Health Technology Assessment
Dépistage du cancer colorectal : connaissances scientifiques actuelles et impact budgétaire pour la Belgique

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Federaal Kenniscentrum voor de gezondheidszorg
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Centre fédéral d'expertise des soins de santé (KCE).
62 Rue de la Loi
B-1040 Bruxelles
Belgium

Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85

Email : info@centredexpertise.fgov.be
Web : http://www.centredexpertise.fgov.be

Health Technology Assessment Dépistage du cancer colorectal : connaissances scientifiques actuelles et impact budgétaire pour la Belgique

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CHRIS DE LAET, MATTIAS NEYT, IMGARD VINCK, MURIELLE LONA, IRINA CLEEMPUT, STEFAAN VAN DE SANDE

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Auteurs :	Chris De Laet, Mattias Neyt, Imgard Vinck, Murielle Lona, Irina Cleemput, Stefaan Van De Sande
Experts externes :	Norbert Blanckaert (UZ Leuven), Jerôme de Roubaix (Communauté française), André Dufour (SSMG), Frans Govaerts (Domus Medica), Stefaan Gryspeerdt (SZ Roeselaere), Michel Melange (UCL Mont Godinne), Marc Polus (CHU Sart Tilman), Peter Suenaert (UZ Antwerpen), Eric Van Cutsem (UZ Leuven), Elizabeth Van Eycken (Registre National du Cancer), Pieter Vandenbulcke (Vlaamse Gemeenschap)
Validateurs :	Jean Faivre (CHU Dijon, France), Marc Peeters (UZ Gent), Marjolein Van Ballegooijen (Erasmus University Medical Center Rotterdam, Pays-Bas)
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PREFACE

Le cancer colorectal constitue en ordre de fréquence la troisième cause de cancer chez les hommes et la deuxième chez les femmes. Il occupe aussi la deuxième position en ce qui concerne la mortalité par cancer. L'occurrence du cancer colorectal augmente avec l'âge, et chaque année, le diagnostic de ce cancer est posé chez environ 7700 Belges. La durée de vie après diagnostic ainsi que le traitement du cancer colorectal sont très étroitement liés au stade de la maladie au moment du diagnostic: plus la tumeur est localisée, meilleur est le pronostique. Ces éléments justifient d'examiner l'intérêt d'un programme de dépistage.

La plupart des recommandations, y compris celles de la Commission Européenne, insistent sur un dépistage de ce cancer à partir de l'âge de 50 ans environ. Cependant, les décideurs internationaux ont jusqu'à présent été très réticents à initier des programmes de dépistage, essentiellement en raison de la faible sensibilité du test le plus utilisé – la détection de sang dans les selles - et d'un taux de participation potentiellement bas. Au cours des dernières années, un certain nombre de pays européens ont démarré un programme pilote pour évaluer la faisabilité d'un dépistage organisé du cancer colorectal.

Faut-il en lancer un également en Belgique ? Si les décideurs politiques considèrent comme prioritaire un programme de dépistage du cancer colorectal au niveau communautaire et fédéral, alors ce rapport fournit les bases scientifiques pour avancer dans cette direction. Indiscutablement, un tel programme doit être organisé de façon professionnelle et être accompagné d'un contrôle de la qualité. Un programme de dépistage mal organisé est en effet potentiellement plus néfaste que l'absence de programme et constitue un gaspillage de ressources.

Le programme de dépistage du cancer colorectal a par ailleurs un prix. L'évaluation de son impact budgétaire est présentée dans ce rapport et peut aussi apporter un éclairage utile à la décision.

Jean-Pierre CLOSON
Directeur Général Adjoint

Dirk RAMAEKERS
Directeur Général

Résumé du rapport

Ce rapport Health Technology Assessment (HTA) fait la synthèse des « données probantes » scientifiques sur l'efficacité et le rapport coût-efficacité du dépistage du cancer colorectal . Il examine également de quelle manière un programme potentiel de dépistage du cancer colorectal peut être introduit efficacement en Belgique. A cet effet, nous évaluons systématiquement la littérature scientifique, nous décrivons les directives existantes concernant le dépistage et la surveillance et nous effectuons une estimation de l'impact budgétaire résultant de l'introduction d'un tel programme. Nous discutons aussi des principales incertitudes liées à l'introduction de ce dépistage en Belgique.

Conclusions

Pourvu que les exigences organisationnelles soient rencontrées, le dépistage du cancer colorectal satisfait clairement aux critères classiques de Wilson et de Jungner ainsi qu'à l'extension récente de ces critères qui traite des questions pratiques et éthiques. Ces nouveaux critères soulignent principalement que les programmes de dépistage devraient se dérouler de manière concertée avec des garanties de qualité et un contrôle de qualité, être accessible à tous et contenir une information complète et facilement compréhensible sur les avantages attendus et les inconvénients possibles. L'objectif est que chacun puisse décider en toute liberté et en toute connaissance de cause de participer au programme.

Pour le dépistage du cancer colorectal, nous constatons que, dans le passé, seul le dépistage opportuniste était d'usage dans la plupart des pays. Ces dernières années, un certain nombre de pays ont initié des projets pilotes de dépistage organisé. Le but principal de ces projets pilotes est de déterminer la forme optimale de dépistage pour ces pays.

En Belgique, le cancer colorectal est la troisième forme la plus fréquente de cancer chez les hommes et la deuxième forme chez les femmes ; ce cancer représente la deuxième cause de mortalité due au cancer. L'apparition du cancer colorectal augmente avec l'âge et chaque année, le cancer colorectal est diagnostiqué chez environ 7.700 belges. La survie après le diagnostic et le traitement du cancer colorectal est fortement associée au stade de la maladie au moment du diagnostic: le diagnostic est d'autant meilleur que la tumeur est bien localisée. C'est la raison principale pour laquelle la détection précoce du cancer colorectal devrait être envisagée.

La plupart des cancers colorectaux apparaissent chez des individus sans indication apparente de risque élevé mais un quart des cancer colorectaux apparaissent chez les personnes présentant un risque élevé connu, soit lié à des antécédents familiaux, soit lié à des antécédents personnels. Ce groupe (selon nos estimations environ 15% de la population) ne rentre pas en ligne de compte pour un programme de dépistage. Néanmoins, il est important que ces individus bénéficient d'un suivi. Dès lors, nous avons donné, dans ce rapport, un aperçu des directives qui existent pour les personnes à risque accru.

Au niveau mondial, il existe de nombreuses directives sur le dépistage et le suivi du cancer colorectal et nous décrivons plusieurs d'entre elles. Toutes les directives recommandent le dépistage à partir de 50 ans, mais elles ne se prononcent pas sur la limite d'âge supérieure et ni sur les techniques optimales de dépistage. Lorsque le FOBT (*Fecal Occult Blood Test* ou recherche de sang occulte dans les selles) est choisi comme test de dépistage, alors le FOBT non-rehydraté effectué par le patient à domicile est choisi de manière unanime. Toutes les directives conseillent aussi la colonoscopie totale comme premier choix chez les personnes présentant un risque accru. Les directives pour le suivi des personnes à risque accru ne sont pas unanimes sur la stratification exacte du risque et sur les limites d'âge étant donné que la plupart des recommandations pour les sous-groupes de population sont principalement le reflet des pratiques empiriques. Bien que toutes les directives plaident pour un dépistage, les décideurs politiques à l'étranger ont été jusqu'à présent réticents à introduire des programmes nationaux de dépistage, surtout en raison de la sensibilité faible du test utilisé, le gFOBT (*guaiac based FOBT*).

L'efficacité du dépistage de la population a été examinée chez les hommes et les femmes à partir de l'âge de 45 ou 50 ans et jusque l'âge de 75 ans. Il n'existe des preuves suffisantes de haute qualité que le dépistage réduit la mortalité liée au cancer colorectal que pour le gFOBT. La diminution estimée de cette mortalité est d'environ 15% dans les méta-analyses des essais contrôlés randomisés (RCT). Pour les autres techniques qui peuvent être considérées comme tests de dépistage primaires comme le iFOBT (*immunochemical FOBT*), la sigmoïdoscopie flexible, la colonoscopie, la colonoscopie virtuelle et la détection de l'ADN dans les selles, il n'y a pas encore actuellement de données probantes directes garantissant que le dépistage de masse réduise la mortalité liée au cancer colorectal. Toutes ces études soulignent l'importance cruciale du *"taux de participation"* afin d'atteindre effectivement les objectifs d'une réduction de la mortalité liée au cancer colorectal.

Les évaluations économiques les plus fiables sont basées sur des données cliniques probantes provenant des RCT, alors que d'autres évaluations économiques sont principalement basées sur des hypothèses qui sont pour le moins purement spéculatives et parfois non crédibles. Les évaluations économiques montrent que le dépistage gFOBT annuel ou biennal (suivi par une colonoscopie pour les participants avec un test positif) est une intervention coût efficace. Les ratio incrémentaux de coût efficacité (Incremental Cost Effectiveness Ratio ou *ICER*) varient entre € 2.000 par année de vie gagnée et € 30.000 pour des sous-groupes spécifiques (jeunes). Ces ICER sont principalement sensibles à la fréquence du dépistage (le test répété tous les 2 ans a un meilleur ICER que le test annuel), à la sensibilité et la spécificité du test (le test non réhydraté qui est moins sensible mais plus spécifique a de meilleurs ICER) et au coût du test de dépistage (aussi bien le FOBT que la colonoscopie subséquente). Ces évaluations économiques montrent aussi que le choix du groupe cible optimal (tranches d'âge) a une influence importance sur le ICER. Cela vaut également pour le taux de participation dans le cas du dépistage initial et pour le taux d'acceptation des individus avec FOBT positif à subir la colonoscopie (aussi appelé *compliance*). A l'heure actuelle, il n'y a pas de données probantes indiquant que le iFOBT est plus coût efficace. Toutes les évaluations économiques évaluant la colonoscopie comme technique de dépistage primaire sont basées sur des hypothèses hautement optimistes surtout en ce qui concerne le taux de participation.

Des programmes de dépistage ont été testés dans différents pays, mais il n'y a, pour le moment, que quelques pays comme la Finlande et l'Australie qui possèdent un programme national pour le dépistage du cancer colorectal. Dans les pays avec un programme national ou régional, le FOBT est utilisé comme test (principalement le gFOBT biennal).

Afin d'estimer les conséquences financières de l'introduction d'un programme de dépistage gFOBT biennal en Belgique, nous avons effectué une analyse de l'impact budgétaire basée sur les données de la littérature internationale et, pour autant que cela soit possible, sur les données belges de coûts. Nous avons développé 2 scénarios. Dans le premier scénario, le médecin est la figure centrale. Ainsi, chaque individu reçoit une lettre l'invitant à consulter son généraliste afin de recevoir de l'information et des conseils sur le programme de dépistage. Si l'individu est prêt à participer, il reçoit de son généraliste le kit test avec les instructions pour l'utilisation à domicile et pour l'envoi. Les résultats sont communiqués au participant et à son généraliste. Le suivi et la prescription éventuelle d'une colonoscopie se font par le généraliste. Ce scénario est à comparer dans les grandes lignes avec le modèle français et nous l'appelons par la suite *"le modèle médecin généraliste"*. Dans le deuxième scénario, l'individu reçoit le kit test à la maison, avec les instructions sur le programme, les critères d'inclusion, et le manuel d'utilisation pour le kit. Dans ce scénario, le participant consulte le généraliste seulement lorsque le test FOBT est positif afin d'obtenir de l'information, des conseils et la prescription d'une colonoscopie. Nous l'appelons par la suite *"le modèle mailing"*

Etant donné les incertitudes actuelles concernant les données, nous avons effectué des analyses de sensibilité probabilistes et les résultats ont été exprimés avec des intervalles de confiance de 95% (IC). Les coûts annuels liés à un programme de dépistage gFOBT répété tous les 2 ans pour les hommes et les femmes entre 50 et 74 ans seraient de 35 millions d'euros (€35.000.000) pour le premier tour de dépistage dans le modèle du

médecin généraliste (IC: 18-52 M€). Les coûts estimés par cancer colorectal détecté sont d'environ € 50.000. Un programme semblable avec les mêmes effets dans le cadre du " modèle mailing " coûterait environ 20 M€ (IC: 14-26 M€) et le coût par cancer colorectal détecté serait ici d'environ € 29.000.

L'incertitude la plus importante pour le coût total du programme est le taux de participation qui a un effet important sur le nombre de tests exécutés (FOBT et colonoscopies). Pour ce paramètre crucial, nous ne disposons pas de chiffres relatifs à la situation belge et les chiffres provenant de l'étranger sont très divergents. Un taux minimum de participation est important, non seulement en ce qui concerne les coûts mais également pour la pertinence sociale du programme. Il est difficile de donner un seuil précis de participation mais il se situe vraisemblablement dans un intervalle de 40 à 50%. D'autres incertitudes importantes résident dans les coûts du programme (coûts du mailing, campagne, etc.) qui sont très dépendants de l'organisation du programme. Par ailleurs, il subsiste aussi des incertitudes concernant la compliance vis-à-vis de la colonoscopie après un FOBT positif et les pourcentages de détection de cancers colorectaux et d'adénomes par colonoscopie après un FOBT positif. Notre analyse de l'impact budgétaire estime le nombre de colonoscopies dans le cadre du programme FOBT biennal avec l'Hemoccult II à environ 10.000 colonoscopies par an au cours du premier tour du dépistage et un peu moins de colonoscopies au cours des années suivantes. Comparativement, ce nombre représente 10% du total des 100.000 colonoscopies effectuées chaque année en Belgique.

Recommendations et Agenda de Recherche

Ce rapport Health Technology Assessment montre que le dépistage du cancer colorectal avec test guaiac FOBT répété tous les 2 ans, suivi par une colonoscopie lorsque le test est positif, peut être un programme de dépistage coût efficace pour les individus de 50 ans et plus. En outre, ce type de dépistage est conforme à la recommandation du Conseil Européen du 2 décembre 2003.

Avant qu'un tel programme ne puisse être introduit de manière efficace, un certain nombre de problèmes doivent être abordés et solutionnés. C'est pourquoi, nous recommandons que la première étape soit la mise sur pied de quelques programmes pilotes qui puissent analyser quelques unes de ces incertitudes sur le terrain.

Si les décideurs politiques compétents au niveau fédéral et au niveau communautaire retiennent le dépistage du cancer colorectal comme une priorité pour la politique des soins de santé, la décision d'introduire à terme un programme de dépistage du cancer colorectal peut être appuyée par le présent rapport scientifique. Cette décision doit aussi intégrer les aspects organisationnels qui incluent:

- la portée du dépistage (catégories d'âge)
- les objectifs du dépistage (participation minimale et compliance)
- horizon temporel pour une introduction complète (2 à 4 ans semble être raisonnable étant donné le temps nécessaire pour les programmes pilotes)
- financement du programme
- organisation de la gestion du programme (gestion séparée du dépistage du cancer colorectal ou gestion commune avec d'autres programmes de dépistage)
- contrôle de qualité et système d'enregistrement du dépistage
- éventuelle collaboration internationale (européenne)

Afin d'éliminer les incertitudes actuelles sur l'implémentation d'un programme de dépistage, nous recommandons la mise sur pied de quelques programmes pilotes. Nous partons de l'hypothèse que ces projets pilotes dureront environ 2 à 4 ans et qu'ils feront l'objet d'évaluations intermédiaires. Ces projets doivent tester la faisabilité pratique du programme en mettant l'accent sur:

- le design du programme: ces modèles (modèle médecin généraliste et/ou modèle mailing) fonctionnent-ils dans le contexte belge et quelle est l'influence de ce choix sur le taux de participation?
- organisation et implémentation d'un système d'enregistrement du dépistage
- comment assurer que les colonoscopies nécessaires puissent être exécutées (capacité de colonoscopies) et comment en assurer le contrôle de qualité

Les projets pilotes doivent aussi examiner spécifiquement les incertitudes:

- participation, compliance et acceptation du programme en Belgique
- prévalence d'un risque accru de cancer colorectal dans la population
- taux positifs et sensitivité/spécificité du FOBT dans la pratique quotidienne
- pourcentages de détection des cancers colorectaux et d'adénomes
- inconvénients et effets secondaires liés au screening
- optionnel: test de la performance du iFOBT dans la pratique

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ABBREVIATIONS

Acronym	Full text
ACCP	European Advisory Committee on Cancer Prevention
ACG	American College of Gastroenterologists
ACP	American Collega of Physicians
ACPGBI	Association of Coloproctology for Great Britain and Ireland
ACS	American Cancer Society
AFAP	Attenuated Familial Adenomatous Polyposis
AGA	American Gastroenterological Association
AGEQ	Association des Gastro-Entérologues du Québec
AGEQTF	Quebec Association of Gastroenterology Task Force
AGREE	Appraisal of Guidelines Research and Evaluation
AHRQ	Agency for Healthcare Research and Quality USA (formerly AHCPR)
AHTAC	Australian Health Technology Advisory Committee
AJCC	American Joint Committee on Cancer
ANAES	Agence Nationale d'Accréditation et d'Evaluation en Santé – France; nowadays: HAS - Haute Autorité de Santé
AR	Absolute Risk
ASCO	American Society of Clinical Oncology
ASGE	American Society for Gastrointestinal Endoscopy
AUD	Australian dollars
BSG	British Society of Gastroenterology
CBO	Centraal BegeleidingsOrgaan, nowadays Kwaliteitsinstituut voor de Gezondheidszorg CBO - Nederland
CDC	Centers for Disease Control and prevention (US)
CDN	Canadian dollars
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-effectiveness Analysis
CEBM	Centre for Evidence-Based Medicine
CER	Control Event Rate
CG	Control Group
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CPG	Clinical Practice Guidelines
CR	Crude (all ages) incidence rate (n/100.000 person years)
CRC	Colorectal Cancer
CRCT	Cochrane Central Register of Controlled Trials
CRD	Centre for Reviews and Dissimination
CT	Computerised Tomography
CTC	Computerised Tomography Colonography
CTFPHC	Canadian Task Force on Preventive Health Care
Cum Se	Cumulative Sensitivity (after primary screening and re-screening)
DALY	Disability Adjusted Life Years
DARE	Database of Abstracts of Reviews of Effectiveness
DCBE	Double Contrast Barium Enema
DKFZ	Deutsche Krebsvorschungszentrum
DKK	Danish Krone
DPCP	Detectable Pre-Clinical Phase
DRE	Digital Rectal Examination
EDD	Extensive Distal Diverticulosis
EER	Experimental Event Rate

ESR	Age standardised incidence rate, using the European Standard Population (n/100.000 person years)
EU	European Union
FAP	Familial Adenomatous Polyposis
FDR	First Degree Relative
FIT	Faecal Immunochemic Test = iFOBT
FNR	False Negative Rate
FOBT	Faecal Occult Blood Test
FPR	False Positive Rate
FS	Flexible Sigmoidoscopy
GCP	Good Clinical Practice
gFOBT	Guaiac Faecal Occult Blood Test
GP	General Practitioner
HAS	Haute Autorité de Santé
HC/PR	Health Care/Prevention Recommendations
HCR	Health Care Recommendation
HMO	Health Maintenance Organization
HNPCC	Hereditary Nonpolyposis Colorectal Cancer
HTA	Health Technology Assessment
IBD	Inflammatory Bowel Disease
ICER	Incremental Cost-Effectiveness Ratio
ICSI	Institute of Clinical Systems Improvement
ICT	ImmunoChemical Test = iFOBT
iFOBT	Immunochemical Faecal Occult Blood Test
IKC	Integraal Kanker Centrum (Netherlands)
ITS	Intention To Screen
ITT	Intention To Treat
JNCI	Journal of the National Cancer Institute
M2 - PK	M2 Pyruvate kinase
MOH	Ministry of Health (NZ)
MRI	Magnetic Resonance Imaging
MSI	Microsatellite instability
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute (USA)
NGC	National Guidelines Clearinghouse
NHC	National Health Committee (NZ)
NHS	National Health Service (UK)
NHS EED	NHS Economic Evaluation database
NNS	Number Needed to Screen
NPV	Negative Predictive Value
NSU	National Screening Unit (NZ)
NZ	New Zealand
NZD	New Zealand dollars
NZGG	New Zealand Guidelines Group
NZHTA	New Zealand Health Technology Assessment
OECD	Organisation for Economic Cooperation and Development
oFOBT	office-based FOBT
OMGE	Organisation Mondiale de Gastro-Entérologie
OR	Odds Ratio
p.a.	per annum
PCR	Polymerase Chain Reaction
PPV	Positive Predictive Value

QALY	Quality Adjusted Life Years
RCT	Randomized Controlled Trial
RR	Relative Risk
RRR	Relative Risk Reduction
SD	Standard Deviation
SDR	Second Degree Relative
Se	Sensitivity
SEER	Surveillance, Epidemiology and End Results registry
SG	Screening Group
SIGN	Scottish Intercollegiate Guidelines Network
SFED	Société Française d'Endoscopie Digestive
Sp	Specificity
TCE	Total Colon Evaluation
TCR	Two Close Relatives
TDR	Third Degree Relative
TPR	True Positive Rate
UICC	Union Internationale Contre le Cancer - International Union Againt Cancer
UK	United Kingdom
UMHS	University of Michigan Health System
US	United States of America
USD	United States dollars
USPSTF	U.S. Preventive Services Task Force
VA	Veterans Affairs
WGO	World Gastroenterlogy Organisation
WHO	World Health Organization
WSR	Age standardised incidence rate, using the World Standard Population (n/100.000 person years)

GLOSSARY

Term	Description
Absolute risk	The observed or calculated probability of an event in the population under study.
Absolute risk difference	The difference in the risk for disease or death between an exposed population and an unexposed population.
Absolute risk reduction	The difference in the absolute risk (rates of adverse events) between study and control populations.
Adherence	Refers, in a general sense, to the completion of a screening test or procedure
Adjustment	A summarizing procedure for a statistical measure in which the effects of differences in composition of the populations being compared have been minimized by statistical methods
Association	Statistical dependence between two or more events, characteristics, or other variables. An association may be fortuitous or may be produced by various other circumstances; the presence of an association does not necessarily imply a causal relationship.
Asymptomatic	Asymptomatic people are those who do not have one or more symptoms (e.g., rectal bleeding) that may be due to a disease (e.g., colorectal cancer).
Before and after study	A situation in which the investigator compares outcomes before and after the introduction of a new intervention.
Bias Systematic error	Deviation of results or inferences from the truth, or processes leading to such deviation. Any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth.
Blind(ed) study Masked study	A study in which observer(s) and/or subjects are kept ignorant of the group to which the subjects are assigned, as in an experimental study, or of the population from which the subjects come, as in a nonexperimental or observational study. Where both observer and subjects are kept ignorant, the study is termed a double-blind study. If the statistical analysis is also done in ignorance of the group to which subjects belong, the study is sometimes described as triple blind. The purpose of "blinding" is to eliminate sources of bias.
Case control study	An epidemiological study involving the observation of cases (persons with the disease, such as colorectal cancer) and a suitable control (comparison, reference) group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the past history of the people in the two groups with regard to how frequently the attribute is present (= retrospective comparison).
Case-series	Report of a number of cases of disease.
Causality	The relating of causes to the effects they produce. Most of epidemiology concerns causality and several types of causes can be distinguished. It must be emphasized, however, that epidemiological evidence by itself is insufficient to establish causality, although it can provide powerful circumstantial evidence.
Cohort study	An epidemiological study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed in different degrees, to a factor or factors hypothesised to influence the probability of occurrence of a given disease or other outcome. Studies usually involve the observation of either a large population, or for a prolonged period (years), or both.

	Follow-up of exposed and non-exposed defined groups, with a comparison of disease rates during the time covered.)
Co-interventions	Interventions other than the treatment under study that are applied differently to the treatment and control groups. Cointervention is a serious problem when double blinding is absent or when the use of very effective non-study treatments is permitted.
Co-morbidity	Coexistence of a disease or diseases in a study participant in addition to the index condition that is the subject of study.
Comparison group	Any group to which the index group is compared. Usually synonymous with control group.
Compliance	Refers to completion of all tests or examinations when sequential offers are made to the same persons regardless of whether they completed a prior test
Confidence interval	The range of numerical values in which we can be confident (to a computed probability, such as 95%) that the population value being estimated will be found. Confidence intervals indicate the strength of evidence; where confidence intervals are wide, they indicate less precise estimates of effect. The larger the trial's sample size, the larger the number of outcome events and the greater becomes the confidence that the true relative risk reduction is close to the value stated. Thus the confidence intervals narrow and "precision" is increased. In a "positive finding" study the lower boundary of the confidence interval, or lower confidence limit, should still remain important or clinically significant if the results are to be accepted. In a "negative finding" study, the upper boundary of the confidence interval should not be clinically significant if you are to confidently accept this result.
Confounding	A situation in which the measure of the effect of an exposure on risk is distorted because of the association of exposure with other factor(s) that influence the outcome under study.
Confounding variable, Confounder	A third variable that indirectly distorts the relationship between two other variables, because it is independently associated with each of the variables.A variable that can cause or prevent the outcome of interest, is not an intermediate variable, and is associated with the factor under investigation. A confounding variable may be due chance or bias. Unless it is possible to adjust for confounding variables, their effects cannot be distinguished from those of factor(s) being studied.
Continous screening	Periodic provision of an opportunity for diagnostic testing to a population of individuals who are asymptomatic and at increased risk for disease (or perception of increased risk)
Control event rate	The percentage of the control/nonexposed group who experienced outcome in question.
Cost-benefit analysis	A form of economic evaluation in which an attempt is made to value the consequences or benefits of a medical intervention in monetary terms so that these may be compared with the costs.
Cost-effectiveness analysis	A form of economic evaluation in which the consequences or benefits of medical interventions are measured in terms of an appropriate health effect, such as life years saved, without placing a monetary value on such effects. These are balanced against the monetary cost of the intervention.
Cost-minimisation analysis	A form of economic evaluation in which it can be shown that outcomes are identical and, therefore, only costs are compared.
Cost-utility	A form of economic evaluation in which the consequences or benefits

analysis	of medical interventions are adjusted by health state preferences or utility weights, such as in quality adjusted life years (QALYs) or disability adjusted life years (DALYs).
Coverage	The number, percent, or proportion of eligible people reached by a program, i.e. completed at least one test or examination when sequential offers are made to the same people, regardless of whether they completed a prior test
Cross-sectional study	A study that examines the relationship between diseases (or other health related characteristics), and other variables of interest as they exist in a defined population at one particular time.
Day patient	A person who is admitted and discharged from hospital on the same day.
Descriptive study	A study concerned with, and designed only to describe the existing distribution of variables, without regard to causal or other hypotheses.
Determinant	Any definable factor that effects a change in a health condition or other characteristic.
Diagnostic test efficacy	The impact and usefulness of a diagnostic test expressed in terms of its technical properties.
Dose-response relationship	A relationship in which change in amount, intensity, or duration of exposure is associated with a change-either an increase or decrease-in risk of a specified outcome.
Effectiveness	A measure of the extent to which a specific intervention, procedure, regimen, or service, when deployed in the field in routine circumstances, does what it is intended to do for a specified population. A measure of the benefit resulting from an intervention for a given health problem under usual conditions of clinical care for a particular group; this form of evaluation considers both the efficacy of an intervention and its acceptance by those to whom it is offered, answering the question, "Does the practice do more good than harm to people to whom it is offered?"
Efficacy	A measure of the benefit resulting from an intervention for a given health problem under the ideal conditions of an investigation; it answers the question, "Does the practice do more good than harm to people who fully comply with the recommendations?"
Efficiency	The effects or end results achieved in relation to the effort expended in terms of money, resources and time. The extent to which the resources used to provide a specific intervention, procedure, regimen, or service of known efficacy and effectiveness are minimised.
Elective services	Non-urgent services for conditions which do not need immediate treatment. This includes services for patients with semi-urgent or non life-threatening chronic conditions that tend to be stable or slowly deteriorate over time.
Epidemiology	The study of the distribution and determinants of health-related states or events in specified populations.
Evidence based	Based on valid empirical information.
Evidence table	A summary display of selected characteristics (e.g., methodological design, results) of studies of a particular intervention or health problem.
Exclusion Criteria	Conditions which preclude entrance of candidates into an investigation even if they meet the inclusion criteria.
Experimental event rate	The percentage of intervention/exposed group who experienced outcome in question.
External validity	Refers to the appropriateness by which the results of a study can be

	applied to non-study patients or populations.
False negative result	A negative test result in a person who does have the condition being tested for.
False positive result	A positive test result in a person who does not have the condition being tested for.
Final truth determination	Use of a reference standard to provide an accurate or "truth" diagnosis for verification of positive and negative diagnoses by a screening or diagnostic test (see also "reference standard").
Follow-up	Observation over a period of time of an individual, group, or initially defined population whose relevant characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	Applicability of the results to other populations.
Gold standard	A method, procedure, or measurement that is widely accepted as being the best available.
Grey literature	That which is produced by all levels of government, academics, business and industry, in print and electronic formats, but which is not controlled by commercial publishers.
High risk groups	Usually refers to groups that have been identified as having a higher than average incidence of the disease in question.
Histology	The microscopic study of the minute structure and composition of tissues.
Internal validity	Refers to the integrity of the experimental design of a study.
Incidence	The number of new cases of illness commencing, or of persons falling ill, during a specified time period in a given population.
Indicator	An item of quantitative or qualitative information reported to enable the monitoring of a condition or the performance of an organisation.
Intention to treat Intention to screen	A method for data analysis in a randomised controlled trial in which individual outcomes are analysed according to the group to which they were randomised, even if they never received the treatment to which they were assigned. By simulating practical experience it provides a better measure of effectiveness (versus efficacy).
Interviewer bias Observer bias	Systematic error due to interviewer's c.q. observer's subconscious or conscious gathering of selective data.
Likelihood ratio	Ratio of the probability that a given diagnostic test result will be expected for a patient with the target disorder rather than for a patient without the disorder.
Matching	The process of making a study group and a comparison group comparable with respect to extraneous factors.
Mean	Calculated by adding all the individual values in the group and dividing by the number of values in the group.
Median	Any value that divides the probability distribution of a random variable in half. For a finite population or sample the median is the middle value of an odd number of values (arranged in ascending order) or any value between the two middle values of an even number of values.
Meta-analysis	The process of using statistical methods to combine the results of different studies. The systematic and organised evaluation of a problem, using information from a number of independent studies of the problem.
Metachronous tumor	If a tumor with the same histology is identified in the same site at least two months after the original diagnosis (with pre-operative complete colonoscopy or one negative post-operative colonoscopic follow-up to rule out synchronous tumor), this is called a metachronous primary tumor.
Misclassification	The erroneous classification of an individual, a value, or an attribute

	into a category other than that to which it should be assigned.
Morbidity	Illness.
Mortality rate	The number of deaths from a specified disease that are diagnosed or reported during a defined period of time in a given population.
Multiple regression	Analysis of data that takes into account a number of variables simultaneously.
Natural history	The course of a disease from onset to resolution.
Negative predictive value	The probability a person does not have the disease when the screening test is negative.
Number needed to Screen	The number of patients who would need to be screened, for a given period of time, in order to prevent a single event (i.e. death from colorectal cancer). The smaller the NNS, the fewer people need to be screened to prevent an event. The NNS often varies markedly with risk factors such as age and in general with incidence of the disease in that population.
Number Needed to Treat	The number of patients who must be exposed to an intervention before the clinical outcome of interest occurs; for example, the number of patients needed to treat to prevent one adverse outcome.
Odds	A proportion in which the numerator contains the number of times an event occurs and the denominator includes the number of times the event does not occur.
Odds ratio Cross-product ratio Relative odds	A measure of the degree or strength of an association. In a case control or a cross-sectional study, it is measured as the ratio of the odds of exposure (or disease) among the cases to that among the controls.
Opportunistic screening	The key feature that distinguishes opportunistic screening from screening programs is the lack of a quality process, including routine monitoring and evaluation. Opportunistic screening usually occurs when a person who is presenting to the health system for another reason is asked a question or offered a test in order to detect the presence or confirm the absence of a specific condition. Opportunistic screening may be organised to a greater or lesser degree. However, because there are no attendant quality processes, its safety, effectiveness and costeffectiveness cannot be assessed and guaranteed.
Outpatient	A person who goes to a health care facility for a consultation, and who leaves the facility within three hours of the start of the consultation. An outpatient is not formally admitted to the facility.
Population based screening program	A population-based screening program is one in which screening is systematically offered by invitation to a defined, identifiable population; this requires a means of identifying and inviting the target population, for example through a population register.
Population screening programs	Population screening programs involve screening entire populations or a large and easily identifiable group within a population. The target population group for screening may be defined geographically or by some other characteristics such as gender, age or ethnicity. The New Zealand cervical and breast screening program are examples of population screening programs.
Positive predictive value	The probability that a person actually has the disease when the screening test is positive.
Power	The ability of a study to demonstrate an association if one exists.
Precision	The range in which the best estimates of a true value approximate the true value.
Predictive value	In screening and diagnostic tests, the probability that a person with a positive test is a true positive (i.e., does have the disease), or that a

	person with a negative test truly does not have the disease. The predictive value of a screening test is determined by the sensitivity and specificity of the test, and by the prevalence of the condition for which the test is used.
Prevalence	The number of events in a given population at a designated time (point prevalence) or during a specified period (period prevalence).
Primary care	First contact, continuous, comprehensive and coordinated care provided to individuals and populations undifferentiated by age, gender, disease or organ system.
Prognosis	the possible outcomes of a disease or condition and the likelihood that each one will occur.
Prognostic factor	Demographic, disease-specific, or co-morbid characteristics associated strongly enough with a condition's outcomes to predict accurately the eventual development of those outcomes. Compare with risk factors. Neither prognostic nor risk factors necessarily imply a cause and effect relationship.
Prospective study	Study design where one or more groups (cohorts) of individuals who have not yet had the outcome event in question are monitored for the number of such events which occur over time.
Providers	Organisations and health professionals providing health services.
Random sample	A sample that is arrived at by selecting sample units in such way that each possible unit has a fixed and determinate probability of selection.
Randomised controlled trial	An epidemiologic experiment in which subjects in a population are randomly allocated into groups - rather than by conscious decisions of clinicians or patients - to receive or not receive an experimental preventive or therapeutic procedure, manoeuvre, or intervention. Randomised controlled trials are generally regarded as the most scientifically rigorous method of hypothesis testing available in epidemiology. If the sample size is large enough, this study design avoids problems of bias and confounding variables by assuring that both known and unknown determinants of outcome are evenly distributed between treatment and control groups.
Recall bias	Systematic error due to the differences in accuracy or completeness of recall to memory of past events or experiences.
Reference standard	An independently applied test that is compared to a screening or diagnostic test being evaluated in order to verify the latter's accuracy. A reference standard, therefore, provides an accurate or "truth" diagnosis for verification of positive and negative diagnoses. It is sometimes described as providing "final truth determination".
Referral filter bias	The sequence of referrals that may lead patients from primary to tertiary centres raises the proportion of more severe or unusual cases, thus increasing the likelihood of adverse or unfavorable outcomes.
Relative risk	The ratio of the risk of disease or death of those exposed to the risk compared to the risk among those unexposed, in a specified period of time. It is a measure of the strength or degree of association applicable to cohort studies and RCTs.
Relative risk reduction	The proportional reduction in rates of events between experimental and control participants in a trial. If there was an increase in the rate of events in the experimental group, the term would then be relative risk increase.
Reliability Repeatability Reproducibility	The results of a test or measure are identical or closely similar each time it is conducted.
Repeat screening	Rescreening offers made only to persons completing a prior test or

	examination
Retrospective study	Study design in which cases where individuals who had an outcome event in question are collected and analyzed after the outcomes have occurred (see also Case-control study).
Risk factor	An exposure or aspect of personal behaviour or lifestyle, which on the basis of epidemiologic evidence is associated with a health-related condition. Patient characteristics or factors associated with an increased probability of developing a condition or disease in the first place. To compare with prognostic factors. Neither risk or prognostic factors necessarily imply a cause and effect relationship.
Screening	Screening is the examination of asymptomatic people in order to classify them as likely or unlikely to have the disease that is the object of screening. The aim of screening is to detect disease before it is clinically apparent, and for this to improve the outcome for people with the disease.
Secondary care	Surgical and medical services that are generally provided in a hospital setting. In many cases, access to these services is by referral from a primary care health professional such as a general practitioner.
Selection bias	Any error in selecting the study population such that the people who are selected to participate in a study are not representative of the reference population or, in analytic studies the comparison groups are not comparable. A bias in assignment or a confounding variable that arises from study design rather than by chance. These can occur when the study and control groups are chosen so that they differ from each other by one or more factors that may affect the outcome of the study.
Sensitivity	Sensitivity is the proportion of truly diseased persons, as measured by the gold standard, in a screened population who are identified as diseased by a screening test. Sensitivity is a measure of the probability of correctly diagnosing a case, or the probability that any given case will be identified by the test.
Sensitivity analysis	A method to determine the robustness of an assessment by examining the extent to which results are affected by changes in methods, values of variables, or assumptions.
Sequential screening	Rescreening offers made to the same persons regardless of whether they completed a prior test.
Specificity	The proportion of truly nondiseased persons, as measured by the gold standard, who are so identified by the diagnostic test under study. It is a measure of the probability of correctly identifying a non-diseased person with a screening test.
Stratification	Division into groups. Stratification may also refer to a process to control for differences in confounding variables, by making separate estimates for groups of individuals who have the same values for the confounding variable.
Strength of Inference	The likelihood that an observed difference between groups within a study represents a real difference rather than mere chance or the influence of confounding factors, based on both p values and confidence intervals. Strength of inference is weakened by various forms of bias and by small sample sizes.
Surveillance, Epidemiology and End Results (SEER) registry	A set of geographically defined, population-based, central cancer registries in the United States, operated by local non-profit organisations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers

	to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.
Survival curve	A graph of the number of events occurring over time or the chance of being free of these events over time. The events must be discrete and the time at which they occur must be precisely known. In most clinical situations, the chance of an outcome changes with time. In most survival curves the earlier follow-up periods usually include results from more patients than the later periods and are therefore more precise.
Symptomatic	Symptomatic people are those who have one or more symptoms (e.g., rectal bleeding)
Synchronous tumor	If a tumor with the same histology is identified in the same site within 2 months after the original diagnosis (with pre-operative complete colonoscopy or one negative post-operative colonoscopic follow-up to rule out synchronous tumor), this is called a synchronous primary tumor.
Systematic review	Literature review reporting a systematic method to search for, identify and appraise a number of independent studies.
Term	Definition
True negative	A test correctly identifies a person without the disease.
True positive	A test correctly identifies a person with the disease.
Validity	The extent to which a variable or intervention measures what it is supposed to measure or accomplishes what it is supposed to accomplish.

1 GENERAL INTRODUCTION TO CANCER SCREENING

1.1 DEFINITION OF SCREENING

In medicine, screening is typically a strategy used to identify disease in a primarily unsuspecting population. Unlike in curative medicine, in screening a test or intervention is performed on individuals without any known clinical indication of disease. The intention is to identify disease in an earlier stage, thus enabling earlier intervention and management in the hope to reduce mortality and suffering from disease.

However, there remains a certain overlap with pre-emptive searching for disease in suspected population subgroups at more than average risk and surveillance of those with confirmed disease or genetic predisposition, as we will discuss further on.

1.2 PRINCIPLES OF SCREENING

The principles underlying an effective screening intervention were originally developed by Wilson and Jungner in 1968[1], and these are summarized below:

1. The condition should be an important health problem for the individual and community.
2. There should be an accepted treatment or useful intervention for patients with the disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development for latent to declared disease, should be adequately understood.
8. There should be an agreed policy for referring for further examination and whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a "once and for all" project.

The essence of these principles is that the target disease process should be a common problem that has a better outcome when treated at an early stage, and that the test employed is acceptable and sufficiently sensitive, specific, and inexpensive to be cost-effective.

Although these original principles remain largely valid, other considerations are to be made. In its 'Report on the Dutch consensus development meeting for implementation and further development of population screening for colorectal cancer based on FOBT'[2], the Dutch National Health Council[3] extended the

Wilson & Jungner criteria, adding additional criteria on practical[4] and ethical[5] issues:

11. Treatment started at an early stage should be of more benefit than treatment started later.
12. The time between test and result and between result and treatment must be as short as possible.
13. The recruitment procedure should not limit people in their freedom to participate or not in the screening program.
14. Potential participants should receive adequate information about pro and cons of participation. Benefits and risks should also be well known to health care providers[6].
15. Public education should promote a broad accessibility of the program. It should however not include a moral pressure effect.
16. There should be quality assurance (QA) and quality control (QC) procedures for the whole screening program.
17. Screening programs are concerted actions meeting organisational and managerial requirements.

1.3 PITFALLS AND POSSIBLE HARMS

To many people, screening intuitively seems an appropriate thing to do, because catching disease earlier seems better. However, no screening test is perfect. There will always be problems with incorrect results and adverse effects. Before a screening program is implemented, it should thoroughly be studied to ensure that putting it in place would do more good than harm.

1.3.1 Biases

Various factors can cause the screening test to appear more successful than it really is. A number of different biases can distort the results[7-13]:

1. Length-time bias arises from the fact that intermittent screening tests will tend to pick up slow-growing, indolent disease that is likely to have a better prognosis than the rapidly advancing disease, which is more likely to appear with symptoms between screening intervals. As a consequence, screening in general may tend to detect some cancers that would not have killed the patient or even not have been detected prior to death from other causes.
2. Lead-time bias arises from early diagnosis itself. By screening, we intend to diagnose a disease earlier than it would be without screening. Even if in both cases a person dies at the same time, the survival time since diagnosis is longer with screening, simply because in the latter case we diagnosed disease earlier. No additional life has been gained but, looking at raw statistics, screening will appear to increase survival time: this gain is called lead time. If we do not pay attention to what 'survival time' actually means in this context, we might attribute success to a screening test that does nothing but advance diagnosis.
3. Selection bias can arise from the fact that not everyone necessarily will participate in a screening program. There can be factors that differ between those willing to get tested and those

who are not. If people with a higher risk of a disease are more eager to be screened, for instance women with a family history of breast cancer joining a mammography program, then a screening test could cause the disease related mortality to look worse than in non-participants. This is because more people with the disease will participate, resulting in a higher incidence, in the screened population, of people dying from it. Selection bias may also make a test look better than it really is. If a test is more available to young and healthy people (for instance if people have to travel a long distance to get checked) then less people in the target population would be detected with disease, and the test will seem to make a positive difference.

4. Volunteer bias is a special kind of selection bias, created by the fact that screening invitations tend to be more readily accepted by health-conscious individuals who are likely to have a better outcome for reasons other than early detection of the disease. In other words, individuals with a strong interest in health issues are more likely to participate, whereas the risk of these individuals may be lower, due to a more healthy lifestyle.
5. Overdiagnosis bias: screening may identify abnormalities that would never cause a problem in a person's lifetime. An example of this is prostate cancer screening[8, 14]. It has been said that "more men die with prostate cancer than from it". Autopsy studies have shown that a high proportion of men who have died in other ways, have prostate cancer when the prostate is examined under a microscope. Aside from issues arising from unnecessary treatment (prostate cancer treatment is by no means without risk), overdiagnosis makes a study look good at picking up abnormalities, even though they are sometimes harmless.
6. Observation bias or observer bias is error introduced into measurement when observers overemphasize what they expect to find and fail to notice what they do not expect. This is why medical trials are normally double-blind rather than single-blind.

The overall effect of these biases tends to exaggerate the beneficial effect of screening. To prove that screening is producing a real benefit, it is essential to carry out population-based randomized controlled trials in which the group randomized to screening is analyzed as a whole and includes those who refuse the invitation to be screened and those who develop cancers that are not detected by screening (intention-to-screen principle).

1.3.2 End points in RCTs on cancer screening

The most widely accepted end point in randomized cancer screening trials is *disease-specific mortality*. Only if the *disease-specific mortality* in the whole of this group is significantly lower than in the randomly selected group, that is not offered screening, can we be sure that the screening process is producing a truly beneficial effect on disease outcome. The validity of this end point, however, rests on the assumption that cause of death can be determined accurately. An alternative end point is *all-cause mortality*, which depends only on the accurate ascertainment of deaths[15].

Major inconsistencies were identified in disease-specific and all-cause mortality endpoints in randomized cancer screening trials[15]. Because all-cause mortality is

not affected by bias in classifying the cause of death, it should be examined when interpreting the results of randomized cancer-screening trials. The use of *surrogate outcome measures* in screening trials always bears a risk of biasing conclusions.

So, the real question to be answered before spending considerable public health resources on the implementation of a mass screening program, is whether one should consider *overall mortality*[16-18] and quality of survival[19] as the only hard outcome measure of interest, especially in case of unsatisfactory screening uptake.

1.3.3 Adverse effects

Although screening may lead to an earlier diagnosis, not all screening tests have been shown to benefit the person being screened[20-24]. Like any medical test, the tests used in screening are not perfect. The test may miss people who have the disease (false negative) or may appear positive for those without disease (false positive). Besides misdiagnosis and overdiagnosis, other potential adverse effects of screening are:

1. Stress and anxiety caused by a false positive screening result[25].
2. Unnecessary further investigation and treatment of false positive results.
3. Prolonging knowledge of an illness if nothing can be done about it.
4. A false sense of security caused by false negative results, which may even delay final diagnosis.
5. Overuse/waste of medical resources.
6. Unnecessary and uncomfortable procedures looking for a disease that is unlikely.

1.3.4 Target population and appropriateness of screening

It is often assumed that screening applicants are asymptomatic but this is not necessarily so: a screening offer may be more readily accepted by a patient with unreported symptoms. Indeed, a study[26], published in 2005, on 563 consecutive individuals with a positive fecal occult blood test (FOBT) in the Scottish arm of the national colorectal cancer screening pilot has shown that 439 (78,0 %) had one or more lower gastrointestinal symptoms and 124 (22,0 %) were symptom free. Taking adenoma and carcinoma together, 322 (57,2 %) of the subjects were found to have colorectal neoplasia, and 128 (22,7 %) had a completely normal colon, the remaining 113 having minor colorectal lesions. Rectal bleeding was the most common symptom, followed by recent change in bowel habits, abdominal pain, tenesmus, rectal pain besides unexplained weight loss or anaemia. This undoubtly raises the question whether the FOBT was being ordered appropriately, but this issue will be dealt with in the chapter on clinical effectiveness and potential harms of CRC screening.

1.4 SCREENING VERSUS SURVEILLANCE

The New Zealand Guidelines Group[27] defines screening and surveillance as follows:

1. Screening is the examination of asymptomatic individuals in order to classify them as unlikely or likely to have a disease. A national screening program is an example of a population preventive strategy, where everyone in a particular age-group is invited to participate. Such strategy has the potential to identify a high proportion of individuals with early disease in a given population. This proportion depends on the uptake of screening and the sensitivity of the test chosen. Even in cancer screening programs where uptake is high and the screening test is very sensitive, the vast majority of individuals who take part will not have cancer, so that the potential benefits of screening are available to a relatively small group.
2. Surveillance, as opposed to screening, refers to monitoring individuals known to have a disease or to be at increased risk for a disease. For this population the potential benefit of surveillance is higher than that of screening in the population at large, because the prevalence of the disease is higher in this population. Thus, the benefit-to-risk ratio of surveillance is more favourable than the benefit-to-risk ratio of screening. Therefore, for example, individuals who believe themselves to be at increased risk of developing colorectal cancer (CRC) may be more willing to accept the risks associated with surveillance.

Others[28, 29] more restrictively define 'surveillance' as monitoring of patients known to have a specific disease or a genetic predisposition to it and 'screening' as the examination of individuals not (yet) known to have it, irrespective of the risk (average or increased). In this definition screening can either refer to a population based screening program (average risk screening, population or mass screening), or to targeted screening for individuals with established risk factors or personal concerns about it (also called sensitive screening). Both methods imply different objectives and thus different requirements: if the aim is to reduce the burden of disease on a community the approach needed is population screening; this requires the use of a test associated with a high uptake and low cost. If, on the other hand, the aim is to respond to an individual's request for information regarding his disease status, the emphasis must be on a test of high sensitivity and specificity[30].

1.5 IMPLICATIONS FOR COLORECTAL CANCER SCREENING

In dealing with guidelines for CRC screening, one must recognize that in many countries sensitive case finding on an individual basis forms the foundation of so-called screening[31]. Implementation of CRC mass screening programs is indeed tedious, expensive and requires several barriers to be overcome. It might therefore seem logical in some countries to concentrate public health resources on a selected sub-population, in which screening appears to be most meaningful and probably more cost-effective.

Returning to definitions, we have to recognize that the demarcation line between surveillance and targeted screening remains fuzzy: should we consider a proven genetic predisposition as a pre-clinical phase of the disease and thus needing surveillance (follow-up)? And what should be done for patients with a

'high risk category' family history and with an inconclusive genetic predisposition test? Should we label them for targeted screening or for surveillance? However, from the clinical point of view, such questions remain chiefly academic.

Based on the above considerations we framed a general classification scheme for CRC screening and surveillance (Table 1).

Table 1: Classification of CRC screening & surveillance

Classification	(Sub)population involved	CRC risk category
Mass / population screening	Asymptomatic or unreported symptoms Personal and family history negative	Average risk (Low risk)
Targeted / sensitive screening	Positive or suspected family history Strong personal concerns	Possible increased or high risk
Surveillance	Positive personal history = presence of related disease or proven genetic predisposition	Increased risk or high risk (hereditary)

Key messages

- **In population screening programs the target disease should be a common problem that has a better outcome when treated at an earlier stage.**
- **The test used should be acceptable and sufficiently sensitive, specific, and inexpensive as to be cost-effective.**
- **To prove that screening really is beneficial, it is essential to carry out population-based randomized controlled trials in which the group randomized to screening is analyzed as a whole and includes those who refuse the invitation to be screened (intention-to-screen principle) and those who develop cancers that are not detected by screening.**
- **Typically, lead-time bias, length-time bias and selection bias can skew the results of screening trials.**
- **The use of surrogate outcome measures rather than hard outcome measures always bears a risk of biased conclusions.**
- **Overdiagnosis can cause stress and discomfort through unnecessary diagnostic procedures or even unnecessary treatment and its complications. It can also make a study look well performing at picking up abnormalities, even though they might be harmless.**
- **Potential harms of screening are mainly unnecessary investigation and treatment of false positive results and a false sense of security caused by false negative results, which may even delay final diagnosis.**
- **Mass or population screening programs imply different objectives and thus different requirements compared to targeted screening. For mass screening programs to be successful, utmost care should be devoted to a proper organisation and a suitable test in order to maximise participation rates and minimise potential harms.**
- **In many countries sensitive case finding on an individual basis historically forms the foundation of colorectal cancer screening.**

2 EPIDEMIOLOGY OF COLORECTAL CANCER

2.1 INTERNATIONAL CLASSIFICATION

Invasive colorectal cancer (CRC) is a malignant disease that starts in the colon or in the rectum. This definition covers ICD-10 codes[32] C18 (Colon), C19 (RectoSigmoid) and C20 (Rectum) but not C21 (anus and anal canal). In Belgium these ICD-10 codes are used for recording causes of death.

In clinical record registries such as the minimal data sets, however, the ICD-9-CM[33] coding system is still being used. Here, colorectal cancers are covered by codes 153.0 to 154.8 (with exclusion of codes 153.5 = malign neoplasm of appendix and 154.3 = malign neoplasm of anus, unspecified).

Topographical (location) and morphological (histology) features of neoplastic lesions are registered by means of the International Classification of Diseases for Oncology (ICD-O) coding system, currently in its third revision[32]. This is widely used by cancer registries and in anatomopathological protocols of resection specimens.

2.2 INCIDENCE

Colorectal cancer is the third most common malignant neoplasm in the world and the second cause of cancer death, with lung cancer being the first cause of death. Worldwide, colorectal cancer is diagnosed every year in around 1 Million men and women, and about 500.000 die every year from the disease (Table 2). If the westernised countries are combined (North America; those in northern, southern, and western Europe; Australia and New Zealand), colorectal cancer represents 12,6% of all incident cancer in men and 14,1% in women[34, 35].

Table 2: Colorectal cancer worldwide, in Western Europe and in Belgium (Globocan 2002)

	MEN			WOMEN		
	Cases	Age-Standardized Rate (/100.000)	Deaths	Cases	Age-Standardized Rate (/100.000)	Deaths
World	550.465	20,1	278.446	472.687	14,6	250.532
Western Europe	64.886	42,9	29.968	60.122	29,8	30.823
Belgium	3.304	37,0	1.732	3.130	26,8	1.764

From Globocan 2002, International Agency for Research on Cancer (http://www.dep.iarc.fr/ accessed May 16th, 2006)

In 2004 in Europe[36], there were an estimated 2.886.800 incident cases of cancer diagnosed and 1.711.000 cancer deaths. The most common incident form of cancer on the European Continent in 2004 was lung cancer (381.500 cases, 13,2% of all incident cases), followed by colorectal cancer (376.400, 13%) and breast cancer (370.100, 12,8%). Lung cancer was also the largest cause of cancer death (341.800 deaths, 20% of all deaths), followed by colorectal (203.700, 11,9%), stomach (137.900, 8,1%) and breast (129.900, 7,6%)

The risk of colorectal cancer begins to increase after the age of 40 and starts to rise more importantly after the ages of 50 to 55; thereafter the risk continues to rise, approximately doubling with each succeeding decade[37, 38]. Increase is more slowly in women and, at every age, women have a lower incidence of colorectal cancer than men[34].

The incidence data for Belgium in table 2 were based on older data from Flanders 1997 – 1998 and might be underestimated. More recent data from Flanders show slightly higher incidence numbers[39]: in the years 2000 - 2001, a total of 8.513 cases of invasive colorectal cancer were diagnosed in Flanders in those two years combined, 4.595 in men and 3.918 in women.

In Flanders colorectal cancer is the third most common cancer in men (after prostate and lung cancer) while it is the second most common cancer in women, only after breast cancer (Figure 1).

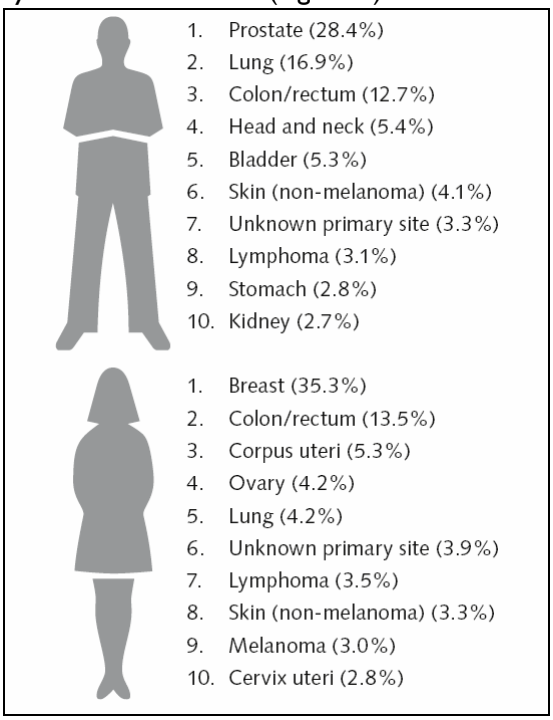

Figure 1: Most frequent cancers in Flanders (source: Vlaams Agentschap Zorg en Gezondheid[39])

Figure 2 presents crude numbers of colorectal cancers by gender and age group in Flanders for the period 2000 - 2001. In absolute numbers, most colorectal cancers occur around the age of 70 - 74 in men and around the age of 75 - 79 in women.

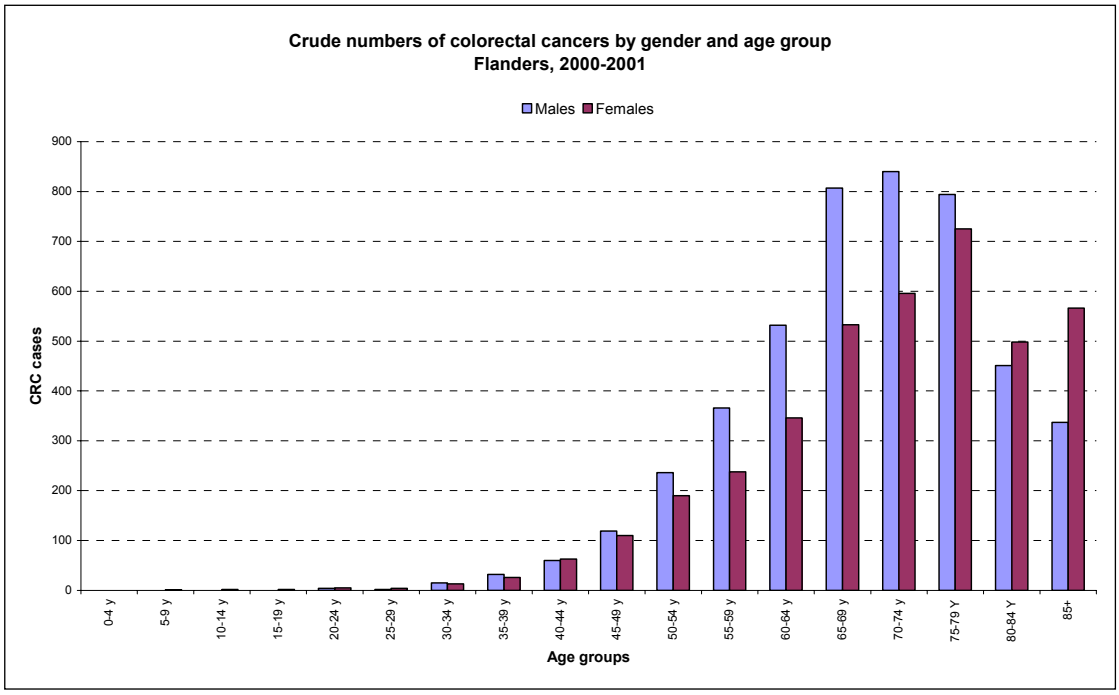

Figure 2: Crude numbers of colorectal cancers by gender and by age group, Flanders, 2000 - 2001

Extrapolation of the Flemish incidence data to the Belgian population (population January 1st, 2006) would correspond to approximately 7.500 colorectal cancer cases in Belgium for the year 2006 (Table 3), 4.000 colorectal cancer cases in males and 3.500 in females.

Table 3: Estimated colorectal cases in Belgium 2006

CRC extrapolation 2006, All ages		
Males	**Females**	**M + F**
4.180	3.608	7.716
Subgroup from 50 to 70 y		
1.642	1.120	2.762
40,0%	31,0%	35,8%
Subgroup from 60 to 70 y		
1.067	706	1.773
26,0%	19,6%	23,0%
Subgroup from 50 to 75 y		
2.352	1.626	3.977
57,3%	45,1%	51,5%
Subgroup from 55 to 75 y		
2.142	1.452	3.595
52,1%	40,3%	46,6%

The age intervals most considered in foreign screening programs are either from 50 - 70 or from 60 - 70. However, some cases occur before the age of 50 and many cases occur after those ages: for Belgium, the implementation of those age limits would correspond to approximately 38% and 24% of total number of CRC cases respectively, with a higher proportion in men than in

women (Table 3). Expanding those age limits from 50 to 75 would correspond to more than half of the CRC cases in Belgium.

Age-specific incidence rate is the number of new cases per year in a specific 5-year age group per 100.000 inhabitants in the same age group. Age-specific incidence rates by gender for colorectal cancer in Flanders, years 2000 - 2001, are presented in Figure 3. Incidence data were calculated on the basis of the annual absolute incidence and age-specific population data from the National Institute of Statistics (NIS).

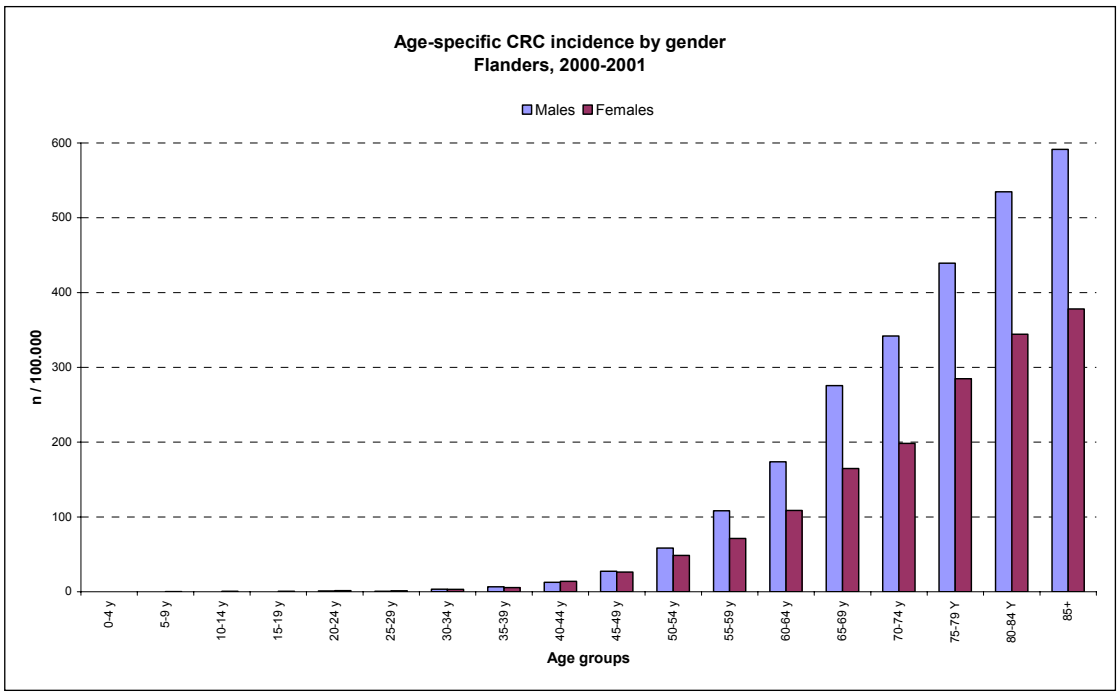

Figure 3: Age-specific colorectal cancer incidence by gender, Flanders, 2000 - 2001

2.3 PRIMARY TUMOR LOCALISATIONS

The Flemish registration also provides data on primary tumor localisations, and, especially in view of the different options for screening, this is important to consider, since not all techniques are equally able to detect abnormalities in all parts of the colon.

Distribution by localisation in Flanders 2000 - 2001 is shown in Figure 4. However, it should be recognised that the exact primary localisation was unknown in 17% (colon, not otherwise specified).

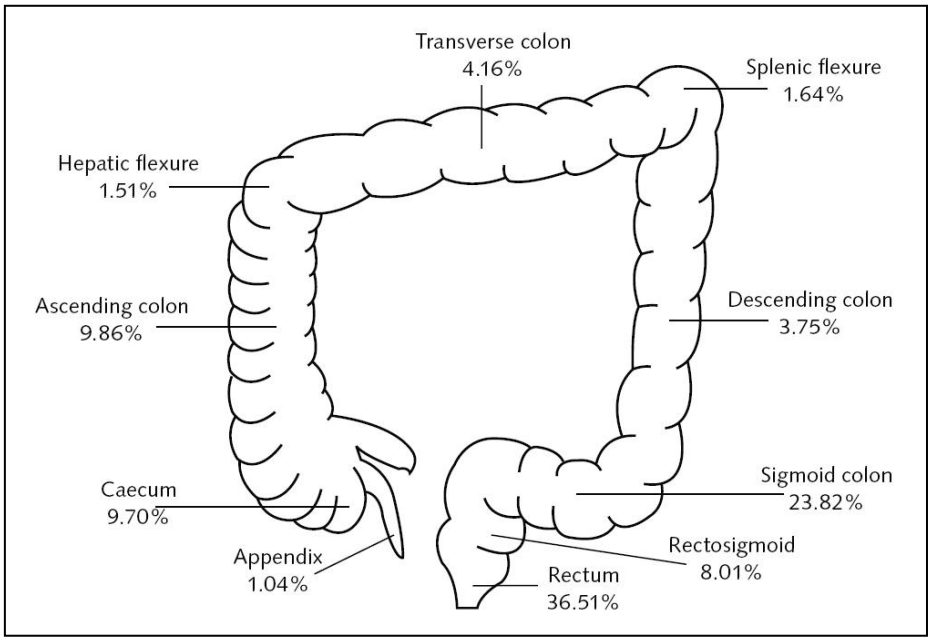

Figure 4: Invasive colorectal primary tumor localisations (n = 7.091, including appendix) in Flanders 2000 – 2001 (source: Vlaams Agentschap Zorg en Gezondheid[39])

2.4 STAGING

The TNM staging system (Tumor, Node, Metastasis)[40, 41] of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (Union Internationale Contre le Cancer - UICC) is now the standard for colorectal cancer staging widely used by national, regional, and local tumor registries in the United States and internationally. In short, it is the international language of colorectal cancer staging in all disciplines. The TNM system has three additional advantages over other staging systems. First, it is data-driven and has a process in place for continuous improvement based on ongoing expert review of existing data. Second, it has a comprehensive set of definitions and rules of application that ensure uniform use. Third, it is multidisciplinary in design and is pertinent to all modern techniques of stage evaluation.

Figure 5 shows the distribution of colorectal cancer TNM stages in males and females in Flanders for the years 2000 - 2001. Stage distributions in males and females show a very comparable pattern. These data also show that the stage distribution is very similar in the different age categories (not shown). This staging illustrates the extent of colorectal cancer at the time of diagnosis and enabled the classification of patients into prognostically comparable categories. Although the importance of good staging is well-recognised, these data were not always passed on to the cancer registry. In addition, these data may have been incomplete or missing from the medical files. These are possible reasons why the cancer registry encountered an important percentage of missing data. With the introduction in 2003 of financial reimbursement for multidisciplinary oncological consultations, it might be expected that these data will be more complete in the future because payment is only made if these data are completed.

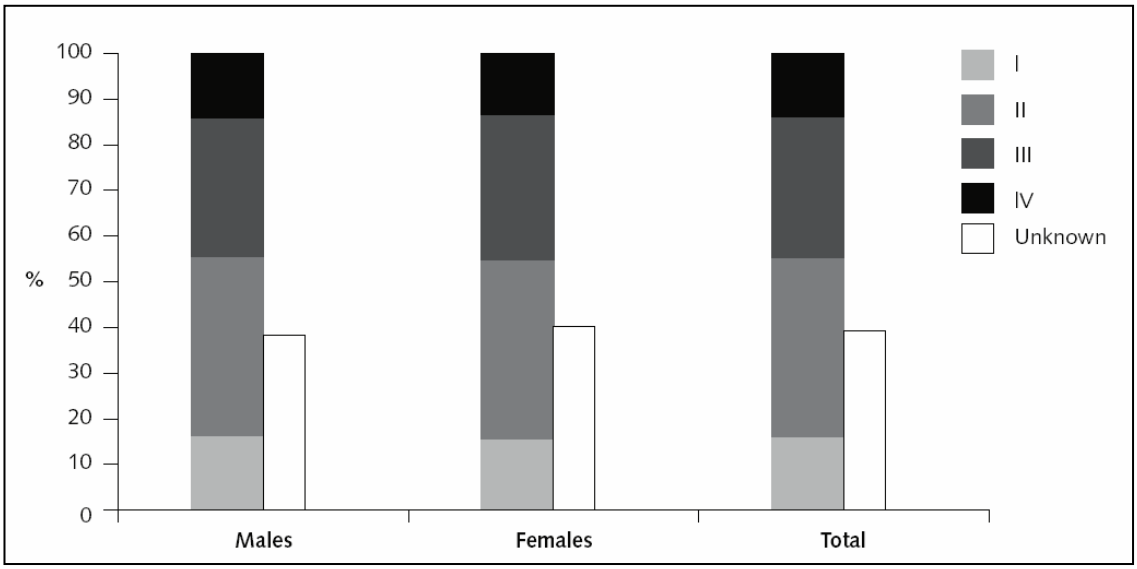

Figure 5: Colorectal cancer stages in 2000 - 2001, TNM 5th edition 1997 (source: Vlaams Agentschap Zorg en Gezondheid[39])

The older Dukes staging system[42] for CRC and its later modifications (mainly the Modified Dukes-Astler-Coller staging - MAC[43, 44]) is a pathological staging based on resection of the tumor and measures the depth of invasion through the mucosa and bowel wall. It does not take into account the level of nodal involvement or the grade of the tumor. It is, however, still widely used in surgical publications in Belgium and other European countries.

Based on different sources[40, 41, 45, 44] we produced a comprehensive overview of the TNM stages for CRC and their correlates with Dukes' and MAC classifications (Table 4).

Table 4: CRC staging systems: TNM, MAC & Dukes

UICC AJCC staging	TNM - correlate	TNM – description	Modified Astler-Coller (MAC)	Dukes
Stage 0	**Tis** N0 M0	Carcinoma in situ (intraepithelial or intramucosal carcinoma)	N/A	N/A
Stage I	**T1**, N0, M0	Tumor invades the submucosa	A	A
	T2, N0, M0	Tumor invades the muscularis propria	B1	
Stage IIA	**T3**, N0, M0	Tumor invades through the muscularis propria into the subserosa or into the nonperitonealized pericolic or perirectal tissues	B2	B
Stage IIB	**T4**, N0, M0	Tumor directly invades other organs or structures (T4a) or perforates the visceral peritoneum (T4b)	B3	
Stage IIIA	T1-T2, **N1**, M0	Tumor confined to the submucosa-muscularis propria with lymph node metastasis in one to three lymph nodes	C1	C
Stage IIIB	T3-T4, **N1**, M0	Tumor through the bowel wall with lymph node metastasis in one to three lymph nodes	C2,C3	
Stage IIIC	Any T **N2** M0	Any tumor with lymph node metastasis in four or more lymph nodes	C1,C2,C3	
Stage IV	T1-T4, N0-N2, **M1**	Distant metastases	D	N/A

2.5 MORTALITY AND SURVIVAL

In Flanders, a total of 6,991 patients died of colorectal cancer in the period 2000-2003 (data kindly provided by 'Vlaams Agentschap Zorg en Gezondheid). After standardising for age, there are yearly about 12 colorectal cancer deaths per 100.000 inhabitants registered (Figure 6). This mortality rate remained rather constant throughout those years. These rates turn out to be somewhat higher than those released by the NCI-SEER in the USA, possibly due to a difference in stage distribution at diagnosis between the USA and Flanders. The same observation was made for Europe as a whole by the Istituto Nazionale per lo Studio e la Cura dei Tumori, Italy[46]. Apparently there are wide variations in diagnostic and surgical practice between Europe and the USA.

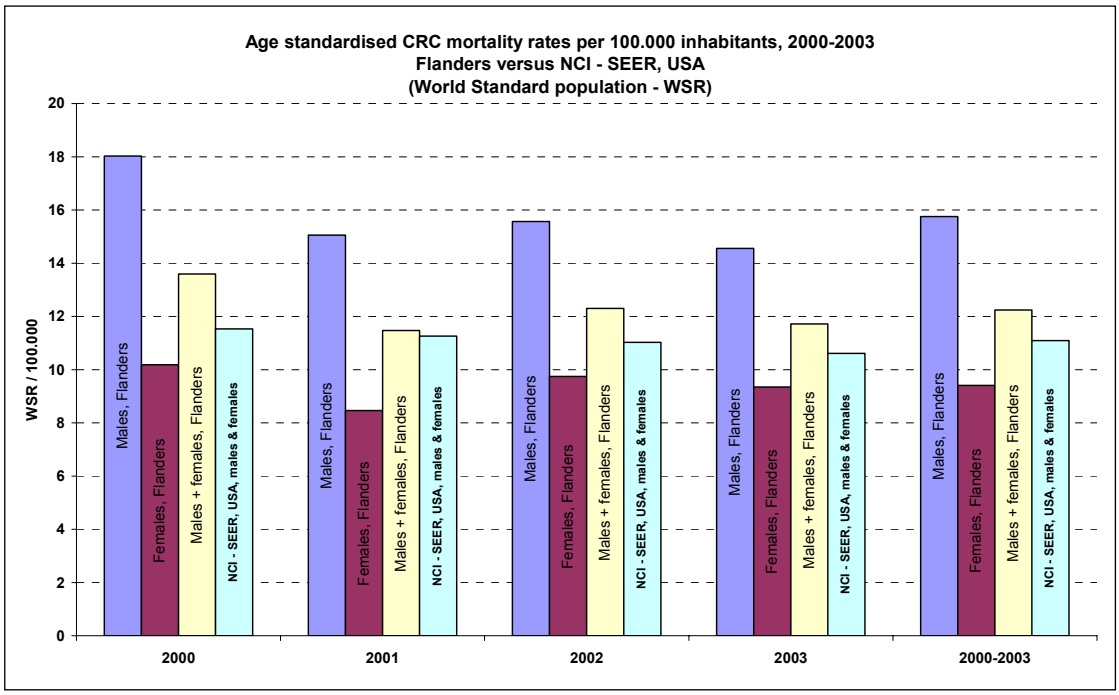

Figure 6: Age standardised (world standard population) CRC mortality rates per 100.000, Flanders 2000-2003 (source: Flemish Agency for Care and Health) compared to age standardised (world standard population) CRC mortality rates per 100.000, USA 2000-2003 (source: NCI-SEER, USA)

Stratified by gender and age, Flemish mortality data for the year 2003 show that, together with increasing incidence, also the mortality rates increased clearly with age (Figure 7). Although in absolute numbers more elderly women died from colorectal cancer (Figure 8), the age-specific mortality rate was higher in men, due to the demographic reality that there are more elderly women left at those ages.

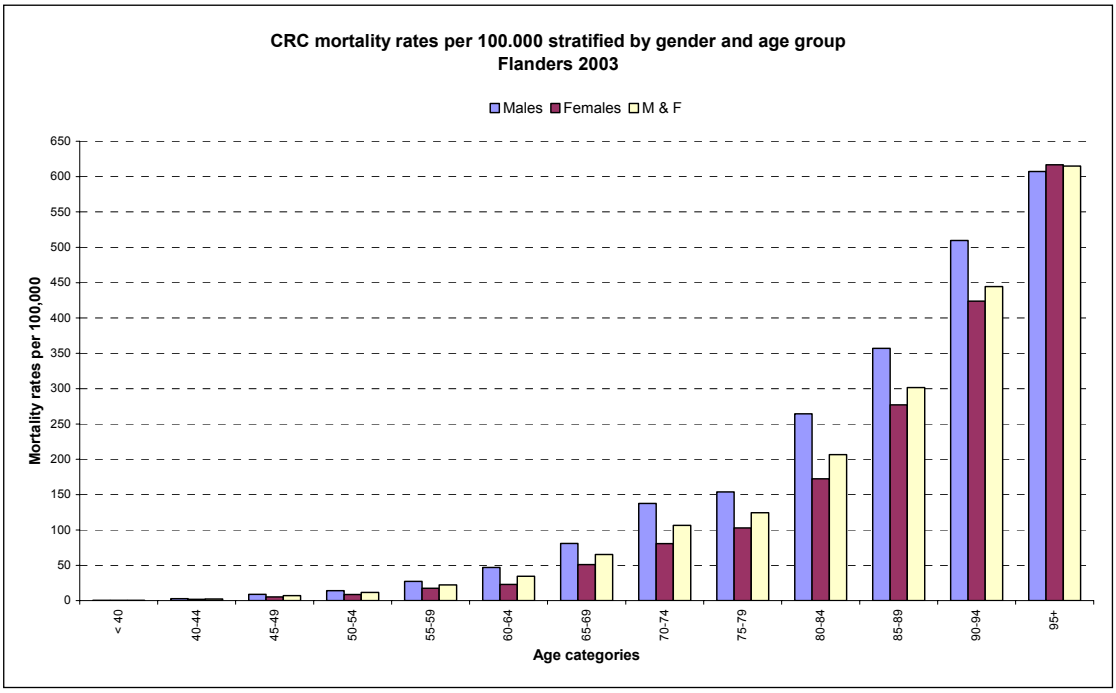

Figure 7: Flanders CRC mortality rates per 100.000, stratified by gender and age group, 2003 (source: Vlaams Agentschap Zorg en Gezondheid)

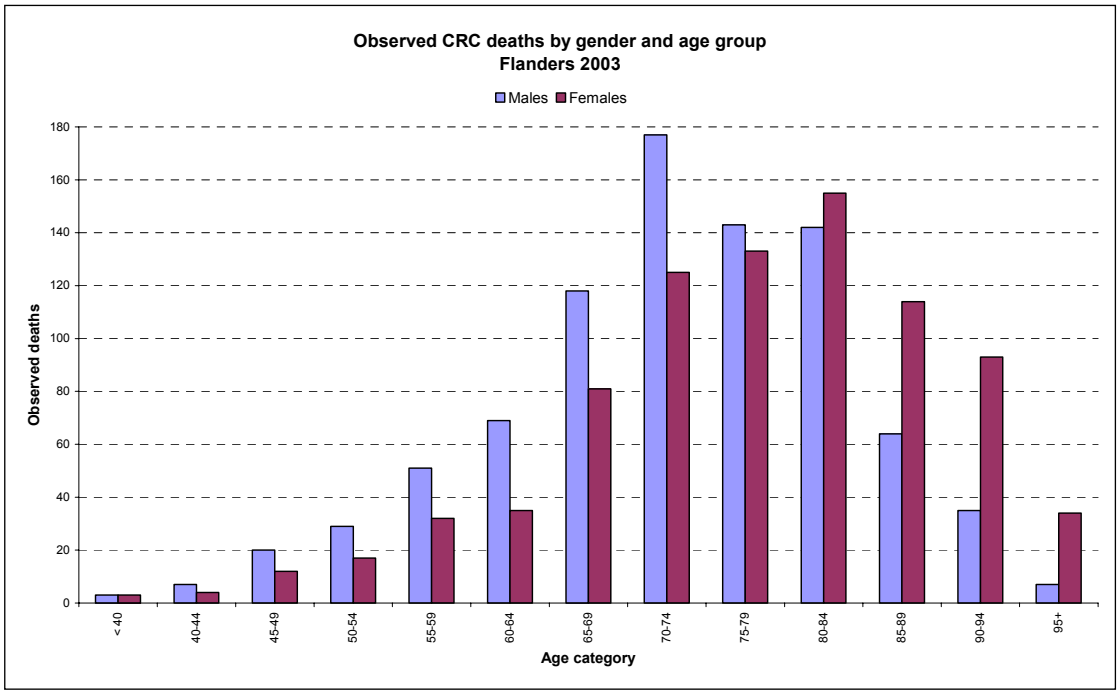

Figure 8: Flanders observed CRC deceases by gender & by age group, 2003 (source: Vlaams Agentschap Zorg en Gezondheid)

Global 5-year survival in Flanders[39], calculated using the actuarial method (life table method), was 46% in men and 47% in women. CRC relative 5-year survival

was 57% in both males and females. Relative survival is a frequently used parameter in cancer epidemiology and forms a good approach to disease-specific survival. The relative survival rates reflect an estimate of the expected survival of cancer patients, in which causes of death other than cancer have been left aside. Relative 5-year survival is calculated by dividing the observed survival by the expected survival in a group of people with the same gender and age structure from the general population.

Stage at diagnosis (TNM staging, 5th edition) is a strong predictor of survival[43, 41], as illustrated by Figure 9 and Figure 10 showing the observed and relative survival curves respectively of patients with CRC by stage.

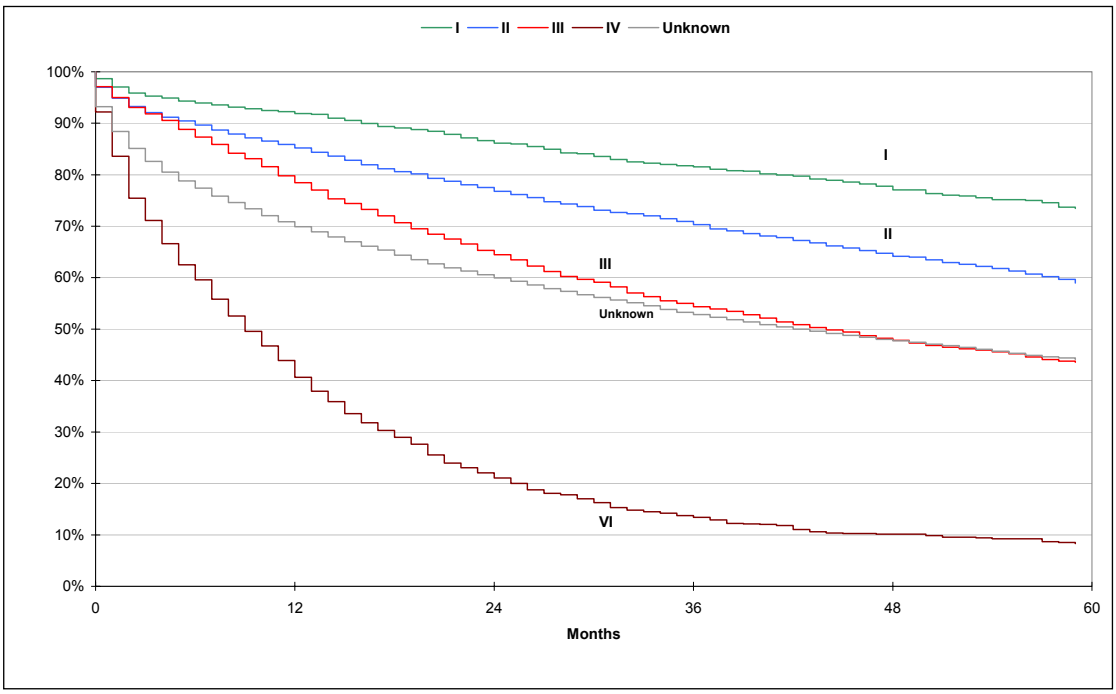

Figure 9: Invasive colorectal cancers: observed survival by stage over 5 years, 1997 – 2001 (source: Vlaams Agentschap Zorg en Gezondheid[39])

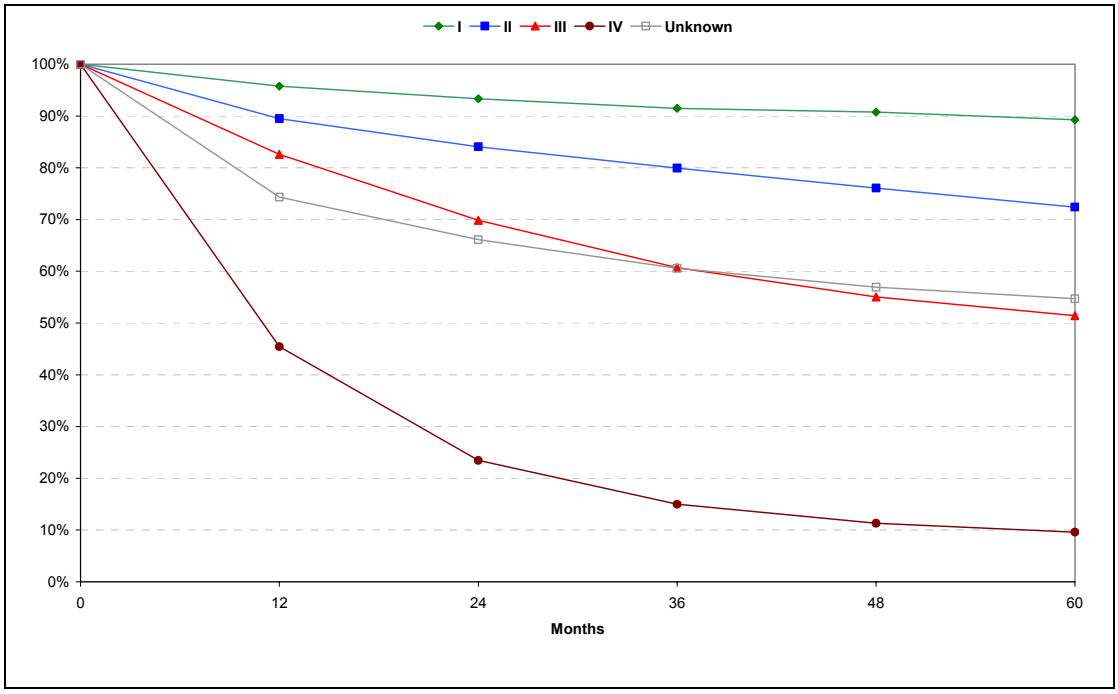

Figure 10: Invasive colorectal cancers: relative survival by stage over 5 years, 1997 – 2001 (source: Vlaams Agentschap Zorg en Gezondheid[39])

This high impact of stage at diagnosis on survival is present in both genders as illustrated by Figure 11. The same observation applies to age groups 40 - 60 y and 60+ (not shown).

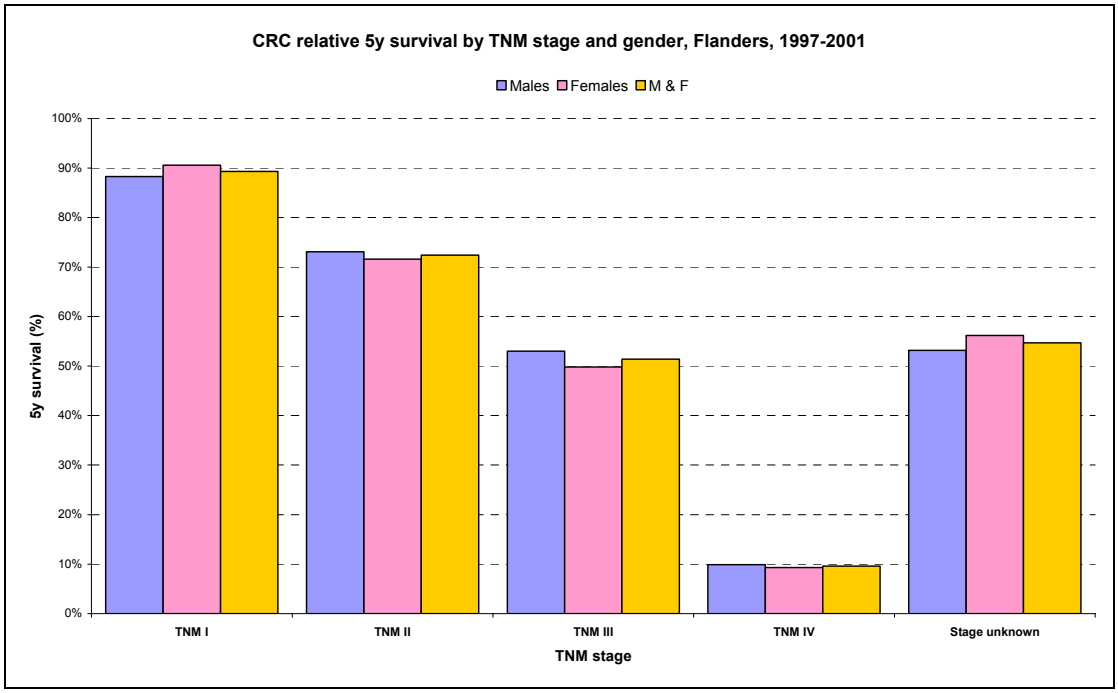

Figure 11: CRC relative 5-year survival by TNM stage and gender, 1997 – 2001 (source: Vlaams Agentschap Zorg en Gezondheid[39])

For comparison, more differentiated data, based on TNM staging, 6th edition (Figure 12) were published by the American Joint Committee on Cancer

(AJCC)[45]: data came from a total of 119.363 patients, diagnosed with colon adenocarcinoma in the SEER (Surveillance, Epidemiology, and End Results) national cancer registry from January 1st, 1991 through December 31th, 2000. The SEER program is a population-based tumor registry that collects patient records from multiple sites across the United States. These data essentially show a similar importance of stage at diagnosis as observed in Flanders.

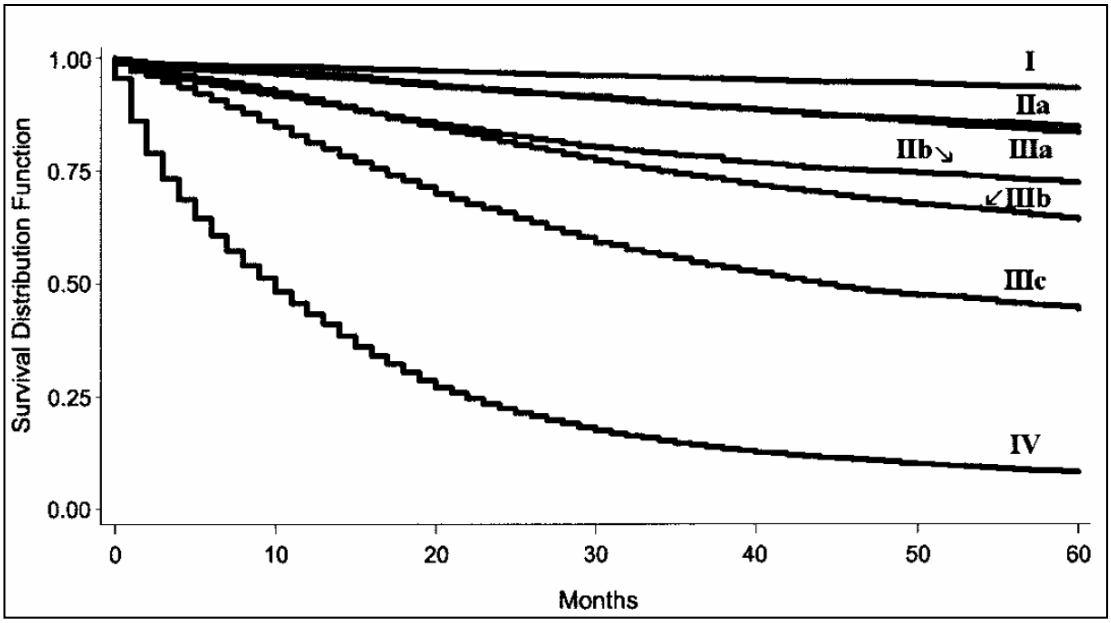

Figure 12: Five-year survival by the AJCC 6th edition system stages I-IV (source: The National Cancer Institute - USA - http://www.cancer.gov/)

Key messages

- **Colorectal cancer is the third most common malignant neoplasm in the world and the second cause of cancer death.**
- **Colorectal cancer incidence typically rises after the age of 40 in both genders, but more slowly in women and, at every age, women have a lower incidence of colorectal cancer than men.**
- **Accurate tumor staging (TNM staging) is very important as stage is a strong predictor of survival, independent from age and gender.**
- **In Flanders (2000 - 2001) crude 5-year survival was 46% in men and 47% in women. Colorectal cancer relative 5-year survival was 57% in males and females.**

3 RISK STRATIFICATION FOR COLORECTAL CANCER

3.1 INTRODUCTION

The majority, about 70 - 75% of patients with colorectal cancer, have sporadic disease, with no apparent evidence of having inherited the disorder. The remaining 25 - 30% of patients has a family history of colorectal cancer that suggests a genetic contribution, common exposures among family members, or a combination of both[47]. Limiting screening or early cancer detection to only these persons at increased risk would obviously miss the majority of colorectal cancers.

Specific genetic mutations have been identified as the cause of inherited cancer risk in some CRC-prone families. High penetrance dominant genes yielding clinical syndromes such as familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC - Lynch syndrome) are estimated to account for approximately 5% to 6% of colorectal cancer cases overall[48, 47]. It is likely that other yet undiscovered major genes and background genetic factors contribute to the development of colorectal cancer.

Moderate familial clustering, on the other hand, represents a heterogeneous group attributable to a combination of genes, environment, and chance.

This chapter does not deal with personal lifestyle, dietary nor environmental risk factors. An excellent overview of these aspects can be found in the SIGN National clinical guideline on management of colorectal cancer[49], on the National Cancer Institute website[38] (USA) or on the Australian Cancer Network website[50].

3.2 PERSONAL AND FAMILIAL HISTORY ELEMENTS INDICATING INCREASED CRC RISK

Patients with the following history are to be considered as having a moderate-to-high lifetime risk of developing CRC[51-54, 29, 55, 27, 56-58]:

3.2.1 Personal history of adenomatous polyps

A personal history of adenomatous polyps is associated with an increased risk of future development of additional polyps and of colorectal cancer. This risk increases with sizes greater than 1 cm for any adenomatous polyp, the number of polyps, and villous or tubulovillous histology[59-62].

Efforts to identify causes of CRC and to develop effective preventive measures have led to the hypothesis that adenomatous polyps (adenomas) are precursors for the vast majority of colorectal cancers. Evidence supporting the adenoma-carcinoma sequence in colorectal cancer is summarized in Table 5[63].

Table 5: Evidence Supporting the Adenoma—Carcinoma Sequence in Colorectal Cancer[63]

1.	Adenomas and carcinomas are frequently contiguous
2.	The anatomical distribution of adenomas and carcinomas is similar
3.	Adenomas > 2 cm in diameter have a 50% risk of harboring invasive malignancy
4.	The prevalence of adenomas is similar to that of carcinomas, and the average age of adenoma patients is about five years younger
5.	In about one third of all surgical specimens resected for carcinoma, synchronous adenomas will be found
6.	Familial adenomatous polyposis (FAP) is unequivocally premalignant
7.	Adenomas and carcinomas share similar patterns of chromosomal abnormality and genetic mutation
8.	There is indirect but strong evidence that colonoscopy and polypectomy are associated with a reduced incidence of carcinoma

In effect, measures which reduce the incidence and prevalence of adenomas may result in a subsequent decrease in the risk of colorectal cancer[64]. In addition, the *'National Polyp Study (US)'* data suggest that adenoma prevalence results from a dynamic process of both formation as well as regression of adenomas[65].

All publicatons[59, 60, 66, 67, 61, 62] concur on:

1. Patients with only one or two tubular adenomas < 1 cm with only low-grade dysplasia should have their next follow-up colonoscopy in 5 to 10 years. The precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, and the preferences of the patient and judgment of the physician).
2. Patients with 3 to 10 adenomas, or any adenoma > 1 cm, or any adenoma with villous features, or high-grade dysplasia should have their next follow-up colonoscopy in 3 years provided that piecemeal removal has not been done and the adenoma(s) are completely removed.
3. Patients who have more than 10 adenomas at one examination should be examined at a shorter (< 3 years) interval established by clinical judgment, and the clinician should consider the possibility of an underlying familial syndrome.
4. Patients with sessile adenomas[67] that are removed piecemeal should be considered for follow up at short intervals (2 to 6 months) to verify complete removal. Once complete removal has been established, subsequent surveillance needs to be individualized based on the endoscopist's judgment. Completeness of removal should be based on both endoscopic and pathologic assessments.
5. Patients with small rectal hyperplastic polyps should be considered to be at average risk, and therefore the interval before the subsequent colonoscopy should be 10 years. An exception is patients with a hyperplastic polyposis syndrome[66]. They are at increased risk for adenomas and colorectal cancer and need to be identified for more intensive follow up.

3.2.2 Personal history of colorectal cancer

Patients with resected colorectal cancer are at risk for recurrent cancer and metachronous neoplasms in the colon[68-70]. Patients with endoscopically resected TNM Stage I colorectal cancer, surgically resected Stage II and III cancers, and Stage IV cancer resected for cure (isolated hepatic or pulmonary metastasis) are candidates for endoscopic follow-up.

3.2.3 Personal history of endometrial or ovarian cancer

Women with endometrial and ovarian cancer diagnosed prior to age 60 years are at mildly elevated risk for colorectal cancer. Risk is highest for women with the primary diagnosis prior to age 50 years[71]. However, this observation is based on data that did not exclude patients with Hereditary Nonpolyposis Colorectal Cancer (HNPCC) who may account for some of the observed risk[72].

3.2.4 Personal history of long standing active inflammatory bowel disease involving the colon

Also at increased risk are individuals with a personal history of long standing active inflammatory bowel disease (IBD) involving the colon[73-80], such as long-standing (8 - 10 years) chronic ulcerative colitis[74, 75] or Crohn's colitis[81, 76, 78].

One cross-sectional study[82] examined the relationship between distal diverticulosis and risk for colorectal neoplasia in 502 patients undergoing first-time colonoscopy for any indication. Patients with prior polypectomy, colonic resection, or inflammatory bowel disease were excluded. Patients completed a survey about risk factors for CRC prior to colonoscopy. Endoscopists, blinded to study objective and survey results, recorded the size, extent (none, few, or many), and location of diverticuli and polyps. Overall comparison of patients with extensive distal diverticulosis (EDD) versus few or no diverticuli revealed no differences in the risks of any neoplasia or advanced neoplasia, either distally (26,0% vs. 25,4%; 12,9% vs. 8,8%, respectively) or proximally (25% vs. 18,4%; 6.0% vs. 4,9%). However, compared to women with few or no distal diverticuli, women with EDD were more likely to have any neoplasia and advanced neoplasia, both distally (34,6% vs. 16,3%; p = 0,03, and 23,1% vs. 5,7%; p = 0,003) and proximally (30,8% vs. 14,9%; p = 0,049, and 11,5% vs. 4,3%, p = 0,13). Adjustment for age did not affect results for advanced distal neoplasia (OR = 3,2; CI: 1,18 - 13); however, adjustment for the presence of a distal neoplasm eliminated the increased risk of proximal neoplasia associated with EDD (OR = 1,31; CI: 0,43 - 4,02). Hence, distal diverticulosis appears not to be independently associated with proximal neoplasia in men or women.

3.2.5 Acromegaly

Recently, it has become apparent that patients with acromegaly have an increased prevalence of colorectal adenomas and cancer[83-90]. That this increased risk might be related to serum growth hormone and/or IGF-1 levels is supported by recent observational epidemiological studies in the non-acromegalic population that have demonstrated an association between serum IGF-1 and the risk of colorectal cancer[91-98].

3.2.6 Ureterosigmoidostomy patients

Neoplasia at the anastomosis of the ureters and colon in patients with any urinary diversion that mixes urine and stool (ureterosigmoidostomy and its

variations) occurs in about 24% of patients at 20 years of follow up. The earliest recorded is 10 years after ureterosigmoidostomy[99]. The observation that the mean latent period for the development of adenomas is 19,8 years and for carcinomas is 25,8 years suggests that the adenoma-carcinoma sequence takes a mean of six years[100-104]. It is uncertain whether the neoplasms arise from the intestinal or the ureteric epithelium or from the anastomosis itself.

3.2.7 Family history of colorectal cancer

Individuals with a family history of colorectal cancer are at increased risk of developing colorectal cancer. This risk is greater when associated with early age of onset or multiple affected relatives[105-113]. Furthermore, there is increasing awareness among relatives of patients with colorectal cancer that they may be at increased risk for this disease and consequently there is rising demand for targeted screening[29, 114].

Family history risk factors for CRC include:

1. One first-degree relative (FDR = parents, siblings and children) diagnosed before age 60.
2. Two FDR diagnosed at any age.
3. A single FDR diagnosed after age 60 may put patients at a very slightly increased risk. The U.S. Multisociety Task Force on Colorectal Cancer recommends starting routine screening at age 40 for patients with a family history of colorectal cancer in a single FDR diagnosed over the age of 60[55, 56].
4. Individuals who have FDR with adenomatous polyps may be at increased risk for the development of colorectal cancer[115, 116]. When two family members have adenomatous polyps, regardless of the age of diagnosis, targeted screening is appropriate. As the age of diagnosis in the FDR decreases, the risk to the individual compared to the average population increases.

3.2.8 Hereditary high risk

Certain patients are considered to be at high risk for development of colorectal cancer. Relevant hereditary conditions include[108, 117-119, 113, 47]:

1. Familial polyposis coli / familial adenomatous polyposis (FAP)[120, 121, 117] and variants.
2. Non-polyposis hereditary colorectal cancer (NPHCC - Lynch syndrome)[122-125].

Additional syndromes continue to be defined as new genes are linked to the development of colonic polyps and cancer[126, 119, 127-129].

3.3 ESTIMATIONS OF RELATIVE (RR) AND ABSOLUTE RISK (AR)

3.3.1 The Fuchs study, 1994

Most recommendations on targeted screening of patients with a familial history of CRC are based on the findings of the study by Fuchs[107] et al. that provided relative risks for colorectal cancer according to number of affected relatives. This study was conducted in 2 prospective cohort studies (Nurses' Health

Study and the Health Professionals Follow-up Study) where individuals (32.085 men and 87.031 women who had not previously been examined by colonoscopy or sigmoidoscopy) provided information on their family history. The two cohorts were followed for the development of colorectal cancer over 6, respectively 8 years. The results are presented in Table 6.

Table 6: Estimations of RR and AR of developing CRC - Fuchs et al. - 1994

Family History	Relative Risk for CRC
No family history	1
One first-degree relative with colorectal cancer	1,72 (95% CI: 1,34 - 2,19)
More than one first-degree relative with CRC	2,75 (95% CI: 1,34 - 5,63)
Subject ≤ 45 y with ≥ 1 affected first-degree relative diagnosed with CRC at any age	5,37 (95% CI: 1,98 - 14,6)

The cumulative lifetime risk of CRC in the general population combined with the RR of colorectal cancer and the prevalence of different groups of subjects with family history of colorectal tumor or inflammatory bowel disease (IBD) allows the calculation of cumulative risks in these groups.

3.3.2 Focused search for articles on risk estimations in familial CRC

We performed an additional Medline search (see appendix) for journal articles focusing on risk estimations in familial CRC, limited to the years 2000 - 2006 (October, 31st).

This yielded 35 publications dealing with familial aggregation estimated from family studies based on an index person and, on abstract review, we retained 16 of them for further evaluation.

The remaining 19 articles were discarded as they either studied specific genetic polymorphisms[130-133], had too small a study population[134], were simple review articles[135] or chiefly treated non-related issues: pharmacological, surgical issues, etc.

3.3.3 Primary studies

Evidence-based counseling and prevention are not available so far for hereditary cancer prone persons, through lack of data based on clinical trials. Indeed, there are very few high-risk persons in the population as a whole. Population trials on cancer prone persons are feasible, but vast numbers have to be pre-screened to identify the few people with a high hereditary risk and willing to accept screening within a controlled trial. In 2001 the results of a randomized trial conducted in France were published[136]. The trial was based on colonoscopic screening for colorectal cancer on a subgroup of high-risk group persons determined by familial history analysis. Only 1,2% of all healthy volunteers attending screening centers reached the arbitrary high-risk level defined as a RR > 4. Among the 77 members of the French Institutional Preventive Center Network, 37 took part in this protocol. During the first 3 years, 850.000 persons were interviewed at these 37 Health centers. The enrollment process was particularly time-consuming, since a large amount of information had to be delivered to the participants. The mean rate of recruitment of eligible candidates was far lower than predicted, averaging only 1,4/1.000 interviewed instead of the 9/1.000 expected. However, this mean figure was based on inclusion rates ranging from 0,06/1.000 to 7/1.000 among the different centers. The low rates of recruitment were mainly due to the intercenter heterogeneity

(differences in commitment and in resources), and to the fact that the acceptability of undergoing a colonoscopy turned out to be lower than predicted.

Others studies are population-based prospective cohort studies[137-139] or retrospective population studies[140-142, 123, 143].

To determine to what extent individuals with various family histories of colorectal cancer are at risk a prospective, observational study of high risk families, followed up over 16 years, was carried out in a tertiary referral family cancer clinic in London[139]. 1.678 individuals from families registered with the cancer clinic were classified according to the strength of their family history: HNPCC (if they fulfilled the Amsterdam criteria[144, 58]), and one, two, or three affected first degree relatives (moderate risk). Colonoscopy was initially offered at five year intervals or three year intervals if an adenoma was detected. The incidence of adenomas with high risk pathological features or cancer was analysed by age, the extent of the family history, and findings on previous colonoscopies. The cohort was flagged for cancer and death. Incidence of colorectal cancer and mortality during > 15.000 person years of follow-up were compared with those expected in the absence of surveillance. High risk adenomas and cancer were most common in families with HNPCC (on initial colonoscopy 5,7% and 0,9%, respectively). In the families with moderate risk, these findings were particularly uncommon under age 45 (1,1% and 0%) and on follow-up colonoscopy if advanced neoplasia was absent initially (1,7% and 0,1%). The incidence of colorectal cancer was substantially lower than the expected incidence in the absence of surveillance when the family history was taken into account: 80% in families with moderate risk (p = 0,00004), and 43% in families with HNPCC (p = 0,06). The study showed clearly that colonoscopic surveillance reduces the risk of colorectal cancer in people with a strong family history; members of families with HNPCC require surveillance with short intervals. Individuals with a lesser family history may not require surveillance under age 45, and if advanced neoplasia is absent on initial colonoscopy, surveillance intervals may be lengthened. This would reduce the demand for colonoscopic surveillance.

In a multicenter, prospective controlled cohort trial[138] 200 patients with normal Flexible Sigmoidoscopy (FS) and 200 patients with diminutive adenomas on FS were matched for age and gender. Diminutive adenomas (< 10 mm in diameter) are frequently found during colon cancer screening with FS and the trial aimed to assess the predictive value of these diminutive adenomas for advanced adenomas in the proximal colon. All patients underwent colonoscopy. The presence of advanced adenomas (adenoma ≥ 10 mm in diameter, villous adenoma, adenoma with high grade dysplasia, and colon cancer) and adenomas (any size) was recorded. Before colonoscopy, patients completed questionnaires about risk factors for adenomas. The prevalence of advanced adenomas in the proximal colon was similar in patients with diminutive adenomas and patients with normal FS (6% vs. 5,5%, respectively - RR 1,1; 95% CI: 0,5 - 2,6). Diminutive adenomas on FS did not accurately predict advanced adenomas in the proximal colon: sensitivity was 52% (95% CI: 32% - 72%) and specificity, 50% (95% CI: 49% - 51%); positive predictive value was 6% (95% CI: 4% - 8%) and negative predictive value was 95% (95% CI: 92% - 97%). Male gender (odds ratio 1,63; 95% CI: 1,01 - 2,61) was associated with an increased risk of proximal colon adenomas. The authors concluded that diminutive adenomas on sigmoidoscopy may not accurately predict advanced adenomas in the proximal colon.

A Swedish study focused on secondary cancers in 68.104 cases of CRC from the Swedish Family-Cancer Database[142]. In 1.113 patients a secondary CRC was diagnosed; 25 of them had a family history of CRC. Cases of secondary CRC with a family history were diagnosed up to 10 years before sporadic cases. The RR of all secondary CRCs was 2,21 compared with the first CRC. Familial secondary CRCs had a 2-fold risk compared with the sporadic forms. Age of onset was the most important covariate of secondary CRCs; the relative risk at ages 15 - 39 years was 27 compared with the first CRC. Familial CRC was associated with a high risk of small-intestinal, endometrial, and gastric cancers apart from CRC, all typical of HNPCC. Among familial cases, 36% of secondary CRCs and 100% of endometrial cancers came from families that fulfilled the Bethesda criteria for HNPCC[145, 58]. Only 12 families conformed to the Amsterdam criteria; in family members, the risk of secondary CRC was 127-fold and that of endometrial cancer 257-fold. Other sites that were in excess among all secondary cancers were many cancers linked to HNPCC and, additionally, breast, prostate, thyroid and other endocrine, skin, and genital cancers. The authors concluded that the high risk of secondary cancer after early-onset CRC calls for evaluation of family history and clinical surveillance.

Adenoma prevalence and cancer risk in familial non-polyposis colorectal cancer was further studied in Sweden[123]. Over a period of 10 years, 304 subjects at risk were included in ongoing surveillance with regular colonoscopies. To compile the medical findings and experience generated during this period, a retrospective cross sectional study was performed. Subjects were classified into three family groups: families with HNPCC (Lynch syndrome), families with hereditary colorectal cancer (HCC, non-Lynch syndrome) and a third group of families with only empirical risk estimates based on a family history of two close relatives (TCR) with CRC. The risk population was studied with regard to age at onset, prevalence, number, cancer risk, size, dysplasia, and distribution of adenomas. A comparison was made within the family groups and with a reference group representing the general population. In total, 195 adenomas and six cancers were detected among 85 individuals. The relative risk of having an adenoma in the whole risk population compared with the general population was 2,6. Subjects from TCR families had most adenomas and HNPCC subjects had the least. A shift from proximal adenomas to distal carcinomas in families with HCC and TCR suggested a higher cancer risk in distal adenomas in these syndromes. HNPCC families showed a younger age at onset and adenomas with a higher degree of dysplasia. In HNPCC there was a similar localisation of adenomas and carcinomas, suggesting a high risk of cancer in all adenomas. The study showed that there was clear overrepresentation of adenomas in all three family types compared with the reference population. In HNPCC there was earlier onset of adenomas and faster progression to cancer. Families with HCC, and even more so TCR subjects, had a later onset and lower risk of cancer from proximal adenomas. Based on these results, surveillance protocols in Sweden have been revised.

A retrospective review of the French Calvados Cancer Registry 1993 - 1998, published in 2004[143], showed that colon cancer had a familial or genetic component but not rectal cancer: RR 1,47 (95% CI: 1,16-1,96; *p* value 0,004) vs. RR 0,98 (95% CI: 0,67-1,40). The familial/genetic component appeared stronger for proximal colon cancer than for distal colon cancer, but only among women: RR 2,24 (95% CI: 1,35-3,50) vs. RR 1,45 (95% CI: 0,83-2,36).

Another French population study[140] aimed to estimate the lifetime risk (0 - 74 y) of CRC in the general population (males versus females) and in first degree relatives of patients with sporadic colorectal cancer or adenoma. The lifetime

risk of CRC was 1/23 in men and 1/40 in women. In males, 0,5% in the 55 - 59 age group and 4,5% in the 70 - 74 age group developped a CRC. The corresponding values in females were 0,4% and 2,5%. The cumulative risk at age 74 varied between 7,7% (one family member affected) and 25,6% (two affected) in males, and 4,3% and 14,3% respectively in females. The risk in the 40 - 44 year age group for individuals with one first degree relative affected before 45 years of age was 0,5%, similar to that of those aged 45 - 49 with one first degree relative affected with a colorectal cancer or a large adenoma (> 1 cm). The study results suggested that screening in the general population should start at 50 or 55. In individuals with one affected first degree relative before age 45, or with at least two affected first degree relatives, the lifetime risk appeared high enough (over 10%) to warrant colonoscopic screening and relatives of these patients should enter screening programs at age 40 to 44.

Family history as a risk factor for colorectal cancer in Inflammatory Bowel Disease (IBD) was studied in a population-based cohort study of 19.876 individuals with ulcerative colitis or Crohn's disease born between 1941 and 1995[137]. Familial CRC was associated with a more than 2-fold risk of CRC (RR = 2,5, 95% CI: 1,4 - 4,4) and an increase in absolute risk (AR) of CRC at 54 years from 3,8% to 6,9%. Patients with a first-degree relative diagnosed with CRC before 50 years of age had a higher RR (9,2, 95% CI: 3,7 - 23) and the highest AR (29%). No association with familial IBD was observed.

Finally, a retrospective analysis of the Surveillance Epidemiology and End Results (SEER) program database for the period 1974 through 1995 identified 101.734 white and African-American women, age ≥ 25 yr, with prior cervical, endometrial, or ovarian cancer[141]. Subsequent follow-up demonstrated no increased risk of colorectal cancer in women with cervical cancer. For endometrial cancer patients, increased risk of colorectal cancer was confined to women whose diagnosis of endometrial cancer was before age 50, but the increased risk was substantial in this group (RR 3,39; 95% CI: 2,73 - 4,17). For ovarian cancer patients, increased risk for colorectal cancer was substantial for those diagnosed with ovarian cancer before age 50 (RR 3,67; 95% CI: 2,74 - 4,80), and there was some increased risk for women diagnosed at ages 50 - 64 yr (RR 1,52; 95% CI: 1,25 - 1,83).

3.3.4 Systematic reviews with meta-analysis

Some of the retrieved publications were based on systematic reviews of the literature with meta-analysis[146, 147, 48, 114, 148, 47].

The Web published NCI Colorectal Cancer (pDQ) Genetics update[47] recalls the estimated relative and absolute risks of developing CRC based on a systematic review and meta-analysis of familial colorectal cancer risk by Johns & Houlston[146], published in 2001 (Table 7).

Table 7: Pooled estimates of RR and AR of developing CRC - Johns et al. - 2001

Family History	Relative Risk for CRC	Absolute Risk of CRC by age 79*
No family history	1	4%*
One first-degree relative with colorectal cancer	2,3 (95% CI: 2,0 - 2,5)	9%@
More than one first-degree relative with colorectal cancer	4,3 (95% CI: 3,0 - 6,1)	16%@
One affected first-degree relative diagnosed with colorectal cancer before age 45	3,9 (95% CI: 2,4 - 6,2)	15%@
One first-degree relative with colorectal adenoma	2,0 (95% CI: 1,6 - 2,6)	8%@

*Data from SEER database
@The absolute risks of CRC for individuals with affected relatives was calculated using the relative risks for CRC and the absolute risk of CRC by age 79*

The AHRQ Systematic Evidence Review[147] on CRC screening in adults (2002) gives additional figures on increased CRC risk with prior diagnosis of endometrial or ovarian cancer[141], particularly for cancers occurring below age 50; a history of breast cancer, however, increases risk only slightly, if at all (Table 8).

Table 8: Relative Risk of Colorectal Cancer - AHRQ - 2002

Risk Factors	Relative Risk (95% CI:)
Family history of colorectal cancer in a first-degree relative before age 60[149]	Range 1,7 - 4,0*
Family history of adenomatous polyps in a first-degree relative before age 60[150]	1,8 (1,2 - 2,7)
Personal history of endometrial cancer[151, 141]	
Diagnosis before age 50	3,4 (2,7 - 4,2)†
Diagnosis age 50 – 64	0,93 (1,2 - 1,8)
Personal history of ovarian cancer[151, 141]	
Diagnosis before age 50	3,7 (2,7 - 4,8)
Diagnosis age 50 – 64	1,5 (1,2 - 1,8)
Personal history of breast cancer[152]	1,1 (1,0 - 1,2)

* For patients age 40 - 60; older patients appear to have lower risk.
† 95% confidence interval CCI:.

The American Society for Gastrointestinal Endoscopy (ASGE) Clinical Updates[48] also documents on life time risks for average, moderate and increased risk conditions (Table 9).

Table 9: ASGE stratification on CRC risk - 2004

Risk level	Lifetime risk of CRC
Average	
Age > 50 y	5% - 6%
Moderate	
Chronic colitis due to ulcerative colitis or Crohn's disease	20%
Familial risk: 1st degree relative with CRC	10% - 20%
High	
Familial polyposis	≈ 100%
HNPCC	80%

Familial aggregation, a primary theme in genetic epidemiology, can be estimated from family studies based on an index person. The excess risk due to the presence of affected family members can be classified according to whether disease in the relatives is considered a risk factor for the index person (type I relative risk) or whether the disease status of the index person is considered a risk factor for the relatives (type II relative risk). Type I relative risks are useful in clinical counselling settings when an individual wants to know his/her disease risk given his or her family history. Type II relative risks can be used to quantify the risk of disease to relatives of an affected individual and then identify subjects eligible for screening. A meta-analysis of published colorectal cancer studies reporting a measure of familial association[114] with application of multilevel linear regression to model age-specific relative risks showed that the pooled type I relative risk of colorectal cancer given any affected first-degree relative (based on 20 studies) was 2,26 (95% CI: 1,86 - 2,73) and decreased with the age of the individual. The pooled type II estimate (based on seven studies) was 2,81 (95% CI: 2,05 - 3,85).

Finally, Butterworth et al. from the Cambridge Public Health Genetics Unit recently published a systematic review[148] of the literature on familial risks of colorectal cancer. Fifty-nine studies were identified including 47 that estimated the relative risk of developing colorectal cancer given at least one affected first-degree relative. Pooled risk estimates are summarized in Table 10.

Table 10: Pooled estimations of RR and Lifetime Risk of developing CRC - Butterworth et al. - 2006

Family History	Relative Risk for CRC	Lifetime risk at 50 years
One first-degree relative with colorectal cancer	2,24 (95% CI: 2,06 - 2,43)	3,4% (95% CI: 2,8 to 4,0)
More than one first-degree relative with colorectal cancer	3,97 (95% CI: 2,60 - 6,06)	6,9% (95% CI: 4,5 to 10,4)

3.3.5 Economic evaluations

Recently, a preliminary economic analysis of family history assessment to detect increased risk for colorectal cancer was published by Ramsey et al[111]. The authors developed a decision model to compare costs and outcomes for two scenarios: (a) standard population screening starting at age 50; (b) family history assessment at age 40, followed by screening colonoscopy at age 40 for those with a suggestive family history of colorectal cancer. The analysis was conducted

using the health insurer perspective. Using U.S. population estimates, 22 million would be eligible for family history assessment, and one million would be eligible for early colonoscopy; 2.834 invasive cancers would be detected, and 29.331 life years would be gained. The initial program cost would be USD $900 million. The discounted cost per life year gained of family history assessment versus no assessment equals USD $58.228. The results were most sensitive to the estimates of life expectancy benefit from earlier screening, the cost of colonoscopy, and the relative risk of colon cancer in those with a family history. The authors concluded that the cost-effectiveness of family history assessment for colorectal cancer approaches that of other widely accepted technologies; yet, the results are sensitive to several assumptions where better data are needed. Because of the relatively high prevalence of family history in the population, careful analysis and empirical data are needed.

3.3.6 Conclusion

Individuals with a family history of colorectal cancer are at increased risk of developing colorectal cancer and warant colonoscopic surveillance starting before 50 years of age. This risk is greater (and the targeted screening should start earlier) when associated with early age of onset or multiple affected relatives.

3.4 RISK STRATIFICATION

The American Gastroenterological Association (AGA) recommends[55] that clinicians determine an individual patient's risk status for the development of CRC well before the earliest potential initiation of screening (typically around age 20 years, but earlier if there is a family history of FAP). The individual's risk status determines when screening should be initiated and what tests and frequency are appropriate. Risk stratification can be accomplished by asking several questions aimed at uncovering the risk factors for colorectal cancer[28]: (1) Has the patient had colorectal cancer or an adenomatous polyp and at what age? (2) Does the patient have an illness (e.g., inflammatory bowel disease) that predisposes him or her to colorectal cancer? (3) Has a family member had colorectal cancer or an adenomatous polyp? If so, how many, was it a first-degree relative (parent, sibling, or child), and at what age was the cancer or polyp first diagnosed? A positive response to any of these questions should prompt further efforts to identify and define the specific condition associated with increased risk.

For patients with a positive family history the New Zealand Guidelines Group (NZGG) proposes a risk stratification in 3 categories[27], taking however 55 years as cut-off age instead of the 60 years used in the US:

1. **Category 1**: Individuals with a slight increase in risk of CRC due to family history (up to 2-fold compared with the general population): one FDR with CRC diagnosed over the age of 55 years.
2. **Category 2**: Individuals with a moderate increase in risk of CRC (3-to 6-fold compared with the general population):
    a. One FDR with CRC diagnosed under the age of 55 years.
    b. Two FDR on the same side of the family with CRC diagnosed at any age.

3. **Category 3**: Individuals with a potentially high risk of CRC: more than 6-fold compared with the general population or ≥ 50% lifetime risk:
    a. A family history of FAP, HNPCC, or other familial CRC syndromes[117, 139].
    b. One FDR plus two or more FDR or second-degree relatives (SDR), all on the same side of the family, with a diagnosis or CRC at any age.
    c. Two FDR, or one FDR plus one or more SDR, all on the same side of the family, with a diagnosis of CRC and one such relative (1) was diagnosed with CRC under age of 55 years, (2) developed multiple bowel cancers, or (3) developed an extra-colonic tumor suggestive of HNPCC (i.e., endometrial, ovarian, stomach, small bowel, upper renal tract, pancreas, or brain).
    d. At least one FDR or SDR diagnosed with CRC in association with multiple bowel polyps.
    e. A personal history or one FDR with CRC diagnosed under the age of 50, particularly where colorectal tumor immunohistochemistry has revealed loss of protein expression for one of the mismatch repair genes (hMLH1 or hMSH2).

Although family history is used extensively to estimate the risk of colorectal cancer, there is considerable potential for recall bias and inaccuracy[153-155]. One study[156] has quantified the inaccuracy of interview in identifying people at risk of colorectal cancer due to a family history. Colorectal cancer was substantially underreported and so family history information should be interpreted with caution. On the other hand, information on individual and family CRC risk must be communicated very cautiously. Little investigation on psychological impact of such information has been done so far and further investigations are needed to develop and adjust risk information provided to the individual in order to avoid misunderstanding, especially as this information is going to be revealed to family members. Counselling support should be offered to those individuals who experience psychological distress[134].

The risks of genetically mediated colorectal cancer are variable and depend on the specific germ line mutations. Some mutations are associated with a 100% lifetime risk of developing cancer, while others are associated with only a mild increase in risk. Although there are overlapping clinical features in many of these syndromes, they can be distinguished by the age at cancer diagnosis, inheritance pattern, number and distribution of polyps, specific histological features of the cancers, and the presence of distinctive extra-colonic features (e.g. the Amsterdam & Bethesda criteria[118, 109, 157-160, 58, 47]). The introduction and refinement of genetic testing[161-164, 129, 165, 47, 166] has provided a new and invaluable tool for the diagnosis and assessment of cancer risk for suspected cases of hereditary colon cancer.

3.5 PREVALENCE OF A FAMILY HISTORY OF COLORECTAL CANCER IN THE GENERAL POPULATION

Robust estimates of the prevalence of a family history of colorectal cancer in the general population are essential to inform planning of provision for

colonoscopic surveillance and for clinical genetics services. However, there is a paucity of high-quality data.

In a 2001 Journal of Medical Screening publication, Sandhu et al.[54] performed a cross-sectional analysis of CRC and self reported family history based on data from a large population based study in Norfolk, United Kingdom. Of the 30.353 participants, 2.069 (6,8%) participants had reported a family history of colorectal cancer in at least one first degree relative. The prevalence of colorectal cancer in those with a family history was 1% and 0,5% in those without. Of the 151 participants with prevalent colorectal cancer, 14,6% reported a family history of the disease.

In a 2006 publication in Genetics in Medicine, Ramsey et al.[167] queried survey questions from the National Health Interview Survey, an annual nationwide survey of approximately 36.000 households in the United States, to determine the prevalence of persons reporting one or more first-degree relatives with breast, colorectal, lung, prostate, or ovarian cancer. Breast cancer was the most common condition noted for family members (7,74% of respondents), followed by lung cancer (7,10%), colorectal cancer (4,96%), prostate cancer (4,68%), and ovarian cancer (1,79%).

Mitchell et al.[168] used computerized record linkage to assess systematically the family history of 160 cancer-free community subjects and thereby provide prevalence data independent of participant recall. The data set comprised 2.664 first- and second-degree relatives of study subjects, with 148.068 years at risk. Of people in the 30-70 years age range, 9,4 (95% CI: 5,8 to 14,9) per cent had a first-degree relative affected by colorectal cancer, and 28,8 (95% CI: 22,3 to 36,2) per cent had an affected first- or second-degree relative. Between 0 and 3,1 per cent of study subjects merited colonic surveillance, depending on the stringency of the guidelines used.

Key messages

- **About 70-75% of patients with colorectal cancer have sporadic disease, with no apparent evidence of having inherited the disorder. The remaining 25-30% of patients has a family history of colorectal cancer that suggests a genetic contribution, common exposures among family members, or a combination of both.**
- **Individuals with a family history of colorectal cancer are at increased risk of developing colorectal cancer and targeted screening should start earlier than 50 years in those subgroups. The risk is greater when associated with early age of onset or multiple affected relatives.**
- **Approximately 5 to 6% of colorectal cancers will occur in individuals that are to be considered at high hereditary risk for development of colorectal cancer: HNPCC, FAP, AFAP, and variants.**
- **A personal history of adenomatous polyps is associated with an increased risk of future development of additional polyps and of colorectal cancer. This risk increases with sizes greater than 1 cm for any adenomatous polyp, the number of polyps, villous or tubulovillous histology and grade of dysplasia.**
- **Patients with resected colorectal cancer are at risk for recurrent cancer and metachronous neoplasms in the colon.**
- **Patients with a personal history of long standing active inflammatory bowel disease involving the colon, such as long-standing (8 - 10 years) chronic ulcerative colitis or Crohn's colitis have a predisposition for colorectal cancer.**

4 GUIDELINES ON COLORECTAL CANCER SCREENING AND SURVEILLANCE

4.1 INTRODUCTION

A quick explorative Medline search, focusing on "colorectal cancer" combined with either "screening" or "surveillance" and with addition of the search term 'guideline$' for the field 'publication type' yielded 45, respectively 24 citations if restricted to the years 2000 – 2006. Subsequently we searched additional guidelines sources (see appendix for details).

We retrieved guidelines on average risk screening as well as on surveillance and management of groups at increased risk of colorectal cancer, however limited to the years 2000 - 2006.

Older or rescinded guidelines, as well as guidelines and recommendations in other languages than English, Dutch or French were disregarded. Excluded were also guidelines exclusively restricted to treatment of CRC or genetic testing for hereditary colorectal cancer.

As a result of those searches, 20 full-text guidelines & recommendations were obtained, including, for some of them, their NGC appraisals.

4.2 GENERAL PRINCIPLES

Clinical practice guidelines (CPG) are defined as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (Oxford Centre for Evidence-Based Medicine - CEBM[169, 170]).

1. Good CPG provide graded recommendations about a specific health problem, based on the best evidence available at the time they are derived by means of a systematic review of the scientific literature and representing consensus opinion of experts gathered[171] through Consensus development conferences, Expert Consensus Committees, Delphi method, Nominal Group Technique, etc. The former (the systematic review) implies the application of rating schemes for appraisal of the strength of reviewed evidence[172, 173], the latter (the consensus opinion) a shared framework for their development, reporting and assessment[174]. Ideally, each guideline consists of an algorithm or decision pathway outlining diagnostic, therapeutic and supportive care management, a manuscript discussing important issues related to the algorithm, and references providing data on which the recommendations are based[58]. Furthermore, a good guideline should consider all relevant disciplines and stakeholders, as well as the local circumstances in which healthcare is delivered[175]. It is however essential that these recommendations are continuously updated and revised to reflect new data and new clinical information.
2. To ensure that clinical guidelines improve patient care they should meet minimum quality criteria[176, 177]. In the mid nineties a group of researchers from 13 countries developed the Appraisal of Guidelines Research and Evaluation (AGREE) Instrument. The objectives of the project were to provide a framework to create

a coordinated international approach to the appraisal of clinical guidelines and to identify potential areas for harmonization of guideline development[178, 174].

Health Care/Prevention Recommendations (HC/PR), on the other hand, are issued by regional, national or supranational (EU, WHO,…) governmental advisory committees involved with public health and chiefly address the public, politicians and the public health administrations of the respective countries. They focus on implementation of cancer screening programs within the frame of the general priority setting on the use of healthcare resources, screening coverage and compliance, quality assurance at all levels and good public information about benefits and risks[179]. Although grounded on published scientific evidence, structured grading of the evidence generally is not their main concern.

Table 11 gives an overview of the 20 retrieved guidelines and recommendations on CRC screening and surveillance. Some of them solely deal with average risk screening (mass screening), others include recommendations on increased risk screening and/or surveillance topics.

Table 11: Retrieved guidelines & recommendations concerning average & increased risk CRC screening & surveillance (N=20)

Scope	Nr.	Type	Title	Issued by	Year published	Last update
Average risk screening only	1	CPG	Health Care Guideline: Colorectal Cancer Screening[180].	Institute for Clinical Systems Improvement (ICSI)	1995	2006
	2	HC/PR	The Quebec Association of Gastroenterology position paper on colorectal cancer screening - 2003[181].	Quebec Association of Gastroenterology (AGEQ) Task Force	2003	2003
	3	CPG	Screening for colorectal cancer: recommendations and rationale[182].	U.S. Preventive Services Task Force (USPSTF)	1996	2002
	4	HC/PR	Recommendations on cancer screening in the European Union[179, 183].	EU Advisory Committee on Cancer Prevention	2000	2000
Average risk screening Increased risk screening Surveillance	5	CPG	ASGE guideline: colorectal cancer screening and surveillance[184].	Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE)	2000	2006
	6	CPG	Colorectal Cancer Screening[58].	National Comprehensive Cancer Network (NCCN)	1995	2006
	7	CPG	Report on the Belgian consensus meeting on colorectal cancer screening[185].	Belgian Gastroenterologists community	2005	2005
	8	CPG	Prevention and screening of colorectal cancer[186].	Finnish Medical Society Duodecim.	2004	2005
	9	CPG	Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer[50]	Australian Cancer Network Colorectal Cancer Guidelines Revision Committee	1999	2005
	10	CPG	Adult preventive health care: cancer screening[187].	University of Michigan Health System (UMHS)	2004	2004
	11	CPG	American Cancer Society guidelines on screening and surveillance for the early detection of adenomatous polyps and colorectal cancer - update 2004[56].	American Cancer Society (ACS)	2002	2004

	12	CPG	WGO - OMGE Position Statement: Colorectal Cancer Screening and Surveillance[188].	Guidelines & Statements Committee of the World Gastroenterology Organisation (WGO-OMGE)	2002	2004
	13	CPG	Colorectal cancer screening and surveillance: clinical guidelines and rationale - update based on new evidence[55].	U.S. Multisociety Task Force on Colorectal Cancer (AGA/ASGE/ACP/ACG)	1997	2003
	14	CPG	Preventive health care, 2001 update: colorectal cancer screening[28].	Canadian Task Force on Preventive Health Care (CTFPHC)	1994	2001
Increased risk screening Surveillance	15	CPG	Guidelines for colonoscopy surveillance after polypectomy[61, 62].	US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society	1996	2006
	16	CPG	Guidelines for colonoscopy surveillance after cancer resection: a Consensus Update[69].	US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society	1996	2006
	17	CPG	Surveillance and management of groups at increased risk of colorectal cancer[27].	New Zealand Guidelines Group (NZGG)	2004	2004
	18	CPG	Management of Colorectal Cancer - A national clinical guideline[49].	Scottish Intercollegiate Guidelines Network (SIGN)	2003	2003
	19	CPG	Follow-up na poliepectomie - Herziene richtlijn[189].	Kwaliteitsinstituut voor de Gezondheidszorg (CBO - NL)	1987	2002
	20	CPG	Guidelines for colorectal cancer screening in high risk groups[190].	British Society of Gastroenterology (BSG) Association of Coloproctology for Great Britain and Ireland (ACPGBI)	2002	2002

4.3 POSITION PAPER ON CANCER SCREENING IN THE EUROPEAN UNION

In its Position Paper on cancer screening in the European Union[179], published in 2000, the Advisory Committee on Cancer Prevention recommended that (quote) "FOBT screening should be seriously considered as a preventive measure, based on the observation that colorectal cancer is a major health problem in many European countries. The decision on whether or not to embark on these screening programs must depend on the availability of the professional expertise and the priority setting for healthcare resources. If screening programs are implemented they should use FOBT test and colonoscopy should be used for the follow-up of test positive cases. Screening should be offered to men and women aged 50 years to approximately 74 years. The screening interval should be 1 or 2 years. Other screening methods such as immunological tests, FS and colonoscopy can at present not be recommended for population screening. (…) These recommendations address the people, the politicians and the health administrations of the Member States, the European Commission and the European Parliament."

In addition, the European Council Recommendation of 2 December 2003 on cancer screening ruled a general recommendation framework for cancer screening, citing 3 screening tests fulfilling the requirements of the recommendation (quote): "(1) PAP smear screening for cervical cancer precursors starting not before the age of 20 and not later than the age of 30; (2) mammography screening for breast cancer in women aged 50 to 69 in accordance with European guidelines on quality assurance in mammography; and (3) fecal occult blood screening for colorectal cancer in men and women aged 50 to 74. However, indicated age ranges are to be understood as maximum ranges, subject to national epidemiological evidence and prioritisation; smaller age ranges may be appropriate."

4.4 RATING SCHEMES FOR THE STRENGTH OF EVIDENCE AND RECOMMENDATIONS

Rating or grading consists of using a system that assigns a weighted value (e.g., levels or grades) to distinguish high from low quality research studies and/or strong from weak bodies of evidence or recommendations. Systems have been developed for different types of studies or evidence pertaining to therapy, prevention, diagnosis, prognosis and harm.

Unfortunately, not all guidelines include evidence rating and, moreover, different evidence-grading hierarchies are applied by various guideline developing agencies. Thus every guideline should be checked for its 'Evidence Grading System'. Details of all rating systems referred to in this report can be found in appendix.

4.5 AVERAGE RISK SCREENING (N = 14)

4.5.1 Review of retrieved guidelines

Table 2 in appendix gives an overview of the reviewed guidelines on average/low risk CRC screening. All of them recommend that CRC screening should be offered to average/low risk patients ≥50 years and otherwise asymptomatic, and that colonoscopy should be used for the follow-up of test positive cases. Screening benefits include reduction in colorectal cancer mortality, possible reduction in cancer incidence through detection and removal

of colorectal adenomas and, potentially, treatment of early colorectal cancers may involve less invasive surgery[24].

Except for five of them (nrs. 2, 5, 8, 11 & 12), all provide evidence rating and recommendation grading. Only four of them (Nrs. 5, 8, 9 and 14) recommend home-administered FOBT as first choice screening method, requiring the patient to collect and submit 3 stool test cards, each card with 2 separate stool samples from each of 3 consecutive bowel movements[191]. The others do not recommend a single specific screening method. Single office-based FOBT (oFOBT) obtained at the time of a digital rectal examination (DRE) is univocally disapproved[192, 193].

There is less agreement on optimal ages of initiation and cessation of screening (≥ 50, 50 - 70, 50 - 75, 50 - 80?)[194] nor on which test and which modalities to choose. In the following overview the general preferences are underlined:

1. FOBT frequency: annual or biennial.
2. Which particular FOBT to use and how many stool samples are to be collected per testing round, (mainly) for iFOBT brands.
3. Cutoff limits for number of coloured readings needed to consider a test positive are rarely discussed.
4. Unrehydrated vs. rehydrated guaiac FOBT (gFOBT). However, rehydration, used to increase sensitivity of the FOBT, comes at the cost of decreased specificity[195, 196] and has become generally disapproved.
5. gFOBT (Hemoccult II) vs. more sensitive immunochemical testing (iFOBT), based on the use of a specific antibody[197-201, 196, 202-205]. However, for screening purposes, any gain in sensitivity is of interest only if specificity and positive predictive value are satisfactory. Moreover, extra costs, if existing, must be acceptable for the society.
6. Dietary restrictions and their extent or no restrictions at all[206, 207]. Following on this, the American Cancer Society stated[56] that 'there is no justification for repeating fecal occult blood test in response to an initial positive finding'.
7. Duration of campaign, optimal number of screening rounds, as well as the length of follow-up after stopping FOBT campaigns[208, 209].

4.5.2 Conclusions

Although all these guidelines recommend to offer screening to average risk individuals aged 50 years and over, the low sensitivity of the common guaiac screening test Hemoccult II added to observed moderate compliance rates[210-215], even with participation enhancement strategies[216-218], make practitioners and public health deciders reluctant to set up a national population screening program. Indeed, most of the guidelines and recommendations favor a more differentiated approach, leaving the ultimate choice of the screening method to the patient after being given full information about the advantages and disadvantages associated with each approach. This undoubtedly reflects a tendency among gastroenterologists towards more targeted screening strategies based primarily on colonoscopy.

4.6 TARGETED SCREENING IN CASE OF A POSITIVE FAMILY HISTORY (N = 10)

This guideline category explicitely excludes people whose family history fulfils criteria for HNPCC or other autosomal dominant genetic syndromes associated with colorectal cancer susceptibility. It also excludes people who carry mutations in colorectal cancer susceptibility genes (for example, APC-genes or DNA mismatch repair genes), irrespective of the family history: these cases are dealt with in the section on guidelines & recommendations on CRC surveillance in case of high personal risk.

Table 3 in appendix gives an overview of the reviewed guidelines on sensitive CRC screening in case of an increased family history risk. Six of them (nrs. 1-2,4,6,9-10) are very elaborate in providing detailed guidelines for every identifiable subgroup at increased risk.

There is a general consensus that individuals with a family history of colorectal cancer are at increased risk of developing colorectal cancer and the evidence for this is shown in the previous chapter. This risk is greater when associated with early age of onset in the affected relative or with multiple affected relatives[105-113].

There is unanimity among the reviewed guidelines on total colonoscopy as the first choice screening method. There is less consensus on risk stratification, cut-off ages and screening frequency.

4.7 SURVEILLANCE IN CASE OF HIGH PERSONAL RISK (N = 11)

Surveillance guidelines and recommendations for this category of individuals are out of the scope of this report as they are to be considered as guidance on follow-up treatment.

The interested reader can refer to the references in table 4 in appendix for more details.

Key messages

- **All guidelines recommend that CRC screening should be offered to average (low) risk patients ≥ 50 year and otherwise asymptomatic.**
- **All guidelines recommend that colonoscopy should be used for the follow-up of test positive subjects.**
- **Guidelines disagree on optimal ages of screening (≥ 50, 50 - 70, 50 - 75, 50 - 80) and on which test and which modalities to choose.**
- **Screening benefits include reduction in colorectal cancer mortality, possible reduction in cancer incidence through detection and removal of colorectal adenomas and potentially less invasive therapy due to early treatment of colorectal cancers.**
- **If FOBT is chosen as primary mass screening test, unrehydrated home-administered FOBT is univocally recommended, requiring the patient to collect and submit 3 stool test cards, each card with 2 separate stool samples from each of 3 consecutive bowel movements.**
- **Single office-based FOBT obtained at the time of a digital rectal examination is disapproved.**
- **There is no justification for repeating FOBT after an initial positive finding.**
- **In many countries experts and public health decision makers are reluctant to set up a systematic national population screening program because of low sensitivity of the common guaiac screening test Hemoccult II added to observed moderate compliance rates, even with participation enhancement strategies.**
- **All guidelines recommend total colonoscopy as the first choice screening method for population subgroups at increased CRC risk as well as for surveillance.**
- **Guidelines are not concordant on risk stratification, cut-off ages and screening or surveillance frequency, nor on evidence rating scales.**
- **Screening recommendations for populations subgroups at increased risk are empiric and combine the known effectiveness of available screening tools with the observed risks associated with a positive family history of CRC.**

5 CLINICAL EFFECTIVENESS OF MASS SCREENING FOR COLORECTAL CANCER

5.1 INTRODUCTION

Screening and surveillance of colorectal cancer (CRC) appear to be topics of major interest in medical & public health communities worldwide, with increasing Medline citation numbers in the past 10 years (Figure 13).

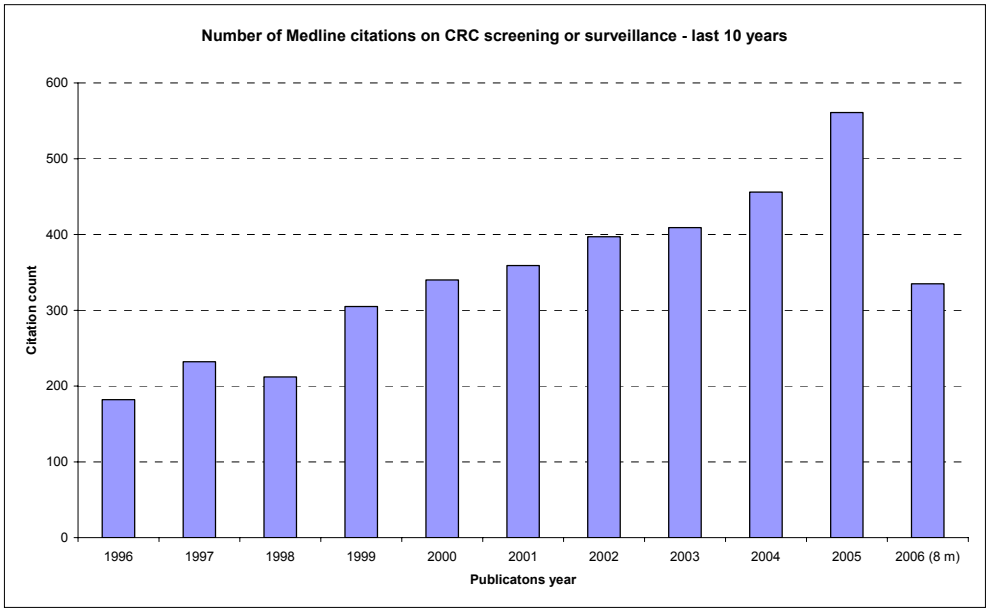

Figure 13: Medline citations on CRC screening or surveillance in last 10 years

A quick explorative Medline search, focusing on "colorectal cancer" combined with either "screening" or "surveillance" and limited to the last two years, yielded 896, respectively 139 citations if restricted to core clinical journals (see appendix).

After a first selection on systematic reviews our attention quickly focussed on an exhaustive systematic review from the New Zealand Health Technology Assessment group (NZHTA), published in 2005[219] and covering the literature between January 1997 and October 2004. This review in itself was an update of a previous systematic review from 1998[220]. The NZHTA review considered all screening options available, but concentrated on fecal occult blood test (FOBT), guaiac tests as well as on immunochemical FOBT, and flexible sigmoidoscopy (FS). For the other techniques a lack of available RCTs with appropriate outcome variables was reported.

In order to include more recent evidence we performed an incremental search of the scientific literature to cover the period since October 2004. However, much of the evidence presented in this chapter will be based on this previous systematic review.

5.2 INCREMENTAL SEARCH ON CLINICAL EFFECTIVENESS OF COLORECTAL SCREENING

The core searches on CRC screening of the NZHTA rapport were repeated, all searches being limited to the years 2004 (October to December) to 2006

(October, 31st). Searches were not limited by language, but languages other than English, French, German or Dutch were discarded. Earlier papers, found by hand searching of reference lists from papers, were reviewed where required to provide background material.

Gray literature, including internet websites were searched for ongoing clinical trial information, guidelines, screening programs of other health systems, and details of tests mentioned in recent literature.

It is important to consider that the main research question for this HTA project is the effectiveness and cost-effectiveness of population screening for colorectal cancer. Hence, our core search was looking for interventions and strategies directed towards a population at average colorectal cancer risk. A population with an increased risk for colorectal cancer was not the original target for this HTA evaluation. Nevertheless, our Scientific Steering Committee suggested giving consideration to population subgroups at increased or high CRC risk. Therefore, an additional search was performed on risk assessment and screening guidelines for identifiable patient groups. These were treated in the chapters on risk stratification and existing guidelines.

After discussion within the Scientific Steering Committee we also decided to focus our evaluation on two screening methods, FOBT and colonoscopy, while the other screening methods could be treated in less detail.

More information on the search strategies used is given in appendix.

5.2.1 Results

A total of 509 additional articles were identified by the core search strategy. Based on abstract review and hand searching of the reference lists, 56 articles were retrieved as full text for further assessment.

5.2.1.1 Systematic reviews and meta-analyses on CRC screening & surveillance

Only two new systematic reviews reported on clinical effectiveness of average risk FOBT screening; two meta-analyses on polyp detection rates with CT-colonography; the other eight concerned risk assessment and surveillance of patient groups at increased risk.

- Clinical effectiveness of FOBT screening: one meta-analysis[209] and one Cochrane review update (updated 12 august 2005)[24];
- CT-colonography: two meta-analyses, one on 24 within-subject endoscopic verification studies[221] and the other on 33 prospective studies of adults undergoing CT colonography with colonoscopy or surgery as the gold standard[222];
- Colonoscopic surveillance of HNPCC: a systematic review based on 3 cohort studies[223];
- CRC risk assessment in Crohn's disease: two meta-analyses on population-based cohort studies[81, 76];
- CRC risk assessment of malignant polyps: a pooled-data analysis of 31 original studies regarding malignant polyps[224];
- CRC risk assessment and familial aggregation: a meta-analysis of 20 published colorectal cancer studies reporting a degree of familial association[114];

- CRC risk assessment and MSI testing: a meta-analysis on original reports of both MSI and mutation analysis on the same subjects[225];
- CRC risk assessment and tumor M2-PK: a pooled-data analysis of 6 studies reporting on M2-PK measurement in the feces[226];
- CRC risk assessment with hyperplastic polyps: a meta-analysis of studies that compared the prevalence of proximal neoplasia and proximal advanced neoplasia in patients with distal hyperplastic polyps versus controls[227].

5.2.1.2 RCTs on CRC screening

5 new RCTs were identified, 4 concerning screening compliance and screening strategies, 1 concerning 2 regimes for bowel preparation for CT-colonoscopy:

- CRC screening compliance, iFOBT vs. gFOBT[228];
- CRC screening, strategies for increasing adherence[229, 230];
- CRC screening, strategy comparison[210];
- CT-colonoscopy, bowel preparation[231];

5.2.1.3 Other studies on CRC screening & surveillance

- CT-colonoscopy & computer aided polyp detection program, a cohort study[232];
- Genetic CRC risk assessment, a retrospective controlled study[233];
- Fibrosigmoidoscopic adenoma & CRC detection rate, a case control study[234];
- Colonoscopic post-polypectomy surveillance, a case control study[235];
- Two publications on CRC screening implementation and screening pilots[228, 236].

5.3 RATIONALE OF COLORECTAL CANCER SCREENING

Before considering an intervention such as screening in apparently healthy individuals there should be sufficient evidence that the benefits of screening will be more important than the potential harms. Moreover, there are several other conditions that need to be fulfilled before considering the establishment of regional or country-wide screening programs. To be appropriate for screening, a disease should be serious (relating to burden, incidence, cost-effectiveness and ethics), treatment given before symptoms become apparent should be more beneficial in terms of reducing morbidity or mortality and the prevalence of the preclinical disease should be high enough among the population being screened (see Wilson and Jungner criteria[1] and the Dutch National Council for Public Health criteria[2], discussed earlier).

In the systematic review of the New Zealand HTA this was implemented as:[219].

1. The condition is a suitable candidate for screening.
2. There is a suitable test.
3. There is an effective and accessible treatment or intervention for the condition identified through early detection.
4. There is high quality evidence, ideally from RCTs, that a screening program is effective in reducing mortality or morbidity.
5. The potential benefit from the screening program outweighs the potential harm.
6. The health care system will be capable of supporting all necessary elements of the screening pathway, including diagnosis, follow-up and program evaluation.
7. There is consideration of social and ethical issues
8. There is consideration of cost-benefit issues.

5.3.1 First criterion

For the *first criterion*, the condition should be a suitable candidate for screening, it is important that the condition is well-defined and that its incidence is well understood. For colorectal cancer this condition appears to be fulfilled. Another important aspect is the natural history of the disease: the hypothesis is that most colorectal cancers begin as adenomatous polyps and progress over the years to carcinoma through what is called an 'adenoma-carcinoma sequence'. There is a large amount of evidence supporting this theory. Therefore, in theory, there should indeed be an early stage at which most colorectal cancers, or its precursor adenomatous polyps, could be detected and prevented from developing. However, there is also evidence that not all colorectal adenomas evolve to cancers and autopsy studies found adenomas in up to 40% in individuals over the age of 60[237-243].

For the prognosis of the patient, the most important factor is the stage at which colorectal cancer is diagnosed[45, 219], as was extensively discussed in the chapter on the epidemiology of colorectal cancer.

5.3.2 Second criterion

For the *second criterion*, availability of a suitable test, different screening test options are to be considered: FOBT, flexible sigmoidoscopy (FS) or a combination of both, colonoscopy and its even more sophisticated counterpart, virtual colonoscopy or CT colonography, and double contrast barium enema (DCBE). Other, upcoming techniques are based on molecular stool analysis[244-246, 55, 247-258, 126, 259-264, 127].

5.3.3 Third criterion

The *third criterion* is that treatment is effective and accessible for all those who are identified through the screening program. This is no place for a discussion of the various therapeutic options and their effectiveness, but the conditions of availability and accessibility appear to be fulfilled in Belgium.

5.3.4 Forth criterion

The *forth criterion*, the presence of high quality evidence, ideally from RCTs, that a screening program is effective in reducing mortality or morbidity, will be addressed while evaluating the evidence for the various screening strategies.

5.3.5 Criteria five to eight

These criteria will be evaluated all through this HTA report. To do this, however, it is important that the screening pathway is well-defined and well-understood. A simple representation of the screening pathway for colorectal cancer is shown in figure 14.

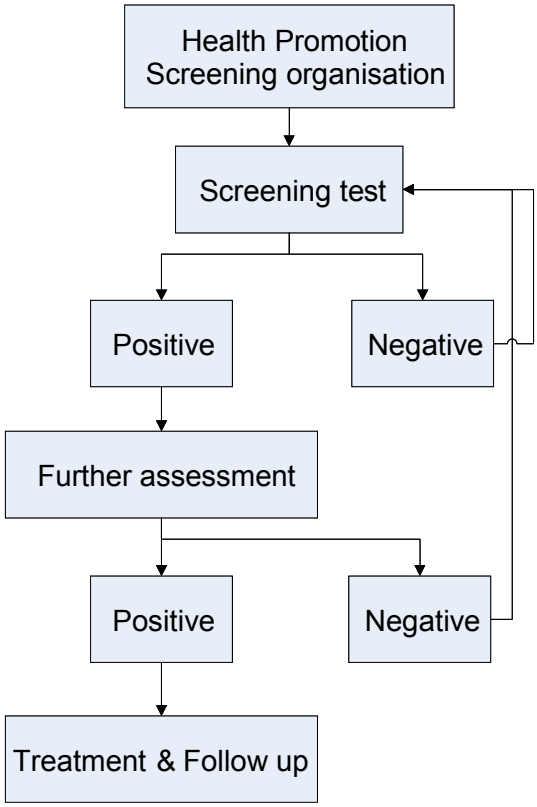

Figure 14 : The colorectal screening pathway adapted from Kerr et al.[219]

5.4 STRATEGIES AND TESTS CONSIDERED

An essential element for a screening program to become acceptable and successful is the availability of a suitable screening test or strategy. A test should ideally be safe, simple, reliable, valid, cheap, highly sensitive and highly specific. Moreover, it should also be generally perceived as acceptable by the target population as to result in an optimal participation in screening (in the literature participation is also referred to as compliance or adherence).

Clinical sensitivity and specificity are often used to compare the diagnostic capabilities of a test and they traditionally rely on the performance of a given test, used at a specific test threshold, when compared to a reference or 'gold' standard that is supposed to give the 'true' diagnosis. In short, with a highly sensitive test the probability that the test will indeed be positive when the person has the condition (as determined with the reference standard) will be

high, thereby minimising the number of false negatives. A highly specific test means that there will be a high probability that the test will have a negative result if indeed the person does not have the condition, thereby minimising the number of false positives.

Other measures of assessing diagnostic performance in screening tests are the predictive values (positive and negative predictive value). These measures can be useful in clinical settings, as they indicate the probability that a person with a given test results will indeed have or not have the disease, but they are specific for the population in which they are used as they depend on the population prevalence of the condition. Therefore, they should not be used while comparing tests that were used in different populations. The same is true for concepts such as the 'Number Needed to Screen' (NNS) as those numbers are dependent upon the population in which the intervention is applied.

Most trials of screening strategies have been conducted in men and women aged 50 and up to ages 70 to 75. The obvious reason, of course, is to apply the test in a population with sufficiently high prevalence of detectable malformations.

5.4.1 Fecal occult blood tests (FOBT)

Fecal occult blood testing (FOBT) is based on the nature of colorectal cancer and larger polyps to bleed intermittently. Presence of blood in the stool is therefore an indicator of cancer. The bleeding, however, is intermittent and blood is unevenly distributed throughout the stool. Additionally, the amount of bleeding is dependent on the size of the polyp(s) or cancer. Screening for the presence of blood in the stool is far less sensitive for polyps than for cancer[265].

Approximately two thirds of colorectal cancers bleed in the course of a week[266, 267, 197], thereby naturally limiting the potential clinical sensitivity of FOBT: at the moment the cancer does not bleed it can not be detected by FOBT. Moreover, non-malignant lesions can also bleed and there are still other causes for the presence of blood in the stool, thereby also limiting the potential specificity. FOBT is therefore, by definition, a non-specific test giving information on the probability of the presence of colorectal cancer. It provides no information on the localisation of the source of bleeding, but it has the advantage of being a non-invasive test. Therefore, a positive test result will necessarily call for an invasive procedure afterwards[268].

Most information in the literature is found on the classical FOBT, the so-called guaiac FOBT (gFOBT). Van Deen[269] is generally credited with the discovery that gum guaiac, a natural resin extracted from the wood of Guaiacum officinale, is useful in detecting occult blood. The heme portion of hemoglobin, if present in the fecal specimen in its free form or bound to protein (globin, myoglobin, and some cytochromes), has peroxidase activity which catalyzes the oxidation of alpha guaiaconic acid (active component of the guaiac paper) by hydrogen peroxide (active component of the developer) to form a highly conjugated blue quinone compound. Degradation products of heme, that are formed in the intestine, lack peroxidase activity and, as a result, are not detected by the test. Heme enters the proximal gastrointestinal tract as hemoglobin or myoglobin in food or as red cells from bleeding lesions, and relatively little is absorbed by the small intestine. However, in the colon, heme is modified by the microflora so that it loses its peroxidase activity, and consequently guaiac tests are more sensitive for distal (colonic) than for proximal (gastric) bleeding pathology.

To perform the test, fecal matter needs to be collected and applied to a testing kit. Guaiac-based FOBTs use sticks or spatulas to collect specimens from stools

that have not contacted toilet bowl water ('dry specimen collection'); specimens are then smeared on test cards that need to be developed afterwards. Nearly all FOBT manufacturers make analytical sensitivity claims (in vitro detection limits). The analytical sensitivity of a test represents the smallest amount of substance that can accurately be measured in a biological sample. Examples of these sensitivity claims from manufacturers' product sheets are listed in Table 12.

Table 12: in vitro detection limits of commercially available FOBTs

Product	Type	Manufacturer	In vitro detection limits
Hemoccult® * † Hemoccult® II *	guaiac	Beckman Coulter Inc.	50% at 300 µg Hb/gm feces
Hemoccult® SENSA® * Hemoccult II® SENSA® *	guaiac		75% at 300 µg Hb/gm feces
Hemoccult® ICT (immuno) **	immuno		~30 µg human Hb/gm feces
FlexSure® OBT **	immuno		300 µg human Hb/gm feces
Magstream HemSp ® **	immuno		300 µg human Hb/gm feces
Instant-View® FOBT II ***	immuno	Alpha Scientific Desings Inc.	50 µg human Hb/gm feces
InSure® **	immuno	Enterix, Inc.	50 µg human Hb/gm feces
ImmoCARE® ** ColonCARE® **	immuno	Care Products, Inc.	30 µg human Hb/gm feces
HemeSelect® **	immuno	Fujirebio (Japan)	300 µg human Hb/gm feces
Immudia HemSp ® **	immuno		
OC-Hemodia® **	immuno	Eiken Chemical (Japan)	40 µg human Hb/gm feces
MonoHaem® **	immuno	Nihon Pharmaceuticals (Japan) Chemicon International, Inc.	~1 - 2 mg Hb/gm feces
Sure Vue® *	guaiac	Fisher Scientific Co. Inc.	10 mg Hb/gm feces
Coloscreen® ES *	guaiac	Helena Laboratories Inc.	~ 0,3 mg Hb/gm feces
Sure Vue® ES *	guaiac	Fisher Scientific Co. Inc.	~ 0,3 mg Hb/gm feces
HemaPrompt® *	guaiac	Aerscher Diagnostics Inc.	2 mg Hb/gm feces
Hemostick®****	immuno	Ventec S.A. (Belgium)	~ 100 µg human Hb/gm feces
Actim Fecal Blood®*****	immuno	Medix Biochemica (FN)	25-50 µg human Hb/gm faeces

† Hemoccult® and Hemoccult II® are similar except for card design; Hemoccult® is now discontinued.

Sources: * http://www.hemoccultfobt.com/healthcare/health_products.htm
** Blue Cross and Blue Shield Association http://www.bsbs.com
*** http://www.meditechinternational.com/instant_cancerCE.html
**** Ventec S.A. Av. Du Pré Aily 10, 4031 Angleur - tel: 04/361 42 32
***** Lucron Bioproducts B.V.B.A. Willemsdorp 2 B-9840 De Pinte

The observation that colorectal neoplasms and polyps do not bleed continuously has been the basis for the standard testing procedure for guaiac tests, whereby two samples of fecal matter are applied to the test kit on three consecutive days, leading to 6 samples to be studied. Hemoccult II slides come

in an 'all in' patient kit with 3 double windowed specially prepared, stabilized guaiac test cards, 6 stool spatulae and a vial with hydrogen peroxide developer. They are designed for patients to easily collect serial specimens at home from bowel movements over three days. After the patient prepares the Hemoccult II test, it may be returned in person or by mail to the laboratory, hospital or medical office for development and interpretation. Hemoccult II Sensa is a guaiac based but more sensitive and more readable test than Hemoccult II. However, there is no consensus on the number of those samples that need to be positive to call the test round positive. Different trials used different positivity thresholds, inevitably leading to different test characteristics in terms of sensitivity and specificity.

Although gFOBT can in theory detect bleeding from any part of the alimentary tract, it is somewhat more selective for the large bowel over the upper gastrointestinal tract. False positives can occur with gFOBTs as a result of dietary factors and ingestion of certain medications. Non-human hemoglobins from meat, other dietary components with peroxidase activity (e.g., radishes, turnips, broccoli, spinach,…), and bleeding due to medications (e.g., salicylates) may give false-positive results, whereas an excess of vitamin C may give false-negative results[270]. Therefore, dietary and drug restrictions are often recommended prior to sampling (table 13), although there is little evidence that these precautions are required[195]. Moreover, there are concerns whether such restriction also reduces the probability that patients will complete the test[206], thus endangering optimal patient adherence to the screening program.

Table 13: Recommended drug and diet guidelines with guaiac FOBTs

Drug Guidelines
For seven days before and during the stool collection period, avoid non-steroidal anti-inflammatory drugs such as ibuprofen, indomethacin, naproxen or aspirin (more than one adult aspirin a day) as well as corticosteroids, phenylbutazone, reserpine, anticoagulants, anti-metabolites, and cancer chemotherapeutic drugs.
Acetaminophen can be taken as needed.
For three days before and during the stool collection period, avoid vitamin C in excess of 250 mg a day from supplements, and citrus fruits and juices.
Avoid alcohol in excess and the application of antiseptic preparations containing iodine (povidone/iodine mixture)
Diet Guidelines
For three days before and during stool collection period, avoid red meats (beef, lamb and liver).
Eat a well balanced diet including fibre such as bran cereals, fruits and vegetables, but avoid radishes, turnips, broccoli, spinach, citrus fruits and juices.

Source: http://www.hemoccultfobt.com/docs/PI_HOS_462489.E-web.pdf

Some reports suggest that delaying development of Hemoccult cards for at least three days will decrease the number of false positives caused by plant peroxidases and obviate the need for diet restriction of fruits and vegetables[254].

In their position paper on the interpretation and follow-up of FOBTs, Ransohoff and Lang[195] argue that any person with a positive result who did not restrict diet or medications pre-test should still undergo diagnostic work-up, rather than resubmitting repeat FOBTs after diet and medication restrictions. Likewise, the American Cancer Society likewise states that there is no justification for repeating fecal occult blood test in response to an initial positive finding[56].

Aside from the classical guaiac FOBT there has been the development of immunochemical FOBTs (iFOBT) specifically designed to detect human hemoglobin in dried fecal samples. They contain polyclonal anti-human hemoglobin antibodies that react with the globin portion of undegraded hemoglobin. Because they are specific for human blood in feces, no special dietary restrictions are required[270]. Restrictions on intake of drugs that easily induce gastro-intestinal erosions and hemorrhage, however, remain.

Hemoglobin from upper G.I. bleeding (i.e., oral cavity, oesophagus, stomach or small intestine) is generally degraded by bacterial and digestive enzymes before reaching the large intestine and is therefore rendered immunochemically non-reactive. Conversely, hemoglobin from lower G.I. bleeding (i.e., caecum, colon or rectum) undergoes less degradation and can therefore remain immunochemically reactive. Thus, immunochemical fecal occult blood tests which detect undegraded hemoglobin have, in theory, increased biological specificity for lower G.I. bleeding and any associated pathology[270], and therefore could lower the overall cost of detecting these disorders by lowering colonoscopy rates[196, 202-205]. However, we have to keep in mind that all fecal occult blood tests are subject to certain limitations inherent to lesions that bleed intermittently with non-uniform distribution of blood in feces. There is much variation between iFOBT tests and they are more expensive. They are also less studied than the classic gFOBT test.

Immunochemical FOBTs require sample collection from 2 stools (InSure OC-Hemodia), 3 stools (HemeSelect, FlexSure OBT, MonoHaem), or 1 stool (Instant-View, immoCARE)[270]. For InSure the sample is collected by brushing the surface of the stool while in the toilet bowl water, avoiding the gFOBT requirement for dry specimen collection, which is easier to handle and thus claimed to be more patient friendly and thereby increase screening compliance[201].

The test formats for several iFOBTs require minimal processing and involve developing a test strip with controls and reading a colour reaction. Some iFOBT formats require more extensive laboratory processing (HemeSelect, OC-Hemodia). In the case of the InSure, all tests are exclusively developed by a private laboratory company (U.S.). Magstream 1000[271, 196, 202] and Hem SP[272, 273] provide automatic instrumental test development and reading with adjustable sensitivity threshold.

Advantages and disadvantages of iFOBT compared with gFOBT are summarized in Table 14.

Table 14: Advantages and disadvantages of iFOBT compared with gFOBT

Advantages of fecal immunochemical test (iFOBT) compared with gFOBT	
Improved specificity	iFOBTs will not react with non-human hemoglobin, vitamins, drugs, or peroxidase from food sources. They also showed to be non-reactive with blood from the upper gastrointestinal tract provided bleeding is occult.
Potential increase in patient compliance	Since no dietary restrictions are needed, iFOBT may be more acceptable to the consumer than current gFOBT tests.
Disadvantages of an fecal immunochemical test (iFOBT) compared with gFOBT	
Limited clinical testing	No prospective, controlled trials of iFOBT screening and colorectal cancer incidence or mortality outcomes have been reported. However, if iFOBTs perform at least as well as gFOBT, it is likely that iFOBTs used for CRC screening would have at least the same efficacy in decreasing colon cancer mortality as gFOBTs[270].
Same sensitivity limitations	While iFOBTs have advantages over gFOBTs, they are still tests for occult blood, which may leak intermittently and may occur from sources in the colon and rectum other than cancers or large adenomas. Data indicate that the problem for detection created by intermittent bleeding is less marked with immunochemical than with guaiac tests because higher test sensitivity is not accompanied by significant degradation of specificity, as is the cause with guaiac tests. In addition, because bleeding from adenomas occurs infrequently, the potential for CRC prevention through adenoma detection and removal is likely to be lower with this and all FOBT methods than with endoscopic and imaging screening modalities. However when used annually, as recommended, the program sensitivity of FOBT is very high.
More expensive	See Table 15

Table 15 lists available FOBT test kits in Belgium[274], leaving some choice depending on availability of regional colonoscopy resources.

Table 15: Choice of FOBT depending on colonoscopy resources

Regional resources	**Recommended FOBT**	**Trade name**	**Belgian supplier**	**Price per test round (VAT incl.)**
Colonoscopy resources limited	Guaiac test with high specificity	Hemoccult® II	Laméris	2,06 €
	Fecal Immunochemical test (FIT)	Instant-View® Hemostick® Actim Fecal Blood®	Obelis Ventec Lucron Bioproducts	± 7 €
Colonoscopy resources readily available	Guaiac test with high sensitivity	Hemoccult® Sensa®	Laméris N.V.	2,14 €

The Instant View FOBT II test comes in a set of fecal collection tubes, pre-filled with extraction buffer, with sampling stick and corresponding one-step lateral flow chromatographic immunoassay test cassettes (Instant View FOBT II casette

test) or dip strips (Instant View FOBT II dip strip test). Hemostick comes in a set of collection cards and a test kit for development.

5.4.2 Flexible sigmoidoscopy

Flexible sigmoidoscopy (FS) is an invasive endoscopic technique using medical fibre optics. A 60 cm long flexible endoscope visualises the rectum and the left side of the colon. The preparation involves the administration of two enemas on the day of the examination and the procedure is usually performed without sedation[275, 194]. It is an invasive technique but offers the possibility for sampling lesions identified during the procedure (polypectomy). The technique is rather simple to learn[276] and in some countries, such as in the UK, performed by trained nurses[277-279]. However, the randomized US Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial demonstrated a considerable variability in the rates of positive screens and in polyp and adenoma detection rates among FS examiners performing the procedures using a common protocol[280]. This potential variation in technical quality may have a profound impact on the effectiveness of FS on the early detection and prevention of colorectal cancer. In reaction, an international multi-society task group published in 2005[281] a set of consensus and evidence based recommendations to assist the development of continuous quality improvement programs around the delivery of FS for colorectal cancer screening.

Another important drawback with FS is that only the distal portion of the colon can be seen. Although the major proportion of carcinomas occurs distally, up to 30 to 40% of the tumors originate more proximally, as illustrated by the Flemish cancer registry data in the chapter on epidemiology. It is argued, however, that many patients with proximal cancers also have concomitant adenomas or CRC within reach of the flexible sigmoidoscope (see also table 17); if those lesions are identified by FS a full colonoscopic examination will follow thereby detecting those proximal lesions. Several studies[282-284] explored the prevalence and location of advanced colonic neoplasms (i.e., adenomas ≥ 10 mm in diameter, villous adenomas, adenomas with high-grade dysplasia, or cancer) and their risk in asymptomatic patients with and without distal neoplasia. Subjects with advanced distal histology and those older than 65 years appear to be at increased risk of advanced proximal neoplasia[282].

In a systematic review and meta-analysis of screening colonoscopy, Lewis et al.[285], studied detection rates of proximal adenomatous polyps with screening sigmoidoscopy: distal adenomatous polyps, including diminutive distal adenomatous polyps, were associated with an increased prevalence of synchronous proximal neoplasia. However, 2 to 5 % of patients undergoing screening colonoscopy had isolated advanced proximal neoplasia. Even more patients had isolated nonadvanced proximal neoplasia, indicating the limits of sensitivity of FS as a screening technique for CRC.

Some data also suggest that with ageing, the prevalence of more proximal lesions might increase. A recently published retrospective prevalence study[286] reported on the prevalence of overall adenoma, advanced neoplasia (i.e. adenomas of at least 10 mm in diameter, villous adenomas, adenomas with high-grade dysplasia), and CRC in 1.177 average-risk Israeli Jews enrolled for colonoscopy (initiated by the patients or their family doctors) and aged 40 - 80 yr. Excluded were those with cancer-related symptoms or alarm signs and those with a personal or family history of colorectal neoplasia. Stratification by age groups included a main group of screenees aged 50 - 75 yr (the acceptable age

range for screening) and two smaller groups of young (aged 40 - 49 yr) and elderly participants (aged 76 - 80 yr). Results are summarized in Table 16.

Table 16: Prevalence of adenoma, advanced neoplasia and CRC by age group[286]

Age group	Sample size	Non-advanced adenoma			Advanced neoplasia*			Invasive CRC		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
40 - 49 y	183	16	8,7%	4,6% - 12,8%	2	1,1%	0,0% - 2,6%	0	-	-
50 - 75 y	917	145	15,8%	13,5% - 18,2%	50	5,5%	4,0% - 6,9%	11	1,2%	0,5% - 1,9%
76 - 80 y	77	11	14,3%	6,5% - 22,1%	9	11,7%	4,5% - 18,9%	2	2,6%	0,0% - 6,2%

* adenomas at least 1 cm in diameter, villous adenomas, adenomas with high-grade dysplasia

Overall, in 21% of the 206 cases with proximal neoplasia, no distal neoplasia was detected in the rectum, sigmoid, and descending colon up to the splenic flexure. However, when only the rectum and sigmoid colon were considered, 43% of the cases with proximal neoplasia had no distal lesions. Furthermore, the study indicated a possible proximal shift in neoplastic lesions in older ages (Table 17).

Table 17: Odds Ratio for Proximal Neoplasia According to the Findings of Neoplasia in the Distal Colon

	B	Sig.	OR	95% CI
Distal colon 1	0,901	0,0004	2,462	1,497 - 4,049
Age (/year)	0,066	0,000003	*1,069*	*1,036 - 1,102*
Distal colon 2	0,506	0,0648	1,659	0,969 - 2,84
Age (/year)	0,058	0,0000004	*1,06*	*1,034 - 1,087*

B = logistic regression coefficient. Distal colon 1 defined as rectum, sigmoid and left colon until the splenic flexure and distal colon 2 defined as rectum and sigmoid colon.

Of course, one should emphasize that this study was done on Israeli Jews having different ethnic variation features, higher rates of malignant conversion from adenoma to carcinoma, and higher rates of flat adenomas. Furthermore, conclusions are based on retrospective data only.

Another issue also concerns potential inadequacy of FS[287]. Using data from 55.791 individuals screened as part of the Colon Cancer Prevention (CoCaP) program[a] of Kaiser Permanente of Northern California, Doria-Rose et al.[288] evaluated the likelihood of having an inadequate (< 40 cm) examination by age and sex, and estimated the risk of distal CRC according to depth of sigmoidoscope insertion at the baseline screening examination. In 1994 and 1995 reports from all sigmoidoscopies performed in KP facilities were entered into a CoCaP computerised database. These reports included patient's reported medical history and indications for examination (screening versus symptoms), plus endoscopist's recorded indications for examination and results, including depth of insertion, limitations of the examination (due to spasm/pain, stool, or angulation), and number and depth of any polyps identified. Histological findings from any removed or biopsied polyps were linked back to the sigmoidoscopy data form. Additional demographic data (age and sex) and provider data (gastroenterologist, non-gastroenterologist physician, or nurse) were obtained from other KP databases, and incident cases of CRC to 31 December 2000

[a] the CoCaP program offers a screening FS to all KP members aged 50 years and older once every 10 years.

were identified using the KP Tumor Registry. Either patient or endoscopist report that the examination was being done as a result of symptoms resulted in exclusion. If a patient had more than one sigmoidoscopy during this time period, only the first was considered. Patients at high risk of developing CRC were excluded, based on the presence of inflammatory bowel disease, prior colorectal polyps or cancer, or history of CRC in more than one first degree relative or one first degree relative diagnosed at age 55 years or younger. Additionally, subjects who had CRC diagnosed at baseline were excluded, as identification of a lesion suspected of being cancer often results in termination of the examination prior to the maximal possible depth of insertion. Finally, those who had no indication of insertion depth recorded on the sigmoidoscopy report were also excluded.

Incidence rates of distal CRC (that is, cancers of the rectum and sigmoid colon, ICD-0-2 codes C18.7, C19.9, and C20.9) were calculated by categories of sigmoidoscopy depth of insertion and examination limitations (pain, suboptimal bowel preparation and angulation of the colon). Rates were calculated by dividing the number of distal CRC cases by the total amount of person-time at risk. Study subjects were followed until 31 December 2000 or until the time of death, KP membership termination, or CRC diagnosis. Poisson regression was used to estimate the rate ratios, with 95% CI for sigmoidoscopy depth of insertion and examination limitations. All Poisson models were adjusted using indicator variables for age (as parameterised above), sex, and family history of CRC.

Older individuals were at a much greater risk of having an inadequate examination (RR for age 80+ years compared with 50 - 59 years: 2,6 (95% CI: 2,3 - 3,0), as were females (RR 2,3 - 95% CI: 2,2 - 2,5); these associations were attenuated but remained strong if further adjusted for examination limitations (pain, stool, and angulation). There was an approximate threefold increase in the risk of distal CRC if the baseline sigmoidoscopy did not reach a depth of at least 40 cm; a smaller increase in risk was observed for examinations that reached 40 - 59 cm. The authors concluded that older individuals and women are at an increased risk of having inadequate sigmoidoscopy and recommended that, because of inadequate sigmoidoscopy results in an increased risk of subsequent CRC, physicians should consider steps to maximise the depth of insertion of the sigmoidoscope or, failing this, should consider an alternative screening test.

5.4.3 Colonoscopy

Colonoscopy is also an invasive endoscopic technique but using a longer endoscope than FS, enabling direct visualisation of the entire colon. The preparation of the patient involves dietary restrictions and the administration of laxatives the day before the procedure, while the procedure is usually performed under sedation[275, 194].

Colonoscopy is currently seen as the gold standard investigation for the colon and has the advantage of allowing taking samples for pathologic examination and performing immediate polypectomy with the potential for preventing subsequent colorectal cancer. A landmark study in this field was the U.S. National Polyp Study that compared a cohort of subjects undergoing periodic colonoscopy for polyp surveillance with historical controls[64]. In this study 1.418 patients who had undergone total colonoscopy and removal of adenomas underwent one or more follow up colonoscopies during an average follow-up period of six years and the incidence of colorectal cancer in this group was

compared with that in three reference groups including two cohorts in which polyps had not been removed. Ninety-seven percent of the subjects were followed up for a total of 8.401 person years, and the majority (80%) had one or more follow-up colonoscopies. During this time five asymptomatic early-stage colorectal cancers were detected by colonoscopy and no symptomatic cancers were detected. When compared with the reference group this represented a much lower rate of diagnosis of colorectal cancer than would have been expected, and the conclusions were that colonoscopic surveillance in adenoma patients reduces the incidence of and subsequent mortality from colorectal cancer. Although this is generally considered a landmark study, the conclusions must be interpreted with caution as the comparison group was not derived from the same population as the cases and this is likely to have led to an overestimation of the efficacy of colonoscopy. In addition, it is difficult to extrapolate from polyp surveillance to screening asymptomatic populations.

Performance characteristics of colonoscopy are widely known to be operator dependent and mainly polyps, but even cancers might be missed if the examination is unconsciously incomplete: in a variable proportion (5 to 30%) of cases the caecum is not reached[49] and the localisation of the tumor can be inaccurate[49]. Most clinically significant adenomas missed on colonoscopy appear to be located behind a fold or near the anal verge[289].

Although gastroenterologists agree that colonoscopy is not infallible, there is no clarity on the numbers and rates of missed polyps[290, 277, 291, 292, 289]. In a recently published systematic review[293] summary estimates were obtained of the polyp miss rate as determined by tandem colonoscopy. Six studies with a total of 465 patients could be included. Results are summarized in Table 18.

Table 18: Systematic review of polyp miss rate determined by tandem colonoscopy[293]

Size	No. Polyps (missed/total)	Pooled miss rate	95% CI
Any	370/1.650	22%	19% - 26%
adenomas ≥ 10 mm	2/96	2,1%	0,3% - 7,3%
adenomas 5 to < 10 mm	16/124	13,0%	8,0% - 18,0%
adenomas 1 to < 5 mm	151/587	26,0%	27,0% - 35,0%
non adenomatous polyps ≥ 10 mm	0/8	0,0%	0,0% - 36,9%
non adenomatous polyps ≥ 10 mm	83/384	22,0%	18,0% - 26,0%

Thus, colonoscopy rarely misses polyps ≥ 10 mm, but the miss rate increases significantly in smaller sized polyps. However, the available evidence is based on a small number of studies/patients with heterogeneous study designs and inclusion criteria.

The colonoscopic examination also carries some risks[294-299] such as bowel perforation or post-procedure bleeding and, on rare occasions, severe electrolytic imbalances related to aggressive bowel preparation and needing hospitalization[300-314]. Risks are significantly higher in therapeutic colonoscopy (polypectomy, biopsies,…) than in merely diagnostic endoscopies[295, 297, 299], but overall the risks of colonoscopy are definitely higher than from either FOBT or FS.

In a prospective study conducted by the SFED (Société Française d'Endoscopie Digestive) in January 2003, questionnaires were sent to all gastroenterologists practicing in France (N=2.901). They were asked to reply to items concerning colonoscopies and sigmoidoscopies performed on two workdays chosen in

advance. The response rate was 32.8%. Data were extrapolated to establish estimates for the entire year and are presented in Table 19 (not published, but downloadable slideshow from the SFED website[315]).

Table 19: Estimated complication rates of colonoscopies in France 2002 - 2003

Complication category	Percentage
Hemorrhage	0,28%
Anesthetical problems	0,05%
Perforation	0,07%
Septicaemia	0,01%
Other	0,06%
TOTAL COMPLICATIONS ($N_{estimated}$ = 4.962 / 1.041.953 colonoscopies)	0,47%

Several factors might improve the quality (complication rates) and sensitivity (missing rates) of colonoscopy: (1) examiners should receive adequate training, (2) caecal intubation rates should be high, (3) caecal intubation should be verified by specific landmarks in all cases, (4) failure to reach the caecum should be followed by barium enema or virtual colonoscopy, and (5) meticulous examination would appear to improve sensitivity for cancer detection[316].

Whether and when colonoscopy with negative findings has to be repeated is not well defined. To determine the duration and magnitude of the risk of developing colorectal cancer following performance of a negative colonoscopy Singh et al[317] performed a population-based retrospective analysis of individuals with neoplasia-negative colonoscopic evaluations. A cohort of 35.975 patients who had been evaluated between April 1, 1989, and December 31, 2003, were identified using Manitoba Health's physician billing claims database. Standardized incidence ratios (SIRs) were calculated to compare CRC incidence in the cohort with that in the general population of the same province. Stratified analysis was performed to determine the duration of the risk reduction. Patients with a history of CRC prior to the index colonoscopy, inflammatory bowel disease, resective colorectal surgery, and lower gastrointestinal endoscopy within the 5 years before the index colonoscopy were excluded. Cohort members were followed up from the time of the index colonoscopy until diagnosis of colorectal cancer, death, emigration from Manitoba, or end of the study period on December 31, 2003. Results are summarized in Table 20.

Table 20: Standardized incidence ratios (SIR) after negative index colonoscopy versus control[317]

Follow up time	SIR	95% CI
6 months	0,69	0,59 - 0,81
1 year	0,66	0,56 - 0,78
2 years	0,59	0,48 - 0,72
5 years	0,55	0,41 - 0,73
10 years	0,28	0,09 - 0,65

The proportion of right sided CRC was significantly higher in the colonoscopy cohort than the rate in the Manitoba population (47% vs. 28%; P< 0,001). The study concluded that the risk of developing CRC remains decreased for more than 10 years following the performance of a negative colonoscopy and that there is a need to improve the early detection rate of right-sided colorectal neoplasia in usual clinical practice.

In a small population based case-control study in Germany[318]; including 380 cases and 485 controls, detailed history and results of previous colonoscopies were obtained by interview and from medical records and adjusted relative risks of colorectal cancer among subjects with a previous negative colonoscopy compared with those without previous colonoscopy were estimated according to time since colonoscopy. Subjects with previous negative colonoscopy had a 74% lower risk of CRC than those without previous colonoscopy (OR 0,26; 95% CI 0,16 to 0,40). This low risk was seen even if the colonoscopy had been done up to 20 or more years previously. Particularly low risks were seen for rectosigmoid cancer (OR 0,13; 95% CI 0,04 to 0,43) and for rectal cancer (OR 0,19; 95% CI 0,09 to 0,39), and after a negative screening colonoscopy at ages 55 to 64 (OR 0,17; 95% CI 0,08 to 0,39) and ≥ 65 (OR 0,21; 95% CI 0,10 to 0,41). The authors concluded that subjects with negative findings at colonoscopy are at very low risk of colorectal cancer and might not need to undergo repeat colonoscopy for 20 years or more, if at all. The possibility of extending screening intervals to 20 years or more might reduce complications and increase the feasibility, compliance and cost-effectiveness of colonoscopy based screening programs.

5.4.4 Double contrast barium enema (DCBE)

With this conventional radiological technique, a liquid barium mixture is instilled into the colorectum and afterwards air is insufflated, followed by x-ray examination in various positions[275, 194]. The patient usually prepares with dietary restrictions and an enema or laxatives the day before. It is a standard radiological technique and was considered as a potential screening tool. It does have the advantage of a higher sensitivity compared to FOBT, the ability to visualise the entire colon compared to FS and a better safety and lower cost compared to colonoscopy. It does not permit, however, to take samples meaning that colonoscopy will still be needed when suspicious lesions are detected by DCBE. The Scientific Steering Committee considered DCBE as an obsolete technique for mass screening purposes.

5.4.5 Virtual colonoscopy

Virtual colonoscopy (also known as CT colonography, CT pneumocolon, MRI colonoscopy) refers to essentially preoperative (i.e. diagnostic) radiological tumor staging techniques[319] using computer generated images of the colon constructed from data obtained from an abdominal CT[194, 320-323] or MRI examination[324-327].

The preparation is similar to standard colonoscopy. Air or carbon dioxide is insufflated into the colon and data are acquired by the scanner, generating images of the colon. Data are presented as two-dimensional images while suspicious areas can be rendered as three-dimensional images[328]. Sedation is normally not required although mild discomfort is reported from the insufflation of air during the procedure[231].

Theoretically, virtual colonoscopy has several potential advantages over endoscopic colonoscopy for use in colorectal cancer diagnosis and potentially even screening. It enables to visualise the entire colon non-invasively and can also identify malignancies in areas that are difficult to assess with colonoscopy. Therefore, it has been argued that, in a diagnostic setting, it might be the favoured examination technique when colonoscopy failed, was incomplete or when the performance of a colonoscopy was contra-indicated or refused by the patient[329, 330]. It is a rapidly evolving technique as witnessed by the wealth of

publications in recent years and future potential developments include possibilities to simplify patient preparation, thereby increasing patient comfort[231].

Disadvantages of virtual colonoscopy are that, as with DCBE, there is a certain radiation exposure with CT colonography and no samples can be taken during the examination and neither can polyps be removed. Therefore a conventional colonoscopy may still be needed after positive results from virtual colonoscopy. Radiologist experience with the technique may also influence accuracy and test performance[275, 194]. High resource costs for both equipment and radiologist training may be important barriers to the widespread use of virtual colonoscopy.

5.4.6 Other techniques

Detection of DNA mutations associated with colorectal carcinogenesis in stool, using amplification techniques such as PCR is an emerging technology[331-341, 252, 256, 258, 262, 263, 342]. Unlike blood, DNA is stable in fecal matter and is shed continuously by colorectal carcinomas. In theory, therefore, DNA stool sampling could become an attractive test if performance characteristics are good. It might also allow for the detection of carcinomas in other parts of the gastrointestinal tract. Disadvantages of current DNA stool sampling techniques are that the tests are expensive and time-consuming and that few data are available regarding the use of this technology in screening settings[246].

5.5 EVIDENCE FOR PERFORMANCE OF STRATEGIES AND TESTS IN SCREENING CONDITIONS

Another important criterion for a screening program to become acceptable is that there is high-quality evidence, ideally from RCTs, that a screening program is effective in reducing mortality and morbidity. The main reason for this requirement is that other study designs always carry the risk of being influenced by bias, mainly because of different prognosis of subjects in the comparison groups due to initial selection bias. An RCT, because of its initial randomisation is the only possibility to avoid this prognostic unbalance. Randomisation is, of course, not the only requirement and the study design and conduct should be of good quality to avoid other types of biases, for example by using blinded allocation and/or blinded assessment of outcomes to avoid observation bias (see introduction chapter). Blinded allocation can be difficult in screening circumstances, but investigators should make sure that outcome assessment is similar for both groups. Loss to follow-up should be minimized and the losses that do occur should be explained and analysed wherever possible. To keep the original randomisation, the analyses should also be conducted on an 'intention to screen' basis and participants should be kept in their original group even if they failed to comply with screening. Apart from breaking the randomisation, eliminating those who did not comply with the protocol may also bias the result in favour of the intervention.

Table 21 and 22 summarize primary study characteristics and core evidence related to clinical effectiveness of different screening interventions, based on nowadays available publications and considering CRC mortality as hard outcome (Table 21), respectively surrogate endpoints (Table 22) as assessed by the NCI in 2006.

Table 21: Effect of Screening Intervention on Mortality from Colorectal Cancer *(source: National Cancer Institute - PDQ summaries, USA, 2006)

	FOBT	Sigmoidoscopy	Digital rectal exam (DRE)
Study design	RCTs	Case-control studies, RCTs in progress	Case-control studies
Internal Validity	Good	Fair	Fair
Consistency	Good	Fair	Good
Magnitude of Effects	15% - 33%	About 50% for left colon	No effect
External Validity	Fair	Poor	Poor

*There are no data on the effect of other screening interventions (i.e., FOBT/sigmoidoscopy, barium enema, colonoscopy, computed tomographic [CT] colonography, and stool DNA mutation tests) on mortality from colorectal cancer.

Table 22: Effect of Screening Intervention on surrogate endpoints (CRC or adenoma detection) (source: National Cancer Institute - PDQ summaries, USA, 2006)

	FOBT/ FS[343, 210].	FS[344, 284].	Barium Enema[345].	Colonoscopy [346, 283].	CT Colonography[320, 329].	Stool DNA Mutation Tests[248].
Study design	Randomized controlled studies	Case-control studies	Ecologic and descriptive studies	Ecologic and descriptive studies	Ecologic and descriptive studies	Studies in progress
Internal Validity	Fair	Poor	Fair	Fair	Fair	Unknown
Consistency	Poor	Fair	Poor	Poor	Poor	Unknown
Magnitude of Effects on Surrogate Endpoints	No difference in diagnostic yield between sigmoidoscopy + FOBT vs. sigmoidoscopy alone	About 45% decrease in detection rate of cancers compared to colonoscopy	Barium enema detects about 30% - 50% of cancers detected by colonoscopy	About 3% of patients with no distal adenomas have advanced proximal neoplasia. There is a 3-fold increase in this rate in patients with distal adenomas.	CT colonography may have similar sensitivity to colonoscopy in certain centers.	Unknown
External Validity	N/A	Poor	N/A	N/A	Poor	Unknown

5.5.1 Guaiac Fecal Occult Blood Tests (FOBT)

Guaiac FOBT (Hemoccult[b] and Hemoccult II) was tested as a screening tool in a few large trials (Table 23, summarizing main characteristics of those trials[c]). The Nottingham RCT[347, 348] and the Funen RCT[349-352, 208] used FOBT as a biennial screening tool, although the definition of a positive test (number of samples testing positive) differed. The other large long term trial, the Minnesota RCT[353-358] used annual and biennial screening, and most of the FOBTs were rehydrated, thereby increasing sensitivity at the expense of specificity[219]. A fourth large trial is the Göteborg trial[359-362], with over 30.000 participants; hard outcome data

[b] Hemoccult® and Hemoccult II® are similar except for card design; Hemoccult® is now discontinued.

[c] Data were extracted from most recent publications

(CRC mortality), however, are not published yet. Because of this the trial was not included in the review from the NZHTA. It was however included in a Cochrane review were the reviewers retrieved the mortality data directly from the researchers involved[24].

Another study, the Burgundy study, a French controlled study[207, 209] published in June 2004, was excluded for review by the NZHTA team mainly because of the absence of random allocation. Nevertheless, in this very large population-based study, using nonrehydrated Hemoccult without dietary restriction, all residents of several small geographical areas (12 administrative districts in Burgundy for the screening group and 17 other administrative districts corresponding to a population of a similar size for the control group) were allocated either to screening or to no screening. This involved inviting 45.642 subjects between the ages of 50 and 74 years, while a control group of similar size was followed without being informed of the study nor receiving any programmed screening. Uptake in the first round was 52.8% and increased slightly in subsequent rounds since those who clearly refused to participate were not invited again. Overall 69% of the invited population participated at least once. Screen positive proportion was 2,1% in the first round and 1,4% on average thereafter, and the overall colorectal cancer mortality reduction was 16% in an intention to screen analysis and 33% in those who participated (at least once).

We need to be careful, however, when comparing these trials as there were important differences in screening intensity (annual vs. biennial), test usage (non rehydrated vs. rehydrated), the definition of positivity (number of samples out of 6 that need to be positive), and ages (although all ages were between 45 and 80).

In spite of these caveats, the Cochrane review (most recent update 12 August 2005[24]) estimated the colorectal cancer mortality reduction through offering a (annual or biennial) Hemoccult screening program at 16% (95% CI: 7 - 23%) on an 'intention to screen' basis, and at 23% (95% CI: 11 - 43%) adjusting for screening attendance. On a population level they estimated that if 10.000 people were offered a biennial Hemoccult screening program, and when two-thirds actively attend for at least one of the screening test, there would be 8,5 CRC deaths prevented (95% CI: 3,6 - 13,5 CRC deaths) over 10 years.

The NZHTA[219] and the Cochrane systematic review[24] conclude that there is high quality evidence of reduction in CRC mortality, possible reduction in CRC incidence through detection and removal of colorectal adenomas and earlier detection of cancers potentially leading to less invasive surgery. They stress however that very little information is available from those trials, or from other studies about the potentially harmful effects of screening other than the direct complications of follow up colonoscopy in case of positive FOBT finding.

Table 23: Summary of Findings from gFOBT Screening Trials

Study	1. Nottingham[348, 363]	2. Funen[350, 351, 208]	3. Göteborg[359-362]	4. Minnesota[354, 357, 358]	5. Burgundy[364, 207]	Towler B. & Cochrane CDSR[24]
Study type	RCT	RCT	RCT	RCT	Controlled trial	Meta-analysis
Methodologic characteristics	1. Central randomisation of households of subjects identified from GP records; randomisation adequate	1. Random allocation of individuals identified from population register; couples randomised together; adequate	1. Central randomisation of Göteborg inhabitants; adequate	1. Individual random allocation of volunteers; randomisation adequate	1. Non randomly allocated groups from defined areas to screen (12 Burgundy districts) or control groups (17 Burgundy districts) Recruitment by GPs or mailing if failed	Includes listed studies plus results of FOBT arm of the National Polyp Study, New York
	2. Analysis by intention to screen.	2. Analysis by intention to screen	-	2. Analysis by intention to screen.	-	
	3. Blinded, standardised outcome assessment of CRC mortality, including deaths from complications of treatment	3. Blinded standardised assessment of CRC mortality, including deaths from complications of treatment; 5% of deaths reviews were unblinded[a]	3. Outcome assessment by one doctor not involved in the trial; deaths from complications of treatment not reported	3. Blinded, standardised assessment of CRC mortality; deaths from complications of treatment not reported; criteria used not stated or referenced	3. Blinded, standardised assessment of CRC mortality; deaths from complications of treatment included[b]	
	4. Trial group comparability: age, sex & overall mortality balance demonstrated.	4. Trial group comparability: age, sex balance demonstrated	4. Trial group comparability: age, sex balance demonstrated	4. Trial group comparability: age, sex, and residence balance demonstrated	4. Trial group comparability: age & sex balance demonstrated.	
Recruitment, all	152.850	61.933	68.308	46.551	91.199	351.398
Recruitment, screening Group	76.466	30.967	34.144	Annual 15.570 / Biennial 15.587	45.642	185.708
Recruitment, control group	76.384	30.966	34.164	15.394	45.557	165.690
Age range	45 – 74 y	45 – 74 y	60-64 y	50-80 y	45 – 74 y	45-80

Study	1. Nottingham[348, 363]	2. Funen[350, 351, 208]	3. Göteborg[359-362]	4. Minnesota[354, 357, 358]		5. Burgundy[364, 207]	Towler B. & Cochrane CDSR[24]
Screening period	1981 – 1995	1985 – (continuing)	1982 – 1983 1st round 1984 – 1985 2nd round	1976 – 1982 (phase 1) 1986 – 1992 (phase 2)		1988 – 1998	-
Number of screening rounds	3 – 6 rounds	9 rounds (aug. 2002)	2 rounds	11 rounds	6 rounds	6 rounds	-
Frequency	Biennial	Biennial	2nd screening after 16-22 months	Annual	Biennial	Biennial	-
FOBT test	Hemoccult II unrehydrated	Hemoccult II unrehydrated	Hemoccult II 51% rehydrated 1st round 100% rehydrated 2nd round	Hemoccult II 82.5% rehydrated		Hemoccult II unrehydrated	Most Hemoccult II rehydrated
Dietary restrictions	No	Yes	Yes	Yes		No	
Total person-years of observation, screening group	844.419	431.190	-	240.325	240.163	476.911	-
Total person-years of observation, control group	843.463	430.755	-	237.420		477.773	-
Follow-up, median (years)	11,7	17	8,3	13		11	-
Follow-up, range (years)	8,4 – 18,4		-				-
Lost to recruitment (%)	2.599 / 152.850 1,7% of recruitment[24]	< 6 persons[24]	< 100 persons[24]	11,2% screening[357] 11,5% control[357]	10,9% screening[357] 11,5% control[357]	? ("5,6% of population")	
Compliance	60% 1st round	67% 1st round	66% 1st round 58% 2nd round	90% at least 1 round		69,5% at least 1 screening round 38,1% 5 to 6 screening rounds	67%
Reported positivity rate FOBT	2,1%, first round 1,54% all rounds	1,0%	unrehydrated: 1,9% rehydrated: 5,8%	unrehydrated: 2,4% rehydrated: 9,8%		unrehydrated: 2,1% initially 1,4% on average in the 5 successive rounds	

Study	1. Nottingham[348, 363]	2. Funen[350, 351, 208]	3. Göteborg[359-362]	4. Minnesota[354, 357, 358]		5. Burgundy[364, 207]	Towler B. & Cochrane CDSR[24]
Cumulative risk of a positive test among screenees	1.977 / 76.224 2,6%	1.888 / 30.762 6,1%		2,7%	2,8%	4,1%	-
FOBT sensitivity for CRC, reported by authors	64,0%	46,0%	81%	Rehydrated: 92% Unhydrated: 81%		41%	
Cumulative CRC incidence per 1000 person-years, screening group	1,51	2,06	-	1,8	1,9	1,47	-
Cumulative CRC incidence per 1000 person-years, control group	1,53	2,02	-	2,18		1,46	-
% Localised CRC ($T_1N_0M_0$), screened	20%	36%	21%	33%[354]	29%[354]	29%	-
% Localised CRC ($T_1N_0M_0$), control	11%	11%	15%	25%[354]		24%	-
Relative CRC mortality reduction in screening group (95% CI)	13% (3% – 22%)	11% (-1% – 22%)	12% (-0,1% – 31%)	32% (15% – 45%)	17% (-3% – 34%)	17% (2% – 29%)	16% (7% – 23%)
Relative CRC mortality reduction among screenees* (95% CI)	27% (10% – 43%)	34% (19% – 46%)	-	-	-	33% (19% – 44%)	23% (11% – 43%)
Absolute risk reduction for death from CRC	1,2 (0,3 – 2,1)	1,7 (-0,2 – 3,6)	-	3,7 (1,5 – 5,9)	2,0 (-0,2 – 4,2%)	1,1 (0,1 – 2,1)	0,85

Study	1. Nottingham[348, 363]	2. Funen[350, 351, 208]	3. Göteborg[359-362]	4. Minnesota[354, 357, 358]		5. Burgundy[364, 207]	Towler B. & Cochrane CDSR[24]
per 1.000 in screening group[c], (95% CI)							
Number needed to screen in screening group, over follow-up time[c] (95% CI)	834 (473 – 3.484)	595 (280 – ∞)	-	268 (169 – 644)	499 (234 – ∞)	903 (472 – 10.449)	1.173 (741 – 2.807)
Relative risk reduction for overall mortality[c], point estimate (95% CI)	0% (-2% – 1%)	0% (-2% – 2%)	-	0% (-3% – 3%)	1% (-2% – 4%)	-	-
Absolute risk reduction for overall mortality per 1.000[c], point estimate (95% CI)	-0,6 (-5,1 – 3,8)	1,4 (-6,3 – 9,1)	-	0,6 (-9,9 – 11,1)	2,4 (-8,1 – 13,0)	-	-

* At least 1 screening completed

a Case notes revealed that patient had been in the screening group

b CRC was considered as the cause of death when occuring ≤ 30 days post CRC surgery, in case of clinically or histologically demonstrated recurrence, or if patient received palliative treatment without evidence of another underlying cause of death

c Using UBC Clinical Significance Calculator: http://www.healthcare.ubc.ca/calc/clinsig.html

A recently published meta-analysis of controlled trials on colorectal cancer screening by FOBT[209] reviewed in depth the effectiveness of screening for CRC with FOBT and they also included the French study results, not taken up in previous meta-analyses. The aim was to consider the reduction in mortality during or after screening and to try to identify factors associated with a significant mortality reduction. A meta-analysis of four controlled trials, selected for their biennial and population-based design, was conducted. The main outcome measurements were mortality (RR and 95% CI) of biennial FOBT during short (10 years, i.e. five or six rounds) or long-term (six or more rounds) screening periods, as well as after stopping screening and follow-up during 5 - 7 years. The meta-analysis used the Mantel-Haenszel method with fixed effects when the heterogeneity test was not significant, and to additionally test for potential impact of heterogeneity they excluded each of the studies in turn. Analysis was on an 'intention to screen' basis. Although the quality of the four trials was high, only three were randomized (Nottingham, Funnen and Minnesota), and one (Minnesota) used rehydrated biennial FOBT associated with a high colonoscopy rates (28%) due to the higher sensitivity and the lower specificity of the rehydrated test. A meta-analysis of mortality results showed that subjects allocated to screening had a 14% reduction of CRC mortality during a 10-year period (RR 0,86; CI: 0,79 - 0,94), although CRC mortality was not decreased during the 5 to 7 years after the 10-year (six rounds) screening period, nor in the last phase (8 - 16 years after the onset of screening) of a long-term (16 years or nine rounds) biennial screening. Whatever the design or the period of ongoing FOBT, CRC incidence neither decreased nor increased, although it was reduced for 5 - 7 years after the 10-year screening period. Neither the design nor the clinical or demographic parameters of these trials could be shown to be independently associated with CRC mortality reduction. Whatever the endpoint chosen for mortality assessment in the meta-analysis, there was never a significant decrease in overall mortality from all causes. This is, however, not surprising because CRC mortality represents only a small proportion of overall mortality in both the intervention groups and the control groups (range 2,84 to 3,59%). The authors concluded that biennial FOBT screening decreased CRC mortality by 14% when performed over 10 years, without evidence-based benefit on CRC mortality when performed over a longer period.

In conclusion: performing an annual fecal occult blood test (FOBT) is one of several recommended options for colorectal cancer screening in the average risk population beginning at age 50. Annual or biennial screening with gFOBT has been shown in large, randomized trials to have a significant and beneficial effect on colorectal cancer incidence and mortality, but there was never a significant decrease in overall mortality from all causes. Furthermore, while the specificity of these tests is generally high, sensitivity is poor. Complicated dietary restrictions prior to testing and sampling instructions may limit patient compliance.

5.5.2 Immunochemical Fecal Occult Blood Tests

Newer immunochemical FOBTs (iFOBT) are reported to have improved performance characteristics compared to guaiac tests without a need for dietary restrictions. However, no large scale prospective RCTs of iFOBT screening and CRC incidence or mortality outcomes have been reported so far. On the other hand, if iFOBTs perform at least as well as gFOBT, it is likely that iFOBTs used for CRC screening would have at least the same efficacy in decreasing CRC mortality as gFOBTs[270].

The screening guidelines of the American Gastroenterological Association[55] note that (quote) "newer guaiac-based and immunochemical tests are available that have improved sensitivity and appear to maintain acceptable specificity". In April 2002 the American Cancer Society Colorectal Cancer Advisory Group concluded that (quote) "the evidence showing improved specificity with immunochemical tests, and the lack of requirements to adhere to dietary restrictions prior to the test, was sufficiently persuasive to update the guideline (...) to include the following statement: in comparison with guaiac-based tests for the detection of occult blood, immunochemical tests are more patient-friendly, and are likely to be equal or better in sensitivity and specificity"[365]. The USPSTF evidence review for its guidelines refers only to guaiac-based tests used in studies of FOBT screening and mortality outcomes[275]. A joint committee representing the World Health Organization and the World Organization for Digestive Endoscopy published a report on choice of FOBT for colorectal cancer screening[197] quoting: "The Hemoccult Sensa is the recommended gFOBT due to low cost, greater sensitivity than Hemoccult II, but better specificity than rehydrated Hemoccult II. Reliable compliance but poor colonoscopy resources are more compatible with the higher specificity of Hemoccult II. However, if compliance is uncertain or unreliable but colonoscopy resources are sufficient, iFOBT may be considered."

One Chinese controlled study[366], the Jiashan trial, was identified in the New Zealand systematic review as having compared a 'once only' immunochemical FOBT test to no screening. All residents of Jiashan County aged 30 years or older were enrolled in the study, and 21 townships in the county were randomized to either a screening (n = 10 townships) or control (n = 11 townships) group. Participants in the screened group submitted a one-article-per-slide stool sample and completed a structured risk-assessment questionnaire from which their attributive degree value was computed. According to the study protocol, 4.299 participants were defined as high risk and underwent diagnostic evaluation with 60-cm FS and, in some cases, an additional screening with colonoscopy. From 1989 to 1996, cumulative mortality from colon cancer was 90 (95% CI: 83 - 97) per 100.000 in the screened group and 83 (95% CI: 76 - 90) per 100.000 in the control group (p = 0,222). Mortality from rectal cancer during this time was 110 (95% CI: 102 - 118) per 100.000 in the screened group, which differed significantly from the control group mortality rate of 161 (95% CI: 152 - 170) per 100.000 (p = 0.003). The iFOBT was also accompanied with a questionnaire on colorectal cancer risk factors, making it difficult to interpret the results. The population in this trial was also younger (40 - 49) than in the guaiac FOBT trials. The only direct evidence from this trial was that a reduction in rectal cancer may be achievable using this test.

Three case-control studies of iFOBT screening and CRC incidence or CRC death have been published by the same corresponding authors in Japan[367]. They found that cases diagnosed with advanced colorectal cancer were significantly less likely than controls to have been screened within the previous 2 or 3 years. Similarly, Saito et al[368, 369] found that deaths from CRC were significantly less likely in those screened with iFOBT versus those not screened. Across studies, the risk reductions ranged from approximately 40 to 60%. As they did for gFOBTs when compared to subsequent randomized, controlled trials[370], available case-control studies of iFOBT screening likely overestimate the actual benefit.

A recent cluster-randomized trial in Italy aimed at assessing the effect of the type of fecal occult blood, gFOBT or iFOBT on screening compliance[198]

concluded that compliance was more likely with the immunochemical than the guaiac test, independent of the test kit provider. Guaiac tests showed a higher variability of the results among centres. This issue will be discussed in detail further on in present report (section on screening acceptability and compliance).

The Blue Cross and Blue Shield association assessed, in its Assessment Program Volume 19, No. 5 July 2004[270], iFOBTs versus gFOBTs with 2 objectives: (1) to evaluate whether there is sufficient evidence to evaluate the performance of iFOBTs in general, or of specific iFOBTs, and to compare performance to standard gFOBTs and (2) to examine the evidence on patient compliance with various iFOBT formats to determine if compliance is more likely with any or with a specific iFOBT versus gFOBTs. Seven studies met the selection criteria[371-377]. Because none of the studies enrolled an average-risk CRC screening population all studies were assigned a quality rating of "Fair." No major flaws in any of the studies changed that rating; lesser quality items were considered by adding a plus or minus sign to the rating. All studies calculated performance characteristics based on one FOBT screening procedure, with sampling according to the manufacturer's directions. No studies were designed to estimate programmatic screening performance characteristics i.e., annual screening over several years.

Four studies compared iFOBTs to the Hemoccult II gFOBT; 2 studies compared iFOBTs only to Hemoccult Sensa; and 1 study compared 2 different iFOBTs including the only published evaluation of the InSure iFOBT performance characteristics (n = 443). The vast majority of comparative data on iFOBTs are derived from studies of FlexSure OBT (n = 2.946) and HemeSelect (n = 1.853), neither of which are currently available in the U.S. Only 1 included study evaluated MonoHaem (n = 81) and none evaluated Instant-View or immoCARE.

Of interest in a colorectal cancer screening program is the yield of early stage cancer and large adenoma. However, numbers of all cancers were low and in several studies were less than 5; stage information was not available in every study. For best estimates of FOBT performance characteristics, the evidence evaluation in this assessment focussed on significant neoplasia, a combination of cancers and large adenomas (i.e., > 1 cm).

In all but 391 patients[378], the FOBT tests compared in each study were run on each patient and the results were matched by patient. Thus, statistical comparisons of proportions from independent samples are inappropriate for determining significant differences between performance characteristics such as sensitivity and specificity. Rather, McNemar's test, which takes paired data into account, is most often used in this situation. However, none of the included studies presented raw data in a format that allowed McNemar's test to be conducted. Two studies compared sensitivities and specificities by McNemar's testing and reported the results. Young et al.[377] found no significant difference in any parameter between InSure and FlexSure OBT tests. Greenberg et al.[374] reported that sensitivity results for neoplasia by Hemoccult Sensa, FlexSure, and HemeSelect were not significantly different from each other, but all were significantly greater than Hemoccult II; for specificity, FlexSure OBT was significantly lower than Hemoccult II.

These publications suggest the following conclusions regarding the comparative performance of gFOBTs and iFOBTs:

- iFOBTs have better (clinical) sensitivity than Hemoccult II but not necessarily better sensitivity than Hemoccult SENSA,
- iFOBTs have better (clinical) specificity than Hemoccult SENSA, but specificity is not clearly as good as or better than Hemoccult II.

However, this overall comparison assumes that iFOBTs as an assay class perform similarly. As shown in Table 12, this may not be the case, and iFOBTs vary in their detection limit, determined by adding known quantities of fresh, human blood. For example, MonoHaem has the highest detection limit for hemoglobin and, judging from 1 small study[371], poor clinical sensitivity compared to Hemoccult II. However, the InSure assay reportedly has a detection limit that is 6 times lower than that of FlexSure but in 1 study[377]. InSure and FlexSure performed equally. Thus, artificially determined detection limits may not predict comparative clinical performance.

Nevertheless, evidence in favor of the substitution of gFOBT by iFOBT is increasing, the gain being more important for high-risk adenomas than for cancers. Automated reading technology allows the choice of the positivity rate associated with an ideal balance between sensitivity and specificity. In a very recently published article Guittet et al.[379] compared the performances of a non-rehydrated gFOBT test (Hemoccult II) and an iFOBT test with automated reading process (Magstream 1000), enabling the comparison between different positivity cut-off points, in an average-risk population sample of the 10.673 individuals aged 50-74 years in the geographic area of Calvados (Normandy, France), who completed the two tests. Patients with at least one test positive were asked to undergo a colonoscopy. Accuracy of both tests was compared by calculating the ratio of sensitivities (RSN) and the ratio of false positive rates (RFP). Using the usual cut-off point of 20ng/ml hemoglobin, the gain in sensitivity associated with the use of iFOBT (50% increase for cancer and 256% increase for high-risk adenoma) was balanced by a drop in specificity. The number of extra false positives associated with the detection of one extra advanced neoplasia (cancer or high-risk adenoma) was 2,17 (95% CI: 1,65 - 2,85). With a threshold of 50ng/ml, iFOBT detected more than twice as many advanced neoplasias as the gFOBT (RSN = 2,33), without any loss in specificity (RFP = 0,99). With a threshold of 75ng/ml associated with a similar positivity rate to gFOBT (2.4%), the use of iFOBT allowed a gain in sensitivity of 90% and a decrease in false positive rate of 33% for advanced neoplasia.

5.5.3 Flexible Sigmoidoscopy (FS)

5.5.3.1 Telemark Polyp Study 1 - NORCCAP

No large-scale RCT has been completed. Only the Telemark Polyp Study in Norway (the Telemark Polyp Study 1 - NORCCAP)[380, 381], which was in fact a small feasibility study, compared a 'once-only FS' screening to no-screening in a control group of individuals. 400 men and women aged 50 - 59 years were randomly drawn from the population registry of Telemark, Norway (in 1983). They were offered a FS and, if polyps were found, a full colonoscopy with polypectomy and follow-up colonoscopies in 1985 and 1989. A control group of 399 individuals, who were unaware of their enrolment, was drawn from the same registry. In 1996 both groups (aged 63 to 72 years) were invited to have a

colonoscopic examination. Hospital files and the files of The Norwegian Cancer Registry were searched to register any cases of CRC in the period 1983 - 1996. In the first round (1983), 324 (81% of intervention group) individuals attended endoscopic screening and 451 (71% of total group) in 1996. From 1983 to 1996, altogether 10 individuals in the control group and 2 in the screening group were registered to have developed CRC (RR 0,2 - 95% CI: 0,03 - 0,95; P = 0,02). Strikingly, a higher overall mortality was observed in the screening group, with 55 (14%) deaths, compared with 35 (9%) in the control group (RR 1,57 - 95% CI: 1,03 - 2,4; P = 0,03). However, before drawing possible conclusions on this, the possible effect of screening on overall mortality should be addressed in larger studies. Currently, a few larger trials are underway, but those are not expected to report mortality results in the near future.

5.5.3.2 UK FS Screening Trial

In the UK FS Screening Trial[279] 170.432 men and women aged 60 to 64 in fourteen centers were sent a questionnaire by mail to ask if they would attend for FS screening if invited. Of 354.262 people to whom this questionnaire was sent, 194.726 (55%) agreed to participate. Interested respondents were excluded if they informed the local trial unit of exclusion criteria missed by their general practitioner, or if they had a strong family history of colorectal cancer (at least two affected close relatives), a temporary health problem that would prevent them from having the screening test, or a worrying bowel symptom that required investigation. Individuals with a strong family history of bowel cancer or suspicious symptoms were managed outside of the trial, because randomisation would not have been in their interest. Finally, 170.432 eligible subjects were randomized using a 2:1 ratio of controls (N = 113.178) to those invited for screening (N= 57.254). The screening protocol involved a FS with removal of all small polyps seen at the time of sigmoidoscopy with colonoscopy reserved for those with high-risk polyps (three or more adenomas, an adenoma greater than 1 cm in diameter, a villous or severely dysplastic adenoma) or invasive cancers. Of the 57.254 individuals invited for screening 40.674 (71%) attended. The attendance rate was higher in men than in women (20.519 of 28.097 (73%) vs. 20.155 of 29.157 (69%, p< 0·001). However, the men and women who attended for screening showed similar age distributions: proportions aged over 60 years: men 8.976 of 20.519 (44%), women 8.839 of 20.155 (44%). Of the 16.580 who did not attend, 7.541 (46%) provided a reason to the unit: 3.324 no longer wanted the test, 547 said they had had a similar test already, 794 were undergoing hospital treatment or awaiting an appointment, 265 had moved away, 97 had died, and 2.514 provided various other reasons.

It should be recognised that this study is essentially a volunteer study. The trial used a two-stage recruitment procedure whereby eligible participants were enrolled only if they responded positively to a questionnaire asking whether they would be likely to accept the offer of screening. 55% of questioned people responded positively, and 71% of those invited for screening (all of whom had replied positively) actually attended. Therefore, as the researchers state, the population coverage achieved was equivalent to 39%.

In the screening group, 2.131 (5,2%) were classified as high-risk and referred straight to colonoscopy; of these 165 for reasons other than high-risk polyps (safety of polypectomy: 31; family history of cancer: 20; suspicious symptoms: 16). 38.525 with no polyps or only low-risk polyps detected were discharged after screening FS. Distal adenomas were detected in 4.931 (12%) and distal cancer in 131 (0,3%). Proximal adenomas were detected in 386 (18%) of those undergoing colonoscopy and proximal cancer in nine cases (0,4%). Of particular

importance was the stage of diagnosis, and it was found that 62% of the cancers were Dukes stage A (TNM stage I). For reference: the Flemish population data 1997 - 2001 showed that only around 15% were stage I.

5.5.3.3 SCORE trial, Italy

In the SCORE trial (the Italian arm of a multicenter randomized controlled trial of "once-only sigmoidoscopy"[382]), similar results were found. In this trial a questionnaire was mailed to a random sample of 236.568 people aged 55-64 years to assess their eligibility for and interest in screening. Those reporting a history of colorectal cancer, adenomas, inflammatory bowel disease, recent colorectal endoscopy, or two first-degree relatives with colorectal cancer were excluded. Eligible, interested respondents were assigned randomly to the control group (no further contact) or the intervention group (invitation to undergo sigmoidoscopy). Screenees with colorectal cancer, polyps larger than 5 mm, three or more adenomas, adenomas 5 mm or smaller with a villous component of more than 20%, or severe dysplasia were referred for colonoscopy. Of the 56.532 respondents (24% of those invited), 34.292 were enrolled and 17.148 were assigned to the screening group. Of those, 9.999 (58%, i.e. 14% of those invited) attended and 9.911 were actually examined by sigmoidoscopy; 88 did not have a FS for various reasons. Distal adenomas were detected in 1.070 subjects (11% [-5.9% - 14.7%] across the trial centers). Proximal adenomas were detected in 116 of 747 (15.5%) subjects without cancer at sigmoidoscopy who then underwent colonoscopy (high risk distal lesions, incomplete sigmoidoscopy, or clinical indication). A total of 54 subjects was found to have colorectal cancer, a rate of 5,4 per 1000 and 54% of these were Dukes' A (TNM stage I). The procedures were relatively safe, with two perforations (one in 9.911 sigmoidoscopy exams and one in 775 colonoscopies) and one hemorrhage requiring hospitalization after polypectomy during colonoscopy. The pain associated with sigmoidoscopy was described as mild or less than expected by 83.3% of the screenees. The authors concluded that sigmoidoscopy screening is generally acceptable to recipients and safe. The high yield of advanced adenomas is consistent with the projected impact of sigmoidoscopy screening on colorectal cancer incidence.

Present evidence related to FS screening indicates that, although it is an effective means of detecting early disease and adenomas, it does tend to miss proximal disease and currently compliance rates are modest. This calls into question the use of FS as a population screening tool, and although the randomized trials are likely to indicate mortality reductions, further work requires to be done to estimate true population compliance. Therefore, larger and properly randomised trials are necessary to assess the impact of FS screening on colorectal cancer incidence and mortality. Three RCTs are currently underway but data will not become available before 2008 for two of them (UK FS Screening Trial and Italian SCORE trial), and only in 2010 for the PLCO (US Prostate, Lung, Colorectal and Ovarian Cancer Screen Trial). Baseline data from those trials, however, indicate that screening using FS is likely to be feasible and acceptable.

5.5.4 FOBT and FS combined

There are very few studies that directly compare different screening methods and of those that exist all address the relative merits of FOBT and FS. No RCTs compared FOBT and FS to no screening.

The Nottingham group carried out a randomized study comparing FOBT with a combination of FOBT and FS[383]. This prospective, randomized study aimed to assess the compliance and neoplasia yield of FOBT and FS compared with that of FOBT alone. From general practitioner registers, 6.371 asymptomatic patients (3.124 men, 3.247 women; age range 50 - 74 years) were invited for screening by means of FOBT testing (3.128 patients) performed at home, or a combination of FOBT and FS (3.243 patients). Compliance with FOBT alone was 50%. In the FOBT+FS, 48% returned the FOBT test but only 20% went on to FS. Despite the poor compliance, the neoplasia yield was four times greater in the FOBT + FS group. Of those who attended for FOBT screening 4% had a positive test and 13% had a neoplastic lesion greater than 1 cm in the rectum or sigmoid colon; the corresponding rate in the FS group was 23%. Overall, 10 individuals were diagnosed with a neoplastic lesion in the FOBT group compared with 31 in the FS group. The conclusion was that FS increases the neoplasia yield but strategies to improve compliance must be identified for this to become a population screening test.

In Sweden a group of 6.367 individuals aged between 55 and 56 were randomized to be offered screening with Hemoccult II or FS[384]. Compliance with the FOBT screening was 59% and with FS 49%. Of those who attended for FOBT screening 4% had a positive test and 13% had a neoplastic lesion ≥ 10 mm in the rectum or sigmoid colon; the corresponding rate in the FS group was 2,3%. Overall, 10 individuals were diagnosed with a neoplastic lesion in the FOBT group compared with 31 in the FS group.

In the Norwegian Colorectal Cancer Prevention (NORCCAP) Screening Study[343] 20.780 individuals aged between 50 and 64 were randomized to be invited for FS only or a combination of FS and FOBT. Compliance was 65% and overall 41 (0,3%) cases of colorectal cancer and 2.208 (17%) adenomas were found. The diagnostic yields in the two groups were identical in terms of CRC or high-risk adenomas indicating that there was very little benefit in adding a FOBT to a screening FS.

Although all three trials did not evaluate morbidity or mortality outcomes, these studies indicate that while compliance with FS tends to be less than for FOBT, the sensitivity of FS is much higher. On the other hand it has to be remembered that all the randomized studies of FOBT screening were based on repeated testing, and a nonrandomized study from Denmark comparing 'once only' FS plus FOBT, with FOBT alone over 16 years, found that the FOBT screening program had a diagnostic yield at least as high as a single FS[352].

To date, the evidence relating to the relative merits of a FOBT program and 'once only' FS is not of particularly high quality, and this question can only be fully resolved by a randomized trial directly comparing these two modalities. Combined testing provided significantly higher detection rates of neoplasms compared to FOBT alone, but there was no additional diagnostic benefit from adding FOBT to FS alone. FS compliance in combination testing with FOBT was low compared to FOBT alone or to FS alone, probably due to acceptability issues and participants knowing their FOBT result prior to being invited for FS. The evidence, therefore, does not support a combined screening strategy in the target population compared to using either FOBT or FS alone. The results of the ongoing trial (NORCCAP) could change this conclusion but results are only expected late 2007.

5.5.5 Colonoscopy

In some countries there is considerable interest in using colonoscopy as a screening tool. Potential advantages are clear. It is highly accurate for the detection of CRC with a sensitivity reported to be as high as 99,0% (95% CI: 97,1% to 99,9%) and a specificity of virtually 100%[329]. It has to be appreciated that sensitivity is not 100% as has been demonstrated by back-to-back colonoscopy studies, which show that adenomas and occasionally carcinomas can be overlooked by even experienced colonoscopists[290]. In addition, a study comparing state-of-the art CT-colography with colonoscopy suggests that the sensitivity of colonoscopy for adenomatous polyps may be as low as 87,5%[320].

There have been no published RCTs on the efficacy of colonoscopy as a screening strategy for colorectal cancer[181, 219]. All data regarding efficacy and risk came from studies of its use as a diagnostic or therapeutic tool limiting the direct relevance of the evidence to the screening context[275, 194]. Conclusions must therefore necessarily be limited. It is clear, however, that colonoscopy has high sensitivity and specificity but also that the risks of physical harm from colonoscopy are higher than from either FOBT or FS. Those are also dependent upon the operators' experience, as discussed before.

The most important study in the literature in terms of estimating the efficacy of screening colonoscopy is a case-control study conducted among U.S. military veterans[385]. The study group consisted of 4.411 veterans deceased of colorectal cancer between 1989 and 1992. The control group was derived from living control patients and dead control patients without colorectal cancer matched by age, sex, and race to each case. Using this study design it was found that colonoscopy reduced death rates from colorectal cancer with an odds ratio of 0,41 (range 0,33 - 0,50) In addition, comparison with the living control group revealed that the protective effects lasted for five years and that polypectomy was particularly protective. Similar results were found when the dead control group was studied. Again it should be emphasized that this study was observational and its design far from perfect, particularly as the indications for colonoscopy in the study group were varied and included investigation of symptomatic patients.

There are, of course, abundant uncontrolled data on screening colonoscopy and perhaps the most useful study was carried out in 13 Veterans Affairs (VA) medical centers to determine the utility of colonoscopy in detecting colorectal neoplasia in asymptomatic individuals aged 50 to 75[283]. Of 17,732 patients screened for participation, 3.196 were enrolled; 3.121 of the enrolled patients (97,7%) underwent complete examination of the colon. The mean age was 62,9 years and 97% were males. An adenoma of at least 10 mm diameter was detected in 7,9% and invasive cancer in 1%. Of 1.765 subjects with no adenomas distal to the splenic flexure 48% had proximal adenomas or cancers. It can be concluded from this study that if colonoscopy were used as a screening tool in men aged between 50 and 75 the participation rate would only be 20% and only 1% of colonoscopies would detect colorectal cancer. Thus, although colonoscopy is widely used to screen asymptomatic individuals on demand (targeted screening), it seems very unlikely that it could ever be used as an effective population screening modality.

5.5.6 Double contrast barium enema (DCBE)

There have been no published RCTs on the efficacy of DCBE as a screening strategy for colorectal cancer[275, 181, 219]. In the National Polyp Study the performance characteristics of DCBE were compared to those of colonoscopy

by examining those who had undergone a prior colonoscopic polypectomy[345]. In this study the DCBE was less sensitive in detecting adenomas than colonoscopy and the sensitivity was associated with the size of the adenomas. This finding was confirmed by other studies[194, 386].

Johnson et al.[386] compared relative sensitivity and specificity of CT colonography with DCBE for the detection of colorectal polyps in a population reflective of a screening setting. In addition the potentially added value of double reading at CT colonography was assessed, using endoscopy as the 'gold standard'. This prospective, blinded study comprised 837 asymptomatic persons at higher than average risk for colorectal cancer who underwent CT colonography followed by same-day DCBE. Examinations with polyps ≥ 5 mm in diameter were referred to colonoscopy. CT colonography readers detected 56% - 79% of polyps ≥ 10 mm in diameter. In comparison, the sensitivity with DCBE varied between 39% and 56% for the 31 polyps ≥ 10 mm. All of the readers detected more polyps at CT colonography than DCBE, but the difference was statistically significant for only a single reader (p = 0,02). Relative specificity for polyps ≥ 10 mm on a per-patient basis ranged from 96% to 99% at CT colonography, and 99%-100% at DCBE. Double-read CT colonography detected significantly more polyps than DCBE (81% vs. 45% for polyps ≥ 1 cm (p ≤0,01), and 72% vs. 44% for polyps 5 - 9 mm (p ≤ 0,01)). The authors concluded that double-read CT colonography is significantly more sensitive in detecting polyps than single-read DCBE.

5.5.7 Virtual colonoscopy

Virtual colonoscopy is a rapidly evolving technology under evaluation as a new method of screening for colorectal cancer. However, up to today there have been no published RCTs on the efficacy of virtual colonoscopy as a screening strategy for CRC and its performance in this field has not yet been studied in typical screening populations[387, 328, 219].

The Blue Cross and Blue Shield Technology Evaluation Center report, Volume 10, nr. 6[387] rightfully underlines that there are many possible methods used in the literature to analyze the diagnostic performance of CT colonography. The 2 most common methods are referred to as a per-polyp analysis and a per-patient analysis. In the per-polyp analysis, the capability of CT to detect all polyps is calculated in terms of sensitivity relative to a reference standard. Specificity cannot be calculated because there is no real denominator for the absence of a polyp. Although a per-polyp analysis gives some insight regarding the technical capability of CT, it is not as relevant as a per-patient analysis in determining its clinical utility. Furthermore, in most studies, the per-polyp analysis gives a misleading estimate of sensitivity as it would be used clinically. The studies usually consider CT colonography to have "matched" a polyp seen on colonoscopy if the size of the polyp seen on CT is within 50% of the size determined on colonoscopy. For example, a polyp measured as 5 mm on CT is considered a positive finding for a polyp measured as 10 mm on colonoscopy. However, this should not be considered as a positive finding in a per-patient analysis, because to allow a 5 mm size threshold to be a "positive" test for detecting 10 mm polyps would require such a threshold to be also applied to the assessment of specificity. Thus, all patients who are accurately identified as having only 5 mm polyps with CT colonography should be counted as "false positive" if one requires a 5 mm threshold to identify a 10 mm polyp. Although CT colonography is considered to be more sensitive for large polyps, clinically this greater sensitivity may not bear out because the interpretation must not only identify a large polyp, but also correctly classify it as a "large" polyp. Thus,

the most relevant analysis for the purpose of assessing screening performance of CT with referral to optical colonoscopy is a per-patient analysis. A per-patient analysis uses the patient as the unit of analysis, and assesses the capability of CT colonography to detect or rule out a patient with at least 1 lesion of a particular minimum size. The per-patient analysis must specify the size threshold for referral, because the rational case for CT colonography relies on only referring patients with a specific threshold size for colonoscopy.

Many studies only calculated per-patient sensitivity and specificity for detection of any polyp regardless of size, a strategy which refers a very high proportion of patients to colonoscopy. A few studies used clearly flawed methods in that different size thresholds were apparently used in the calculations of sensitivity and specificity. For example, in a study by Rex et al.[388], a threshold of any polyp seen on CT, regardless of size, was used to calculate sensitivity to detect a patient with a polyp of 10 mm or larger. However, specificity was calculated based on whether CT showed a false-positive polyp of greater than 10 mm. Other studies were excluded because it was unclear whether they used similar diagnostic thresholds for polyp size in the calculations of sensitivity and specificity.

It is also important to consider the reference standard in assessing the performance of CT colonography. Most studies use colonoscopy as the reference standard; although colonoscopy is imperfectly sensitive, it is highly likely to be close to 100% specific. To the extent that CT colonography detects some polyps that are missed by colonoscopy, these potentially true positives are instead classified as false positives. Thus, both the sensitivity and specificity of CT are downwardly biased from their "true" values when colonoscopy alone is used as a reference standard.

A few studies used unblinded colonoscopy as the reference standard, where the CT colonography findings are sequentially revealed to the colonoscopist, who can then investigate all polyps thought to be seen with CT[320, 389, 329]. By rechecking areas of the colon that CT identified as having polyps, lesions that might be classified as false positive on CT can be correctly reclassified as true positive if a polyp is seen on reexamination with colonoscopy. Although polyps that miss detection by either method are still uncounted, this provides a less-biased estimate of diagnostic performance, and it also allows measurement of the performance of colonoscopy (where colonoscopy performance is based on blinded colonoscopy findings, using unblinded colonoscopy as the reference standard).

Overall, sensitivities are quite variable between studies, from as low as 35% to as high as 100% for detecting patients with 10 mm or larger lesions. The larger studies with more stable estimates of sensitivity ranged from 55% to 94%. Specificities were less variable, and most studies reported specificities greater than 90%. At a smaller size threshold of detection CT colonography was both less sensitive and less specific. Variable performance of CT colonography may be associated with interpreter experience or other technical factors.

Such evidence, however, does not allow conclusions on the effect of CT colonography in improving health outcomes. Positive findings on CT colonography require referral for colonoscopy to confirm findings and remove polyps. The appropriate minimum size of polyp that should be referred and the appropriate screening interval are unknown. It would defeat the purpose of initial noninvasive screening to refer patients with any polyp for colonoscopy, because the prevalence of polyps is so high that a large proportion of patients would need to undergo both procedures. Because known polyps are left

behind, and sensitivity for small polyps is known to be less than colonoscopy, CT colonography is meant to be used more frequently than colonoscopy in a screening program.

The performance of CT colonography as a (diagnostic) test has varied widely across studies[194, 246, 270, 219] and the reasons for these discrepancies are poorly defined. In order to clarify this Mulhall et al.[222] conducted a systematic review on the test performance of CT colonography compared to colonoscopy or surgery with assessment of variables that may affect its performance. The PubMed, Medline, and Embase databases and the Cochrane Controlled Trials Register were searched for English-language articles published between January 1975 and February 2005. Prospective studies of adults undergoing CT colonography after full bowel preparation, with colonoscopy or surgery as the gold standard, were selected. To be included, studies needed to use state-of-the-art technology[d]. The evaluators of the colonographies had to be unaware of the results of the gold standard test. Data on sensitivity and specificity overall and for the detection of polyps less than 6 mm, 6 to 9 mm, and greater than 9 mm in size were abstracted. Sensitivities and specificities weighted by sample size were calculated, and heterogeneity was explored by using stratified analyses and meta-regression. Thirty-three studies provided summary statistics on 6.393 patients. The sensitivity of CT colonography was heterogeneous but improved as polyp size increased. Characteristics of the CT colonography scanner, including width of collimation, type of detector, and mode of imaging, explained some of this heterogeneity. In contrast, specificity was homogenous (Table 24). The studies differed widely, and the extractable variables explained only a small amount of the heterogeneity. Obviously, only a few studies examined the newest CT colonographic technology.

Table 24: Meta-analysis of per patient sensitivity and specificity of virtual colonoscopy[222]

	Sensitivity		Specificity	
Polyp size	**Estimate**	**95% CI**	**Estimate**	**95% CI**
polyps < 6 mm	48%	25% - 70%	92%	89% - 96%
polyps 6 to 9 mm	70%	55% - 84%	93%	91% - 95%
polyps > 9 mm	85%	79% - 91%	97%	96% - 97%

The heterogeneity of virtual colonoscopy raises concerns about consistency of performance and about technical variability in daily imaging practice. These issues must be resolved before CT colonography can be advocated for generalized application for diagnostic, let alone screening purposes.

[d] including at least a single - detector CT scanner with supine and prone positioning, insufflation of the colon with air or carbon dioxide, collimation smaller than 5 mm, and both 2 - dimensional and 3 - dimensional views during scan interpretation

With regard to CT Colonography (CTC) for the detection of colorectal polyps and neoplasms, the ICSI Technology Assessment Committee[328] concluded in its active HTA report, approved in 2004 and reviewed bi-annually[e]:

1. CTC is a safe procedure with minor side effects reported. There is however radiation exposure[f]. The optional use of an intravenous and/or intraluminal contrast agent would potentially increase the morbidity and mortality risk.
2. A single study with a screening population found good sensitivity and specificity for CTC compared with conventional colonoscopy when images were interpreted by trained radiologists who had read a minimum of 25 CTC studies. There were no significant differences between the sensitivities of CTC and conventional colonoscopy for the detection of adenomas > 5 mm or ≥ 10 mm (all sensitivities approximately 90%). The specificity of CTC 79,6% for adenomas > 5 mm and 79,6% for adenomas ≥ 10 mm. The CTC procedure in this study included technical variations (i.e., use of 2 oral contrast agents, a multi-detector CT scanner, thin collimation, and a 3-dimensional "fly-through" analysis for primary review). It is unclear which, if any, of these variables contributed to the improved sensitivity of neoplasm detection. At present, this protocol is not uniformly used as many centers performing CTC do not have the required hardware or software.
3. In a screening population, with the present data acquisition and interpretation protocols, it is unclear how CTC compares with conventional colonoscopy in terms of sensitivity and specificity due to limited available data. CTC is potentially useful for patients unwilling to undergo conventional colonoscopy or other procedures, who have failed conventional colonoscopy (incomplete examination of the colon), or who cannot be sedated. However, patients with positive findings on CTC (approximately 15% of the population) will require conventional colonoscopy to obtain biopsy specimens.
4. CTC appears to be superior, in terms of detection of colorectal polyps and neoplasms, to no examination, fecal occult blood test, double-contrast barium enema, and FS. CTC has not been proven to be superior to conventional colonoscopy.
5. Patient acceptance of CTC appears to be at least as good as acceptance of conventional colonoscopy. Due to variations in study protocols, it is unclear how sedation at conventional colonoscopy and bowel relaxants at CTC may affect patient ratings.

5.5.8 Other techniques

There have been no published RCTs on digital rectal examination as a screening strategy for colorectal cancer. A case-control study showed no effect on colorectal cancer mortality[390].

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[e] and revised, if warranted.
[f] approximately 20 mSv.

There were also no published RCTs of the use of stool DNA mutation tests as a screening strategy for colorectal cancer. Those DNA mutation tests were recently assessed in a prospective study of 4.404 asymptomatic persons who all received colonoscopy[339, 246]. Hemoccult II was compared to a stool DNA testing based on a panel of markers assessing 21 mutations. Conducted in a blinded way among a subgroup of 2.507 participants the DNA panel had a much better sensitivity than Hemoccult II for all stages of colorectal cancers with a similar specificity.

A cost-effectiveness analysis of colorectal cancer screening with stool DNA testing in the general population 50 to 75 years of age in Taiwan[342], compared with annual FOBT, FS every 5 years, and colonoscopy every 10 years or not screening at all, concluded that, in countries with a low or intermediate incidence of colorectal cancer, stool DNA testing is less cost-effective than the other currently recommended strategies for population-based screening, particularly targeting at asymptomatic subjects.

Fecal DNA testing may provide enhanced sensitivity for detection of CRC in comparison with FOBT, but its high cost limits its use for generalized screening. Rectal mucin testing requires additional evaluation to determine its sensitivity and specificity in comparison with guaiac-based FOBT. Serum tests, such as proteomics, nuclear matrix proteins, and serum DNA, are still in their infancy, but remain a hope for the future[264].

5.6 POTENTIAL HARMS OF CRC SCREENING

5.6.1 False positive results, overinvestigation and complications of colonoscopy

Screening comes at a cost, and the cost is not only financial but can also be measured in terms of morbidity and mortality. The question of financial cost is dealt with in the section on economic evaluation, but the issues on morbidity and mortality are as important. While performing a FOBT is unlikely to cause physical morbidity and FS is very safe, the possibility of complications of the subsequent colonoscopy for those with a positive test and of surgery for those who are diagnosed with cancer should not be overlooked. Estimates of post-screening colonoscopy harms depend on the trial: for the Minnesota trial there would be 28 percent of the participants having at least one colonoscopy (the Minnesota trial used rehydrated Hemoccult increasing sensitivity at the expense of specificity and had therefore higher colonoscopy rates) and there would be 0,34 pro mille colonoscopy complications (perforations or hemorrhage). Considering screening harms from the Göteborg RCT (non rehydrated FOBT) there would be only 6 percent participants needing a colonoscopy, resulting in 0,18 pro mille complications.

Small adenomas (i.e., < 1 cm in diameter) are unlikely to bleed and are unlikely to harbor malignancy[391-393]. Positive screening tests for fecal blood that are followed by colonoscopy and the discovery of small adenomas are likely to reflect false-positive test results due to diet or non-neoplastic gastrointestinal bleeding and the coincidental discovery of adenomas. As a result, Ransohoff and Lang (1990)[394] suggest that, (quote) "The identification of persons with small adenomas should not be assumed to be an important beneficial outcome of FOBT screening, because the clinical significance of small adenomas is not clear, the mechanism of detection is serendipity, and only a minority of persons with small adenomas are identified." The authors further suggest that more intensive surveillance beyond average risk guidelines following removal of small adenomas is unnecessary in such patients.

On the other hand, there is the issue of overinvestigation in the group with false-positive tests. Despite the fact that the guaiac tests are very insensitive for upper gastrointestinal bleeding, there remains some concern.

5.6.2 False-negative results

In addition, false-negative results caused by the low sensitivity of the FOBT and the propensity of sigmoidoscopy to miss proximal cancers might falsely reassure individuals (i.e. the "certificate of health effect") and lead to delayed cancer diagnosis and poorer outcome.

Some patients present with fully developed cancers within 1 - 4 yr of a colonoscopy that apparently cleared the colon of neoplasia. These events may result in medical-legal action against gastroenterologists, generally based on an assumption of negligent technical performance of the procedure. Alternative explanations for the development of interval cancers include variable growth rates of colorectal cancers, the inherent miss rate of the procedure, even when optimal examination techniques are used, and the possibility of flat lesions that are not readily detected by standard colonoscopic techniques. Issues relevant to reduction of medical-legal risks associated with interval cancers after clearing colonoscopy include informed consent, documentation of cecal intubation, appropriate description of preparation, documentation of examination time and technique, and attention to potential atypical neoplasms[292].

5.6.3 Studies on CRC screening harms

The Nottingham group has addressed these forgoing issues by examining the investigation and treatment-related mortality and the stage at presentation of the interval cancers[296]. There were no colonoscopy-related deaths and five deaths after surgery for screen-detected cancers; this represents a 2% operative mortality at a time when mortality after elective colorectal cancer surgery in the United Kingdom was estimated to be around 5% by a large national audit[395]. Furthermore, the stage distribution of the interval cancers (cancers that were diagnosed after a negative FOBT or colonoscopy) was similar to that of the cancers in the control group, but the survival was significantly better than that for the control cancers. Nevertheless, these concerns have been highlighted by the finding that all-cause mortality is not affected by colorectal cancer screening and indeed, in the Nottingham study it was found to be even increased in the group offered screening[15]. However, colorectal cancer only accounts for around 2% of all deaths, and a 15% reduction in disease-specific death rate could only be expected to reduce all-cause mortality by 0,3%. To demonstrate a difference of this size with statistical power would require a trial too big to be feasible. Furthermore, unlike the difference in disease-specific mortality, the excess of all-cause deaths observed in the group offered screening was not statistically significant and therefore likely to represent a chance finding.

To try to rationalize the fear that ignoring a positive FOBT in the face of “a normal colonoscopy” might be seen as negligent, if significant upper gastrointestinal pathology is missed, the Nottingham group looked at a cohort of 283 FOBT positive cases without neoplastic disease diagnosed at colonoscopy[396]. Fourteen (5%) of these underwent upper gastrointestinal endoscopy because of symptoms, and one was found to have gastric carcinoma. The rest, who were asymptomatic, were followed up for a median period of five years and only one, who had persistent symptoms after a previous partial gastrectomy, was subsequently diagnosed as having gastric cancer. Thus, the evidence supports a strategy of reassuring the majority of those who have a

negative colonoscopy and reserving upper gastrointestinal endoscopy only for those with relevant symptoms.

5.6.4 Psychological morbidity

Another important adverse effect of screening relates to psychological morbidity. In colorectal cancer screening there has been relatively little work done in this field, but there are two studies of certain importance. In the Swedish randomized study of FOBT screening a questionnaire was administered to 2.932 participants and it was found that 4,7% experienced '*worry*' from the invitation letter sufficient to influence daily life, and that this increased to 15% after a positive test[397]. However, worry decreased rapidly after the screening process was over and at one year 96% declared that they had appreciated the opportunity to be screened. As part of the Nottingham trial a similar study was carried out using validated measures of psychiatric morbidity, and this was found to be highest in those with a positive test result. But, in those with false-positive tests the psychiatric morbidity measure declined the day after colonoscopy and remained low one month later[21]. Thus it appears that the screening process does cause anxiety, but that is short lived in case of negative follow up examinations.

5.6.5 Inappropriate use of screening tests

Finally, there is the question of appropriateness of screening. Evaluating the effect of FOBT screening in the U.S. may be complicated by the generally inappropriate use of these tests by a significant proportion of physicians. In one study[398, 399] a questionnaire was mailed to U.S. gastroenterologists chosen at random from a national database; responses were obtained from 1,828 (24%). The FOBT tests of choice were Hemoccult II (72%) or Hemoccult Sensa (22%) and 78% of respondents reported providing patients with advice about dietary restrictions before either performing or ordering a FOBT. However, 86% reported performing FOBTs on a single stool specimen obtained from digital rectal exam. Similarly, results of the National Health Interview Survey reported that approximately half of FOBT testing is performed with single samples taken during a physical examination rather than with the home kit[400].

A single in-office FOBT is likely to be less sensitive than the FDA-approved 3-card home-performed FOBT because only one sample is taken[275] and evidence substantiating its use is lacking. Based on these results, it seems possible that physicians may not rigidly adhere to guidelines regarding the patients' performance of FOBTs. Moreover, physicians frequently use the FOBT for reasons other than colorectal cancer screening, such as for hematemesis, melena, heartburn, or dyspepsia (Sharma et al. 2000), for which the test has not been validated. Despite the apparent lack of consistent use in practice, the use of FOBT can be accurately evaluated only when it is used for validated indications (CRC screening) and with the manufacturer's approved performance instructions.

A recent study in the Veterans Health Administration (VHA) health system[191] aimed to ascertain whether FOBT testing was being ordered appropriately. The records of 500 consecutive primary care patients at a single VHA facility, for whom FOBT had been ordered, were reviewed to determine whether the FOBT was appropriate and, if not, the reason why. It appeared that 18% of the sample had severe comorbid illness, 13% had signs or symptoms of gastrointestinal blood loss, 7% had a history of colorectal neoplasia or inflammatory bowel disease (high risk), 5% had undergone colonoscopy within

prior 5 yr, and 3% were younger than 50 yr of age. Overall, 35% of the patients had at least one reason that the FOBT was inappropriate and at least 19% of the patients should not have undergone any colorectal cancer test for screening or diagnosis. In addition, data suggested that FOBT was actually being used for diagnosis instead of screening. Screening patients unlikely to live long enough to develop and die from colorectal cancer provides no benefit and places these individuals at unjustifiable risk. Additionally, inappropriate screening utilizes resources that could be used to improve screening and follow-up for eligible individuals.

5.7 SCREENING ACCEPTABILITY, ADHERENCE AND COMPLIANCE

Ultimately, the effectiveness of any screening program depends on patients' risk perception and hence perceived acceptability of the proposed test and its consequences in case of positive testing, starting in principle with a colonoscopy. All those factors decisively influence patient compliance[401]. Lieberman[402] compared the cost-effectiveness of five screening programs for CRC and concluded that compliance was the most important determinant of program effectiveness in all five programs.

5.7.1 Definitions

The terms adherence, compliance and coverage are used interchangeably in the literature[403], and in the economic literature participation is often used with the same meaning.

- *Adherence* in a general sense refers to the completion of a colorectal cancer screening test or procedure.
- *Compliance* refers to completion of *all tests* or examinations when sequential offers are made to the same persons regardless of whether they completed a prior test.
- *Coverage*[g] refers to completion of *at least one test* or examination when sequential offers are made to the same people, regardless of whether they completed a prior test.

Continuous screening is defined as the periodic provision of an opportunity for diagnostic testing to a population of individuals who are asymptomatic and at increased risk for disease (or a perception of increased risk)[404]. With regard to continuous screening we have to distinguish:

- *Sequential screening*: refers to rescreening offers made to the same persons regardless of whether they completed a prior test.
- *Repeat screening*: refers to rescreening offers made only to persons completing a prior test or examination and who remain eligible, e.g. are still alive, still reside in the geographic area, and are free of CRC.

[g] Definitions for "coverage" and "compliance" are from a summary of an NCI preapplication meeting for an RFA (CA-89-05) on worksite health promotion interventions (January 1989).

5.7.2 Effects of risk perception and risk communication on cancer screening behaviors

Perceived risk has been used to explain cancer screening behaviors as well as in interventions to promote cancer screenings. However, the literature on perceived risk in relation to cancer screening behaviors has not been examined systematically across cancer sites and the following terms have been used synonymously: perceived risk, risk perception, perceived susceptibility, perceived vulnerability, and subjective risk.

As noted by several authors[405, 406], perceived risk is a central construct in a number of theories of health behavior[407], e.g., the Health Belief Model[408-413], the Precaution Adoption Model[414, 415], the Transactional Model of Stress and Coping[416-421], the Self-regulation Model of Health Behavior[422], and the Protection Motivation Theory[423-428]. Risk perception derives from threat appraisal, which is considered to be a major motivating factor in preventive and protective health behaviors. Threat appraisal is based on beliefs about disease risk and severity[429, 430]. As defined by Weinstein and Klein[431], perceived risk relates to one's belief about the likelihood of personal harm. Because risk perception may be an important motivator of a number of health-related behaviors, it is important to understand both the determinants of risk perception and the patterns of association between perceived risk and specific health-related behaviors to develop effective risk communication messages to encourage the adoption of behaviors that will improve health status.

In the case of screening tests or procedures with established efficacy and effectiveness, the goal of risk communication is to encourage or persuade persons to be tested. For screening procedures in which the risks and benefits are uncertain, e.g., mammography screening for women in their forties or prostate-specific antigen testing, the goal of risk communication is informed decision making. Risk communication about screening behaviors will take different forms, depending on the strength of the scientific evidence establishing the risks and benefits associated with the tests or procedures in question.

In a very elaborate 1999 JNCI Monograph review, Vernon[432] summarizes and synthesizes research findings on risk perception and risk communication as they relate to cancer screening behaviors. The focus was on cancers for which there is evidence that screening reduces mortality, i.e., cervical, breast, and colorectal cancers.

The following questions were addressed in Vernon's review:

1. Is perceived risk associated with relevant cancer screening behaviors?
2. What factors are associated with perceived risk?
3. Is the relationship between perceived risk and cancer screening behaviors modified by other factors?
4. Have interventions to change perceived risk been effective in modifying risk perceptions?
5. Are these changes related to subsequent cancer screening behaviors?

There was consistent evidence that perceived risk was associated with mammography screening, but there were insufficient data on these associations for cervical or colorectal cancer screening behaviors. There was some evidence that perceived risk mediated the association between other variables and

screening behaviors[408, 415, 424, 433-439]: e.g. perceived susceptibility[414] and barriers[435], social[440, 441], cognitive[429], attitudinal variables[440], personal moral obligation - "I think I should have a screening test"[429], etc. However, because of the small number of studies, findings are best viewed as hypothesis generating.

Studies of interventions to modify risk perceptions provided some support for the view that they are modifiable[442-446, 439], but there was conflicting evidence that these changes were related to subsequent cancer screening. Methodologic studies of how best to measure perceived risk are needed. Because most data on the correlates of perceived risk were cross-sectional, it is difficult to determine whether perceived risk is a cause or an effect in relation to cancer screening. Longitudinal studies that measure perceived risk in defined populations with different cancer screening histories and that include follow-up for screening and repeated measurements of risk perception are needed to clarify this relationship.

5.7.3 Factors influencing CRC screening adherence

5.7.3.1 Systematic review on participation in CRC screening (JNCI, 1997)

In a 1997 JNCI systematic review[403] more than 132 empiric studies were included to evaluate the published literature on adherence to CRC screening with either FOBT or sigmoidoscopy. Specifically, the review addressed the following questions: 1) prevalence of FOBT and sigmoidoscopy; 2) interventions to increase adherence to FOBT and sigmoidoscopy; 3) correlates or predictors of adherence to FOBT and sigmoidoscopy; and 4) reasons for nonadherence. Although selection criteria varied somewhat for the four questions, at the minimum, the investigators had to describe the study population, the setting, and the data collection methods. Because this was the first systematic review of the topic, a wide range of study designs, varying in rigor, was included.

Study characteristics included program circumstances where all eligible persons were offered a test (including the study arm of randomized clinical trials on FOBT efficacy), intervention studies of methods to increase adherence as well as intervention studies to evaluate the effects of diet restrictions, length of testing, or type of test on adherence.

Population characteristics included patient populations, community-populations, worksite populations and others (e.g. FDRs of CRC patients and other volunteers, high-risk patients, members of voluntary organizations, etc.). In a few reports, the study population was not clearly described.

Most studies measured behavior prospectively in response to an invitation to undergo CRC screening. Community-based studies were further classified as media campaigns or surveys. In media campaigns, persons were offered an opportunity to pick up a kit, or kits were handed out to "all comers" in a variety of settings, e.g., shopping malls and drug stores. Surveys measured self-reported past behavior using different time periods, e.g., ever use or use during the past year.

Overall, 101 studies reported adherance to CRC screening; 11 studies (231.365 individuals) examined adherence rates for FOBT re-screening; 22 studies (at least 75.790 individuals) reported adherence rates for screening sigmoidoscopy; 3 studies (at least 8.672 individuals) assessed adherence rates for sigmoidoscopy re-screening; and 18 studies (at least 74.677 individuals) reported adherence rates following interventions to increase screening results. The numbers of individuals in the remaining studies were not specified in the review.

In this very heterogeneous collection of studies (study type and design, population studied, screening recruitment and methods, etc.) adherence rates to FOBT ranged from 0 to 98% in the USA and Canada, from 10 to 92% in Europe, and from 2 to 95% in other countries. The rates of adherence to sigmoidoscopy ranged from 2 to 69%. The rates for FOBT re-screening were 39 to 90% for coverage, 23 to 60% for compliance, and 56 to 94% for repeats. Adherence to re-screening by sigmoidoscopy ranged from 34 to 79% for coverage and from 16 to 64% for compliance.

Reported adherence rates were generally consistent with the statement that the longer the interval between tests, the higher the adherence to rescreening. Data from the Minnesota Colon Cancer Control Study[354] showed a consistent decline in adherence with greater frequency of testing (annual versus biennial) and as persons were asked to complete more tests. The yield from offering initial nonparticipants another opportunity to be screened is low. In the Nottingham study Hardcastle et al.[348] reported that only 6% of those refusing the first FOBT completed a subsequent test; other investigators also found low adherence to FOBT among initial nonparticipants offered a second chance to be tested[447, 448, 364].

'Health motivation' was the most consistent positive correlation to FOBT test completion (positive in 7 of the 9 studies). Knowledge of cancer and knowing someone with colorectal cancer also appeared positively correlated. Demographic and medical history variables have not been adequately tested to clearly show statistical differences; however, patients who were female, had a higher education level, or had a higher income, were more likely to complete the FOBT test. With sigmoidoscopy, there were very few studies examining correlates. There were some data to suggest that patients who were male, had a higher education level, or had a higher income, were more likely to have had sigmoidoscopy. The perceived susceptibility to colorectal cancer was also positively correlated with having had a sigmoidoscopy (all 3 studies were positive).

Reasons given for nonadherence to the FOBT included practical reasons; no current health problems; the test was embarrassing or unpleasant; and the patient did not want to know of any health problems. The reasons given for nonadherence to the sigmoidoscopy test were: no current health problems; practical reasons; worry about pain or complications of the test; and the patient did not want to know of any health problems.

5.7.3.2 Previous screening experiences

Previous screening experiences appear to have a potentially negative impact on adherence to CRC screening programs, as was reported in a study assessing adherence to sequential and repeat CRC screening among older adult members of an independent practice association-type health maintenance organization (HMO) in two consecutive rounds of screening[404]. In the first screening round, FOBTs were sent to 1.565 subjects randomly assigned to receive usual care or one of four behavioral interventions intended to encourage testing and varying in intensity. Overall, 647 (41%) subjects completed and returned their tests. In the second screening round, all persons received a mailed FOBT kit and a reminder letter approximately 2 weeks after the kit was mailed, regardless of treatment group status in round 1. Compliance, i.e. completion of all sequential tests or examinations offered to the same people regardless of prior participation, was 23%. Among persons who completed a test in the first round, 56% completed a second test (i.e., repeat screening). Of particular interest was

the finding that second round adherence, regardless of adherence status in the first round, was similar across the four groups that received interventions of different intensity in the first round; the range was 28%–33% and there was no pattern across groups. Surprisingly, when the analysis was limited to repeat screening, completion of a second test was lowest in the group who received the most intense intervention in the first round.

Logistic regression analysis results showed that first-round testing was a significant independent predictor of serial adherence for subjects older than 65 years of age (OR = 10,8) and those younger than 65 years of age (OR = 10,9). Furthermore, a significant negative association between exposure to first-round intervention and serial adherence (OR = 0,5) was found among younger subjects. Among first-round adherers, age was significantly and positively related to repeat adherence (OR = 1,6). However, exposure to first-round intervention and having an abnormal FOBT result were significantly and negatively associated with repeat adherence (OR = 0,5 and OR = 0,4, respectively). The results of this study indicate that previous screening is a strong predictor of serial adherence, and special efforts may be required to achieve high levels of serial and repeat adherence among younger adults. Additional research is needed to understand why persons with abnormal screening test results are unlikely to engage in repeat screening.

5.7.3.3 Age, gender and ethnicity

Patterns of participation by age and sex (and screening center) were studied in another Italian RCT study[210] of five different methods of offering two different colorectal screening tests - FS and a FOBT - in a sample of the general population aged 55 to 64 year, at average CRC risk. People with previous CRC, adenomas, IBD, a recent (≤ 2 years) colorectal endoscopy or FOBT, or 2 FDR with colorectal cancer were excluded. Of 28.319 people sampled, 1.637 were excluded and 26.682 were randomly assigned to a screening arm. Participation rates were estimated in a multivariable model after mutually adjusting for the effects of the covariates (age, sex, center, and screening arm) on participation. The participation rate in the sigmoidoscopy groups was higher among men than among women (OR = 1,22, 95% CI =1,14 to 1,32) and lower among subjects aged 60 – 64 years than among subjects aged 55 – 59 years (OR = 0,89; 95% CI = 0,82 to 0,95). Among the subjects invited for FOBT screening, fewer men than women actually took the test (OR = 0,82, 95% CI = 0,74 to 0,90). Overall, more subjects who had been sent a FOBT kit actually took the test than subjects who were allocated to the sigmoidoscopy followed by biennial FOBT group (OR = 1,11, 95% CI = 1,00 to 1,22, P = ,0498). Participation rates in all other screening arms were similar to that for the sigmoidoscopy followed by biennial FOBT arm. Overall, subjects aged 60 – 64 years had lower screening participation rates than subjects aged 55 – 59 years (OR = 0,94, 95% CI = 0,89 to 0,99), independent of screening modality. If restricted to subjects in the older age group, the participation rate to the invitation for FOBT was higher than the participation rate to sigmoidoscopy screening (OR = 1,09, 95% CI = 1,01 to 1,18). Among subjects who had sigmoidoscopy, a statistically significantly higher proportion of women than men reported having painful experience with the test. In addition, the proportion of examinations that could not be completed because of bowel adhesions was statistically significantly higher among women than among men. Similar findings were previously reported[449]. These findings suggest that specific interventions that address barriers to attendance among women as well as aspects related to test performance in women should be implemented in any mass screening program that adopts sigmoidoscopy.

The 2001 California Health Interview Survey (CHIS 2001 - a random-digit dial telephone survey) has provided an opportunity to examine the use of CRC screening tests in California's ethnically diverse population[450]. Data of this survey were used to evaluate 1) rates of CRC test use, 2) predictors of the receipt of tests, and 3) reasons for non-use of CRC tests. CHIS 2001 responses from 22.343 adults aged ≥ 50 years were analyzed. CRC test use was defined as receipt of a FOBT in the past year and/or receipt of an endoscopic examination in the past 5 years. Nearly 54% of California adults reported recent receipt of a CRC test. Insurance coverage and having a usual source of care were the most important predictors of CRC testing. Latinos age < 65 years were less likely to be tested than whites (RR 0,84; 95% CI: 0,77 - 0,92). Men were more likely to be tested than women, an effect that was greater among individuals age 50 - 64 years (RR 1,28; 95% CI: 1,23 - 1,32) than among individuals age ≥ 65 years (RR 1,19; 95% CI: 1,15 - 1,23). Women were more likely than men to say that their physician did not inform them the test was needed and that CRC tests were painful or embarrassing. Results of this Californian study indicated a need for physicians to recommend CRC testing to their patients and that assuring that all individuals have both health insurance and a usual source of care would help address gaps in overall population's adherence to CRC tests.

It is reassuring to see that the patterns of participation by age and sex reported in the Segnan study are similar to findings in the United States[403, 450] and elsewhere in Europe[451]. Although the health care systems and, presumably, attitudes regarding health behavior such as screening differ among these geographical areas, the effect of age and sex remain fairly predictable. This consistency among different areas should make cross-cultural generalization of these findings easier.

5.7.3.4 Physician prompts

In a 1999 review on cancer screening decisions McCaul et al[452] discuss three topics: (a) physician prompts that may elicit compliant screening behavior, (b) the independent and joint effects of risk perceptions and worry, and (c) the screenees personal costs and benefits of getting screened. Overall, the data suggest that each of these factors will influence screening adherence. So, for example, people are more likely to seek screening if a physician recommends adherence, if they feel personally vulnerable and worry about cancer, if insurance covers the screening, and if they believe that the test is an effective early detection procedure. Future research needs to include studies comparing theories, longitudinal rather than cross-sectional studies, and true RCT experiments. We also need to know more about why physicians are such powerful change agents and the trade-offs of increased personal risk versus exacerbating worry. Practical recommendations for promoting cancer screening include encouraging physician interventions, explaining risk, and lowering the costs while emphasizing the benefits of screening.

A more recent review[453] concluded that a positive attitude towards screening and physician recommendation result in high adherence while fear of finding cancer and the belief that cancer is fatal result in low adherence.

5.7.3.5 Effects of dietary restrictions, length of testing, type of FOBT and method of screening offering

Several investigators evaluated the effect on adherence of requiring dietary restrictions before performing the test[454-460]. Although most investigators found

only a modest effect, if any[454-456, 458], Robinson et al.[459] reported a substantial effect.

Robinson et al.[459, 372] and Thomas et al.[461] evaluated length of testing, i.e., the number of days respondents were asked to collect stool samples. Robinson et al.[459] found no effect of 3- versus 6-day testing, but in a follow-up study[372] of 1- versus 3-day testing using Hemeselect, respondents were more likely to complete the 1-day test. Thomas et al.[461] found a statistically significant effect of 3- versus 6-day testing, but the magnitude of the difference was small (58% and 54% for 3- and 6-day testing, respectively).

Type of test, e.g., Hemoccult or Colo-Screen, did not affect adherence[462, 458]. In a recent cluster-randomized trial in Italy, aimed at assessing the effect of the type of fecal occult blood testing, gFOBT or iFOBT, on screening compliance[198], 130 general practitioners (GPs) consenting to participate were sampled. Half of them were randomly allocated to gFOBT (Hemo-Fec) and half to iFOBT (OC-Hemodia). 20% of each participating GPs' 50 to 75 year old patients were selected (n=7.332) and randomly divided into 2 equally sized groups. One half was invited to be screened at the GP's office and the other to the nearest gastroenterology ward. The principal outcome measurement was the percentage of returned tests. The immunochemical test had a compliance of 35,8% and the guaiac of 30,4% (RR 1,20; 95% CI: 1,02 - 1,44). The difference was mostly due to a higher probability of returning the sample: 94% and 89% for iFOBT and gFOBT, respectively (RR 1,06; 95% CI: 1,02 - 1,10). The guaiac test had a higher prevalence of positives (10,3% versus 6,3%, RR 0,60; 95% CI: 0,43 - 0,84). There was a higher variability in the results obtained with the guaiac test compared with the immunochemical (p = 0,0017). The authors concluded that compliance was more likely with the immunochemical than the guaiac test, independent of the provider. Guaiac tests showed a higher variability of the results among centres.

Also in 2005, Segnan et al[210] presented the results of a well-conducted randomized trial of five different methods of offering two different colorectal screening tests - FS and a FOBT - to an average-risk population in Italy. The five screening arms comprised 1) a mailed FOBT kit, 2) a FOBT offered in the clinic, 3) a one-time FS, 4) a one-time FS followed 2 years later by a FOBT, and 5) the subject's choice of a FS or a FOBT. The trial was designed to allow estimation of the participation rates with respect to the screening test offered and the method of offering, as well as comparisons of the rates at which clinically relevant neoplasms were detected. The novel aspects of this study include comparing the offer of an explicit choice between screening tests (i.e., screening arm 5) with recommendations of a specific test (i.e., screening arms 1, 2, and 3) as well as with the option of doing both tests (i.e., screening arm 4). Equally novel is the comparison of two methods of distributing the FOBT kits: by direct mail or during a clinic visit. This innovative study design is useful for understanding, from a practical point of view, whether such strategies make a difference in the acceptance of screening by those at average risk of the disease. With regard to acceptance of screening, the authors' main finding is that mailed FOBT kits elicited the highest acceptance rate compared with all four of the offers of screening in a clinic setting. A related finding in the United States - that direct mailing of FOBT kits on a population basis led to increased screening rates[463] - complements this result. This method lends itself to a variety of organizational structures within a health care system, because the offers can be clinic-based or come from a public health agency with equal ease. The other strategies studied by Segnan et al[210] had about equal acceptance rates. This finding implies that those given a choice between the two screening test

methods did not accept screening at a higher rate than those not given a choice. Together these results suggest that a relatively efficient way to increase participation in CRC screening may be to use exclusively mailed invitations, with the option of including a FOBT kit in the mailing, but prudence is called for a straightforward extrapolation of such conclusions to a Belgian population, generally used to a general practitioner based healthcare guidance, as in France. The authors also report considerable variation by study site in the differential participation between a FOBT and FS, in that subjects from the larger study centers preferred sigmoidoscopy slightly more than a FOBT, whereas subjects from the smaller study center strongly preferred a FOBT over sigmoidoscopy. Additional study of this phenomenon would be useful. For example, were the practitioners in the larger centers more in favor of endoscopy and vice versa? Or was subject preference a function of the characteristics of their respective populations (e.g., more men in the larger centers)?

5.7.3.6 Healthcare system factors, personal insurance status, cultural and various psychosocial influences

Healthcare system factors and personal insurance status[464-466], in addition to cultural and psychosocial influences[448, 467, 404, 468-471], play a considerable role in patient's adherence to screening programs. Affect-related personality traits (neuroticism, extraversion, optimism, worry, and self-deceptive enhancement) can negatively influence screening adherence[397].

Finally, Taylor et al.[472] studied quality of life and trial adherence among participants in the prostate, lung, colorectal, and ovarian cancer screening trial. Participants (N = 432; 217 in the control arm and 215 in screening arm) were accrued from the Georgetown University PLCO site from May through December 1998. Screening-arm participants were interviewed by telephone at baseline (prescreening), shortly after notification of screening results (short-term follow-up), and 9 months after notification of screening results (intermediate-term follow up). Control-arm participants completed a baseline and 1-year follow-up assessment. Logistic regression analyses were conducted. Participants reported high levels of HRQL and satisfaction with their decision to participate. Screening-arm participants with abnormal screening results had a higher level of intrusive thoughts about cancer than those with all normal results (OR = 2,9; 95%CI: 1,3 to 6,3) at the short-term follow-up but not at the intermediate-term follow-up (when abnormal test results were known to be false positive; OR = 1,9, 95%CI: 0,89 to 4,2). Trial adherence was statistically significantly better among participants who had received all normal results in the previous year's screening tests (93,7% versus 78,7%; OR = 3,7; 95%CI = 1,1 to 12,0) than in those who received at least one abnormal result. In the control arm, adherence (defined as returning annual questionnaires) was positively associated with education (OR = 3,4; 95%CI = 1,4 to 8,4) and sex, with women being more likely to return questionnaires than men (OR = 2,1; 95% CI = 1.05 to 4.4). These results suggest several methods for improving adherence in this and other subgroups.

5.7.4 Promoting CRC screening adherence

Different methods of enhancing patient adherence to screening programs have been explored: physician/nurse talk, and/or reminder postcard, and/or reminder phone call[473]; survey by telephone 4 months later followed by a second FOBT mailing[448, 467, 468]; authorizing support staff to order fecal occult blood tests in a general internal medicine clinic[474]; direct mailing of FOBT kits and a questionnaire about colorectal cancer screening[463]; educational video, mailed to

patients' homes before a physical examination[475]; reminder-feedback and educational outreach intervention in primary care practices[476]; organizational level interventions, such as a team approach to colorectal cancer screening[477]; using an educational multimedia computer program in a university-affiliated, community-based Internal Medicine outpatient practice[478]; provider recommendation to FDRs of CRC patients[479], but a single optimal strategy cannot be determined from the currently available data[194].

Attempts to promote CRC screening have used both a public health model that targets entire communities, e.g., mass media campaigns, and a medical model that targets individuals, e.g., general practice patients. Most of these efforts, however, did not include systematic evaluation of strategies to increase adherence[403]. The data on FOBT adherence show that the median adherence rate to programmatic offers of FOBT can reach between 40% and 50%, depending on the type of population offered the test, e.g., patients or employees in employer-sponsored programs. Approximately 50% of those initially offered testing in unselected populations will respond to minimal prompts or interventions[403]. A salient issue for FOBT, however, is whether or not the behavior can be sustained over time. Fewer studies examined adherence to sigmoidoscopy. Here, adherence was highest in relatives of CRC cases and in employer-sponsored programs offered to workers at increased risk of CRC. At present, we know very little about the determinants of CRC screening behaviors, particularly as they relate to rescreening[403].

In the 1997 Vernon review[403] the most intensive strategies delivered to well-defined populations of eligible persons rarely increased adherence above 50%. In studies that delivered minimal or relatively impersonal interventions, adherence ranged from approximately 10% to 30%[454, 480, 467, 456, 468]. In general, adherence was lowest when persons were asked to pick up a test kit or to mail in a reply card in order to receive a kit[454, 481, 482]. Various strategies ranging from the use of a letter signed by one's own physician and including FOBT kits in the mailing[480, 483] to intensive follow-up with instructional telephone calls[467, 468] were effective at increasing adherence, compared with a control group, to approximately 50%. Nichols et al.[482] evaluated the inclusion of an educational booklet in conjunction with five different contact strategies and found no effect of the booklet. A second mailed follow-up reminder increased adherence in all studies reporting its use[481, 456, 459]. Thompson et al. found that a simple reminder postcard was as effective as more complex interventions, some of which were based on the Health Belief Model[473].

Zapka et al.[475] tested, in a primary care RCT setting, the effect of an educational video about CRC, the importance of early detection, and screening options, mailed to patients' homes before a physical examination, on performance of colorectal cancer screening, particularly sigmoidoscopy. Overall screening rates were the same in the intervention and control groups (55%). In regression modelling, intervention participants were nonsignificantly more likely to complete sigmoidoscopy alone or in combination with another test (odds ratio 1,22; 95% CI: 0,88 to 1,70). Intervention dose (viewing at least half of the video) was significantly related to receiving sigmoidoscopy with or without another test (odds ratio 2,81; CI: 1,85 to 4,26). However, recruitment records showed that at least 23% of people coming for periodic health assessments were currently screened by a lower-endoscopy procedure and therefore were not eligible. Furthermore, the primary care sample studied consisted primarily of middle-class white persons who had high screening rates at baseline and the trial was conducted during a period of increased health insurance coverage for lower-endoscopy procedures and public media attention to colon cancer

screening. As a result, the results may not be generalizable to other populations. Under these limitations, a mailed video showed no effect on the overall rate of colorectal cancer screening and only modestly improved sigmoidoscopy screening rates among patients in primary care practices.

5.7.5 Conclusions

In choosing which screening test to adhere to, an important element to consider is patient's preferences[484, 485]. In order to have a high level of uptake any CRC screening program requires proper education and information of the public on the risk factors for CRC and the alternative screening tools[55, 56, 185, 486, 58]. This implies a substantial amount of initial planning and resource allocation, including defining roles of the different health professionals and including training of the community of general practitioners[185] and even gastro-enterologists[398, 487].

Key messages

- **All studies investigating the effectiveness of CRC screening in average risk populations have been conducted in males and females starting from age 45 or 50 and up to age 75.**
- **There is high quality evidence from RCTs that screening with guaiac FOBT reduces CRC mortality. The estimated CRC mortality reduction due to screening with gFOBT is around 15%. There is, however, no evidence for overall mortality reduction.**
- **There is no direct evidence from RCTs that screening with iFOBT reduces CRC mortality. In theory, iFOBT should have improved performance characteristics compared to gFOBT. However, there is conflicting evidence regarding the comparative performance of iFOBT and gFOBT, partly due to important differences and detection limits between tests.**
- **There is currently no evidence from large RCTs that screening with FS reduces CRC mortality. However, 3 large trials are currently running but results are not anticipated before 2008.**
- **There is no direct evidence to support combined screening using FOBT and FS.**
- **Although colonoscopy is a highly sensitive diagnostic technique, there is no direct evidence that screening an average risk population using colonoscopy reduces CRC mortality.**
- **Although virtual colonoscopy is a rapidly evolving and reliable diagnostic technique, there is no direct evidence that screening an average risk population using virtual colonoscopy reduces CRC mortality.**
- **Patient participation is of crucial importance in population based CRC screening and while planning screening programs consideration should be given to methods to optimize adherence and minimise harms. This involves careful selection of screening strategy in combination with information and education of the public and involved clinicians on potential benefits and harms, but leaving the ultimately choice on whether or not to be screened to the individual.**

6 ECONOMIC EVALUATION OF CRC SCREENING: LITERATURE REVIEW

6.1 INTRODUCTION

The aim of this chapter was to conduct a detailed and critical appraisal of research evidence in the international literature, analysing the cost effectiveness of screening programs for colorectal cancer. We mainly focused on 2 types of screening tests: FOBT and colonoscopy, as recommended by the Scientific Steering Committee.

As for the chapter on effectiveness, and after a first check of the literature we decided to take as a starting point the same exhaustive systematic review from the New Zealand Health Technology Assessment group (NZHTA), published in 2005[219], and covering the literature between January 1997 and October 2004. This review in itself was an update of a previous systematic review from 1998[220]. The NZHTA review considered all screening options available, but concentrated on fecal occult blood tests (FOBT), guaiac tests as well as immunochemical FOBT, and Flexible Sigmoidoscopy (FS). For all other techniques, a lack of available RCTs with appropriate outcome variables was reported.

In order to include more recent evidence we performed an incremental search of the economic literature to cover the period since October 2004. However, much of the evidence presented in this chapter will be similar to evidence already presented in the NZHTA systematic review.

We conducted several searches of the literature on the cost-effectiveness of colorectal cancer screening in Medline (OVID and Pubmed), Embase, the Cochrane Library of Systematic Reviews and CRD (Dare, NHS EED, HTA). Preliminary searches were done in June 2006 and searches were repeated on October 31st, 2006 for completeness. Economic evaluations that came out of the general search on effectiveness (see chapter 5) were also included. Details of the searches can be found in appendix. No language restrictions were applied and the searches were limited to the years 2004 till 2006.

Overall, 341 different articles on economic evaluations were found in those searches, and those were obviously partly overlapping with articles from 2004 already included in the NZHTA report. Based on title and abstract we selected 14 new articles not included in the NZHTA report. Full text articles were retrieved for these 14. Partial economic evaluations were excluded from our review. Full economic evaluations were defined according to the Drummond criteria[488]: study types included were cost-minimisation analyses, cost-effectiveness analyses, cost-utility analyses and cost-benefit analyses. From the 14 full text articles, 7 new studies were included in this incremental review. Together with the 15 primary studies included in the NZHTA report, this means that we considered 22 studies for this review.

The economic evaluations were appraised in terms of their design, methods, data sources, key results, sensitivity of the model to value changes in variables, limitations and conclusions. Data were extracted using a structured data extraction form (also see tables in appendix).

6.2 INCLUDED STUDIES

The NZHTA report identified and appraised the evidence for the effectiveness and cost-effectiveness of fecal occult blood test (FOBT) screening, the comparison of guaiac versus immunochemical FOBT, flexible sigmoidoscopy (FS) and combined FOBT and FS screening, relative to no screening. For lack of hard evidence from RCTs it did not take into account other strategies like colonoscopy (or virtual colonoscopy) or other newly developed strategies. After discussion with the Scientific Steering Committee, however, we decided that colonoscopy could be considered as a potential option for colorectal cancer screening in Belgium. Therefore, we also included articles on the economic evaluations of colonoscopy as a screening tool.

With regard to cost-effectiveness, the NZHTA report[219] included 15 primary studies of high quality (published as full original reports) and 3 secondary research studies (systematic reviews and meta-analyses) published in the time period 1997-2004. Many of the included articles studying FOBT screening have a strong grounding in RCTs (the Funen RCT, the Nottingham RCT, the Minnesota RCT, the Göteborg RCT and later also the Burgundy trial, which although controlled was not randomised). The earlier studies used preliminary RCT outcomes and costs and they made simulations to project long-term results of cost-effectiveness. The recent studies are more often based on measured outcomes derived from the longer follow-up time of these RCTs. Key outcome parameters considered for the review are cost per life year, cost per disability-adjusted life year (DALY) and cost per quality-adjusted life year (QALY) gained.

Table 25 lists the 15 studies included in the NZHTA review.

Table 25: Economic evaluations appraised in the New Zealand HTA

Whynes DK, Neilson AR, Walker AR, Hardcastle JD., 1998[489]	Fecal occult blood screening for colorectal cancer: is it cost-effective?
Whynes DK, 1999[490]	Cost-effectiveness of fecal occult blood screening for colorectal cancer: results of the Nottingham trial.
Gyrd-Hansen D, Sogaard J, Kronborg O, 1998[491]	Colorectal cancer screening: efficiency and effectiveness.
Gyrd-Hansen D, 1998[492], will be called 1998b further in this chapter	Fecal occult blood test: a cost-effectiveness analysis.
Gyrd-Hansen D, 1999[493]	The relative economics of screening for colorectal cancer, breast cancer and cervical cancer.
Helm JF, Russo MW, Biddle AK, Simpson KN,, 2000[494]	Effectiveness and economic impact of screening for colorectal cancer by mass fecal occult blood testing.
Sonnenberg A, Delco F, Inadomi JM., 2000[495]	Cost-effectiveness of colonoscopy in screening for colorectal cancer.
Frazier AL, Colditz GA, Fuchs CS, Kuntz KM., 2000[496]	Cost-effectiveness of screening for colorectal cancer in the general population
Loeve F, Brown ML, Boer R, van Ballegooijen M, van Oortmarssen GJ, Habbema JD., 2000[497]	Endoscopic colorectal cancer screening: a cost-saving analysis.
Flanagan WM, Le Petit C, Berthelot J-M, White KJ, Coombs BA, Jones-McLean E., 2003[498]	Potential impact of population-based colorectal cancer screening in Canada.
Van Ballegooijen M, Habema, JDF., Boer, R., 2003[499]	A comparison of cost-effectiveness of fecal occult blood tests with different test characteristics in the context of annual screening in the medicare population.
Berchi C, Bouvier V, Reaud J-M, Launoy G., 2004[271]	Cost-effectiveness analysis of two strategies for mass screening for colorectal cancer in France
O'Leary BA, Olynyk JK, Neville AM, Platell CF., 2004[500]	Cost-effectiveness of colorectal cancer screening: comparison of community-based flexible sigmoidoscopy with fecal occult blood testing and colonoscopy.
Whynes DK., 2004[501]	Cost-effectiveness of screening for colorectal cancer: evidence from the Nottingham fecal occult blood trial
Stone CA, Carter RC, Vos T, John JS., 2004[502]	Colorectal cancer screening in Australia: an economic evaluation of a potential biennial screening program using fecal occult blood tests.

We have examined the 15 articles from the point of view of potential screening strategies that could be implemented in Belgium (FOBT and colonoscopy) and we have selected 14 articles out of those 15 studies. One article[497] has been rejected from our analysis as the study is mainly dealing with sigmoidoscopic colorectal cancer screening and it did not take into account FOBT or colonoscopy screening as an alternative choice.

Table 26 lists the studies retained from the incremental literature search. As mentioned previously we have focussed on economic evaluation studies that compared no screening versus at least one of the two screening strategies we considered for Belgium: FOBT and colonoscopy. We finally retained seven primary research studies for this report: three studies were conducted in USA, and the other in Singapore, France, Israel and Taiwan. We decided to include one study from 2003 that was originally excluded from the New Zealand HTA report[503]. We kept this study in our review because it compared different

screening strategies including colonoscopy. Only one of the included studies[504] was based on a newly published controlled trial (the Burgundy trial in France). The publication from Ramsey et al.[111] is not about mass screening but a study on how to detect individuals with increased risk based on family history assessment through GP questioning. Therefore, this study will not be evaluated in this chapter.

Table 26: Economic literature KCE incremental search (2004-2006)

Leshno M, Halpern Z, et al., 2003[503]	Cost-effectiveness of colorectal cancer screening in the average risk population."
Lejeune C, Arveux P, et al., 2004[504]	Cost-effectiveness analysis of fecal occult blood screening for colorectal cancer
Wong SS, Leong APK, et al., 2004[505]	Cost-effectiveness analysis of colorectal cancer screening strategies in Singapore: a dynamic decision analytic approach.
Ramsey SD, Burke W, et al., 2005[111]	Family history assessment to detect increased risk for colorectal cancer: conceptual considerations and a preliminary economic analysis.
Ladabaum U, Song K., 2005[506]	Projected national impact of colorectal cancer screening on clinical and economic outcomes and health services demand
Maciosek MV, Solberg LI, et al., 2006[507]	Colorectal cancer screening health impact and cost effectiveness
Wu GHM, Wang YW, Yen AMF, Wong JM, Lai HC, Warwick J, et al., 2006[342]	Cost-effectiveness analysis of colorectal cancer screening with stool DNA testing in intermediate-incidence countries.

6.3 ECONOMIC LITERATURE REVIEW

The detailed evidence tables of these economic evaluations can be found in appendix

6.3.1 Methodology

6.3.1.1 Data

The clinical and cost data for the studies comparing FOBT screening versus no screening are in the first place drawn from the three major RCTs (Funen-1 (Denmark), Nottingham (UK) and Minnesota (US)). A recent study[504] was based on the controlled Burgundy trial. These data were supplemented by values from literature, national incidence/mortality data, and relevant cost data based on the specific health care systems. In contrast with the RCT based FOBT studies, the scenarios analysing immunochemical FOBT and/or colonoscopy (and other screening alternatives) are not supported by data from RCTs.

Almost all studies are cost effectiveness analyses. Only Whynes[489, 490] and Stone[502] performed a cost utility analysis. The study by Whynes et al. expressed results as costs per Quality Adjusted Life Year gained (QALYs) and the quality of life data were taken from earlier empirical investigations[508, 509]. The study by Stone et al. calculated costs per disability adjusted life years (DALYs) using the Burden of Disease methodology[510].

6.3.1.2 Perspective of the studies

The perspective of almost all included studies is that of the third-party payer in a governmentally funded health system. Although the study of Frazier[496] claims to use a societal perspective, only direct costs to the health care system were

included. Only two studies incorporated indirect costs. From the studies comparing no screening with FOBT screening, only Gyrd-Hansen[491, 493] analysed the influence of including production losses. Maciosek[507], who estimated the average value of offering patients a choice of screening tools, adjusted cost estimates to reflect the cost of patient time for screening and follow-up.

6.3.1.3 Time window

Health interventions, and especially screening campaigns, produce most of the costs immediately or in the very short term, whereas health benefits and/or cost savings accumulate over a far longer period. Evaluating the costs and effects of screening programs over a short period would only underestimate the cost effectiveness of the program, making it apparently less favourable. As a result, costs and effects incurred by screening programs should be calculated over the long term.

The studies analysing FOBT screening are based on long term follow up data from RCTs with a long follow-up. All but one, i.e. the study of Helm[494] which was based on 10-year follow-up data, used modelling techniques to simulate results further in the future up to end of life. From the other non-RCT-based studies, all but one developed models with a timeframe of 20 years up to lifetime. Only O'Leary[500] applied a 10-year timeframe.

6.3.1.4 Currencies

For practical reasons all costs will also be presented in Euro, next to the original currency. Exchange rates used are those of October 26th, 2006 (table 27).

Table 27: Exchange rates (October 26th, 2006)

1,00 USD (United States Dollars)	0,789804 EUR
1,00 GBP (United Kingdom Pounds)	1,48812 EUR
1,00 CAD (Canadian Dollars)	0,703149 EUR
1,00 AUD (Australian Dollars)	0,602639 EUR
1,00 DKK (Dannish Kroner)	0,134155 EUR
1,00 ILS (Israel New Shekels)	0,184473 EUR
1,00 SGD (Singapore Dollars)	0,503717 EUR (October 30th)

6.3.2 Interventions and comparisons

For our overview, the cost effectiveness studies have been divided into three categories, i.e. studies comparing FOBT with no screening, studies looking at guaiac-based FOBT versus immunochemical FOBT, and studies taking into account colonoscopy. Since this overview is about mass screening for a population at average risk, the study on family history assessment[111] will not be considered in this chapter.

6.3.2.1 FOBT compared with no screening

Intervention and population

The studies comparing FOBT with no screening are the following: Whynes et al.[489, 490], Gyrd-Hansen et al.[491, 493], Helm et al.[494], Flanagan et al.[498], Whynes[501], Stone et al.[502], Lejeune et al.[504]. Table A 4.1 provides an overview of these studies. Whynes and Gyrd-Hansen both have two separate published studies

which were based on the same methodology and data. Therefore, we considered these studies as a single study.

The core scenario in all studies was characterized by biennial screening, i.e. subjects completing the initial screen, and for whom no abnormalities had been detected, were offered a re-screen after two years. Most of the studies also analysed annual screening either in their base case scenario or as part of a sensitivity analysis.[491, 489, 493, 490, 494, 498] One study even included screening intervals of 1,5 and 3 years since it considered that specific outcomes of the Danish RCT could be generalized to screening programs with alternative screening intervals within a range of 2 years ±1 year (Gyrd-Hansen). Participants with positive test results were further investigated by colonoscopy or in some studies by DCBE (Gyrd-Hansen, Helm) where colonoscopy failed or was not acceptable. After a negative colonoscopy, participants would not be invited for screening for a period of 10 years, provided no polyps were found (Flanagan).

The target population exists primarily of individuals aged between 50 and 74 years.(Whynes, 1998, 1999; Gyrd-Hansen, 1998, 1999; Flanagan, 2003; Lejeune, 2004), while a few studies also include younger patients (starting at 45 years)(Helm, 2000; Whynes, 2004). Gyrd-Hansen (1998, 1999) and Stone questioned the optimal target population by performing subgroup analyses for different target populations.

Cost items

Costs may vary widely over the several studies due to country differences, year of pricing, items included, etc. Therefore it is important to mention which costs have been included and their price.

All studies of course include the cost of FOBT and, for positive FOBTs, the costs for colonoscopy. FOBT costs lie within the range of €3,3 and €9,8 with two exceptions of €16,5 and €24,6 due to the inclusion of GP visits costs[h]. For colonoscopy, the difference is even more noticeable (€130 - €995)[i]. Several studies also included costs produced by follow-up investigations. This follow-up program was assumed to consist of colonoscopy every three years after finding a polyp (Gyrd-Hansen, 1998, 1999; Helm). In the Canadian study, follow-up colonoscopies are performed at three, five, and 10-year intervals if polyps were found (Flanagan). The Australian and French studies include an additional expense from increased follow-up activities which amount to respectively €528 and €843 over a 5-year period.

The costs for setting up a national screening campaign should also be taken into account. Gyrd-Hansen and colleagues (1998) mention a fixed cost per year of €27.144,[j] based on the average yearly costs incurred over the initial 8 years of the Funen-1 trial in which 30.967 persons were offered screening. Costs of coordinator and secretaries were assumed to vary with number of invited

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[h] 9DKK + 11,5DKK + 8DKK = €3,71 (for respectively FOBT cost, mailing and test analysis) (Gyrd-Hansen); 10$ = €7,9 (Helm); CAD4,65 – 9,30 and CAD6 - 8 = €7,5 – 12,1 = €9,8 on average (for resp. the test kit and processing) (Flanagan); £3,29 = €4,9 (test kit, administration, return postage) (Whynes, 2004); AUD41 = €24,6 (test kit, transport, processing and GP visit) (Stone, 2004); 12.52€ (test, GP and mailing) and €4 (test analysis) = €16,52 (Lejeune, 2004).

[i] 1000DKK = €130 (Gyrd-Hansen); $1260 = €995 (Helm); CAD350 - 425 = €245 - €298 (Flanagan); £187 = €279 (Whynes, 2004); AUD1000 = €600 (Stone, 2004); €526 (Lejeune, 2004).

[j] Computer assistant 16.800DKK, software 150.000DKK, offices 36.000DKK and inventory 6000DKK (208.800DKK = €27.144). It is assumed that costs of software, offices and inventory are independent of the size of the program.(Gyrd-Hansen, 1998, 1999)

persons per screening round and were included as a mark-up of €2,55 (19,65DKK) per invitation, corresponding to the calculated mark-up at the fourth screening round in the Danish study (Gyrd-Hansen, 1998, 1999). Flanagan used a sample of approximately 7 million people in the simulation, and included a cost for head office, satellite and promotion of €10.500.000 – 21.000.000 per year. In the Australian study[502], with a population of 18 million people, infrastructure costs amount €4.740.000 (AUD7.900.000). Lejeune mentions organizational costs of €1,26 per target individual.

Treatment costs are a following cost component. Several studies took into account the cost differences according to the stage of colorectal cancer. In the study of Helm, costs attributable to treatment of colorectal cancer from diagnosis until death or 15 years were assumed to be about €38.150 ($48.300) for Dukes' stage A and B, €53.300 ($67.500) for stage C, and €46.850 ($59.300) for stage D. In the Australian study this was €8400 (AUD14.000) for stage A and B, €13.200 (AUD22.000) for stage C, and €11.400 (AUD19.000) for stage D. In the French study, treatment costs were €17.579[k], €21.858, €31.110, and €17.384 for respectively stage I to IV colorectal cancer (see chapter on epidemiology for details about staging of colorectal tumors).

Gyrd-Hansen (1998, 1999) made the opposite reasoning. Cost savings of €15.470 (119.000DKK) were taken into account for patients who did not develop a cancer as a result of screening. For patients who would develop cancer with or without the screening program, they argue trial evidence has shown that treatment costs of screen-detected cancers do not differ significantly from the treatment costs of symptomatic cancers[511-513]. Since the introduction of screening programs has no effect on the costs of treatment for these patients, these could be left out of the analysis. The treatment of screen-detected cancers would only incur a cost because it takes place earlier in time. The lead time, however, which is estimated at 2,1 years[514], makes this effect minimal. For cancers avoided, the cost of a hospital day on the surgical ward was estimated at €552,5 (4250DKK) and the average number of bed-days was 28 for a cancer patient.

Another important cost component, often forgotten in economic evaluations, are those caused by complications. Flanagan modelled complications associated with colonoscopy, i.e. perforation (0,17%), hemorrhage (0,03%) and death (0,02%)[515]. However, no costs associated with the first two side-effects were mentioned. Only the Australian study by Stone explicitly mentioned a cost of €9000 (AUD15.000) per perforation.

Cost-effectiveness ratios

The estimated incremental cost effectiveness ratio (ICER) of FOBT screening versus no screening lies in the range of €1975 per life-year saved (study of Helm et al. relying on the Nottingham trial) and €30.000 per disability adjusted life year (the study of Stone et al. for a target population of 45-49 years). All evaluated screening programs therefore, seem to be cost-effective health care interventions using commonly accepted threshold ranges for ICERs.

The study of Whynes (1998, 1999) estimated that based on the median eight-year follow-up of the Nottingham trial, cost per QALY gained as a result of

[k] For treating stage A colorectal cancer a cost of 15.579 was mentioned in the article, probably due to a typing mistake. Since the confidence interval mentioned by Berchi was €14.063 - €21.095 and mean estimate €17.579, the latter was probably the correct amount.

CRC screening using hemoccult was approximately €8470 (£5685) for males and €7380 (£4951) for females. Longer-term simulations, which relied on modelling, estimated these costs at approximately €3050 (£2047) per QALY gained for males and €2040 (£1371) per QALY gained for females. Screening in women was more cost-effective than screening of men mainly due to the longer life expectancy.

Gyrd-Hansen analysed alternative programs depending on combinations of different target populations, i.e. inviting different age groups, and screening intervals. Fifty-four of the 60 programs were found to be inefficient as being subject to extended dominance. The estimated incremental costs per life-year gained of the identified programs lying on the 'efficiency frontier' ranged from €2210 to €5525 (17.000 – 42.500DKK). The six most efficient programs evaluated included biennial screening of 65-74 year olds, of 60-74 year-olds, and of 55-74 year olds; screening 55-74 year olds every 1,5 years; and annual screening of 55-74 year-olds and 50-74 year-olds. The highest incremental cost occurred when expanding the program from screening the 55–74 year olds every year to include also the 50–54 year olds in the program.

Helm estimated costs per life year saved to be on average approximately €16.195 ($20.500) for screening based on the Minnesota protocol, €2150 ($2700) for screening based on the Funen-1 protocol, and €1975 ($2500) for screening based on the Nottingham protocol. The high estimate for the Minnesota-based result was probably explained by the smaller survival benefit associated with the trial's 'healthy volunteer' recruitment and the practice of FOBT rehydration, which increased the number of false positive results and generated substantial numbers of unnecessary endoscopic investigations.

The Canadian study[498] estimated the incremental cost per life year saved due to FOBT screening, compared with no screening, at €8335 (CAD11.907). The most recent study of Whynes and colleagues (2004) was in line with previous long-term simulations (see above). A screening program based on the Nottingham trial protocol was estimated to have an incremental cost-effectiveness ratio of €2360 (£1584) (Whynes, 2004).

The Australian study[502] estimated net cost per DALY at €7200 (AUD12.000) for a target population of individuals aged 55-69 years. This cost per DALY was lower for older age groups, i.e. €3180 (AUD5300) and €3980 (AUD6600) for respectively 70-74 and 75+ year olds, and higher for younger persons, i.e. €14.400 (AUD24.000) and €30.000 (AUD50.000) for respectively 50-54 and 45-49 year old persons.

Finally, the French study of Lejeune estimated the incremental cost per life year gained at €4705 when calculated over a 10-year period and €3357 when this period was extended to 20 years.

Sensitivity analysis

Robustness of results is checked through sensitivity analysis. In several studies, cost items, discount rates, screening intervals, age, compliance, sensitivity and specificity of the screening tests, survival, and complications were varied to see how results could be influenced. All but one (Stone) only performed one way-sensitivity analysis.

Helm only performed sensitivity analysis on costs derived from the 10th and 90th percentile of charges. The ICER was found to vary within about 50% of the base values. Costs per life year saved ranged from approximately €9000 to €25.675 (baseline €16.195) for screening based on the Minnesota protocol, €1250 to

€3300 (baseline €2150) for screening based on the Funen-1 protocol, and €1000 to €3300 (baseline €1975) for screening based on the Nottingham protocol. Also in the Canadian study[498], the cost effectiveness ratio remained favourable even under high-cost scenarios, i.e. €12.900 ($18.445) instead of €8335 ($11.907).

With respect to which cost items have the largest impact on results, Whynes and colleagues (2004) doubled testing, investigation, and treatment costs which increased the ICER with 59,6, 27,5, and 12,9 percent respectively. In the initial study, doubling FOBT costs raised the ICER by 30 percent relative to the base estimate.(Whynes, 1998, 1999) The French study results are relatively similar. Colorectal cancer treatment costs did not influence the ICERs, but, changes in the costs of FOBT and colonoscopy had a stronger impact. A decrease in the FOBT cost from €3,20 to €1,60 led to an 11,1 percent reduction in the ICER. According to the lowest and highest value of the colonoscopy costs, i.e. €225 and €830, ICERs ranged from €2929 to €3817 per LYG. Finally, also Gyrd-Hansen found that the cost of colonoscopy had a significant effect on the estimated cost per life year saved. Tripling this cost, i.e. from €130 to €390 (3000DKK), increased the ICERs by 40-45 percent (Gyrd-Hansen, 1998, 1999).

Concerning the influence of discounting, results are not surprising. In the study of Whynes (2004), results were found to be relatively insensitive to plausible variations in the assumed discount rate for costs but more sensitive to variations in the discount rate for benefits. Discounting benefits by the same rate as costs, i.e. 6 percent instead of 2 percent, raised the ICER by 77,4 percent. When benefits are undiscounted, the ratio falls by 25,5 percent. The fact that changing the discount rate on costs does not influence results greatly is due to the fact that these occur mainly in the short term. Benefits of screening programs, on the contrary, occur in the future which is the reason why discounting them has a greater impact on results.

Regarding the periodicity of the screening test a biennial screening program is favoured. The study of Gyrd-Hansen (1998, 1999) provided six efficient screening programs. The biennial screening program provided better ICERs than the annual screening program. For example, in a target population of 55-74 year old persons, the incremental cost effectiveness ratio was €2990 (23.012DKK) and €4610 (35.471DKK) for respectively biennial and annual screening. The cost per life-year gained from biennial screening was €8335 (CAD11.907) and this increased to €9450 (CAD13.497) under annual screening (discounted at 5%). Both biennial and annual screening remained cost-effective under the high-cost sensitivity analysis, respectively €12.900 (CAD18.445) and €13.925 (CAD19.893).(Flanagan) In the Australian study, annual screening was associated with an ICER of €12.000 (AUD20,000) per DALY gained instead of €10.200 (AUD17.000) for biennial screening.(Stone) However, annual screening was found to increase both the cost and yield of screening compared with the biennial approach, and Whynes (1998, 1999) concluded these two effects compensated for each other and as a result had little impact on the ICER.

Two studies (Gyrd-Hansen (1998, 1999) and Stone estimated the influence of changing the age of the target population in the main analysis (see above). With regard to cost effectiveness, older age groups had better outcomes than younger ones (45-49 and/or 50-54). Other studies explored the influence of changing target groups as part of their sensitivity analysis. In the Canadian study, the increased cost of screening before age 50 was not warranted, given the small gain in life expectancy, and screening after age 75 showed no significant gains in life expectancy. Starting to screen at age 50 and ending at age 74 was shown to be more cost-effective than starting later or ending earlier (Flanagan).

In the French study, the 55-64 age group presented the best cost effectiveness ratio (€2980), with very small differences comparing to other age groups (maximum €3923).

With respect to compliance and participation, results are diverse and some results should be interpreted with caution. In the study of Whynes (1998, 1999) results appear relatively insensitive to the different assumptions in three simulations regarding compliance. Increased compliance increased survival gains, although at the expense of additional detection, treatment and follow-up costs and the effects appear largely compensatory. This reasoning is correct in their specific research setting in which organisational costs of the screening program were not included. If these costs would be included, it would probably be important (depending on the size of fixed costs and the target population) to have a high participation and/or compliance in order to spread the fixed costs over a larger population. Another study mentioned the major influences on the uncertainty of the health benefits were the size of the mortality reduction and the screening participation rate. In the study by Stone the FOBT positivity rate and the participation rate had the greatest impact on the cost estimates. However, it should be emphasised that these sensitivity analyses were performed for total health benefits and costs separately and not with regard to the ICER.

In the Canadian study[498], biennial screening was less cost-effective when the participation rate was reduced from 67% to 50%, i.e. €10.980 (CAD15,688) instead of €8335 (CAD11.907). In the French study[504], effectiveness and ICER were strongly related to the acceptability rate. With a 10 percent absolute increase of the acceptability rate, the ICER was reduced by 20,1 percent. On the other hand, a decrease of the acceptability rate of 20 percent resulted in an increase of the ICER by 86,0 percent.

Sensitivity and specificity of the FOBT test were analysed in two studies. High specificity of FOBT was found to be instrumental in avoiding the high costs of investigating false positives. The cost per QALY doubled if FOBT specificity decreased by 10 percent. (Whynes, 1998, 1999) In the French study, a reduction in specificity from 99 to 90 percent resulted in an increase of the cost effectiveness ratio by 19,3 percent. Increasing sensitivity from 60 to 70 percent only decreased the ICER from €3357 to €3203 per LYG (Lejeune).

Finally, the survival estimate and complications were examined in some studies. Gyrd-Hansen (1998, 1999) estimated that a 1 percent decrease in the excess survival rate generated a 4-4,9 percent increase in incremental costs. Using the highest Kaplan-Meier survival estimate with a survival advantage of 1,34 years instead of 1,12 years compared to the controls, the ICER decreased with 23,3 percent relative to the base estimate (Whynes, 2004). As a result, and being expected, survival estimates are relatively important. According to Flanagan, deaths due to the complications of colonoscopy had minimal impact on the estimated mortality reduction. For every 178 CRC deaths avoided in the simulated cohort, one death due to complications was incurred.

6.3.2.2 Guaiac-based and immunochemical FOBT

Intervention and population

Several studies have compared the unhydrated Hemoccult II test with alternative faecal occult blood tests. Among these alternatives are rehydrated Hemoccult II, Hemeselect, Hemoccult II Sensa and immunochemical FOBT Magstream. The following reports, studying several of these alternatives, will be

discussed: Gyrd-Hansen et al (1998b)[492], Van Ballegooijen et al. (2003)[499], and Berchi et al (2004)[271]. Table A 4.2 provides an overview.

The interval of screening varied across studies. Whereas Gyrd-Hansen (1998b) evaluated both one- and two-year screening strategies, Van Ballegooijen looked at annual screening, while Berchi analysed biennial screening. People with a positive screening test were supposed to undergo a colonoscopy. Follow-up, if included, consists of one colonoscopy performed every three years (Berchi).

The target population also differs across studies. Whereas the French and Danish study focus on individuals aged between 50/55 and 74 years of age (Berchi; Gyrd-Hansen 1998b), the US study incorporates a relatively older population of 65-79 years old individuals. Only Gyrd-Hansen (1998b) made an analysis with respect to age by changing the starting age of the population eligible for screening from 55 to 50.

Cost items

Costs for both FOBT and colonoscopy are included in all studies. The Danish and US study did not differentiate initially between guaiac and immunochemical FOBT costs, which are €3,9 (30DKK) and €3,56 ($4,5) for the two studies respectively (Gyrd-Hansen, 1998b; Van Ballegooijen). The French study includes a cost of €8,84 and €10,98 for respectively immunologic and guaiac FOBT (Berchi). These cost ranges are in line with previously mentioned FOBT costs. For colonoscopy, Gyrd-Hansen and colleagues include a relatively low cost, i.e. €143 (1100DKK) (Gyrd-Hansen, 1998b), which is 10% higher than in their study comparing FOBT with no screening (Gyrd-Hansen, 1998). The cost of €514 ($650) and €457 for the US (Van Ballegooijen) and French study (Berchi) are about at the average of the cost range for colonoscopy found in the previous part. The cost of €514 was the estimated mean observed in the Calvados screening experience in which the costs ranged from €150 to €1000 depending on whether colonoscopy was practised in a surgery or in a private clinic (Berchi).

The US and French study explicitly mentioned the follow-up procedure. In the US study, diagnostic follow-up was performed after positive test results. Surveillance follow-up depended on the size of detected adenomas, i.e. after 5 years if one or two adenomas <1cm were found, after 3 years if three or more adenomas or an adenoma >1cm was found, and repeated after 5 years after a negative surveillance (Van Ballegooijen). In the model of Berchi, follow-up by colonoscopy was performed every three years.

With respect to the costs of organising and managing the screening campaign, only Berchi explicitly included these costs which amount to a total annual cost of €63.256 or €0,38 per individual.(Berchi) In contrast to the previous study of Gyrd-Hansen and colleagues comparing FOBT with no screening,(1998, 1999) they did not mention campaign costs this time.

Next, treatment costs were included. Treatment costs included in the French study of Berchi were exactly the same to those of the previous mentioned French study of Lejeune, i.e. €17.579, €21.858, €31.110 and €17.384 for respectively stage A, B, C and D. Based on literature, Van Ballegooijen assumed that the average payment level was about €21.200 ($26.800) for the initial treatment of colorectal cancer, €1660 ($2100) annually for continuing care cost following initial cancer treatment, and €17.150 ($21.700) for terminal care costs for those who die of colorectal cancer.

Finally, treatment costs for complications, as well as their influence on health benefits, were not modelled.

Cost-effectiveness ratios

In the Danish study, the most cost effective screening programs were biennial screening of 55-74 year olds using unrehydrated Hemoccult II (€2275 (17.500DKK) per LYG), annual screening of 55-74 year olds using unrehydrated Hemoccult II (€3900 (30.000DKK) per LYG), annual screening of 50-74 year olds using unrehydrated Hemoccult II (€5070 (39.000DKK) per LYG), annual screening of 50-74 year olds using HemeSelect (€9270 (71.300DKK) per LYG) and annual screening of 50-74 year olds using rehydrated Hemoccult II (€17.950 (138.100DKK) per LYG). Higher sensitivities of the rehydrated H-II test, the Hemoccult Sensa test, and the HemeSelect test were at a cost of lower specificity (Gyrd-Hansen, 1998b).

The results of the study of Van Ballegooijen (2003) were performed for a hypothetical immunochemical FOBT assumed to have comparable sensitivity to Hemoccult SENSA but with higher specificity. If a specificity of 98% for IFOBT was assumed, the test would be economically preferred to Hemoccult II at the current level of payment and be preferred to Hemoccult Sensa even at a much higher payment level. On the one hand, this hypothetical approach limits the current practical use of the study. On the other hand, it shows how future improvements in the specificity of iFOBTs may be associated with significant improvements in cost-effectiveness.

The French study results did not compare guaiac and immunochemical FOBT versus no screening but versus each other. The incremental cost-effectiveness of substituting Magstream for Hemoccult was estimated to be €7458 per life year saved after 10 years of screening and €2980 per life year saved after 20 years of screening.

Sensitivity analysis

As for the previous studies, results are sensitive to the costs of testing. If in the Danish study, FOBT test costs increased to €5,2 (40DKK) instead of €3,9 (30DKK) and diagnostic test costs (follow-up colonoscopy) increased to €208 (1600DKK) instead of €143 (1100DKK), the incremental cost of applying annual screening of 50-74 year olds using HemeSelect or rehydrated Hemoccult II would increase to about €16.200 (124.800DKK) and €25.850 (198.800DKK), respectively (instead of 71.300DKK and 138.100DKK) (Gyrd-Hansen, 1998b).

Also in the French study, cost-effectiveness ratios were positively correlated to the costs of colonoscopy. When the latter increased from €457 to €1000, cost effectiveness ratios increased 1,5-fold. On the other hand, a decrease in the cost of colonoscopy from €457 to €150 led to a 93% decrease of the cost-effectiveness ratio when comparing to the basic scenario (Berchi). On the contrary, cost-effectiveness ratios were negatively and less strongly correlated to the costs of treatment. A 20% increase of the costs of treatment led to a 2% decrease of the cost-effectiveness ratio for 20 years of biennial screening and a 20% decrease of the costs of treatment entailed a 4% increase of the cost-effectiveness ratio (Berchi). A stronger sensitivity of results to test costs and in a lesser extent to treatment costs is in line with previous findings.

Sensitivity analysis on the applied discount rate was performed in the French study. However, only costs were discounted at several rates. Benefits were not involved. When the costs were not discounted, less favourable ICERs were provided. The corresponding figures after 10 and 20 years of screening were respectively €4141 (instead of €2980) and €8.983 (instead of €7458).(Berchi)

As for the studies comparing FOBT with no screening, the periodicity of screening provides better cost effectiveness results for biennial screening compared to an annual screening program. The average costs per life-year for the unhydrated Hemoccult II test of €2275 (17.500DKK) at a 2-year screening interval rose slightly to €2730 (21.000DKK) when the screening interval was one year (Gyrd-Hansen, 1998b).

Rather surprisingly, and in contrast to other studies including campaign costs, one study mentioned the incremental cost-effectiveness ratios were positively correlated to participation rates. In the study of Berchi, a decrease in participation from 43,7 to 20% led to a 50% decrease in incremental cost effectiveness ratios, and an increase in participation to 60% led to a 1,3-fold higher incremental cost-effectiveness ratio for 10 years of biennial screening and a 1,5-fold greater for 20 years of screening.

When sensitivity and specificity were analysed, specificity again seemed to be a very important determining factor for cost effectiveness results. The incremental cost of introducing the rehydrated H-II test could be as low as €5200 (40.000DKK) or as high as €17.950 (138.100DKK), depending on whether the specificity is 95,7% or 90,4%. Gyrd-Hansen (1998b) and Berchi both changed sensitivity and specificity while keeping one of the two factors constant. With a 90% specificity and screening lasting 20 years, the cost-effectiveness ratio was €26.107/YLS if sensitivity was taken to be 70%, while it was only €13.102/YLS with sensitivity at 90%. With a 70% sensitivity, the cost-effectiveness ratio was even negative (-€3607/YLS) with a 100% specificity (Berchi), meaning that screening would be cost-saving.

6.3.2.3 FOBT and colonoscopy

Intervention and population

In the following studies, both FOBT and colonoscopy have been analysed. Other screening strategies such as flexible sigmoidoscopy, FOBT in combination with flexible sigmoidoscopy, Double Contrast Barium Enema (DCBE), detection of altered human DNA in a stool test and virtual colonoscopy have also been modelled in these studies. For the scope of our report, however, only results concerning FOBT and colonoscopy are discussed. The included studies are the following: Sonnenberg et al (2000)[495], Frazier et al (2000)[496], Leshno et al (2003)[503], Wong et al (2004)[505], O'Leary et al (2004)[500], Ladabaum et al (2005)[506], Maciosek et al (2006)[507], and Wu et al (2006)[342]. Table A 4.3 provides an overview of these studies.

Whereas in the studies comparing FOBT with no screening the core scenario was biennial screening, all studies in this part analyse annual screening and only one discusses biennial screening. Similar as before, patients with positive FOBT results undergo colonoscopy and in the case of normal results, annual FOBT is resumed 10 years after colonoscopy. Follow-up varies across studies depending on, for example, whether or not a distinction is made between small and large adenomas. If an adenomatous polyp is found, surveillance colonoscopy is repeated every 3 years until they are no longer found (Sonnenberg), or 5 years for patients with small adenomas (Wu). If a high risk polyp or colorectal carcinoma is detected, then polypectomy or surgical resection is performed and surveillance colonoscopy is done a year later (Leshno). With respect to the colonoscopy screening strategy, colonoscopy is performed every 10 years. Two studies also analysed a once-only colonoscopy scenario (Leshno, Frazier).

Concerning the target population, all but one start screening at the age of 50 and no subgroup or incremental analysis with respect to age categories were performed.

Cost items

As in previous parts, we first mention the costs for FOBT and colonoscopy. For FOBT, not all studies explicitly mentioned which type of test was included in their study. Sonnenberg included a cost of €2,8 ($3,5) for a nonhydrated test. Wong included a cost of €5 (SGD10) and €15 (SGD30) for respectively guaiac and immunochemical FOBT. O'Leary took into account a cost of €15,8 (AUD16,4) for a rehydrated test. Frazier did not make a difference between the cost of rehydrated and unrehydrated FOBT (€30/$38). The other two US studies took into account an amount of €15,8 ($20) and €14,2 ($18) (Ladabaum and Maciosek). In the Israeli study, the cost was €7,2 (40ILS) (Leschno). An extremely low cost of €0,5 ($0,6) was used in the Taiwanese study (Wu). Concerning colonoscopy, included costs for the US and Australia are in the same range of €450 - €650, with one exception of about €800.[l] Costs in the Singapore, Israeli and Taiwanese studies were lower at respectively €370 (SGD740), €144 (800ILS) and €52 ($66) (Wong, Leshno, Wu).

With respect to the costs of a national screening campaign, only the Australian study mentioned to include an administration costs for the program of €45 (AUD75) per invited person (O'Leary).

The costs for colorectal cancer treatment were included in different ways. Sonnenberg included a more general cost of €35.730 ($45.228) without making a distinction between several cancer stages. Frazier, Leshno and Ladabaum differentiated costs for localized, regional, and metastasised colorectal cancer treatment. These costs were relatively much lower in the Israeli study in comparison with the US studies.[m] In the Taiwanese study, cost for early and late CRC, and terminal costs for CRC were respectively €2460 ($3118), €6090 ($7706), and €6040 ($7647). Wu, O'Leary and Wong differentiated between stages A, B, C and D colorectal cancer with completely different costs. Whereas in the Singapore study, costs were €10.000 (SGD20.000) for treating stage A and B cancer and €17.500 (SGD35.000) for stage C and D, this was respectively about €9190 (AUD15.318), €17.880 (AUD29.804), €13.810 (AUD23.021), and €3360 (AUD5596) for stage A to D cancers in the Australian study. O'Leary also mentioned costs separately for surgery for adenoma removal, chemotherapy, and radiotherapy. However, in their model it seems they used aggregated costs per stage. The study of Maciosek used an alternative, but less transparent, approach of net costs. These net costs were the value of resources used in providing the preventive service plus any follow-up services, minus the resource savings from averted disease or injury. This aggregated approach did not mention treatment costs separately.

Whereas the majority of the previous mentioned studies forgot to include costs caused by complications, six studies explicitly included them in this part. However, as for treatment costs, big differences are observed. Whereas Ladabaum includes a cost of €20.540 ($26.000) for endoscopy complications,

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[l] $696 = €550 (Sonnenberg), AUD897 = €538 (O'Leary), $820 = €648 (Ladabaum), $572 = €452 (Maciosek). $1012 = €799 (Frazier).

[m] Costs for localized, regional, and distant colorectal cancer treatment are respectively €17.380 ($22.000), €34.680 ($43.900), and €46.050 ($58.300) (Frazier); €7920 (44.000ILS), €15.300 (85.000ILS), and €30.600 (170.000) (Leshno); €36.340 ($46.000), €53.720 ($68.000), and €56.090 ($71.000) (Ladabaum).

this is exactly half this amount for perforations (€ 10.270), and only about €3450 ($4360) for bleedings in another US study (Sonnenberg). In the Australian study, a similar cost of €9460 (AUD15.777) is incorporated for perforations (O'Leary). Again, costs are much lower for the Israeli, Singapore and Taiwanese studies, i.e. respectively €2700 (15.000ILS), €4350 (SGD8706), and €1278 ($1618) (Leshno, Wong, Wu).

Finally, only Maciosek adjusted calculations for time costs which amount to €86 ($109) for annual FOBT and €43 ($55) for colonoscopy performed every 10 years.

Cost-effectiveness ratios

For providing a correct overview of the most cost effective interventions, screening strategies not being considered as an option for the current Belgian situation are also provided in this part since several of the included studies analyse a wider range of strategies.

In the study of Sonnenberg, and under base-case conditions, the ICER of colonoscopy compared with no screening was only slightly greater than that of FOBT compared with no screening, i.e. about €8675 ($10.983) versus €7670 ($9705). Compared with annual FOBT screening, colonoscopy costs more but also saves more life-years at an ICER of €8990 ($11.382) over FOBT. Guaiac FOBT was also the most cost effective test in the Singapore study with an incremental cost of €81 (SGD162) per life year saved. The third study in favour of FOBT was the US study from Ladabaum with an ICER of €6400 ($8100) per life-year gained for FOBT and €14.850 ($18.800) for colonoscopy when comparing both strategies to no screening. In the Taiwanese study, both FOBT and colonoscopy screening were dominant when comparing to no screening (Wu).

The Australian study of O'Leary provided less favourable results for rehydrated FOBT. When comparing with no screening, the incremental cost per life-year saved were €24.710 (AUD41.183) and €28.140 (AUD46.900) for biennial and annual FOBT screening, respectively. This was only €10.080 (AUD16.801) for flexible sigmoidoscopy screening and €11.570 (AUD19.285) for colonoscopy screening, both performed every 10 years. Frazier also provided most favourable results for sigmoidoscopy. Screening strategies without sigmoidoscopy were excluded by simple or extended dominance.

Maciosek estimated the cost-effectiveness ratios to €10.530 ($13.300), €14.900 ($18.900), and €6980 ($8800) per life year saved for respectively FOBT, sigmoidoscopy and colonoscopy. This provided an estimate of €9440 ($11.900) per life year saved based on a weighted average which reflected the current relative delivery of FOBT (48%), sigmoidoscopy (9%), and colonoscopy (43%) in 2003.

Leshno reported completely different results. Only two strategies, i.e. one time colonoscopic screening and annual FOBT in combination with flexible sigmoidoscopy every 5 years (FOBT+SIG), were on the efficiency frontier.[n] FOBT+SIG had an ICER of €228 (1268ILS) per life-year saved compared to one time colonoscopic screening. Other strategies were eliminated by simple dominance.

n The authors mistakenly used the term 'cost-effectiveness frontier' instead of 'efficiency frontier.

Sensitivity analysis

Rather surprisingly, Wong did not perform sensitivity analysis on his cost effectiveness outcomes and Ladabaum only performed such an analysis on the demand for health services. Three studies did not perform sensitivity analysis with respect to FOBT or colonoscopy compared to no screening. The Israeli study only performed sensitivity analysis on the ICER of colonoscopy compared with FOBT+SIG, the Taiwanese study identified the influential parameters on the ICER for stool DNA testing compared with no screening, and Frazier performed the analysis on the ICER of rehydrated FOBT with 5-yearly sigmoidoscopy versus no screening.

O'Leary performed a sensitivity analysis on costs. The cost of the screening program was an important determinant of the cost-effectiveness of FOBT. The ICER of biennial FOBT screening was increased slightly from €24.710 (AUD41.183) to €29.295 (AUD48.824) if administrative costs for the screening program increased from €45 (AUD75) to €60 (AUD100) but decreased dramatically to €9455 (AUD15.758) if these costs were omitted. With respect to discounting there were no surprising results, i.e. outcomes were better when not discounting the benefits, the opposite happened for costs, and there was a relatively larger influence on the ICER of discounting benefits compared to costs.

Only two studies performed sensitivity analysis changing screening intervals. O'Leary already compared annual and biennial FOBT screening in their base analysis, which provided better cost effectiveness outcomes for the 2-yearly screening schedule. Sonnenberg changed both the frequency of FOBT and colonoscopy. If the frequency of colonoscopy is increased to once every 5 years, the incremental cost-effectiveness of colonoscopy compared with FOBT increases from a baseline value of about €8990 ($11.382) to €21.750 ($27.529). In combination with a lower efficacy (50% instead of 75%) and an 80% compliance (instead of 100%) the ICER would even increase to about €43.100 ($54.561). Shortening the interval of repeated colonoscopy also affects the ICER of FOBT which increases from €7670 ($9705) to €16.390 ($20.746). Reducing the frequency of screening with FOBT from once annually to once every 3 years slightly increased the ICER form €7670 ($9705) to €7775 ($9843), as costs savings became partly negated by fewer life-years saved through early cancer detection (Sonnenberg).

Furthermore, according to Sonnenberg, FOBT is particularly sensitive to changes in the compliance rate of repeated testing because it is done more frequently than colonoscopy. For instance, a decrease of compliance with annual test repetition to 90% (base case 100%) increases the ICER of FOBT to about €11.680 ($14.788) (base case €7670 ($9705)). Low compliance with colonoscopy after a positive result on FOBT also renders the initial screening technique less efficacious and increases its associated costs per saved life-year. If only 75% (base case 100%) of positive FOBTs were followed by colonoscopy, the incremental cost-effectiveness ratio of FOBT would increase to €8120 ($10.281). Also in the study of O'Leary, ICERs improved if compliance increased. Finally, Maciosek found that adherence was less influential on results than gains in life expectancy and net costs. However, exact outcomes were not presented.

Sonnenberg also analysed the influence of changing test characteristics. Improvement of test sensitivity results in detection of cancers at an earlier stage and reduced mortality from colorectal cancer. Improved specificity results in

fewer colonoscopies performed after false positive results on FOBT. Within the ranges tested in the sensitivity analysis, the overall influence on the ICER exerted by the sensitivity or specificity of FOBT did not exceed €1580 ($2000).

6.4 CRITICAL APPRAISAL OF THE STUDIES

In this part, we will discuss general and some specific problems with the studies included in this overview.

Only two studies performed a cost utility analysis (Whynes, 1998, 1999; Stone). Gyrd-Hansen and colleagues decided to ignore the impact on quality of life (QoL) because it was judged that the main outcome of the screening program was life years gained (Gyrd-Hansen, 1998). The most important reason not to adjust for QoL appears to be that QoL data are not readily available. Whynes evaluated the QoL following surgery for colorectal cancer and found that a QoL coefficient for surviving patients lies within the range 0,948–0,981[509]. These small factors may indicate adjustment would not be expected to have a great impact on results. However, as mentioned by Flanagan, there may also be ethical issues related to the impact of screening on QoL. False positive FOBT results may increase anxiety in otherwise healthy individuals. Screening may adversely affect the QoL, given that cancers are detected earlier. Patients live longer with knowledge of their disease and, further, the life-years gained may not be lived in perfect health. On the other hand, the life-years gained may be lived in less severe states of the disease. Further research to determine the impact of mass screening on QoL is clearly necessary as these data are missing.

The majority of studies have taken the perspective of a third-party payer. Consequently, no indirect costs such as patient time, travel costs, informal carer costs, etc. were included. Also not included were the effects on general consumption and productivity, which would be relevant from a societal perspective[219]. Although these costs should not be underestimated, they are mostly omitted in studies. When included, it would be desirable to present results separately to enhance consistency and comparability across studies. Indirect costs may be a decisive factor if decision makers have no preference based on other included factors.

Transparency is also an issue. Sources of cost data are often not well described. A lack of detail on cost data means it is not always clear which costs have been included. For example, all studies took into account the cost for FOBT. However, it was not always clear if this was just the cost for the test kit, or if the mailing and test analysis were also included. Or, beyond the immediate investigation of positive FOBT results, several studies did not specify the assumed nature or frequency of follow-up investigations.

A limitation to the majority of the studies is that they omitted program-related expenses such as the costs of health promotion, recall systems and extra administrative overheads (Whynes, 1998, 1999, 2004, Helm, Sonnenberg, Frazier, Leshno, Wong, Ladabaum, Maciosek, Wu). Stone argued it was assumed that the program was in steady-state, in order to provide estimates of ongoing annual costs and exclude the higher implementation costs, as well as increased detection of cancer associated with the introduction of a screening program. However, when evaluating a mass screening campaign for colorectal cancer, these costs are real and should be taken into account.

The disutility and potential negative health effects associated with complications of colonoscopy were not included in about half of the studies. If the FOBT result is positive, i.e. a false or true positive, colonoscopy test is performed. This can, however, lead to complications such as perforation or bleedings, or

even in a small percentage of cases, death. Both the influence on benefits and costs should be taken into account.

A very important problem concerns the participation rate and compliance. First of all, some studies, based on their sensitivity analysis, argue compliance did not have a major influence on the ICERs. However, this was due to omitting campaign costs from the analysis. If fixed costs would be included in the analysis, having a high participation and/or compliance would have a positive influence on results because these relatively large fixed costs would be divided over a larger population participating in the screening.

Moreover, the values for participation/compliance rates incorporated in the studies may be questioned. Many studies used 100% compliance in their base case analysis. This obviously does not reflect reality and therefore results should be interpreted with caution. From the studies comparing FOBT to no screening, the core scenario was characterized by biennial screening with a 60-67% participation in the first screening round and about 90% participation in subsequent screening rounds and compliance follow-up by colonoscopy. These numbers are based on population based randomized controlled trials. It is difficult to assess, however, how participation and compliance with an advertised national screening program could be expected to behave. As mentioned by Flanagan, participation rates in organized breast cancer screening programs in Canada in 1997–98 were well below the target of 70%, with estimates ranging from 12% to 55% across provinces after as much as 10 years of program implementation[516]. Also Helm referred to a review which concluded that even the most intensive strategies in well defined populations rarely increase FOBT participation to more than 50% of the eligible population[403]. This uncertainty has not been tackled extensively in most studies.

Uncertainty in general was handled poorly. The models tried to reproduce mean estimates but did not take into account the full uncertainty on the input data as for example reported in the original RCTs. In addition, almost all studies performed one-way sensitivity analysis. As a result, the influence of combined uncertainty in the input variables (test characteristics, compliance, test costs, campaign costs, health benefits, etc…) was not taken into account. A few multi-way sensitivity analyses were presented and show the major influence of changing several factors at the same time. Unfortunately, none of the studies performed probabilistic sensitivity analysis applied on all input variables at the same time, which should be part of an economic evaluation according to the Belgian guidelines[517].

Another problem relates to the comparability of study results: differences in cost items included, country variations in cost levels, possibly different cost estimation methods, year of pricing, different discount rates, etc. Costs for the included variables in the US studies are, for example, much higher than in the Singapore, Israeli or Taiwanese studies. Special attention should be paid at the costs of testing and discount rates on benefits since, according to the one-way sensitivity analysis, they have a large impact on results. Fortunately, almost all studies discounted health benefits and costs. With regard to transferability to the Belgian situation, cost data are within the ranges mentioned in most of the studies, i.e. €539 for diagnostic colonoscopy, €568 for colonoscopy and biopsy, and €656 for colonoscopy in combination with polypectomy. FOBT costs in Belgium are €2,06 for the test kit or €44,47 with inclusion of development cards and two GP visits.

The studies included in the first part of our overview, comparing FOBT with no screening, based compliance rates on RCT data. All results indicate that

screening individuals in a target population between 50/55 and 74 years of age is cost effective. Results may, however, overestimate cost effectiveness in real-world conditions. First of all, as mentioned before, participation and compliance in real-world settings are often lower than in RCTs. Secondly, several studies have not explicitly included campaign costs and/or impact of complications (Whynes, 1998, 1999, 2004; Gyrd-Hansen, 1998, 1999; Helm, Lejeune).

From the studies comparing guaiac FOBT and immunochemical FOBT, the US study[499] cannot have direct policy implications. The major limitation of this study is the use of a hypothetical immunochemical FOBT with properties that do not currently exist amongst immunochemical FOBTs[219]. This hypothetical immunochemical FOBT was assumed to have comparable sensitivity to Hemoccult SENSA but with higher specificity. Furthermore, 100% compliance was assumed. Based on other aspects such as compliance and including campaign costs the French study[504] is the most complete one. Both the Danish and French study (Gyrd-Hansen, 1998b; Berchi, 2004), however, provide better cost effectiveness results for gFOBT than for iFOBT.

From the studies in the third part, i.e. assessing both FOBT and colonoscopy as a screening strategy, Sonnenberg, Leshno and Wong applied a 100% compliance rate in the base case which does not reflect real-world conditions. Furthermore, all but one, i.e. O'Leary, did not explicitly include campaign costs thereby overestimating cost effectiveness of screening campaigns. The cost-effectiveness estimates presented by Maciosek focus only on the average ICER of offering patients a choice of CRC screening tools rather than on the incremental value of each screening tool relative to another or compared with no screening. Compliance levels were also assumed to be the same, whatever the strategy chosen. Only O'Leary both included program administration costs and reasonable compliance levels, i.e. 60% for FOBT and 42% for colonoscopy. Looking at other aspects of the study, they have also included costs of complications and distinguished treatment costs according to stage of colorectal cancer. The only major problem with this study is that they evaluated against rehydrated FOBT, as most studies in this part did, while it is clear from the studies on gFOBT that cost effectiveness results are in favour of unrehydrated FOBT.

6.5 CONCLUSION

Which screening test is most appropriate is function of several factors such as the acceptability and safety of a test, the evidence for its clinical effectiveness, as well as economic considerations.

Until now, only guaiac–based FOBT has been the subject of large RCTs with published results on clinical outcomes and on costs. Based on the point estimates from economic studies, unrehydrated Hemoccult II test, followed by colonoscopy for subjects with positive FOBT results, is a cost effective option. Results also show that a screening program based on gFOBT is likely to be more cost effective than iFOBT. The high specificity, which avoids unnecessary colonoscopies, seems to be a determining factor for cost effectiveness. If more favourable evidence is provided for other types of FOBT, they may become an alternative in the future.

Concerning the periodicity of the program, biennial screening is more cost effective than annual screening and the implication of periodicity on logistic requirements should not be underestimated. With respect to the target population, CRC screening is mostly proposed to subjects aged 50-74 years. It should be mentioned, however, that a screening program starting later, for

example at age 55 rather than the commonly mentioned 50 years, would be more cost effective.

In the presence of scarce resources, a sensible decision-making process taking into account economic considerations is necessary. The combination of a widening of the target population and increasing the periodicity of screening can have a large impact on budgets and necessary capacity in a country. A trade-off between health gains and costs, both considering acceptability and affordability, is therefore necessary. To be able to provide the best available trade-off, investigation of age, periodicity and the other influential factors in a pilot program is recommended before implementing a full national program.

Key messages

gFOBT

- **All available economic evaluations show that annual or biennial gFOBT followed by colonoscopy for screen positive participants is a cost effective intervention. However, estimates for the Incremental Cost Effectiveness Ratio (ICER) range from approximately 2000 € per Life Year Gained to 30.000 € per Disability Adjusted Life Year in a young target population.**
- **ICERs for gFOBT are mainly sensitive for the frequency of screening (biennial testing has better ICERs than annual screening), sensitivity and specificity of the test (the less sensitive but more specific non-rehydrated test had better ICERs than the more sensitive rehydrated test), and for the cost of testing.**
- **Choosing the right target population for gFOBT mass screening has an important influence on the ICERs: best ICERs are obtained at ages between 55 and 74. Below and above these ages ICERs are less favourable.**
- **The ICERs are very dependent on participation and compliance if program costs are included in the economic evaluation.**

iFOBT

- **There is no evidence for a better ICER from any of the studied iFOBT tests vs. gFOBT, when comparing screening strategies to no screening.**

Colonoscopy

- **All economic evaluations of colonoscopy as a screening tool are based on overly optimistic and unrealistic assumptions (especially regarding compliance).**

7 ORGANISATION OF COLORECTAL CANCER SCREENING IN VARIOUS COUNTRIES

7.1 INTRODUCTION

In 2003 the European Commission recommended to use FOBT as a screening tool for colorectal cancer in men and women between 50 and 74[183]. Following this recommendation different pilot programs were launched in several European member states in order to determine the best screening strategy and the feasibility of a national screening program. In some European countries, however, initiatives were already taken at the end of the nineties.

Only a few countries have adopted colorectal cancer screening as a public health policy. In several countries such as Germany, the Czech Republic, France, and the UK, FOBT screening or screening by endoscopy as a population screening has been introduced on the regional level. Several countries have programs conform the EC recommendations; others have ignored these recommendations and offer colonoscopy or sigmoidoscopy as a screening tool.

Also outside Europe, national colorectal cancer screening guidelines gave birth to several initiatives.

In this chapter, an overview of screening programs, pilot studies or public health programs in and outside Europe will be given. Recommendations and guidelines with regard to surveillance programs for high risk groups have been described in a previous chapter. As far as particular organised surveillance programs for high risk groups exist, they will be highlighted in this chapter. Information was collected from national and/or local governmental websites, and from private agencies when relevant. In order to validate or add to this information, contact was made with one or more experts in the specific country.

Table 28 summarizes the available screening programs and pilots in different countries.

Table 28: overview of CRC screening programs in various countries.

Countries	National/regional program/pilot	Time interval	Test (options)	Age	Participation %
Netherlands	Pilot	2 yearly	Comparison 2 FOBT's (Hemoccult II and OC-Sensor mu)	50-74	/
Finland	Nat. Prog.	2 yearly	FOBT (unrehydrated Hemoccult II)	60-69	75 % (2005)
Germany	Reimbursement rules	FOBT: annually Colonoscopy 10 yearly	FOBT or Colonoscopy	50-54 =>FOBT 55+ => colonoscopy	/
Scotland	Pilot	2 yearly	FOBT	50 - 69	2000-2003: 55 % 2003-2005:53 %
Czech Rep.	Nat. Prog.	2 Yearly	FOBT	50+	20% (2004)
France	Pilot	2 yearly	FOBT	50 -74	26% (2004)
UK	Nat. Prog. (2006)	2 yearly	FOBT (Hemoccult II)	60-69	2000-2002: 58,5 % 2003-2005: 51,9%
Australia	Nat. Prog.	2 yearly	iFOBT	55-65	45 %
Canada	Pilots	2 yearly/ annually	FOBT (unrehydrated Hemoccult II)	50-74	
Italy	Regional programs	/	- Lombardia: biennial FOBT	Lombardia: 50-74	29 % (2005)
			- Piemonte: FS or biennial FOBT	Piemonte: 59-69 (FOBT); 58 (FS)	
			- Toscana: biennial iFOBT	Toscana: 50-70	51,9 % (2004)
			- Valle d'Aosta: biennial iFOBT	Val d'Aosta: 50-74	59 %
			- Emilia-Romagna: biennial FOBT	Emilia-Romagna : 50-69	
			- Umbrië: FOBT	Umbrië: 50-74	
			- Veneto: biennial FOBT/ FS	Veneto: 50-69 (FOBT); 60 (FS)	69,5 % (2005) : FOBT 48 % : FS
USA	Regional Programs	/	- Annual FOBT	50+	
			- FS every 5 y		
			- Annual FOBT +sigmoidoscopy every 5 y		
			- DCBE every 5-10 y		
			- Colonoscopy every 7 to 10 y		

7.2 THE NETHERLANDS

7.2.1 Average risk groups

In accordance with the advise of the Dutch National Health Council[3], the national colon carcinoma screenings trial workgroup (COCAST)[518], the Dutch cancer society working group on colon cancer[519] and the Dutch program for cancer control[520], a pilot project for colorectal cancer population screening has been launched on 31 may 2006 for the regions Amsterdam and Nijmegen and will last for approximately one year[o]. The aim is to implement a FOBT screening program in two comprehensive cancer centres[521] and to measure the effectiveness of the screening program. Within the pilot project 2 different FOBT's (Hemoccult II and oc-Sensor mu) will be compared to determine which one is the most appropriate to screen the Dutch population. Additionally, the project aims at finding out how to improve the screening protocol and how population screening for colorectal cancer in the Netherlands can be best organised[2].

The target group includes asymptomatic individuals between 50 and 74. A total of 20.000 individuals from the above mentioned regions will be invited to participate in this pilot.

Participants will receive an invitation letter accompanied by an FOTB test, operation instructions and a leaflet. The FOTB test can be done at home and has to be sent to the laboratory in a postage–free envelope for analysis. Each participant receives a written result within 2 to 3 weeks. Whenever the result is positive, the participants' GP will receive a copy of the result, and the participant will be informed that the GP also received this result. Participants with a positive result are invited for a consultation with a physician–researcher or a nurse–researcher in the research unit Amsterdam[522] or Nijmegen[523]. Advice on the interpretation of the result and guidance on advisable follow-up examinations will be given to the participant. The advised follow-up for participants with a positive result is through colonoscopy.

Following the second advice of the above mentioned committees, there's a current study proposal to directly compare FOBT with sigmoidoscopy[524]. The aim of the study is to evaluate the attendance and feasibility of the two forms of FOBT (a replication of the Dutch FOBT implementation trial in a different setting), to evaluate the attendance and feasibility of sigmoidoscopy for screening and to compare the two forms of FOBT and sigmoidoscopy.

In november 2006 a one year pilot population screening project starts in the region of Rijnmond (Rotterdam and neighbouring villages)[525]. 15.000 men and women aged from 50 to 75 years will be invited for colorectal cancer screening. The aim of the project is to find out which method is the most appropriate for a colorectal population screening program. Therefore individuals from the target group are randomly allocated into 3 groups. Two groups will receive a home test kit with 2 different FOBT's for each group. The third group will be invited for sigmoidoscopy. Results are expected by the end of 2007.

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[o] The project is a collaboration of the departments stomach-, bowel and liver diseases of the Academic Medical Centre Amsterdam (AMC), the universitary Medical centre St Radboud Nijmegen (UMCN), the integral cancer centre Amsterdam (IKA) and the integral cancer centre East (IKO). The project is financed by ZonMW, the Netherlands organisation for health research and development

7.2.2 Groups at increased or high risk

High risk groups represent approximately 15 % of colorectal cancer cases in the Netherlands. Periodic surveillance colonoscopies are being performed in people at increased or high risk:

- Carriers of genetic mutations such as Hereditary NonPolyposis Colon Cancer (HNPCC) and Familial Adenomatous Polyposis (FAP)
- Family risk of colorectal cancer
- Individuals suffering from diseases that are linked to an increased risk for colorectal cancer (personal history of CRC, Crohn and Colitis Ulcerosa)

There's a registry-guided surveillance program used by the Dutch Hereditary Colorectal Cancer Registry. Personal and family data, pathology reports, and treatment outcomes are collected for this registry. The family physician is responsible for maintaining surveillance among the family members.

STOET[526] aims at the prevention of hereditary cancer tumours. Families at risk for hereditary cancer have to be referred to a "Polikliniek Erfelijke Tumoren" by the GP or a specialist. If their risk status has been confirmed by a geneticist this can be registered at STOET. If family history shows that a person is at high risk, he/she will be advised to get examined annually or every two years, and for individuals older than 60 every five years. Mostly examinations will start between the age of 20 and 25. The relative at risk will be referred by the GP to get a policlinical consultation with a gastroenterologist, an internist or a surgeon. In a first consultation the advisability of regular preventive examinations will be discussed. The periodic examination could be either colonoscopy, or sigmoidoscopy combined with a double contrast barium enema.

7.3 FINLAND

7.3.1 Average risk groups

In Finland, the Ministry of Social Affairs and Health made a recommendation in 2003 to the municipalities to run a randomized feasibility study with FOBT (unrehydrated Hemoccult – II) screening for colorectal cancer as a public health policy that is repeated every second year[527]. Health care in Finland is decentralised, organised by municipal authorities. It is up to them to decide whether to start colorectal cancer screening. The municipals also pay the actual screening costs. The organisational costs are centrally paid.

For the first six years of introduction, each age cohort is randomized to screening or "the usual care" (no screening) at the age of 60-64 years. The program is a centralized public health policy with gradual or stepped initial phase covering 15% of the municipal specific population in the first year and 50% in the sixth year. In 2004 the first 23 municipalities started with more than 5.000 screened individuals in a target population of 35.000. The individuals are selected by random sampling from the population register for invitees and controls by municipality and by birthcohort. The ultimate target population is approximately 500.000 individuals at 60-69 years of age. Screening is being gradually expanded to cover this whole age group. Initially it has focused specifically on 60, 62 and 64 year-olds. The non-invited controls will gradually

be screened only after the six-year implementation period. The effects of screening will be evaluated, comparing the incidence of CRC and the mortality from CRC in those invited to screening with controls. In that way the implementation of colorectal cancer screening in Finland meets the criteria for a randomized controlled trial and the requirements for a public health program. This provided an opportunity to evaluate the program after five years and to further adjust the screening strategy or to implement FOBT.

The screening program uses FOBT (unrehydrated Hemoccult – II), a sample collection procedure performed on three consecutive days. People in the target group receive and return the tests by post. A Colorectal Screening Centre based in the city of Tampere handles the distribution of FOBT's, interpretation of results and contact with people tested. It provides advice and guidance for people whose test results reveal the presence of blood in their stool samples to ensure they undergo further testing arranged by their local health centre.

The tests are free of charge for the people being screened. The cost of screening is estimated at 8 euro per invitation including the test and mail charges, analysing the tests and providing the participants with written test results and possible referrals for further examinations. In 2004, 4539 were invited for screening; 75 % participated.

7.3.2 Groups at increased or high risk

Nation-wide preventative colonoscopic surveillance for mutation carriers in HNPCC families has been organized since the early 80's by the Finnish HNPCC registry[528].

7.4 GERMANY

7.4.1 Average risk groups

In Germany there's no national screening program but different screening options are being offered and paid by the statutory health insurance[529, 530]:

- Annual FOBT test for individuals from 50 to 54 years old
- Colonoscopy every 10 years from the age of 55 (since october 2002)

If the individual does not opt for a colonoscopy, the statutory health insurance will refund FOBT every two years from the age of 55.

In 2003, 500.000 patients underwent colonoscopy screening[531].

All examinations are documented. A central institution collects the completed data sheets, and an electronic version of the standardised colonoscopy protocol is being prepared.

Since the implementation of the colonoscopy screening program, the national commission of physicians and health services (Der Bundesausschuss Ärzte und krankenkassen) has formulated a quality handbook with regard to the structure and the screening process[532]. The following standards have been set:

- The performing of colonoscopies is only allowed if permission of the "Kassenärztlichen Vereinigungen" is given
- Colonoscopy needs to be done by skilled physicians (such competent physicians are gastroenterologists, internists with skills in sigmoido/colonoscopy, ...), having performed at least 200 colonoscopies and 50 polypectomies in the 2 years before the request of the authorisation
- For the prolongation of the authorisation physicians have to perform yearly at least 200 entire colonoscopies and 10 polypectomies
- Emergency medical material has to be available
- To assure the quality of hygiene, hygienic-microbiological controls of the cleaning of the endoscope have to be performed
- Solely colonoscopies of the entire colon ("bis zum Zoekum bzw. Ileum") can be accounted for as screening colonoscopies
- The completeness of the examination should be proven by documentation of photographs

A condition for reimbursement of the examination is a documentation on the indication, on the parameters of the process (e.g. the completeness of the examination, polypectomy, entire removal of polyps, complications) and on the result.

In Saarland[533] a study of the "Deutsche Krebsvorschungszentrum" (DKFZ) and The "Centralinstitut für die Kassenärztlichen Versorgung" examines the efficacy of a colonoscopy screening program.

7.4.2 Groups at increased or high risk

There is no organised screening program for high risk groups. For patients at risk such as patients with a positive FOTB test or with a positive family history, a colonoscopy before the age of 56 is recommended and can be repeated earlier than after 10 years if needed[530]. These colonoscopies are also reimbursed by the national health insurance.

7.5 ITALY

In Italy, the regions and self-governing provinces are responsible for the planning of health services. Health care decisions are decentralized while the State must monitor the situation to ensure that all citizens receive essential health services[534]. The "Agreement between State and Regions" of March 2005 set up the National Prevention Plan 2005-2007. Development of mammography, cervical and colorectal screening programs are among the priority objectives. The plan is coordinated by the National Prevention and Disease Control Centre (CCM), within the Ministry of Health[535]. The goal is to overcome the obstacles that have prevented a homogeneous development of cancer screening programs in Italy. Although screening has been shown to be effective in reducing colorectal cancer mortality, there continue to be difficulties in

implementing a standardised program at the national level. Two of the most important issues are the lack of a single scale of priorities shared by all regions, and the differences in organisational capacities. Within each region, the health service is controlled by local health departments (more than 200 nationwide). In some of them the need for cancer screening programs and prevention in general is not considered as urgent a priority as providing assistance to sick patients.

A second problem is related to the organization of screening programs: a multidisciplinary approach is needed in order to have successful programs. Unfortunately there is a lack of collaboration between clinicians and public health services.

Regional screening programs started in Tuscany, Veneto, Piemonte and Basilicata. During 2004, active programs adopting FOBT, FS or a combination of both, increased to 18[536]. The overall attendance rate was 51,3 %[P]; positivity rate was 5,4 % at first and 3,9 % at repeat screening. In the three FS programs the attendance rate was 31,9 %.

The "Centro per lo studio e la prevenzione oncologica" (CSPO)[537] (a scientific institute of the Tuscany region in Italy) analyzes fecal samples within the colorectal screening program performed in the Florence District. The program involves subjects of both genders between 50 and 70 years of age, using a biennial immunologic fecal occult blood test (iFOBT) done at home for the initial screening. The screening program started in 2000. The results from this project demonstrated the feasibility of a biennial FOBT screening program and aims to extend the screening program nationally in 2007[538].

In Veneto[539] screening programs for Colorectal cancer are presently running in 7 out of 22 Local Health Units: in 5 Local Health Units a FOBT strategy was adopted and in 2 Local Health Units sigmoidoscopy screening programs are ongoing. About 30% of the target population is presently covered by screening. Compliance ranges from 54% to 72% in FOBT programs and is about 48% in the FS screening program, started in July 2003.

In Piemonte[540] individuals aged 58 years old are invited to undergo a sigmoidoscopy. Subjects who refuse FS can be screened by biennial FOBT. For the subjects aged between 59 and 69 years at the beginning of the program, biennial FOBT is offered.

In Turin FOBT screening activity started in April 2004 and FS screening started in January 2003. In Basilicata a biennial FOBT screening program for individuals from 50 to 70 started in September 2004[541]. Other regional screening programs exist in Umbrië[542]. Local Pilot projects have been carried out or they are ongoing in Valle d'Aosta[543], in Cremona, Bolzano and in Abbiategrasso (Milan).

7.6 CZECH REPUBLIC

7.6.1 Average risk groups

The Czech Republic ranks high among other countries in incidence and mortality of colorectal cancer. The Czech screening program (2000) has been

[P] The attendance rate was adjusted as subjects reporting that they already had a recent screening test outside the program were excluded. However, there was a small difference between between the absolute and the adjusted attendance rate.

designed according to the EU recommendations and focused on asymptomatic individuals aged over 50, with first FOBT, provided and interpreted by GP's, and if positive patients are referred for colonoscopy performed by a gastroenterologist. The expenses are covered by health insurance[544].

After 4 years the global data show that about 20% of the targeted population participates in the program. 97% of GPs in the country joined the program and 20 % of them reached 50% FOBT coverage of targeted population. The data from practices show that 80-90 % of patients return the test within three months. However, 10-20 % refuse colonoscopy when FOBT was positive.

7.6.2 Groups at increased or high risk

People at high risk of having colorectal cancer are recruited by GPs or gastroenterologists for an early colonoscopy or FOBT testing at age of 40 and further on a yearly basis although the approach can vary individually.

7.7 FRANCE

7.7.1 Average risk groups

In 1998, the "Agence nationale d'accréditation et d'évaluation en santé" (ANAES) recommended in a consensus conference the introduction of an organised screening program for individuals between 50 and 74 years by means of a FOBT test every two years[545]. In 2002, 22 departments (out of 95) have been selected for a pilot project. Following the positive experience in those departments, colorectal cancer screening with FOBT was extended to 50 departments in 2005 and is planned to be nationally implemented by 2007. Between 2002 and 2004, 2.700.000 persons were invited and 716.000 participated (+/ 26%)[546]. The average participation rate in departments with an activity of more than 1 year and having invited more that 80 % of the population of the department was 33 %. It also appeared that the participation rate increases with the duration of the program. In the department Haut – Rhin a participation rate of 53,13 % (2006) was reached [547].

A coupled strategy is used[548]. First, invitation letters are sent to individuals from the target group by a central administration, the "structure de gestion départemental"[549]. An information leaflet and a brief questionnaire are included to the invitation letter in order to identify the persons that have to be excluded from the screening program. Furthermore a self-adhesive label with the identification data is sent to the individual. The individual has to get the test from the GP, who has to explain the objectives of the test to allow the patient to grasp its use and the consequences in case of a positive test result. The test will be realised at the individual's home. Afterwards individuals have to send the test to a central laboratory for analysis[550] (centre de lecture). These laboratories send the test results to the central administration. The central administration forwards the results to the patient and the GP. Those with a positive test result are recommended to undergo a colonoscopy. Individuals who underwent a colonoscopy are excluded from screening for the next 5 years.

If persons did not get tested after the first invitation letter, a reminder with a test is sent by mail by the central administration to those individuals from the eligible target population that did not explicitly refuse to undergo the test. The GP has to indicate the persons that are not eligible to get screened or the persons that refused the test to the central administration. GP's are paid a fixed

amount per package of realised test and for the transmission of the information mentioned above.

The central administration assures the education of GPs, they coordinate the management of the invitations and they register the follow-up of the screened individuals. They gather all the information that is necessary for the evaluation at the national level and they transfer the data to the 'Institut de Veille Sanitaire"[551] that is charged with the evaluation of the screening program at the national level.

In order to guarantee a rigorous organisation of the screening program several quality indicators have been set. There are some requirements in order to be recognised as a central laboratory:

- Personnel that is adequately educated to interpret FOBT
- Performing an internal quality control
- Interpreting the tests following certain modalities (for instance double, simultaneous interpretation by 2 qualified laboratory technicians)
- Guaranteeing that results are sent at last 2 working days after the reception:
    - Having obtained the permission of the post office to store and send the samples
    - Having obtained a convention with health insurance and the "structure de gestion"

GP's receive specific colorectal cancer screening training. Those who don't participate to the education program are excluded from the screenings program.

7.7.2 Groups at increased or high risk

5 groups of persons are excluded from the screening program:

- Persons having had a recent digestive symptomatology should have a coloscopic or other examination offered
- Persons having had a normal colonoscopy less than 5 years ago
- Persons with a history of colorectal cancer or colorectal polyps and that are following a endoscopical control program
- Persons having a parent with colorectal cancer before the age of 65 or having two parents with colorectal cancer. A screening by colonoscopy from the age of 45 (or 5 years prior to age of diagnosis in index case) is recommended
- In case of severe extra-intestinal disease (ethical motive) or if screening is not indicated at that moment (for example in case of depression: ethical and efficacy motive)

7.8 UK

7.8.1 Average risk groups

Several pilot projects[552, 553] have preceeded the national Bowel Cancer Screening Program[554] that was scheduled to start in april 2006 and to be rolled-

out over the next three years. The deadline however could not be met, because it takes about six months to commission the screening centres. A central budget has been announced of 18,5 million € for 2006/7 and 37 million € for 2007/8. However no funding has been provided yet[555]. Uptake, defined as the proportion of those invited who returned an adequate kit in the first phase of screening was 58,5 % in the first round (2000-2002) of the pilot and 51,9 % (127.746 were invited) in the second round (february 2003-april 2005)[556]. Uptake of colonoscopy was 80,5 % in the first round and 82,8 % in the second round.

In the national program men and women aged 60 to 69 registered with the NHS will be invited to take part in FOBT screening every two years. This age range is narrower than in many other countries because of concerns about the capacity of the National Health Service to deliver sufficient numbers of colonoscopies without affecting the symptomatic service[30]. People over 70 can request a screening kit by calling a freephone helpline when the program reaches their area. Five program hubs will operate a national call and recall system to send out fecal occult blood (guaiac FOBT) test kits, analyse samples and dispatch results. The population expected to be covered by each programme hub is 10 million people.

The program hubs will have the following functions:

- Responsibility for up to 20 screening centres
- Call/recall of population for initial screening
- Assembly and dispatch of kits to invited population
- Laboratory – test the returned kits
- Dispatch of test results to individuals within 48 hours of receipt
- Book appointments at specialist screening nurse clinics for people receiving an abnormal result (nurse positive clinics) at local screening centre with result letter within one week of result
- Provide a help line
- Have overview of screening centres/clinic space
- Facilitate polyp surveillance for screening patients

The first screening centres are situated in Wolverhampton, Norwich, Liverpool and Torbay. By March 2007, all five program hubs and around fourteen local screening centres will be established. Screening centres will be selected based on a global rating scale. The parameters are waiting times and patient experience, adequate number of accredited colonoscopists to provide timely colonoscopy per year and ability to offer all patients a colonoscopy within two weeks of a nurse positive clinic appointment. In order to achieve a high level of quality control, a system of accreditation will be introduced[557]. Screening centres will link not only to the program hub but also to local hospitals and cancer centres where the planning will take place for associated treatments such as pathology, surgery, further imaging, oncology and palliative care.

Competence and performance of colonoscopists will be evaluated by submission to a regular audit of practice that will include observation of two colonoscopies by tri-split video. Quality indicators are: a completion rate with photographic evidence of ileo caecal valve > 90 %, an adenoma detection rate of at least 35 %, complete polyp resection of over 90 % of those excised, correct

identification of tumour location in more than 95 % of the cases. Indicators for safety measures are a perforation rate less than 1 pro mille, low post-polypectomy complications such as bleeding and perforation, and low rate of complications requiring hospital admission.

Furthermore a national information technology system, with electronic patient records that incorporate family data and a training program for additional endoscopists, including nurse endoscopists and expansion of overall workforce is being prepared.

GPs are not directly involved in the implementation of the NHS Bowel Cancer Screening Program, but they will be notified when invitations for bowel cancer screening are being sent out in their area. They will also receive a copy of the result letters sent to their patients.

Men and women eligible for screening will receive an invitation letter explaining the program and an information leaflet. About a week later, a FOBT kit will be sent out along with step-by-step instructions for completing the test at home and sending the samples to the hub laboratory. The test will then be processed and the results sent within two weeks.

Different information tools were used in the UK. There was a media campaign[558] with regard to bowel cancer in order to stimulate people to live healthier. The cancer screening program was also announced at the BBC news[559]. Moreover information leaflets and posters that explain stepwise the symptoms of bowel cancer are available[560].

7.8.2 Groups at increased or high risk

Protocols for the surveillance of high risk groups recommending early screening with colonoscopy and genetic counseling or testing for patients with genetic syndromes are available from the NICE cancer service guidance[561].

7.9 SCOTLAND

7.9.1 Average risk groups

The Bowel cancer screening pilot in Scotland started in 2000 in NHS Tayside[562], NHS Grampian[563] and NHS Fife[564]. All individuals aged between 50 and 69 years old and registered at a GP's practice were invited to participate. The pilot is now in its third phase, which is the first phase of national roll-out[565]. A guaiac-based test was used, but in the second round, a sensitive immunological test was employed in a reflex "two tier" approach in an attempt to reduce the false positive rate. In the first round, the participation rate was 55 %, the positivity rate was 2,7% and the cancer detection rate was 2,1/1000 screened. In the second round these figures were 53 %, 1,9 % and 1,2/1000 respectively. In the first round the positive predictive value of a positive test was 12 % for cancer and 36,5 % for adenoma; these fell to 6,8 % and 29,5 % in the second round[566].

In August 2005, the Scottish Executive Health Department (SEHD) announced a new initiative to help tackle bowel cancer, with the roll-out of a national bowel cancer FOBT screening program. The program will commence in 2007 and will be phased in gradually over a 3-year period to all NHS boards throughout Scotland, targeting all eligible individuals (male and female) aged between 50–74 years. With the aim to implement a national bowel screening program, the program will operate from a screening centre based in Dundee, consisting of a call-recall office, laboratory and helpline telephone service for individuals.

Individuals with an overall positive result will be referred to a local hospital where a pre-assessment will be undertaken by an NHS board-based nurse, and will be offered a colonoscopy examination, if appropriate. This arrangement may differ in some areas, for example in island NHS board areas.

The National Screening Coordinator based within National Services Division (NSD) will have a responsibility to monitor and coordinate the screening program; however, the screening program will be integrated with the existing local colorectal services to ensure equity for all patients.

As with all screening services, the national bowel screening program will require to quality assure the service that is provided and should be integral within existing quality assurance procedures and must meet the program's nationally set clinical standards. NHS Boards will be responsible for ensuring the quality and performance of care for the patients within their Board area who are referred for further investigation and treatment.

Bowel Cancer UK has been contributing to preparatory work on the clinical standards being done by NHS Quality Improvement Scotland (NHS QIS)[567]. The draft standards cover key elements of the bowel screening program such as the call-recall system, the screening process, the laboratory process and reporting, pre-colonoscopy and histopathology and the neoplasia yield.

7.9.2 Groups at increased or high risk

Protocols for the surveillance of high risk groups are available from the SIGN guidance on Bowel Cancer. Moreover there's a high risk (HNPCC and FAP) genetics program in place nationwide[568]

7.10 BELGIUM

Today primary prevention of colorectal cancer in Belgium focuses on a healthy life style. In that scope several initiatives have been taken in order to increase awareness. The "Stichting tegen Kanker" and the "Vlaamse Kankerliga" for instance edited several brochures[569] on the prevention of colorectal cancer. More generally the "Vlaams Instituut voor Gezondheidspreventie"[570] offers information on healthy food issues.

A national screening program for colorectal cancer screening has not yet been implemented. There are, however, emerging initiatives in the Flemish community to set up pilot projects in order to study the feasibility of colorectal screening in Belgium.

Nowadays screening for colorectal cancer is disparately performed in several hospitals. The Saint-Joseph hospital (Liège)[571] for instance promotes virtual colonoscopy as a screening technique for people older than 50.

In a consensus meeting on colorectal cancer screening, the Belgian gastro-enterologists advocated the implementation of population screening for colorectal cancer in line with current national and European cancer screening programs. They recommended that mass screening should be made annually by FOBT(Hemoccult) test in all Belgian people ≥ 50 years old (except for increased risk categories). Colonoscopy is recommended as follow up in case of positive tests or in people at increased or high risk.

7.11 AUSTRALIA

7.11.1 Average risk groups

Efforts leading to a national screening program started in 1989 when professional bodies collaborated in drawing-up guidelines for screening and surveillance for colorectal cancer. An evidence-based consensus process undertaken in 1996 and 1997 recommended that the evidence supporting population screening justified consideration of screening as part of formal health policy but that issues around the detail of the screening process and its feasibility needed to be addressed[572]. After a special allocation of funds from the government in 2002, the federal department agreed to plan a pilot screening program involving nearly 70,000 individuals aged 55 to 74 at three sites: parts of Melbourne and Adelaide and in Mackay, Queensland[573].

Results of the pilot were formally analysed and reported to the government in 2005[574]. Many of the outcomes of the pilot were positive, including: population participation at 45%, referral to colonoscopy after a positive test at 95%, waiting time for colonoscopy after positive test at median 30 days, caecal intubation rate at colonoscopy at 95%, incremental cost per life year saved of $22,000. Data collection processes, however, were not complete.

As a consequence it was decided that in late 2006, a formal national screening program would start[575]. Initially, screening utilising Fecal Occult Blood Tests (iFOBTs called ' Bayer Detect™) will be offered to Australians turning 55 or 65 years of age on a biennial basis, and those who participated in the successful pilot program that ran from November 2002 to June 2004. The test will be mailed directly to eligible participants by a national register, will be free of charge, will be performed at home and returned by mail. If the person returns a positive test, has symptoms or is identified to be at high risk, they will be directed to the primary care practitioner to organize appropriate action, usually colonoscopy through usual-care processes. There will be a single national registry[576] that tracks outcomes across the whole screening pathway and adherence to the pathway will be closely monitored. Mainstream health services will be used wherever feasible.

An evaluation of the national bowel cancer screening program will be completed prior to the 2008 budget with the aim of extending bowel cancer screening, if successful on clinical grounds, to all Australians over 55 and Indigenous Australians over 45 years of age.

In June 2006 the Australian Government minister for Health launched a media campaign "It's Crunch Time"[577] targeting employers and retail outlets. It's Crunch Time targets employers and community to help raise awareness of the early warning signs of bowel cancer. The aim of the initiative is to prevent bowel cancer through early detection and increased public education and awareness of the risk factors associated with the disease.

7.11.2 Groups at increased or high risk

Registries provide a useful focal point for coordinating the management of high risk groups for colorectal cancer. It is difficult for any individual practitioner to offer comprehensive management that is family-based and provides continuity of support to successive generations, encompassing diagnosis, genetic counseling/testing, cancer screening and treatment. Therefore several State-based familial cancer registers have been established in Australia. These facilitate the management of familial colorectal cancer by providing or supporting the maintenance of a meticulous, confidential and secure database on behalf of the present and future generations of a family, the liaison with relevant health care professionals, providing educational support and counseling, coordinating genetic counselling and testing etc.

The Familial Cancer Program is a state-wide service providing a comprehensive service to families with a history of breast, ovarian, colorectal and other related cancer syndromes[578]. The program, run by genetic services of Western Australia incorporates counselling, education, genetic testing and management for individuals/families with a history of cancer

7.12 USA

Currently there is no national screening program in the USA. A recent study of the Centers for Disease Control and prevention (CDC) demonstrated that approximately 41,8 million average-risk people aged 50 or older have not been screened for colorectal cancer according to national guidelines. The U.S. health care system has enough capacity to conduct widespread screening of the unscreened population, using FOBT and diagnostic colonoscopy for those with a positive FOBT. Currently, 18 states require coverage of colorectal cancer screening tests[579]. A few other states require that they be offered or available throughout Medicare Supplemental policies. Many states refer to the guidelines of the American cancer society and from the age of 50 years onward, individuals without family history or hereditary risk should have five different screening options:

- Annual FOBT test with their GP. If the test is positive, the follow – up should be a colonoscopy
- Flexible sigmoidoscopy every 5 years
- Annual FOBT + sigmoidoscopy every 5 years
- Double contrast barium enema every 5-10 years
- Colonoscopy every 7 to 10 years

To increase colorectal cancer screening, in August 2005, the CDC awarded cooperative agreements to five sites to establish colorectal cancer screening demonstration programs for low-income U.S. men and women aged >50 years who have inadequate or no health insurance coverage for colorectal cancer screening. Screening services in these programs are expected to begin by early April 2006.

The demonstration program sites are:

- Statewide: Nebraska Department of Health and Human Services[580] : primary screening with gFOBT; colonoscopy for high risk persons and for follow-up of positive gFOBT with a focus on African – American population
- County-based: the Research Foundation of SUNY at Stony Brook, New York (Suffolk County): primary screening with colonoscopy
- County-based: Seattle and King County, Washington (Seattle and King County): primary screening with gFOBT; colonoscopy for high risk persons and for follow–up of positive gFOBT with a focus on American – Indian population
- City-based: Missouri Department of Health and Senior Services (St. Louis): primary screening with gFOBT; colonoscopy for high risk persons and for follow-up of positive gFOBT with a focus on African – American population

- City-based: Maryland Department of Health and Mental Hygiene (Baltimore)[581]: primary screening with colonoscopy with a focus on African – American population

The program sites also will provide diagnostic follow-up; conduct public education and outreach; establish standards, systems, policies, and procedures; develop partnerships; collect and track data; and evaluate the effectiveness of the demonstration program.

CDC also provides funding to 21 state programs to implement specific colorectal cancer prevention strategies through National Comprehensive Cancer Control Program[q] (NCCCP)[582] initiatives. In that scope the Northwest Ohio Colorectal Cancer Task Force[583] developed and promoted two colorectal cancer screening clinics in Lima. St. Rita's Med-Care Health Clinic screens largely indigent, uninsured, and underserved patients, including referrals from the Allen County Community Health Center. Screenings at this location are subsidized by St. Rita's Medical Center, the Lima hospital that owns the clinic. Insured patients are screened at the West Central Ohio Surgery and Endoscopy Center, which is affiliated with a local gastroenterology group practice. Clinic patients can obtain screening services via physician referral or self-referral; the goal of the clinics is to screen each patient within 2 weeks of his or her referral, a wait far less than that experienced in many parts of the United States.

The CDC recently funded the Cancer Research and Prevention Foundation to assist 14 states in the delivery of a 1-day colorectal cancer Dialogue for Action conference. These conferences are designed to encourage attendees to work with providers, healthcare systems, and the public to address barriers to colorectal cancer screening in their states.

Several educational and promotional efforts have been undertaken. CDC created and implemented the Screen for Life: National Colorectal Cancer Action Campaign[584] to promote colorectal cancer screening among all persons aged >50 years and encourage them to discuss screening options with their health-care providers.

On the local level too, poster campaigns[585] and television spots have been used to raise and/or increase awareness. During the months of march and april there is specific attention for bowel cancer. Several campaigns offer a free FOBT test[586].

7.13 CANADA

7.13.1 Average risk groups

Based on a 2002 technical report that acknowledged that there would be potential benefits to a national colorectal screening program the Canada's National Committee recommended that colorectal cancer screening should be made available in an organised and structured environment and under the following conditions:

- Clear, concise and understandable information for patients and physicians on the risks and the benefits of screening and on the administration of the test

[q] collaborative process through which a community and its partners pool resources to promote cancer prevention, improve cancer detection, increase access to health and social services, and reduce the burden of cancer.

- Informed consent following personal consultation with family practitioner or equivalent
- Standardised protocols and procedures with a single entry test and options for follow-up
- Systematic tracking and evaluation of all screening invitations (if used, testing frequency, results (including false positive and false negative rates), follow-up, and outcomes)

Based on current evidence, the National Committee recommends,

- Screening be offered to a target population of adults aged 50 to 74 years of age, using unrehydrated Hemoccult II or equivalent as the entry test
- Individuals be screened at least every two years**,** recognizing that annual screening would have slight improvement in mortality reduction over biennial, but require increased resources
- Positive tests be followed up by colonoscopy, with options of barium enema and flexible sigmoidoscopy where appropriate (e.g. patient preference/availability of services)

Despite the recommendations of the National Committee the government has not yet adopted a national screening program[587]. There was however a pilot program in Alberta offering biennial screening to individuals over 50[588]. In order to implement the recommendations of the National Committee, the Alberta cancer board has hosted an expert panel involving representatives from several disciplines, including representatives from Alberta Health and Welness and the two large regional health authorities in the province.

Almost half of the colorectal cancers of Canada are located in the province of Ontario[589]. Cancer Care Ontario, in collaboration with the Ontario Ministry of Health and Long-Term Care, the Institute for Clinical Evaluative Sciences, and the Ontario Association of Medical Laboratories conducted a one-year pilot project of population-based screening for colorectal cancer using the Fecal Occult Blood Test (FOBT)[590]. The pilot project took place from March 2004 to March 2005 in 12 randomly selected regions in Ontario. The main goal of the project was to determine the best way to encourage Ontario residents aged 50 to 75 years and at average-risk of colorectal cancer, to be screened. The pilot compared two methods of recruitment: through recommendations from the family doctor to be screened, and through promotion and activities of the local public health unit.

The project also looked at:

- variations in recruitment rates among the diverse geographic, socio-demographic, and linguistic communities of Ontario, including Northern Ontario and among non-English speakers
- attitudes about colorectal cancer screening with FOBT among primary care physicians, public health units, and persons who are eligible for screening
- selected indicators of system-capacity and resource-utilization, such as follow-up rates, waiting times for follow-up investigation, and cost of promotion and recruitment
- effectiveness of various strategies to promote screening

- other implementation and feasibility issues

Despite strong evidence about early detection and prevention of colorectal cancer deaths through screening with the fecal occult blood test (FOBT), statistics show that Ontario's screening participation rates include only 15% in eligible individuals.

The results of the project will be used to inform the development of a provincial colorectal cancer screening policy, enhancing the potential for high-quality, accurate, and timely population-based colorectal cancer screening and follow-up program in Ontario

In March 2006, Toronto launched a program to train nurses to perform flexible sigmoidoscopy. So far the program has trained six nurses at two sites in Toronto. In addition, the report from a one-year pilot project on FOBT has recently been submitted to the Ministry of Health and Long-Term Care (MOHLTC) with a request for funding for a provincial FOBT screening program. The design of the program is similar to that in the UK with a central program office, regional offices and colonoscopy hubs. There are also plans for an information system, quality assurance and ongoing monitoring of participation rates, positivity rates, referral rates, adverse events and evaluation of outcomes.

In order to raise public awareness for colorectal cancer a National Colorectal Cancer Campaign was set up in 1997 and has become a national campaign[591].

7.13.2 Groups at increased or high risk

The Ontario familial colon cancer registries collect personal and family health information from Ontario residents who have a family history of colorectal cancer. The registries participate in Cancer Family Registries (CFR), an international assembly made up of 10 participating sites from Australia, the United States and Canada.

7.14 NEW ZEALAND

7.14.1 Average risk groups

The implications of a program for colon cancer screening for New Zealand were examined in 1998 by a National Working Party on Screening for Colorectal Cancer[592]. The working party recommended against establishing a national population based screening program for colorectal cancer with FOBT, given the modest potential benefit, the considerable commitment of health sector resources and the small but real potential for harm. There was also a lack of evidence from randomised controlled trials that a screening program with other modalities such as flexible sigmoidoscopy, colonoscopy or double contrast barium enema will reduce the incidence of people dying from colorectal cancer.

In order to update the conclusions of the working party on colorectal cancer screening, the New Zealand Ministry of Health's national screening unit requested New Zealand Health Technology Assessment (NZHTA) to undertake a systematic review of the new (since 1997) evidence on colorectal cancer screening[219].

Consistent with the findings of the Working Party on Screening for Colorectal Cancer, high quality evidence was found that FOBT screening with the guaiac-based FOBT Hemoccult reduces mortality from colorectal cancer. FOBT as a screening test however raised several issues concerning other aspects of how

to conduct a FOBT screening program, such as how many positive slides should be considered as a positive test and what dietary advice should be given to screening participants. As a result of the HTA report, it appears that little additional evidence on these matters has emerged since it was considered by the working party in 1998.

With regard to the comparison between immunochemical FOBT and the guaiac tests there is limited definitive evidence regarding superior immunochemical FOBT performance over the guaiac tests. Consequently one should wait for further reliable evidence before drawing definitive conclusions.

The introduction of flexible sigmoidoscopy in a national screening program cannot currently be justified since there are currently no data on long-term incidence and mortality. Currently there are some ongoing trials.

7.14.2 Groups at increased or high risk

Genetic services in New Zealand providing a comprehensive range of clinical genetic services, including genetic counselling and referral for patient support are limited. They are based in Wellington (Northern Regional Genetic Services), Auckland (Central Regional Genetic Services) and Christchurch (Southern Regional Genetic Services). A national familial bowel cancer registry has historically been managed through the Northern Regional Genetic Service. A Southern registry, with functional links to the northern service, is now operational in Christchurch.

Key Messages

- **Currently there are only a few countries with a national colorectal cancer screening program.**
- **In those countries where a national screening program is available FOBT (mostly guaiac, always biennial) is used as a primary screening tool.**
- **Organised surveillance programs for high risk groups are fragmentarily available.**

8 IMPLEMENTATION SCENARIOS AND BUDGET IMPACT

8.1 SCENARIOS

To estimate the budget impact of mass screening for colorectal cancer we analysed two general implementation scenarios. It should be emphasised that the goal of these analyses is limited to budget impact estimation and that they should not be considered as a cost-effectiveness analysis of screening tests. These cost-effectiveness analyses are described in chapter 6.

In a first scenario an individual from the target group receives an invitation by mail to participate in the screening program and to visit his GP for delivery of the test kit. During a first visit the GP identifies the pre-screening risk of the individual. Individuals who are at high risk for colorectal cancer should be followed up for this risk (surveillance) and are therefore excluded from the mass screening program. For average risk individuals, the GP provides extensive information about the aims, consequences and drawbacks of CRC screening, and if they agree to participate they are given the FOBT test kit. After completion of the test the participant receives his result through the GP. If the test is positive the participant is advised to undergo colonoscopy and referred for the procedure. This scenario is further called the ***'GP system'***.

In a second scenario, an individual from the target group is again invited by mail to participate in the screening program, but in this scenario the letter contains the test kit, together with detailed information about the nature of the program, consequences, exclusion criteria, and instructions for use of the test kit. The test is performed by the individual and mailed to the laboratory. The results are mailed to the participant and the GP. If positive, the participant is advised to visit his GP, where the participant is counselled and referred for colonoscopy. This scenario is further called the ***'mailing system'***.

Both scenarios will be presented for a target group aged 50-74 and a target group aged 55-74. A distinction is made between the first round of screening and the second and subsequent rounds of screening. This distinction is important because the introduction of a previously non-existing screening program induces a higher detection rate of cancer that will not be reached once the program is running for several years.

The budget impact as well as the cost per CRC detected of both scenarios in both age groups is estimated by means of an economic model. The analyses are performed from a third payer perspective.

8.1.1 Baseline analysis: biennial screening with unrehydrated gFOBT

As most evidence is available in literature for a biennial screening strategy with unrehydrated gFOBT, this will be our ***baseline analysis***. Apart from data from the literature (mostly for clinical variables), data from national databases (e.g. for costs of procedures, population size) are used in the model. It is assumed that, at the start of the screening program, half of the population in the target group is being offered screening in the first year and the other half in the second year. Therefore, the first screening round is defined as the first and second year of the screening program, the second round as the third and fourth year. Results are identical in the two years of the same screening round.

All parameters and variables included in the model are presented in table 30. Uncertainty is accounted for in the model by including all estimated variables with their respective distributions. Estimates and distributions are derived from literature or from expert opinion if no data were directly available from literature. This approach allows probabilistic sensitivity analyses and the construction of confidence intervals around the point estimates for total costs and costs per CRC detected resulting from the model. Parameters for which precise data are available, such as costs of specific procedures, are included in the model without a distribution.

The basis for the assumed value and distribution of each variable in the model is briefly explained in the following paragraphs.

8.1.1.1 Exclusion of individuals at high risk

Mass screening is targeted at individuals at average risk. Therefore individuals at increased or high risk should not be included in mass screening but offered regular health care. In both the GP and mailing system, individuals at high risk are excluded from mass screening. In the GP system the GP performs a pre-screening risk-stratification and informs the patients about the eligibility for mass screening. In the mailing system, the accompanying letter will clearly state that individuals who are already being followed-up for their increased CRC risk should not participate. In case of doubt they would be adviced to contact their GP.

We do not have precise data on the actual number of individuals that will be excluded for this reason. A few studies estimated the prevalence of having a family history of CRC in at least one first degree relative at 5 to 10% (see chapter 3.5). In the literature it is assumed that about 25 to 30% of cancers occur in individuals at increased risk. Assuming on average a doubling of the risk in this group, this would correspond to a proportion of 14 to 18% of the population that should be excluded from mass screening. We therefore used a point estimate of 16% with an uncertainty ranging from 14% to 18% in a Beta-distribution.

8.1.1.2 Participation

Participation is defined as going to the GP in the GP system or returning the test kit to the laboratory in the mailing system. In RCTs participation to FOBT in the first round of screening ranges from 60% to 69,5% (see table 23). The Cochrane meta-analysis[24] reported 67%. Real world experiences in different countries (see table 28), however, indicate more variation in participation, ranging in Europe from 20% in the Czech Republic to 75% in Finland. In chapter 5 we showed that the median participation rate to programmatic offers of FOBT is between 40 and 50%, and that approximately 50% can be obtained with minimal prompting. For the budget impact model we used a point estimate of 45% with an uncertainty ranging from 15% to 75% in a Beta-distribution.

8.1.1.3 Compliance

Compliance is defined as accepting colonoscopy after a positive FOBT result. In our model, compliance with colonoscopy is assumed to be 87,5%, with uncertainty limits ranging from 80% to 95% in a Beta-distribution. This assumption is based on experience in other countries (see chapter 7), on expert opinion and supported by evidence from the Burgundy and the Funen trial that report a compliance rate with colonoscopy after a positive FOBT of 85% and 82% respectively (see table 29).

8.1.1.4 Sensitivity

Whereas we judged that participation rates from RCTs could not be directly extrapolated to real life screening conditions, this is probably less so for other parameters of screening performance. Sensitivity estimates from the RCTs that used unrehydrated gFOBT[362, 358, 351, 363, 207, 208] range from 41% in France to 81% in Göteborg and Minnesota. In our model, we used a point estimate of 50% for sensitivity of FOBT and a range from 40 tot 80% in a Beta-distribution. The proportion of CRC missed (false negatives) is one minus sensitivity.

8.1.1.5 Positivity rate

The positivity rate, or the percentage of positive FOBT results, was taken from the same RCTs using unrehydrated gFOBT[362, 358, 351, 363, 207, 208]. Specifically reported positivity rates for the first round of screening ranged from 1,9% in Göteborg to 2,4% in Minnesota, with two trials reporting 2,1% positivity rate in the first round (Nottingham and Burgundy). Therefore we chose 2,1% as a point estimate for the first round of screening with uncertainty ranging from 1,9 to 2,4% in a skewed Beta-distribution. For subsequent rounds of screening a lower point estimate of 1,5% was assumed with uncertainty ranging from 1,4 to 1,6 in a Beta-distribution based on information from RCTs (see tables 29 and 35).

8.1.1.6 Colonoscopy detection rates (Cancer, Adenoma, negative)

After a positive FOBT, colonoscopy is used as the golden standard to evaluate the colon. During this evaluation not only CRC is found but also adenomata or other disorders. From the RCTs, CRC and adenomata ≥ 10mm are reported. Table 29 gives an overview of the (colonoscopic) findings in 3 RCTs over all screening rounds combined[348, 207, 208] and from a study of Allison[593] that compared the performance of several FOBT tests and of a combination of tests by identifying screened patients who had colorectal neoplasms diagnosed (carcinoma or a polyp ≥ 10mm in diameter) in the two years after screening. It should be appreciated that combined with the reported positivity rates of FOBT, those numbers lead to an apparent incidence that is two to three times higher than the incidence reported in cancer registries. This is due to the inherent property of screening that it increases apparent incidence by detecting cancer earlier.

Table 29: Observed performance characteristics of FOBT and colonoscopy

	Burgundy	Nottingham	Funen	Allison
Colonoscopy after pos FOBT	85%		82%	
Reported Sensitivity	41%	64%	46%	37%
Positivity rate (average)	1,5%	1,5%	1,5%	2,46%
CRC after positive FOBT	9,9%	11,5%	10,4%	6,6%
Adenoma (>10mm) after positive FOBT	14,3%	34,6%	22,2%	16,67%
CRC incidence in those screened	0,15%	0,18%	0,15%	0,16%
CRC incidence in those screened corrected for sensitivity of FOBT	0,36%	0,28%	0,33%	0,43%

Approximations of detection rates after positive FOBT made for the Dutch consensus development meeting used similar estimates[2]: 10% for CRC and 30% for adenoma. In a French survey of colonoscopies (unpublished but presentation available at the SFED website[315]) the incidence was 4% for CRC and 35% for all polyps, but these colonoscopies were carried out for various reasons and not

only after a positive FOBT. We therefore used a central estimate of colonoscopy detection rates of 10% for CRC (in a Beta-distribution ranging from 5 tot 15%) and of 20% for adenomata (in a skewed Beta-distribution ranging from 10 to 35%)

8.1.1.7 Complication rates from colonoscopy after positive FOBT

Reporting of complication rates differs in the RCTs. In the Minnesota trial there would be 0,034% complications from colonoscopy (perforations and hemorrhage). In the Göteborg RCT the complication rate was 0,018%. A recent large series of colonoscopies in Poland[594] showed overall complication rates of 0,1% (including mainly perforation, bleeding, cardiovascular events and a few other complications), while perforation rate was 0,01%. In the French series of colonoscopies performed for all reasons and not merely screening (see table 19), reported perforation rate was 0,07% and hemorrhage 0,28% and an overall complication rate of 0,47% using a broad definition of 'complications'. However, as mentioned in chapter 5 complication risk is significantly higher in therapeutic colonoscopy than in diagnostic endoscopies, due to the higher rate of polypectomies and biopsies. For the purpose of this budget impact model we accept a large variability in the complication rate parameter and we estimated only the cost of perforation. To apply this we used a perforation rate of 0,05% ranging from 0,01 to 0,1% in a skewed Beta-distribution.

8.1.1.8 Costs

Wherever possible, known Belgian costs have been applied. This is especially so for GP visits, cost of colonoscopy (with associated bowel preparation, sedation, anaesthesia and anatomopathology), cost for FOBT test kits and the lab. These costs were obtained from the Belgian national reimbursement tariffs (RIZIV-INAMI). For this analysis we also assumed that the FOBT testing would be entirely covered by the screening program. It should be noted that models where the cost of the test kits are not covered by the program, or where price-volume negotiations with the distributor lead to lower prices for the test, result in lower estimates for budget impact and cost per CRC detected. The cost of the complication of perforation during colonoscopy was based on costs used in published economic evaluations (see evidence table of chapter 6) and on Belgian expert opinion.

For other costs, such as up-front campaign cost (media, flyers, setting up infrastructure) and mailing costs no hard data were available. These were estimated, based on grey literature and expert opinion. For uncertain cost estimates, a distribution was defined by the multiplication of the point estimate for costs with a factor drawn from a skewed Beta-distribution with mean 1, minimum 0,5 and maximum 2. This means that an uncertainty range is defined of 0,5 times the mean cost to 2 times the mean cost.

An overview of the assumptions and parameter values is presented in table 30.

Table 30: Overview of modelling variables and their distribution assumptions (baseline analysis: unrehydrated gFOBT two-yearly)

Variable	Uncertainty
Individuals excluded for mass screening	Beta-distribution: mean: 16%, minimum: 14%, maximum: 18%
Participation rate	Beta-distribution: mean: 45%, minimum: 15%, maximum: 75%
Compliance colonoscopy after positive FOBT	Beta-distribution: mean: 87,5%, minimum: 80%, maximum: 95%
Sensitivity FOBT	Skewed beta-distribution: mean: 50%, minimum: 40%, maximum: 80%
Positivity rate: 1st round 2nd round	 Skewed beta-distribution: mean: 2,1%, minimum: 1,9%, maximum: 2,4% Beta-distribution: mean: 1,5%, minimum: 1,4%, maximum: 1,6%
Colonoscopy detection rates: Colorectal cancer Adenoma	 Beta-distribution: mean: 10%, minimum: 5%, maximum: 15% Skewed beta-distribution: mean: 20%, minimum: 10%, maximum: 35%
Complication rates from colonoscopy after positive FOBT	Skewed beta-distribution: mean: 0,05%, minimum: 0,01%, maximum: 0,1%
Costs Fixed campaign costs* Mailing costs* Costs colonic perforation* GP visit (excl. non refundable part) ° FOBT° Colonoscopy with biopsy or polypectomy° Purely diagnostic colonoscopy°	 2.000.000€ GP system: 1€ Mailing system: 5€ 15.000 € 19,06 € GP system: 44,47€ (incl. 2 GP visits) Mailing system: 6,35 € 656,42€ 485,83€

* uncertainty defined by multiplication of the point estimate (reported in table) by a factor drawn from a skewed beta-distribution with mean 1, minimum 0,5 and maximum 2.
° precise figures from national reimbursement scheme

8.1.2 Comparison of 3 different FOBTs

Although most information in the literature is about the guaiac Hemoccult II, some comparative information exists for the comparison between different FOBTs in the same population. For the purpose of this budget impact analysis we used a comparison of Hemoccult II, Hemoccult II Sensa (a more sensitive guaiac test) and HemeSelect, an immunochemical test for human hemoglobin.

The variables and assumptions for this analysis that differ from those of the baseline analysis are shown in table 31.

Information on the positivity rate, CRC detection rates and sensitivity of the different tests was derived from one study [593]. Cost data were obtained from the Belgian reimbursement scheme and personal communication from the distributors of the tests in Belgium. No exact price information was available for Belgium for the cost of the HemeSelect at the time of this study. Its cost was therefore assumed to be about 6 times higher than for the gFOBT tests. To account for the uncertainty of this point estimate, the cost of 12 € was multiplied by a factor drawn from a skewed beta-distribution with mean 1, minimum 0,5 and maximum 2.

Table 31: Overview of modelling variables and distribution assumptions for sensitivity analysis (comparison 3 FOBTs)

Scenario comparing three FOBTs	
Positivity rate:	Beta-distribution:
Hemoccult II	α = 198, β = 7867 (mean: 2,46%)
Hemoccult II Sensa	α = 1073, β = 6831 (mean: 13,58%)
HemeSelect	α = 440, β = 7053 (mean: 5,87%)
Colonoscopy detection rates:	Series of conditional beta distributions:[r] α_1 = number of colorectal cancers, α_2 = number of adenomata, α_3 = false positives
Hemoccult II	α_1 = 13, α_2 = 33, α_3 = 152
Hemoccult II Sensa	α_1 = 27, α_2 = 72, α_3 = 974
HemeSelect	α_1 = 22, α_2 = 68, α_3 = 350
Sensitivity:	Beta-distribution:
Hemoccult II	α = 13, β = 22 (mean: 62,86%)
Hemoccult II Sensa	α = 27, β = 7 (mean: 20,59%)
HemeSelect	α = 22, β = 10 (mean: 31,25%)
Costs:	
Hemoccult II	2,06€
Hemoccult II Sensa	2,14€
HemeSelect*	12€

* uncertainty defined by multiplication of the point estimate (reported in table) by a factor drawn from a skewed beta-distribution with mean 1, minimum 0.5 and maximum 2.

[r] Series of conditional beta distributions[595]: First π_1 is drawn from a beta $\left(\alpha_1, \sum_{j=2}^{k} \alpha_j\right)$. Next, for each π_j in turn, j = 2, …, k-1, draw φ_j from a beta $\left(\alpha_j, \sum_{i=j+1}^{k} \alpha_i\right)$, and then set $\pi_j = (1 - \sum_{i=1}^{j-1} \pi_i)\varphi_j$. Finally, set $\pi_k = 1 - \sum_{i=1}^{k-1} \pi_i$

8.2 RESULTS

8.2.1 Baseline analysis

The results of the baseline analysis for the age group of 50 to 74 years are presented in table 32. For the age group of 55 to 74 years results are presented in table 33.

8.2.1.1 First screening round of a biennial screening program

In the first screening round, a biennial mass screening program with unrehydrated gFOBT in all individuals between 50 and 75 years of age is expected to cost the Belgian government 20 to 34,7 million € per year, depending on the scenario chosen. The mailing system is less expensive than the GP system. Mass screening leads to the detection of 989 colorectal cancers per year in the first round. This is about 13% of the total number of CRCs that are diagnosed in Belgium without screening, a proportion which is considerably higher than the 3,7% that would be expected in this population considering that only half the population is reached each year and considering the incomplete compliance. This is of course due to the earlier detection of CRC through the screening. The expected average cost per colorectal cancer detected is 22.771 € for the mailing system and 37.576 € for the GP system.

Table 32: Results baseline analysis age group 50-74

50-74	**GP system**		**Mailing system**	
	1st & 2nd year			
Budget impact	34.694.320 €		19.960.480 €	
95% CI	17.636.130 €	51.533.840 €	14.007.280 €	26.421.150 €
Neoplasms detected				
CRC	989		989	
	380	1.795	380	1.795
adenoma	1.975		1.975	
	769	3.810	769	3.810
Cost per neoplasms detected				
CRC	37.576 €		22.771 €	
	24.620 €	60.569 €	12.132 €	43.285 €
CRC + adenoma	12.265 €		7.431 €	
	8.488 €	17.578 €	4.287 €	13.564 €
	3rd year			
Budget impact	33.158.810 €		18.363.540 €	
95% CI	16.895.710 €	49.113.960 €	13.095.000 €	24.112.550 €
Neoplasms detected				
CRC	707		707	
	268	1.271	268	1.271
adenoma	1.412		1.412	
	536	2.669	536	2.669
Cost per neoplasms detected				
CRC	50.271 €		29.488 €	
	32.980 €	81.589 €	15.206 €	56.530 €
CRC + adenoma	16.405 €		9.621 €	
	11.371 €	23.628 €	5.489 €	18.141 €

Restricting the screening program to people between 55 and 75 years of age diminishes the budgetary impact of both scenarios (table 33). In this age group,

the GP system has an expected cost of almost 26,5 million € per year for 741 CRC detected per year in the first screening round. The mailing system would cost around 15,5 million € per year to the government for the same number of colorectal cancers detected. The expected cost per colorectal cancer detected is respectively 38.376 € and 23.570 € for the GP and mailing system.

The number of neoplasms detected was set equal between the GP and the mailing system in the model because we had no indication to assume that the mailing system would lead to a higher participation rate than the GP system in Belgium. A number of studies, however, have shown higher participation rates for direct mailing of kits to the population[463, 210]. By assuming the participation rate of the mailing system and the GP system to be identical, we chose for a conservative approach. Indeed, with a higher participation rate in the mailing system, the estimated cost per CRC detected would be lower, making the difference with the GP system even larger.

Table 33: Results baseline scenario age group 55-74

55-74	**GP system**		**Mailing system**	
	1st & 2nd year			
Budget impact	26.497.220 €		15.457.430 €	
95% CI	13.654.540 €	39.128.920 €	10.947.810 €	20.438.140 €
Neoplasms detected				
CRC	741		741	
	285	1.345	285	1.345
adenoma	1.480		1.480	
	576	2.855	576	2.855
Cost per neoplasms detected				
CRC	38.376 €		23.570 €	
	25.069 €	62.130 €	12.480 €	44.633 €
CRC + adenoma	12.525 €		7.691 €	
	8.638 €	18.026 €	4.440 €	14.116 €
	3rd year			
Budget impact	25.346.690 €		14.260.870 €	
95% CI	13.155.100 €	37.324.980 €	10.256.960 €	18.658.130 €
Neoplasms detected				
CRC	530		530	
	201	953	201	953
adenoma	1.058		1.058	
	401	2.000	401	2.000
Cost per neoplasms detected				
CRC	51.390 €		30.606 €	
	33.511 €	83.165 €	15.711 €	59.450 €
CRC + adenoma	16.769 €		9.984 €	
	11.599 €	24.231 €	5.660 €	18.833 €

8.2.1.2 Second screening round

The total budget impact of 2-yearly gFOBT screening is higher in the first two years of the screening program than in subsequent years. This is due to the fact that in the first and second year, during which each time half of the target population is screened in our model, a higher number of FOBTs will be positive compared to subsequent years. In the first year, recently developed colorectal cancers as well as latent CRC since more than 2 years can be detected. In the third and fourth year, only the recently developed cancers during the past two

years in individuals who have already been screened before, or in people entering the screening program can be detected. Therefore, the number of colonoscopies needed will be lower in the subsequent years.

For the group 50- to 74-year-olds, the total budget impact of a biennial CRC screening program is 33,1 million € per year for the GP system and 18,4 million € per year for the mailing system in the second screening round. Due to the high fixed costs associated with the screening campaign, the difference in expected total costs between the first and second screening round is not very high. The number of colorectal cancers detected, however, is lower in the second round (707 in the second round compared to 989 in the first round). As a consequence, the average cost per colorectal cancer detected is much higher in the second round than in the first round. The cost per colorectal cancer detected is 50.271 € in the GP system and 29.488 € in the mailing system.

Restricting the screening program to people between 55 and 75 years of age would lower the budget impact to 25,3 million € per year in the GP system and 14,3 million € per year in the mailing system, but slightly increase the cost per colorectal cancer detected. This is due to the fact that the decrease in number of CRC detected is relatively larger than the decrease in the budget impact. The cost per CRC detected in this age group is 51.390 € in the GP system and 30.606 € in the mailing system. It should be understood, however, that in our model we used similar positivity rates and detection rates of CRC and adenomata for this older age group, while in real live, these rates are likely to be higher in older age groups. As a consequence, the actual cost per CRC detected in 55- to 74-year-olds might be lower and hence the difference between the costs per CRC detected of the two strategies smaller.

8.2.1.3 Comparing screening strategies in different age groups

From a comparison between the target populations defined by age, we can conclude that screening 55- to 74-year-olds is expected to be less expensive for the government but also less effective in detecting colorectal cancers (table 34). The expected incremental cost of screening 50- to 74-year-olds as compared to 55- to 74-year-olds in the GP system is 8,2 million € per year in the first screening round. This would lead to an additional 248 CRC detected. In the mailing system, the expected incremental cost is 4,5 million € per year for the same additional number of CRC detected. The incremental cost, from a governmental point of view, of detecting one additional colorectal cancer in the first screening round would be 33.053 € in the GP system and 18.157 € in the mailing system if age limits were extended from 55-75 to 50-75.

In subsequent screening rounds, the expected incremental cost of screening 50- to 74-year-olds as compared to screening only 55- to 74-year-olds is 7,8 million € per year in the GP system and 4,1 million € in the mailing system. This would lead to an additional 177 CRCs detected in both systems. The incremental cost per CRC detected of screening 50- to 74-year olds as compared to screening 55- to 74-year olds would be 44.136 € in the GP system and 23.179 € in the mailing system. The incremental cost, effectiveness and cost-effectiveness figures are presented in table 34.

Table 34: Incremental cost-effectiveness, in terms of cost per CRC detected, of screening different age groups

	Cost GP system		Cost mailing system		CRC detected	
1st round						
50-74	34.694.320 €		19.960.480 €		989	
55-74	26.497.220 €		15.457.430 €		741	
Incremental value	8.197.100 €		4.503.050 €		248	
95% C.I.	3.955.395 €	12.481.470 €	3.074.823 €	6.054.114 €	95	450
Cost / add. CRC detected	33.053 €		18.157 €			
95% C.I.	23.037 €	56.621 €	10.959 €	37.515 €		
2nd round						
50-74	33.158.810 €		18.363.540 €		707	
55-74	25.346.690 €		14.260.870 €		530	
Incremental value	7.812.120 €		4.102.670 €		177	
95% C.I.	3.752.111 €	11.800.700 €	2.817.188 €	5.515.838 €	67	319
Cost / add. CRC detected	44.136 €		23.179 €			
95% C.I.	31.119 €	75.324 €	13.604 €	49.341 €		

The relevance of these figures is limited to showing that extending the population from 55- to 74-year-olds to 50- to 74-year-olds is associated with an additional cost per additional CRC detected. Whether the additional yield in terms of CRC detected is worth the extra costs depends, among other, on the savings associated with avoiding treatment and the value of life years gained and/or quality of life impairment avoided.

8.2.2 Comparison between different FOBTs

The results of the model that compared different FOBTs are presented in Table 35. We only present the results for the first round in a mailing system and for the age group of 50 to 74 years, as the results for the GP system, subsequent rounds and the more limited age group are similar as far as the relation between the different tests is concerned.

The Hemoccult II test has the lowest budgetary impact, with a total cost to the government of 20,8 million € per year in the first screening round. The Hemoccult II is, however, the least effective in detecting CRC. The Hemoccult II Sensa has the highest budget impact and is the most effective for detecting CRC, however at the cost of more false positives. The expected cost of screening with the Hemoccult II Sensa in all people between 50 and 75 years of age is 48,4 million € per year in the first screening round and the expected number of colorectal cancers detected is 1.609.

Table 35: Results comparison of 3 different FOBTs age group 50-74, mailing system

mail system, 50-74, 1st round	Hemoccult II		Hemoccult II Sensa		HemeSelect	
Budget impact	20.775.180 €		48.413.650 €		43.728.670 €	
95% CI	14.438.980 €	27.165.250 €	28.100.340 €	68.689.030 €	29.759.050 €	58.844.440 €
neoplasms detected						
CRC	755		1.609		1.383	
	283	1.474	680	2.897	591	2.578
adenoma	1.934		4.291		4.272	
	795	3.471	1.942	7.129	1.876	7.168
cost per neoplasms detected						
CRC	31.373 €		32.085 €		35.188 €	
	15.526 €	59.743 €	21.097 €	48.371 €	18.931 €	62.034 €
CRC + adenoma	8.413 €		8.516 €		8.311 €	
	5.198 €	14.511 €	6.611 €	11.554 €	5.273 €	13.938 €

The estimates of the incremental cost per additional CRC detected of the Hemoccult II Sensa and the HemeSelect, as compared to the Hemoccult II, are presented in Table 36. The incremental cost per CRC detected is lower for the Hemoccult II Sensa than for the HemeSelect test. The incremental cost of the Hemoccult II Sensa relative to the Hemoccult II is 32.363 € per additional CRC detected. For HemeSelect, the incremental cost per CRC detected is 36.564 €. This means that the Hemoccult II Sensa is expected to be more cost-effective – in terms of cost per CRC detected- than the HemeSelect, relative to the classical Hemoccult II and at considered prices. Note that the incremental number of CRC detected is not significantly different from 0 for HemeSelect. This means that there is still considerable uncertainty if HemeSelect will lead to more CRC cases detected than Hemoccult II.

Table 36: Incremental cost-effectiveness, in terms of cost per CRC detected, of different FOBTs from the governmental perspective (first round mailing system, age group 50-74 years)

	Cost (Budget impact)	Number of CRC detected	Incremental cost of test relative to Hemoccult II		Incremental number of CRC detected		Cost per additional CRC detected
Hemoccult II	20.775.180 €	755					
HemeSelect	43.728.670 €	1.383	22.953.490 €		628		36.564 €
95% C.I.			13.571.080 €	34.368.620 €	-89	1.627	
Hemoccult II Sensa	48.413.650 €	1.609	27.638.470 €		854		32.363 €
95% C.I.			12.849.240 €	43.103.940 €	120	1.944	

From this analysis it is not possible to conclude whether Hemoccult II or Hemoccult II Sensa is the most cost-effective test for mass screening in the target population. Such conclusion would require an estimate of the costs and outcomes of the current situation without mass screening and the outcomes – in terms of number of life years gained- with mass screening. The estimation of the costs of CRC diagnosis without screening is hampered by the fact that the number of people undergoing colonoscopy for the detection of CRC after a true *or* false positive FOBT cannot be derived from the national databases. Given the importance of this information for the cost-effectiveness estimate, as

clearly illustrated in the literature review in chapter 6, it did not seem appropriate to attempt to model the current situation.

The incremental cost of HemeSelect and Hemoccult II Sensa is high due to the high price of the first relative to the Hemoccult II and due to the increased number of colonoscopies generated by both. With the implementation of a mass screening program with one of those tests the demand for these tests will increase dramatically. This would offer the government the possibility to negotiate with the industry about the price of the tests. Lower prices will lower the expected budget impact and hence the average cost per CRC detected.

8.2.3 Sensitivity analysis

The confidence intervals around the estimated costs of the different implementation scenarios are large due to the uncertainty in a number of modelling parameters. The relative impact of the uncertainty in the different modelling parameters on the estimated **total cost** of the screening program is illustrated by means of an influence diagram in figure 15 for the baseline analysis applying a mailing system. The lengths of the bars represent the relative importance of the variable for the results. They result from the 1000 Monte Carlo simulations ran on our model for the probabilistic sensitivity analysis.

The by far most important uncertainty in all screening scenarios is participation. Uncertainty in the participation rate is the most decisive factor for the variability in the total cost estimate. In the mailing system also mailing costs, fixed campaign costs and compliance with colonoscopy after a positive FOBT influence the total cost estimate of mass screening for CRC. In the GP system the participation rate is the single most important uncertain factor in the model.

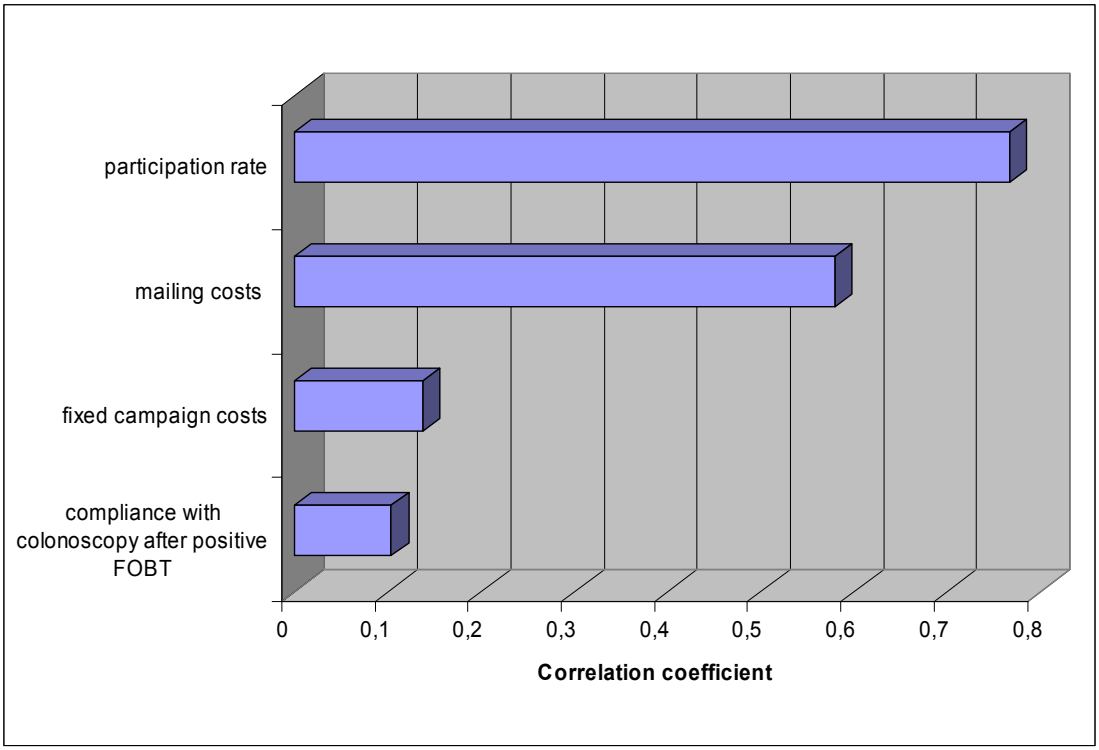

Figure 15: Influence diagram, representing the sensitivity of the total cost estimate in the first screening round to uncertain modelling parameters in the mailing system (age group 50-74 years)

If we assume that our point estimate for participation is accurate, and fix this variable at the value of 45% in the GP system, where participation is the single most important uncertain factor, the most influential uncertain factors are (in order of importance): fixed campaign costs, mailing costs, compliance with colonoscopy after positive FOBT and positivity rate of FOBT in the first screening round.

The uncertainty in the **cost per CRC detected** depends in first instance on the uncertainty in the detection rate of CRC after a positive FOBT in both the GP and mailing system. This was the most important factor in the GP system, whereas in the mailing system also the uncertainty around the participation rate, mailing costs, campaign costs and compliance with colonoscopy after positive FOBT added to the uncertainty in the cost per CRC detected (Figure 16).

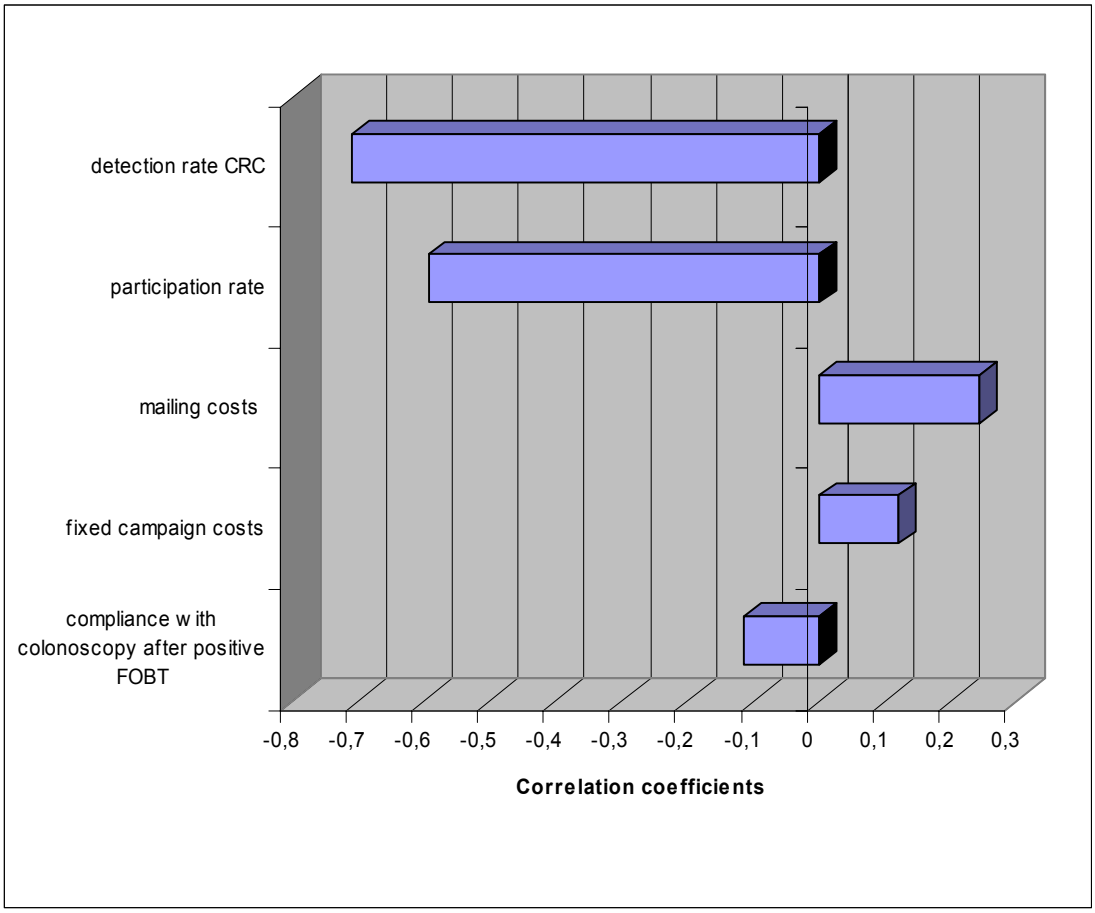

Figure 16: Influence diagram representing the sensitivity of the estimated cost per CRC detected in the first screening round to uncertain modelling parameters in the mailing system (age group 50-74 years)

8.3 CAPACITY NEEDS

Implementing a mass screening program requires resources, not only in terms of money but also in terms of capacity. One of the major requirements is sufficient capacity to perform colonoscopies.

From our baseline model with Hemoccult II, we concluded that 9890 colonoscopies per year would have to be performed in the first screening

round. In subsequent screening rounds a capacity of 7065 would be required. Currently around 100.000 colonoscopies are performed in Belgium each year, for all indications.

The model that compares the costs and effects of Hemoccult II, Hemoccult II Sensa and HemeSelect based on the results of one specific study revealed a much higher capacity need for the other FOBTs: 63.936 additional colonoscopies for Hemoccult II Sensa and 27.656 for HemeSelect.

Key messages

- **The expected budget impact of a mailing system is lower than that of a GP system.**
- **In a biennial screening program with gFOBT, the budget impact and the number of colorectal cancers detected will be higher in the first round than in subsequent rounds. The cost per CRC detected increases in subsequent screening rounds.**
- **Screening a population between 50 and 75 years of age will be more expensive than screening a population between 55 and 74 years of age, but will obviously detect more CRC.**
- **Mass screening with Hemoccult II is the least expensive strategy but detects fewer cancers than the more sensitive strategies based on Hemoccult II Sensa or HemeSelect.**
- **Participation rate is the most important uncertainty for the total costs of a colorectal cancer screening program.**
- **Implementation of a mass screening program based on Hemoccult II will require a yearly capacity of 10.000 colonoscopies equivalent to 10% of the number of colonoscopies currently performed each year in Belgium.**
- **The more sensitive the FOBT test used in a mass screening program, the higher the capacity need for colonoscopy.**

9 CONCLUSIONS AND RECOMMENDATIONS

The purpose of this HTA on Colorectal Cancer (CRC) Screening was to evaluate whether, and under which conditions, CRC screening could become an effective and cost-effective method to reduce the burden of CRC in Belgium. Therefore, we analysed and evaluated the available evidence about CRC screening. We also evaluated the uncertainties surrounding CRC screening and identified areas where specific additional data are necessary before such a program can successfully be implemented in this country.

9.1 CONCLUSIONS

Provided that the organisational conditions are met, colorectal cancer screening clearly fulfils the original Wilson and Jung criteria and also the more recent extended criteria regarding practical and ethical issues. These extensions of the criteria mainly emphasize that screening programs should be concerted actions, with adequate quality assurance, broadly accessible and with full information about potential benefits and harms but without any moral pressure on individuals to participate. In the case of CRC screening we observed that in most countries opportunistic screening, historically, is the main form of screening. Recently, however, several countries started pilot projects to find out how to organise a programmed mass screening for CRC.

In Belgium, colorectal cancer is the third most common cancer in men and the second most common cancer in women. It is also the second most common cause of cancer death. Its incidence rises with age and every year CRC is diagnosed in approximately 7700 Belgians. Even though men have, at every age, a higher incidence of CRC, the absolute number of CRC in women is also high because of their longer life expectancy. Survival after the diagnosis of CRC is strongly associated with stage of disease at diagnosis: the more localised the tumor, the better the prognosis. Therefore, early identification of the malignancy through screening is considered important.

Most CRC occur sporadically, i.e. in individuals without apparent evidence of increased risk. However, about 25 to 30% of CRC occur in individuals who are known to be at increased risk, either through a family history of CRC occurrence or through personal predisposing conditions. Although to date no exact numbers are available for Belgium, it can be estimated that this population amounts to about 15% of the general population, assuming an average twofold risk in this subpopulation as a whole. Those individuals should not be the target of mass screening programs but nevertheless should be cared for. Therefore, we included in this report reviews of general recommendations for risk stratification for CRC and of guidelines for taking care of individuals at increased or at high risk. Those individuals should be referred to appropriate regular healthcare.

Many guidelines on CRC screening and surveillance are available worldwide, including the position paper on cancer screening in the European Union, and we described many of those. All guidelines recommend CRC screening to be offered to low risk patients starting at age 50, and all guidelines also recommend using colonoscopy for the follow-up of individuals with a positive screening test. However, guidelines disagree on optimal age span of screening and on optimal screening techniques. If FOBT is chosen as screening technique the unrehydrated home-administered FOBT is univocally recommended. All guidelines also recommend total colonoscopy as the first choice method for individuals at increased CRC risk as well as for surveillance. Guidelines on

surveillance and follow-up of individuals at increased risk disagree on exact risk stratification and cut off ages and most recommendations for population subgroups are mainly empiric. Although all guidelines recommend screening, policy makers in many countries have been reluctant to implement national screening programs for fear of the low sensitivity of the commonly used guaiac FOBT (gFOBT).

Effectiveness of mass screening has been investigated in average risk males and females starting from the age of 45 or 50 and up to the age of 75 years. Only for the guaiac FOBT there is high quality evidence that screening reduces CRC mortality. The estimated reduction attributable to screening is around 15% in RCTs in intention to treat analyses and around 33% in per protocol analyses. For other techniques considered for primary screening, such as the immunochemical FOBT (iFOBT), flexible sigmoidoscopy, colonoscopy, virtual colonoscopy or DNA detection methods in stool there is currently no direct evidence of CRC mortality reduction in mass screening circumstances. All studies on mass screening emphasize the crucial importance of a high participation rate to reach the goals for CRC mortality reduction. Although there is high quality evidence that FOBT based screening can reduce CRC mortality, there is no evidence for overall mortality reduction.

The strongest economic evaluations are, obviously, based on the clinical evidence available, while other economic evaluations are mainly based on assumptions that are at least speculative: all economic evaluations of colonoscopy as a screening tool were based on overly optimistic and unrealistic assumptions, especially regarding participation. The available economic evaluations show that annual or biennial gFOBT followed by colonoscopy for screen positive participants is a cost effective intervention. Incremental cost effectiveness ratios (ICERs) range from approximately €2000 to €30.000 per life year gained. Those ICERs are mainly sensitive to the frequency of screening (biennial testing has better ICERs than annual testing), to the sensitivity and specificity of the test (the less sensitive unrehydrated test has better ICERs) and, as expected, to the cost of testing (both FOBT and subsequent colonoscopy). Those economic evaluations also show that choosing the optimal target population (age range) has an important influence on the ICER as have the participation rate with the screening program and compliance with colonoscopy after a positive FOBT, at least in those evaluations where program costs were incorporated. From none of the economic evaluations there is evidence for a better ICER for the iFOBT tests, but this depends of course on the performance characteristics and price of iFOBT and this could change in the future.

In various countries around the world screening programs are being tested, but currently there are only a few countries with an established national CRC program, such as Finland and Australia. In those countries with national or regional screening programs FOBT (mostly guaiac, always biennial) is the screening method chosen. Although most guidelines emphasise the importance of surveillance for individuals at increased risk for CRC, organised surveillance programs are only fragmentarily available.

To evaluate the financial consequences of implementing a biennial gFOBT based screening program in Belgium, we conducted a budget impact analysis. The model used to estimate the budget impact was based on international literature, and whenever possible on Belgian prices. We considered two extreme scenarios. In a first scenario the General Practitioner (GP) is the key person. The invited individual goes to his/her GP for information and counselling and distribution of the test kit, and when results are available returns to this GP for

follow-up. This scenario is roughly comparable to the French model. In the second scenario, the individual receives the invitation and the test kit by mail, with instructions on whether to participate and how to use the test kit. In this scenario, the participant only visits the GP in case of positive FOBT for information and counselling and referral for colonoscopy. This scenario is roughly comparable to the Finnish and Australian models. Those alternatives should be considered as two extremes that could be modified when implementing an organised program. A call-centre, for example, could be necessary in the 'mailing system' approach, to help patients resolve specific questions about the screening program and their eligibility to participate. Moreover, in the Belgian Healthcare system not every patient has his/her regular GP since patients are allowed to choose freely from the medical care available; this causes potential problems in both scenarios. We included up-front program costs, and used costing assumptions that were either based on existing tariffs and prices or on published data and expert opinion. Because of the important uncertainties about screening performance assumptions and some of the costs we conducted a probabilistic sensitivity analysis and results are shown with 95% confidence intervals (CI) from these analyses. In a baseline analysis with biennial screening for all men and women aged 50-74 years of age, the yearly cost during the first round for the GP based scenario would be around M€35 (€35.000.000) with uncertainty ranging from M€18 to M€52. The main uncertainty is the participation rate with an important influence on number of tests (FOBT and colonoscopy). Estimated cost per CRC detected would be around €50.000. A similar program with the same effect but based on the direct mailing system would cost M€20 (14 – 26), and cost per CRC detected would be around €29.000.

The results of the budget impact analysis heavily depend on some of the assumptions. The most important of these is the participation rate, especially for the cost of the program but also for the cost per CRC detected. There is important uncertainty about this parameter which is of crucial importance to a CRC screening program. Other important uncertainties are program costs (mailing, campaign, etc). Those costs will clearly depend on the organisation of the program. Other uncertainties are related to compliance with colonoscopy after positive FOBT and CRC detection rates through colonoscopy after positive FOBT. Those issues should be field-tested in Belgium. Regarding capacity, our budget impact analysis shows that in the biennial FOBT scenario with Hemoccult II, around 10.000 colonoscopies per year would be necessary in the first screening round, and slightly less in subsequent years. Compared to the 100.000 colonoscopies performed yearly in Belgium this would represent 10%.

9.2 RECOMMENDATIONS AND RESEARCH AGENDA

This HTA report shows that CRC screening using a biennial guaiac FOBT screening followed by colonoscopy in case of a positive FOBT in individuals aged 50 years and older (exact age range to be defined) can be a cost-effective mass screening program when properly organised. Therefore, we recommend introducing such a screening program in Belgium. However, before such a program can be successfully implemented, a series of key issues need to be addressed and resolved. We recommend the implementation of a few pilot screening programs to investigate these issues.

A political decision on whether to implement a CRC screening program can be made based on the existing information to date in consultation with the competent authorities on the federal and regional levels and in collaboration

with the stakeholders. This decision should also address organizational issues including quality control and setting up a screening registry, the scope of the screening such as age groups to be included, target goals such as minimal participation and compliance rates, the timeframe for full implementation (presumably within two to four years, allowing the pilot projects to deliver the necessary information), and the funding of CRC screening.

Additionally, a clear clinical pathway for individuals at increased CRC risk should be designed and communicated to the population and to clinicians, GPs as well as gastroenterologists and gastroenterologic surgeons to ensure that individuals who are outside the scope of the mass screening program will adequately be referred to standard care conforming to the existing guidelines.

Together with this process, a screening management organization should be defined and implemented, preferably not only for CRC screening but conjointly for different mass screening programs, and international (European) cooperation might be considered. This screening management organization should also take care of the indispensable quality assurance and organize the most cost-efficient way to deliver FOBT screening. Whether this screening management organization would be located at the federal or at the community level is a political decision.

To address the uncertainties surrounding the implementation of a FOBT based screening program we recommend the implementation of a few pilot screening programs. We estimate that these pilot programs should run for two to four years with intermediate evaluations. Those pilot programs should address and test the design of the program, the organisation and implementation of a screening registry, negotiations with suppliers on the price of test kits to be used in a screening program, and the colonoscopy capacity as well as quality assurance.

The pilot programs should also specifically address the following uncertainty issues: participation rates, compliance and acceptance of the screening program in Belgium, prevalence of increased CRC risk, positivity rates and sensitivity-specificity of FOBT in real world circumstances, CRC and adenoma detection rates by colonoscopy after positive FOBT, and harms caused by the screening program.

Moreover, these pilot programs should assess the feasibility of both the 'GP system' and/or the 'mailing system' in the Belgian context, and the impact of this choice on participation rates in the screening program. Optionally the performance of iFOBT compared to gFOBT could be tested in selected areas.

Based on the results of the pilot projects either the initial goals of the mass screening program might have to be adapted (e.g. concerning participation) or the program might have to be redefined (e.g. a call-centre is needed to increase efficiency of the program). Re-evaluation of the organizational and financing issues might be necessary as a consequence of such decisions.

10 APPENDICES

APPENDIX FOR CHAPTER 3

MEDLINE SEARCH FOR CRC RISK STRATIFICATION

Medline search (October, 31st 2006) on risk estimations in increased groups with familial CRC history

#	Search History	Results
1	colorectal cancer.mp.	29.497
2	family history.mp.	25.178
3	relative risk.mp.	29.428
4	absolute risk.mp.	1.561
5	lifetime risk.mp.	1.163
6	3 or 4 or 5	31.551
7	1 and 2 and 6	73
8	limit 7 to yr="2000 - 2006"	35
9	from 8 keep:	16

APPENDIX FOR CHAPTER 4

SEARCH FOR GUIDELINES ON CRC SCREENING AND SURVEILLANCE

Table 1: Medline citations on CRC screening & surveillance guidelines from 2000 to October, 31st 2006

	Search History	Results
1	colorectal cancer.mp.	29.497
2	screening.mp.	227.044
3	surveillance.mp.	77.004
4	2 or 3	298.365
5	1 and 4	5.123
6	guideline$.pt.	14.513
7	5 and 6	45
8	limit 7 to yr="2000 - 2006"	24

Subsequently we searched the following guidelines sources:

- The Cochrane Collaboration - Colorectal Cancer group
- NGC - National Guidelines Clearinghouse
- NCI - National Cancer Institute (USA)
- AGA - American Gastroenterological Association
- ACG - American College of Gastroenterologists
- ACS - American Cancer Society
- ASGE - American Society for Gastrointestinal Endoscopy
- ASCO - American Society of Clinical Oncology
- US-PSTF - United States Preventive Services Task Force
- Canadian Task Force on Preventive Health Care
- NZGG - New Zealand Guidelines Group
- NHMRC – Australian National Health and Medical Research Council – Australian Cancer Network
- SIGN - Scottish Intercollegiate Guidelines Network (SIGN)
- British Society of Gastroenterology (BSG) & Association of Coloproctology for Great Britain and Ireland (ACPGBI)
- ANAES - Agence Nationale d'Accréditation et d'Evaluation en Santé - France
- CBO - Centraal Begeleidings Orgaan, nowadays Kwaliteits Instituut voor de Gezondheidszorg CBO - Netherlands
- WGO - OMGE - World Gastroenterlogy Organisation - Organisation Mondiale de Gastro-Entérologie
- ICSI - Institute for Clinical Systems Improvement

EVIDENCE TABLES GUIDELINES FOR SCREENING AND SURVEILLANCE

Table 2: Guidelines & Recommendations on Average risk CRC screening (N = 14)

Nr	Title	Issued by	Type	Target population	Screening methods / options considered	Interval	Supporting evidence classes & quality rating	Rating system	Conclusions	Grades of recommendation
1	Health Care Guideline: Colorectal Cancer Screening[180].	Institute for Clinical Systems Improvement (ICSI)	CPG	The patient must meet all four of the following criteria: - 50 to 80 years old or if African American 45 to 80 years old; - No personal history of polyps and/or colorectal cancer; - No family history of colorectal cancer in one first-order relative diagnosed before age 60 or two first-order relatives diagnosed at any age - No family history of adenomatous polyps in one first-order relative diagnosed before age 60 - A single first order relative diagnosed with colorectal cancer or adenomatous polyp after age 60 may put the patient at a slightly increased risk and may warrant starting colon cancer screening at age 40	One of the following methods based on joint decision making by patient and provider: 1. FOBT 2. FS or colonoscopy 3. Combination of FS or colonoscopy and FOBT. 4. Total colon evaluation: colonoscopy, double contrast barium enema - DCBE or CT colonography.	1. Annual FOBT 2. FS or colonoscopy every 5 years. 3. Combination of FS or colonoscopy every 5 years and annual FOBT. 4. TCE: 5 years (5 - 10 years for colonoscopy)	FOBT: A+ FS: A - , Bø, Cø/ - , Dø Colonoscopy: Aø, C+/ø, Dø, M FOBT & FS: Cø/ - BCBE: C -	See Appendix 2 Appendix 2 (ISCI:)	1. Annual or biennial routine FOBT done for large, average risk, randomly selected populations reduce mortality rates for colorectal cancer. 2. FOBT, even when combined with FS, fails to detect colorectal cancer in at least 24% of those with cancer. 3. Mortality from colorectal cancer can be decreased by FS examination every 5 years. Additionally, a distal villous or tubulovillous adenoma increases the likelihood of an advanced neoplasm. 4. Colonoscopy has been shown to reduce the incidence of colorectal cancer in a population of patients with adenomatous polyps. There is, however, no evidence of reduction of colorectal cancer mortality in an average risk population by randomized trial, non-randomized trial, or case-control studies through the use of colonoscopy as no studies have been published directly addressing the question. Cost-effectiveness estimates suggest a possible benefit. 5. Screening DCBE can image the entire colon and detect cancers and large polyps almost as well as colonoscopy or FS.	1. Grade I 2. Grade II 3. Grade III 4. Grade IV 5. Grade III
2	WGO-OMGE Position	Guidelines &	CPG	Men and women ≥	1. FOBT	1. FOBT annually	Evidence	None	All men and women age 50 and older should be	Not included

Nr	Title	Issued by	Type	Target population	Screening methods / options considered	Interval	Supporting evidence classes & quality rating	Rating system	Conclusions	Grades of recommendation
	Statement:Colorectal Cancer Screening and Surveillance[188].	Statements Committee of the World Gastroenterology Organisation (WGO-OMGE)		50 y. old	2. FS 3. FOBT & FS combined 4. Colonoscopy 5. DCBE with FS	with a sensitive guaiac or immunochemical test 2. FS every 5 years 3. FOBT & FS combined (preferably) 4. colonoscopy every 10 years 5. DCBE with FS every 5 - 10 years	discussed but not rated		offered screening for adenomatous polyps and cancer with one of the follow options: Fecal occult blood testing annually with a sensitive guaiac or immunochemical test, FS every 5 years, preferably both combined, colonoscopy every 10 years, or DCBE with FS every 5 - 10 years. People with 1 or 2 first-degree relatives with colorectal cancer or an adenomatous polyp under age 60 should be offered screening beginning at age 40 with one of the above options. A family history consistent with FAP or HNPCC requires genetic counselling, possibly genetic testing and more intense surveillance at a younger age.	
3	The Quebec Association of Gastroenterology position paper on colorectal cancer screening - 2003[181].	Quebec Association of Gastroenterology Task Force (AGEQTF)	HC/PR	Patients ≥ 50 y. old at low CRC risk and otherwise asymptomatic	1. FOBT 2. FS 3. Colonoscopy 4, DCBE 5. Virtual colonoscopy	1. Annually or biennially 2. 5 to 10 yearly 3. 5 to 10 yearly 4. 10 yearly 5. Not mentioned	1. FOBT: Level I / Grade A 2. FS: II-2 / Grade B 3. Colonoscopy: Level II (diagnosis CRC/polyps & polypectomy) / Grade C for screening 4. BCBE: II-3 (diagnosis CRC/polyps) / Grade C for screening 5. Virtual colonoscopy: insufficient evidence	See Appendix 2 (CTFPHC)	There exists Level I evidence that screening reduces the mortality from CRC (A recommendation) and the cost effectiveness of a screening program compares favourably with initiatives for breast and cervical cancer. Fecal occult blood testing (FOBT), endoscopy (including sigmoidoscopy and colonoscopy), barium enema and virtual colonoscopy were considered. Although most clinical efficacy data are available for FOBT and sigmoidoscopy, there are limitations to programs based on these strategies. FOBT has a high false positive rate and a low detection yield, and even a combination of these strategies will miss 24% of cancers. Colonoscopy is the best strategy to both detect and remove polyps and to diagnose colorectal cancer, with double contrast barium enema also being a sensitive detection method. The Task Force recommended the establishment, in Quebec, of a screening program with 5- to 10-yearly double contrast barium enema or 10-yearly colonoscopy for individuals aged 50 years or older at low risk. The program should include outcome monitoring, public and professional education to increase awareness and promote compliance, and central coordination with other provincial programs. The program should be evaluated; specific billing codes for screening for colorectal cancer would help facilitate this. Formal feasibility, effectiveness and cost-effectiveness studies in Quebec are now warranted.	Recommendation A on a screening program for CRC

Nr	Title	Issued by	Type	Target population	Screening methods / options considered	Interval	Supporting evidence classes & quality rating	Rating system	Conclusions	Grades of recommendation
4	Screening for colorectal cancer: recommendations and rationale[182].	U.S. Preventive Services Task Force (USPSTF)	CPG	Men and women ≥ 50 y. old	1. home FOBT 2. FS 3. home FOBT + FS 4. Colonoscopy	1. FOBT yearly 2. FS every 5 y. 3. home FOBT + FS 4. Colonoscopy every 10 y.	1. FOBT: Direct evidence, Level I, internal validity good, external validity good 2. FS: Direct evidence, Level II, internal validity good, external validity fair 3. FOBT and FS: Direct evidence not sure, Level II, internal validity fair, external validity fair 4. BCBE: No direct evidence, Level III, internal validity fair, external validity fair 5. Colonoscopy: Direct evidence not sure, Level II, internal validity fair, external validity fair	See Appendix 2 (UPSTF)	The USPSTF strongly recommends that clinicians screen men and women aged 50 and older who are at average risk for colorectal cancer. For those at higher risk, such as those with a first-degree relative diagnosed with colorectal cancer before age 60, it is reasonable to begin screening at a younger age. Screening options for colorectal cancer include home fecal occult blood test (FOBT), FS, the combination of home FOBT and FS, colonoscopy, and double-contrast barium enema. The choice of screening strategy should be based on patient preferences, medical contraindications, patient adherence, and resources for testing and follow-up There are insufficient data to determine which particular screening strategy is best in terms of the balance of benefits and harms or cost-effectiveness. Studies reviewed by the USPSTF indicate that colorectal cancer screening is likely to be cost effective (costing less than $30,000 per additional year of life gained) regardless of which screening method is used.	Grade A
5	Recommendations on cancer screening in the European Union[179].	EU Advisory Committee on Cancer Prevention (ACPG)	HC/PR	Men and women aged 50 to approximately 74 y.	FOBT screening test + colonoscopy for the follow-up of test positive cases	annually or biennially	Evidence discussed but not rated	None	As colorectal cancer is a major health problem in many European countries fecal occult blood screening should be seriously considered as a preventive measure. The decision on whether or not to embark on these screening programs must depend on the availability of the professional expertise and the priority setting for healthcare resources. If screening programs are implemented they should use the fecal occult blood screening test and colonoscopy should be used for the follow-up of test positive cases. Screening should be offered to men and women aged 50 years to approximately 74 years. The screening interval should be 1 or 2 years. Other screening methods such as immunological tests, FS and colonoscopy can at present not be recommended for population screening.	No grading (HC/PR)

Nr	Title	Issued by	Type	Target population	Screening methods / options considered	Interval	Supporting evidence classes & quality rating	Rating system	Conclusions	Grades of recommendation
6	ASGE guideline: colorectal cancer screening and surveillance[184].	Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE)	CPG	Men and women ≥ 50 y. old	1. Preferred modality: colonoscopy Alternatives: 2. FOBT 3. FS 4. FOBT + FS	1. colonoscopy every 10 y 2. FOBT yearly 3. FS every 5 y 4. FOBT yearly and FS every 5 y	Evidence discussed but not rated	See Appendix 2 (UPSTF)-grading	Colonoscopy is the preferred modality for CRC screening in average risk patients (B). Alternative methods for CRC screening in average-risk patients include: - yearly FOBT (A), - FS every 5 years or combined yearly FOBT and FS every 5 years (B). Single digital rectal examination FOBT (SRE-FOBT)has a poor sensitivity for CRC and should not be performed as a primary screening method (A). Studies evaluating virtual colonoscopy and fecal DNA testing for CRC screening have yielded conflicting results and therefore cannot be recommended (A).	Colonoscopy: grade B FOBT: grade A FS or FOBT + FS: grade B
7	Colorectal Cancer Screening[58].	National Comprehensive Cancer Network (NCCN)	CPG	Men and women ≥ 50 y. old with: - No history of adenoma - No history of inflammatory bowel disease - Negative family history: not having a first degree relative or two second degree relatives with colorectal cancer or clustering of HNPCC related cancers in the family.	1. Colonoscopy (preferred) 2. FOBT+ FS 3. DCBE Colonoscopy if 2 or 3 positive	1. Colonoscopy (preferred) 2. FOBT annually + FS every 5 y 3. DCBE every 5 y	Evidence given but not explicitly rated	See Appendix 2 (NCCN categories of consensus)	1. Colorectal cancer risk assessment in persons without known family history is advisable by age 40 years to determine the appropriate age for initiating screening. 2. Individuals with a negative family history for colorectal neoplasia and associated hereditary syndromes, and a negative personal history of colorectal neoplasia, HNPCC associated cancers, and inflammatory bowel disease, represent the group at average risk for development of colorectal cancer. 3. It is recommended that average risk screening begin at age 50 after discussion of the available options. 4. Currently recommended options include annual FOBT (category 1) and FS every 5 years using a 60 cm or longer scope, or colonoscopy every 10 years. 5. The NCCN panellists prefer colonoscopy as a screening modality for individuals at average risk. 6. Double-contrast barium enema every 5 years is an alternative option.	Category 2A
8	Report on the Belgian consensus meeting on colorectal cancer screening[185].	Belgian Gastroenterologists community	CPG	All Belgians ≥ 50 y. old, with exclusion of increased risk categories	FOBT (Hemoccult) + colonoscopy for the follow-up of test positive cases	Annually	Evidence given but not explicitly rated	None	The results of several randomised population-based studies have shown that screening for colorectal cancer by FOBT can reduce colorectal cancer mortality. The time has come to implement well-organised FOBT screening of the average-risk population. In order to have a high level of uptake this program requires a substantial amount of initial planning and resource allocation, including defining roles of the different health	No grading

Nr	Title	Issued by	Type	Target population	Screening methods / options considered	Interval	Supporting evidence classes & quality rating	Rating system	Conclusions	Grades of recommendation
									professionals ,training of the community of general practitioners together with proper education and information of the public on the risk factors for CRC and the alternative screening tools.	
9	Prevention and screening of colorectal cancer[186].	Finnish Medical Society Duodecim.	CPG	Patients ≥ 50 y. old at low CRC risk and otherwise asymptomatic	FOBT (Hemoccult) + colonoscopy for the follow-up of test positive cases	Not stated	1. FOBT: Grade A 2. Cost-effectiveness: Grade B	A. Strong research-based evidence. Multiple relevant, high-quality scientific studies with homogenic results. B. Moderate research-based evidence. At least one relevant, high-quality study or multiple adequate studies. C. Limited research-based evidence. At least one adequate scientific study. D. No research-based evidence. Expert panel evaluation of other information.	1. The results of large trials involving screening with FOBT indicate a reduction in mortality from colorectal cancer, but such screening results in colonoscopy being performed on a large proportion of the screened population. The cost-effectiveness of screening is controversial. Only about 50% of those invited can be expected to attend screening. 2. The use of colonoscopy for screening of asymptomatic individuals is indicated only in cases with marked familial susceptibility to cancer or if an adenoma has earlier been removed endoscopically. 3. Follow-up after the initial investigations is not indicated in persons with a single small tubular adenoma in the rectum or in patients above 75 years of age.	1. FOBT: Grade A 2. Cost-effectiveness: Grade B
10	Adult preventive health care: cancer screening[187].	University of Michigan Health System (UMHS)	CPG	Men and women ≥ 50 y. old	1. FOBT 2. FS 3. FOBT & FS	FOBT: annually FS: every 5 years FOBT & FS:	FOBT: Grade A FS: Grade A FOBT& FS: Grade	A. Randomized controlled	FOBT annually FS every 5 years FOBT/FS annually/every 5 years	FOBT: Grade A FS: Grade A FOBT/FS: Grade

Nr	Title	Issued by	Type	Target population	Screening methods / options considered	Interval	Supporting evidence classes & quality rating	Rating system	Conclusions	Grades of recommendation
					combined 4. Colonoscopy 5. DCBE	annually/every 5 years Colonoscopy: every 10 years DCBE (acceptable modality, but not recommended): every 5 years	B Colonoscopy: Grade B DCBE: Grade B	trials B. Controlled trials, no randomization C. Observational trials D. Opinion of expert panel	Colonoscopy every 10 years DCBE: acceptable modality, but not recommended	B Colonoscopy: Grade B DCBE: Grade B
11	American Cancer Society guidelines on screening and surveillance for the early detection of adenomatous polyps and colorectal cancer - update 2004[56].	American Cancer Society (ACS)	CPG	Average risk patients ≥ 50 y.	1. FOBT 2. FS 3. FOBT and FS 4. Double Contrast Barium Enema (DCBE) 5. Colonoscopy	1. FOBT: annually 2. FS: every 5 years 3. FOBT and FS: annual FOBT and FS every 5 years 4. DCBE: every 5 years 5. Colonoscopy: every 10 years	The type of evidence is not specifically stated for each recommendation	None	The following options are acceptable choices for colorectal cancer screening in average-risk adults: FOBT, FS, FOBT + FS, DCBE, colonoscopy. Since each of the following tests has inherent characteristics related to accuracy, prevention potential, costs, and risks, individuals should have an opportunity to make an informed decision when choosing a screening test.	Not included
12	Colorectal cancer screening and surveillance: clinical guidelines and rationale - update based on new evidence[55].	U.S. Multisociety Task Force on Colorectal Cancer (AGA/ASGE/ACP/ACG)	CPG	Average risk patients ≥ 50 y. and otherwise asymptomatic	1. FOBT 2. FS 3. FOBT and FS 4. Colonoscopy 5. Double Contrast Barium Enema (DCBE)	1. FOBT: annually 2. FS: every 5 years 3. FOBT and FS: annual FOBT and FS every 5 years 4. Colonoscopy: every 10 years 5. DCBE: every 5 years	Evidence given but not explicitly rated	None	Men and women at average risk should be offered screening with one of the following options beginning at age 50 years. The rationale for presenting multiple options is that no single test is of unequivocal superiority and that giving patients a choice allows them to apply personal preferences and may increase the likelihood that screening will occur. The strategies are not equal with regard to evidence of effectiveness, magnitude of effectiveness, risk, or up-front costs. FOBT: yearly screening using a guaiac-based test with dietary restriction or an immunochemical test without dietary restriction. Two samples from each of 3 consecutive stools should be examined without rehydration. Patients with a positive test on any specimen should be followed up with colonoscopy. FS: every 5 years. Combined FOBT and FS: FOBT every year combined with FS every 5 years. When both tests are performed, the FOBT should be done first. Colonoscopy: every 10 years.	Not included

Nr	Title	Issued by	Type	Target population	Screening methods / options considered	Interval	Supporting evidence classes & quality rating	Rating system	Conclusions	Grades of recommendation
									DCBE: every 5 years.	
13	Preventive health care, 2001 update: colorectal cancer screening[28].	Canadian Task Force on Preventive Health Care (CTFPHC)	CPG	Asymptomatic patients ≥ 50 y. old with no other risk factors	1. FOBT 2. FS 3. FOBT + FS 4. Colonoscopy	Not stated	1. Level I 2. Levels II-2 & III 3. Level I 4. Level II-3	See Appendix 2 (CTSPHC-grading)	1. Screening with FOBT (Hemoccult): There is good evidence to include screening with Hemoccult test in the periodic health examination of asymptomatic patients over age 50 with no other risk factors. However, there remain concerns about the high rate of false-positive results, feasibility and small clinical benefit of such screening. The number needed to screen for 10 years to avert 1 death from colorectal cancer is 1173. For patients being screened with Hemoccult, it is recommended that they avoid red meat, cantaloupe and melons, raw turnips, radishes, broccoli and cauliflower, vitamin C supplements and aspirin and non-steroidal anti-inflammatory drugs for 3 days before fecal samples are collected. However, a recent meta-analysis of 4 randomized controlled trials found no improvement in positivity rates or change in compliance rates with moderate dietary restrictions. 2. Screening with sigmoidoscopy or a combination of FOBT and FS. 3. There is insufficient evidence to include or exclude colonoscopy as an initial screening in periodic health examination. Although colonoscopy is the best method for detecting adenomas and carcinomas, it may not be feasible to screen asymptomatic patients because of patient compliance and the expertise and equipment required and the potential costs. On the other hand, if colonoscopy were an effective screening strategy when performed at less frequent intervals, these issues might be of less concern.	1. FOBT: Grade A 2. FS: Grade B 3. FOBT + FS: Grade C 4. Colonoscopy: Grade C
14	Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer[50]	Australian Cancer Network Colorectal Cancer Guidelines Revision	CPG	Asymptomatic patients ≥ 50 y. old with no other risk factors	FOBT + colonoscopy for the follow-up of test positive cases	Not stated	Level I	See Appendix 2 (NHMRC-grading)	1. Organised screening with FOBT, performed at least once every two years, is recommended for the Australian population over 50 years of age. 2. Given the uncertainties relating to the most	FOBT strongly recommended

Nr	Title	Issued by	Type	Target population	Screening methods / options considered	Interval	Supporting evidence classes & quality rating	Rating system	Conclusions	Grades of recommendation
		Committee							effective means of implementing such a program and to the feasibility, acceptability and cost-effectiveness of such a program in the Australian setting, the program should commence with preliminary testing involving a number of pilot and feasibility studies.	

Table 3: Guidelines & recommendations on CRC screening in case of a positive family history (N = 11)

Nr.	Title	Issued by	Last update	Target population	Recommendations	Starting at age	Interval	Supporting evidence classes	Rating system
1	ASGE guideline: colorectal cancer screening and surveillance[184].	Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE)	2006	At least 1 FDR with CRC diagnosed < 60 y	Colonoscopy	40 y or 10 y younger than affected relative (whichever is younger)	If normal, repeat every 3-5 y	Grade B	See Appendix 2 (UPSTF)-grading
				At least 1 FDR with CRC diagnosed ≥ 60 y	Benefit of earlier colonoscopy for patients with one first-degree relative diagnosed with CRC at an advanced age is unclear	40 y?	If normal, repeat every 10 y		
				At least 1 FDR with adenomatous polyp < 60 y	Colonoscopy	40 y or 10 y younger than affected relative (whichever is younger)	If normal, repeat every 5 y		
				• At least 1 FDR with adenomatous polyp ≥ 60 y • At least 1 SDR or third degree relative (TDR) with cancer or polyps	Uniphase screening colonoscopy	Age individualized	If normal, switch to average risk screening		
2	Colorectal Cancer Screening[58].	National Comprehensive Cancer Network (NCCN)	2006	• 1 FDR with CRC < 50 y & ≥ 2 FDR with CRC at any age	Check criteria for a defined syndrome (high risk surveillance) If not meeting: colonoscopy	40 y or 10 y younger than affected relative (whichever is younger)	Repeat every 1-5 y	Category 2A	See Appendix 2 NCCN categories of consensus
				• 1 FDR with CRC ≥ 50 y OR ≥ 2 SDR with CRC at any age	Consider colonoscopy		Repeat every 5 y		
3	Report on the Belgian consensus meeting on colorectal cancer screening[185].	Belgian Gastroenterologists community	2005	• 1 FDR with adenoma or CRC ≥ 60 years old • 2 FDR with adenoma or CRC ≥ 60 years old • 1 FDR with adenoma or CRC < 60 y	Colonoscopy	• 40 y • 30-35 y • 10 y earlier than the age at diagnosis of the younger ill family member	• If normal, repeat at least every 10 y • If normal, repeat every 3-5 y • Repeat every 5 years	Evidence discussed but not explicitly rated	N/A

4	Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer[50]	Australian Cancer Network Colorectal Cancer Guidelines Revision Committee	2005	• 1 FDR with CRC diagnosed at 55 years or over (included in category 1 – RR up to 2-fold) • 1 FDR with CRC diagnosed under 55 years (RR 3 to 6-fold) • ≥ 2 FDR with CRC diagnosed at any age (RR 3 to 6-fold)	• Colonoscopy • FS and DCBE or CT colonography may be offered if colonoscopy is contraindicated for some reason.	50 y. or 10 years younger than the age of first diagnosis of bowel cancer in the family, whichever comes first.	Repeat every 5 y.	III-2	'Recommended'
5	American Cancer Society guidelines on screening and surveillance for the early detection of adenomatous polyps and colorectal cancer - update 2004[56].	American Cancer Society (ACS)	2004	Either CRC or adenomatous polyps in any FDR < 60 y, or in ≥ 2 FDR at any age (if not a hereditary syndrome). CRC in relatives more distant than FDR does not increase risk substantially above the average risk group	Colonoscopy	Age 40, or 10 y before the youngest case in the immediate family	Every 5-10 y	Evidence discussed but not explicitly rated	N/A
6	Surveillance and management of groups at increased risk of colorectal cancer[27].	New Zealand Guidelines Group (NZGG)	2004	Category 3 risk: • 1 FDR plus ≥ 2 FDR or SDR, all on the same side of the family, with a diagnosis or CRC at any age • 2 FDR, or 1 FDR plus ≥ 1 SDR, all on the same side of the family, with a diagnosis of CRC and one such relative (1) was diagnosed with CRC under age of 55 y, (2) developed multiple bowel cancers, or (3) developed an extra-colonic tumor suggestive of hereditary nonpolyposis colorectal cancer (i.e., endometrial, ovarian, stomach, small bowel, upper renal tract, pancreas, or brain) • At least 1 FDR or SDR diagnosed with CRC in association with multiple bowel polyps • 1 FDR with CRC diagnosed < 50 y, particularly if colorectal tumor immunohistochemistry has revealed loss of protein expression for one of the mismatch repair genes (hMLH1 or hMSH2)	Suspect hereditary disease and refer patient to: • A genetic specialist/family cancer clinic or familial bowel cancer registry for further risk assessment and possible genetic testing • If yes → see surveillance; if no → colonoscopy	40 y or 10 y younger than affected relative (whichever is younger),	Repeat every 1-5 y	Grade 5	See Appendix 2 NZGG National Health Committee evidence grading hierarchy

				Category 2 risk: 1 FDR with CRC diagnosed < 55 y or ≥ 2 FDR on the same side of the family with CRC diagnosed at any age	Colonoscopy(1). Fully inform individuals about their risk of developing CRC and the reason for this recommendation (2). Individuals should be informed that colonoscopy is generally a safe procedure, but it is an invasive procedure with some rare but recognised risks (3).	50 y or 10 y younger than the earliest diagnosis in the family, whichever comes first	Every 5 y	Grade 3 for (1) Grade 5 for (2) and (3)	
				Category 1 risk: 1 FDR with CRC diagnosed ≥ 55 y	No specific screening recommendations are made for this group at this time given the slight increase in risk, the uncertainty regarding the age at which this additional risk is expressed, and the concern regarding the appropriateness of colonoscopy as a screening procedure in this group (1). Prompt investigation of lower bowel symptoms is advised (2). Individuals requesting information should be fully informed regarding their absolute risk of developing CRC and advised of the reasons for this recommendation (3).	N/A	N/A	Grade 5 for (1),(2) & (3)	
7	Adult preventive health care: cancer screening[187].	University of Michigan Health System (UMHS)	2004	≥ 2 FDR with CRC or 1 FDR with CRC or adenomatous polyps diagnosed at < 60 y	Colonoscopy	40 y or 10 y younger than the earliest diagnosis in the family, whichever comes first	Every 5 y	Evidence discussed but not explicitly rated	N/A
8	Colorectal cancer screening and	U.S. Multisociety Task Force on Colorectal Cancer	2003	One FDR with CRC or adenomatous polyp at age ≥ 60 y, or 2 SDR with CRC	Average risk screening	40 y	N/A		

				1 SDR or any TDR with CRC	Average risk screening	50 y	N/A		
9	Management of Colorectal Cancer - A national clinical guideline[49].	Scottish Intercollegiate Guidelines Network (SIGN)	2003	High risk: • 3 family members with CRC • ≥ 2 with CRC and 1 with endometrial CA in at least 2 generations, 1 diagnosed at ≤ 50 y and 1 FDR of the other 2	(Colonoscopy (Discuss gynaecological screening for endometrial or ovarian CA (Oesophago-duodeoscopy (OGD) for gastric CA screening (Consider screening for other cancers which may occur in specific families and are part of the HNPCC spectrum	At first consultation or 5 y younger then the youngest affected relative	Colonoscopy & OGD every 2 y from 30-70 y	Grade D	See Appendix 2 SIGN
				Moderate risk: • 1 FDR with CRC < 45 y. or 2 FDR with CRC, one < 55 y or 2 (one with CRC < 55 y) or 3 family members with CRC or endometrial CA , who are FDR of each other and one being a FDR of the consultant • 1 FDR with CRC < 45 y • 2 FDR with CRC, one < 55 y	Colonoscopy	At first consultation or at 30-35 y, whichever is the later	If first colonoscopy clear, repeat at 55 y		
10	Guidelines for colorectal cancer screening in high risk groups[190].	British Society of Gastroenterology (BSG) Association of Coloproctology for Great Britain and Ireland (ACPGBI)	2002	2 FDR with CRC 1 FDR < 45 y with CRC	Colonoscopy	At first consultation or at age 35-40 y whichever is the later	If initial colonoscopy clear then repeat at 55 y	Grade B	See Appendix 2 BSG & ACPGBI
11	Preventive health care, 2001 update: colorectal cancer screening[28].	Canadian Task Force on Preventive Health Care (CTFPHC)	2001	≥ 1 FDR with polyps or CRC but not meeting the criteria for HNPCC	Colonoscopy	40 y	Not stated	Grade C, Level III	See Appendix 2 USPSTF/CTSPHC grading

Table 4: Guidelines & recommendations on CRC surveillance in case of high personal risk (N = 12)

Nr.	Title	Issued by	Year	Familial Adenomatous Polyposis (FAP) & related	Hereditary Non-Polyposis Colon Cancer (HNPCC)	Personal history of CRC resection	Personal history of colonpolyps	Inflammatory bowel disease (IBD)	Miscellaneous
1	Colorectal Cancer Screening[58].	National Comprehensive Cancer Network (NCCN)	2006	1. Family history of FAP → FS or colonoscopy beginning at age 10-15 y. Repeat every 12 m until age 24 y; every 2 y until age 34 y; every 3 y until age 44 y then every 3-5 y thereafter. Consider substituting colonoscopy every 5 y beginning at age 20 in addition to the FS. 2.In case of: Personal history of adenomatous polyposis (> 10 adenomas, or > 15 cumulative adenomas in 10 y) either consistent with recessive inheritance or with adenomatous polyposis with negative APC mutation testing; Family history of sibling with MYH polyposis and asymptomatic (counseling and testing for the familial mutations is recommended); Biallelic MYH mutation positive and small adenoma burden manageable by colonoscopy and polypectomy → Begin colonoscopy at age 25-30 y and every 3-5 y if negative (consider shorter intervals with advancing age) → Consider upper endoscopy and side viewing duodenoscopy at age 30-35 y and repeat every 3-5 y. 5. Patients with duodenal adenomas are treated as FAP. 6. Dense polyposis or large polyps not manageable by polypectomy needs counseling regarding surgical options Recommendations 2A	1. Colonoscopy at age 20-25 y or 10 y younger than the youngest age at diagnosis in the family, whichever comes first. Repeat every 1-2 y. Consider periodic evaluation for associated intra-abdominal malignancies. 2. If adenom(s) found: endoscopic polypectomy with follow-up colonoscopy every 1-2 y depending on: location, character, surgical risk, patient preference. 3. For women: screening for endometrial cancer with transvaginal ultrasound and office endometrial sampling annually starting by age 30-35 y or 5-10 y earlier than the earliest age of first diagnosis of these cancers in the family, and screening for ovarian cancer with concurrent transvaginal ultrasound (preferrably day 1-10 of cycle for premenopausal women) + CA-125 every 6-12 m. Recommendations 2A	Curative intent resected CRC → colonoscopy in 1 y, within 3-6 m if there was no or incomplete preoperative colonoscopy. If adenoma found → repeat colonoscopy in 1-3 y. If normal → repeat colonoscopy in 2-3 y Recommendations 2A	1. Low risk adenoma = ≤ 3 polyps, < 1 cm, tubular) → repeat colonoscopy within 3-6 y, if normal repeat every 5 y. 2. Advanced or multiple adenomas = high-grade dysplasia/carcinoma in situ OR larger than 1 cm OR villous (> 25% villous) OR number > 3 and ≤ 10 → repeat colonoscopy within 3 y, if normal repeat every 3-5 y. 3. > 10 adenomas or > 15 cumulative adenomas in 10 y → consider a polyposis syndrome 4. Incomplete polypectomy → Repeat colonoscopy within 3-6 m (timing depending on endoscopic and pathologic findings). Recommendations 2A	1. Starting at 8-10 y after onset of symptoms, colonoscopy every 1-2 y. When clinically quiescent, 4 quadrant biopsies every 10 cm with > 30 total samples using large cup forceps (preferred). Additional extensive sampling of strictures and masses. Endoscopic polypectomy when appropriate with biopsies of surrounding mucosa for the assessment of dysplasia. 2. Information regarding the value of endoscopic surveillance of long-standing Crohn's disease is limited. Surveillance is at the discretion of the physician. Optimal management of Crohn's related dysplasia remains undefined. Patient and physician preference should be considered. Extent of resection for Crohn's-related dysplasia needs to be based upon the individual findings. Recommendations 2A	Personal history of ovarian or endometrial cancer at age < 60 y → start colonoscopy at age 40 y or at age of diagnosis of ovarian/endometrial cancer. Repeat colonoscopy at 5 year intervals if normal. Recommendations 2A

Nr.	Title	Issued by	Year	Familial Adenomatous Polyposis (FAP) & related	Hereditary Non-Polyposis Colon Cancer (HNPCC)	Personal history of CRC resection	Personal history of colonpolyps	Inflammatory bowel disease (IBD)	Miscellaneous
2	ASGE guideline: colorectal cancer screening and surveillance[184].	Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE)	2006	1. FAP with positive genetic test result in proband: offer genetic testing with counseling. In relatives with positive genetic testing, annual FS beginning at age 10-12 y with colectomy when polyps develop. If no polyps are detected, annual FS until age 40 y, then every 3-5 y. Relatives with negative genetic test results are assumed not to be affected; however, they can be offered FS every 7-10 y until age 40 y then colonoscopy every 5 y. 2. FAP with negative genetic test result in proband: annual FS in all potentially affected relatives beginning at age 10-12 y as outlined above. Recommendation grade B	Colonoscopy every 1-2 y beginning at age 20-25 y, or 10 y younger than the earliest age of diagnosis of CRC in the family, whichever is earlier. Annual colonoscopy should be performed after age 40 y. Recommendation grade B	1. Prior colon cancer: high quality clearance of remainder of the colon at or around time of resection, followed by colonoscopy at 1 y after curative resection, then at 3 y and then 5-y intervals if results are normal 2. Prior rectal cancer: colonoscopy: clearance of remainder of colon at or around time of resection, followed by colonoscopy at 1 y and 4 y after resection, then at 5-y intervals. 3. After low anterior resection, if no pelvic radiation or no mesorectal excision: FS every 3-6 m for 2-3 y. Recommendation grade B	1. Prior colonic adenomas ≤ 2 small tubular adenomas (< 1 cm) and only low-grade dysplasia → surveillance colonoscopy every 5 y 2. 3-10 adenomas → surveillance colonoscopy every 3 y 3. > 10 adenomas → surveillance colonosocpy within 3 y 4. Large sessile polyp with potentially incomplete excision: repeat colonoscopy within 2-6 m. Negative surveillance colonoscopy → repeat every 5 y. Recommendation grade B	Patients with UC or extensive Crohn's colitis, greater than one third colonic involvement, should undergo surveillance colonoscopy every 1-2 y beginning 8 to 10 years after disease onset. Biopsy specimens of the colon in patients with documented pancolitis should be obtained in all 4 quadrants every 10 cm from the cecum to the rectum, to obtain a minimum of 32 biopsy samples. In patients with less extensive colitis, biopsy specimens can be limited to the microscopically involved segments. The presence of high-grade dysplasia or multifocal low-grade dysplasia in flat mucosa is an indication for colectomy. Recommendation grade B	Not included

3	Guidelines for colonoscopy surveillance after polypectomy[61, 62].	US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society	2006	Not included	Not included	Not included	1. Patients with small rectal hyperplastic polyps should be considered to have normal colonoscopies, and therefore the interval before the subsequent colonoscopy should be 10 years. An exception is patients with a hyperplastic polyposis syndrome. They are at increased risk for adenomas and colorectal cancer and need to be identified for more intensive follow up. 2. Patients with only one or two small (< 1 cm) tubular adenomas with only low-grade dysplasia should have their next follow-up colonoscopy in 5 to 10 years. The precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, and the preferences of the patient and judgment of the physician). 3. Patients with 3 to 10 adenomas, or any adenoma > 1 cm, or any adenoma with villous features, or high-grade dysplasia should have their next follow-up colonoscopy in 3 years providing that piecemeal removal has not been done and the adenoma(s) are completely removed. If the follow-up colonoscopy is normal or shows only one or two small tubular adenomas with low-grade dysplasia, then the interval for the	Not included	Not included

4	Guidelines for colonoscopy surveillance after cancer resection: a Consensus Update[69].	US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society	2006	Not included	Not included	1. Patients with colon and rectal cancer should undergo high quality perioperative clearing. In the case of nonobstructing tumors, this can be done by preoperative colonoscopy. In the case of obstructing colon cancers, computed tomography colonography with intravenous contrast or double contrast barium enema can be used to detect neoplasms in the proximal colon. In these cases, a colonoscopy to clear the colon of synchronous disease should be considered 3 to 6 months after the resection if no unresectable metastases are found during surgery. Alternatively, colonoscopy can be performed intraoperatively. 2. Patients undergoing curative resection for colon or rectal cancer should undergo a colonoscopy 1 year after the resection (or 1 year following the performance of the colonoscopy that was performed to clear the colon of synchronous disease). This colonoscopy at 1 year is in addition to the perioperative colonoscopy for synchronous tumors. 3. If the examination performed at 1 year is normal, then the interval before the next subsequent examination should be 3 years. If that colonoscopy is normal, then the interval before the next subsequent examination should be 5 years. 4. Following the examination at 1 year, the intervals before subsequent examinations may be shortened if there is evidence of hereditary nonpolyposis colorectal cancer or if adenoma findings warrant earlier colonoscopy. 5. Periodic examination of the rectum for the purpose of identifying local recurrence, usually	Not included	Not included	Not included

Nr.	Title	Issued by	Year	Familial Adenomatous Polyposis (FAP) & related	Hereditary Non-Polyposis Colon Cancer (HNPCC)	Personal history of CRC resection	Personal history of colonpolyps	Inflammatory bowel disease (IBD)	Miscellaneous
5	Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer[50]	Australian Cancer Network Colorectal Cancer Guidelines Revision Committee	2005	FS annually or biennially from age 12–15 years to 30–35 years until polyposis develops. Colonoscopic screening is appropriate for families with attenuated FAP, as recto-sigmoid sparing surgery can be done in this variant of the disease. Once a causative APC mutation has been identified for the family, genetic testing may be used to distinguish mutation-positive and mutation-negative family members.	Screening of mutation carriers or individuals affected with HNPCC-related tumours in Amsterdampositive families should be by full colonoscopy performed annually or at least once every two years, beginning at the age of 25 years or five years earlier than the age of diagnosis of the youngest affected member of the family (whichever is the earliest). Screening first-degree relatives of affected members in Amsterdam positive families where the mutation status is unknown is similar, although colonoscopy can be reduced to two-yearly. More distant relatives can be offered 5-yearly colonoscopy.	Intensive follow up for CRC should be considered for patients who have had potentially curable disease, although optimal investigation and pathways are yet to be firmly established.	All polyps should be at least sampled, and preferably removed. Synchronous polyps should be sought and removed. All patients with colorectal neoplasia completely removed at colonoscopy should then be considered for colonoscopic surveillance according to the following protocols: • within 1 y. following incomplete or possible inadequate examination, for example in a subject with multiple adenomas (level II evidence) • at 3 y. with large adenomas (>1 cm), adenomas with high-grade dysplasia, villous change in adenomas, three or more adenomas, or aged 60 or more with a first-degre relative with colorectal neoplasia (level II evidence) • at 4 to 6 y. in subjects without the risk factors outlined above. (level III-3).	-	-

6	American Cancer Society guidelines on screening and surveillance for the early detection of adenomatous polyps and colorectal cancer - update 2004[56].	American Cancer Society (ACS)	2004	Family history of familial adenomatous polyposis (FAP): counseling to consider genetic testing; If the genetic test is positive, colectomy is indicated. Early surveillance with endoscopy, starting at puberty. These patients are best referred to a center with experience in the management of familial adenomatous polyposis (FAP)	Family history of hereditary non-polyposis colon cancer (HNPCC) → colonoscopy at 21 y and counseling to consider genetic testing. If the genetic test is positive or if the patient has not had genetic testing, repeat colonsocopy every 1-2 years until age 40, then annually. These patients are best referred to a center with experience in the management of hereditary non-polyposis colon cancer (HNPCC)	Personal history of curative-intent resection of colorectal cancer: colonoscopy within 1 year after cancer resection; if normal, repeat examination in 3 years; if normal then, repeat examination every 5 years.	1. People with single, small (< 1 cm) adenoma: colonoscopy 3-6 years after the initial polypectomy; if the exam is normal, the patient can thereafter be screened as per average risk guidelines. 2. People with a large (1 cm+) adenoma, multiple adenomas, or adenomas with high-grade dysplasia or villous change: colonoscopy within 3 years after the initial polypectomy; if normal, repeat examination in 3 years; if normal then, the patient can thereafter be screened as per average risk guidelines	Cancer risk begins to be significant 8 years after the onset of pancolitis, or 12-15 years after the onset of left-sided colitis → colonoscopy with biopsies for dysplasia, every 1-2 years. These patients are best referred to a center with experience in the surveillance and management of inflammatory bowel disease.	Not included

Nr.	Title	Issued by	Year	Familial Adenomatous Polyposis (FAP) & related	Hereditary Non-Polyposis Colon Cancer (HNPCC)	Personal history of CRC resection	Personal history of colonpolyps	Inflammatory bowel disease (IBD)	Miscellaneous
7	Surveillance and management of groups at increased risk of colorectal cancer[27].	New Zealand Guidelines Group (NZGG)	2004	1. Offer referral to a genetic service for consideration of genetic testing within the context of appropriate counseling to: • Individuals with a clinical diagnosis of FAP • All at-risk family members if a family-specific genetic mutation has been identified at the age when sigmoidoscopic surveillance would normally begin 2. Sigmoidoscopy 1- to 2-yearly from the age of 12 to 15 y is recommended for asymptomatic individuals with an identified disease-causing FAP mutation and for all at-risk members of families with FAP if genetic testing is not available or is noninformative. 3. Increase the interval for sigmoidoscopic surveillance to 3-yearly at 35 y if previous examinations have been normal. Consider cessation at 55 y. 4. If attenuated FAP is suspected, colonoscopy is advised. Depending on the family history this may begin as late as 18 y and continue beyond 55 y. 5. Gastroduodenoscopy to detect duodenal adenomas at 1- to 3-yearly intervals from 30 to 35 y is commonly advised, as most advanced duodenal adenomas develop after the age of 40 years. The Spigelman Criteria may be used to guide surveillance interval. Recommendations all grade 3 except for 5. (grade 5)	1. Offer referral to a genetic service for consideration of genetic testing, within the context of appropriate counselling, to all at-risk members of families with HNPCC, at the age when colonoscopic surveillance would normally begin. 2. For bowel surveillance colonoscopy is recommended 2-yearly from the age of 25 years (or from an age 5 years before the earliest age at which CRC was diagnosed in the family, whichever comes first). Consider annual colonoscopy in known mutation carriers. 3. Endometrial cancer is the most common extracolonic malignancy. Surveillance with annual transvaginal ultrasound (+/- endometrial aspiration biopsy) is usually advised for known mutation carriers and at-risk members of families with HNPCC as determined by the Amsterdam Criteria if there is a family history of uterine cancer and/or genetic testing is noninformative The efficacy of these surveillance tools remains uncertain in premenopausal younger women. Recommendations all grade 5, except for 2. (grade 3)	1. Follow-up after resection of CRC with curative intent is recommended as it allows practitioners to monitor treatment outcome and is consistent with the preference of individuals with CRC. 2. All such individuals should have specialist follow-up over the time period in which the majority of recurrences (local or metastatic) are most likely to occur (3-5 years). Follow-up should be appropriate to the clinical context. In deciding on intensity and duration of follow-up, age and comorbid conditions should be considered. Follow-up should occur in conjunction with, and subsequently be continued by, the individuals general practitioner. 3. Individuals free of recurrent CRC for 3 to 5 years should be entered into a colonoscopy surveillance program. Colonoscopy should be performed at 3- to 5-yearly intervals. 4. All individuals with CRC should be informed of the uncertain efficacy of follow-up with regard to survival benefit. All recommendations grade 5	1. Adenoma size > 10 mm: colonoscopy after 3 years - if negative subsequent colonoscopy after 3-5 y 2. > 3 adenomas: Colonoscopy after 3 years - if negative subsequent colonoscopy after 3-5 y 3. Villous lesions and/or severe dysplasia: Colonoscopy after 3 years - if negative subsequent colonoscopy after 3-5 y 4. Adenomas with no high-risk features and significant family history of CRC: colonoscopy after 3 y 5. Adenomas with no high-risk features and no family history of CRC: colonoscopy after 5-6 y; consider discontinuing surveillance if subsequent surveillance colonoscopy normal. All recommendations grade 3	1. After 8 to 10 years, individuals with ulcerative colitis (UC) should undergo colonoscopy with serial biopsies (as detailed below) to define disease extent, both macroscopic and microscopic. All those with significant disease extending proximal to the sigmoid colon should be enrolled in a surveillance program. 2. Colonoscopy is recommended 2-yearly for individuals with UC after 10 years' disease duration. At colonoscopy, 2 to 3 biopsies should be taken from each of 10 sites (caecum, proximal and distal ascending colon, proximal and distal transverse colon, proximal and distal descending colon, proximal and distal sigmoid colon, and rectum). Additional biopsies should be taken from any mass lesions, but not from pseudopolyps. 3. If high-grade dysplasia (HGD) is present on biopsy (and confirmed on histological review), the individual should be referred for colectomy. If low-grade dysplasia (LGD) is found in the absence of significant inflammation, shorten the surveillance interval to 1 year and refer for surgery 4. All individuals with extensive colorectal Crohn's disease should undergo surveillance procedures as detailed for individuals with extensive UC. Recommendations grade 3, for Crohn's disease grade 4	1. Individuals with hamartomatous polyps of the large or small bowel, or those with a first-degree relative known to have multiple polyps alone or associated with CRC, should be referred to the appropriate bowel and genetic specialists. 2. Individuals identified to have hyperplastic polyps beyond the rectosigmoid junction with risk features should be referred to the appropriate bowel and genetic specialists. Risk features include: • Unusual numbers (> 20) • Unusual size (> 10 mm) • Location in the proximal colon • Presence of high-grade dysplasia • Coincidental adenomas • A first-degree relative with high-risk hyperplastic polyps • A first-degree relative with CRC Recommendations all grade 5

Nr.	Title	Issued by	Year	Familial Adenomatous Polyposis (FAP) & related	Hereditary Non-Polyposis Colon Cancer (HNPCC)	Personal history of CRC resection	Personal history of colonpolyps	Inflammatory bowel disease (IBD)	Miscellaneous
8	Colorectal cancer screening and surveillance: clinical guidelines and rationale - update based on new evidence[55].	U.S. Multisociety Task Force on Colorectal Cancer (AGA/ASGE/ACP/ACG)	2003	People who have a genetic diagnosis of FAP, or are at risk of having FAP but genetic testing has not been performed or is not feasible, should have annual sigmoidoscopy, beginning at age 10-12 years, to determine if they are expressing the genetic abnormality. Genetic testing should be considered in patients with FAP who have relatives at risk. Genetic counseling should guide genetic testing and considerations of colectomy.	People with a genetic or clinical diagnosis of HNPCC or who are at increased risk for HNPCC should have colonoscopy every 1-2 years beginning at age 20-25 years, or 10 years earlier than the youngest age of colon cancer diagnosis in the family, whichever comes first. Genetic testing for HNPCC should be offered to first-degree relatives of persons with a known inherited mismatch repair (MMR) gene mutation. It should also be offered when the family mutation is not already known, but 1 of the first 3 of the modified Bethesda Criteria is met.	Patients with a colon cancer that has been resected with curative intent should have a colonoscopy around the time of initial diagnosis to rule out synchronous neoplasms. If the colon is obstructed preoperatively, colonoscopy can be performed approximately 6 months after surgery. If this or a complete preoperative examination is normal, subsequent colonoscopy should be offered after 3 years, and then, if normal, every 5 years.	Patients who have had 1 or more adenomatous polyps removed at colonoscopy should be managed according to the findings on that colonoscopy. Patients who have had numerous adenomas, a malignant adenoma (with invasive cancer), a large sessile adenoma, or an incomplete colonoscopy should have a short interval follow-up colonoscopy based on clinical judgment. Patients who have advanced or multiple adenomas (> 3) should have their first follow-up colonoscopy in 3 years. Patients who have 1 or 2 small (< 1 cm) tubular adenomas should have their first follow-up colonoscopy at 5 years. Future evidence may clarify the intervals more precisely. The timing of the subsequent colonoscopy should depend on the pathology and number of adenomas detected at follow-up colonoscopy. For example, if the first follow-up colonoscopy is normal or only 1 or 2 small (< 1 cm) tubular adenomas are found, the next colonoscopy can be in 5 years.	In patients with long-standing, extensive inflammatory bowel disease, surveillance colonoscopy with systematic biopsies should be considered. This applies to both ulcerative colitis and Crohn´s colitis because the cancer risk is similar in both diseases.	Not included

Nr.	Title	Issued by	Year	Familial Adenomatous Polyposis (FAP) & related	Hereditary Non-Polyposis Colon Cancer (HNPCC)	Personal history of CRC resection	Personal history of colonpolyps	Inflammatory bowel disease (IBD)	Miscellaneous
9	Management of Colorectal Cancer - A national clinical guideline[49].	Scottisch Intercollegiate Guidelines Network (SIGN)	2003	1. Genetic testing for APC gene mutation analysis 2. Yearly FS beginning at puberty 3. Colonoscopy every 2 to 3 years. Recommendation grade C	Gene carriers (HNPCC genes) and untested primary relatives of gene carriers: § Colonoscopy at first consulation or or 5 y younger then the youngest affected relative § Discuss gynaecological screening for endometrial or ovarian CA § Oesophago-duodeoscopy (OGD) for gastric CA screening § Consider screening for other cancers which may occur in specific families and are part of the HNPCC spectrum § Repeat colonoscopy & OGD every 2 y from 30-70 y. Recommendation grade C	Patients who have undergone curative CRC resection should be offered formal follow-up in order to facilitate detection of metastatic disease. Colonoscopic surveillance should be carried out as for adenomatous polyps Where the clinician suspects intraluminal recurrence, prompt colonoscopy is indicated. Recommendation grade A	1. ≤ 2 adenomas < 1 cm: surveillance colonoscopy at 5 years; if normal cease surveillance 2. ≥ 3 adenomas or at least one ≥ 1 cm or at least one showing severe dysplasia: surveillance colonoscopy at 3 years; if subsequently normal on two consecutive cases, cease surveillance 3. in case of uncertainty about complete removal of adenoma(s): follow-up colonoscopy ≤ 1 y 4. Colonoscopic surveillance should continue until age and fitness of the patient dictate that it should cease (consensus patient & doctor!) Recommendation grade D	1. Patients with left-sided colitis or pancolitis of 10 years duration should undergo 3 yearly colonoscopy with mucosal biopsies and biopsy of any suspected lesion. 2. The frequency of colonoscopy should increase to yearly when the disease has been present for 20 years or when indeterminate dysplasia has been diagnosed. Recommendation grade D	Not included
10	Guidelines for colorectal cancer screening in high risk groups[190].	British Society of Gastroenterology (BSG) Association of Coloproctology for Great Britain and Ireland (ACPGBI)	2002	1. FAP and variants: genetic testing + FS + OGD at puberty, repeat FS yearly 2. Juvenile polyposis and Peutz-Jegher: genetic testing + colonoscopy + OGD at puberty, repeat FS yearly	At risk HNPCC, or more than 2 FDR (refer to clinical geneticist) as well as documented MMR gene carriers: Colonoscopy +/- OGD at 25 y or five years before earliest CRC in family; gastroscopy at age 50 or five yrs before earliest gastric cancer in family; repeat colonoscopy and gastroscopy two yearly	1. Colonoscopy within 6 months of resection only if colon evaluation pre-op incomplete 2. Liver scan within two years post-op 3. Colonoscopy five yearly until 70 y	1. Low risk: 1-2 adenomas, both < 1 cm: colonoscopy - no surveillance or five years-cease follow up after negative colonoscopy 2. Intermediate risk: 3-4 adenomas OR at least one adenoma > 1 cm: colonoscopy every 3 years until two consecutive negative colonoscopies, then no further surveillance 3. High risk: > 5 adenomas or > 3 with at least one > 1 cm: annual colonoscopy until out of this risk group then interval colonoscopy as per Intermediate risk group 4. Large sessile adenomas removed piecemeal: colonoscopy or FS (depending on polyp location) 3 monthly until no residual polyp; consider surgery	1. Ulcerative colitis and Crohn's colitis: colonoscopy + biopsies every 10 cm, starting for pan-colitis eight years and for left-sided colitis 15 years from onset of symptoms; repeat 3 yearly in second decade, 2 yearly in third decade, subsequently annually 2. IBD + primary sclerosing cholangitis (pSC) +/- orthoptic liver transplant (OLT): colonoscopy with biopsy every 10 cm at diagnosis of PSC; repeat yearly	1. Uretero-sigmoidostomy: FS 10 yrs after surgery; repeat annually 2. Acromegaly: colonoscopy at 40 years; repaet 5 yearly

Nr.	Title	Issued by	Year	Familial Adenomatous Polyposis (FAP) & related	Hereditary Non-Polyposis Colon Cancer (HNPCC)	Personal history of CRC resection	Personal history of colonpolyps	Inflammatory bowel disease (IBD)	Miscellaneous
11	Follow-up na poliepectomie - Herziene richtlijn[189].	Kwaliteitsinstituut voor de Gezondheidszorg (CBO - NL)	2002	1. Genetic counseling and testing is recommended for all family members with a familial history compatible with criteria for HNPCC, FAP or attenuated FAP. Follow-up frequency should be dictated by the outcome of such testing (recommendation level 3). 2. Such genetic counseling and testing is optional for all family members with a familial CRC history or a sporadic CRC at young age. In these cases colorectal surveillance after 3 y is advisable, however supported by little data (recommendation level 4). 2. Such genetic counseling and testing is optional for all family members with a familial CRC history or a sporadic CRC at young age. In these cases colorectal surveillance after 3 y is advisable, however supported by little data (recommendation level 4).3. There is no need for intensivated surveillance in case of colorectal polyps found at young age in combination with a negative familial history (recommendation level 4).	1. Genetic counseling and testing is recommended for all family members with a familial history compatible with criteria for HNPCC, FAP or attenuated FAP. Follow-up frequency should be dictated by the outcome of such testing (recommendation level 3). 2. Such genetic counseling and testing is optional for all family members with a familial CRC history or a sporadic CRC at young age. In these cases colorectal surveillance after 3 y is advisable, however supported by little data (recommendation level 4).3. There is no need for intensivated surveillance in case of colorectal polyps found at young age in combination with a negative familial history (recommendation level 4).	Not included	1. CRC risk augments with number of adenomata (level 3). 2. Many adenomata found on follow-up colonoscopy were already present at indexcolonoscopy (level 3). 3. If ≤ 2 adenomata found at indexcolonoscopy → first FU-colonoscopy at 6 y; if ≥ 3 polys, after 3 y (level 3). 4. Patients with cumulative 1 adenoma at 65 y→ no need for further FU-colonoscopy (level 3). 5. In case of 2 cumulative adenomata at 65 y: continue till 75 y. For ≥ 3: lifetime FU colonoscopy warranted (level 4). 6. A completely resected adenoma does not recur (level 4). 7. All resected polyps need histological examination before setting up a surveillance strategy (level 4). 8. DCBE for FU after polypectomy is indicated if endoscopist doubts complete removal of all polyps (level 4). 9. Patients with high risk family history of CRC: more frequent FU warranted (level 4).	Not included	Not included

Nr.	Title	Issued by	Year	Familial Adenomatous Polyposis (FAP) & related	Hereditary Non-Polyposis Colon Cancer (HNPCC)	Personal history of CRC resection	Personal history of colonpolyps	Inflammatory bowel disease (IBD)	Miscellaneous
12	Preventive health care, 2001 update: colorectal cancer screening[28].	Canadian Task Force on Preventive Health Care (CTFPHC)	2001	1. genetic counseling should be performed prior to genetic testing 2. FS beginning at puberty 3. Individuals from families where the gene mutation has been identified but are negative themselves, require screening similar to the average risk population 4. For at risk individuals where the mutation has not been identified in the family or where genetic testing is not available, screening with annual or biennial FS should be undertaken beginning at puberty	1. Based on Level III evidence, the Task Force recommends screening with colonoscopy in individuals from HNPCC kindreds 2. The ages when screening should begin and the frequency at which colonoscopy should be performed are unclear.	Not included	Not included	Not included	Not included

RATING SCHEMES FOR THE STRENGTH OF EVIDENCE & RECOMMENDATIONS

Centre of Evidence Based Medicine (CEBM - UK)

Very detailed levels of evidence and grades of recommendation, adapted for reviewing different kinds of studies, were established by the NHS R&D Centre of Evidence Based Medicine[596] (latest version, March 2002**)**. In depth discussion of these various criteria remains outside the scope of this report.

Grade of recommendation	Level of Evidence	Therapy: whether a treatment is efficacious/ effective/harmful	Therapy: whether a drug is superior to another drug in its same class	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analysis
A	1a	SR (with homogeneity*) of RCTs	SR (with homogeneity**) of head-to-head RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
	1b	Individual RCT (with narrow Confidence Interval‡)	Within a head-to-head RCT with clinically important outcomes	Individual inception cohort study with > 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
	1c	All or none§		All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses‡‡
B	2a	SR (with homogeneity*) of cohort studies	Within a head-to-head RCT with validated surrogate outcomes‡‡‡	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
	2b	Individual cohort study (including low quality RCT; e.g., <80% follow-	Across RCTs of different drugs v. placebo in similar or different	Retrospective cohort study or follow-up of untreated control	Exploratory** cohort study with good††† reference standards;	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited

		up)	patients with clinically important or validated surrogate outcomes	patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only	CDR† after derivation, or validated only on split-sample§§§ or databases		review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
	2c	"Outcomes" Research; Ecological studies		"Outcomes" Research		Ecological studies	Audit or outcomes research
	3a	SR (with homogeneity*) of case-control studies	Across subgroup analyses from RCTs of different drugs v. placebo in similar or different patients, with clinically important or validated surrogate outcome		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
	3b	Individual Case-Control Study	Across RCTs of different drugs v. placebo in similar or different patients but with unvalidated surrogate outcomes		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
C	4	Case-series (and poor quality cohort and case-control studies§§)	Between non-randomised studies (observational studies and administrative database research) with clinically important outcomes	Case-series (and poor quality prognostic studies ***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"; or non-randomised studies with unvalidated surrogate outcomes	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

These levels were generated in a series of iterations among members of the NHS R&D Centre for Evidence-Based Medicine (Bob Phillips, Chris Ball, Dave Sackett, Brian Haynes, Sharon Straus and Finlay McAlister).

Notes

1. Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because of:
    - EITHER a single result with a wide Confidence Interval (such that, for example, an ARR in an RCT is not statistically significant but whose confidence intervals fail to exclude clinically important benefit or harm)
    - OR a Systematic Review with troublesome (and statistically significant) heterogeneity.
2. Grades of recommendation are shown as linked directly to a level of evidence. However levels speak only of the validity of a study not its clinical applicability. Other factors need to be taken into account (such as cost, easy of implementation, importance of the disease) before determining a grade. Grades that are currently in the guides link closely to the validity of the evidence - these will change over time to reflect better concerns that we highlight in the text of the guide or related CATs.

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category)
‡	See comment #2 for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
‡‡	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and equally or more expensive.
†††	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (eg 1-6 months acute, 1 - 5 years chronic)
‡‡‡	Surrogate outcomes are considered validated only when the relationship between the surrogate outcome and the clinically important outcomes has been established in long-term RCTs.

SIGN

The Scottish Intercollegiate Guidelines Network (SIGN[49]) published (2001) concise rating schemes for appraisal of the strength of evidence given by reviewed scientific articles. Different grades of recommendation relate to the strength of the evidence on which they are based:

I. Levels of Evidence:

- **1++** : High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
- **1+** : Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
- **1−** : Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
- **2++** : High quality systematic reviews of case control or cohort studies or high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
- **2+** : Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
- **2–** : Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- **3** : Non-analytic studies, e.g. case reports, case series
- **4** : Expert opinion

II. Grades of recommendation:

The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

- **A** : At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; *or a* body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
- **B** : A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
- **C** : A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
- **D** : Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

New Zealand Guidelines Group (NSGG)

The evidence-grading hierarchy used by the initial 1998 National Health Committee working party:

- **Grade 1:** RCT (randomised controlled trials can control for various forms of bias associated with screening).
- **Grade 2:** Non-RCT (randomisation is needed to minimise bias and confounding).
- **Grade 3:** Non-randomised historical cohort studies, case-control and other population studies (compare current outcomes due to intervention with previous outcomes, which may permit inappropriate groups to be compared).
- **Grade 4:** Case series (data are derived from a group of unselected individuals, and are limited in value).
- **Grade 5:** Expert (consensus) opinion (not evidence per se, but may have value where evidence is not likely to be or become available).

British Society of Gastroenterology (BSG)

Association of Coloproctology for Great Britain and Ireland (ACPGBI)

I. Categories of evidence

- **Ia:** Evidence obtained from meta-analysis of **ra**ndomised controlled trials.
- **Ib:** Evidence obtained from at least one randomised controlled trial.
- **IIa**: Evidence obtained from at least one well designed controlled study without randomisation.
- **IIb**: Evidence obtained from at least one other type of well designed quasi-experimental study.
- **III**: Evidence obtained from a well designed non-experimental descriptive study, such as comparative studies, correlation studies, and case studies.
- **IV**: Evidence obtained from expert committee reports or opinions or clinical experiences of respected **a**uthorities.

II. Grading of recommendations

The strength of each recommendation is dependent upon the category of the evidence supporting it, and is graded according to the following system.

- **A**: Evidence categories Ia and Ib.
- **B**: Evidence categories IIa, IIb, III.
- **C**: Evidence category IV.

U.S. Preventive Services Task Force (UPSTF)

the Canadian Task Force on Preventive Health Care (CTFPHC)

I. Quality of evidence rating according to 5 levels):

- **I** - Evidence from at least 1 properly randomized controlled trial (RCT).
- **II-1** - Evidence from well-designed controlled trials without randomization.
- **II-2** - Evidence from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
- **II-3** - Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included here.
- **III** - Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

II. Grades of Recommendation:

- **A**: The USPSTF strongly recommends that clinicians routinely provide the clinical preventive action to eligible patients. (The USPSTF found good evidence that the clinical preventive action improves important health outcomes and concludes that benefits substantially outweigh harms.)
- **B**: The USPSTF recommends that clinicians routinely provide the clinical preventive action to eligible patients. (The USPSTF found at least fair evidence that the clinical preventive action improves important health outcomes and concludes that benefits outweigh harms.)
- **C**: The USPSTF makes no recommendation for or against routine provision of the clinical preventive action. (The USPSTF found at least fair evidence that the clinical preventive action can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.)
- **D**: The USPSTF recommends against routinely providing the clinical preventive action to asymptomatic patients. (The USPSTF found at least fair evidence that the clinical preventive action is ineffective or that harms outweigh benefits.)
- **I**: The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing the clinical preventive action. (Evidence that the clinical preventive action is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.)

Institute of Clinical Systems Improvement (ICSI - USA)

Evidence is classed and graded as described below.

I. Classes of Research Reports :

A. Primary Reports of New Data Collection:

- **Class A:** Randomized, controlled trial
- **Class B:** Cohort study
- **Class C:** Non-randomized trial with concurrent or historical controls; Case-control study; Study of sensitivity and specificity of a diagnostic test; Population-based descriptive study
- **Class D:** Cross-sectional study; Case series; Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

- **Class M:** Meta-analysis; Systematic review; Decision analysis; Cost-effectiveness analysis
- **Class R:** Consensus statement; Consensus report; Narrative review
- **Class X:** Medical opinion

II. Conclusion grades

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system (defined in Section I, above) and are assigned a designator of +, -, or ø to reflect the study quality. Conclusion grades are determined by the work group based on the following definitions:

- **Grade I:** The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.
- **Grade II:** The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.
- **Grade III:** The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results from different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

- **Grade Not Assignable (N/A):** There is no evidence available that directly supports or refutes the conclusion.

The symbols +, –, ø, and N/A found on the conclusion grading worksheets are used to designate the quality of the primary research reports and systematic reviews:

- **+** indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis;
- **–** indicates that these issues have not been adequately addressed;
- **ø** indicates that the report or review is neither exceptionally strong or exceptionally weak;
- **N/A** indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

National Comprehensive Cancer Network (NCCN - USA)

Categories of Consensus

The NCCN Guidelines Steering Committee has devised a set of Categories of Consensus. These annotations contain two dimensions: the strength of the evidence behind the recommendation and the degree of consensus about its inclusion:

- **Category 1**: the recommendation is based on high-level evidence (i.e., high-powered randomized clinical trials or meta-analyses), and the Guideline Expert Panel has reached uniform consensus that the recommendation is indicated. In this context, uniform means near unanimous positive support with some possible neutral positions.
- **Category 2A**: the recommendation is based on lower level evidence, but despite the absence of higher level studies, there is uniform consensus that the recommendation is appropriate. Lower level evidence is interpreted broadly, and runs the gamut from phase II or large cohort studies to individual practitioner experience. Importantly, in many instances, the retrospective studies are derived from clinical experience of treating large numbers of patients at a member institution, so panel members have first-hand knowledge of the data. Inevitably, some recommendations must address clinical situations for which limited or no data exist. In these instances the congruence of experience-based opinions provide an informed if not confirmed direction for optimizing patient care. These recommendations carry the implicit recognition that they may be superseded as higher level evidence becomes available or as outcomes-based information becomes more.
- **Category 2B**: the recommendation is based on lower level evidence, and there is non-uniform consensus that the recommendation should be made. In these instances, because the evidence is not conclusive, institutions take different approaches to the management of a particular clinical scenario.

This non-uniform consensus does not represent a major disagreement, rather it recognizes that given imperfect information, institutions may adopt different approaches. A Category 2B designation should signal to the user that more than one approach can be inferred from the existing data.

- **Category 3**: including the recommendation has engendered a major disagreement among the panel members. The level of evidence is not pertinent in this category, because experts can disagree about the significance of high level trials. Several circumstances can cause major disagreements. For example, if substantial data exist about two interventions but they have never been directly compared in a randomized trial, adherents to one set of data may not accept the interpretation of the other side's results. Another situation resulting in a Category 3 designation is when experts disagree about how trial data can be generalized. A Category 3 designation alerts users to a major interpretation issue in the data and directs them to the manuscript for an explanation of the controversy.

National Health & Medical Research Council (NHMRC – Australia)

Levels of evidence

- **I** - Evidence obtained from a systematic review of all relevant randomised controlled trials
- **II** - Evidence obtained from at least one properly designed randomised controlled trial
- **III-I** - Evidence obtained from well-designed pseudo randomised controlled trials (alternate allocation or some other method)
- **III-2** - Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, casecontrol studies, or interrupted time series with a control group
- **III-3** - Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
- **IV -** Evidence obtained from case series, either post-test or pre-test/post-test.

Strength of recommendations

The strength of recommendations are determined by a expert advisory panel taking into account the level of evidence, quality of studies, size of effect and clinical importance for all the included studies, and ranges from 'Strongly recommended' to 'Strongly not recommended'. These levels of recommendation are modified from The Canadian Task Force on the Periodic Health:

- **Strongly recommended** : clinically significant level I in favour of clinical question — strongly recommended in favour.

- **Recommended** : clinically significant lower levels (e.g. II, III-1, III-2) in favour of clinical question — less strongly recommended in favour.
- **Equivocal** : lack of higher levels of evidence (e.g. III-3 or IV) OR equivocal level I or II evidence for and against clinical question — no recommendation for or against, as evidence is inconclusive — recommend further research.
- **Not recommended** : clinically significant lower levels (e.g. II, III-1, III-2) against the clinical question — weak recommendation against.
- **Strongly not recommended** : clinically significant level I against the clinical question — strong recommendation against.

APPENDIX FOR CHAPTER 5

INITIAL EXPLORATIVE SEARCH FOR EVIDENCE

Medline citations on CRC screening & surveillance form 2005 to Sept. 2006

#	Search History	Results
1	colorectal cancer.mp. [mp=ti, ot, ab, nm, hw]	28.785
2	screening.mp. [mp=ti, ot, ab, nm, hw]	22.1768
3	surveillance.mp. [mp=ti, ot, ab, nm, hw]	74.511
4	2 or 3	290.767
5	1 and 4	4.942
6	limit 5 to yr="2005 - 2006"	896
7	limit 6 to "core clinical journals (aim)"	139

INCREMENTAL CORE SEARCHES FOR EVIDENCE 2005-2006

Principal sources of information

The following databases were searched:

Bibliographic databases

- CRCT - Cochrane Central Register of Controlled Trials
- CDSR - Cochrane Database of Systematic Reviews
- CRD - Database of Abstracts of Reviews of Effectiveness (DARE)
- CRD - Health Technology Assessment database (HTA)
- CRD - NHS Economic Evaluation database (NHS EED)
- Ovid - Medline & PubMed
- Embase
- Cinahl
- BNI
- Econlit

Inclusion criteria

1. Studies were included if they compared the clinical effectiveness of:
    - fecal occult blood test (FOBT) screening, either immunochemical FOBT (iFOBT) screening or guaiac FOBT (gFOBT) screening;
    - colonoscopic screening.

Publications included primary research (published as full original reports) and secondary research (systematic reviews and meta-analyses).

For primary research studies relevant to the effectiveness of screening tests for CRC only randomised controlled trials (RCTs) were included, with the

exception of studies on colonoscopic screening where consideration was also made of study designs with lower levels of evidence to reflect the "best evidence" available on the subject. Those studies were mainly observational studies and diagnostic accuracy studies.

2. Secondary research studies reporting systematic reviews or meta-analyses of RCTs were included if they contained a methods section describing how the relevant studies were identified.
3. RCTs and other original studies on CRC screening participation and patient compliance were also included for documentary purposes.

Exclusion criteria

1. Non-systematic reviews, correspondence, editorials, expert opinion articles, comments, articles published in abstract form only, conference proceedings, studies that did not clearly describe their methods/results, and exclusively animal studies.
2. Studies on CRC screening in specific non-European ethnic (sub)groups.
3. All searches were limited to the years 2005 - 2006 and were completed on October, 31st 2006.

NOTE

Following tables (and counts) are limited to the years 2005-2006 (October, 31st). However, searches were also performed for the last three months of 2004, with elimination of those publications referred to in the NZHTA report, 2005.

Ovid MEDLINE 1966 to Present incl. In-Process & Other Non-Indexed Citations

#	Search History	Results
1	exp colorectal neoplasms/	98.806
2	(colo$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	96.785
3	((bowel or intestin$) adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	23.607
4	(sigmoi$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	3.199
5	((caec$ or cec$) adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	1.967
6	(rect$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	28.102
7	1 or 2 or 3 or 4 or 5 or 6	134.787
8	mass screening/	54.473
9	screen$.mp.	299.229
10	8 or 9	299.230
11	7 and 10	9.577
12	limit 11 to yr="2005 - 2006"	1.557

Embase

#	Search History	Results
1	'colorectal cancer'/exp	27.173
2	'colorectal tumor'/exp	9.622
3	'mass screening'/exp	84.881
4	('colorectal cancer'/exp) OR ('colorectal tumor'/exp)	36.575
5	('mass screening'/exp) AND (('colorectal cancer'/exp) OR ('colorectal tumor'/exp))	4.356
6	('mass screening'/exp) AND (('colorectal cancer'/exp) OR ('colorectal tumor'/exp)) AND [embase]/lim	3.439
7	('mass screening'/exp) AND (('colorectal cancer'/exp) OR ('colorectal tumor'/exp)) AND [2005-2006]/py	950
8	(('mass screening'/exp) AND (('colorectal cancer'/exp) OR ('colorectal tumor'/exp)) AND [embase]/lim) AND (('mass screening'/exp) AND (('colorectal cancer'/exp) OR ('colorectal tumor'/exp)) AND [2005-2006]/py)	781

BNI & Archive

#	Search History	Results
1	(colo$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	318
2	((bowel or intestin$) adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	47
3	(sigmoi$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	1
4	(rect$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	16
5	screen$.mp.	5.381
6	1 or 2 or 3 or 4	346
7	5 and 6	121

CINAHL

#	Search History	Results
1	exp colorectal neoplasms/	3.793
2	(colo$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	4.228
3	((bowel or intestin$) adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	561
4	(sigmoi$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	247
5	((caec$ or cec$) adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	20
6	(rect$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	558
7	1 or 2 or 3 or 4 or 5 or 6	4.969
8	screen$.mp.	26.488
11	7 and 8	1.239
12	limit 11 to yr="2005 - 2006"	265

CCRT

#	Search History	Results
1	exp colorectal neoplasms/	2.237
2	(colo$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	3.134
3	((bowel or intestin$) adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	357
4	(sigmoi$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	82
5	((caec$ or cec$) adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	5
6	(rect$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	1.108
7	1 or 2 or 3 or 4 or 5 or 6	3.940
8	mass screening/	1.138
9	screen$.mp.	7.778
10	8 or 9	7.778
11	7 and 10	344
12	limit 11 to yr="2005 - 2006"	40

CDSR

#	Search History	Results
1	(colo$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	120
2	((bowel or intestin$) adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	25
3	(sigmoi$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	6
4	((caec$ or cec$) adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	1
5	(rect$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	41
6	screen$.mp.	1.936
7	1 or 2 or 3 or 4 or 5	137
8	6 and 7	59

DARE

#	Search History	Results
1	(colo$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	79
2	((bowel or intestin$) adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	1
3	(sigmoi$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	0
4	((caec$ or cec$) adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	0
5	(rect$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	21
6	screen$.mp.	669
7	1 or 2 or 5	83
8	6 and 7	17

CRD - NHS EED & HTA database

#	Search History	Results
1	colorectal cancer/All fields AND screening/All fields	140
2	limit to 2005-2006	17

Econlit

#	Search History	Results
1	(colo$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	23
2	((bowel or intestin$) adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	3
3	(sigmoi$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	0
4	((caec$ or cec$) adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	0
5	(rect$ adj (cancer$ or neoplas$ or malign$ or carcino$ or adeno$ or polyp$ or tubul$ or vill$ or tum$)).mp.	1
6	1 or 2 or 5	26
7	screen$.mp.	1.163
8	1 and 7	15
9	limit 8 to yr="2005 - 2006"	0

APPENDIX FOR CHAPTER 6

INCREMENTAL COST EFFECTIVENESS SEARCHES 2004 - 2006

Details of searches conducted October 31st, 2006.

MEDLINE, OVID Search Engine limited to the years 2004-2006

#	Search History	Results
1	exp colorectal neoplasms/	97.924
2	(colorectal adj (carcino$ or adeno$)).tw.	12.965
3	(colon$ adj (cancer or neoplas$ or malignan$ or carcino$ or adenocarcino$ or polyp$)).tw.	31.240
4	(bowel adj (cancer or neoplas$ or malignan$ or carcino$ or adenocarcino$ or polyp$)).tw.	1.850
5	(sigmoid adj (cancer or neoplas$ or malignan$ or carcino$ or adenocarcino$ or polyp$)).tw.	282
6	((caecum or cecum) adj (cancer or neoplas$ or malignan$ or carcino$ or adenocarcino$ or polyp$)).tw.	31
7	((rectal or rectum) adj (cancer or neoplas$ or malignan$ or carcino$ or adenocarcino$ or polyp$)).tw.	10.486
8	(colorectal adj (cancer or neoplas$ or malignan$ or polyp$)).tw.	29.882
9	((caecal or cecal) adj (cancer or neoplas$ or carcino$ or adenocarcino$ or malignan$ or polyp$)).tw.	247
10	((rectal or rectum) adj adenoma).tw.	60
11	((colorectal or colon or sigmoid or bowel or caecal or caecum or cecal or cecum) adj adenoma).tw.	680
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	112.299
13	mass screening/ or screen$.tw.	265.613
14	12 and 13	7.622
15	Limit 14 to yr="2004 - 2006"	1.748
16	exp Costs and Cost Analysis/	128.319
17	Cost$.mp.	248.660
18	16 or 17	255.141
19	15 and 18	190
	comment: 13 duplicates so finally 177 unique records	177

EMBASE, limited to the years 2004-2006

#	Search History	Results
1	('mass screening'/exp OR 'mass screening') AND [2004-2006]/py	18.630
2	('colon cancer'/exp OR 'colon cancer') AND [2004-2006]/py	17.237
3	colorectal AND ('cancer'/exp OR 'cancer') AND [2004-2006]/py	14.032
4	colorectal AND ('carcinoma'/exp OR 'carcinoma') AND [2004-2006]/py	5.197
5	#2 OR #3 OR #4	20.933
6	('economic evaluation'/exp OR 'economic evaluation') AND [2004-2006]/py	27.996
7	#1 AND #5 AND #6	188

CDSR (Cochrane Database of Systematic Reviews), no time limit

#	Search History	Results
1	colorectal neoplasm.mp. [mp=title, short title, abstract, full text, keywords, caption text]	4
2	colorectal neoplasm$.mp. [mp=title, short title, abstract, full text, keywords, caption text]	24
3	colorectal cancer.mp. [mp=title, short title, abstract, full text, keywords, caption text]	81
4	colon cancer.mp. [mp=title, short title, abstract, full text, keywords, caption text]	40
5	colorectal carcinoma.mp. [mp=title, short title, abstract, full text, keywords, caption text]	11
6	colon carcinoma.mp. [mp=title, short title, abstract, full text, keywords, caption text]	8
7	rectal carcinoma.mp. [mp=title, short title, abstract, full text, keywords, caption text]	12
8	rectal cancer.mp. [mp=title, short title, abstract, full text, keywords, caption text]	22
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	116
10	colorectal carcinoma.mp. [mp=title, short title, abstract, full text, keywords, caption text]	11
11	9 or 10	116
12	screening$.mp. [mp=title, short title, abstract, full text, keywords, caption text]	989
13	mass screening.mp. [mp=title, short title, abstract, full text, keywords, caption text]	30
14	12 or 13	989
15	cost$.mp. [mp=title, short title, abstract, full text, keywords, caption text]	2265
16	15 and 14 and 11	25

CRD (Dare, NHS, EED, HTA), and limited to the years 2004-2006

('colorectal cancer' OR 'colorectal carcinoma' OR colon cancer' OR colon carcinoma' or rectum cancer or rectum carcinoma) AND screening AND cost$: result 161 articles

EVIDENCE TABELS ECONOMIC EVALUATIONS

Table 1: overview of economic evaluations of FOBT

Study, country, analytic technique	Perspective, Trial	Interventions and population	Cost items included Year of pricing	Sensitivity analysis	Result
Whynes et al. (1998, 1999) United Kingdom CUA Time window Discount % Based on trial data up to a median follow-up of eight years. Markov-based model to estimate longer-term ICERs. Discount rate: 6%	UK National Health Service, Based on outcomes of Nottingham RCT	No screening versus biennial FOBT screening using guaiac-based FOBT (unrehydrated Hemoccult II). Target population aged between 50 and 74 years	Invitation and FOBT testing, diagnosis, investigation, treatment and follow-up. Year of pricing: 1995-1996	One-way sensitivity analysis: - FOBT costs (+10%) - COL costs (+10%) - Double the cost differential between treating early- and late-stage cancer - effect of annual screening - survival gains early-stage detection (-10%) - discount rate survival gains (3%), - sensitivity (+10%) and specificity (-10%) - compliance 5 different scenarios	Cost per QALY based on 8-year follow-up: (scenario 1) - 5685 for males - 4951 for females Cost per QALY considering lifetime costs and outcomes (scenario 3) - 2047 for males - 1371 for females 1£ = €1.49

Study, country, analytic technique	Perspective, Trial	Interventions and population	Cost items included Year of pricing	Sensitivity analysis	Result
Gyrd-Hansen et al (1998, 1999) Denmark CEA Time window Discount % Estimation of costs and effects was performed by modelling over a period of 36 years Discount rate: 5%	National health care perspective, Based on outcomes of Funen-1 RCT	No screening versus FOBT screening (unhydrated Hemoccult-II) Screening intervals: 3, 2, 1.5 and 1 year. Individuals between 50 years and 75 years. Target groups: 70–74, 65–74, 65–69, 60–64, 60–69, 60–74, 55–59, 55–64, 55–69, 55–74, 50–54, 50–59, 50–64, 50–69 and 50–74 years	Variable costs: FOBT costs (9 DKK), mailing costs (11.5 DKK), test analysis (8 DKK), COL costs (1000 DKK), physician consultation (100 DKK), coordinator and secretary costs (19.65 DKK) Fixed costs: Computer assistant (16 800 DKK), software (150 000 DKK), offices (36 000 DKK), inventory (6000 DKK) Treatment and follow-up: Cost savings due to avoided treatment (119 000 DKK), follow-up (COL every 3 years until the age of 75 years) Year of pricing: 1993	one-way and multi-way sensitivity analyses on: - FOBT costs (20 DKK), - COL costs (3000 DKK), - effect of adenoma follow-up, - excess survival rate, - discount rate, - scope of analysis (production losses, future unrelated health costs) Scenario analysis: 60 possible CRC screening programs (combining various screening intervals and target groups)	The six most efficient programs: - 65-74 biennial: 17 000 DKK - 60-74 biennial: 18 896 DKK - 55-74 biennial: 23 012 DKK - 55-74 1.5 years: 28 802 DKK - 55-74 annual: 35 471 DKK - 50-74 annual: 42 500 DKK 1 DKK = €0.13
Helm et al. (2000) USA CEA Time window Discount % Costs and effects were calculated over a period of 10 years. Discount rate: 3%	Not explicitly mentioned (estimated costs and corresponding Medicare payments). Data alongside 3 trials: - Minnesota RCT (US) - Funen-1 RCT (Denmark) - Nottingham RCT (UK)	No screening versus annual (Minnesota) or biennial (Funen and Nottingham) FOBT. Relevant cohort of US population - cohort aged 45-75 years for the Nottingham and Funen-1 trial results; - cohort aged 50-80 years for the Minnesota trial results.	Cost of detection: - FOBT costs ($10); diagnostic COL ($1260), Colonoscopy, polypectomy, pathology ($1930), FSIG ($430), DCBE ($220), surgical pathology ($110) Cost of treatment: from diagnosis until death or 15 years - $48 300 for Dukes' stage A and B (local), - $67 500 for stage C (regional), - $59 300 for stage D (remote) - follow-up (COL every 3 years) Year of pricing: 1997	Sensitivity analysis only on costs, derived from the 10th and 90th percentile charges.	Incremental cost effectiveness per life-year saved: - $20 500 (range: 11 400 – 32 500) in the US trial, - $2700 (range: 1600 - 4200) in the Danish trial, - $2500 (range: 1300 - 4200) in the UK trial. 1$ = €0.79

Study, country, analytic technique	Perspective, Trial	Interventions and population	Cost items included Year of pricing	Sensitivity analysis	Result
Flanagan et al. (2003) Canada CEA Time window Discount % Costs and effects were calculated over a period of 25 years. Discount rate: 5%	Payer's perspective (government) Primarily based on the Funen RCT (used parameter estimates from the other trials (Minnesota and Nottingham) where appropriate)	No screening versus biennial CRC screening using FOBT (unrehydrated Hemoccult II). Individuals aged 50-74 years	Head office, satellite and promotion (per year) CAD15 000 000 - CAD30 000 000 Cost of detection: FOBT kit (CAD4.65 - CAD9.30), Processing (per FOBT) (CAD6 - CAD8), Consultation (per positive FOBT) (CAD123.7 - CAD161.1), Colonoscopy (per positive FOBT or follow-up to polyps) (CAD350 - CAD425) Cost of treatment: - Polypectomy (CAD147) - other treatment costs from base CRC model Complications - Perforation (0.17%), hemorrhage (0.03%), and death (0.02%). Follow-up - COL (performed at three, five, and 10-year intervals if polyps were found) Year of pricing : not explicitly stated	One way sensitivity analysis: - costs - annual screening - participation (76% → 50%) - age cohort (start ages from 40 to 60 and end ages from 60 to 90) - discount rate (0%, 3% and 5%)	The ICER of biennial screening was CAD11 907. The ICER of annual screening was CAD13 497. When costs increased, the ICER was CAD18 445 with biennial screening and CAD19 893 with annual screening. When the participation rate was reduced from 67% to 50%, the biennial screening became less cost effective (CAD15 688). 1 CAD = €0.71

Study, country, analytic technique	Perspective, Trial	Interventions and population	Cost items included Year of pricing	Sensitivity analysis	Result
Whynes (2004) UK CEA Time window Discount % Duration of follow-up in trial: 11 years Discount rate: 6% for costs and 2% for benefits	UK National Health Service, Based on outcomes of Nottingham RCT	No screening versus biennial FOBT screening for CRC using 3-day Hemocult (initially Hemoccult 3- or 6-day sample collection, Facatwin/Feca EIA (Feca), or both Feca and Hemoccult) Individuals, aged 45-74 years	- FOBT costs (£3.29 for costs of the test kit, administration and return postage) - test developed by nurse (£0.19) - COL (£187) - mean treatment cost (£4340 (CI: 3977 - 4702) Year of pricing: 2002	One-way sensitivity analyses: - discount rate (0% and 12%) - survival estimate (1.34 years instead of 1.12 years) cost items (doubled) - cost testing - cost investigation - treatment cost	Under conservative assumptions, the incremental cost of screening per life year gained was £1584 (CI: 717 - 8612). 1£ = €1.49
Stone et al. (2004) Australia CEA and CUA (DALY) Time window Discount % Long-term horizon Discount rate: 3%	Australian government Based on meta-analysis of the properties of the FOBTs used in the Nottingham (UK), Funen-1 (Denmark) and the Göteburg (Sweden) RCTs. The Minnesota RCT was excluded (because of the high positivity rate of their FOBT).	Biennial guaiac based FOBT compared with the status quo of minimal opportunistic screening. Individuals aged 55-69 years Marginal analysis on including younger and older age groups.	Gross costs (screening program costs only) included: - infrastructure (AUD 7.9 million), - FOBT screens (FOBT kit, transport, processing, GP visit: AUD 41), - diagnostic work-up (Colonoscopy AUD 1000; Initial visit + follow up: AUD 176), - cost of complications (0.17%/COL perforations (AUD 15 000)). Net costs included: - projected treatment savings (stage A&B: AUD 14 000; C: AUD 22 000; D: AUD 19 000; palliation: AUD 25 000), - savings from reduced de facto screening by colonoscopy (AUD 1000), - additional expense anticipated from increased follow-up activity (AUD 880). Year of pricing: 1996	Multi-way probabilistic sensitivity analysis was performed (using normal, uniform, and triangular distributions)	Gross cost/DALY: 45-49: AUD 56 000 (42 000 - 216 000) 50-54: AUD 29 000 (22 000 - 97 000) 55-69: AUD 17 000 (13 000 - 52 000) 70-74: AUD 12 000 (9000 - 36 000) 75+: AUD 15 000 (11 000 - 46 000) Net cost/DALY: 45-49: AUD 50 000 (40 000 - 223 000) 50-54: AUD 24 000 (20 000 - 96 000) 55-69: AUD 12 000 (10 000 - 47 000) 70-74: AUD 5300 (4500 - 29 000) 75+: AUD 6600 (5400 - 33 000) 1 AUD = €0.60

Study, country, analytic technique	Perspective, Trial	Interventions and population	Cost items included Year of pricing	Sensitivity analysis	Result
Lejeune et al. (2004) France CEA Time window Discount % Modelling over a 10 and 20-year period, or until the age of 85, or until death. Discount rate: 3%	The French healthcare insurance system Burgundy trial	No screening versus biennial screening using FOBT (Hemoccult-II). Individuals aged 50 to 74 years.	- organizational costs (€1.26 per target individual) (incl. labour costs and equipment); - invitations (€0.65 per target individual), (incl. conception and printing of the letter and of the information leaflet sent, preparing the mailing, the cast of postage, training the GP and informing the entire medical profession), - cost screening test (€12.52 per test) (incl. cost of test, remuneration GP for offering the test, cost of mailing the test or the reminder letter), - test analysis (€4 per test) (incl. overhead costs, capital expenditure, running costs, and labour costs), - COL (€526). In the case of polypectomy, the cost was €641. Some other costs were obtained from published sources. - Treatment cost: stage I: €15 579, Stage II: €21 858 , Stage III: €31 110, stage IV: €17 384 - Follow-up: €843 per patient (over a 5-year period) Year of pricing: 2002	One-way sensitivity analysis: - acceptability rate FOBT (+10ppt, -10ppt, -20ppt) - diagnostic performance FOBT (sensitivity: 60 → 70%, specificity: 99 → 90%) - cost of test kit (-50%) - COL (min: €225 ; max: €830) - polypectomy (min: €330 ; max: €1000) - treatment: Minimum st.I: €14 063; st.II: €17 486; st.III: €24 888; st.IV: €13 907 Maximum st.I: €21 055; st.II: €26 230; st.III: €37 332; st.IV: €20 861 - starting and end ages - undiscounted LYG	ICER: - €3357 / LYG (over 20 years) - €4705 / LYG (over 10 years)

Table 2: overview of economic evaluations with guaiac and immunochemical FOBT

Study, country, Analytic technique	Perspective, Trial	Interventions and population	Cost items included Year of pricing	Sensitivity analysis	Result
Gyrd-Hansen et al (1998b) Denmark CEA Time window, Discount % Costs and effects were modelled over a 36-year period. Discount rate: 5%	Third-party payer perspective. - unrehydrated Hemoccult II: data from the Funen-1 RCT. - rehydrated Hemoccult II: data from the Minnesota RCT and the Göteborg trial. - HemeSelect and Hemoccult II Sensa: data derived from the literature.	Screening of 55-74 year olds at one- and two-year intervals, as well as screening 50-74 year-olds annually. No screening versus screening with: - unhydrated Hemoccult II (H-II) test alternative FOBT: - rehydrated Hemoccult II test - Hemeselect - Hemoccult II Sensa	Costs of screening tests, diagnostic tests, and treatment, as well as overhead costs such as costs of equipment, personnel, and facilities. - COL (1100DKK) - FOBT (30DKK) Year of pricing: 1993	One-way sensitivity analyses: - cost of COL (1600DKK) - cost of FOBT (40DKK) - sensitivity and specificity	Unhydrated Hemoccult II is the most cost-effective FOBT test. The most cost-effective screening programs were: - biennial screening of 55-74 year olds using unrehydrated Hemoccult II: 17,500 DKK/LYG - annual screening of 55-74 year olds using unrehydrated Hemoccult II: 30,000 DKK/LYG - annual screening of 50-74 year olds using unrehydrated Hemoccult II: 39,000 DKK/LYG - annual screening of 50-74 year olds using HemeSelect: 71,300 DKK/LYG - annual screening of 50-74 year olds using rehydrated Hemoccult II: 138,100 DKK/LYG 1 DKK = €0.13

Study, country, Analytic technique	Perspective, Trial	Interventions and population	Cost items included Year of pricing	Sensitivity analysis	Result
Van Ballegooijen et al (2003) USA CEA Time window, Discount % Costs and effects were followed for the entire life of each person. Discount rate: 3%	Third-party payer perspective. Data for this study were mainly derived from US Studies, including the Minnesota RCT.	This study compared the cost-effectiveness of annual screening versus no screening of individuals aged 65-79 years using: - guaiac-based FOBTs Hemoccult II and HemoccultSENSA - hypothetical immunochemical FOBT assumed to have comparable sensitivity to HemoccultSENSA but with higher specificity (95% and 98%).	- guaiac FOBT: $4.50 - iFOBT: assumptions on price ($4.5, $18, $27 and $28) - diagnostic colonoscopy: $650 - diagnostic colonoscopy plus biopsy: $683 - polypectomy: $750 treatment costs: - $26 800 for the initial treatment of colorectal cancer, - $2100 annually for continuing care cost following initial treatment, - $21 700 for terminal care costs for those who die of CRC. Follow-up Year of pricing: 2002	Multi-way sensitivity analysis on - iFOBT payment levels and - iFOBT test characteristics Threshold analysis on the cost effectiveness under different assumptions about iFOBT performance characteristics - increased sensitivity of iFOBT versus gFOBT (+25, 50, 75, and 100%) - specificity (95% and 98%)	If we assume a specificity of 98% for iFOBT, it is a test that would be economically preferred to Hemoccult II at the current level of payment and be preferred to Hemoccult Sensa even at a much higher payment level.
Berchi et al (2004) France CEA Time window, Discount % Population screened over 20 years. Discount rate: 5% (only on costs)	Third-party payer perspective. - Epidemiological and cost data were based on a screening program in Calvados (France). - Data on characteristics of the gFOBTs were based on the Funen-I RCT. - Data on the characteristics of the iFOBT were derived from Zappa et al. (2001), based on a trial in Florence (Italy)[597].	Biennial CRC screening of individuals aged 50 to 74 years with Guaiac-based FOBT Hemoccult versus immunochemical FOBT Magstream.	- costs of organising and managing the campaign (total annual cost of €63 256 or €0.38 per individual) - cost of testing (€8.84 immunologic, €10.98 guaiac), - COL costs (€457.35) - costs follow-up (colonoscopy performed every three years) - treatment costs: stage A: €17 579 stage B: €21 858 stage C: €31 110 stage D: €17 384 - follow-up costs (COL 3-yearly) Year of pricing: not explicitly reported.	One-way sensitivity analysis: - participation rate, - cost of Hemoccult test, - cost of COL, - cost of CRC treatment, - sensitivity and specificity, - natural history of CRC, - discount rate (only on costs)	The incremental cost-effectiveness of screening using Magstream versus Hemoccult was estimated to be €7458/LYS after 10 years and €2980/LYS after 20 years of screening.

Table 3: overview of economic evaluations with colonoscopy

Study, country, Analytic technique	Perspective	Interventions and population	Cost items included Year of pricing	Sensitivity analysis	Results
Sonnenberg et al. (2000) USA CEA Time window, Discount % Lifetime modelling Discount rate: 3%	Third-party payer perspective.	The study compared the cost-effectiveness of: - FOBT (annual), - flexible sigmoidoscopy (every 5 years), - and colonoscopy (every 10 years) versus each other and versus no screening Individuals of 50 years of age.	- FOBT costs ($3.5) - COL costs ($696) - polypectomy ($1004) - bleeding ($4360) - perforation ($13 000) - care for colorectal cancer ($45 228) Year of pricing: 1998	One-way sensitivity analysis: Sensitivity FOBT (30-50%, base 40%), specificity FOBT (70-99%, base 97.5%), screening interval FOBT (1-3 years), screening interval COL (3-10 years), surveillance interval after polypectomy (1-5 years), annual incidence of adenomas (1-6%, base 1%), efficacy of COL in preventing CRC (50-100%), compliance (base 100%) Multi-way sensitivity analysis: Frequency of COL (5years), efficacy COL (50%, instead of 75%), and compliance with repeated colonoscopy was reduced to 80% (instead of 100%).	Additional cost per extra life-year saved was $9705 for FOBT over no screening. Colonoscopy offered an additional cost per extra life-year saved of $11 382 over FOBT. 1$ = €0.79

Study, country, Analytic technique	Perspective	Interventions and population	Cost items included Year of pricing	Sensitivity analysis	Results
Frazier et al. (2000) USA CEA Time window, Discount % Lifetime modelling Discount rate: 3%	Third-party payer perspective. (not societal perspective as mentioned in the study)	The study compared no screening with the following strategies: - annual guaiac FOBT: two types, i.e. rehydrated (RFOBT) and unrehydrated (UFOBT) were considered - COL (10-yearly) - annual FOBT + SIG (5-yearly) - annual FOBT + SIG (10-yearly) - five-yearly flexible sigmoidoscopy - 10-yearly flexible sigmoidoscopy - DCBE every five years - DCBE every ten years 1-time screens at 55 years of age: - SIG, DCBE, and COL SIG_1: SIG followed by COL if high-risk adenomatous polyp diagnosed SIG_2: SIG followed by COL if either low- or high-risk polyp diagnosed at SIG 50-year-old individuals	- FOBT costs ($38) - COL costs ($1012) - COL + polypectomy ($1519) Predicted lifetime costs: - localized cancer ($22 000) - regional cancer ($43 900) - distant cancer ($58 300) Year of pricing: 1998	Two base-case analysis were performed with 60% and 100% compliance (results only presented for 60%) One-way sensitivity analysis was performed on several variables but only results of the influence on the ICER of RFOBT + sigmoidoscopy every 5years were presented.	For white men (outcomes for black men and white and black women not reported due to constraints of space) the ICERs were: - SIG_1 at age 55 versus no screening: $1200 - SIG_2: at age 55 versus SIG_1 at age 55: $11 000 - SIG_1 every 10y versus SIG_2: at age 55: $15 800 - SIG_2 every 10y versus SIG_1 every 10y: $16 100 - UFOBT + SIG_2 every 10y versus SIG_2 every 10y: $21 200 - UFOBT + SIG_2 every 5y versus UFOBT + SIG_2 every 10y: $51 200 - RFOBT + SIG_2 every 5y versus UFOBT + SIG_2 every 5y: $92 900 1$ = €0.79

Study, country, Analytic technique	Perspective	Interventions and population	Cost items included Year of pricing	Sensitivity analysis	Results
Leshno et al. (2003) Israel CEA Time window, Discount % Screening and/or surveillance continued until 79 years of age. Discount rate: 3%	Third-party payer.	6 screening strategies: - no screening - one-time COL - COL repeated at a 10-year interval (COL-10) - annual FOBT - annual FOBT and flexible SIG in a 5-year interval (FOBT+SIG) - annual detection of altered human DNA in a stool test. Individuals aged 50 years	- cost FOBT (40 ILS) - COL (800 ILS) - COL + polypectomy (1000 ILS) - major complications (15 000 ILS) - treatment localized CRC (44 000 ILS) - treatment regional CRC (85 000 ILS) - treatment distant CRC (170 000 ILS) Year of pricing: 2000	One- and two-way sensitivity analysis: Cost COL + polypectomy (800, 1350 ILS), cost complications (10 000, 25 000 ILS), treatment localized CRC (35 000 ILS), treatment regional CRC (70 000, 100 000 ILS), effectiveness in treatment localized CRC (70, 90%), effectiveness in treatment regional CRC (60, 70%), probability major complications COL (0.10, 0.23, 0.30%), compliance follow-up COL (40, 60, 100%), prevalence polyps at age 50 (5, 10, 17%), lesions in lower colon (40, 60, 80%), time horizon (30, 32.5, 35 years), compliance FOBT and COL	FOBT+SIG had a C/E ratio of 1268 ILS per life-year saved compared to one time colonoscopic screening 1 ILS = €0.18
Wong et al. (2004) Singapore CEA Time window, Discount % The model starts with the population at age 50 and progresses over a time horizon of 50 years. No discounting	Not reported	no screening versus: - annual guaiac FOBT, - annual immonechemical FOBT, - 5-yearly DCBE, - 3-yearly FSIG, - 10-yearly COL Individuals aged 50 to 70 years.	- cost gFOBT (SGD10) - cost iFOBT (SGD30) - cost DCBE (SGD80) - cost FSIG (SGD240) - cost COL (SGD740) - COL + polypectomey (SGD800) - treatment stage A or B (SGD20 000) - treatment stage C or D (SGD35 000) - cost of complications (SGD8706) Year of pricing: not mentioned	No	Guaiac Fecal Occult Blood Test (FOBT) is most cost effective test at SGD162.11/LYG 1SGD = €0.50

Study, country, Analytic technique	Perspective	Interventions and population	Cost items included Year of pricing	Sensitivity analysis	Results
O'Leary et al. (2004) Australia CEA Time window, Discount % A 10-year time-frame. Discount rate: 5%	From the perspective of the government-funded health system.	No screening versus: - flexible SIG (every 10 years) - COL (every 10 years) - annual and biennial FOBT (rehydrated hemoccult) Individuals aged 55-64 years	- FOBT (AUD26.40) - pathology tests (AUD70) - COL (AUD897) - COL with polypectomy (AUD1325) - surgery for adenoma removal (AUD5717) - chemotherapy (AUD9063) - radiotherapy (AUD7980) - perforation (AUD15 777) - cost detection when no screening (AUD83.90) - cost of treatment stage A: AUD15 318 stage B: AUD29 804 stage C: AUD23 021 stage D: AUD5596 - GP visit: AUD28.75 - specialist visit: AUD67.65 - investigation cost when no screening: AUD1463 - investigation cost when screening: AUD1395 - program administration cost: AUD75.13 per invited person Year of pricing: 2001	One-way sensitivity analysis: - adenoma > 10mm progressing to cancer - discount costs (0, 10%) - discount outcomes (0, 10%) - cost COL (AUD718, 1076) - administrative cost screening program (AUD0, 100) - compliance screening program (40, 100% versus baseline 42% for COL and SIG and 60% for FOBT)	ICER per extra life year compared with no screening: - Flexible sigmoidoscopy: AUD16 801 - colonoscopy: AUD19 285 - Biennal FOBT: AUD41 183 - Annual FOBT: AUD46 900 1AUD = €0.60

Study, country, Analytic technique	Perspective	Interventions and population	Cost items included Year of pricing	Sensitivity analysis	Results
Ladabaum et al. (2005) USA CEA Time window, Discount % Individuals progress through the model for 50 one-year cycles, until age 100 years or death. Discount rate: 3%	Third party payer perspective.	No screening versus: - annual FOBT, - flexible SIG (every 5 years) - FOBT/FSIG combined, - COL (every 10 years) emerging strategies: - faecal DNA testing (every 5 years) with different test performance characteristics (F-DNA-base and F-DNA-optimized), - virtual colonoscopy every 10 years, modelled with midrange published values (VC-base) and a good case scenario (VC-Pickhardt) Individuals aged 50 years. Screening and surveillance were performed from age 50 years up to and including age 80 years.	- FOBT ($20) - COL ($820) - COL + biopsy or lesion removal ($1200) - endoscopy complication ($26 000) - CRC treatment localized ($46 000) regional ($68 000) distant ($71 000) Year of pricing: 2003	No sensitivity analysis on cost-effectiveness estimates	Compared with no screening, cost per LYG: - FOBT: $8100, - FSIG: $17 300, - FOBT/FSIG: $18 700 - COL: $18 800, - F-DNA-base: $73 200, - F-DNA-optimized: $31 000, - VC-base: $28 700 - VC-Pickhardt: $26 600 1$ = €0.79

Study, country, Analytic technique	Perspective	Interventions and population	Cost items included Year of pricing	Sensitivity analysis	Results
Maciosek et al. (2006) USA CEA Time window, Discount % Lifetime horizon Discount rate: 3%	Societal perspective	no screening versus screening with: - annual FOBT, - SIG every 5 years - COL every 10 years People aged 50 years and older.	- Cost FOBT: $18, - Cost COL $572, - COL with tissue removal: $796 Net costs: (derived from Vijan study)[598] - value of resources used in providing the preventive service - plus any follow-up services, - minus the resource savings from averted disease or injury. Discounted net costs: - FOBT: $183 - COL: $323 Adjustment for time cost: - $109 for annual FOBT - $55 for 10-year COL Year of pricing: 2000	One-way sensitivity analysis - discount rate - adherence with screening and follow-up	ICER: - FOBT: $13 334/LYG - SIG: $18 869/LYG - COL: $8840/LYG Weighted average : $11 947/LYG Weights = relative delivery of FOBT (48%), SIG (9%) and COL (43%) in 2003 1$ = €0.79

Study, country, Analytic technique	Perspective	Interventions and population	Cost items included Year of pricing	Sensitivity analysis	Results
Wu et al. (2006) Taiwan CEA Time window, Discount % Cohort followed for 25 years Discount rate: 3%	third-party payer perspective	No screening versus: - stool DNA testing (triennial, five-yearly, and ten-yearly) - no screening - annual FOBT - flexible sigmoidoscopy (5-yearly) - colonoscopy (10-yearly) Population aged 50 to 75 years.	Screening: - FOBT ($0.6) - Colonoscopy ($66.2) Treatment and confirmation: - Pathological examination ($20.6) - Biopsy ($13.2) - Polypectomy ($42.4) - Initial cost for early CRC ($3117.6) - Initial cost for late CRC ($7705.9) - Continuing cost for CRC ($176.5) - Terminal Care for CRC ($7647.1) - Complication cost for perforation ($1617.6) - Complication cost for death ($2735.3) Year of pricing: 2004	One-way sensitivity analysis identifying the influential parameters on ICER for stool DNA testing compared with no screening: - the prevalence of colorectal neoplasm at age 50 years, - transition rates, - sensitivity and specificity of screening tool, - cost of per unit of stool DNA testing, - compliance to screening tool, - referral rate to diagnostic colonoscopy, - cost of treatment - discount rate	10-yearly colonoscopy and yearly FOBT are the most cost-effective strategies which are more effective and less costly than no screening. The ICERs were: - FOBT: dominant, - colonoscopy: dominant, - sigmoidoscopy: $2087, - stool DNA testing every three years: $9794, - stool DNA testing every five years: $9335, - Stool DNA testing every ten years: $7717

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