Collaborating with

Health Economic Evaluation Of Alternatives To Current Surveillance In Colorectal Adenoma At Risk Of Colorectal Cancer

SHORT REPORT

Ethna McFerran &

Prof Frank Kee

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EVIDENCE BRIEF

Why did we start?

The global burden of colorectal cancer (CRC) is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030. CRC incidence and mortality rates vary up to 10-fold worldwide, reflecting variation in lifestyles, especially diet. Better primary prevention, and more effective early detection, in screening and surveillance, are needed to reduce the number of patients with CRC in future[1]. The risk factors for CRC development include genetic, behavioural, environmental and socio-economic factors. Changes to surveillance, which offer non-invasive testing and provide primary prevention interventions represent promising opportunities to improve outcomes and personalise care in those at risk of CRC.

What did we do?

By systematic review of the literature, we highlight gaps in comparative effectiveness analyses of post-polypectomy surveillance. Using micro-simulation modelling we assessed the costs and benefits of non-invasive, faecal immunochemical testing in surveillance programmes, to optimise post-polypectomy surveillance programmes, and in an accompanying sub-study, explore the value of adding an adjunct diet and lifestyle intervention.
The acceptability of such revisions was exposed to patient preference evaluation by discrete choice experiment methods. These preferences were accompanied by evidence generated from the prospective evaluation of the health literacy, numeracy, sedentary behaviour levels, body mass index (BMI) and information provision about cancer risk factors, to highlight the potential opportunities for personalisation and optimisation of surveillance. Additional analysis examined the optimisation of the Irish screening programme facing colonoscopy constraints, highlighting the attendant potential to reduce costs and save lives within current capacity.

What answer did we get?

Modelling suggests the potential to use intensive non-invasive faecal immunochemical testing (FIT) based surveillance as an alternative to colonoscopy-based surveillance. The clinical viability of this approach is likely related to long-term acceptability of high-frequency FIT.

Preliminary modelling results show that the addition of diet and lifestyle interventions to surveillance programmes, could potentially generate up to an additional 8 Quality-adjusted life years (QALYs) per thousand persons, the additional cost per additional QALY of a hypothetical 10% increase in the dwell time (achieved by such programmes) was estimated to be in the range of £32,035 to £64,145, with additional gains likely in co-morbid conditions.

Participant's preferences for the inclusion of such programmes showed that people involved in surveillance were in the main unaware of their risk status, and were risk and cost averse, preferring the status quo, in considering revised surveillance programmes. Significant discordance, however, was found between perceived risk versus the known risk of CRC (based on screening programme identifiers), with low levels of recall of information provided within the current surveillance programme, regarding diet and lifestyle CRC risk factors. Subgroups of participants (around 25%) are willing to change behaviours, preferring to do so with the support of phone or email based diet and lifestyle interventions and to utilise non-invasive testing, at earlier intervals of testing. No strong identifiers of this group were evident,

however, our findings did show co-morbid conditions were prevalent amongst the study participants, suggesting that the benefits of such programmes may have extended reach.

Simple changes to BowelScreen (the Irish CRC Screening programme) could save lives, reduce costs and relieve pressure on colonoscopy capacity. The extent of the potential improvements depends in part on the acceptability of lengthening the screening interval, highlighting the importance of considering a full range of alternatives when conducting cost-effectiveness analyses and programme planning.

What should be done now?

In light of the evidence generated which tackles a previously under-studied area of care, the health economics evidence in adenoma surveillance, we identified that no previous evaluation of the cost-effectiveness of colonoscopy compared with other tests had been carried out. We took action to address the evidence gaps, evaluating FIT, non-invasive testing, and provide evidence of cost-effectiveness reporting by sub-group. We highlight the potential evidence on the cost-effectiveness of combined aspirin and colonoscopy in chemoprevention of CRC and its likely role in the prevention of premature mortality due to other causes. We suggest that a focus on the opportunity for practice change in surveillance, at this teachable moment, to include greater personalised prevention. Future efforts should consider the potential role of shared decision making for the types of testing used and the inclusion of supportive behaviour change interventions accompanied by personalised information provision, and aspirin chemoprevention, in those with co-morbid conditions, all of which may enhance CRC prevention outcomes.

Evidence from our modelling suggested that local re-appraisal of BowelScreen, the Irish CRC screening programme, would likely lead to more lives which could be saved within existing colonoscopy capacity constraints if BowelScreen were to trade off a reduction in screening frequency against an increase in population coverage and adopt a more efficient FIT cut-off. We remain in consultation with the Irish National Screening Programme to discuss these findings.

Background

Colorectal Cancer (CRC)

Neoplasia is not the result of single or even multiple genomic alterations in a single cell, but the aggregate of all of the molecular changes in a community of tumour cells, including those affecting signal transduction and gene regulatory networks, which in many cases are related to the environment within which malignant cells reside[2]. In the case of CRC, in May 1927, Lockhart-Mummery and Dukes discovered the relationship of CRC to pre-existing adenomas, when they demonstrated that CRCs were associated with residual adenomatous tissue[3], which lead Morson to describe the ''polyp-cancer'' sequence for CRC[4], and later to Vogelstein and colleagues revealing the somatic mutations that accompanied this sequence[5]. These concepts related to the natural history of the disease were validated by the results of the National Polyp Study results in 1993, showing that CRC was prevented by identifying and removing adenomas[6].

Mutations in oncogenes, tumour suppressor genes and genes related to DNA repair lead to the onset of CRC[7], which, depending on the origin of the mutation can be classified as sporadic, inherited and familial. The majority of CRCs are sporadic[8,9], following an adenoma-carcinoma sequence[5,10], while a minority are thought to develop through an alternative serrated polyp pathway, recognised in the last decade as important premalignant lesions, accounting for between 15% and 30% CRCs[11]. Aberrations of the normal colon epithelial cell cycle, as described by Gonzalez-Pons et al, may lead to one of three main molecular mechanisms that cause aberrant gene expression, which is the precursor to colon carcinogenesis: microsatellite instability (MSI), chromosomal instability (CIN), and the CpG island methylator phenotype (CIMP)[12], as shown in Table 1.

Table 1 - Key characteristics of the three major CRC pathways [12]

	Chromosomal instability (CIN)	**Microsatellite instability (MSI)**	**CpG island methylation (CIMP)**
Prevalence	80–85%	15–20%	Up to 20%
Molecular Events	Characterized by aneuploidy, inactivation of APC/b-catenin, clonal accumulation of genetic alterations in oncogenes and tumour suppressor genes, and allelic losses and gains	Mutations/epi-mutations in the mismatch repair genes result in extensive insertions and/or deletions in microsatellites	Hypermethylation of multiple promoter CpG island loci, such as hMLH1. BRAF mutations

Clinical Features	Associated with poor prognosis	Associated with proximal tumour location, lower staging, high-grade differentiation, and abundance of tumour infiltrating lymphocytes	Correlates with proximal tumour location, higher prevalence in females, and BRAF mutations

The estimated average time from adenoma onset to cancer incidence, the mean dwell time, varies from 10.6 years to 25.8 years[13]. As a consequence of these discoveries into the biology of the condition, interrupting these changes by screening or surveillance, and removal of these lesions has become a key feature in public health efforts to reduce the burden of CRC.

In addition, as shown in Figure 1, there is a growing understanding of the mechanisms by which the gut microbiome may influence not only the initiating events of carcinogenesis but also its progression[14,15]. Aberrant microbiota (dysbiosis) may induce colonic carcinogenesis by producing a chronic inflammation, with Fusobacterium spp, Bacteroides fragilis and enteropathogenic Escherichia coli among the bacteria that are thought responsible for this multiphase process[7]. Whilst it remains unknown whether a specific bacterium or, a microbial community, acting sequentially or synergistically, are responsible for CRC, the microbiome composition is greatly influenced by dietary patterns[7], and as a modifier of the gut microbiota and its metabolism, a critical element in the maintenance of intestinal health[16]. Consequently, there persists an essential role in consideration of the impact of diet and lifestyle on CRC risk and its prevention.

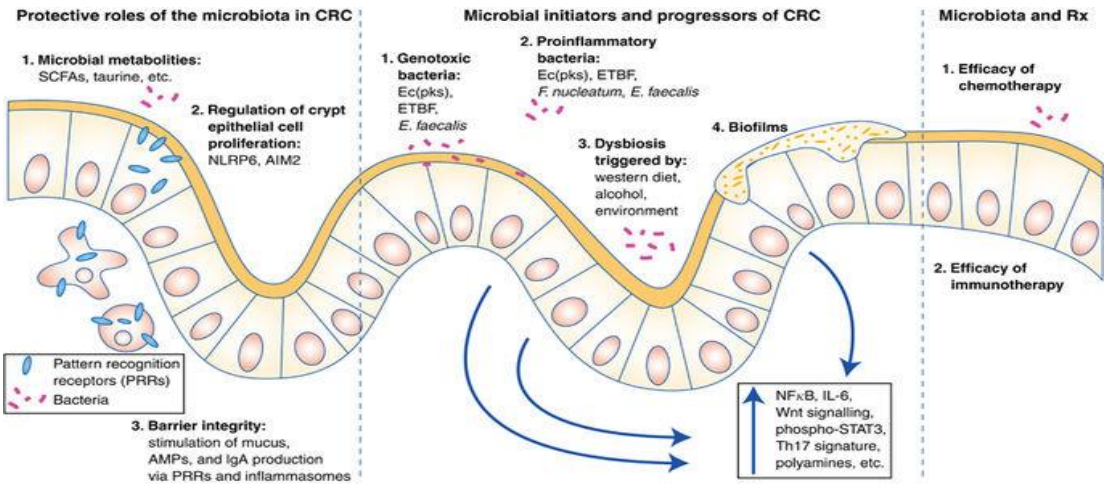

Figure 1 - Roles of the microbiota in CRC prevention, initiation, progression, and therapy

Colonic epithelial cells are depicted with the mucus layer (dark yellow) facing the gut lumen. (Left) Bacteria have multiple protective roles against CRC, including the production of anti-inflammatory metabolites and regulation of crypt epithelial cell proliferation. Most notably, bacteria have integral roles in the maintenance and repair of the colonic epithelial barrier, by triggering controlled innate immune responses through pattern recognition receptors (PRRs) on host cells. Disruption of PRR signalling leads to breaches of the epithelial barrier and excessive inflammation that may instead promote tumorigenesis. (Middle) Multiple avenues by which bacteria may initiate or promote CRC tumorigenesis are also depicted, including the direct

genotoxicity of specific bacteria, as well as the pro-inflammatory effects triggered by either specific microbes, a dysbiotic microbiota as a whole, and/or colonic biofilms. (Right) Immune responses to commensals have also been proposed to be essential for the efficacy of multiple chemotherapies and immunotherapies[14].

Surveillance

Most cancer screening programmes feature surveillance following the removal of polyps[17–19]. The purpose of this surveillance is for the early detection of colonic lesions[20–22]. Surveillance by colonoscopy was evaluated by the National Polyp Study in the late 1980s[23], and delivered the first definitive evidence on its benefits. Since then colonoscopy has formed the main approach to the ongoing assessment of CRC risk[6]. Current surveillance guidelines use risk stratification based on predictive attributes of adenomas removed on screening colonoscopy examination[24]. The risk is categorised as high or low-risk based on size, histology, and multiplicity in the majority of guidelines, with some countries further specifying an intermediate risk group[20,22,25,26].

The purpose of this risk stratification is to permit the adaptation of surveillance intensity to anticipated CRC risk. It has been suggested that risk stratification is imperfect[27,28], since surveillance may be overused for low-risk subjects and underused for high-risk subjects[29]. In data from the largest and most comprehensive analysis of colonoscopy practice in the United States, those in surveillance were thought to be at higher risk than the average population, with the reported detection rate of large polyps higher for adenoma surveillance examinations than for average-risk screening (OR 1.18; 95% CI, 1.16 to 1.21). The results are however reported for undifferentiated risk groups[30]. In contrast, results from a large UK-based, multicentre cohort study suggested that in some subgroups (intermediate risk by UK guidelines), the incidence of CRC was significantly less than that of the general population (standardised incidence ratio 0·51, 95% CI 0·29–0·84)[31]. Consequently, if the CRC risk is lower than that of the general population, then it is unclear if the continued provision of post-polypectomy surveillance is justified[32]. Thus, colonoscopy resource consumption may be optimised if aligned by risk[27].

Experts in CRC continue to discuss whether some patients really need surveillance and whether further lengthening of intervals can be recommended in others[33]. This debate is inhibited somewhat by the absence of clearly reported outcomes, over multiple surveillance tests, in each risk group. Fear is given as a predictor of nonadherence to colonoscopy and in the clinical context, fear of missed lesions, rather than risk, has been found to prompt overuse of surveillance in some clinicians[34,35]. However, colonoscopy capacity is limited[36,37], and the

anticipated growth in the numbers directed to surveillance, combined with a growing interest in simpler, less invasive tests[38], and with better algorithms to guide individualized testing[37], has led to non-invasive alternatives are becoming increasingly relevant to policy development[39].

By using non-invasive tests in people under-going surveillance, colonoscopy could then be reserved for those who test positive with the non-invasive tests and used to obtain biopsy proof of diagnosis; as in primary screening. If cancer is not suspected by the non-invasive surveillance test then a colonoscopy and associated costs and risks could be avoided. By implementing such a two-step approach in surveillance there is the potential to personalise ongoing monitoring and to preserve scarce colonoscopy capacity.

The ability to offer surveillance by non-invasive methods has been further advanced by the improved efficacy of newer faecal immunochemical tests (FIT). Although no trials have yet reported on the potential role of faecal immunochemical testing (FIT) in this setting, it has demonstrated benefit in surveillance for interval cancers in other HR groups (e.g. Family history of CRC)[40]. Within the context of balancing too little surveillance, which jeopardises CRC prevention goals, with overuse of surveillance chancing unnecessary harms and inefficient use of colonoscopy resources[41], FIT may provide a feasible alternative, not previously evaluated[42].

Diet and lifestyle risks in CRC development

Dietary factors including a high intake of red and processed meats[43], highly refined grains and starches, and sugars are associated with an increased risk of CRC[44]. Specifically, in a recent meta-analysis[43], the consumption of red and processed meats was associated with an increase of risk of CRC (RR for 100 g/day increment=1.12; 95% CI=1.04–1.21) and for colon cancer (RR per 100 g/day=1.19 (95% CI=1.10–1.30). For a range of foods and ages, Figure 2 summarises the dose-response relationship to the associated risk of CRC, from a recent analysis.

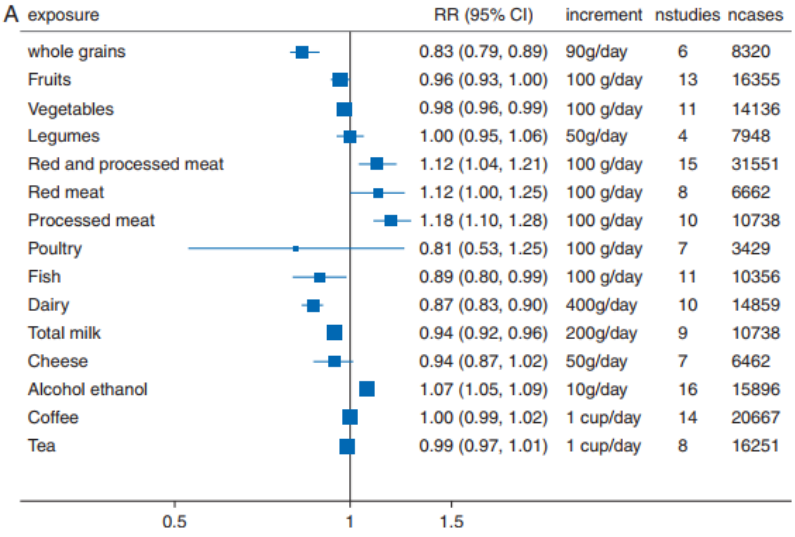

Figure 2 – Dose-response meta-analysis of foods and beverages and risk of colorectal cancer[43]

A plant-based diet with abundant fruits and vegetables, legumes[45], which are rich in Vitamin B6, along with moderate amounts of dairy, limited red and processed meats, refined grains and added sugar may protect against adenoma development[46], and is associated with a lower risk of CRC.

With obesity rates soaring worldwide, affecting more than 2.1 billion people, nearly thirty percent of the global population is estimated to be overweight or obese[47], and so it is important to consider the associated morbidity risks. There is a strong association between obesity and the risk of CRC[48,49], the pooled relative risks of CRC for the obese vs. normal weight category of BMI were 1.334 (95% CI, 1.253–1.420) in a recent meta-analysis, while for the highest vs. lowest category of waist circumference the relative risks were 1.455 (95% CI, 1.327–1.596). There was significant heterogeneity across studies in relation to risks associated with obesity, but not among studies of waist circumference[50]. In the context of post-polypectomy surveillance, a higher BMI is significantly associated with the risk of multiple metachronous adenomas with 5 years of surveillance colonoscopy[51]. The mechanisms connecting obesity to CRC are still debated. Potential etiologic pathways involve metabolic syndrome, insulin resistance and modifications in levels of adipocytokines, growth factors, steroid hormones and immune function. Insights are also emerging about the role of other biological factors, such as gut microbiota or bile acids[52,53].

While obesity has been associated with the risk for colorectal adenoma, the risk can be mitigated by physical activity and body weight reduction and behaviour changes[54,55]. The key mechanisms associated with the protective role of physical activity seem to be linked to increased insulin sensitivity, lower insulin levels, decreased body mass, and decreased

adipose tissue volume, leading to a reduction of chronic inflammation. Reduction of alcohol consumption and avoiding tobacco use are also likely to reduce CRC incidence[56].

The US Preventive Services Task Force (USPSTF) recently revised its view on the role of aspirin for the prevention of CRC, providing a limited recommendation for chronic disease prophylaxis, including CRC prevention, specifically among US adults between ages 50 and 59 with a >10%, 10-year risk of cardiovascular events. However, the present USPSTF stance does not endorse aspirin use for the sole purpose of cancer prevention[57]. In addition, grape seed extract and silibinin, a flavonolignan extracted from milk thistle, and other nutrients including eicosapentaenoic acid and curcumin have also been a focus for research of chemo-preventive agents[56,58].

Currently, however, awareness of relevant lifestyle factors for CRC remains low in people at increased risk of the disease, highlighting the need for further exploration of behavioural changes to reduce CRC risk[59,60]. Primary prevention through changes to diet and lifestyle, should substantially reduce the risk of CRC and augment the results of screening and surveillance.

Aims and Objectives

A review of the previous work was conducted:

1. To assess if there is sufficient evidence to evaluate a programme of personalised surveillance in patients with colorectal adenoma according to risk sub-group.
2. To compare the effectiveness of surveillance colonoscopy with alternative prevention strategies.
3. To assess the trade-off between costs (resource use), benefits and adverse effects that need to be considered in a decision to adopt or reject personalised surveillance.

A validated, internationally tested and applied micro-simulation model (used in National programme evaluations in the US and the Netherlands) was used in collaboration with experts based in the NCI CISNET CRC modelling group, Erasmus MC and Memorial Sloan Kettering Cancer Center:

1. to assess if intensive risk-stratified FIT-based surveillance should be considered as an alternative to colonoscopy-based surveillance post-polypectomy.
2. to estimate the cost and effects of behaviour changes to diet & lifestyle for those in post-polypectomy surveillance.
3. to assess if Ireland's colorectal screening programme can save more lives, save money and live within existing colonoscopy capacity constraints?

A discrete choice experiment was conducted to consider Personal and Public Involvement, specifically to:

1. elicit how patients with adenoma trade-off risk-benefit between different surveillance options;
2. examine the patient and healthcare-related characteristics that could influence these choices;
3. determine whether preferences of patients with adenoma vary by health literacy or other non-health related factors;
4. examine the concordance of these preferences with studies of adherence to exercise programmes for individuals with pre-cancerous detected lesions.

Methods

In each micro-simulation model, we used MISCAN-Colon, a validated model[61], used primarily for evaluations of screening. It has been used to identify improvements to cancer control interventions in prevention, screening, and treatment, and their effects on population trends in incidence and mortality[62,63]. The model's structure, its underlying assumptions and calibration are widely published and are publicly available[64].

By way of overview, MISCAN-Colon is a stochastic, semi-Markov model which simulates the life histories of a representative population from birth to death. MISCAN uses the Monte Carlo method to simulate all events in the programme. As each simulated person ages, 1 or more adenomas may develop, based upon a natural history model, along the adenoma-carcinoma sequence first described by Muto, Morson and Vogelstein[4,5,10]. Adenomas progress from small (≤5 mm) to medium (6 to 9 mm) to large (≥10 mm) size. Of those who develop adenomas, some will progress into preclinical cancer, from stages I to IV. At each stage, it is assumed that CRC may be diagnosed because of symptoms. Survival following a clinical diagnosis is determined by the stage at diagnosis, the localization of cancer, and the person's age[65].

Screening and surveillance testing affects some of the simulated life histories, whereby some cancer cases will be prevented by the detection and removal of adenomas; and in other cases, cancers will be detected at an earlier stage resulting in improved survival. These clinical tests and assessments can also result in serious complications, over-diagnosis and overtreatment of CRC, (the detection and treatment of disease that would not have been detected or resulted in death without screening)[66]. Comparisons are made of all life histories with and without screening and surveillance.

As such, MISCAN-Colon quantifies the effects of screening and surveillance interventions on both health and economic outcomes. The strength of the model for this analysis is its flexibility to enable the user to adjust a surveillance–scheme after detection of an adenoma[64].

In evaluation 1. to assess if intensive risk-stratified FIT-based surveillance should be considered as an alternative to colonoscopy-based surveillance post-polypectomy, reference strategies were adapted from the current UK BSG guidelines[26], offering colonoscopy after 1 year in high risk, after 3 years in intermediate risk, and those with low risk returning either to the screening programme (RTS) in 2 years or for another surveillance colonoscopy at 5 years. In addition, two variations of US recommendations were modelled using 3-year interval in high

risk and 5 or 10-year intervals in low-risk groups. Since there is no clear evidence of an appropriate interval for FIT in surveillance in any given subgroup, alternative scenarios were developing for the analysis and proceeded from the assumption that testing should be offered at least as often as screening (starting at least at every 2 years), and then progressively intensifying its use, on the basis that those in surveillance ought to be at greater risk than an average person offered screening tests, and to further distinguish the benefit of intensifying surveillance for each subgroup. With the frequency of testing shortened to a maximum of 0.5-year intervals in all risk groups. Further details of all strategies evaluated available on request.

In evaluation 2: to estimate the cost and effects of behaviour changes to diet & lifestyle for those in post-polypectomy surveillance, broad assumptions of the potential benefit were considered by assessing the potential impact of a 5% or 10% increase in adenoma dwell time (or a reduced CRC incidence rate) attendant on favourable dietary behaviour change on CRC incidence and mortality in a post-polypectomy surveillance population. Costs were derived from two published intervention trials, BeWel[59] and The Primrose study[67], giving two cost scenarios to estimate the additional cost per additional quality-adjusted life year of providing interventions which positively change behaviour in surveillance. Further details available on request.

In evaluation 3: to assess if Ireland's colorectal screening programme can save more lives, save money and live within existing colonoscopy capacity constraints, we estimated the required colonoscopy capacity by simulating a close proxy of the current BowelScreen programme using a biennial FIT test and a cut-off of FIT200 ng Hb/ml in persons aged 60-69. Subsequently, we varied the screening interval, start age and FIT cut-off levels in a series of alternate scenario models. We considered screening intervals of 1, 2, 3, 4 and 5 years. In addition to the current BowelScreen start and stop age of 60 and 70 years respectively, we also simulated higher and lower screening start ages of 45, 50, 55, 60, 65 and 70 years, with stop ages of 70, 75, 80 years or close approximations thereof depending on the screening interval. We calculated the colonoscopy requirement of the current strategy and assessed all alternate strategies in terms of their colonoscopy requirements relative to the current programme. We then calculated the relative costs and benefits of each strategy, including the relative difference in CRC deaths prevented. Further details available on request.

Further user-led involvement utilised discrete choice methods and is explained in the PPI section below.

Personal and Public Involvement (PPI)

Both qualitative (focus group) and quantitative methods (discrete choice experiment (DCE)) were used to understand the preferences of patients with a history of adenoma removal, for hypothetical alternative surveillance scenarios which add diet and lifestyle interventions and offer the option of non-invasive testing. The DCE attributes and levels were designed in two phases during the development of a study protocol. Protocol development followed good practice methods outlined in the updated ISPOR Conjoint Analysis Experimental Design Task Force[68]. The study received a favourable ethical review, and approval by the Wales REC 6 (REC Reference: 15/WA/0374), prior to invitation and recruitment. All participants provided informed consent to participate in this study.

Development Phase 1

A purposive review of the literature related to CRC screening and surveillance (focusing on diet, lifestyle and physical activity interventions), provided a shortlist of prospective attributes for the DCE vignettes, which in turn are described by a series of discrete levels. Informed by the methods for attribute design[69], the attributes and levels were selected to ensure that analysis could examine a range of factors that affect decision making; including health literacy, risk perception, perceived barriers and benefits, CRC knowledge, attitudes and deliberation[70].

Development Phase 2

These vignettes co-created using focus group discussion and appraisal by members of a patient-user forum, ensuring that the attributes selected in phase 1 were collectively considered the most relevant to decision making to the types of participants who will complete this survey, taking into account:

- appropriateness of attributes and levels,
- believability of options,
- ability to stay focused on the vignettes,
- the potential for response fatigue.

Further iterative improvements (as described below Table 2) were made to attributes and levels, the study questionnaire and vignettes, to produce the final version of the vignettes used for recruitment to the study. The final attributes and levels are presented in Table 2, further justification for these levels available on request.

Table 2 – Study attributes and levels

Attributes/ Characteristics*	Levels
Diet & Lifestyle Programme [59,71–73]	1 on 1 support[71,72] / Group based training / Phone/ e-mail based support[72,73] / No support
How much the package decreases your chance of dying from cancer (Continuous scale)	Levels were presented on a continuous relative risk reduction scale within a range: presented in the vignette as *25, 30, 35, 50, 65, 75, 80%*
Combined in a package with test	'Moderately/ non-invasive' OR 'Highly/ invasive'
Next test to check for new or recurrent polyps in	17 months /21 months /24 months /28 months /42 months
Out of Pocket (OOP) Cost (Continuous scale)	£0 / £15 / £30 / £45+ per calendar month

*PPI based changes included: Change of title "attribute" to "characteristics' to promote use of plain language; amendment to remove the term 'false negatives' and subsequently replaced with a worded example – 'up to 3 people in 10 will be falsely reassured and could delay presenting' or 'up to 2 people in 10 will be falsely reassured and could delay presenting'. Clarification also provided that the numeracy questions are not there to test intellect, and TV package question was made optional.

The study had 5 attributes with between 2 and 7 levels, i.e.: 2^1, 4^2, 5^1, 7^1, giving a full factorial design of 1120 potential vignette profiles, this would not be feasible to present a single individual. Consequently, to create profiles for the choice vignettes, I employed an experimental (fractional factorial, D-efficient) design which was selected and derived using Ngene (a professional suite of design software). This software uses Bayesian optimisation, calculating the most efficient design of vignettes to maximise the power to elicit patients' preferences in the survey instrument. This reduces the number of scenarios to a manageable number whilst maintaining orthogonality, precluding collinearity between attributes but the least decrement in statistical power[74].

The final experimental design consisted of two survey blocks, each containing eight choice vignettes. Each subject was randomly assigned to one of the two blocks. Checks were conducted to verify that attribute-level combinations were plausible and logical[68].

A study questionnaire was included, which invited respondents to complete a series of questions, including medication use by comorbidity indication, which was used to generate a multi-morbidity score >2[75]. Further responses collected data on; information provision about CRC risk factors, literacy and numeracy, sedentary time (by TV watching hours), height, weight, readiness to change (health behaviours) ratings and self-affirmation statements[76–85]. The full study survey is available on request. The DCE vignettes were presented electronically as part of the study questionnaire via an online survey platform (Qualtrics), with recruitment to the study carried out between November 2015 and July 2017. Recruitment was facilitated anonymously by the NI Colorectal Cancer Screening programme. The study team provided sealed invite letters, in unique ID numbered envelopes to the NI Colorectal Cancer Screening programme office, which addressed and posted

the letters to 283 high risk and 917 intermediate-risk persons in surveillance (totalling 1200 invitees) over 3 stages of recruitment. All participants received a written participant information letter with a unique participant ID in the post, explaining the study and inviting them to participate in an online based survey.

Findings

- **Systematic Review**

From the review we believe the salient points from the review of the limited number of previous studies in cost-effectiveness evaluations of colonoscopy based surveillance programmes to be:

(a) Colonoscopy capacity can, at lower levels, prohibit the ability of health systems to offer colonoscopy based surveillance to low-risk groups[86].

(b) Compared with a ten-year low-risk colonoscopy, offering a five-year colonoscopy to low-risk groups was above US thresholds at $296,266/ quality-adjusted life year[87].

(c) Compared to a three-year high-risk colonoscopy, there is evidence to support offering a one-year high-risk* colonoscopy[88] – *for persons aged 60 years entering surveillance.

(d) Aspirin combined with surveillance colonoscopy generated greater life years saved than aspirin or colonoscopy alone and in given its role in the prevention of premature mortality due to other causes, this combination merits further evaluation.

There were quality and reporting issues with a number of the papers evaluated. These shortcomings suggest that questions remain regarding the cost-effectiveness of post-polypectomy surveillance programmes.

This informed the work of the subsequent micro-simulation modelling, specifically in relation to the management of adenoma surveillance. Further details of this review is available on request, and has been published in peer reviewed journal - https://academic.oup.com/epirev/article/39/1/148/3574073

Evaluation 1

A microsimulation modelling study using MISCAN to assess if intensive risk-stratified FIT-based surveillance should be considered as an alternative to colonoscopy-based surveillance post-polypectomy: estimates of effectiveness and cost-effectiveness

Results

Two screen start ages (50 years and 60 years respectively) were considered, to generate a suitable surveillance entrant. In each case the policy-relevant features are highlighted, namely how outcomes vary across strategies defined by (i) current guidelines using colonoscopy based programmes, (ii) by the use of FIT; (iii) by the use mixed testing programmes, and (iv) by the use of "lifetime" surveillance.

Start Age 50 Years

Figure 3 shows the results of the primary analysis. The efficient frontier is made up of three strategies, all of which use colonoscopy in high risk and intermediate risk patients, at 1 and 3-year intervals, respectively. The strategies differ only in terms of the modelled test and the intervals for low-risk persons, with BSG2, colonoscopy at five years being most effective, and with FIT 50 ng Hb/ml at either 1 or 2-year intervals also representing efficient approaches. Of these two strategies FIT 50 ng Hb/ml at 1-year intervals is more effective.

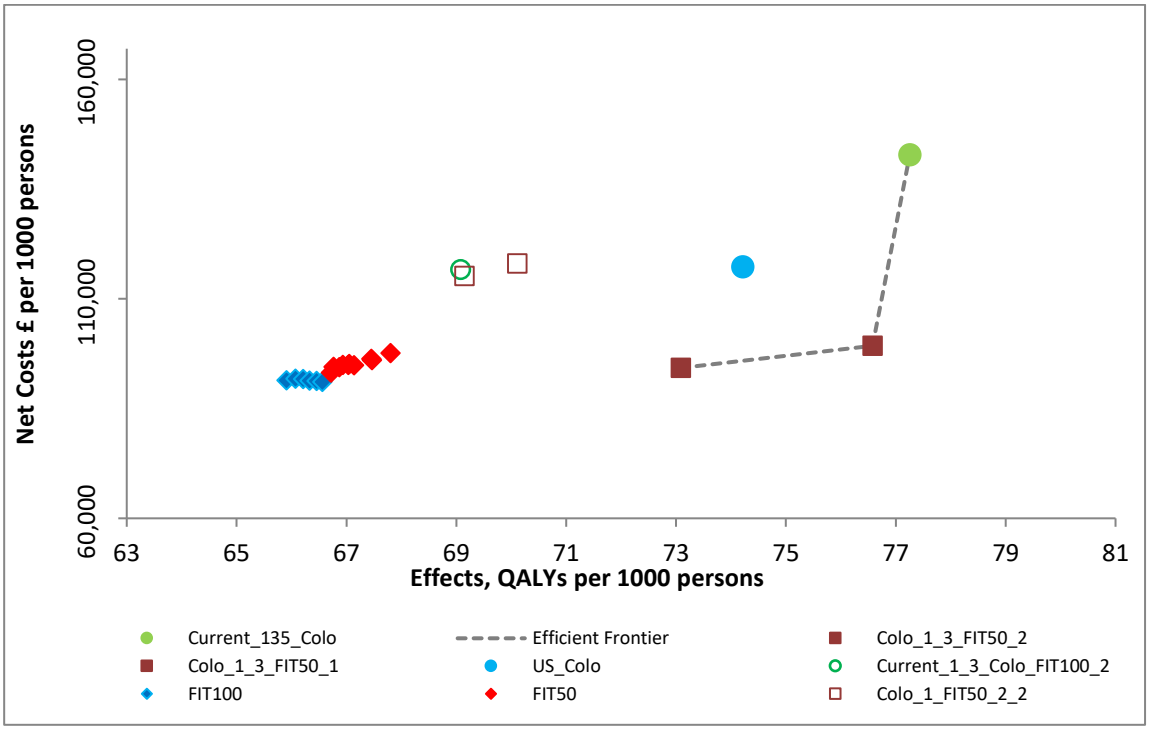

Figure 3– Primary analyses, Strategies Modelled for Surveillance, 50 years entering screening

Surveillance by Current Guidelines

When the two current guideline approaches to surveillance were compared, that is, colonoscopy in high risk and intermediate risk at 1 and 3 years respectively in both strategies. With either FIT100 ng Hb/ml testing (BSG1), or colonoscopy at 5 years (BSG2) offered in the low-risk group, BSG1 was found to be inefficient, that is, it was less effective and more costly, therefore offering BSG2 should be the preferred strategy. This indicates also that the management of the low-risk state is an important driver for the effectiveness of the overall programme.

Surveillance by FIT based programmes

FIT based strategies of surveillance are less effective than colonoscopy based alternatives, and in general FIT100 strategies are less effective than FIT50 strategies. In the primary analyses, all FIT-only strategies are inefficient and dominated.

Surveillance by mixed and lifetime surveillance programmes.

In the secondary analysis, when FIT-based strategies of surveillance were considered for lifetime use, FIT was more efficient and dominated colonoscopy-based strategies, with two FIT-based strategies forming the cost-effectiveness frontier, one of which produced greater absolute QALY gain than colonoscopy.

The two efficient strategies were lifetime FIT 50 ng Hb/ml testing at 0.5-year intervals in all risk groups, which provided the most cost-effective alternative. As shown in Figure 4, the second efficient strategy is lifetime FIT 100 ng Hb/ml at 0.5-year intervals in all risk groups.

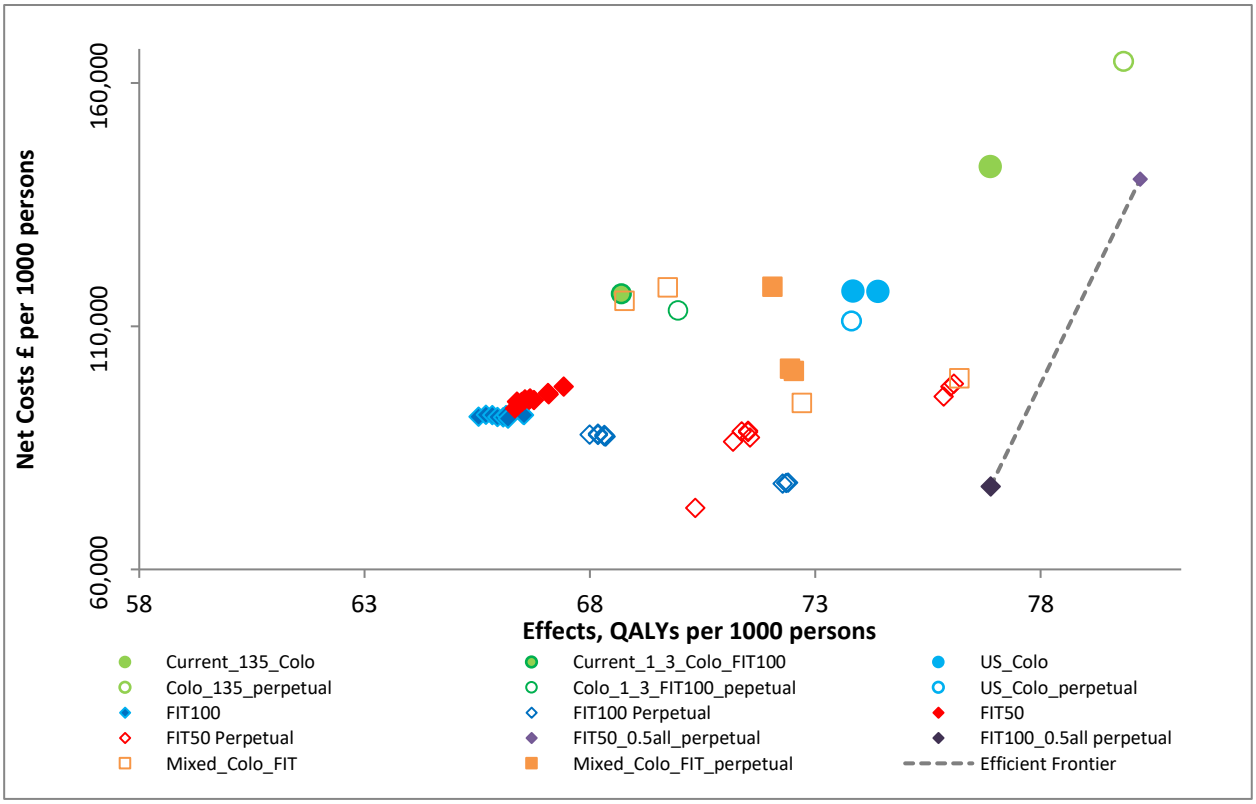

Figure 4 – All Strategies Modelled including lifetime testing, 50 years entering screening

For ease of comparison, Table 3, provides an abridged results table of efficient strategies in primary and secondary analyses.

Table 3 – Efficient surveillance strategies in 50-year-old screen entrants

Test Type (Strategy)	Interval of Test (Yr.)			Per 1000 persons, Compared to no intervention			NHB at £20k	ICER Efficient Strategies	Efficient (Primary Analyses)	Efficient Overall
				ΔQALY gain	Net Cost	No. of Colonoscopies				
Standard Evaluations										
	High	Inter-mediate	Low	-	-	-				
Colo/Colo/FIT50	1	3	2	73.1	94,265	645	708,457	1,290	Y	
Colo/Colo/FIT50	1	3	1	76.6	99,329	704	742,310	1,450	Y	
Colo	1	3	5	77.3	142,847	854	748,893	64,064	Y	
Further Evaluations For Lifetime Surveillance										
FIT100 perpetual	0.5	0.5	0.5	77.3	77,078	616	749,048	0,998		Y
FIT50 perpetual	0.5	0.5	0.5	80.6	140,238	872	781,235	19,021		Y

Start Age 60 Years

The results of all strategies modelled for entrants at 60 years are available by request, which includes the respective ICERs for the primary and secondary analyses.

As shown in Figure 5, in the primary analyses for 60-year-old entrants, the efficient frontier is made up of four strategies: FIT100 ng Hb/ml at 1 year intervals for all risk groups; colonoscopy in high risk and intermediate risk, at 1 and 3 years respectively, with a colonoscopy at five years in low-risk groups; or with FIT 50 ng Hb/ml at either 1 or 2 year intervals.

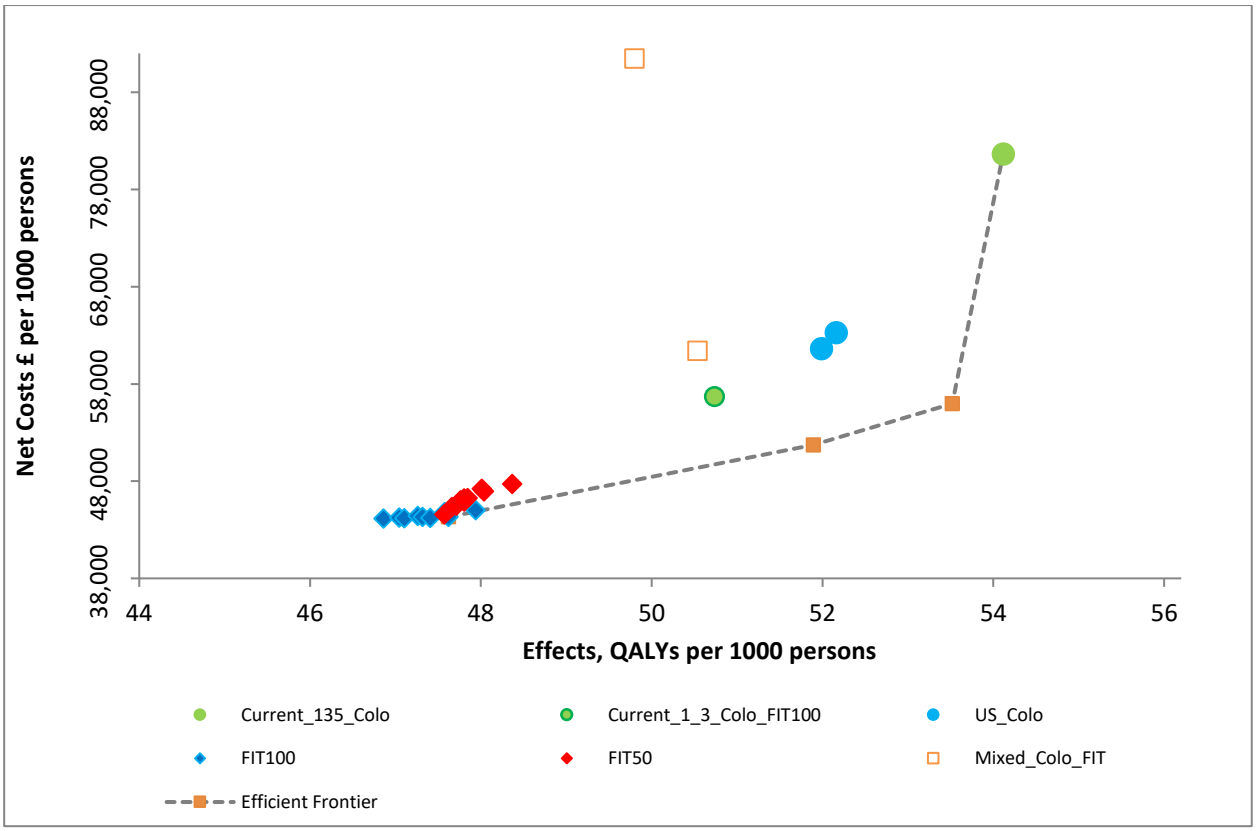

Figure 5 – Primary analyses, Strategies Modelled for Surveillance, 60 years entering screening

Surveillance by Current Guidelines

In the 60 year old entrants to screening, despite an absolute QALY difference of 3. 38 QALYs per thousand persons between the two current UK guideline approaches to surveillance, the use of FIT100 ng Hb/ml compared with using colonoscopy at 5 years in the low-risk group, is inefficient, and therefore the 5 year colonoscopy for low risk should be preferred. Neither of the US guideline approaches to colonoscopy surveillance was efficient when modelled in the context of FIT-based primary screening.

Surveillance by FIT based programmes

In the 60-year entrant age group, one FIT based strategy for surveillance is efficient, i.e. using FIT100 ng Hb/ml at 1-year intervals in all risk groups. In the primary analyses, the remaining FIT only strategies were not efficient.

Surveillance by mixed and lifetime surveillance programmes.

As shown in the primary analyses, one FIT strategy was effective along with two mixed FIT and colonoscopy strategies and one colonoscopy alone strategy. In these analyses mixed testing programmes used FIT50 to optimise the effectiveness of LR surveillance.

When FIT was considered for lifetime use in secondary analyses, using repeat testing irrespective of test outcomes, FIT once again becomes more efficient and dominates both mixed FIT/ colonoscopy and colonoscopy alone strategies.

In the modelled lifetime strategies, two FIT programmes were dominant and result in cost-effective alternatives. Once again FIT 50 ng Hb/ml testing at 0.5-year intervals in all risk groups performed better than colonoscopy alone and provides the most cost-effective alternative, as shown in Figure 6. The alternative efficient strategy is FIT 100 ng Hb/ml at 0.5-year intervals in all risk groups.

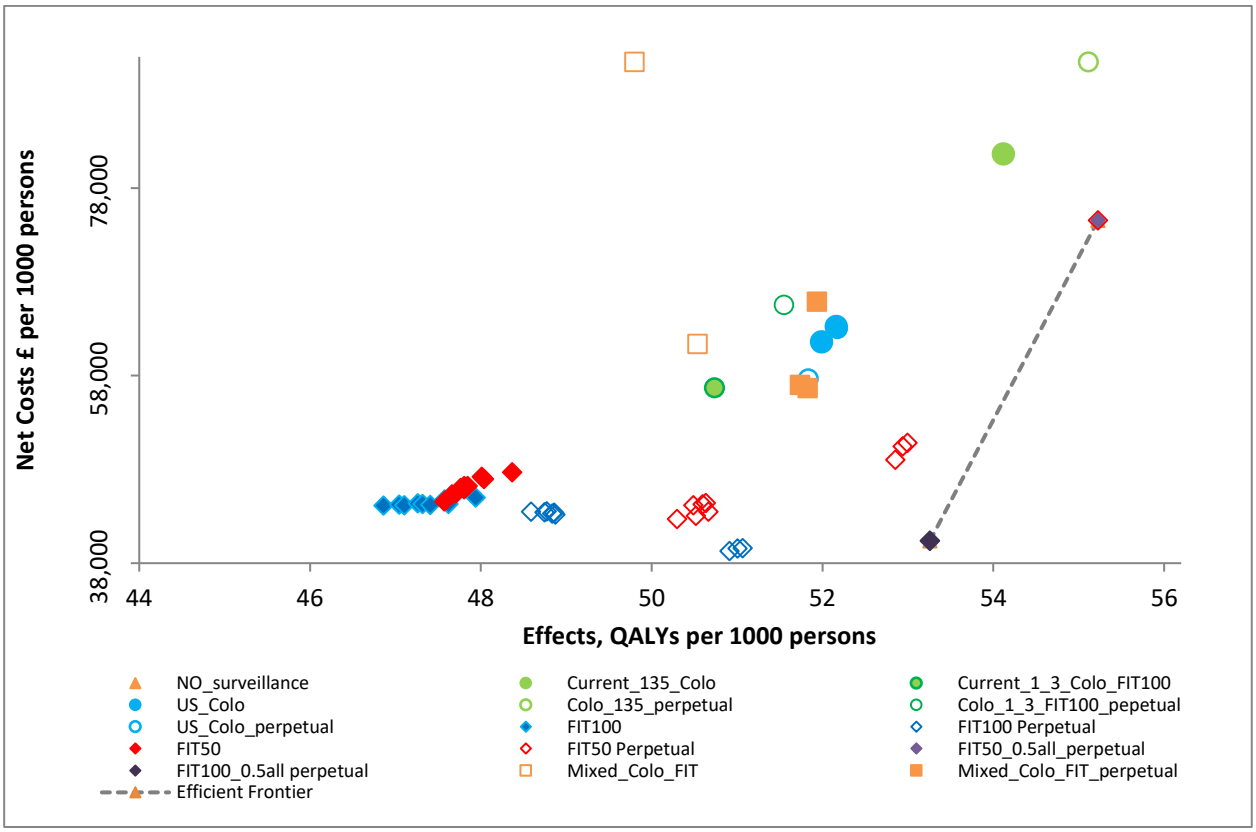

Figure 6 – All Strategies Modelled including lifetime testing, 60 years entering screening

In sensitivity analyses, consideration was given to adherence. Across the range of adherence assumptions, there was no material change to the results, with FIT remaining a cost-effective alternative when used in programmes which involve intensive "perpetual" testing.

Given that the assumptions do not directly parallel the intermediate risk UK guidelines (regarding the inclusion of at least one lesion of greater than 10mm), this may result in some individuals by guideline categorisation versus simulated categorisation, potentially receiving more intensive testing than current guidelines suggest. Accordingly, sensitivity analyses were conducted which modified the subgroup classifications (available by request). The results of which show minimal differences in outcomes which do not affect the relative outcome rankings. Moreover given that the most cost-

effective strategy was lifetime FIT 50 ng Hb/ ml at 0.5-year intervals for all risk groups, variations in the subgroups do not translate to a change in the overall outcomes for this strategy.

This work is undergoing preparation for publication.

Evaluation 2

A Modelling Study to Estimate the Cost and Effects of Behaviour Changes to Diet & Lifestyle for Those in Post-Polypectomy Surveillance

Results

Those strategies which modelled a 10% increase in dwell time produced the most effective results and returned the greatest QALY gains. When all results were compared as mutually exclusive alternatives, two strategies formed an efficient set and were presented on an efficient frontier, using FIT 100ng Hb/ ml at 0.5 year intervals for all risk groups with a 10% increase in dwell time, and FIT 50ng Hb/ml at 0.5 year intervals, with a 10% increased dwell time, these results are in line with the strategies which were cost-effective in the base case analysis. As shown in Figure 7, the strategies which modelled a lower, age-specific CRC incidence by 5% and 10%, in general, show a lower QALY gain than their base case comparators, but with higher net costs.

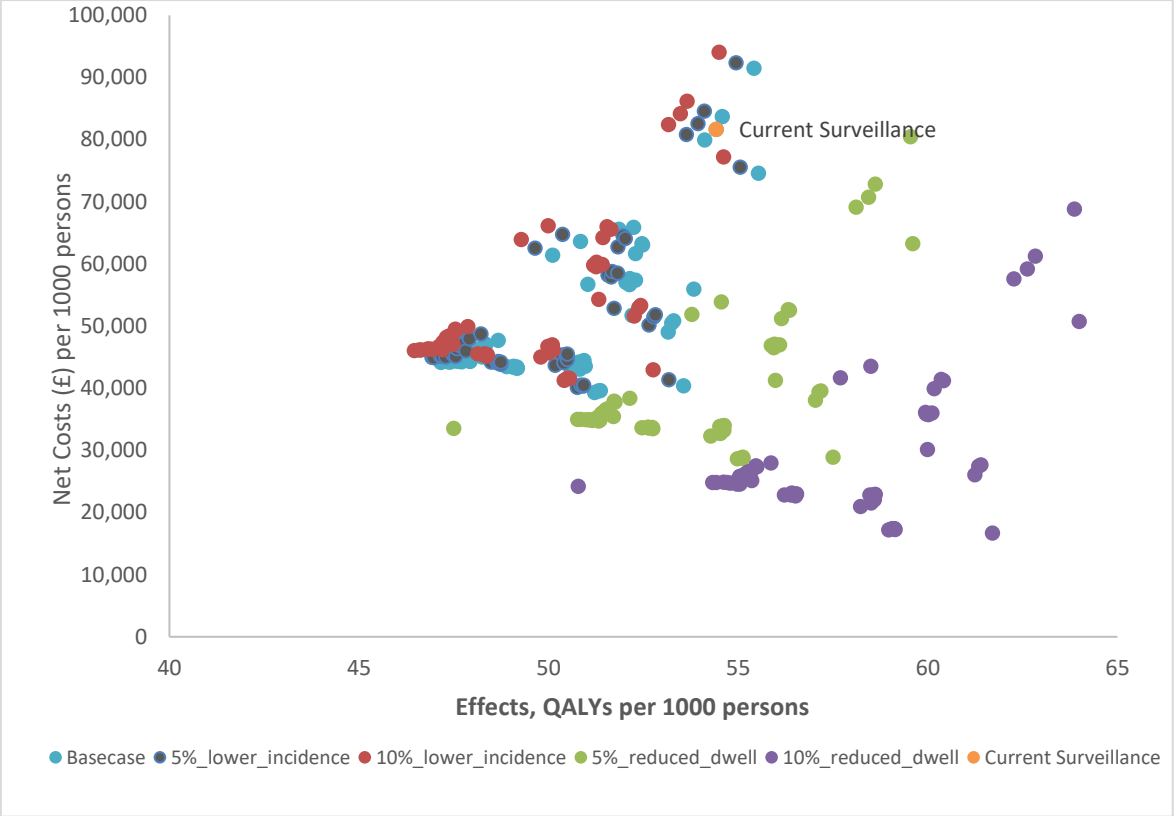

Figure 7 – Cost and effect of all strategies modelled

Subsequently, I selected two strategies; the impact of a 10% increase in dwell time on both current UK guideline surveillance practice (Colonoscopy at 1, 3, 5 year intervals in HR/ IR/ LR respectively), and a highly-effective, lifetime FIT programme (offered at 0.5 year intervals for all risk groups) to estimate the additional cost per additional QALY, as shown in Table 4.

In each strategy, there was a net gain of approximately 8 additional QALYs per 1000 persons, compared to their parallel base case models. In both strategies, the modelled 10% increased dwell time resulted in an overall cost saving compared to their base case comparators. This was added to the total intervention costs for each cost scenario, giving estimated additional costs per additional QALY, with and without the travel costs, and alternatively for the Primrose scenario.

Table 4 – Effects of a 10% increase in dwell time

	Strategy	
	(1) FIT50_0.5ALL	**(3) Colo_135 Current Surveillance**
Change in QALY / 1000 persons	+8.47	+8.20
Net Cost Difference (£) (10% longer dwell time model minus base case model / 1000 persons)	-23,818	-22,488

Additional Cost/ additional QALY / 1000 persons (including cost difference above)			
A	In £, based on BeWel[59] Total cost (without travel costs)	61,686 (40,777)	63,808 (42,235)
B	In £, based on Primrose intervention[67], alternative Cost	32,035	33,215

Based on total costs from the BeWel study the estimated additional costs per additional QALY (including the relative savings benefit) exceeds £60,000 in each strategy (A1 / A2). When travel costs were removed, the additional cost per additional QALY falls to £40,777, in the most effective strategy (A1). Based on the costings from the Primrose intervention, the additional cost per additional QALY is lower at £32,035 (B1) in the most effective strategy.

Notwithstanding the costs of the intervention, as shown in Figure 1, the outcomes from the parallel strategy that modelled 10% lower CRC incidence were more costly. Based on the model outcomes only, the cost for strategies 1 and 3 (FIT50 lifetime testing at 0.5-year intervals and current surveillance) would increase by £2,615 / 1000 persons and £2,538 / 1000 persons respectively, for direct screening and surveillance. In each case, these strategies resulted in slightly lower QALY gains for their respective strategies of -0.92 and -0.94 QALYs, as shown in Table 5, and might be considered to be inefficient. This is representative of the trend across all strategies modelled using the lower aged based CRC incidence assumptions.

Table 5 - Relative change accrued relative to Base case for 10% CRC incidence reduction

	Strategy	
	(1) FIT50_0.5ALL	**(3) Colo_135 Current Surveillance**
Change in QALY / 1000 persons	-0.92	-0.94
Net Cost Difference (£) (5% reduced CRC Incidence model minus base case model / 1000 persons)	2,615	2,538
Relative Change in LYG overall		

A closer examination of the model outputs for the incidence reduction strategies modelled showed reductions in all CRC treatment costs; however, there were increases in the ongoing screening

costs, as a consequence of more people remaining in this part of the model (with fewer incident cases to detect, the cost was incurred without benefits).

This work is undergoing preparation for publication.

Evaluation 3

Can Ireland's Colorectal Screening Programme Save More Lives, Save Money And Live Within Existing Colonoscopy Capacity Constraints? Findings From The MISCAN Micro-Simulation Model

Results

An overview of all simulated strategies is available on request, this reports characteristics of each strategy in terms of the FIT cut-off, interval and age range modelled along with the estimated colonoscopy requirements, costs, effects and total CRC deaths prevented. Figure 8. shows the estimated costs and effects of all 315 simulated strategies according to FIT cut-off and capacity requirements. Strategies with FIT cut-offs of 50, 100 and 200 ng Hb/ml are shown with round, triangular and square markers respectively. Strategies that are within the colonoscopy capacity of the current strategy are shown with solid markers, whereas those exceeding current capacity are shown with hollow markers. The current strategy is shown as the black square. The black dotted lines correspond to the costs and effects of the status quo. The efficient frontier is shown with the grey dotted line. Note that the efficient set is solely composed of strategies with a FIT cut-off of 50 ng Hb/ml. This indicates that the lowest cut-off generally yields strategies that are more effective and less costly than higher cut-offs. Table 6 provides a summary of the moves between previous policy positions in the past, and potential future alternatives considered.

Scope within Ireland's Current Colonoscopy Capacity

Figure 8. shows that while many strategies exceed the current colonoscopy a capacity, there are 126 that do not. The figure shows that a considerable portion of these feasible strategies lie to the right of the status quo, indicating that there are alternatives that are both feasible and more effective than

the current strategy. A small number of these strategies also lie below the current strategy, indicating that some are also cost-saving relative to BowelScreen's current configuration.

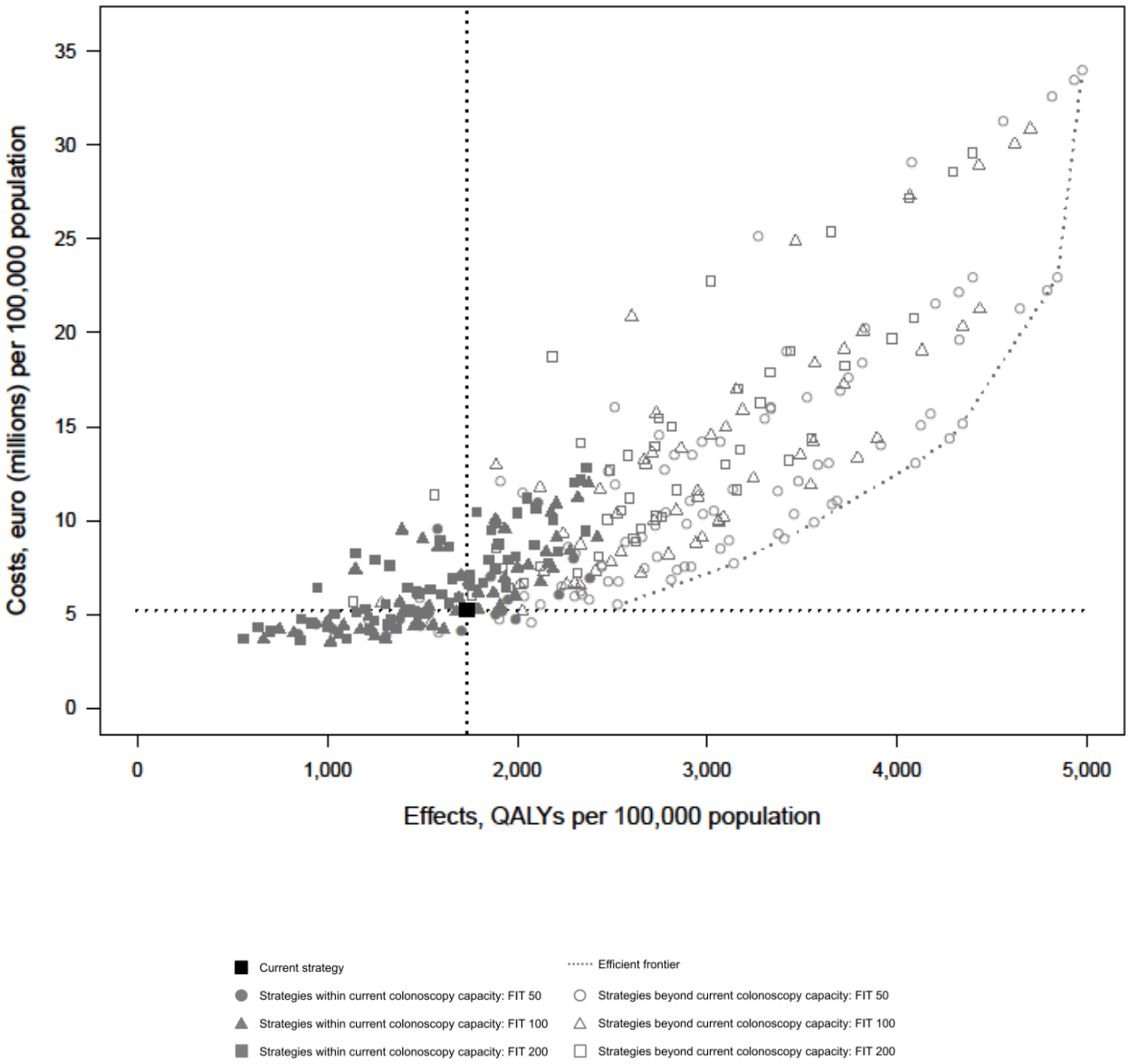

Figure 8 – All Strategies by FIT cut-off and colonoscopy capacity

Decisions reducing colonoscopy capacity requirements

Figure 9. presents a subset of the strategies displayed in Figure 1, but with the axes rescaled for clarity. It shows the three policy positions taken by BowelScreen to date and the planned future expansion. Firstly, Point 1 shows strategy originally recommended by the HIQA HTA. Secondly, the restriction of the screening to 60-69 years adopted at BowelScreen's introduction is shown by Point 2. The 2014 increase in the FIT cut-off to 100 ng Hb/ml is shown by Point 3. Point 4 represents the

currently planned restoration of the screening age range to 55-75. Whilst the planned expansion of the screening age range would generate more QALYs relative to the current programme, it would still be less effective than the initially recommended strategy employing the FIT cut-off of 100 ng Hb/ml between ages 55-75.

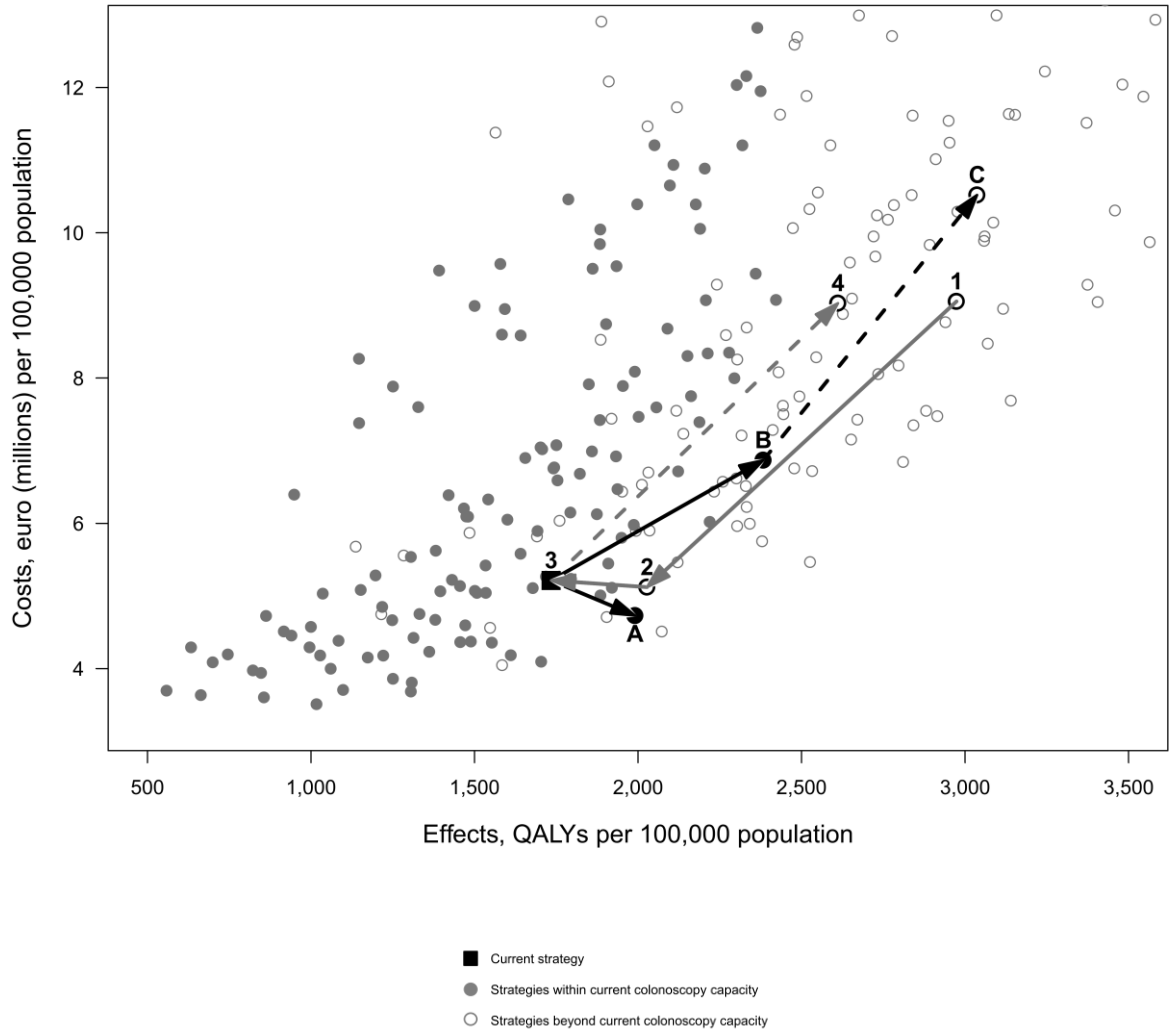

Figure 9- Past Policy Changes and Future Policy Options

Potential policy alternatives

Figure 9. also depicts three possible policy alternatives to the status quo. Both options A and B are within the current colonoscopy capacity and so are feasible now. Option A uses a FIT cut-off of 50 ng Hb/ml with a screening interval of 4 years between ages 60-72. It dominates the current policy as it offers an estimated 15% more QALYs, 13% more CRC deaths prevented, 9% less costs and requires 6% less colonoscopies. Option B is the optimally cost-effective of the currently feasible strategies, as it

maximises NHB. It uses a FIT 50 ng Hb/ml cut-off with a 5 year screening interval between ages 55-75. This strategy provides an approximate 37% gain in QALYs, 29% increase in CRC deaths prevented, a 32% cost increase and result in a modest 2% reduction to the required colonoscopies relative to the current strategy.

Table 6 – Summary of Policy Positions

Identifier	Strategy	Age range	Interval	Cut off	QALYs per 100,000	Cost (€) per 100,000	Colonoscopies per 100,000	Change in QALYs (%)	Change in Costs, (%)	Change in Colonoscopies (%)
1	Initial HIQA Recommendation	55-74	2	100	2,974	9,055,871	101,699	71	74	119
2	Age restriction	60-70	2	100	2,027	5,121,535	66,250	17	-2	43
3	Approximation of current strategy using 200 ng HB/ml	60-70	2	200	1,734	5,214,017	46,372	0	0	0
4	Planned age expansion	55-75	2	200	2,611	9,031,347	73,537	51	73	59
A	Max NHB with cost saving	60-72	4	50	1,991	4,729,132	34,884	15	-9	-25
B	Max NHB within capacity	55-75	5	50	2,383	6,869,370	45,430	37	32	-2
C	Optimised (Max NHB) with expanded capacity	60-75	4	50	3,037	10,521,322	70,579	75	102	52
D	Max overall Net Health Benefit	50-80	1	50	4,844	22,926,425	366,809	179	340	691

BowelScreen's current commitment to restore the initially-planned screening age range of 55 to 74 does not make mention of any planned changes to the screening interval or FIT cut-off. Consequently, this change implies a future increase in the colonoscopy screening capacity. The model permits us to examine if this implied capacity increase could be used more effectively. An alternative service expansion represented by Strategy C which uses a FIT 50 ng Hb/ml cut-off with 4-year intervals between ages 50-74. This strategy would provide a 16% QALY gain relative to the planned age expansion (Strategy 4), but would also be 16% more costly.

Finally, the overall optimally cost-effective strategy among all simulated without any colonoscopy capacity constraint is shown in Figure A1 in the appendix as Point D. This strategy uses a FIT 50 ng Hb/ml threshold, an annual screening interval between ages 50-80. This strategy would require a considerable increase in colonoscopy capacity of 691% relative to the status quo. It would cost 340% more but would yield an estimated 179% more QALYs and 119% more CRC deaths would be prevented than the current policy.

This work is undergoing preparation for publication.

Personal and Public Involvement (PPI) Findings

Discrete choice experiment on alternate colorectal adenoma surveillance packages: results of the 'My follow up' study

Results

A total of 231 participants responded to the survey, response rate = 19.25%. Complete data were available for DCE analysis for n=182 participants.

Participants' demographic characteristics & questionnaire results

Table 7 shows the characteristics of the sample. The sample comprised of a majority of male (77.3%) and married respondents (79.5%, versus 47% of the general NI population[89]) with a mean age of 63.4 years. 27.5% of respondents indicated that they had completed a university degree or higher, which is slightly higher than NI average (23.65% with level 4 qualifications[89]). 38.9% of participants reported that they were unaware of their own CRC risk status, and 40.7% believed themselves to be either at low risk or no longer at risk of CRC following polypectomy.

Of those who provided height and weight data, from which estimated BMI was calculated, average BMI was 28.7 (categorised as overweight). Comorbidities (details on request), were identified by self-reported medication use for a range of conditions including 53.2% for high blood pressure, 48.5% for high cholesterol, 20.8% for cardiac problems, 10.8% for diabetes. 75 participants (32.8%) used medications for more than 2 conditions, and 4.8% were taking medications for more than 4 conditions.

Table 7 – Participants' demographic characteristics & questionnaire results

Patient Characteristics	N	%	Mean	Std. Error	95% Confidence Interval	
					Lower	Upper
Age (Years)			63.4	1.2	61.0	65.8
BMI[$]			28.7	0.4	27.9	29.6
Gender						
Male	177	77.3				
Female	49	21.4				
Marital Status						
Married	182	79.5				
Highest Education						
University/ higher degree*	63	27.5				
Morbidity						
Frequency of Multi-morbidity Score >2[75]	75	32.8				
Lifestyle						
Hours/week spent watching TV[84]			17.9	2.6	12.8	23.0
£ Spend Per Month on TV/ internet package			24.5	3.8	16.8	32.1
Willingness to change score (scale 1-10)			6.5	0.6	5.3	7.7
Exercise 30 mins+ >3 times in the last week*	50	21.8				
Household income (£)						

Not reported	91	39.7	
<10k	14	6.1	
10-30k	74	32.3	
30-50k	38	16.5	
>50k	12	5.2	
Personal Reported understanding of CRC risk (Respondents selected one response) Following colonoscopy I now believe that my risk of CRC is:			
No longer at risk	7	3.1	
Low risk	85	37.6	
Intermediate risk	31	13.7	
High risk	15	6.6	
'I don't really know if I'm honest'	88	38.9	
How was your last colonoscopy result communicated?			
Clinic appointment not on the same day	31	13.7	
By letter in the post	87	38.5	
On the day by my nurse/ endoscopist	85	37.6	
By phone call	4	1.8	
I don't remember	18	7.9	

*the highest category presented $ based on 115 respondents

Multinomial logit (MNL) regression

As a result of the coding used in the statistical model, a higher coefficient shows higher influence (utility) in the participants' preference, whilst a negative coefficient reflects a reduction in well-being (disutility) associated with the attribute level.

After multivariate adjustment it was evident from the MNL model that participants indicated strong preferences for surveillance programmes which maximize risk reduction (β= -0.62 (for 25% reduction in risk), Standard Error (SE) 0.13 as opposed to 0.67 (for 80% reduction in risk), SE 0.15, p = 0.00); and for non-invasive testing (β= 0.13, SE 0.08, p = 0.003). Relative to no support, respondents preferred surveillance programmes with the inclusion of phone or email support for diet and lifestyle changes (p = 0.016). Relative to a 42-month interval of testing, to which people were significantly averse (β= -0.49, SE 0.20, p = 0.000) participants preferred early repeat testing at intervals of 17 and 24 months. Specifically the preference for the 24 month interval was greater than the 17 month interval (β= 0.20, SE 0.15, p = 0.007, and β= 0.17, SE 0.17, p= 0.044 respectively). The model also shows the participant cost aversion (β= -0.38, SE 0.17, p 0.000 for a £45 OOP cost). Detailed model results are available on request. However, the MNL results also indicated that respondents had significant preferences for the status quo (β 0.85, SE 0.13, p = 0.000), while all else being equal participants were significantly less likely to favour invasive testing (β= -0.13, SE 0.08, p= 0.00).

Random parameter logit (RPL)

Detailed results from an RPL (EC) model are available on request. In general, preference heterogeneity across the sample is more effectively accommodated in the RPL EC modelling. As in the MNL

model, the RPL (EC) model indicated that participants were significantly more likely to favour programmes that offered phone/ email based support for diet and lifestyle change and a greater risk reduction.

In the RPL (EC) model, participants preferences for a 17-month testing interval were clear and significant (β= 0.25, SE 0.10, p= 0.007). There is little evidence to confirm the participant preferences for non-invasive testing as the error bars for both invasive and non-invasive testing cross the null. Participants were significantly less likely to favour the more costly programmes (β= -0.59, SE 0.10, p = 0.000). Similarly, there was a significant preference for the status quo.

When all parameters were normalised, the full RPL model indicated that participants favour phone/ email based support for diet and lifestyle programme (β= 0.33, SE 0.16, p = 0.039), details on request. The participants' aversion to risk became more pronounced, with the range of the coefficients extending. The findings in respect of testing frequency, cost aversion and preference for the status quo remained unchanged (when the RPL results are compared to the MNL model). The differences in preferences can be more readily visualized in the illustration of preference weights, with their respective standard errors, as estimated from the full RPL model, as shown in Figure 10.

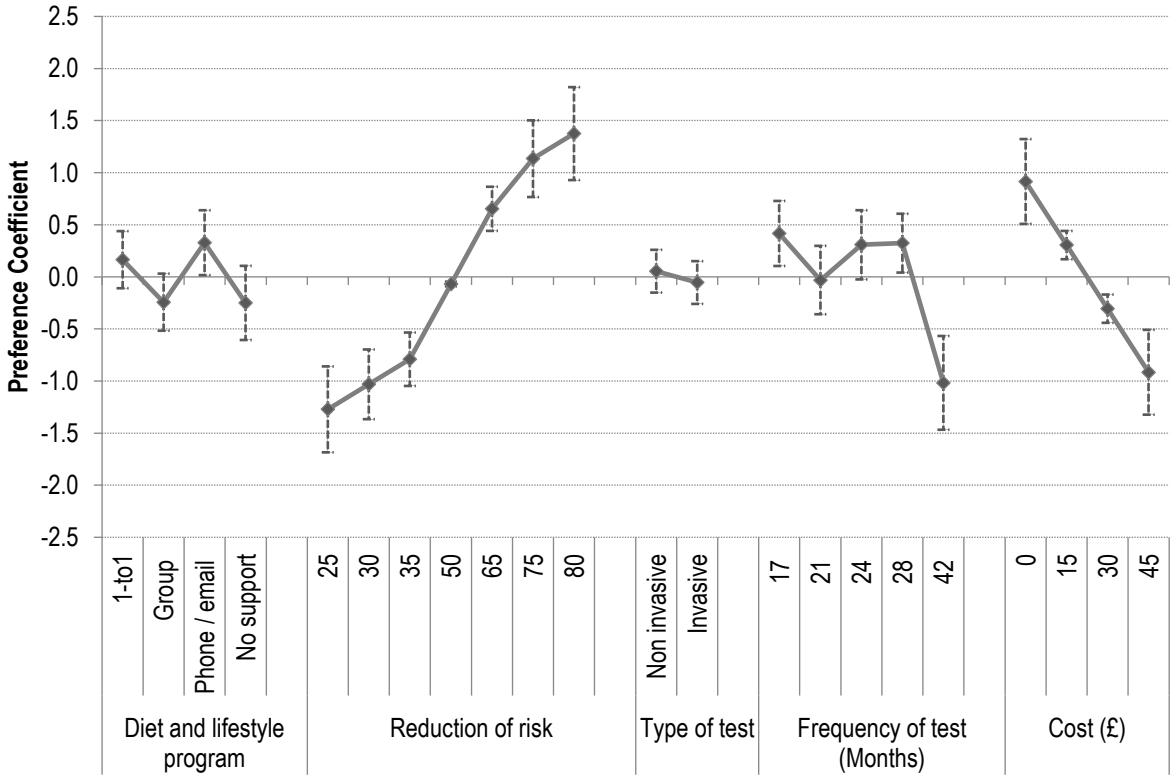

Figure 10 – Preference weights for the RPL model

Figure 10 illustrates that group based support was not preferred with a negative preference weight, 1 to 1 and phone/ email support were preferred, however, the standard error for 1 to 1 support crossed

zero, and is not significant. There is a clear trend for risk aversion. Test type preferences, as estimated in the full RPL model, in each case crossed zero and had non-significant results. For the interval of testing 42 months is not preferred, within the shorter intervals, significant preference for the 17-month interval was shown. Participant cost aversion remains significant.

Relative Importance

To allow the ranking of preferred programme attributes, as shown in Figure 11, on the basis of parameter values (coefficients), relative attribute importance was derived from the full RPL model (details on request). The relative importance estimates are based on the differences in the most preferred and the least preferred level of the attribute. Importance weights for reduction of risk, OOP costs and frequency interval of testing were statistically significant. These importance rankings highlight that participants attached a greater importance to risk minimisation than each of the other attributes, followed by cost, the frequency of testing, diet and lifestyle programme, and test type was the least important attribute. The

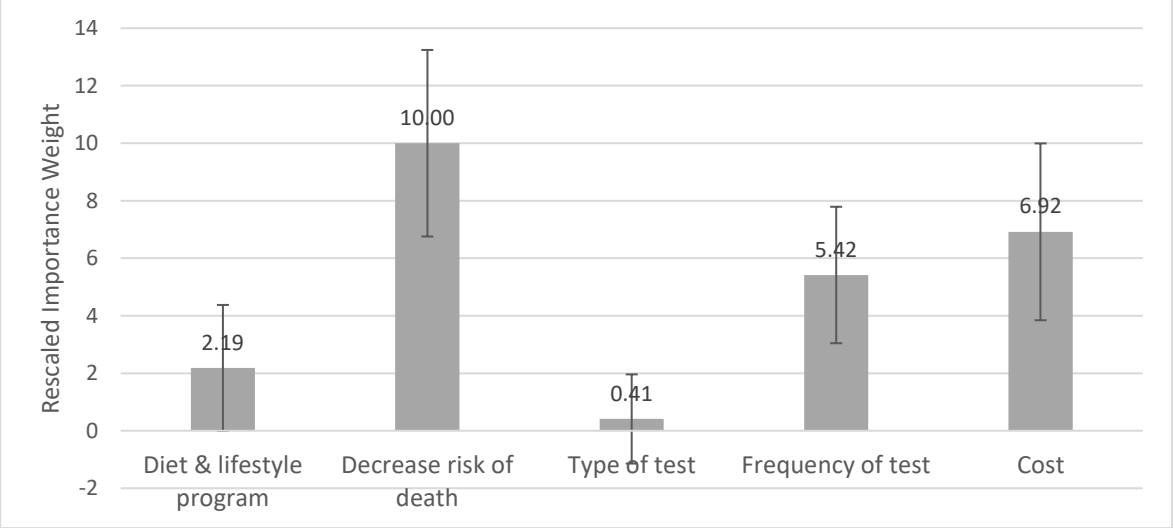

Figure 11 - Relative Importance of attributes (RPL model)

Latent Class (LC) modelling

Given that a preference for inclusion of phone or email support for diet and lifestyle changes was evident in both the MNL and RPL models, LC modelling was used to explore the possibility of subgroups or latent classes within the sample. The AIC and BIC were used to determine the optimal number of subgroups. Using LC modelling, the AIC and BIC suggest that 3 sub-groups best characterize the underlying latent class membership among participants, details on request. Characteristics of the 3 discernible classes (subgroups) were shown to be:

i) Class 1 (membership probability 0.268) - those participants significantly preferring phone/ email support, 17-month interval, non-invasive testing, who were risk and cost averse. The class also had a significant aversion to the status quo.

ii) Class 2 (membership probability 0.484) - those preferring the status quo, who were risk and cost averse.

iii) Class 3 (membership probability 0.247) - those significantly averse to non-invasive testing (p=<0.05), who were risk and cost averse.

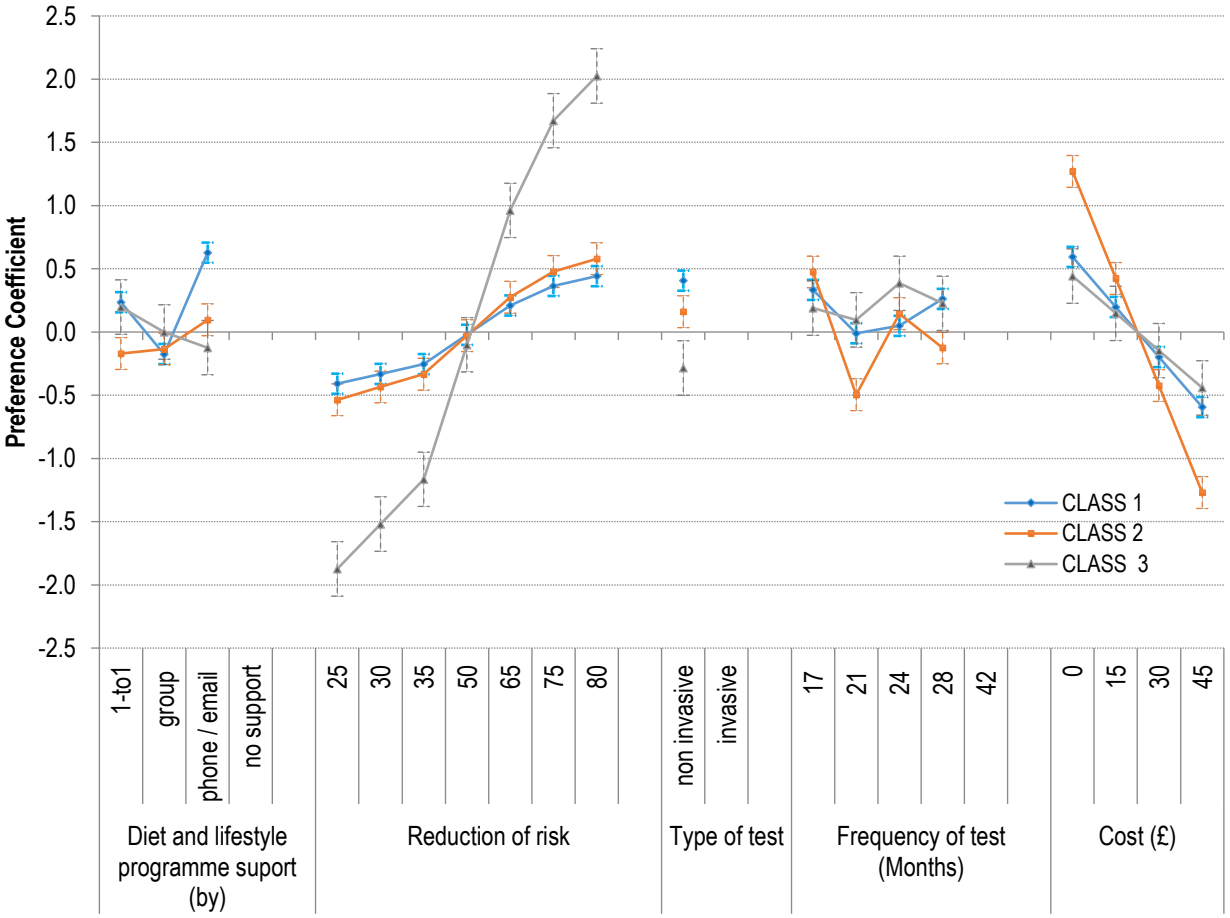

Figure 12 - Preference Weights by LC Model Class

As shown in Figure 12, based on the LC model differences noted in preferences we estimated the relative importance weights, to characterize the between-group differences. The most important attribute differs by class, with Class 1 considering the diet and lifestyle the more important attribute, while Class 2 considered costing the most important attribute and Class 3 considered reduction of risk the most important attribute (details on request). Comparison of the estimated relative importance results of RPL with the LC shows that the RPL based greater relative importance attribute is shared with Class 3 only (details on request).

Other participant characteristics including the willingness to change (lifestyle) scores, perceived risk of CRC, education status, BMI, multi-morbidity, literacy, numeracy and self-affirmation scores were not shown to be significantly linked to class membership in the 3 class LC model [details on request].

Maximum Acceptable Risk

Given that in all models participants were significantly risk-averse, post hoc analysis was carried out to examine the risk/ benefit trade-offs that would be acceptable to participants, across attributes. Consequently, based on the full RPL model, the mean levels of risk reduction that participants were willing to forgo, in exchange for enhancements in various attribute levels were estimated, (details on request, MAR results have negative signs, due to the framing of the DCE questions).

For all versions of support for diet and lifestyle interventions, participants were willing to trade off risk to receive the package, although there were no significant trade-off weights found. Results imply that participants would be willing to accept a 12% reduction in their risk of CRC, to receive phone/ email based support. Results also imply that participants are willing to accept a 2.25% reduction in their risk of CRC for switching from an invasive to a non-invasive test.

Participants were willing to accept significant reductions in their risk, in exchange for receiving their next test, to check for new or recurrent polyps, at intervals earlier than 42 months. For example, for a move from 42, to 17-month test interval, respondents indicated they were willing to accept 29% reduction risk (95% CI = -44.61 to -14.37). Participants were willing to trade a 22% reduction in their relative risk to retain the status quo programme.

Comparisons of the MAR by LC class were also made, (details on request) – which showed that in Class 1 participants were significantly likely to trade to receive either 1 to 1 support or phone/ email based support for diet and lifestyle changes, as well as trades of 54% in their reduction in risk to receive non-invasive testing. In Class 2 and 3, however, no significant trades were shown for access to diet and lifestyle support were shown

Willingness to pay (WTP) results

WTP estimates, based on the full RPL model (details on request). In response to the hypothesis that participants were willing to pay for the addition of a diet and lifestyle support intervention, the WTP was estimated for moving from no support for diet and lifestyle changes to each attribute. WTP to receive a 1 to 1 support; group-based support or a phone/ email based programme respectively were: £10.20, £0.18 or £14.21*, (*p>0.05). There were significant WTP for all moves away from a 42-month testing interval, with the greatest, £35.24, for moving to a 17-month programme. The WTP for a non-invasive test was not

significant, £2.67. Additional WTP estimates were modelled based on the LC model classes and compared with RPL model (details on request). In distinguishing WTP, by class, the results show that in Class 1, there was a significant WTP more for all support programmes, and up to £31.14 for access to non-invasive testing, however, in Class 2, there is was no significant WTP for any support programmes, with only a significant WTP for a move from 21 month to a 17 month testing interval (£18.07). In Class 3 no significant WTP estimates result.

Knowledge of CRC risk factors and lifestyle-related behaviours

Respondents were asked to recall how much information, about a series of CRC risk factors, was discussed with them when receiving the results of their colonoscopy test. N=175 responses were recorded (details on request). In general, the majority of respondents indicated that CRC risk factors related to diet and lifestyle risks were not discussed with them when receiving their results. 38.1% of respondents, who had previously indicated they took medications for diabetes, reported they had received information about the associated risk of CRC with Type II diabetes[90], it was unclear, however, if participants were taking metformin, which may have a protective effect[91]. 17.51% reported they had been informed that increased body fatness and abdominal fatness increases their risk of CRC. Less than 25% of respondents recalled being informed about dietary risks of red meat, processed meats of consumption of animal fats or alcohol consumption, or about the benefits of daily exercise. The most commonly recalled information was for diets rich in high fibre and whole grains (35%) and the associated reduction in CRC risk. Comparisons of information given with self-reported awareness of each factor are available upon request.

As shown in Table 7, the respondents reported an average of 17.94 hours per week watching TV, and only 21.8% took part in exercise, of thirty minutes or more, more than three times per week. On a 1-10 scale, where 1 equals not prepared for lifestyle change, 5 willing to consider change, and 10 indicative of having already begun to change lifestyle, participants were asked '*Do you consider yourself to be motivated to make changes in your day to day life to reduce your risk of developing bowel cancer and other illnesses*?' The mean 'willingness to change' score was 6.48. Only 5.06% of respondents scored <5, indicating that the majority of participants were willing to make changes to diet and lifestyle, and 30.9% of respondents scored 10 indicating they are already making changes to reduce their risk of cancer.

Cognitive Reflection Test

Participants were asked to respond to a short series of cognitive reflection test (CRT) questions designed to measure if an individual has a tendency toward limited processing of information. 29.1% of respondents showed low CRT scores, but 32.6% did not respond to these questions (details on request).

Literacy and numeracy

51.8% (n= 72/139) answered correctly, and 48.2% (n= 67) incorrectly, the Berlin Numeracy Test Single Item Format[79], a strong predictor of an individuals' comprehension of everyday risks. Using the Single Item Literacy Screener[78], respondents are asked: how often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy? Of those who responded 83.2% reported never (n=124); 8.7% reported rarely (n=13); 5.4% reported sometimes (n= 8) and 2.6% (n= 4) reported often or always (34.9% of respondents did not answer, n=80). Further details on request.

This work is undergoing preparation for publication.

Conclusion

Having provided the first comprehensive review of the health economic literature in adenoma surveillance, which indicated no previous evaluation of the cost-effectiveness of colonoscopy compared with other tests, such as FIT or another non-invasive testing, and indicating gaps in cost-effectiveness reporting by sub-group, and highlighting the potential evidence on the cost-effectiveness of combined aspirin and colonoscopy in chemoprevention of CRC and its likely role in the prevention of premature mortality due to other causes.

We suggest that a focus on opportunities for practice change, at this teachable moment, include greater personalised prevention and should consider the potential role of shared decision making for both the types of testing used, supportive behaviour change interventions, personalised information provision and aspirin chemoprevention for those with co-morbid conditions, taken together such a revised programme may enhance CRC prevention outcomes.

In addition, evidence from our modelling suggested that local re-appraisal of BowelScreen, the Irish CRC screening programme, would likely lead to more lives which could be saved within existing colonoscopy capacity constraints, if BowelScreen were to trade off a reduction in screening frequency against an increase in population coverage and adopt a more efficient FIT cut-off. We remain in consultation with the Irish National Screening Programme to discuss these findings.

Practice and Policy Implications/Recommendations

- Modelling suggests a potential to use intensive non-invasive faecal immunochemical testing (FIT) based surveillance as an alternative to colonoscopy-based surveillance. The clinical viability of this approach is likely related to long-term acceptability of high-frequency FIT.

- Preliminary modelling results show that the addition of diet and lifestyle interventions to surveillance programmes, could potentially generate up to an additional eight Quality-adjusted life years (QALYs) per thousand persons, the additional cost per additional QALY of a hypothetical 10% increase in the dwell time (achieved by such programmes) was estimated to be in the range of £32,035 to £64,145, with additional gains likely in co-morbid conditions.

- Participant's preferences for the inclusion of such programmes showed people involved in surveillance were in the main unaware of their risk status, were in the main relatively inactive, and when faced with alternative programme options were risk and cost averse. Whilst reports show participants preferring the status quo, in considering revised surveillance programmes – this may reflect limited current policy and practice guidance on primary prevention within surveillance and would appear to be grounded in personal cost aversion.
    - Significant discordance was found between perceived risk versus the known risk of CRC (based on screening programme identifiers), with low levels of recall of information provided within the current surveillance programme, regarding diet and lifestyle CRC risk factors – this identifies a clear need for improvements to the current information provision in clinical practice for those in surveillance.
    - Subgroups of participants (around 25%) are willing to change behaviours, preferring to do so with the support of phone or email based diet and lifestyle interventions and to utilise non-invasive testing, at earlier intervals of testing - the practice implication is that amongst a cohort where co-morbid conditions were prevalent, benefits of prevention programmes are likely to have added value beyond CRC disease prevention and would likely be cost-effective, as such the feasibility of their delivery in primary and supportive care contexts should be explored.

- Simple changes to BowelScreen (the Irish CRC Screening programme) could save lives, reduce costs and relieve pressure on colonoscopy capacity. The extent of the potential improvements depends in part on the acceptability of lengthening the screening interval, highlighting the importance of considering a full range of alternatives when conducting cost-effectiveness analyses and programme planning.

Pathway to Impact

The findings from this research have been presented at a number of national and international conferences to disseminate the results widely.

Consultation with service user groups has taken place to feedback the findings from the DCE work, and this will be followed up by presentations to the NI Screening Programme team and outreach to local clinicians to explore the potential for practice change. Work is ongoing with the Irish CRC Screening programme to explore the potential to revise their screening programme.

We would be keen secure funding to develop and connect local endoscopy services with the focus of exploring digital solutions, as guided by user feedback, to provide information by email or in the clinic, for shared decision making in primary prevention in this area. In due course, as the local screening programme adopts the newer FIT based technology in screening we would be keen to explore the potential for the knowledge translation of the modelling findings into practice, in relation to FIT testing in surveillance, we foresee, in a trial or registry process, the primary care setting providing an optimal environment for active surveillance in by primary and secondary prevention efforts.

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