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Evaluation of the Effectiveness and Cost-Effectiveness of Personalized Surveillance After Colorectal Adenomatous Polypectomy

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11 **colorectal adenomatous polypectomy**

12

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36

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38 Abstract

39 Lifetime risk of developing colorectal cancer is 5% and five-year survival at early-stage is
40 92%. Individuals with pre-cancerous lesions removed at primary screening are typically
41 recommended surveillance colonoscopy. Since greater benefits are anticipated for those
42 with higher risk of colorectal cancer, scope for risk-specific surveillance recommendations
43 exists. This review assesses published cost-effectiveness estimates of post-polypectomy
44 surveillance to consider the potential for personalised recommendations by risk-group.
45 Meta-analyses of incidence of advanced-neoplasia post-polypectomy for low-risk cases were
46 comparable to those without adenoma; with both rates under the lifetime risk of 5%. This
47 group may not benefit from intensive surveillance, which risks unnecessary harms and
48 inefficient use of often scarce colonoscopy capacity. Therefore, greater personalisation
49 through de-intensified strategies for low-risk individuals could be beneficial. The potential
50 for non-invasive testing such as faecal immunochemical tests combined with primary
51 prevention or chemoprevention may reserve colonoscopy for targeted use in personalised
52 risk-stratified surveillance.

53

54 This review appraised evidence supporting a program of personalised surveillance in
55 patients with colorectal adenoma according to risk-group and compared the effectiveness of
56 surveillance colonoscopy with alternative prevention strategies. It assessed trade-offs
57 between costs, benefits and adverse effects which must be considered in a decision to
58 adopt or reject personalised surveillance.

59 Key Words:

60 Colorectal cancer, adenoma, cost-effectiveness, Precision Medicine, early detection, cancer
61 prevention, surveillance

62 Background

63 Lifetime risk of developing colorectal cancer (CRC) is 5% for an average risk individual in the
64 US¹. CRC is the third most common cancer globally and imposes a significant burden of ill-
65 health². Worldwide, CRC deaths form 8.5% of total cancer deaths (694,000 annually)³.
66 Many deaths could be avoided by early detection through screening^{4,5}; as given five-year
67 relative survival rates for CRC detected at a local stage are 92%⁶.

68
69 Screening programs have been widely implemented to manage CRC risk⁷. Such programs
70 employ colonoscopy either as the primary test or as a diagnostic test following a positive
71 finding on a non-invasive stool test, which detects blood or other markers suggestive of
72 cancerous lesions. Colonoscopy offers direct visualisation and examination of the entire
73 colon permitting the identification and removal of polyps leading, it is thought, to the
74 prevention of CRC⁵.

75
76 There are concerns over claims that screening programs reduce mortality or improve
77 survival⁸, based largely on arguments related to lead time bias. Lead time bias occurs when
78 a diagnostic test merely identifies the disease earlier, thus increasing *perceived* survival
79 without significant modification of the disease course⁹. Despite such concerns, a recent
80 meta-analysis of randomised screening trials (which addressed the effect of lead-time bias,)
81 showed that one CRC death is prevented for every 1000 people screened, with this benefit
82 being manifest on average after 9.4 years^{9,10}. Moreover, micro-simulation modeling is
83 reported to show that declines in CRC death rates are consistent with a relatively large
84 contribution from screening¹¹. While there is considerable randomised control trial

85 evidence to support screening overall, the magnitude of benefit available for surveillance (in
86 terms of CRC deaths prevented) is uncertain.

87

88 Post-polypectomy surveillance by colonoscopy has become a common feature of CRC
89 prevention strategies^{12,13}, offering intensive monitoring to individuals with prior
90 precancerous findings at primary screening¹⁴. In the case of colorectal screening,
91 appropriate surveillance after endoscopic diagnosis of an adenoma¹⁵, is typically a strategy
92 of surveillance colonoscopy at intervals of between 3 and 10 years. Surveillance intensity
93 can be adjusted dependent on an individual's estimated CRC risk, as predicted by the
94 number and grade of polyps removed at index colonoscopy. Despite being widely
95 recommended, the evidence that post-polyp surveillance reduces CRC incidence or
96 mortality is lacking and is rarely established for sub-groups¹⁶.

97

98 Up to 85% of CRCs are thought to develop from conventional adenomas¹⁷. Adenomas begin
99 in the glandular tissue lining the colon and while many are benign, some may have
100 malignant potential. Genetic changes in the colon's lining can lead to malignancy as a result
101 of a complex multi-step process in which adenoma is an intermediate stage. A process
102 referred to as the adenoma-to-carcinoma sequence, taking an estimated 7 to 15 years¹⁷⁻²⁰.
103 The long preclinical sojourn time of many adenomas creates the opportunity for successful
104 early detection through screening. Reported adenoma prevalence is estimated at 20-53% in
105 persons over 50 years, with gender differences showing higher prevalence (40%) in men
106 than in women (29%)^{17,21}.

107

108 Colonic polyps were conventionally classified as either hyperplastic or adenomatous, of
109 which the latter were believed to have the potential to progress to carcinoma²². Advances
110 in genetic pathology are alleviating so called 'variant classification' which 'obfuscated the
111 correct classification' of sessile serrated adenomas²³, which unfortunately, were not as
112 readily detected by many screening tests. As new information emerges it is possible that
113 sessile serrated lesions may be responsible for up to 30% of CRC. The implications of the
114 different pathologies for clinical management warrant the vigilance of physicians who may
115 consider follow-up colonoscopies in accordance with sessile serrated adenomas
116 guidelines²⁴⁻²⁷. Although sessile lesions may have greater contribution to CRC than
117 previously thought, this review focuses on the evidence related to adenomatous polyp risk
118 groups.

119
120 Although there is limited decisive evidence from colon-polyp surveillance, current guidelines
121 for post-polypectomy surveillance employ explicit risk stratification by sub-groups, using the
122 predictive features of adenomas detected at screening colonoscopy²⁸. The size, the number
123 of polyps and their histology provide further qualification in differentiating those with
124 tubular features from those with villous features, considered more likely to have cancers
125 develop in them²⁹. For example, US guidelines recommend that individuals with 3-10
126 adenomas undergo a surveillance colonoscopy every 3 years, while those with 1-2 tubular
127 adenomas <10mm receive a surveillance colonoscopy every 5-10 years³⁰. Surveillance
128 colonoscopies account for approximately 25% of colonoscopies among people over 50 years
129 in the US³¹.

130

131 While the surveillance guidelines are clear, conflicting reporting might lead to a conclusion
132 that these persons are at a significantly increased risk, whilst other reports contend that
133 many of the lesions detected at screening are likely to be of low risk. It has been suggested
134 that following initial detection and removal of adenomas, approximately half of people
135 (51.4%) will have further adenomas within 3 years of initial colonoscopy, of which significant
136 numbers may meet at least one criterion for advanced adenoma^{13,32–35}. However, 84% of all
137 polyps removed at colonoscopy in a large screening study of 13,992 participants were less
138 than 10mm. Within a subset of the study population, CRC was detected in 0.03% of
139 participants whose largest polyp was 1-5mm, (1 patient amongst 3744 patients with polyps
140 1-5mm), moreover only 3 of the 74 cancers detected were found as a consequence of
141 detecting advanced adenomas^{17,36}. Consequently, screening typically generates many
142 'positive' findings that ultimately may be of low-risk, accounting for a small portion of
143 cancer cases, meaning that large numbers of patients will be referred to surveillance, the
144 clinical utility of which can be debated^{17,36}.

145
146 Whilst one benefit of surveillance is the possibility to detect lesions of significance, it may
147 expose patients to unnecessary risks as a result of overdiagnosis, that is, the inclusion of
148 'pseudodisease,' that would not become evident before the patient dies of other causes³⁷.
149 For example, it was reported that CRC was diagnosed in 19 of 2915 patients, who were
150 deemed free of remaining lesions at a baseline clearing colonoscopy, over a mean follow-up
151 of 3.7 years (incidence, 1.74 cancers/ 1000 person-years) amongst those in close
152 surveillance. Equating to 0.65% of atypical post-polypectomy surveillance participants
153 developing CRC³⁸, this includes a considerable numbers of individuals who undergo a
154 surveillance test who could therefore be considered subject to over-diagnosis.

155

156 Some regions are adopting resect and discard policies, whereby lesions judged by the
157 clinician performing polypectomy not to be of high risk can be discarded without being
158 evaluated by a pathologist, thus reducing the risk of procedural over diagnosis³⁹. Another
159 obvious means to lower potential overdiagnosis and limit the harms of invasive testing
160 might be to consider an alternative to colonoscopy and to personalise approaches to
161 surveillance by exploring the role of faecal immunochemical testing (FIT)⁴⁰. In a recent
162 systematic review, FIT shows high diagnostic accuracy for detecting CRC and has shown the
163 capability of quantifying and adjusting cut-off concentrations for positivity⁴¹⁻⁴³. Moreover,
164 its acceptability to patients has also been demonstrated⁴⁴. Therefore, FIT could be an
165 appropriate, acceptable and cost-effective surveillance test.

166

167 Decision making requires careful balancing to avoid either too little surveillance, which may
168 jeopardise CRC prevention goals, or lead to overuse of surveillance, chancing unnecessary
169 harms and inefficient use of colonoscopy resources⁴⁵. Health economic evaluations aim to
170 impartially identify, measure and compare the cost and consequences of the different
171 interventions being considered to manage particular clinical problems⁴⁶. Recent economic
172 evaluation in the US estimated an inflection point between conferring benefit and risking
173 harm in the use of colonoscopy in older adults^{47,48}, whereby the anticipated harms of false
174 positives and unnecessary investigations outweighed the benefits of early detection.

175

176 The relevant resource utilisation relates not only to the financial costs of providing
177 surveillance, but also to colonoscopy capacity, which is often constrained in many health
178 systems. Therefore, decision makers need to consider how best to allocate the limited

179 number of colonoscopy examinations to those individuals with the greatest likelihood of
180 benefit.

181

182 Consensus has not yet emerged on what personalised surveillance practice ought to involve,
183 with variation in current guideline recommendations shown in Table 1. For example, Japan
184 does not differentiate its surveillance guidance by risk category; recommending
185 colonoscopy every three years, whereas the UK recommendations vary between annual
186 colonoscopy for high-risk patients and five year colonoscopy (or return to screening) for
187 low-risk patients. Concerns over how best to balance surveillance intensity will be
188 increasingly pressing given anticipated growth in numbers of people being directed into
189 surveillance colonoscopy¹⁴, in part due to demographic aging and changes in the primary
190 screening technology employed.

191

192 Current data suggest that screening colonoscopy may identify patients at low risk of death
193 from colorectal cancer or who may derive greatest value from a single screening test, but
194 who may not benefit from subsequent intensive surveillance^{49,50}. Although meta-analysis of
195 incidence of advanced neoplasia after polypectomy for a low-risk individual is comparable to
196 persons without findings of an adenoma at colonoscopy, absolute risk in both groups was
197 under the average persons' lifetime risk of 5% (low-risk 3.6% vs without adenoma 1.6%)⁵¹.

198 This indicates that the low-risk group may indeed have a CRC risk that is broadly comparable
199 to the average risk population eligible for primary screening. For that reason, there may be
200 arguments for de-intensifying surveillance towards the types of screening frequencies and
201 non-invasive testing technologies used in primary screening, which in turn would lead to
202 greater personalisation of colonoscopy use.

203

204 Existing approaches to the adjustment of surveillance intensity rely on the frequency of
205 testing, that is, through changes to the interval of use of the current technology
206 (colonoscopy), offering, for example, 3 and 5-10 year colonoscopy³⁰. The ability to vary
207 surveillance has been limited to this interval approach. Newer, more effective stool tests
208 may offer the ability to change the type of test offered, which may add flexibility to
209 surveillance programs and as a result reduce the number of colonoscopies required during
210 surveillance.

211

212 Accordingly, this systematic review has three aims:

213

1. To assess if there is sufficient evidence to evaluate a program of personalised
214 surveillance in patients with colorectal adenoma according to risk sub-group.

214

215

2. To compare the effectiveness of surveillance colonoscopy with alternative
216 prevention strategies.

216

217

3. To assess trade-off between costs (resource use), benefits and adverse effects
218 that need to be considered in a decision to adopt or reject personalised
219 surveillance.

218

219

220

221 **Methods**

222 **Data Sources and Search Strategy**

223

The systematic review was conducted according to the Preferred Reporting Items for

224

Systematic Reviews and Meta-analyses (PRISMA) guidance recommendations^{52,53} and the

225

Centre for Reviews and Dissemination guidance⁴⁶. The review has been registered with

226

[PROSPERO](#) – reference: CRD42016033509.

227

228 An initial check for previous reviews on the topic was conducted, as recommended^{46,54}. The
229 search for the key words 'adenoma' AND 'cost' in ANY FIELD (September 2015), was carried
230 out within the Centre for Reviews and Dissemination [database](#) including all databases
231 (DARE, NHS EED and HTA; those most specific to economic evaluations of health and social
232 care interventions)⁵⁵. This search indicated no existing systematic reviews addressing cost-
233 effectiveness within colorectal adenoma surveillance and prevention programs.

234

235 The systematic review search strategy was optimised with help from a Specialist Medical
236 Librarian (RF), informing the choice of available databases and developing the search to
237 meet the needs of the review. The search strategy was run in MEDLINE, MEDLINE in-
238 process and EMBASE. These databases were searched from their inception to February
239 2016, for key words, medical subject heading terms and synonyms of:

240 (a) Colorectal neoplasms OR adenoma.

241 (b) Costs-benefit analysis OR synonyms.

242 (c) Early detection of cancer OR surveillance.

243 Searches a, b and c were then combined with AND, as shown in Web Appendix 1.

244

245 In order to optimise the resultant yield of studies, we expanded the medical subject heading
246 terms, used a modified strategy in each database (MEDLINE / EMBASE) to identify the
247 literature under relevant terms and included techniques for word proximity and suffixes,
248 which optimised database search tools to find relevant papers.

249

250 The titles and abstracts of the studies returned by the database searches were then
251 screened for inclusion by eligibility criteria according to the patient population or the
252 disease being addressed (P) the interventions or exposure (I) the comparator group (C) the
253 outcome or endpoint (O) the study date / time frame (T) and the study design chosen (S) –
254 ‘PICOTS’ criteria⁵⁶, as shown in Table 2. The reference lists of the retrieved studies were
255 searched to find studies not captured by our database searches.

256

257 Study selection was conducted in three stages, as shown in Figure 1, including removal of
258 duplicates (n=264), title and abstract screening against the PICOTS criteria (n=1009) and
259 independent screening of all full text articles (n= 32) to confirm their eligibility, by two
260 reviewers (EMF / JFOM); conducted according to the selection criteria detailed in Web
261 Appendix 2. In order to minimize bias, studies were retained in situations where both
262 reviewers were not in agreement on exclusion, with discrepancies resolved by adjudication
263 with a third reviewer. All excluded papers were codified by ineligibility of PICOTS category.
264 This process resulted in n=7 papers that were fully evaluated for the review.

265

266 **Data Extraction and Identification of Cost-Effectiveness Analyses**

267 We extracted the initial data from each study using the Consolidated Health Economic
268 Evaluation Reporting Standards statement [checklist](#) tool⁵⁷. We have not conducted a meta-
269 analysis as the outcomes of economic evaluations are typically not commensurate for
270 comparison. Some studies reported incremental cost-effectiveness ratios (ICERs) that differ
271 from the conventional interpretation, as the ratio of incremental costs to incremental health
272 effects, relative to the next most effective strategy⁵⁸, whereby strategies that are more
273 costly and less effective are ruled out by simple or extended dominance^{59,60}. In these

274 instances, the ICERs were recalculated from the reported costs and effects and replicated
275 cost-effectiveness estimations were used to re-examine the comparisons and analyses made
276 by the studies, as carried out in another recent review⁶¹. The recalculated results are
277 presented alongside the originally published results in Web Table 1.

278

279 **Results**

280 **Study Descriptions**

281 The systematic review returned 7 papers that were fully evaluated. An overview of the key
282 quality attributes of each paper as assessed in this review is given in Web Table 2, following
283 the Consolidated Health Economic Evaluation Reporting Standards quality indicators^{48,50,52–}
284 ⁵⁷. The studies were published between 1991 and 2011; no studies from more recent years
285 were identified.

286

287 In brief, the search returned a small number of studies and the prevention strategies
288 compared in the studies varied such that not all compared the same alternative
289 interventions. Thus, the potential for cross-comparison of the effectiveness and cost-
290 effectiveness of particular strategies was limited. Whilst some papers compare surveillance
291 by colonoscopy to natural history, others model compared surveillance by colonoscopy to a
292 screening colonoscopy a 10 year interval⁶², or for performing an early 1 year colonoscopy⁶³,
293 whilst other models compared surveillance colonoscopy combined with chemo-
294 prevention^{64,66} and chemo-prevention alone compared to natural history⁶⁵.

295

296 Strategies considered include:

- 297 • one year surveillance by colonoscopy⁶³,

- 298 • a three-year high-risk and five-year low-risk colonoscopy⁶²,
- 299 • a three-year high-risk and ten-year low-risk colonoscopy⁶²,
- 300 • a three-year high-risk and three-year low-risk colonoscopy⁶²,
- 301 • aspirin as chemoprevention alone⁶⁶,
- 302 • aspirin therapy combined with colonoscopy⁶⁶,
- 303 • celecoxib as chemoprevention alone⁶⁵,
- 304 • a three-year high-risk colonoscopy⁶⁵,
- 305 • calcium as chemoprevention alone⁶⁴,
- 306 • calcium therapy combined with colonoscopy⁶⁴,
- 307 • fixed interval / modified interval colonoscopy surveillance⁶⁷.

308 To address the primary aims of the review in a systematic way, the following sections
309 critically address how respective papers' methods, assumptions and outputs support or
310 prohibit clear evidence for each objective.

311

312 **Evidence to support personalised surveillance by sub-group at index colonoscopy**

313 No papers reported cost-effectiveness results disaggregated by high-risk/ low-risk sub-
314 groups. While two studies described clear elements of stratification, identifying high-risk
315 and low-risk subgroups of patients with adenoma, neither reported a comparison of
316 outcomes by these subgroups; rather they reported results as combined group data^{59,64}.

317 Accordingly, this limited what our review was able to determine regarding risk-optimised
318 surveillance strategies.

319

320 The reporting in one paper did permit a step wise comparison of interval change for
321 surveillance by colonoscopy in high-risk and low-risk groups⁶². The ICERs presented

322 indicated that it is beneficial to change from a 10 year interval colonoscopy to a 3 year
323 interval for high-risk individuals⁶², as this strategy was more effective and its ICER of
324 \$5743/QALY indicated that it is a cost-effective policy change, within conventional
325 thresholds thought to be at least \$50,000/QALY⁶⁸. Whilst it is also beneficial to move from
326 10 year interval colonoscopy to 5 year in low-risk individuals, the ICER of \$296,266/QALY is
327 greater than conventionally accepted thresholds for the US⁶⁸. Importantly, these results
328 also indicated that more intensive surveillance by a change from a 5 year to 3 year interval
329 for low-risk individuals resulted in reduced quality adjusted life years, (-0.0023 QALYs). This
330 'disutility of colonoscopy', shows that it becomes more harmful for low-risk individuals to
331 receive a more intensive surveillance strategy of a 3 year colonoscopy⁶².

332

333 **Effectiveness of colonoscopy compared to alternative prevention strategies**

334 An important purpose of this review was to find studies that compared alternatives to
335 colonoscopy-based surveillance. The review found no studies that considered other clinical
336 test strategies in post-polypectomy surveillance other than colonoscopy. All papers
337 retrieved assumed that the default test for surveillance was colonoscopy. There are,
338 however, comparisons of colonoscopy to three types of chemoprevention drugs, all of
339 which compared chemoprevention benefit to no intervention,⁶⁴⁻⁶⁶ or compared
340 colonoscopy combined with chemoprevention to no intervention^{64,66}. A summary of the
341 results from the strategies evaluated for surveillance is shown in Web Table 1.

342

343 In addressing clinical variations in colonoscopy capacity, the most recent paper authored by
344 Wilschut and colleagues,⁵⁹ used micro-simulation modelling with the MISCAN-Colon model
345 ([one of 3 internationally validated models which evaluate screening programs](#)). This

346 included 48 variations of the background screening program within which 2 surveillance
347 strategies were simulated. Although this study presented results for variation in the primary
348 screening strategy, the reported results do not permit comparison of the two surveillance
349 strategies considered. The analysis considered whether it would be appropriate to offer
350 colonoscopy surveillance under increasingly tight colonoscopy capacity constraints. They
351 found that an affordable ICER was achievable for colonoscopy surveillance when capacity
352 was greater than 20 colonoscopies per 1,000 individuals⁵⁹. However, if the capacity of
353 colonoscopy was <5 per 1,000 individuals offering low-risk groups surveillance colonoscopy
354 was no longer considered an effective allocation of a scarce health resource⁵⁹.

355

356 Wilschut et al.'s analysis adds a modelling feature, not commonly employed in the other
357 papers, that permits the simulation of the impact of both primary screening and subsequent
358 surveillance⁵⁹. Moreover, it has the ability to evaluate issues of service capacity, alternate
359 types of testing and a mix of tests which more accurately reflects the complexity of choice
360 facing decision makers. By comparison, the models used in other studies reviewed only
361 characterise limited aspects of the decision problem.

362

363 Hassan et al estimated the benefit of early annual colonoscopy compared with not doing an
364 early annual colonoscopy, since their descriptions are not clear we clarify that they compare
365 providing a 1 year to a 3 year test⁶³. They report an ICER of \$66,136 per life year gained
366 (LYG) for a comparison of annual colonoscopy to no yearly test⁶³ (where 'no test' is
367 modelled as a 3 year test). However, the paper did not report total costs or total effects for
368 the strategies considered; consequently, it was difficult to assess this ICER or its basis. The
369 modelling conducted in this comparison is for persons aged 60 years on entry to the

370 surveillance program. This comparison may have somewhat limited clinical relevance in its
371 chosen setting, as the recommended age to start screening in the US is 50 years⁷. The
372 finding that an annual colonoscopy may be cost-effective relative to a three year
373 colonoscopy is in keeping with the results of an application of the U.K. guidelines in the U.S.
374 which suggested a subset of high risk patients may warrant a one-year clearing
375 colonoscopy⁶⁹.

376

377 **Chemoprevention**

378 Although none of the reviewed studies considered tests other than colonoscopy, a range of
379 chemoprevention strategies were evaluated⁶⁴⁻⁶⁶, one of which demonstrated that a strategy
380 employing aspirin combined with colonoscopy is cost-effective⁶⁶. Focusing on the absolute
381 differences in benefit, this study estimated that compared with no intervention,
382 colonoscopy surveillance accrued +0.0124 life years saved (LYS) whilst aspirin combined
383 with colonoscopy surveillance provided +0.0138 LYS⁶⁶.

384

385 DuPont et al reported ICERs for aspirin alone, colonoscopy surveillance alone and a
386 combined intervention of aspirin with colonoscopy surveillance, which showed an ICERs of
387 \$87,609/ LYS, \$78,226/ LYS, \$60,492/ LYS respectively⁶⁶. These ICERs however appear to
388 have been calculated differently from the conventional interpretation⁵⁸. As such, the
389 reported ICER in the paper effectively becomes an average cost-effect, that is, the ratio of
390 the cost to benefit of an intervention without reference to a comparator⁷⁰. Accordingly, we
391 recalculated the ICERs from the reported costs and effects and the replicated cost-
392 effectiveness estimations plotted on a cost-effectiveness plane. These re-estimated ICERs
393 are reported in Web Table 1 alongside the reported figures from the paper. This

394 reinterpretation of the results indicates that aspirin chemoprevention alone was subject to
395 extended dominance, as was colonoscopy surveillance alone, meaning that they are not
396 preferred from the cost-effectiveness perspective. The combination of 3/5yr colonoscopy
397 combined with aspirin had an ICER of \$73,927/ LYS and as such remains a cost-effective
398 strategy for the US. This result shows that combination therapy is more cost-effective than
399 either intervention alone, which is noteworthy and merits further investigation, given the
400 role of aspirin in the prevention of premature mortality due to other causes.

401

402 Arguedas and colleagues compared colonoscopy surveillance with no surveillance and
403 demonstrated an incremental benefit of 0.01995 LYS (8.48482 life years vs 8.45487 life
404 years), whilst celecoxib was estimated to provide a greater absolute gain in LYS, generating
405 a further 0.00579 LYS relative to colonoscopy surveillance⁶⁵. Although celecoxib
406 chemoprevention was estimated to be more effective than colonoscopy, the ICER of
407 \$1,715,199/ LYS was significantly above US thresholds⁶⁸.

408

409 Notably the DuPont et al, aspirin paper and the Arguedas paper evaluating
410 chemoprevention using celecoxib, shared co-authors and employed similar models^{65,66}.
411 Whilst the DuPont et al title described addressing increased risk for CRC, the Arguedas et al
412 paper described average-risk patients, however both models explained colonoscopy
413 surveillance as colonoscopy 'occurring 3 years after index colonoscopy'^{65,66}. Such
414 description left it unclear if individuals eligible for a 5 year surveillance test were included.
415 Whether these models in fact incorporated only those in the high-risk group, according to
416 US guidelines³⁰, was not fully supported by the parameter estimates for the models. The
417 cited reference for malignant transformation rate (0.10⁶⁵) was taken from published data

418 for untreated polyps, rather than reported high-risk transformation. The probability
419 reported differed in the aspirin analyses, where malignant transformation was reported as
420 0.01, citing one shared reference, consequently in the absence of clear reporting, we cannot
421 draw any firm conclusions about whether all those eligible for surveillance were modelled in
422 either paper.

423

424 The effectiveness of supplemental calcium as a chemoprevention was evaluated by Shaukat
425 et al. That analysis assessed a dose of 1.2g/day for age 50-80 years⁶⁴, not at the 3-4g/ day
426 dose mentioned in the article as providing a reduction in adenoma recurrence of 22%
427 compared to placebo in meta-analyses. The article does not present a clear argument for
428 using the lower dose selection.

429

430 Like DuPont et al, Shaukat et al report an ICER for calcium chemoprevention alone however
431 this strategy is subject to extended dominance and so would not be a preferred strategy and
432 should not have an ICER reported for it⁶⁴. The recalculated ratios of costs and effects were
433 replicated to provide cost-effectiveness estimations which were plotted on a cost-
434 effectiveness plane, reported in Web Table 1. Based on the recalculated ratios the resultant
435 ICER for surveillance colonoscopy was \$20,494 /LYG when compared to natural history, with
436 the combination of calcium chemoprevention and colonoscopy generating an ICER of
437 \$2,823,333 /LYG, based on the 0.0003 incremental LYG reported⁶⁴, an ICER which is once
438 again greater than US thresholds⁶⁸.

439

440 This reassessment of the reported results indicated that surveillance colonoscopy alone is
441 cost-effective, whilst the ICERs indicated that the incremental cost, of additional health

442 benefits from chemoprevention by celecoxib alone or calcium combined with colonoscopy
443 was likely to be very high, relative to the health gains. It can tentatively be claimed that
444 aspirin chemoprevention combined with surveillance colonoscopy appears to be cost-
445 effective, but given the ambiguity regarding risk-groups within the DuPont et al paper, the
446 results merit further investigation to clarify if these are sub-group dependent or if they
447 might apply to all adenoma patients.

448

449 From the review we believe the salient points from the conclusions of these cost-
450 effectiveness evaluations of colonoscopy based surveillance programs to be:

- 451 (a) Colonoscopy capacity can, at lower levels, prohibit the ability of health systems to
452 offer colonoscopy based surveillance to low-risk groups⁵⁹.
- 453 (b) Compared with a ten-year low-risk colonoscopy, offering a five-year colonoscopy to
454 low-risk groups was above US thresholds at \$296,266/ quality adjusted life year⁶².
- 455 (c) Compared to a three-year high-risk colonoscopy, there is evidence to support
456 offering a one-year high-risk* colonoscopy⁶³ – *for persons aged 60 years entering
457 surveillance.
- 458 (d) Aspirin combined with surveillance colonoscopy generated greater life years saved
459 than aspirin or colonoscopy alone and in given its role in the prevention of
460 premature mortality due to other causes, this combination merits further evaluation.

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

464

465 **The trade-off between costs (resource use) and beneficial or adverse effects that need to**
466 **be considered in a decision to adopt or reject personalising surveillance**

467 Cost calculations of the strategies should account for all resources used. Whilst all models
468 included the costs of colonoscopy and polypectomy, program and administration costs were
469 only described in two papers^{59,62}. Only one reviewed study attempted to address the
470 treatment costs, accounting for newer therapies such as oxaliplatin, now recommended in
471 advanced stage cancer, and terminal care costs^{59,71,72}. Where these costs were estimated
472 for the final year of life, there was some uncertainty as to how these were adjusted for
473 according to heterogeneity by stage⁵⁹. There was no consistent approach to adjusting
474 treatment costs according to the stage of disease^{62-64,72}. Adjustments for inflation were also
475 unclear in some of the papers^{59,67}. Use of biologics, such as Cetuximab or Bevacizumab in
476 treatment costs assumptions was not noted.

477
478 Study costs were commonly taken from Medicare fee schedules for colonoscopy,
479 polypectomy, complications and pathology⁶²⁻⁶⁶, or in some cases national reports⁶². Only
480 one study reported the type of distribution used for costs in probabilistic sensitivity
481 analyses⁶². Indirect costs, in the form of lost income to the patient and an escort, were
482 included in only one study⁶³. Somewhat strangely, one study cited a long term arthritis trial
483 for their \$100,000 costs per CRC case, the provenance of which was uncertain given the
484 source cited⁶⁵.

485
486 Resource costs for aspirin were given from a trial with wholesale prices used in sensitivity
487 analyses⁶⁶. Calcium costs were described as constant over the period 2005-2008 prices⁶⁴.

488 There were some inconsistencies in referenced costs for "incurable" CRC⁶⁶, citing a base

489 case scenario (\$40,000) with a maximum in the range (\$100,000) from a source that used
490 this maximum as its base case⁶⁵.

491

492 Health effects were calculated based on the estimated effect of colonoscopy and
493 polypectomy and weighted by the risk of adenoma transformation in all models. The use of
494 a preference-weighted health state classification system such as the EuroQol-5D⁷³ were not
495 consistently reported. No citations were presented for the utility estimates used in some
496 models (for CRC at diagnosis and subsequently)⁵⁹ while in others no measures for utility
497 were given⁶³.

498

499 We noted a large difference in the modelled life expectancy (between 8.45487/ LYS⁶⁵ and
500 12.2847/LYS⁶⁶) under no surveillance of celecoxib and aspirin from two studies that used
501 related models in which the same discount rate was used and individuals were modelled
502 from age 50 in both cases. While the difference in life expectancy may relate to differences
503 in risk subgroups between the analyses the difference still seems large, and was not readily
504 explained^{65,66}. Whilst there is a 6 year gap in publishing, it is unclear whether this difference
505 can be directly attributed to the characteristics modelled, surveillance program or to
506 differences in the quality or practice of colonoscopy techniques over time^{24,74}, or to
507 treatment improvements⁷².

508

509 It is inevitable that colonoscopy carries the risk of missed lesions, given as approximately
510 22% by meta- analyses^{75,76}. Missed polyps clearly have the potential to become interval
511 cancers. Only two of the studies reported a probability of a missed polyp; and there was a

512 noticeably large variation ranging from 0.08-0.21^{62,66} (where reported as a percentage, small
513 adenoma=17.8% and large adenoma=4.6%⁶⁴). The remaining studies have not reported this
514 within model parameters and it this implies it is not assessed within the analyses^{59,63,65}.

515

516 The risk of colonic perforation, as an adverse effect, was considered in all but one of the
517 models⁶³. This was modelled with various probabilities; a base case probability of 0.0006⁶²,
518 0.003 for colonoscopy alone^{65,66}, or 0.02 with polypectomy⁶⁵. The origins of these rates are
519 uncertain from the reported literature. Although relatively rare, perforation can cause
520 significant morbidity and even death (30 day morbidity rates of 21%-53% and mortality
521 rates of 0%-26%, with hospital stay of up to 3 weeks⁷⁷).

522

523 Discussion

524 The main policy-relevant issue emerging from this review was that no studies were found
525 that evaluated the cost-effectiveness of colonoscopy against other tests, such as FIT or
526 other non-invasive testing. Colonoscopy has been the primary approach to post-
527 polypectomy surveillance since the early 1990s but it has not been compared with other
528 tests in the surveillance of patients after polypectomy. This is in spite of the availability of
529 alternatives, such as FIT, which have been compared with colonoscopy in index screening
530 evaluations⁷⁸⁻⁸².

531

532 Critically we acknowledge the gaps in cost-effectiveness reporting by sub-group. Since it is
533 possible to implement different treatment decisions for patients with different
534 characteristics, models should consider the potential for their results to vary across different
535 subgroups to facilitate different policy decisions⁸³. As demand for testing changes over time

536 in screening programs, through the introduction of newer technologies and with trends in
537 adherence and variable adenoma detection rate⁸⁴, these issues require attention from
538 policy makers and modellers to understand and explore the potential of modelling to
539 provide a clear understanding of the risks and benefits in the choice of interventions
540 adopted.

541

542 Prior work has shown that FIT threshold for positivity can be adjusted within a screening
543 program to optimise detection according to available colonoscopy capacity⁸⁵, therefore post
544 polypectomy surveillance could follow such an approach. The role of FIT is being considered
545 in surveillance with a trial in the UK currently comparing FIT vs colonoscopy⁸⁶. FIT offers
546 improved performance over older stool-based testing techniques and its ability to adjust
547 cut-off levels may allow for greater optimisation of resources given colonoscopy capacity
548 constraints.

549

550 The UK NHS Bowel Cancer Screening Programme recently recommended the primary test
551 used be changed from guaiac-based faecal occult blood testing (gFOBT) to FIT⁸⁷⁻⁸⁹. Such a
552 change in the primary test used will likely affect the numbers of patients detected with
553 advanced adenoma, and with it those eligible for surveillance⁹⁰. As part of this change there
554 are planned adjustments to the FIT positivity cut-off value used, in order to continue to
555 optimise the effectiveness of the planned technology in line with capacity changes and
556 service transition. These recommendations have acknowledged the likely systemic effect on
557 colonoscopy capacity; as such it would seem pragmatic to consider not only the adjustment
558 of FIT cut-off for screening but also its role within the surveillance context. Whether

559 surveillance guidelines might be developed or modified to account for colonoscopy capacity
560 is one issue that might be explored in future modelling studies.

561

562 FIT has the potential to be an effective post-polypectomy surveillance test for suitable risk-
563 groups. Reported uses in screening other high-risk groups (e.g. first-degree relatives of
564 patients with CRC) has revealed that annual FIT screening (over 3 years) detected all CRCs
565 and proved equivalent to colonoscopy in detecting advanced neoplasia⁹¹. FIT, when used
566 between scheduled surveillance colonoscopies, has been shown to have detected neoplasia
567 sooner than scheduled surveillances⁹². Interval FIT analyses could be effectively used to
568 detect missed or rapidly developing lesions in surveillance programs⁹². FIT has a useful
569 diagnostic role and it has also been suggested that FIT has a predictive capacity, with
570 interval cancers independently predicted by faecal haemoglobin concentration (FHbC),
571 which may be applied for tailored case management and modification based on FHbC⁹³.

572

573 The use of existing tests such as FIT, in innovative and adaptive ways, might help accrue
574 benefits in more risk appropriate, prescribed and personalised surveillance-based
575 approaches. Addressing and personalising other known features of risk of CRC, such as diet
576 and lifestyle, might offer increased precision and optimise the prevention of CRC. Offering
577 personalised surveillance with diet and lifestyle evaluation as a companion to non-invasive
578 testing alternatives might support adopting a primary care rather than secondary care
579 service design for prevention interventions to address the risk of colorectal cancer^{94,95}.

580

581 In future, there may be more scope for increased personalisation of surveillance programs.
582 Novel blood based tests such as predictive micro-RNAs, or combined biomarkers (β -catenin
583 nuclear localisation, Cox-2 expression and p53 nuclear expression, were significantly
584 associated with adenoma recurrence after 3 years (β -catenin: $p=0.002$; Cox-2: $p=0.001$; p53:
585 $p=0.001$). These tests put forward predictions of adenoma recurrence with high negative
586 predictive value (88.5%) and sensitivity (94.6%), which if validated, would be equivalent to
587 or better than current clinical risk stratification approaches based on adenoma size and
588 frequency^{28,32}.

589

590 **Clinical Issues**

591 The most clinically-relevant issue raised by this review is that of the role of aspirin
592 chemoprevention, recently endorsed by the updated US Preventative Task Force
593 Recommendations⁹⁶ and described as the first pharmacological agent to be endorsed for
594 cancer chemoprevention⁹⁷. We have highlighted that aspirin combined with colonoscopy
595 surveillance results in a reported ICER of \$60, 942 (recalculated to be \$73,927/ LYG), in what
596 we might reasonably infer to be high-risk groups and might be considered a strategy for
597 personalised surveillance. Since some methodological issues were raised in the model
598 reviewed within this paper, we believe it is highly relevant to consider an updated model
599 which addresses the role of aspirin, taking cognisance of the known likelihood of a future
600 precision medicine approach that is based on aspirin's mechanism of action.

601

602 The other key clinical issue highlighted in the review, was how readily results may be
603 affected by differences in capacity of colonoscopy services or may be influenced by other

604 quality assurance issues such as adenoma detection rates. As shown in other evaluations of
605 screening, the adenoma detection rate was recognised as influencing the cost-effectiveness
606 of screening programmes⁸⁴. There are recognised differences in this rate between
607 screening and surveillance, which was significantly higher in surveillance colonoscopies
608 (37%), compared with screening colonoscopies (25%; $P < .001$)²⁴. Future work
609 acknowledging the impact of examination quality as characterised by adenoma detection
610 rates, within decision models or colonoscopy capacity planning would allow robust
611 evaluation of the benefits of surveillance. In so doing, we can more fully evaluate if
612 infrequent high-quality colonoscopy exams are indeed more effective in preventing CRC
613 than are frequent low-quality colonoscopy exams³⁵.

614

615 **Limitations**

616 Potential limitations of the review are that as a result of our search strategy we do not
617 characterise the grey literature related to the economic evaluation of surveillance in
618 colorectal adenoma post-polypectomy surveillance.

619

620 **Conclusion**

621 We suggest a cautious interpretation of the findings of cost-effectiveness of colonoscopy-
622 based post-polypectomy surveillance due to the small number of studies addressing the
623 topic. Based on the reviewed literature we would suggest that future investigations update
624 and confirm the benefits reported, in particular exploring comparisons of the cost-
625 effectiveness of newer testing alternatives, such as FIT or newer tests like micro-RNA. In
626 particular, we suggest examination of where FIT may provide clinically accessible
627 adjustments to cut-off levels, and triage national or regional resources optimally based on

628 national or regional quality indicators and capacity. The insights on cost-effectiveness of
629 combined aspirin and colonoscopy merit further exploration in light of the updated
630 literature on the role of aspirin in chemoprevention and its likely role the in prevention of
631 premature mortality due to other causes. Taken together, these results suggest that there
632 are valuable alternatives to current guidelines which should be explored in updated cost-
633 effectiveness models.

634

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635 **Tables**636 **Table 1** –Guidelines for surveillance following polypectomy

Location	Year	Surveillance Recommendations	Interval	Reference No.
UK / New Zealand	2011	Low Risk - one or two adenomas smaller than 10 mm.	Consider colonoscopy at 5 years or return to screening (by gFOBT)	98,99
		Intermediate Risk - three or four adenomas smaller than 10 mm or one or two adenomas if one is 10 mm or larger.	3 year colonoscopy	
		High-risk - five or more adenomas smaller than 10 mm or three or more adenomas if one is 10 mm or larger.	1 year colonoscopy	
US	2012	No polyps / distal small (<10 mm) hyperplastic polyps.	10 year colonoscopy	30
		1–2 tubular adenomas <10mm	5 -10 year colonoscopy	
		3–10 adenomas	3 year colonoscopy	
		>10 adenomas	<3 year colonoscopy (states - 'no basis for less than 3 years,' < symbol as shown in paper).	
		one or more tubular adenomas >10 mm / one or more villous adenomas / adenoma with high grade dysplasia	3 year colonoscopy	
European Society of Gastrointestinal Endoscopy (ESGE)	2013	Low risk group (patients with 1–2 tubular adenomas <10mm with low grade dysplasia),	Participation in existing National screening programmes 10 years after the index colonoscopy.	100
		High-risk group (patients with adenomas with villous histology or high grade dysplasia or ≥10mm in size, or ≥3 adenomas)	Colonoscopy 3 years after the index colonoscopy	
Australia	2011	Low risk adenomas (patients with one or two small (<10 mm) tubular adenomas).	Colonoscopy at 5 years	101
		High-risk adenomas (three or more adenomas, ≥10mm, or with tubulovillous, or villous histology, or high grade dysplasia)	Colonoscopy at 3 years	
		Multiple (Five or more) adenomas	Follow up at 12 months	
		Possible incomplete excision adenoma	Colonoscopy 3-6 months	
Japan	2015	Uncategorized - Comments: Management of diminutive adenoma (<5 mm) has not been established. In brief, there is no uniform Japanese approach (removal or follow-up) for diminutive adenomas, and controversy remains.	'Follow-up colonoscopy should be performed within 3 years after polypectomy'	102
EU	2012	Low Risk (1–2 small adenomas)	Routine screening	35
		Intermediate Risk (3 or more adenomas or an adenoma ≥10 mm)	3-year interval to the first surveillance colonoscopy	
		High-risk (5 or more adenomas or an adenoma of size 20 mm or larger).	An additional clearing colonoscopy at 12 months may be warranted	
		<i>Cut-off age for stopping surveillance is usually 75 years – does not preclude further surveillance for clinical or other reasons.</i>		
Netherlands	2013	Revised guideline 2002 onwards recommended, patients with three or more patients with fewer than three adenomas	3 years colonoscopy	45,103
			6 years colonoscopy	

637 **Table 2 – PICOTS Criteria Applied**

PICOT Category	Inclusion	Exclusion
Population	Patients diagnosed with (resected) colorectal adenomatous polyp(s)	Patients with diagnosed colorectal cancer or sessile serrated adenomas ^a
Intervention	Interventions given for the management of colorectal cancer risk associated with the presence of a baseline adenoma, i.e. a follow up examination, surveillance test or reassessment by an appropriate means including colonoscopy and comparators listed below;	Interventions not currently in clinical use outside of trial for e.g. novel biomarkers
Comparison	Endoscopy, FOBT, FIT or CTC	Tests in development / biomarker based tests not currently in clinical use outside of trial for e.g. novel biomarkers
Outcome	Incidence of adenoma; recurrent /metachronous adenoma; colorectal cancer; 'positive' tests (in the case of qualitative FOBT, FIT, +/- other investigational tests) where a positive results indicates the need for further clinical investigation to treat/ resect potential lesions detected; Costs, LYG, Quality Adjusted Life Years, Disability Adjusted Life Years or other unit of health gain.	
Time	No time limits were imposed	
Study designs	Economic evaluations where published as academic papers are eligible for inclusion	Case series, case reports, and reports from grey literature and conference proceedings; excluded from the review owing to the high potential for bias. RCTs and controlled trials reported effects and other formats than controlled trials, cohort studies, case-control whilst considered within the quality evaluation within models are not directly included.

638 FOBT = faecal occult blood testing, CTC = computed tomographic colonography, RCTs = Randomised

639 controlled trials

640 ^a Sessile serrated lesions are often added to guidelines addressing the umbrella term polyp/

641 adenoma, clear pathological and molecular distinctions are now recognised, thus we refer

642 to comprehensive recent work on this pathology for further clinical - ^{25,26}.

643

644

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950 Figure 1 - PRISMA Flow Diagram

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