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Pathways to a Cancer-Free Future: a protocol for modelled evaluations to minimise the future burden of colorectal cancer in Australia.

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Pathways to a Cancer-Free Future: a protocol for modelled evaluations to minimise the future burden of colorectal cancer in Australia.

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Abstract

Introduction

With almost 50% of cases preventable and the Australian National Bowel Cancer Screening Program in place, colorectal cancer (CRC) is a prime candidate for investment to reduce burden. The challenge is determining the most effective ways to reduce morbidity and mortality. *Pathways-Bowel* is a multi-stage program that aims to identify best-value investment in CRC control by integrating: expert and end-user engagement; relevant evidence; modelled interventions to guide future research investment; and policy-driven implementation of interventions.

Methods and analysis

Pathways-Bowel is an iterative work program that incorporates a calibrated and validated CRC natural history model for Australia (*Policy1-Bowel*) and assesses the health and cost outcomes and resource use of targeted interventions. Experts help identify and prioritise modelled evaluations of changing trends and interventions and critically assess results to advise on their real-world applicability. Where appropriate the results are used to support public policy change and make the case for optimal investment in specific CRC control interventions. Fourteen high priority evaluations have been modelled or planned, including evaluations of CRC outcomes from: changing the prevalence of modifiable exposures including smoking and body fatness; potential benefits of daily aspirin intake as a form of chemoprevention; increasing CRC incidence in people under 50 years; increasing screening participation in the general population and in Aboriginal and Torres Strait Islander peoples; alternative screening technologies and modalities; and changes to follow-up surveillance protocols. *Pathways-Bowel* is a unique, comprehensive approach to evaluating CRC control; no prior body of work has assessed the relative benefits of a wide variety of interventions across CRC development and progression to produce a list of best-value investments.

Ethics and dissemination

Ethics approval was not required as human subjects were not involved. Findings are reported in a series of papers in peer-reviewed journals and presented at fora to engage the community and policymakers.

Article summary

Strengths and limitations

- *Pathways-Bowel* leverages a fully calibrated natural history microsimulation model for CRC (*Policy1-Bowel*) to model evaluations of existing and hypothetical changing trends and interventions to improve CRC outcomes for Australians.

- This program aims to bridge the gap between end-user priorities, epidemiological and statistical research outputs and practical applicability from health, resource, and health system cost perspectives.
- Findings from the *Pathways-Bowel* program are applicable to Australia; however, the flexibility of *Policy1-Bowel* enables its future adaptation to other settings where location-specific data are available.
- The predictive modelling used is limited by and dependent on the available data sources and assumptions made in the absence of real-world data.
- The overarching *Pathways* program generates evidence on the best-value investments or “best buys” in cancer control across multiple cancers, to inform future decision making.

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Introduction

Background

In Australia, colorectal cancer (CRC) was the third most commonly diagnosed cancer in 2017, with estimated incidence of 63.4 per 100,000 and 45.8 per 100,000 in males and females, respectively (1,2). A small proportion of CRC cases are found in higher-risk patients and associated with strong family history of CRC or hereditary syndromes. Lynch syndrome and Familial Adenomatous Polyposis account for ~3% and less than 1% of new CRC cases, respectively (3–5). The Australian Burden of Disease Study found there were over 95,000 years of healthy life lost due to CRC in 2015 which accounted for 2% of the total disease burden in Australia (6). From 1982 to 2015, CRC incidence and mortality rates decreased (from 58.3 to 57.4 and 32.3 to 19.2 per 100,000, respectively) (7), with noted gender, socio-economic and geographic disparities (8–11). The 5-year overall survival for CRC in Australia has increased from 51% in 1985–1989 to 70% in 2010–2014 (12). However, a recent analysis highlighted increasing CRC incidence in people under 50 years of age, which could be partially attributed to the rising prevalence of harmful risk factors but certain causes are still unknown (13). Nearly half (49.8%) of new CRC cases in Australia are attributable to known modifiable risk factors (14) and therefore could be influenced by primary prevention interventions. Evidence on policies and interventions for preventing bowel cancer through lifestyle change varies widely between risk factors. On current evidence, the best buy in CRC control is increasing participation in Australia’s National Bowel Cancer Screening Program (NBCSP) but fewer than half the eligible population choose to participate. By the 2020, all Australians aged 50–74 will be invited to participate in biennial screening using an immunochemical faecal occult blood test (iFOBT) (12). Further decreases in incidence and mortality of 23% and 36%, respectively, are anticipated by 2040 at current participation rates once full NBCSP implementation is in place (15).

Pathways

In view of the changing landscape of CRC control, “*Pathways to a cancer-free future*” (*‘Pathways’*) was developed to focus investment where the biggest impact can be made at a population level. First described in relation to cervical cancer, it has since grown (16). The *Pathways* model is being applied to five major cancers: cervical, lung, colorectal, prostate, and breast cancer, and to cancers relating to Lynch syndrome with early work commencing in cancers of the ovary, liver and melanoma. It aims to identify the best-value investments, or “best buys”, in cancer control to inform future assessments by decision makers. *Pathways-Bowel* refers to the program of work focused on CRC, with a detailed assessment of high-risk individuals with Lynch syndrome and other Lynch-related cancers currently underway (17), as part of *Pathways-Lynch*. *Pathways-Bowel* will span the

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3 CRC control continuum, from primary prevention to survivorship. It aims to model comparative
4 evaluations of CRC interventions guided by the best available evidence. The results are intended to
5 guide and underpin future research investment and policy implementation. **The aim of the current**
6 **article is to outline the design and objectives of *Pathways*-Bowel and summarise the protocol for**
7 **ongoing and planned modelled evaluations of CRC interventions.**
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13 **Methods and Analysis**

14 *Study design*

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16 *Pathways* as an overarching program has been previously described (16). Since that time, *Pathways*
17 has transformed from a staged approach into a more iterative process. As evaluation results become
18 available, they are immediately reviewed and disseminated as appropriate to support potential
19 policy change.
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24 *Patient and Public Involvement Statement*

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26 Multisectoral stakeholder involvement in *Pathways*-Bowel is achieved via a multidisciplinary
27 Scientific Advisory Committee (SAC) including academics, clinicians, consumers and advisers on
28 policy. The SAC was formed to ensure that there was involvement from all relevant stakeholders
29 outside the core research team and confirm the relevance of modelled evaluations and their
30 translation. The SAC was first convened to discuss CRC in March 2018 and members are consulted
31 based on their area of expertise to guide, critique and support the program and its
32 recommendations. Following critical assessment of the evidence, the SAC and smaller working
33 groups provide guidance on modelled evaluations, ensuring there is involvement from interested
34 parties throughout the process.
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44 *Processes and analysis for modelled evaluations of interventions*

45 Modelling platform: *Policy1-Bowel*

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47 We use a previously developed microsimulation model platform, *Policy-1 Bowel*, to perform
48 predictive modelled evaluations of CRC interventions in Australia (18). The platform has, thus far,
49 been developed to evaluate the NBCSP (15,19,20). The model platform is implemented in C++ and
50 includes several interconnected elements to evaluate the NBCSP (see Figure 1):
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- 53 a) a model of the development of CRC from adenoma (via the adenoma-carcinoma pathway)
54 and sessile serrated lesions (via the serrated pathways) and survival from CRC;
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3 b) a model of screening for average-risk people, including post-screening diagnosis, treatment,
4 and surveillance (Figure 2 summarises the current NBCSP screening delivery pathways
5 incorporated in *Policy1-Bowel*);
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8 c) a multiple-cohort implementation model that simulates the development of polyps and CRC,
9 screening, diagnosis and other downstream NBCSP processes in the target population over a
10 time period of interest; and
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13 d) a population component that applies Australian-specific demographic, economic and health
14 utilities data (including cost and quality-adjusted life-years) to the model outputs to estimate
15 cross-sectional results in a population.
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Policy1-Bowel validation

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21 Extensive calibration of the model has been carried out against a wide range of current NBCSP
22 outputs and other Australian data sources (15). The model has also been validated against the
23 findings of other well-established microsimulation models and multiple large randomised-controlled
24 trials with long-term follow-up (21). Further details of the model used in this work, and descriptions
25 of its development, parameterisation, data sources, calibration, and validation outcomes, have been
26 published previously and technical appendices are available (15,18–20).
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Economic Analysis

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34 The modelled evaluations are conducted and result in economic analyses to develop a business case
35 for investment. *Pathways-Bowel* (and all *Pathways*) uses a common framework so “best buys” can
36 be compared within and between groups. The framework is in development and will be based on
37 similar initiatives internationally (22). The populations of interest are average-risk Australians and
38 sub-groups relevant to the modelled evaluations. For each evaluation, several primary outcomes are
39 considered, including:
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- 45 i) health benefits– e.g. reduction in lifetime risk of CRC incidence and mortality;
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47 ii) harms – e.g. hospitalisations, adverse events of colonoscopy;
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49 iii) resource use – e.g. communications strategies to promote interventions, workforce,
50 screening and diagnostic tests; and
51
52 iv) health-economic outcomes – e.g. discounted and undiscounted lifetime cost, life-years,
53 quality-adjusted-life years, disability-adjusted life years and incremental cost-effectiveness
54 ratio (ICER).
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57 For each intervention, the primary outcomes listed may be expanded or differ. The comparator for
58 analyses is the general population or specific sub-group of interest without the influence of the
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3 intervention being assessed. The potential harms associated with interventions are oftentimes
4 minimal, but *Pathways* will enable their characterisation and quantification. For example, the health
5 benefits and harms for screening would also include colonoscopy-related adverse events and
6 number-needed-to colonoscope per CRC death prevented.
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11 A health services perspective is applied, and efforts be made to expand to the societal perspective
12 including characterisation of out-of-pocket expenses. From a health services perspective, costs
13 incurred by governments and the health system over a person's lifetime (until the age of 89 years)
14 are incorporated. For each evaluation, multiple time horizons may be chosen as appropriate to the
15 specific intervention, but the common time horizon is to 2050 (as this timeline indicates a change
16 within a generation). In terms of an indicative willingness-to-pay (WTP) threshold, \$30,000-
17 50,000/life-year saved has previously been used for evaluations of interventions for CRC and cervical
18 cancer (19,23,24). In *Pathways*, a 5% discount rate and the indicative WTP threshold of \$30,000-
19 50,000/life-year saved, with alternative WTP thresholds included for comparability, are used. Our
20 focus is to quantify and comparing ICERs in all our analyses. One-way and probabilistic sensitivity
21 analyses and uncertainty analyses will be conducted as required to assess the impact of model
22 parameter uncertainties on the key model findings.
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33 Rationale for modelled evaluations of CRC interventions

34 Under the guidance of the SAC, a list of priority modelled evaluations for CRC interventions was
35 compiled. Evaluations were preceded by exploratory scoping reviews of the literature to identify
36 potential interventions and were escalated to a full systematic review as required and determined
37 by the SAC. The ongoing and planned interventions are listed in Table 1 and vary based on the CRC
38 control continuum and the evidence available. These represent the first series of evaluations.
39 Broadly, these evaluations cover interventions to reduce CRC risk, interventions in light of changing
40 incidence trends, modifications to the NBCSP via target age groups, increased participation and
41 alternative screening methods, and improved surveillance management. Findings from these
42 analyses have been and will continue to be reviewed by the SAC as required. At a later date, these
43 evaluations will grow and could include topics of growing public interest, for example the promotion
44 of healthy diet, and extend to the later stages of CRC control as evidence becomes available.
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55 While *Policy1-Bowel* has been developed to run modelled evaluations of the NBCSP, it is a flexible
56 and dynamic model that can be adapted to incorporate both alternative screening interventions as
57 well as interventions addressing other stages of the CRC continuum. *Policy1-Bowel* proves a critical
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3 tool for assessing the “best buys” for CRC. The section below outlines how *Pathways-Bowel* is being
4 used in the contexts of primary prevention, screening and early detection and treatment for CRC.
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8 Primary Prevention: Reducing risk

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10 Promoting healthy behaviours and reducing risk through primary prevention can play an important
11 role in CRC control (14). Targeted primary prevention interventions to reduce CRC risk could address
12 any or all of the following: tobacco use, alcohol use, body fatness, insufficient physical activity,
13 insufficient dietary fibre intake, and excess red and processed meat intake (25–27). The prevalence
14 of most of these risk factors, except tobacco use, has increased in Australians in recent decades but
15 for some key risk factors, such as overweight and obesity, prevalence in children is rising and calls for
16 action are increasing (28). Although evidence is less robust, the use of calcium supplements,
17 consumption of dairy products and wholegrains, and use of hormone therapy by postmenopausal
18 women have been identified as potentially reducing CRC risk (25,29,30). Notably, the 2017
19 Australian clinical practice guidelines for CRC recommend low-dose daily aspirin use for all people
20 aged 50–70 as evidence suggests its potential effectiveness in CRC primary prevention (29,30). More
21 recent studies have begun exploring the role of the gut microbiota in the development of CRC, which
22 can be indirectly affected by diet (31). In practice, evidence-based interventions addressing these
23 risk factors are challenging to evaluate without information on medium to long term CRC outcomes.
24
25 *Pathways-Bowel* will synthesise the existing evidence to determine the likely impact on CRC
26 outcomes in the future. Initially, the priorities in this area (Table 1) are: (1) changing smoking
27 prevalence, (2) changing body fatness prevalence and distribution, and (3) impact of daily aspirin
28 prophylaxis. Other behaviours, such as alcohol consumption and diet, will potentially be added at a
29 later stage.
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44 Screening and Early Detection: NBCSP outcomes

45 Identification and removal of precancerous adenomas can prevent CRC development, and early
46 detection of existing malignancies improves survival, making CRC an ideal candidate for an organised
47 population screening program (32). The NBCSP participation rate over the 2016-2017 biennial period
48 was about 40% nationally (12). Current reported rates of colonoscopy for assessment of individuals
49 with a positive NBCSP-iFOBT test are approximately 66%, with known underreporting (12).
50
51 Recommended screening for people at intermediate or high CRC risk due to family history of CRC
52 and/or hereditary syndromes is more intense, beginning at a younger age, and might include iFOBT
53 and colonoscopy screening depending on level of risk, informed by evidence (33). In addition,
54 ongoing surveillance of individuals with either a positive iFOBT or polyps removed at colonoscopy
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3 follow varying management recommendations based on level of risk and subsequent colonoscopy
4 results (34).
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8 National reports issued by the Australian Institute of Health and Welfare, along with other studies,
9 have drawn attention to NBCSP participation disparities by gender, geographic location, Indigenous
10 status, place of birth and language spoken at home (12,35–37). Interventions to promote CRC
11 screening, used internationally, revolve largely around general population awareness and health
12 organisation or practitioner endorsement of participation and follow-up (38–40). Efforts are now
13 being made by government and not-for-profit organisations to improve NBCSP participation both in
14 the general population and in targeted population subgroups (41–43). Interventions to improve
15 NBCSP participation are likely to be effective and cost-effective investments to improve NBCSP and
16 health outcomes (41,42). Evaluations of interventions to support compliance with recommendations
17 for screening, follow-up and surveillance and to assess the best use of existing health resources
18 could also be conducted, when data on the performance of these interventions are available.
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28 Australia has a national organised screening program (federally funded and near full
29 implementation) that should be taken into account in any modelled evaluation. The priority areas
30 cover predictive modelling of the NBCSP outcomes under a range of conditions or changes in the
31 external environment or program (Table 1). These scenarios are: (1) changing temporal incidence
32 trends, (2) targeting NBCSP participation in population subgroups, (3) targeting NBCSP participation
33 to a broader age range, (4) long-term NBCSP participation at varying rates, (5) long-term NBCSP
34 participation increased by simulated mass-media campaigns, (6) using alternative technologies, and
35 (7) modifying surveillance management.
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44 Treatment

45 Once diagnosed, surgery is generally considered as initial treatment, with or without adjuvant
46 chemotherapy or radiation therapy (44,45). The goal of surgery is to remove any tumour as well as
47 surrounding tissue either laparoscopically or via traditional open surgery (46). Variations in
48 treatment pathways more often relate to adjuvant chemotherapy where there are differences in
49 guidelines and outcomes based on stage, location and genetic mutations, where relevant.
50 Additionally, post-operative complications can occur and impact individuals (47). Metastatic disease
51 is treated with systemic chemotherapy and biological therapies. Bevacizumab, added to the
52 Pharmaceutical Benefit Schedule (PBS) for Australian Government supported subsidies in 2009, can
53 be used in addition to chemotherapy in metastatic CRC cases and has been found to prolong both
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3 progression-free survival (from 7.1 to 9.7 months) as well as overall survival (from 17.7 to 20.5
4 months) in first- and second-line therapy (48). Cetuximab and panitumumab are also PBS-subsidised
5 for use in patients with RAS wild-type CRC (49). Besides these, there have been few modifications to
6 the PBS related directly to therapies for CRC. For CRC, immunotherapy has proven effective in early
7 and advanced microsatellite unstable CRC tumours, which can comprise 15% of all CRC and greater
8 for those under 50 years. Research continues in this area with an active interest in the concept of
9 personalised medicine with therapies for specific CRC subtypes (50). There have been calls for
10 further research into several new immune agents and other therapies for CRC treatment that could
11 potentially change patient outcomes. In future, evaluations of treatment options and their
12 associated outcomes (including post-operative complications) can be conducted as part of
13 *Pathways-Bowel* to determine both the therapeutic- and cost-effectiveness of existing and novel
14 therapies as further evidence becomes available in Australia.

Survivorship

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26 With a 5-year overall survival (2010–2014) of 70% and decline in mortality predicted to continue
27 (12), survivorship issues are growing in relevance and importance. The majority of evidence is
28 focused on patient surveillance for recurrence with differences across available guidelines on the
29 frequency and timing of follow-up tests (51). Survivorship issues for CRC patients include physical,
30 psychological and social challenges as well as ongoing healthcare needs (51–54). Australian evidence
31 has suggested care is highly variable in CRC survivors and disparities by socio-economic group are
32 apparent (53). American guidelines for CRC survivorship have highlighted the role of risk-based
33 health care and there has been a shift in focus to improving patient outcomes through survivorship
34 care plans and coordinated care (51,52). In future, evaluations of survivorship issues and
35 interventions to improve outcomes will be integrated into *Pathways-Bowel*.

Ethics and dissemination

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46 The *Pathways-Bowel* protocol for modelled evaluations has been reviewed and approved by the
47 SAC. No human subjects are involved to perform modelled evaluations and therefore Human
48 Research Ethics Committee was not required. Where epidemiological analyses are planned and
49 require ethics approval, it will be sought. No deviations from the protocol will be conducted without
50 prior review and approval of the relevant working party leads from the SAC.

Preliminary Results

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3 This program formalises an existing ongoing body of research which has already produced outputs.
4 *Pathways-Bowel* officially commenced in early 2017 and is an ongoing collaboration with the SAC
5 and other CRC-specialist researchers. As results become available, they are reviewed and prepared
6 for peer-reviewed publication. Work has initially focused on evaluating the NBCSP from various
7 perspectives using both predictive modelling and epidemiological research (15,19,20,37,41). An
8 evaluation of NBCSP effectiveness and cost-effectiveness at various participation levels showed that
9 increasing participation from 40% to 60% would prevent 83,800 deaths from 2015-2040 and reduce
10 annual expenditure on CRC control within a decade of full NBCSP rollout (15). We also explored the
11 impact of optimistic NBCSP adherence rates, possibly beyond those achievable in practice, to
12 determine whether the impact of such an intervention is substantial and worth pursuing further.
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21 Alternative screening methods using different screening modalities or targeting NBCSP screening age
22 groups have also been evaluated (19,20). The alternative technologies evaluated were plasma DNA
23 testing, faecal DNA testing, computed tomography colonography, flexible sigmoidoscopy, and
24 colonoscopy (20). Extensions to the target age range for the general population were also assessed,
25 including people in their 40s and/or people in their 80s (19). Considering the health outcomes and
26 cost-effectiveness, the studies concluded that the planned NBCSP using biennial iFOBT and targeting
27 people aged 50-74 years is currently the optimal option for CRC screening in Australia, and achieving
28 higher screening participation within that age range will save more lives and improve the long-term
29 cost-effectiveness (19,20). These results had a direct impact on clinical practice and policy as they
30 were used to inform the 2017 “Clinical practice guidelines for the prevention, early detection and
31 management of colorectal cancer”, approved by the National Health and Medical Research Council,
32 and guided recommendations for the NBCSP (30).
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43 In addition to the planned modelled evaluations, epidemiological data will also be assessed to
44 quantify and characterise screening occurring outside the NBCSP, which is anecdotally thought to be
45 considerable and may impact the estimates of the benefits of increasing participation in NBCSP if
46 these individuals are already being screened (55). Further work has been undertaken and continues
47 to inform guidelines and policy in areas of CRC management, such as the updated national
48 surveillance colonoscopy guidelines (34). As additional evidence accumulates for potential
49 interventions, these will be explored in future modelled evaluations and used to inform guidelines
50 and policy change discussions. Notably, the *Policy1-Bowel* platform was used to evaluate a recent
51 pilot mass-media campaign aimed at increasing NBCSP participation which resulted in a \$10 million
52 government investment in a national mass-media campaign (43). This provides a clear
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3 demonstration on the usefulness of *Pathways*-Bowel in guiding investment and policy
4 implementation (41–43).
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8 **Discussion**

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10 The proven ability and future capacity of the *Pathways* program to identify the best-value
11 investments in cancer control is critical in public health decision making. Internationally it has been
12 recognised that demonstrating the cost-effectiveness of public health interventions helps to
13 underpin commitment from policymakers and funders (56). However, the varying methods by which
14 interventions are evaluated makes them difficult to compare and subject to methodological
15 confounding (56). *Pathways*-Bowel is leading by example. *Pathways*-Bowel is a unique, evidence-
16 based, comprehensive approach to CRC control initially focused on screening interventions and their
17 effectiveness in relation to the evolving knowledge of the natural history of CRC. Relevant evidence
18 exists in CRC, but no prior body of work has assessed the relative benefits of interventions across the
19 CRC spectrum in a systematic way using a health economics framework, producing “best buys” for
20 the nation. By providing uniformly obtained, high quality evidence guided by a standardised
21 framework which is in development, *Pathways*-Bowel has the capacity to drive CRC control change
22 and improve outcomes for Australians across the entire spectrum of risk. *Pathways* is a way to
23 assess the impact of many more interventions than could be subject to clinical trials; the
24 interventions can even be complementary, provided they are anchored in the real world.
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37 *Pathways*-Bowel engages and involves researchers, clinicians, consumers, policymakers and other
38 key stakeholders from its outset and throughout the process. Findings are presented in such a way
39 that stakeholders can use the information to guide policy change priorities, funding
40 recommendations and evidence-based advocacy for improved outcomes. Early results are integrated
41 with policy and advocacy efforts through local independent cancer control agencies with a track
42 record in changing policy. The findings may also identify areas where further research could facilitate
43 evaluations and guide research priority setting by funders.
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51 The type of predictive modelling used in the *Pathways* program is not without its limitations. It is
52 dependent on the available data sources and assumptions made in the absence of robust data. In
53 Australia we are fortunate to have high quality data available on CRC incidence and mortality and
54 regular monitoring reports made publicly available on the performance of the NBCSP. These data
55 have been used to develop a robust and sound *Policy1-Bowel* platform. Nevertheless, the modelled
56 results remain predictions. It is through extensive validation with trial outcomes (21), continual
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3 improvement of the model, and input of updated real world information as it becomes available,
4 that the outputs are strengthened.
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8 In terms of health economics, the health services perspective is used which limits the interpretation
9 of results. Economic modelling, by itself, does not explicitly aid policymakers to maximise equity.
10 However, more broadly, the *Pathways*-Bowel program of research embeds equity as a pillar.
11 Through *Pathways*, standard economic analyses are complemented by systematic predictive
12 modelling for specific groups and issues. Although applicable to the Australian general population,
13 the outcomes can be evaluated for other contexts where data are available. Aboriginal and Torres
14 Strait Islander peoples, for example, have seen varying trends in CRC incidence and mortality over
15 time when compared to the Australian population, with significant increase in incidence, no
16 statistically significant trend in mortality, and a lower 5-year relative survival (58%) (57). Evaluations
17 are being conducted for this population group to assess the impact of screening through the NBCSP
18 from age 40 to 74, and modelling of sub-groups can be extended to culturally and linguistically
19 diverse populations living in Australia as required. Overall, the flexibility of the modelling platform
20 used in *Pathways*-Bowel allows for its application to other settings in the future, both for developed
21 and developing countries, and this has already begun for China.
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33 While the current focus is on prevention and screening, *Pathways*-Bowel and the *Policy1-Bowel*
34 platform have the flexibility to evaluate diagnosis, treatment and survivorship interventions as
35 evidence is gathered. The capacity of the model is continually being extended and strengthened with
36 each new modelled evaluation performed. There is much promise in current research to identify
37 optimal approaches to population-based screening for CRC in Australia. The *Pathways* program has
38 already been established based on sophisticated analysis of the associated benefits, harms, and cost
39 factors. The next step, implementation of interventions and policies into practice, is crucial for
40 ensuring the benefits of optimal approaches are realised by those who need it: the Australian
41 population. Evidence-based approaches to inform “best buys” in policy reform, accounting for
42 context, system complexity and stakeholder perspectives, is a fundamental prerequisite for
43 successful and sustained translation of discoveries into real world settings. The *Pathways* program
44 presents the opportunity to continually optimise evidence-based support for cancer control
45 interventions.
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List of figures:

Figure 1: Schematic diagram of the *Policy1-Bowel* microsimulation model platform.

Figure 2: Modelled screening delivery pathway (based on NBCSP) modelled in the *Policy1-Bowel* microsimulation model platform.

Table 1: Priority modelled evaluations for CRC interventions

Evaluation	Focus Area	Status
Impact* of changing smoking prevalence on CRC	Reducing risk of CRC	Ongoing
Impact* of changing body fatness prevalence and distribution on CRC	Reducing risk of CRC	Ongoing
Impact* of daily aspirin prophylaxis on CRC	Reducing risk of CRC	Ongoing
Impact* of NBCSP in the long term due to the increasing CRC incidence in younger cohorts	NBCSP outcomes: Changing temporal trends	Ongoing
Impact* of extending the NBCSP to younger ages for birth cohorts with increasing CRC rate	NBCSP outcomes: Changing temporal trends	Ongoing
Impact* of extending the NBCSP to people aged 40-49 years for the Aboriginal and Torres Strait Islander peoples	NBCSP outcomes: Targeting population subgroups with different CRC risk profiles	Ongoing
Impact* of extending the NBCSP to younger (40-49 years) and/or older (75-84 years) ages of average-risk Australians	NBCSP outcomes: Targeting NBCSP participation to a broader age range	Published
Impact* of the NBCSP at currently observed rates in the long term	NBCSP outcomes: Long-term NBCSP participation	Published
Impact* of increasing NBCSP participation to 60 and 70%	NBCSP outcomes: Increasing NBCSP participation rates	Published
Impact* of optimising NBCSP adherence (iFOBT screening and diagnostic assessment) to 90% and quantifying a maximum threshold for cost-effective investment towards improving NBCSP adherence	NBCSP outcomes: Increasing NBCSP participation rates	Complete
Impact* of mass media campaigns aimed at increasing participation in NBCSP	NBCSP outcomes: Increasing NBCSP participation rates	Complete
Impact* of including twice-off screening colonoscopies at age 40 and 60 in addition to the current NBCSP	NBCSP outcomes: Alternative screening methods	Complete
Impact* of 13 alternative screening approaches involving use of iFOBT, colonoscopy, sigmoidoscopy, computed tomographic colonography, faecal DNA, and plasma DNA for the NBCSP	NBCSP outcomes: Alternative screening methods	Published
Impact* of modifications to colonoscopic surveillance protocols, especially the newly ratified Australian colonoscopy surveillance guidelines to the previous guidelines	NBCSP outcomes: Modifying colonoscopic surveillance management	Ongoing

*The impact of listed evaluations assessed in terms of health outcomes, resource use and costs.

Abbreviations: NBCSP: National Bowel Cancer Screening Program; CRC: Colorectal Cancer; iFOBT: immunochemical faecal occult blood test

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17 Not applicable
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20 **Author statement**

21 KC conceived Pathways and developed the scope of evaluations with EF, JBL, JW, EH, MC and input
22 from the SAC. EF authored the manuscript with input from all co-authors. All authors critically
23 reviewed and contributed to the final manuscript.
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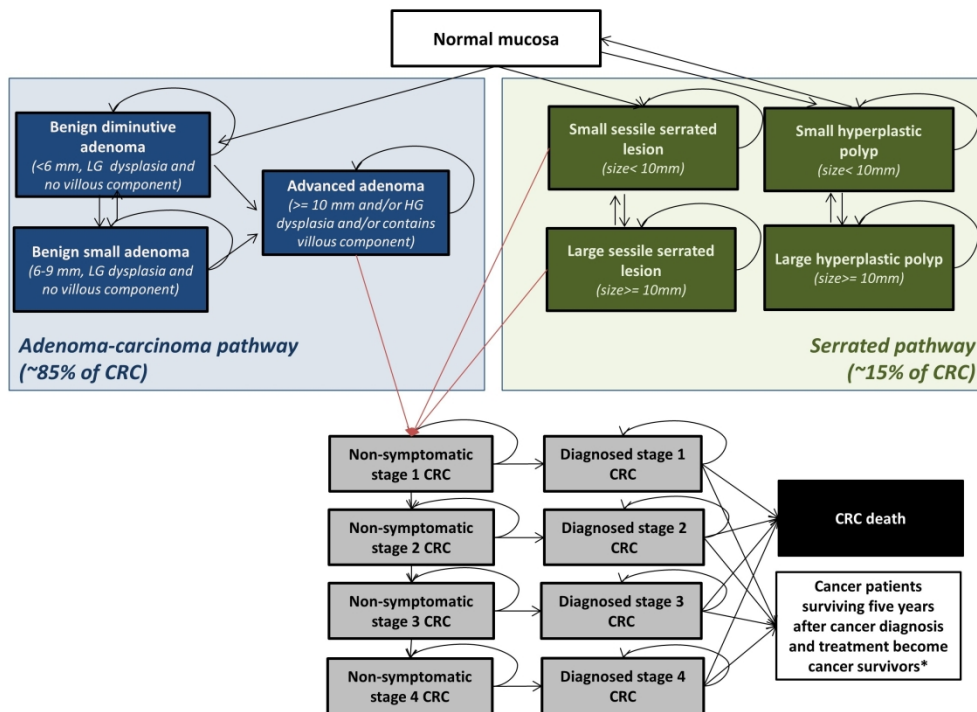


Figure 1: Schematic diagram of the Policy1-Bowel microsimulation model platform.

254x190mm (300 x 300 DPI)

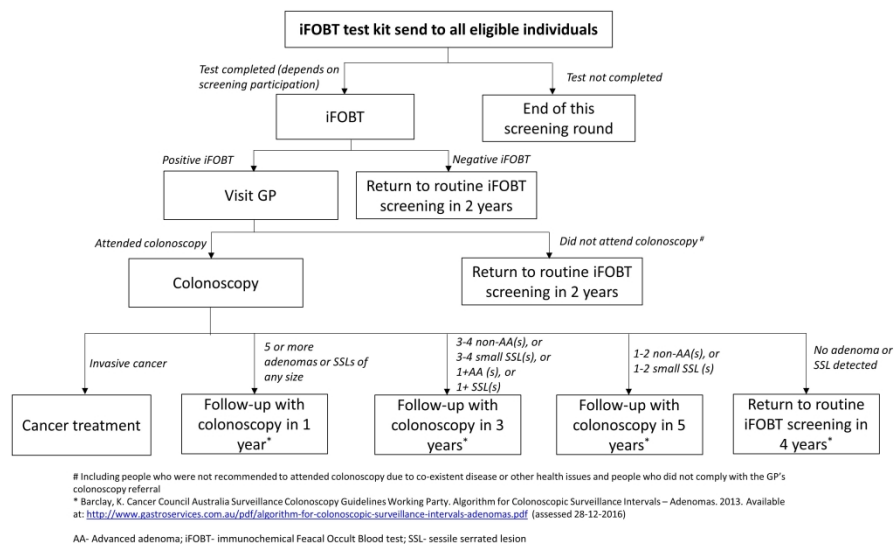


Figure 2: Modelled screening delivery pathway (based on NBCSP) modelled in the Policy1-Bowel microsimulation model platform.

338x190mm (300 x 300 DPI)

BMJ Open

Pathways to a Cancer-Free Future: a protocol for modelled evaluations to minimise the future burden of colorectal cancer in Australia.

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Pathways to a Cancer-Free Future: a protocol for modelled evaluations to minimise the future burden of colorectal cancer in Australia.

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Abstract

Introduction

With almost 50% of cases preventable and the Australian National Bowel Cancer Screening Program in place, colorectal cancer (CRC) is a prime candidate for investment to reduce cancer burden. The challenge is determining effective ways to reduce morbidity and mortality and their implementation through policy and practice. *Pathways-Bowel* is a multi-stage program that aims to identify best-value investment in CRC control by integrating expert and end-user engagement; relevant evidence; modelled interventions to guide future investment; and policy-driven implementation of interventions using evidence-based methods.

Methods and analysis

Pathways-Bowel is an iterative work program incorporating a calibrated and validated CRC natural history model for Australia (*Policy1-Bowel*) and assessing the health cost outcomes and resource use of targeted interventions. Experts help identify and prioritise modelled evaluations of changing trends and interventions and critically assess results to advise on their real-world applicability. Where appropriate the results are used to support public policy change and make the case for optimal investment in specific CRC control interventions. Fourteen high priority evaluations have been modelled or planned, including evaluations of CRC outcomes from the changing prevalence of modifiable exposures, including smoking and body fatness; potential benefits of daily aspirin intake as chemoprevention; increasing CRC incidence in people aged <50 years; increasing screening participation in the general and Aboriginal and Torres Strait Islander populations; alternative screening technologies and modalities; and changes to follow-up surveillance protocols. *Pathways-Bowel* is a unique, comprehensive approach to evaluating CRC control; no prior body of work has assessed the relative benefits of a variety of interventions across CRC development and progression to produce a list of best-value investments.

Ethics and dissemination

Ethics approval was not required as human participants were not involved. Findings are reported in a series of papers in peer-reviewed journals and presented at fora to engage the community and policymakers.

Article summary

Strengths and limitations

- *Pathways-Bowel* leverages a fully calibrated natural history microsimulation model for CRC (*Policy1-Bowel*) to model evaluations of existing and hypothetical trends and interventions to improve CRC outcomes for Australians.
- It aims to bridge the gap between end-user priorities, epidemiological and statistical research outputs, and practical applicability from health, resource, and health system cost perspectives.
- Findings from the *Pathways-Bowel* program are applicable to Australia; however, the flexibility of *Policy1-Bowel* enables its future adaptation to other settings where location-specific data are available.
- The predictive modelling used is limited by and dependent on the available data sources and assumptions made when empirical data are absent.
- The overarching *Pathways* program generates evidence on the best-value investments or “best buys” in cancer control across multiple cancers to inform future decision making.

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Introduction

Background

Colorectal cancer (CRC) was the third most commonly diagnosed cancer in Australia in 2017, with estimated incidence of 63.4 per 100,000 and 45.8 per 100,000 in males and females, respectively (1,2). A small proportion of CRC cases are found in higher-risk patients and associated with strong family history of CRC or hereditary syndromes. Lynch syndrome and Familial Adenomatous Polyposis account for ~3% and less than 1% of new CRC cases, respectively (3–5). The Australian Burden of Disease Study found there were over 95,000 years of healthy life lost due to CRC in 2015 which accounted for 2% of the total disease burden in Australia (6). From 1982 to 2015, CRC incidence and mortality rates decreased (from 58.3 to 57.4 and 32.3 to 19.2 per 100,000, respectively) (7), with noted gender, socio-economic and geographic disparities in these reductions (8–11). The 5-year overall survival from CRC in Australia increased from 51% in 1985–1989 to 70% in 2010-2014 (12). A recent analysis highlighted increasing CRC incidence in people under 50 years of age, which could be partially attributable to the rising prevalence of harmful risk factors, but there are, as yet, no confirmed causes (13). Nearly half (49.8%) of new CRC cases in Australia are attributable to known modifiable risk factors (14) and therefore could be influenced by primary prevention interventions. Evidence on policies and interventions for preventing CRC through lifestyle change varies widely between risk factors. On current evidence, the best buy in CRC control is increasing participation in Australia’s National Bowel Cancer Screening Program (NBCSP)(15) however fewer than half the eligible population are participating. From 2020, all Australians aged 50-74 will be invited to participate in biennial screening using an immunochemical faecal occult blood test (iFOBT) (12). Further decreases in incidence and mortality of 23% and 36%, respectively, are anticipated by 2040 at current participation rates with full implementation of the NBCSP. (15).

Pathways

“*Pathways to a cancer-free future*” (*‘Pathways’*) is a program of research developed to focus investment where the biggest impact can be made at a population level. It aims to identify the best-value investments, or “best buys”, in cancer control to inform future decision making. First described in relation to cervical cancer (16), the *Pathways* model is now being applied to five major cancers: cervical, lung, colorectal, prostate, and breast cancer, and to cancers relating to Lynch syndrome and early work has commenced in melanoma and cancers of the ovary and liver. *Pathways*-Bowel refers to the program focused on CRC, with a detailed assessment of high-risk individuals with Lynch syndrome and other Lynch-related cancers incorporating evidence-based intervention implementation currently underway (17,18), as part of *Pathways*-Lynch. *Pathways*-Bowel will span

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3 the CRC control continuum from primary prevention to survivorship. It aims to model comparative
4 evaluations of CRC interventions guided by the best available evidence to underpin future research
5 investment and policy implementation. **The aim of the current article is to outline the design and**
6 **objectives of *Pathways-Bowel*. *Pathways-Bowel* will inform ongoing and planned modelled**
7 **evaluations of CRC interventions by integrating expert and end-user engagement; relevant**
8 **evidence; modelled interventions to guide future investment; and policy-driven implementation**
9 **of interventions using evidence-based methods.**
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16 **Methods and Analysis**

17 *Study design*

18 *Pathways* as an overarching program was previously described (16). Since that description, *Pathways*
19 has changed from a staged approach to a more iterative process. As modelled evaluation results
20 become available, they are immediately reviewed and disseminated as appropriate to support
21 potential policy change.
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28 *Patient and Public Involvement Statement*

29 Multisectoral stakeholder involvement in *Pathways-Bowel* is achieved via a multidisciplinary
30 Scientific Advisory Committee (SAC) including academics, clinicians, consumers and advisers on
31 policy. The SAC is designed to ensure involvement from relevant stakeholders outside the core
32 research team and confirm the relevance of modelled evaluations and their translation. The SAC was
33 first convened to discuss CRC in March 2018. Since then, members continue to be consulted based
34 on their area of expertise to guide, critique and support the program and its recommendations, thus
35 ensuring there is involvement from interested parties throughout the process.
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43 *Processes and analysis for modelled evaluations of interventions*

44 Modelling platform: *Policy1-Bowel*

45 We use a previously developed microsimulation model platform, *Policy1-Bowel*, to perform
46 predictive modelled evaluations of CRC interventions in Australia (19). *Policy1-Bowel* is a
47 comprehensive platform that synthesises clinical, epidemiological, demographic, behavioural and
48 economic data and has been used to simulate the impact of CRC screening in Australia (15). Existing
49 *Policy1-Bowel* evaluations have assessed a range of screening scenarios and provided estimates of
50 CRC outcomes, resource utilisation and costs. They have, for example, analysed the use of various
51 CRC screening test technologies and target age ranges for the NBCSP to inform Australian guidelines
52 (20,21). The model platform is implemented in C++ and includes several interconnected elements to
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3 evaluate the NBCSP. It incorporates the development of CRC from adenoma (via the adenoma-
4 carcinoma pathway) and sessile serrated lesions (via the serrated pathways) and survival from CRC
5 (see Figure 1). *Policy1-Bowel* then incorporates screening for average-risk people, including post-
6 screening diagnosis, treatment, and surveillance (Figure 2 summarises the current NBCSP screening
7 delivery pathways included). As evaluations are conducted, single- or multiple-cohort approaches
8 are used to simulate the development of polyps and CRC, screening, diagnosis and other
9 downstream NBCSP processes in the target population over a time period of interest. The resulting
10 evaluation is informed by Australian-specific demographic data and economic and health utilities
11 data obtained from national and international literature (including cost and quality-adjusted life-
12 years) to produce cross-sectional results for the population. For modelled evaluations of CRC
13 interventions, data are sourced from national surveys and data collection agencies (e.g. Australian
14 Institute of Health and Welfare: AIHW) and the published literature including meta-analyses,
15 systematic reviews, randomised controlled trials, cohort studies and other relevant publications.
16 Where empirical data are not available, the SAC and other experts are consulted to guide the
17 assumptions used.

30 *Policy1-Bowel* validation

31 Extensive calibration of the model has been carried out against a wide range of current NBCSP
32 outputs and other Australian data sources (15). The model has also been validated against the
33 findings of other well-established microsimulation models and multiple large randomised-controlled
34 trials with long-term follow-up. Further details of the model used in this work, and descriptions of its
35 development, parameterisation, data sources, calibration, and validation outcomes, have been
36 published previously and technical appendices are available (15,19–21).

43 Economic Analysis

44 The modelled evaluations result in economic analyses to develop a business case for investment.
45 *Pathways-Bowel* (and all *Pathways*) uses a common framework so the best value investment, or
46 “best buy”, can be compared within and between analyses. This framework is in development and
47 will be based on similar initiatives internationally (22). The populations of interest are average-risk
48 Australians and sub-groups relevant to the modelled evaluations. For each evaluation, several
49 primary outcomes are considered, including:

- 55 i) health benefits– e.g. reduction in lifetime risk of CRC incidence and mortality;
 - 56 ii) harms – e.g. hospitalisations, adverse events of colonoscopy;
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- iii) resource use – e.g. health costs of CRC (hospitals, workforce, screening and diagnostic tests, program communications etc.); and
 - iv) health-economic outcomes – e.g. discounted and undiscounted lifetime cost, life-years, quality-adjusted-life years, disability-adjusted life years and cost-effectiveness.

For each intervention, the primary outcomes listed may be expanded or differ. The comparator for analyses is the general population or specific sub-group of interest without the influence of the intervention being assessed. The potential harms associated with interventions are often minimal, but *Pathways* will enable their characterisation and quantification. For example, the health benefits and harms for screening would also include colonoscopy-related adverse events and number-needed-to colonoscope per CRC death prevented.

A health services perspective is applied, and efforts are being made to expand to the societal perspective including characterisation of out-of-pocket expenses. From a health services perspective, costs incurred by governments and the health system over a person's lifetime are incorporated. For each evaluation, multiple time horizons may be chosen as appropriate to the specific intervention, but the common time horizon is to 2050 (as this timeline indicates a change within a generation). In terms of an indicative willingness-to-pay (WTP) threshold, \$30,000-50,000 per life-year saved has previously been used for evaluations of interventions for CRC and cervical cancer (20,23,24). In *Pathways*, a 5% annual discount rate and the indicative WTP threshold of \$30,000-50,000/life-year saved are used, with alternative WTP thresholds included for comparability. Our focus is to quantify and compare cost-effectiveness in all our analyses. One-way and probabilistic sensitivity analyses and uncertainty analyses will be conducted as required to assess the impact of model parameter uncertainties on the key model findings.

Rationale for modelled evaluations of CRC interventions

Under the guidance of the SAC, a list of priority modelled evaluations for CRC interventions was compiled. Evaluations are preceded by exploratory scoping reviews of the literature to identify potential interventions, and are escalated to a full systematic review to source evidence for predictive modelling as required and determined by the SAC. The ongoing and planned interventions are listed in Table 1 and represent the first series of evaluations. Broadly, these evaluations cover interventions to reduce CRC risk, interventions in light of changing incidence trends, modifications to the NBCSP via target age groups, increased participation and alternative screening methods, and improved surveillance management. Findings have and will continue to be reviewed by the SAC as required. At a later date, these evaluations will grow and could include topics of growing public

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3 interest, such as the promotion of healthy diet, and extend to later stages of CRC control as evidence
4 becomes available.
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8 While *Policy1-Bowel* has been used to evaluate the NBCSP, it is a flexible and dynamic model which
9 can be adapted to incorporate both alternative screening interventions as well as interventions
10 addressing other stages of the CRC continuum. *Policy1-Bowel* proves a critical tool for assessing the
11 “best buys” for CRC. The section below outlines how *Pathways-Bowel* is being used in the contexts
12 of primary prevention, screening and early detection and treatment for CRC.
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18 Primary Prevention: Reducing risk

19 Promoting healthy behaviours and reducing risk through primary prevention can play an important
20 role in CRC control (14). Targeted primary prevention interventions to reduce CRC risk could address
21 any or all of the following: tobacco use, alcohol use, body fatness, insufficient physical activity,
22 insufficient dietary fibre intake, and excess red and processed meat intake (25–27). Except for
23 tobacco use, the prevalence of these risk factors has increased in Australians in recent decades and
24 for some key risk factors, such as body fatness, prevalence in children is rising and calls for action are
25 increasing (28). The 2017 Australian clinical practice guidelines for CRC recommend low-dose daily
26 aspirin use for all people aged 50–70, as evidence suggests its potential effectiveness in CRC primary
27 prevention (29,30). More recent studies have begun exploring the role of the gut microbiota in the
28 development of CRC, which can be indirectly affected by diet (31). In practice, evidence-based
29 interventions addressing these risk factors are challenging to comprehensively evaluate without
30 information on medium to long term CRC outcomes. *Pathways-Bowel* will synthesise the available
31 evidence from national and international data sources and published evidence to estimate the likely
32 impact on CRC outcomes in the future for modelled evaluations. Initially, the priorities in this area
33 (Table 1) are: (1) changing smoking prevalence, (2) changing body fatness prevalence and
34 distribution, and (3) impact of daily aspirin prophylaxis. Other behaviours, such as alcohol
35 consumption and diet, may be added at a later stage.
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50 Screening and Early Detection: NBCSP outcomes

51 Identification and removal of precancerous adenomas can prevent CRC development, and early
52 detection of malignancies improves survival. The technology for these interventions is effective,
53 available, affordable and acceptable, making CRC an ideal candidate for an organised population
54 screening program (32). The NBCSP participation rate over 2016-2017 period was about 40%
55 nationally (12). Current reported rates of colonoscopy for assessment of individuals with a positive
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3 NBCSP-iFOBT test are approximately 66%, with known underreporting (12). Recommended
4 screening for people at intermediate or high CRC risk due to family history of CRC or hereditary
5 syndromes is more intense, beginning at a younger age, and may include iFOBT and colonoscopy
6 screening depending on level of risk, informed by evidence (33). In addition, ongoing surveillance of
7 individuals with either a positive iFOBT or polyps removed at colonoscopy follows varying
8 management recommendations based on individual risk and colonoscopy results (34).
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15 National reports issued by the AIHW, along with other studies, have drawn attention to NBCSP
16 participation disparities by gender, geographic location, Indigenous status, place of birth and
17 language spoken at home (12,35–37). Interventions to promote CRC screening that are used revolve
18 largely around general population awareness and health organisation or practitioner endorsement
19 of participation and follow-up (38–40). Efforts are now being made by government and not-for-
20 profit organisations to improve NBCSP participation (41–43). Such interventions are likely to be cost-
21 effective investments (41,42). Evaluations of interventions to support compliance with
22 recommendations for screening, follow-up and surveillance and to assess the best use of existing
23 health resources could also be conducted, when data on the performance of these interventions are
24 available.
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34 Australia has a national organised, federally funded screening program that began in 2006. It has
35 undergone phased roll-out, nearing full implementation, and should be taken into account in any
36 modelled evaluation. The *Pathways*-Bowel priority areas cover predictive modelling of the NBCSP
37 outcomes under a range of conditions or changes in the external environment or program (Table 1).
38 These scenarios are: (1) changing temporal incidence trends, (2) targeting NBCSP participation in
39 population subgroups, (3) targeting NBCSP participation to a broader age range, (4) long-term NBCSP
40 participation at varying rates, (5) NBCSP participation increased by simulated mass-media
41 campaigns, (6) using alternative technologies, and (7) modifying surveillance management.
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48 Treatment

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50 Once diagnosed, surgery is generally considered as initial treatment, with or without adjuvant
51 chemotherapy or radiation therapy (44,45). The goal of surgery is to remove any tumour as well as
52 surrounding tissue either laparoscopically or via traditional open surgery (46). Variations in
53 treatment pathways more often relate to adjuvant chemotherapy where there are differences in
54 guidelines and outcomes based on stage, location and genetic mutations. Metastatic disease is
55 treated with systemic chemotherapy and biological therapies. Bevacizumab, added to the
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3 Pharmaceutical Benefit Schedule (PBS) for Australian Government subsidies in 2009, can be used in
4 addition to chemotherapy in metastatic CRC cases and has been found to prolong both progression-
5 free survival (from 7.1 to 9.7 months) and overall survival (from 17.7 to 20.5 months) in first- and
6 second-line therapy (47). Cetuximab and panitumumab are also PBS-subsidised for use in patients
7 with RAS wild-type CRC (48). Besides these, there have been few modifications to the PBS related
8 directly to CRC therapies. Immunotherapy has proven effective in early and advanced microsatellite
9 unstable CRC tumours, which can comprise 15% of all CRC or more for those under 50 years.
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11 Research continues in this area with an active interest in the concept of personalised medicine with
12 therapies for specific CRC subtypes, including the possible use of organoids to predict therapy
13 response (49,50). There have been calls for further research into several new immune agents and
14 other therapies that could change patient outcomes. In future, evaluations of treatment options and
15 their associated outcomes can be conducted as part of *Pathways-Bowel* to determine both the
16 therapeutic- and cost-effectiveness of existing and novel therapies as evidence becomes available in
17 Australia.

28 Survivorship

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30 With 70% 5-year overall survival (2010–2014) and declines in mortality predicted to continue (12),
31 survivorship issues are growing in relevance and importance. Most evidence is focused on patient
32 surveillance for recurrence with differences across available guidelines on the frequency and timing
33 of follow-up tests (51). Survivorship issues include physical, psychological and social challenges as
34 well as ongoing healthcare needs (51–54). Australian evidence has suggested care is highly variable
35 in CRC survivors and disparities by socio-economic group are apparent (53). American guidelines for
36 CRC survivorship have highlighted the role of risk-based health care and there has been a shift in
37 focus to improving patient outcomes through survivorship care plans and coordinated care (51,52).
38 Evaluations of survivorship issues and related interventions to improve outcomes will be integrated
39 into future versions of *Pathways-Bowel*.

48 Preliminary Results

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50 This program formalises an existing ongoing body of research which has already produced outputs.
51 Work initially focused on evaluating the NBCSP using both predictive modelling and epidemiological
52 research (15,20,21,37,41). An evaluation of NBCSP effectiveness and cost-effectiveness at various
53 participation levels showed that increasing participation from 40% to 60% would prevent 83,800
54 deaths from 2015-2040 and reduce annual expenditure on CRC control within a decade of full NBCSP
55 rollout (15). We also explored the impact of optimistic NBCSP adherence rates, possibly beyond
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3 those achievable in practice, to determine whether the impact of such an intervention is substantial
4 and worth pursuing further (55).
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8 Alternative screening methods using different NBCSP screening modalities or different screening age
9 groups have also been evaluated (20,21). The alternative technologies evaluated were plasma DNA
10 testing, faecal DNA testing, computed tomography colonography, flexible sigmoidoscopy, and
11 colonoscopy (21). Extensions to the target age range for the general population included extending
12 to people in their 40s and/or people in their 80s (20). Considering the health outcomes and cost-
13 effectiveness, the studies concluded that the planned NBCSP using biennial iFOBT and targeting
14 people aged 50-74 years is currently the best option for CRC screening in Australia, and achieving
15 higher screening participation within that age range can save more lives and improve the long-term
16 cost-effectiveness (20,21). These results had a direct impact on clinical practice and policy as they
17 were used to inform the 2017 “Clinical practice guidelines for the prevention, early detection and
18 management of colorectal cancer”, approved by the National Health and Medical Research Council,
19 and guided recommendations for the NBCSP (29).
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30 In addition to the planned modelled evaluations, epidemiological data will also be assessed to
31 quantify and characterise screening occurring outside the NBCSP, which is thought to be
32 considerable and may impact estimates of the benefits of increasing participation in NBCSP (56).
33 Further work has been undertaken and continues to inform guidelines and policy in areas of CRC
34 management, such as the updated national surveillance colonoscopy guidelines (34). As additional
35 evidence accumulates for potential interventions, these will be explored in future modelled
36 evaluations and used to inform guidelines and policy change discussions. Notably, the *Policy1-Bowel*
37 platform was used to evaluate a recent pilot mass-media campaign aimed at increasing NBCSP
38 participation; its results prompted a \$10 million government investment in a national mass-media
39 campaign (43). This provides a clear demonstration on the usefulness of *Pathways-Bowel* in guiding
40 investment and policy implementation (41–43).
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50 Discussion

51 The proven ability and future capacity of the *Pathways* program to identify the best-value
52 investments in cancer control is critical in public health decision making. *Pathways* is a way to assess
53 the impact of many more interventions than could be subject to clinical trials; the interventions can
54 even be complementary, provided they are anchored in the real world. Internationally it has been
55 recognised that demonstrating the cost-effectiveness of public health interventions helps to
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3 underpin commitment from policymakers and funders (57). However, the varying methods by which
4 interventions are evaluated makes them difficult to compare and subject to methodological
5 confounding (57).
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10 *Pathways-Bowel* is a unique, evidence-based, comprehensive approach to CRC control initially
11 focused on screening interventions and their effectiveness in relation to the evolving knowledge of
12 the natural history of CRC. There is relevant evidence in CRC, but no prior body of work has assessed
13 the relative benefits of interventions across the CRC spectrum in a systematic way using a health
14 economics framework and producing “best buys” for the nation. By providing uniformly obtained,
15 high quality evidence guided by a standardised framework, which is in development, *Pathways-*
16 *Bowel* has the capacity to drive CRC control change and improve outcomes for Australians across the
17 entire spectrum of risk.
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25 *Pathways-Bowel* engages and involves researchers, clinicians, consumers, policymakers and other
26 key stakeholders from its outset and throughout the process. Findings are presented so stakeholders
27 can use the information to guide policy change priorities, funding recommendations and decisions,
28 and evidence-based advocacy for improved outcomes. Early results are integrated with policy and
29 advocacy efforts through local independent cancer control agencies with a track record in changing
30 policy. The findings may also identify areas where further research could facilitate evaluations and
31 guide research priority setting by funders.
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39 The predictive modelling used in the *Pathways* program is not without its limitations. It is dependent
40 on the available data sources and assumptions made in the absence of robust data. In Australia we
41 are fortunate to have high quality data available on CRC incidence and mortality and regular
42 monitoring reports made publicly available on the performance of the NBCSP. These data have been
43 used to develop a robust and sound *Policy1-Bowel* platform. Nevertheless, the modelled results
44 remain predictions. It is through extensive validation with trial outcomes, continual improvement of
45 the model, and input of updated real world observational information as it becomes available, that
46 the outputs are strengthened.
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54 In terms of health economics, the health services perspective used limits the interpretation of
55 results. Economic modelling, by itself, does not explicitly aid policymakers to maximise equity.
56 However, more broadly, the *Pathways-Bowel* program of research embeds equity as a pillar.
57 Through *Pathways*, standard economic analyses are complemented by systematic predictive
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3 modelling for specific groups and issues. Although applicable to the Australian general population,
4 the outcomes can be evaluated for other contexts where data are available. Aboriginal and Torres
5 Strait Islander peoples, for example, have seen varying trends in CRC incidence and mortality over
6 time when compared to the Australian population, with significant increase in incidence, no
7 statistically significant trend in mortality, and a lower 5-year relative survival (58%) (58). Evaluations
8 are being done for this population group to assess the impact of NBCSP screening from age 40 to 74,
9 and modelling of sub-groups can be extended to culturally and linguistically diverse populations
10 living in Australia as required. Overall, the flexibility of the modelling platform used in *Pathways-*
11 *Bowel* allows for its application to other settings in the future, both for developed and developing
12 countries, and this has already begun for China.

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15 While the current focus is on prevention and screening, *Pathways-Bowel* and the *Policy1-Bowel*
16 platform have the flexibility to evaluate diagnosis, treatment and survivorship interventions as
17 evidence is gathered. The capacity of the model is continually being extended and strengthened with
18 each new modelled evaluation performed. There is much promise in current research to identify
19 optimal approaches to population-based screening for CRC in Australia. The *Pathways* program has
20 already been established based on a comprehensive analysis of the associated benefits, harms, and
21 costs. The next step, implementation of interventions and policies into practice, is crucial for
22 ensuring the benefits of optimal approaches are realised by the Australian population, and has
23 begun for Lynch Syndrome patients (18). Evidence-based approaches to inform “best buys” in policy
24 reform, accounting for context, system complexity and stakeholder perspectives, is a fundamental
25 prerequisite for successful and sustained translation of discoveries into real world settings. The
26 *Pathways* program presents the opportunity to continually optimise evidence-based support for
27 cancer control interventions.

28 29 30 **Ethics and dissemination**

31 The *Pathways-Bowel* protocol for modelled evaluations has been reviewed and approved by the
32 SAC. No human participants are involved to perform modelled evaluations and therefore Human
33 Research Ethics Committee was not required. Where epidemiological analyses are planned and
34 require ethics approval, it will be sought. No deviations from the protocol will be made without prior
35 review and approval of the relevant working party leads from the SAC.

36 37 38 **Study status**

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3 *Pathways-Bowel* officially commenced in early 2017 and is an ongoing collaboration with the SAC
4 and other CRC-specialist researchers. As results become available, they are reviewed and prepared
5 for peer-reviewed publication. The status is outlined in Table 1. The expected completion date for
6 the currently outlined evaluations is 2023.
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For peer review only

List of figures:

Figure 1: Schematic diagram of the *Policy1-Bowel* microsimulation model platform.

Figure 2: Modelled screening delivery pathway (based on NBCSP) modelled in the *Policy1-Bowel* microsimulation model platform.

Table 1: Priority modelled evaluations for CRC interventions

Evaluation	Focus Area	Status
Impact* of changing smoking prevalence on CRC	Reducing risk of CRC	Ongoing
Impact* of changing body fatness prevalence and distribution on CRC	Reducing risk of CRC	Ongoing
Impact* of daily aspirin prophylaxis on CRC	Reducing risk of CRC	Ongoing
Impact* of NBCSP in the long term due to the increasing CRC incidence in younger cohorts	NBCSP outcomes: Changing temporal trends	Ongoing
Impact* of extending the NBCSP to younger ages for birth cohorts with increasing CRC rate	NBCSP outcomes: Changing temporal trends	Ongoing
Impact* of extending the NBCSP to people aged 40-49 years for the Aboriginal and Torres Strait Islander peoples	NBCSP outcomes: Targeting population subgroups with different CRC risk profiles	Ongoing
Impact* of extending the NBCSP to younger (40-49 years) and/or older (75-84 years) ages of average-risk Australians	NBCSP outcomes: Targeting NBCSP participation to a broader age range	Published
Impact* of the NBCSP at currently observed rates in the long term	NBCSP outcomes: Long-term NBCSP participation	Published
Impact* of increasing NBCSP participation to 60 and 70%	NBCSP outcomes: Increasing NBCSP participation rates	Published
Impact* of optimising NBCSP adherence (iFOBT screening and diagnostic assessment) to 90% and quantifying a maximum threshold for cost-effective investment towards improving NBCSP adherence	NBCSP outcomes: Increasing NBCSP participation rates	Complete
Impact* of mass media campaigns aimed at increasing participation in NBCSP	NBCSP outcomes: Increasing NBCSP participation rates	Complete
Impact* of including twice-off screening colonoscopies at age 40 and 60 in addition to the current NBCSP	NBCSP outcomes: Alternative screening methods	Complete
Impact* of 13 alternative screening approaches involving use of iFOBT, colonoscopy, sigmoidoscopy, computed tomographic colonography, faecal DNA, and plasma DNA for the NBCSP	NBCSP outcomes: Alternative screening methods	Published
Impact* of modifications to colonoscopic surveillance protocols, especially the newly ratified Australian colonoscopy surveillance guidelines to the previous guidelines	NBCSP outcomes: Modifying colonoscopic surveillance management	Ongoing

*The impact of listed evaluations assessed in terms of health outcomes, resource use and costs.

Abbreviations: NBCSP: National Bowel Cancer Screening Program; CRC: Colorectal Cancer; iFOBT: immunochemical faecal occult blood test

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20 **Author statement**

21
22 KC conceived Pathways and developed the scope of evaluations with EF, JBL, JW, EH, MC and input
23 on data interpretation from all SAC members: KBut, HH, NT, EB, KBa, KBr, AB, RC, JC, AD, HE, JE, IMF,
24 PG, CHold, CHorn, MAJ, JGK, MAL, BL, GM, SM, BP, DJSJ, LT, KT, MW, RLW, AKW, DW, BKA, FAM. EF
25 authored the manuscript with input from all co-authors: JBL, JW, EH, MC, KBut, HH, NT, EB, KBa, KBr,
26 AB, RC, JC, AD, HE, JE, IMF, PG, CHold, CHorn, MAJ, JGK, MAL, BL, GM, SM, BP, DJSJ, LT, KT, MW,
27 RLW, AKW, DW, BKA, FAM and KC. All authors critically reviewed and contributed to the final
28 manuscript.
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41 **Conflicts of Interest**

42 KC, EF, JW, JBL, EH, MC, NT, KB and HH receive salary support from CCNSW. KC is co-PI of unrelated
43 investigator-initiated trial of cervical screening in Australia ('Compass') conducted by the Victorian
44 Cytology Service, which has received a funding contribution from Roche Molecular Systems and
45 Ventana Inc., USA. All other co-authors have no conflicts of interest to disclose.
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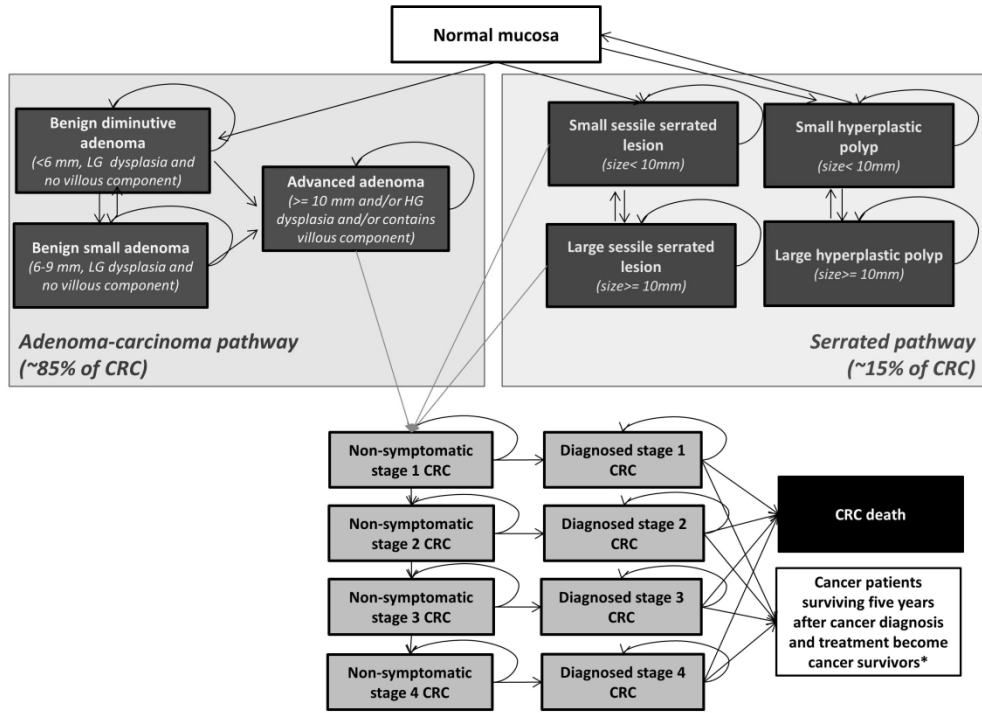


Figure 1: Schematic diagram of the Policy1-Bowel microsimulation model platform.

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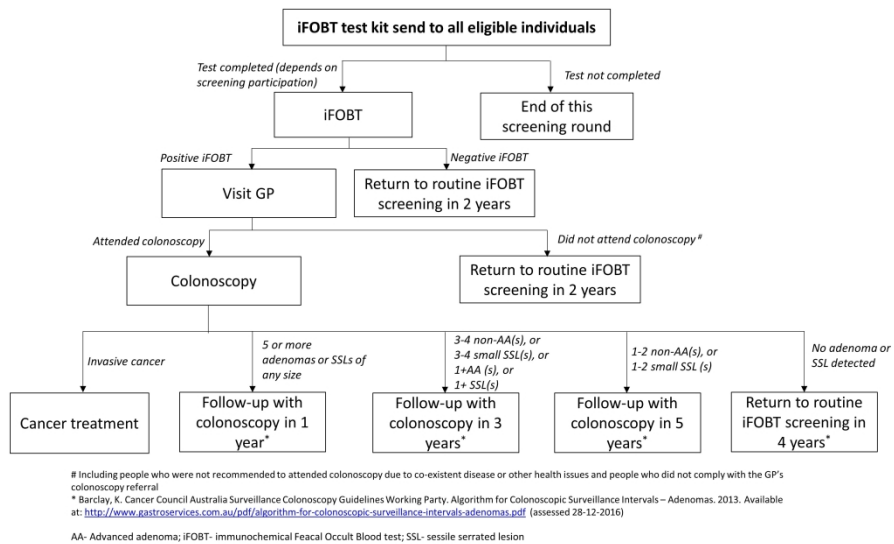


Figure 2: Modelled screening delivery pathway (based on NBCSP) modelled in the Policy1-Bowel microsimulation model platform.

338x190mm (300 x 300 DPI)