EVIDENCE REVIEW

MOONDANCE CANCER INITIATIVE

TOWARDS ZERO DEATHS FROM BOWEL CANCER IN WALES

What could we achieve?

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Moondance Cancer Initiative is a new, not-for-profit company established to find solutions so that more people in Wales survive cancer. We want to help achieve significant and sustained improvements in cancer survival outcomes over the next ten years. What we do:

1. We identify and trial new pathways, practices, and technologies, so that more people in Wales survive cancer
2. We work in partnership with the Welsh health community and beyond – connecting great people across different disciplines, sectors, and regions
3. Our work is evidence-informed, rigorous, and adventurous: we see value in moving quickly, trying and learning
4. We bring funding, research intelligence, and an ethos of collaboration to the table

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List of Abbreviations

ACGBPI	Association of Coloproctology of Great Britain and Ireland
ADR	Adenoma Detection Rate
BMI	Body Mass Index
BSG	British Society of Gastroenterologists
CCE	Colon Capsule Endoscopy
CDH	Community Diagnostic Hub
CEA	Carcinoembryonic Antigen
CRT	Chemoradiotherapy
CT	Computed Tomography
ctDNA	Circulating Tumour DNA
DFS	Disease–Free Survival
ED&D	Early Detection and Diagnosis
EPA	Eicosapentaenoic Acid
FDR	First–Degree Relative
FIT	Faecal Immunochemical Test
HIPEC	Hyperthermic Intraoperative Peritoneal Chemotherapy
HTW	Health Technology Wales
LNCPC	Large Non–Pedunculated Colorectal Polyps
LOS	Length Of Stay
MSI–H	Microsatellite Instability – High
MSS	Microsatellite Stable
NEP	National Endoscopy Programme
NICE	National Institute for Health and Care Excellence
OS	Overall Survival
PHE	Public Health England
RCT	Randomised Controlled Trial
RDC	Rapid Diagnostic Centre
TNT	Total Neoadjuvant Therapy
UKNSC	UK National Screening Committee

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Context of this paper

Colorectal cancer is among the most commonly diagnosed cancers in Wales, with approximately 2300 diagnoses per year. This combination of colon and rectal cancer, often known simply as bowel cancer, it is the second biggest source of cancer mortality, causing over 900 deaths per year in Wales.[1,2]

Yet bowel cancer is also near-unique among cancers in the *number* and *effectiveness* of opportunities we have to prevent people dying from it:

- We have the ability to screen for highly predictive genetic risk factors of bowel cancer[3]
- We have a thorough understanding of the causes of approximately 50% of bowel cancers which are theoretically preventable[4–6]
- Bowel cancer has an extremely long pre-cancer phase of 10–20 years when potentially treatable lesions, polyps, and adenomas can be detected[4]
- We have sensitive screening methods for bowel cancer and pre-cancer in asymptomatic people[7]
- Curative treatment for pre-cancer and early-stage bowel cancer has extremely good outcomes, with the vast majority of patients surviving beyond their cancers[8,9]
- We are aware of numerous lifestyle factors which can improve prognosis and response to treatment in patients with advanced bowel cancer[6]
- A new generation of systemic immunotherapies for advanced-stage bowel cancer may facilitate downstaging to allow resection , and even 'cure' a subset of patients[10,11]

Consensus is growing in the bowel cancer community worldwide that if each of these opportunities were fully taken, in combination with novel innovations for diagnosis and treatment, the number of people that die from bowel cancer could be greatly reduced. Put simply, we believe that Wales can, and should, aspire to move *towards zero deaths* from bowel cancer.

Purpose of this paper

To understand how Wales can move in this direction, we are running the "Towards Zero Deaths from Bowel Cancer in Wales" programme. In this programme, we will:

- Examine the international evidence for opportunities to reduce deaths from bowel cancer
- Consult with healthcare and policy professionals across Wales on this evidence, understanding what they need for outcomes to improve.

- Consult with people who have experienced bowel cancer care in Wales, as a patient or a carer, shaping our plans around their experiences and priorities for change.
- Combining these workstreams, identify our opportunities for change in bowel cancer care in Wales.
- Through a series of workshops, **build** Case for Change for reducing bowel cancer deaths in Wales, before producing and a roadmap, which we can in part support.

Having authored the evidence review and completed our programme of professional consultation, this represents our final evidence analysis, asking: **what could we achieve** in reducing bowel cancer deaths in Wales?

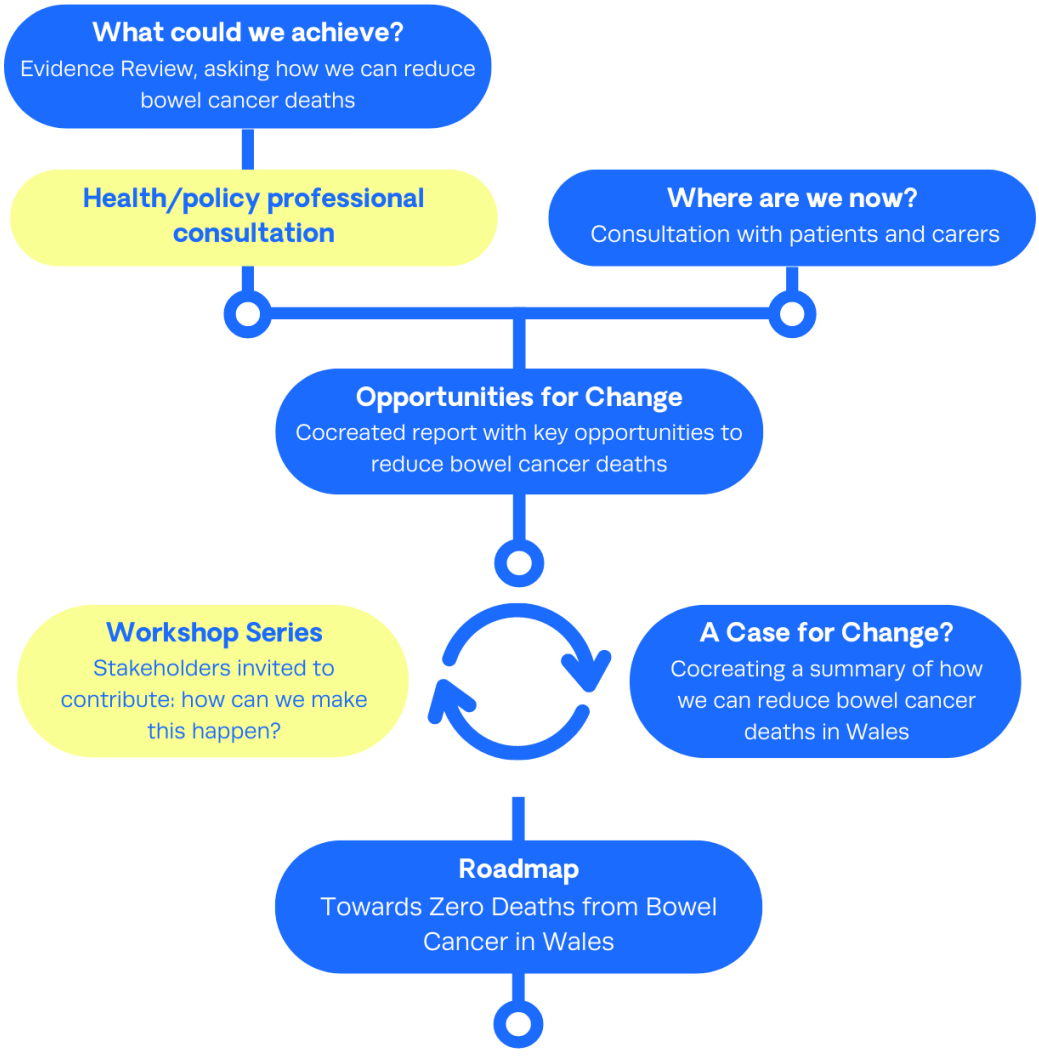

Figure 1. Towards zero deaths from bowel cancer in Wales programme overview

What could we achieve?

Examining the development, diagnosis and treatment of bowel cancer, from genetic risk factors through to advanced disease, we identified nine key areas of opportunity to reduce bowel cancer deaths:

1. Genetic testing to identify people at risk of bowel cancer, and surveillance programmes to diagnose their cancers early.
2. Prescribing aspirin to reduce the risk of bowel cancer in people with Lynch syndrome, and advising people at–risk of bowel cancer of potential benefits pre– and post–diagnosis.
3. Public health measures to reduce the prevalence of behavioural risks, such as smoking, alcohol consumption, and diet.
4. An optimized bowel screening programme, for sensitivity, age range, and uptake, to maximise the early detection of bowel cancer.
5. Improving early presentation and rapid diagnosis of symptomatic cancers, through accessible diagnostics and rapid pathways.
6. Utilising prehabilitation programmes to maximise functional status, and the number of patients eligible for more effective, but more demanding, curative treatments.
7. Maximising the outcomes of curative treatments through neoadjuvant/adjuvant therapies and innovative surgery approaches.
8. Maximising the benefits of systemic therapies for advanced cancers, utilising new innovative modalities, such as immunotherapy.
9. Effectively monitoring for the early detection of treatable recurrence in patients who have finished treatment.

In addition, we will recognize the importance of inequalities in the risk of developing bowel cancer, as well as access to and through healthcare to prevent or treat it; we could achieve much by bringing underserved people and communities up towards the average standard of care.

In this evidence review, we will discuss each of these opportunities, the underpinning evidence, and opportunities for reducing bowel cancer deaths in Wales.

We recognise that the ability of the NHS to realise these opportunities depends on being reasonably resourced, staffed, and organised, and will address questions of practicality later in this programme.

Our aim here is to set the aspiration of what we could achieve in reducing bowel cancer deaths, and to (re)ignite the conversation as to how.

Genetic Surveillance

There are a number of inherited genetic risk factors that are associated with bowel cancer, but the most notable of these is Lynch syndrome, leading affected individuals to have a greater than 50% lifetime risk of developing bowel cancer – greater than 60% in men – often at an early age.[12]

Regular surveillance by colonoscopy (usually every two years) is recommended by bodies such as the National Institute for Health and Care Excellence (NICE), and the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG), to allow early intervention to prevent and treat cancers .[13,14]

Surveillance in people with Lynch syndrome reduces bowel cancer incidence and mortality. A randomised trial of three-yearly surveillance among people with a 50% risk of Lynch syndrome in Finland found that such surveillance reduced bowel cancer incidence by 62.3% within the studied population. Further, all patients were diagnosed at Duke's stage A/B (early stage) compared to half of those without surveillance. Of notable significance was the difference in mortality rate between the surveillance and non-surveillance groups; Zero vs. Nine deaths respectively. All-cause mortality was also reduced by 65.6%.[15] A similar study in the Netherlands found surveillance reduced cancer-deaths by 70%.[16]

Long-term follow-up studies even suggest that, despite a much higher risk of developing cancer, surveillance programmes can eliminate the difference in risk of bowel cancer death between Lynch and non-Lynch patients with otherwise similar genetic backgrounds.[17,18]

Debate continues as to the appropriate surveillance interval; early studies suggested shorter intervals lead to earlier-stage cancer diagnoses.[19] However, larger prospective and retrospective observational studies have failed to demonstrate an association between intervals from 1–3 years and either stage at diagnosis, or 10-year survival.[20,21] In 2021, the European Hereditary Tumour Group (EHTG) and European Society of Coloproctology (ESCP) issued guidance recommending different intervals, dependant on the molecular subtype of Lynch syndrome.[22] Overall, surveillance programmes continue to improve. One programme in France used an optimised surveillance programme, changing the interval depending on bowel preparation, previous findings, and use of chromoendoscopy achieving an increase in the amount of precancers detected (48.1% vs 42.2%), as well as reducing the proportion of patients who subsequently developed bowel cancer (0.3% vs 2.8%).[23]

Surveillance of first-degree relatives (FDRs), including those who do not fulfil every genetic risk criteria of Lynch syndrome, is also recommended, but is much less intensive, ranging from 6-yearly colonoscopy, to yearly participation in Faecal Immunochemical Test (FIT) screening.[24,25]

Identifying people with Lynch syndrome however remains a significant challenge. International best practice, recommended by NICE[14] and the EHTG/ESCP[22] is to test all tumours from patients diagnosed with bowel cancer for Lynch syndrome, and if positive, to perform germline testing, and if also positive, to test all FDRs. Such an approach is considered a cost-effective way of significantly reducing mortality in FDRs of bowel cancer patients.[26,27]

In 2019, Wales committed to testing every patient diagnosed with bowel cancer for Lynch syndrome. A report from the first eight weeks of the programme found that, from 326 referrals received, 49 were diagnosed with Lynch-like conditions, and nine with Lynch syndrome.[28] However, to our knowledge no further information has been published with regards to how many people have been diagnosed with Lynch syndrome in Wales, what proportion of diagnoses are Lynch testing-compliant, what proportion of FDRs are tested, or what surveillance program Lynch syndrome patients are placed upon. Given the prevalence of Lynch syndrome is estimated to be ~1 in 370,[29] and therefore the number of people with Lynch syndrome in Wales is estimated to be around 8,000, it is clear we have a long way to go in providing each of these people with appropriate surveillance.

Facing similar issues, the West London Cancer Alliance launched the Lynch Syndrome Quality Improvement Project (LSQIP).[30] With the support of a project management team, it delivers a number of interventions:

- A small, easy to administer Lynch testing audit, for monitoring quality improvement.
- Appointing a Lynch champion in each MDT, and implementing 'reflex testing' to safety-net patients, and ensure they receive all appropriate testing.
- Provide standardised referral forms for germline testing through primary care, streamlining referral processes.
- Provide online training modules for MDT and primary care, to mainstream knowledge and awareness of genetic counselling practices.

After initial success locally, the project is in the process of being scaled across England, for both bowel and endometrial cancer (the other most common cancer caused by Lynch syndrome).[31]

- *Whilst only about 3% of bowel cancers are caused by Lynch syndrome, surveillance programmes have been shown to vastly decrease incidence and mortality in the affected population.*
- *Despite testing commitments in Wales, we are not aware that there is any data available on Lynch testing or surveillance in Wales. However, the available information suggests that the vast majority of those with Lynch syndrome are currently undiagnosed, and not on surveillance.*
- *We understand that there are opportunities at present in mainstreaming the coordination required for a lynch testing cascade, including keeping patients informed and empowered through primary care, and triggering FDR testing where appropriate. The LSQIP in England is an example of a project addressing these opportunities.*

Aspirin

Aspirin is an inexpensive, easily accessible, over-the-counter painkiller. Evidence has been emerging that aspirin may both reduce the risk of bowel cancer in certain populations, and also improve prognosis in those with the disease.

The evidence is most clear in people with Lynch syndrome, where the CAPP2 randomised controlled trial (RCT) of daily aspirin showed a 44% reduction in bowel cancer incidence in those adhering to the regime, compared to placebo.[32] This led to NICE recommending use of aspirin daily by people with Lynch syndrome.[33]

Evidence is promising but more mixed in non-Lynch populations, which constitute 95-97% of bowel cancer cases. One meta-analysis of observational studies reported a 23% reduction in bowel cancer incidence, consistent across study design, and with protection significantly improving with higher dosage and an increased time taking aspirin.[34] Another meta-analysis reported a reduction of 44% in incidence of bowel cancer, however, margins of error were wide, as not many studies were eligible for inclusion, and statistical significance was not achieved.[35] A third study suggested daily aspirin may even have a mortality reduction equivalent to bowel screening.[36]

On the other hand, another meta-analysis of 18 studies found no significant difference in the survival of pre-diagnosis aspirin users at risk of bowel cancer.[37] SEAFOOD was an RCT that aimed to address this question directly. Adults at risk of bowel cancer were randomised to take Aspirin, EPA (fish oil), or both. At the one-year point, none of the interventions were found to achieve the primary outcome of decreasing the number of people with adenomas, though nonsignificant decreases were observed in total adenoma numbers. In addition, the study only measured outcomes after one year (some evidence suggests 10 years follow-up might be needed to see the effects)[38], and did not assess adenoma rates over time.[39,40] The ongoing STOP-ADENOMA trial aims to continue work with this trial population, following up over a longer period, and analysing

biobank data to understand why some patients responded to aspirin, and others not.[41]

Aspirin used post-diagnosis is more strongly associated with improved outcomes, with three separate meta-analyses reporting a significant decrease in bowel cancer mortality (16–28%) and all-cause mortality (17%).[37,42,43] Add-Aspirin is an ongoing RCT explicitly investigating aspirin as an adjuvant therapy after treatment, which will report recurrence and survival.[44]

Aspirin, even when taken in low doses, is not risk-free, particularly with regards to the increased risk of bleeding. Randomised trials, large-scale observational studies, and systematic reviews, confirm that regular aspirin use does increase risk of hypertension and bleeding-associated adverse events, and has been observed to increase the very small chance of bleeding-associated mortality.[43–45] Such risks should be considered against the potential benefits of aspirin in terms of cancer mortality reduction.

Despite evidence arguably not yet being mature enough for formal recommendation, given the ease-of-access of aspirin, there is a drive toward informing at-risk people of the potential risks and benefits, and making aspirin available to those who choose it, in a manner similar to with prevention of cardiovascular disease.[46]

In 2017, after performing a systematic review of the available evidence, Cancer Council Australia issued guidance recommending that GPs actively consider prescribing aspirin for people in the bowel screening programme (aged 50–70). It also reports that aspirin use may be synergistic with screening for bowel cancer prevention, as it acts primarily in the proximal colon, where bowel screening is less sensitive.[38]

A patient decision aid designed to be given at screening has been designed and tested in Wales.[47] We are unaware whether this has progressed into use.

- *There is clear evidence of aspirin reducing risk in people with Lynch syndrome, and its use is nationally recommended. However, given most people with Lynch syndrome are unlikely to know about their condition, the full benefits of deploying aspirin for this population have not yet been realised.*
- *Evidence mostly supports aspirin as decreasing mortality risk pre-diagnosis in other at-risk populations and when used post-diagnosis.*
- *Though gold-standard evidence is yet to arrive on the subject, some countries have issued guidance recommending the use of aspirin for people at risk of bowel cancer. Alternatively, at-risk people could be advised of the potential benefits and risks.*

Behavioural risk factors

The risk of developing bowel cancer is influenced by lifestyle risk factors; primarily smoking, diet, and exercise. Some studies claim that up 70% of bowel cancer cases are theoretically preventable through changes to lifestyle.[48] However, given the difficulties in changing and measuring public behaviours, the achievable benefits of interventions are difficult to capture.[6]

Smoking is strongly and consistently correlated with bowel cancer risk, with an increased risk of developing bowel cancer of between 14–18%, and a 23–28% increased risk of death from bowel cancer.[49,50] This risk extends to passive smokers, with one meta-analysis reporting a 14% increase in bowel cancer risk associated with passive smoking.[51]

Observational data consistently shows an inverse correlation between colon cancer risk and exercise (though not rectal cancer risk). High numbers of exercise hours per week have been associated with 16–18% *reduction* in colon cancer risk; sedentary behaviours, such as >5 hours watching television per day are conversely associated with a 26% *increased* risk,[52,53] with both patterns consistent across high/low BMI.[54] Generally, participation in exercise has been reported as protective in men and women.[55] Large-scale studies estimate that increases of eight minutes of intense exercise (or 50 minutes in moderate exercise) per day could decrease bowel cancer risk by 34%.[56]

Dietary patterns are also strongly associated with a risk of bowel cancer. Meta-analyses of observational data suggest impacts on bowel cancer risk as follows:

- 12% increased risk per 100g/day red meat
- 7% increased risk per 10g/day ethanol
- 13% reduced risk per 400g/day dairy products
- 17% reduced risk per 90g/day whole grains

Similar results are consistently replicated across several observational studies.[57–59]

However, RCTs of diet changes generally fail to demonstrate reduced bowel cancer risk.[60] A number of factors may be responsible: studies need to be large scale and over a long enough duration to measure changes in the rare event of bowel cancer incidence. Studies cannot guarantee participant adherence to dietary changes, or easily control for other variables such as other dietary changes, smoking more, or exercising less.[58] It is therefore difficult to know how much impact on bowel cancer can be made by dietary public health interventions.

Inequalities (discussed further below) also play a pivotal role, with less deprived people more likely to exhibit healthier, cancer-preventing behaviours.[61,62] This issue is likely to worsen in the near future, given the current pressures on cost of living.[63]

Despite the benefits, especially in relation to cancer, being difficult to measure, public health policies and campaigns can be effective levers to help people live a more healthy lifestyle. With modern public health interventions, such as Peas Please,[64] Veg Power,[65] and Stop Smoking Wales,[66] moving toward a more holistic approach, utilising multiple points of contacts to maximise people's motivation and ability to change their lifestyle (supermarkets, schools, etc.), Wales might have strong foundations upon which to reduce bowel cancer incidence.

Importantly, behavioural risk factors appear to be additive in risk-reduction. In a retrospective study in Germany, participants were given a 'healthy behaviours' score from 0–5, comprising of: not smoking, healthy alcohol intake, exercise, and diet quality. The score's association with bowel cancer risk is shown in Table 1.

Risk Score	Percentage of people	Relative risk of bowel cancer
0/1	8.4%	1.00
2	21.1%	0.85
3	34.6%	0.62
4	26.9%	0.53
5	9.9%	0.33

Table 1. Healthy behaviours score and risk of bowel cancer [67]

As shown in Table 1, there is a maximum possible risk reduction of 67% for people reporting 0/1 healthy behaviours, if they subsequently adopt all 5 health behaviours. Whilst this huge risk reduction is only available to 8.4% of the population, it is worth noting that across the population, each increase in score (i.e. each healthy behaviour adopted) reduces the risk of bowel cancer by 26%. This illustrates the potentially huge beneficial impact of behavioural changes in the risk of bowel cancer.[67]

- *High-quality evidence shows that risk behaviours are potentially an extremely powerful tool to reduce bowel cancer risk and deaths*
- *Whilst there is little evidence available on how any practical approaches will affect bowel cancer outcomes, evidence strongly supports public health as a key approach in prevention. Efforts to improve smoking habits, diet, and exercise in Wales are public health exercises which go beyond the scope of cancer care, and have potentially enormous benefits besides reduction in bowel cancer.*

Screening

Screening involves testing asymptomatic people who are at risk of a specific condition, in the hope of detecting disease at a clinically distinct earlier stage, enabling better treatment. Bowel cancer can be detected at early and pre-cancer stages, at which point cancer can be prevented or much more effectively treated, and as such, screening trials have consistently shown a reduction in bowel cancer incidence, diagnoses at an earlier stage, higher rates of curative therapy, and

lower recurrence after treatment.[68–70] This adds up, with studies reporting between 26% and 34% reductions in cancer deaths, and a 19.1% increase in 1-year survival post-diagnosis.[68,69,71]

Retrospective data shows that mortality is significantly lower in cancers detected via screening: 65.9% reduction in deaths 10 years after diagnosis. This is partially because screening enables the cancer to be diagnosed at an earlier stage – but benefit persists even when accounting for stage. For example, screen-detected stage 3 cancers have been reported to halve the risk of death after 10 years, compared to symptom-detected stage 3 cancers.[70] In summary, the **more bowel cancer we can diagnose through screening, the lower we can drive bowel cancer deaths.**

FIT Optimisation

Of the methods we have for bowel screening, the two most common internationally are 10-yearly colonoscopy, and annual/biennial faecal testing. Colonoscopy is more sensitive at detecting cancer/precancer, and might be expected to reduce incidence and cancer-specific deaths more; however there is a risk of bowel perforation and bleeding with colonoscopy, and it is both more costly and resource-intensive. A new generation of liquid biopsy tests are also being developed for this potential purpose, from bowel-cancer specific options such as Cansense,[72] to multi-cancer detection tests such as GRAIL Galleri, which is being trialled in the NHS currently, with over 140,000 participants targeted.[73] However, evidence for their clinical efficacy is yet to bear out. Consequently, faecal testing is the currently accepted safest and most cost-effective solution for population-level screening.[74–78]

In line with recommendation from the UK national screening committee (UKNSC),[79] Wales currently performs biennial FIT screening. Some modelling studies suggest that annual FIT screening may result in an absolute reduction of 10% in bowel cancer incidence, and 9% in bowel cancer mortality.[76] An RCT (CONFIRM) is currently underway directly comparing annual FIT with 10-yearly colonoscopy, aiming to demonstrate equivalence in cancer incidence/deaths, in a cost-effective and safe manner.[80]

A FIT test quantitatively measures the microscopic concentration of blood in a participant's faeces, a key indicator of bowel cancer development. If a set threshold is surpassed, the participant is referred on for further investigation. The set threshold varies in different international jurisdictions and a lower threshold – i.e., with higher sensitivity – is directly linked to the number of cancers detectable and preventable via screening. FIT sensitivity for bowel cancer and bowel precancer at different thresholds, as reported by studies captured in this review, is shown in Figure 2.[81–87] Whilst not a precise quantitative synthesis, it shows that a 150µg/g threshold is dramatically less sensitive for bowel cancer and precancerous features (through which cancer can be prevented) than thresholds in use in other European countries – shown in Figure 3. This is the threshold

currently in use in Wales – although some plans for optimisation are in place (see below).

Decreasing the FIT threshold from 150µg/g would allow identification of far more precancers/cancers at an early stage, but would come with a resulting increase in demand for screening colonoscopy. Waiting times and capacity for screening colonoscopy are currently a significant challenge in Wales. Whilst requiring significant reorganisation (less resources spent on hospital admissions and expensive drugs for late stage patients, and more investment in diagnostic capacity), it is also worth noting that lower FIT thresholds are universally reported in cost-effectiveness modelling to be overall less costly and more clinically effective.[88,89]

In addition, the benefits of screening could be extended by lowering the age threshold for bowel screening from 58 to 50, in line with both UKNSC guidelines,[79] and comparator countries in Europe, as shown in Figure 3. This would extend the benefits of screening to the 12% of patients diagnosed with bowel cancer who are aged 50–59,[1] as well as preventing cases and late stage diagnoses in people aged 60+.

We are aware of plans in Wales to reduce the FIT threshold to 80µg/g, and age of eligibility to 50 through to 2024. However, this timeline is dependent on screening colonoscopy capacity.[90]

Other reported strategies to optimise bowel screening include:

- **Stratifying patients** by quantitative FIT score, in recognition of the known relationship between FIT score and prognosis (whilst adjusting for other factors, such as gender).[91] For example, patients with non-detectable levels of faecal blood could have their next FIT test delayed.[81]
- Sending people with a certain risk-level **straight for screening colonoscopy**, or taking the higher of two separate FIT measurements, both of which significantly increase precancer detection.[92]

At present, though, it is very unlikely that a strategy for detecting more cancer through screening would not lead to increased demand for screening colonoscopies. On the other hand, each cancer or precancer detected by screening endoscopy is one less detected by symptomatic endoscopy, and likely with less complex needs as a result (e.g. avoiding surgery through endoscopic resection).

One future option for managing this increase in colonoscopy demand could come via Colon Capsule Endoscopy (CCE), where a pill camera is swallowed, to take diagnostic images of the bowel. One trial of CCE in FIT+ screening participants found that it was highly sensitive for colorectal neoplasia (98.2%), and for advanced neoplasia (100%), whilst potentially ruling out 22.8% of patients from colonoscopy.[93] However, evidence for this potential use case is still immature.

Screening Adherence

Another key strategy in detecting more bowel cancer via screening is **increasing adherence to FIT screening** in invited populations. One study in England of patients diagnosed with bowel cancer outside of screening found that, of those at screening-eligible ages, 63.4% of diagnosed patients had never participated in bowel cancer screening.[94]

Numerous interventions have been shown to increase adherence, such as telephone outreach (23%), GP endorsement (17%), and advance notification of receipt (9%).[95–97] Mass media campaigns and community outreach can also be effective.[98] Systematic literature review has identified that blood biomarker-based screening modalities (e.g. Cansense, GRAIL) may be slightly preferable to patients declining to take part in screening, though evidence is mixed.[99]

Digital tools may also be an opportunity here, such as with one study in the USA, where primary care records were analysed by an AI to identify individuals at risk of bowel cancer who were non-adherent to screening, for invitation to screening colonoscopy over the phone by a nurse-led service. Of identified individuals, 68% underwent screening colonoscopy. 70% of these colonoscopies led to clinically significant findings.[100] Ongoing work to increase the digital connectivity across care settings in Wales may help to advance this opportunity.

Whilst the bowel screening programme in Wales typically receiving ~60% participation after the replacement of FOBt testing with FIT, this participation in inequitably skewed, with participation from the most deprived quintile at just 50% in 2019–20, and just 45.7% in the Cardiff and Vale University Health Board.[101]

Reviews note that interventions to increase adherence tend to work additively, and that 80% should be the target of a population screening programme.[102]

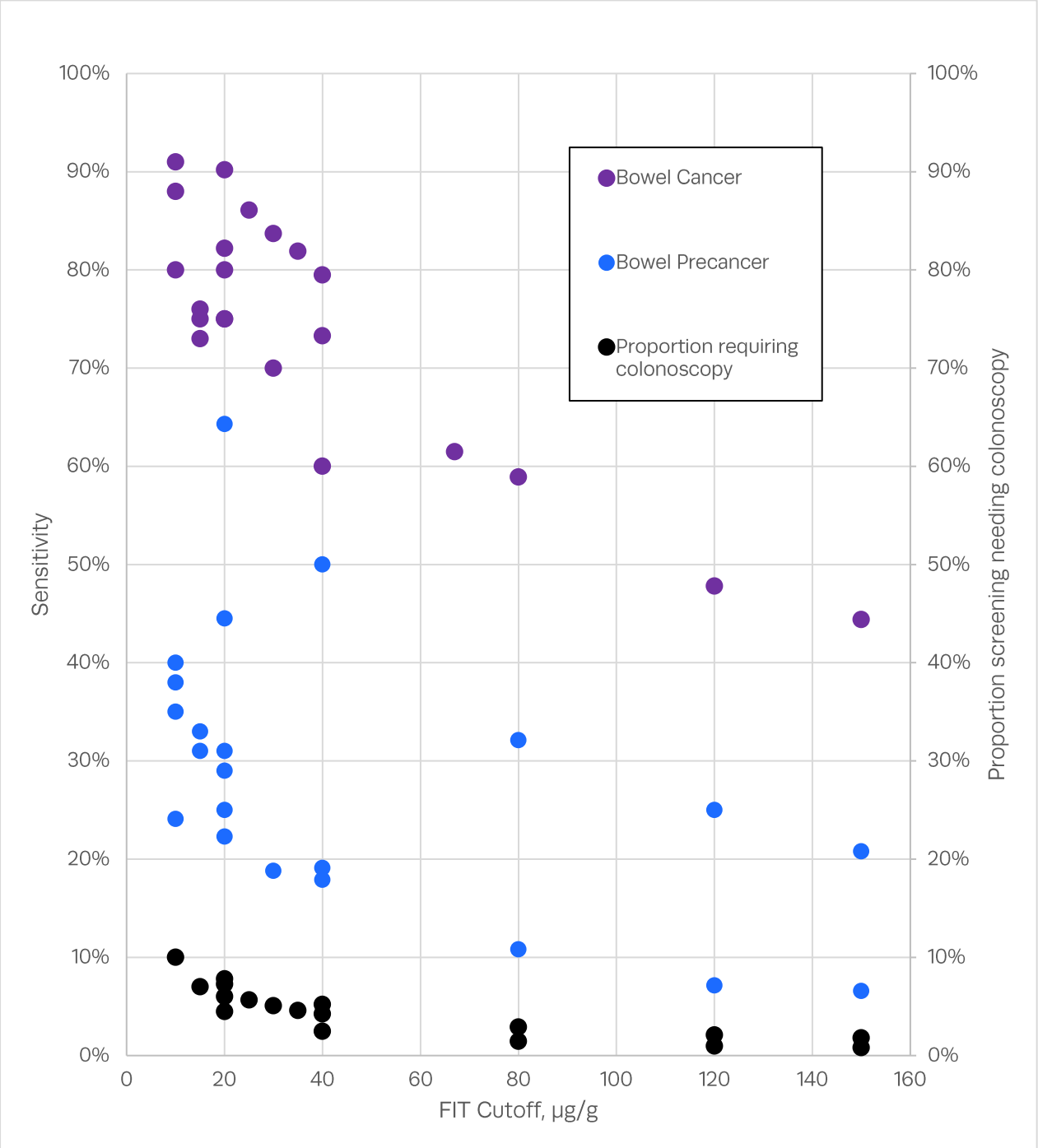

Figure 2. Bowel cancer and precancer sensitivity, and proportion sent for colonoscopy, by FIT threshold.[81–87]

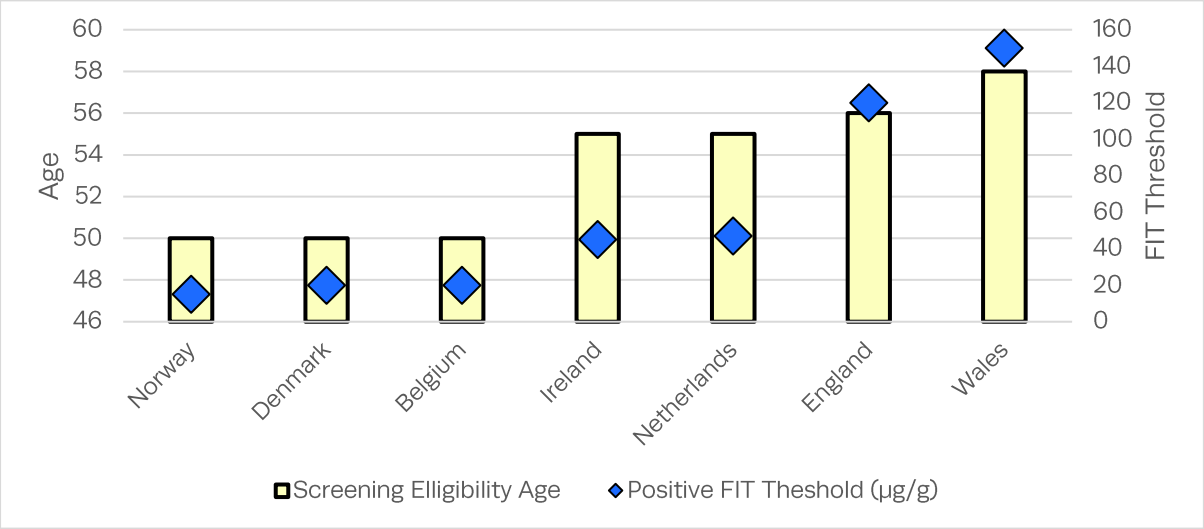

Figure 3. Bowel screening eligibility and threshold for onward referral in Wales and comparable European countries

Endoscopy Optimisation

Finally, **optimizing endoscopy** could represent an opportunity to increase the number of cancers prevented or detected early via screening, by increasing detection rate of pre-cancerous features.

Endocuff Vision is a single use device which fits over the end of the colonoscope. The ADENOMA trial indicated it could increase adenoma detection rate (ADR) by 10.8% in a screening population. NICE have subsequently recommended the device for screening colonoscopies, reporting that the device would become cost-saving when increasing ADR by just 3% or more.[103]

Chromocolonoscopy, involving additional application of fluorescent dye during colonoscopy, has been associated with a two-fold increase in proximal serrated lesion detection (6% vs 12%),[104] higher ADR,[105] more neoplastic lesions detected,[106] and higher sensitivity for early-stage bowel cancer.[107] In Wales, the CONSCOP clinical trial found only a small difference in procedure time with chromocolonoscopy (6.3 minutes), and has led to the CONSCOP-2 trial, where ADR and cost-effectiveness will be assessed.[104,108] CONSCOP utilised 12 out of 24 sites available for screening colonoscopies in Wales, potentially representing a stepping stone to national rollout.[104]

Digital tools may also represent an opportunity in this space, with AI platforms such as CADDIE aiming to assist colonoscopies by monitoring image quality, and highlighting potential polyps.[109] GI Genius™ is a similar tool, currently being tested in the COLO-DETECT trial for the English bowel screening programme, across 8 hospital sites.[110]

- *Screening is arguably our most powerful tool to reduce bowel cancer deaths, with screening-detected cancers far less likely to result in death.*
- *Just ~12% of bowel cancers in Wales diagnosed via screening,*[113]
- *Tactics to increase diagnosis via screening include: decreasing FIT threshold (or similar strategy to increase sensitivity), considering annual FIT testing, increasing screening adherence, and lowering age of eligibility.*
- *There is a risk that screening colonoscopy capacity will be the rate-limiter for improvements in Wales. Nonetheless, the potential for impact on bowel cancer mortality is substantial.*
- *Colonoscopy optimisation may represent another opportunity to prevent and detect more bowel cancer via screening, though we are unsure of uptake of Endocuff vision or chromocolonoscopy in Wales.*

Early detection and diagnosis

The early detection and diagnosis of bowel cancer is absolutely critical for improved outcomes. Stage 1 disease has over 90% 5-year survival, and high rates of curative treatment, compared to stage 2 disease (80%), stage 3 (70%), and stage 4 (10%).[111,112] When bowel cancer is diagnosed as an emergency presentation (EP), the cancer is more likely to be late stage, and the patient has a higher risk of dying.[113,114] One recent study in Wales found that 36% of diagnoses in a tertiary centre were made via EP in 2020, up from 28.6% the year before (though this was worsened by the halt in services during the first COVID lockdown).[115] A publication by the international cancer benchmarking partnership (ICBP) reported that 34.2% of colon cancer and 13.8% of rectal cancer between 2012–2017 was diagnosed via EP, that EP was associated with a 3.9x higher chance of dying from colon cancer within a year of diagnosis, and that 10% increases in EP in Wales would lead to a 7% decrease in 1-year colon cancer survival overall.[116]

Evidence is mounting to suggest that delays to presentation and diagnosis can be key to survival. Indeed, just a 3 month delay to diagnosis has been separately associated with a 3% chance of stage progression,[112] 57% increased risk of all-cause mortality,[117] and a reduction in 10-year survival of 10–16%, depending on age.[118] Another study estimated a delay of just 4 weeks to surgery increased a patient's chance of dying by 6%, and the same delay to adjuvant therapy increased the chance of dying by 13%.[119] These results are supported by a series of real-world studies in Denmark and England, showing treatment delays of more than 12 weeks were associated with 104% and 165% absolute increases in 3-year mortality, and being in the longest quartile for treatment delay with 31% and 95% absolute increases in mortality.[120–123]

Early Presentation

One approach to achieving earlier diagnosis is to **encourage early presentation** by people with symptoms suggestive of bowel cancer. Barriers to prompt presentation include symptom knowledge, and fearful and fatalistic beliefs about cancer, both of which are higher in deprived and ethnic minority communities.[124,125] Surveys in Wales find that, while symptom recognition is comparable to other countries, barrier beliefs such as "worried about wasting a doctors time", "worried about what doctor might find", and "too busy to make time", are more common than elsewhere in the world.[126] In addition, evidence suggests that such barriers have worsened during the coronavirus pandemic, making people less likely to present to their GP with red-flag symptoms.[127] A number of studies have shown how early presentation might be improved,[128] however very little evidence is available on consequent effect on stage at diagnosis or other clinical outcomes. For instance, evaluations of the 'Be clear on cancer' national media campaign reported increased awareness, decreased reporting of psychological barriers, and increased GP presentations, targeted to more deprived communities.[129,130]

Earlier presentation can also potentially be improved by **making access easier**. A new wave of accessible community diagnostic hubs (CDH) aims to encourage early presentation through making diagnostics more accessible as well as faster, though no evidence is available yet on their efficacy.[131]

Prompt Referral and Safety Netting

Memorization, recognition, and cross-referencing of numerous less obvious cancer symptoms can be a difficult exercise for GPs, who only encounter approximately 7 cases of cancer per year.[132]. To meet this challenge, a number of solutions have been developed in recent years to support GP surgeries in recognition and safety-netting of at-risk patients. These are especially important for the growing number of younger bowel cancer patients,[133,134] who can struggle to be referred promptly by their GP.[135]

- Addition of simple risk assessment tools (printed on mouse mats, flip charts, etc.) to 165 UK GPs led to a 26% increase in referrals for colorectal cancers, and the detection of 57 additional cancers in a 6 month period.[136]
- Commercially available automated decision aids, such as C-the-signs and Gateway-C can help to remind GPs when risk-symptoms are present, and have been piloted successfully in English GPs.[137–139]
- The ThinkCancer! platform, developed and tested in Wales, delivers an upskilling intervention to a whole GP surgery, and is being tested in an RCT in 30 Welsh GPs.[140,141]

Symptomatic FIT

FIT testing of symptomatic patients in primary care can be effectively utilised as a diagnostic test to safely manage demand in diagnostic pathways for bowel

cancer. One hypothetical analysis of FIT results from patients awaiting colonoscopy for suspected bowel cancer found that if patients with FIT results below 2µg/g were 'ruled out', colonoscopy demand would reduce by 70%, with no missed cancers.[142] A diagnostic accuracy study in England found that FIT with a 2µg/g threshold could detect 97.7% of bowel cancer cases in patients with high-risk symptoms, and 94.3% with low-risk symptoms.[143]

Symptomatic FIT is recommended by both NICE guidance DG30,[144] and Health Technology Wales (HTW), for patients displaying low-risk bowel cancer symptoms.[145]

An interventional study in primary care in Scotland, using FIT as an additional test for significant bowel disease when referred under NICE NG12 guidelines for cancer suspicion (including high-risk symptoms),[146] found that patients registering over 10µg/g were less likely to be triaged in secondary care, more likely to be urgently referred for colonoscopy, and more likely to have a high-risk adenoma or bowel cancer. Of patients registering less than 10µg/g, only 0.2% went on to develop bowel cancer.[147] One retrospective analysis of bowel cancer diagnoses in Spain found that patients diagnosed via FIT were more likely to be diagnosed at stage 1/2 (51.3 vs 45.5%) and had higher 3-year survival (72 vs 59%).[148] Similarly, unpublished data presented at the Colon Capsule Endoscopy International Conference 2022 suggested that diagnoses by GP referral and screening have increased since introduction of symptomatic FIT, and EP has decreased (>90% of bowel cancer diagnoses in Scotland are now made through a symptomatic FIT pathway).

Retrospective evidence taken from use of symptomatic FIT in Scotland suggests that, where primary care physicians remain concerned after a FIT test returns negative, a second FIT test can be used effectively as a safety net.[149]

In light of a systematic review of evidence up to 2022, the ACPGBI and BSG issued joint guidance, recommending that symptomatic FIT be used to guide all referrals from primary care with suspicion of bowel cancer, though cancer referral pathways could still remain open to those with negative FIT results, but ongoing clinical concern.[150]

After being piloted in Aneurin Bevan Health Board, and in combination with a risk-stratification score in Cardiff and Vale, symptomatic FIT is available to GPs in Wales. In 2022, uptake of symptomatic FIT is high in Welsh health boards, though standardisation and audit of pathways is needed.[151]

Colon Capsule Endoscopy

Another emerging option to safely triage patients and manage colonoscopy demand is CCE. When completed successfully, second-generation CCE has displayed comparable diagnostic accuracy to colonoscopy, and superior to CT colonography (CTC) in polyp detection.[152–154]

One use case for CCE is after incomplete colonoscopy, as an alternative to CTC, for further evaluation of the colon, and diagnostic decision-making. In this setting, it has demonstrated superior diagnostic accuracy to CTC.[155,156] This could translate to better recognition of patients in need of care, and better outcomes, though evidence of effect on time to diagnosis or survival is yet to emerge.

Another use case for CCE, being rolled out in Scotland and piloted in England, is to pair it with symptomatic FIT in a diagnostic pathway, where:

- Undetectable results (<10µg/g) are ruled out.
- Intermediate results (10–100µg/g in England, 10–400µg/g in Scotland) are given CCE, and sent for colonoscopy upon positive findings.
- High risk results (100/400µg/g+, or red flag presentation) are given urgent colonoscopy.

Unpublished evidence from English pilots of over 2,000 capsules have shown no cancers missed in patients receiving CCE, and from the ScotCap study have shown that 39.8% of those receiving CCE were spared colonoscopy. With patient preference comparable between CCE and colonoscopy,[157] and potential to be administered in primary care, this use case may have great value in managing planned secondary care burden.[158,159]

Evidence is yet to emerge on whether this facilitates more rapid diagnosis.

Successful completion rate remains a central challenge to CCE, with completion rates often suboptimal, and reported as low as 57%.[156] However, optimization of bowel preparation for CCE is ongoing, and agents such as prucalopride have recently been associated with an 18.2% absolute increase in completion rate.[160,161]

Rapid Diagnostic Pathways

Another approach is to **streamline diagnostic pathways**, for example via Welsh rapid-diagnostic centres (RDCs) or CDHs, which are based on principles of separated elective care, one-day turnarounds, and broad diagnostic workup. A rapid-access flexible sigmoidoscopy clinic was able to rapidly diagnose 93% of the cancers in one cohort[162]. In another example, an RDC rapid pathway for vague cancer symptoms diagnosed 11 bowel cancers, 8 eligible for curative treatment, of which only 2 would have qualified for bowel cancer-specific referral.[163]

One rapid diagnostic model, which used symptomatic FIT results to triage patients (≤10µg/g excluded, 10–150µg/g referred for diagnostics, ≥150µg/g rapidly referred) achieved a median time from point of suspicion to tissue diagnosis of 23 and 27 days (urgent and normal diagnostic referral); 57.3% of patients were diagnosed stages 1/2 (60.3% in urgent referral patients), with 71.2% of patients ruled out for further investigations, of whom only 0.4% developed bowel cancer.[164–167]

The advent of liquid biopsies (testing for cancer using samples of blood, urine, etc.) may provide another valuable diagnostic tool in this arsenal. Liquid biopsies developed to detect bowel cancer, such as EpiProColon, and Cansense in Wales, generally report similar to slightly inferior diagnostic performance, compared to FIT testing.[168–170] One advantage is that they are usually more patient-acceptable. One study of patients refusing screening colonoscopy found that 97% accepted EpiProColon testing, with just 37% accepting FIT.[170] These tests are continually being developed, and with their low resource intensity and high throughput, are likely to bolster early detection and diagnosis (ED&D) in Wales in the near future.

Ultimately, RDCs aim to create a better conversation between primary and secondary care, using principles of graduated workup to move away from a model where GPs are unable to refer all the patients they are concerned with, as these patients will overwhelm secondary care, and be sent back to primary care with no more answers. This is especially relevant in young people, who experience a high symptom burden, but relatively low incidence of bowel cancer, meaning GPs can be reluctant to refer them onwards.[135]

One solution for these younger low-but-not-no risk patients is the Danish no-yes clinic (NYC). These are similar to RDCs, but operate with an emphasis on quick, low resource intensity tests. With these clinics available, GPs can identify and appropriately refer those at risk of cancer, whilst safely discharging those who are not.[171]

- *Early detection and diagnosis is vitally important to bowel cancer, with diagnostic delays above 3 months associated with significant increases in deaths.*
- *Encouraging early presentation is a key and achievable aim, but little data is available on the clinical benefits achievable by this route, e.g. stage shift, mortality reduction.*
- *High quality evidence and guidance supports the use of symptomatic FIT for bowel cancer referral. We are aware that the National Endoscopy Programme (NEP) are running a programme for engagement with Welsh services.*
- *Emerging evidence supports the use of CCE to safely manage colonoscopy demand. A pilot of CCE in four health boards in Wales has been announced.*
- *High-quality evidence suggests rapid diagnostic pathways, potentially powered by FIT or liquid biopsy testing, could help to diagnose bowel cancer patients with minimal delay.*
- *In December 2021, just 37% of patients started treatment for lower GI cancers within 62 days of suspicion, versus the target in Wales of 95% compliance.*
- *Moondance Cancer Initiative have previously authored a Roadmap for ED&D in Wales and Evidence synthesis on tackling barriers to early presentation, exploring each topic in more depth.*
- *Moondance Cancer Initiative are funding a bowel cancer RDC in the Swansea Bay University Health Board, and we are aware of an ongoing rollout of RDCs across Wales.*

Prehabilitation

Prehabilitation aims to maximise a patient's health and function prior to treatment. It can consist of exercise, smoking cessation, and nutritional and psychological interventions, all delivered in a number of formats.

Better physical function and reduced frailty are strongly associated with reduced bowel cancer mortality after treatment. One retrospective analysis found more physically active patients (matched to controls in every other variable) experienced a 5.9% absolute increase in 10–year disease–free survival (DFS) and an 8% absolute increase in overall survival (OS).[172] Separately, frailty and physical impairment have been linked to higher mortality post treatment, with 70–74% increases in risk of bowel cancer recurrence, and 100–104% increases in risk of mortality across 5 years.[173,174]

Various studies and evidence syntheses agree broadly agree that prehabilitation programmes can improve functional status and reduce frailty pre– and post–surgery. It is shown to improve key indicators such as functional capacity pre–surgery,[175] length of hospital stay (LOS),[176,177] post–operative morbidity,[178] post–surgery 6 minute walking test,[179] quality of life,[179] and post–operation complications[180]. There is also broad agreement that multimodal (e.g. exercise + nutritional + psychological) programmes are more effective than unimodal.[177,179,181]

However, this evidence base is very limited. Firstly, comparators vary, with some studies comparing prehabilitation against standard of care, others with enhanced recovery pathways; in some *re*habilitation is offered as well as *pre*habilitation, in others patients are given only one or another.[175,180,182] Secondly, the prehabilitation intervention itself takes many forms, using different nutritional, exercise, smoking, and/or psychological elements in different combinations, and via various different methods of delivery, such as community, hospital, or home.[176,180,182] All of this makes it difficult to identify best practice, and the likely impact on cancer outcomes.

Nonetheless, guidance and consensus on best practice in prehabilitation is emerging in the UK, with broad agreement that multimodal offerings should be provided, with involvement of allied health professionals (AHPs) (for example, physiotherapists), in a stratified intervention, where information (or a digital platform) can be offered to those with less need of support, with a more intensive, in–person intervention provided for others with greater needs.[183]

Nonetheless, the potential power of prehabilitation has been clearly demonstrated: one pooled analysis of trimodal prehabilitation with enhanced recovery versus enhanced recovery alone, demonstrated a 55% reduction in chances of recurrence after 5 years, rising to 74% when only considering stage 3 patients.[181] This is especially relevant when considering that neoadjuvant therapies (to be discussed below), whilst improving cancer outcomes, can risk decreasing functional status prior to surgery. RCTs continue to evaluate prehabilitation programmes, focussing on additional outcomes such as cost-effectiveness.[184]

- *High-quality evidence shows that prehabilitation is able to improve functional capacity and reduce frailty in cancer patients prior to treatment, which is associated with reduced risk of recurrence and mortality*
- *However, heterogeneity in trial design and comparators means that it is difficult to confirm prehabilitation best practice, or estimate its impact on cancer outcomes*
- *We are aware of prehabilitation services being established in some health boards for bowel cancer patients, which have been limited by resource and staffing constraints, despite relatively low overall costs. At present, there is no national prehabilitation provision.*

Local excision, laparoscopic and robotic surgery

Excision, via endoscopic resection or surgery, and with or without neo/adjuvant therapy, is the standard of care for nonmetastatic bowel cancer, and is mostly carried out with the intention to cure.

Though treatment options are often different for colon and rectal cancer, when both are diagnosed at stage pT1*, **local excision** via endoscopy is the usually preferred treatment method, which has the advantage of reducing invasiveness and morbidity, and of organ preservation, though surgery can be used in 'high-risk' cases. One retrospective study reported that, where appropriate, local excision led to similar rates of recurrence and bowel cancer deaths as surgery. However, for unclear reasons, patients undergoing local excision experienced significantly more overall mortality.[185] Similarly, endoscopic resection is recommended in low-risk rectal cancers diagnosed at stage pT1. However, one recent meta-analysis reported that addition to local excision of surgery and adjuvant (post-excision) chemoradiotherapy led to significantly less recurrence in both low- and high-risk pT1 rectal cancer.[186] Overall, these studies suggest that our ability to identify truly low-risk early cancers, for whom organs can be preserved via local excision without compromising outcomes, is poor. This is a fast-developing field of

* Tumour-node-metastasis (TMN) summarises the stage of a cancer. Tumour (T0-4) summarises the size/extent of the tumour, Node (N0-N3) the number of nearby lymph nodes that have the cancer, Metastasis (M0-1) whether the cancer has spread elsewhere in the body.

research,[187] where patients in Wales may stand to benefit from increased pre-clinical research, and clinical research participation.

For cancers beyond pT1, **laparoscopic**, or 'keyhole', surgery completes this procedure without the large incisions associated with open surgery. Previously, laparoscopy has not been observed to significantly improve long-term recurrence or mortality outcomes when compared to open surgery, both in randomised trials and larger evidence syntheses.[188,189] However, more recent evidence may indicate a benefit: one retrospective analysis of colon cancer patients, matched for background characteristics, found increased 5-year disease-free survival (DFS) (78.2% vs 64.3%) and 5-year OS (86.8% vs 72.1%) for laparoscopic vs open surgery.[190] At present, this benefit is therefore uncertain. Similarly, studies generally fail to demonstrate a significant long-term recurrence or survival benefit of laparoscopy in rectal cancer surgery.[191,192]

Evidence is however more consistent in supporting laparoscopy for reduced post-operative complications and hospital length of stay, and improved functional status after surgery.[193] Such factors can be significant in decisions in minimising the time to starting any adjuvant therapies – and adjuvant therapies can substantially increase chances of long-term survival (see below). Continuing this push toward better organ preservation and reduced invasiveness, natural orifice translumenal surgery is a growing area of interest, research and adoption of which may stand to benefit some patients in Wales.[194,195]

The evidence base for **robotic-assisted, compared to laparoscopic surgery**, is still being established, though there are some positive signs.[196] Studies generally report no significant impact on recurrence,[197–199] and though there are some small-scale reports of long-term mortality benefit, this is in conflict with wider literature reports of no significant differences.[198,200,201] However, early evidence is gathering of better surgical outcomes and functional status post-surgery, such as lower conversion to open surgery,[199,200,202] and shorter LOS (though some studies report no difference), despite longer operation times.[199,200,203,204] Evidence is mixed with regards to resection quality (e.g. R0 margins and lymph node resection), with some studies reporting improvements and others not.[199–201] Overall, it's clear that the evidence is immature, especially in light of the recognised learning curve of robotic surgery, with one single-surgeon study reporting that it took 45-65 cases to stop improving, and attain a consistently high surgery quality.[205] Accordingly, while continuing to monitor the developing evidence on robotic assisted surgery, it seems plausible that there may be a role for robotic surgery in maximising operative quality and post-surgery functional status in some patients, particularly

those with more challenging surgeries, such as in obese patients, or patients requiring surgery in tight spaces.[199,204]

- *Local excision is less invasive than surgery, and preserves function, but our ability to identify low-risk cancers for which it is appropriate it currently limited.*
- *Laparoscopic surgery is shown to improve functional status and recovery, which are important for subsequent adjuvant therapies. Whether it also directly contributes to long-term recurrence/mortality is presently unclear*
- *NBOCA 2021 reports that just over 50% of bowel cancer surgeries in Wales are laparoscopic, and between 1-10% in the UK are by local excision.*[113]
- *The evidence base for robotic-assisted surgery is immature. There are indications that robotic surgery may offer improved recovery compared to laparoscopic surgery in some patients. Mortality outcomes are currently unclear.*
- *NBOCA 2021 reported no robotic bowel cancer surgery in Wales.*[113] *A national robotic assisted surgery programme has however just been announced by the Health Minister (March 2022)*

Systemic Anti-Cancer Treatments and Radiotherapy

Chemotherapy and radiotherapy are the most common non-surgical interventions in cancer, but other types include immunotherapies and targeted therapies. Often, these therapies are offered in combination to try to ensure all cancerous cells are destroyed.

Neoadjuvant/adjuvant approaches in colon cancer

Adding systemic therapy before (neoadjuvant) or after (adjuvant) surgery can play a role in reducing bowel cancer mortality. Presently, neoadjuvant therapy is only recommended for stage 4 colon cancer in the UK, in an attempt to downsize the tumour, facilitating resection. Adjuvant therapy is currently only recommended for stage 3 colon cancer, outside of trials.[9] This recommendation is on the basis of a 20% increase in 5-year DFS in stage 3 patients. The benefit is less certain in stage 2 patients, partially due to the already very high 5-year DFS rate (82-88%). However, numerous trials have examined the benefit of adjuvant therapy for patients with stage 2 bowel cancer, demonstrating for example: 3.6% increase in 5-year OS (QUASAR), and 18% higher chance of achieving 5-year DFS (NSABP C-07).[206] As described above, this uncertainty is likely to be linked to our inability to predict which stage 2 cancers are low-risk, and may not benefit from adjuvant therapy, and which are high-risk, more aggressive, and may benefit from additional treatment.

One recent meta-analysis suggested that, compared to adjuvant therapy, neoadjuvant approaches may increase surgery quality (via improved R0

resection), as well as decrease the risk of mortality.[207] More trials, such as FOxTROT, are underway, investigating this outcome.

In addition, exploratory neoadjuvant approaches for stage III colon cancer using immunotherapy (nivolumab and ipilimumab) in patients with MSI-H colon cancer have demonstrated high response rates when used as a pre-operative therapy with 60% (12/20) having no residual tumour at the time of surgery and 19/20 having a major response, which have the potential to lead to a non-surgical approach for 12-20% of stage II/III colon cancers, if confirmed in ongoing studies.[208]

Optimisation of adjuvant therapies is also underway, for instance with the IDEA international collaboration (5 RCTs) including the UK SCOT trial demonstrating a three-month course gave similar outcomes to a six-month course of chemotherapy, with significantly fewer adverse events, and lower cost.[209]

Whilst the process of formal medication appraisal is outside the scope of 'service improvement', there are clearly real potential patient benefits to be gained from increased participation in such trials.

Data from a recent retrospective analysis, as well as NBOCA 2021, report that only ~61% of stage 3 colon cancer patients eligible for adjuvant chemotherapy actually receive it.[113,210] People with lower functional status were far less likely to receive adjuvant therapy, as well as people from more deprived backgrounds. Laparoscopic surgery was associated with a 28% increased chance of receiving adjuvant therapy. Whilst adjuvant therapy will not be the best choice for all, particularly for more elderly patients, the study suggests adjuvant therapy may be being significantly underutilised, or pre and re-habilitative approaches are not being used or are ineffective at improving fitness for therapy.[210]

Neoadjuvant and definitive approaches in rectal cancer

NICE currently recommends consideration of neoadjuvant radiotherapy for all but stage 1 rectal cancer, indicating that all appropriate options should be discussed, with the patient. It also recommends adjuvant therapy in stage 3 rectal cancer if chemoradiotherapy has not been given previously.[9]

Traditionally, neoadjuvant radiotherapy has been given as 'long-course', delivering small amounts of radiation over 25+ treatments over 5 weeks. However, 'short-course' neoadjuvant radiotherapy is emerging as an option, giving 5 treatments over a week at an increased radiation dose per day. Trials have investigated the effect of delay to surgery (typically over 4 weeks) after receiving short-course radiotherapy, to allow it time to take effect. One meta-analysis comparing this to short-course radiotherapy with no delay found a 25% risk decrease in mortality (nonsignificant, due to small, heterogenous studies), alongside significantly improved response rate, downstaging, and fewer post-op complications.[211] Another trial, which compared a delay to surgery after receiving short-course

radiotherapy, against long-course radiotherapy with no delay, found no decrease in OS or DFS, with reduced treatment burden, which will be less resource intensive for the healthcare system,.[212]

Recent phase III trials have suggested a Total Neoadjuvant Therapy (TNT) approach. Here, recipients receive systemic chemotherapy before or after radiotherapy (either short course or long course) with results suggesting the addition of systemic doses of chemotherapy may increase complete response of the primary tumour, whilst also reducing local and distant recurrence. In patients who appear to achieve a complete clinical response after neoadjuvant therapy it is recommended that the option of a non-surgical, watch and wait or active monitoring approach be discussed with the patient, only deploying surgery if there are signs of tumour growth, thereby sparing patient's function. Recently the RAPIDO and PRODIGE 23 studies have suggested complete pathological response rates of 28% with TNT approaches with short course and long course radiotherapy respectively, in locally advanced rectal cancer. In another promising trial of the TNT approach, stage 2/3 rectal cancer patients treated with chemoradiotherapy followed by consolidation chemotherapy and a watch and wait approach, 53% of patients were spared surgery, with no survival difference compared to those offered surgery straight after their treatment course.[213]

STAR-TREC is a pivotal ongoing phase 3 trial, investigating three treatment options: standard resection surgery, long course-radiotherapy and chemotherapy, or short-course radiotherapy, followed by a 'watch-and-wait'. In this watch and wait approach, the next treatment step is decided by response, with surveillance in place for conversion to local resection.[214]

NBOCA 2021 reported that 36% of those undergoing resection for rectal cancer received neoadjuvant therapy, but with considerable variation, from 14-62%, between UK regions.[113] Besides decreasing this variation in practice, there is clear potential benefit from increased participation in trials of novel approaches.

Immunotherapies for metastatic bowel cancer

Unfortunately, immunotherapies are only considered effective for patients which have the MSI-H subtype, who make up 3-5% of the metastatic bowel cancer population, and not in MSS patients, who make up the remaining 95%+.[215,216] However, they can be transformative for some metastatic patients, most of whom were previously considered only for management and palliative care.

Firstly, immunotherapies give high rates of response and longer duration of response than chemotherapy, potentially opening a wider window for conversion to resectability – though trials are yet to demonstrate this.[10,11] In addition, because immunotherapies 'activate' the immune system, there is hope that a subset of responders to therapy may even represent a group of patients 'cured' long term. Once again, evidence is immature, and yet to fully bear this out.[10]

Next generation therapy combinations are an evolving space with much potential. For example, multiplexed combination therapies which attempt to switch an immune "cold" MSS tumour to an immunotherapy sensitive (immune "hot") tumour or immunotherapy combinations + radiotherapy may increase response rates in MSS patients. Lastly, novel therapies are continually being developed. Two examples are CAR–T cellular therapy, as a means of cure, and the OncoVAX adjuvant vaccine, to protect against MSI–H recurrence.[215,216] There is clear potential benefit here, from increased preclinical research, and patient participation in clinical research, in Wales.

Surgical treatment for peritoneal metastases

In recent years, a combined chemotherapy and surgical technique has been developed to treat metastatic bowel cancer, which has located at the peritoneum (tissue lining the abdomen), where previously only management with chemotherapy was available: cytoreductive and hyperthermic intraperitoneal chemotherapy (HIPEC). This technique has been associated with improved DFS and OS, even leaving patients without recurrence for 5+ years in some cases.[217,218] Debate is ongoing concerning the efficacy of the addition of HIPEC to cytoreduction, and on the correct course of chemotherapy to use.[219] Whilst acknowledging its' risks, the procedure has been recommended for use by NICE in appropriate cases.[220] Currently, cytoreduction surgery with HIPEC is not available to patients in Wales.

- *Adjuvant therapy in colon cancer and neoadjuvant therapy in rectal cancer are recommended, but underutilized interventions, with high-quality evidence showing they can reduce cancer mortality. Increasing functional status, and reducing unwarranted variation will be key to realizing this potential benefit.*
- *A number of novel therapeutic approaches at earlier and later stages of development, such as HIPEC surgery, TNT in rectal therapy, immunotherapy combinations, and novel therapy modalities, may hold huge promise to reduce cancer mortality in bowel cancer patients. In advance of formal appraisal, research participation may be the best way to realize this potential for some Welsh patients in the near-mid future.*
- *Moondance Cancer Initiative is funding a project to increase clinical cancer research participation across three areas of Wales.*
- *Moondance Cancer Initiative is funding a project to investigate the feasibility of implementing cytoreductive surgery with HIPEC in Wales.*

Post-treatment monitoring

Patients remain at risk of recurrence after curative treatment for bowel cancer, and should be monitored in order to catch recurrent disease as early as possible. The FACS trial reported that recurrence in monitored bowel cancer patients was

three times more likely to be resectable than in non-monitored patients, due to being diagnosed earlier.[221] NICE recommends testing for the analyte CEA every six months for three years, as well as two CT scans within three years of curative treatment.[9] In addition, BSG/ACGPI/PHE guidelines† recommend a risk-stratified colonoscopy approach based on a baseline colonoscopy post treatment,[222] as summarised in Table 2:

NICE Guidance	
All Patients	CEA testing every 6 months for 3 years.
All Patients	2 CT scans within 3 years.
BSG/ACPGBI/PGE Guidance, after baseline colonoscopy	
Bowel cancer still present	Resume treatment, surveillance colonoscopy 1 year after this concludes
Large non-pedunculated colorectal polyps (LNCPCs) identified, or R0 resection not achieved	Site check colonoscopy at 2-6 months, and another 1 year later
High risk polyps	Surveillance colonoscopy in 3 years
No high-risk findings	Participate in bowel cancer screening

Table 2. UK guidance for monitoring of bowel cancer patients post-treatment.

This broad **risk-stratified approach** is evidentially supported.[223] Where previous focus was on more intense, regular monitoring, a number of clinical trials (FACS, GILDA, COLFOL) have failed to demonstrate a relationship between monitoring intensity and mortality.[224] Indeed, one retrospective analysis found no overall mortality difference in non-stratified groups of patients who were more, or less adherent to monitoring, and so recommended a risk-stratified approach, adapted to the oncological state of play, comorbidities, and patient preference.[221]

Some innovative approaches to such risk stratification have been suggested. For instance in one retrospective study, stage 1 patients were grouped by risk score based on a series of oncological risk factors. This risk score correlates very well with 3-year recurrence rates, and could be used to identify 20% of the population (risk score 0, DFS 99.1%) not requiring monitoring, as well as 15% of the population (risk score 3-5, DFS 90.0%), who might benefit from more intense monitoring.[225]

At present, no data is available in Wales on how patients are monitored post-treatment, their adherence, or on the proportion of bowel cancer diagnoses and deaths owing to recurrent cancers. Therefore, it is difficult to estimate how much mortality difference can be made by improving monitoring provision. NBOCA 2021 indicated that, in the UK 2017-18, 29% of deaths within 2 years of diagnosis were following local excision or major resection. Not all of these will be due to recurrence, but this figure does help to understand the scope of the affected population.[113]

† These guidelines, produced through consensus seeking research amongst the British Society of Gastroenterology (BSG), the Association of Coloproctology of Great Britain and Ireland (ACGBPI), and Public Health England (PHE), are regarded as best practice in the UK.

The use of FIT has also been investigated to supplement post-treatment monitoring. In a study of 5,938 patients, post-excision of high-risk pre-cancers, yearly FIT tests were offered in addition to a colonoscopy every three years, it was reported that 40% of CRCs and 70% of advanced polyps could be detected earlier with a 10µg/g threshold.[226]

Evidence is emerging that **circulating tumour DNA** (ctDNA) monitoring via liquid biopsy may be an effective tool to identify patients at risk of early recurrence. Studies report that ctDNA positivity post-surgery was highly predictive of recurrence. One found that just 30% of patients identified as ctDNA-positive reached three years of DFS; by contrast 77% of those identified as ctDNA-negative reached 3-year DFS. Another study has similarly shown 33% DFS for ctDNA-positive, and 87% DFS for negative, rectal cancer patients. The quantitative concentration of ctDNA was even strongly correlated with time to recurrence. These results indicate ctDNA as more strongly predictive than the currently recommended CEA testing.[227,228] In another observational study, a ctDNA assay identified 70% of patients with recurrence, with a median lead-time of 8 months to formal diagnosis, much earlier that is possible with current methods.[229]

Research is also ongoing on methods to prevent recurrence in those at risk. One RCT of **Berberine** (an over-the-counter supplement) in patients with resected precancer found that it reduced risk of recurrent adenoma by 23%, and advanced adenoma by 48%, with minimal adverse events observed. No cases of bowel cancer were recorded in the study.[230]

As research into these innovations develops, there are clearly potential benefits to patients in Wales through increasing participation in this research.

- *Post-treatment monitoring can hugely reduce mortality risk, and risk-stratified strategies are being developed to maximize its' benefits*
- *Lack of data in Wales means it is difficult to estimate the impact which could be made on the approximately ~29% of cancer deaths which occur after resection/excision*
- *Innovative approaches, such as FIT or ctDNA monitoring and prophylactic prevention of recurrence may hold significant benefit, and patients in Wales could benefit from increased research participation in this area.*

Inequalities

Whilst not a specific opportunity as defined by an intervention in healthcare, as discussed in examples above, it is important to acknowledge the huge influence that inequalities hold over bowel cancer outcomes. Underserved groups suffer various inequalities in bowel cancer risk, prevention, and treatment:

- Studies in Wales report that young people from more deprived families and schools are more likely to adopt unhealthy behaviours with regards to smoking, alcohol consumption, exercise, and dietary quality, all of which are risks for developing bowel cancer.[61]
- A study in UK women found that a diet associated with reduced bowel cancer risk was less common in participants without degree levels of education, and without professional/managerial socioeconomic status (both measures of deprivation).[62]
- Participation in bowel screening is lower in more deprived Welsh communities, with a >15% difference between the most and least deprived quintiles in 2019–20.[101]
- In the UK, people from more deprived backgrounds report more barriers to timely help-seeking with bowel cancer symptoms, in a pattern which has worsened as a result of the COVID-19 pandemic.[231]
- People with comorbidities and undiagnosed bowel cancer experience longer times from symptoms to tests, and are less likely to receive a timely colonoscopy/sigmoidoscopy.[232]
- People from different ethnic backgrounds are diagnosed with bowel cancer by different routes at different rates. In particular, people identifying as an ethnicity other than White, Black, or Asian, experience significantly less diagnosis by screening, and more by emergency presentation.[233]
- Use of adjuvant chemotherapy was reported in England as less likely in stage 3 colon cancer patients from more deprived backgrounds.[210]

It is important to recognize that these disadvantages in risk, prompt detection and diagnosis, and treatment, are cumulatively experienced by the most deprived communities in Wales.

As a collective result of all these factors, people in the most deprived quintile in Wales suffered an 83% higher risk of death from bowel cancer than the least.[2] Clearly, there are great gains to be made by simply addressing these inequalities.

Solutions to ameliorate inequalities in cancer outcomes are highly unlikely to be one-size-fits-all. However, expertise and experience in addressing these issues are available in Wales, for example in ongoing research to engage Gypsy/Roma communities in bowel screening,[234] or in studies like TIC-TOC, aiming to increase awareness and help-seeking behaviours for cancer in more deprived Welsh populations.[235]

Reflections

In this evidence review we have examined key opportunities along the bowel cancer pathway with potential to help us progress towards zero deaths from bowel cancer in Wales – from public health and awareness, through detection and diagnosis, to treatment and surveillance. We recognise that this is a snapshot of a fast-developing field, and there may be further interventions with potential which arise in the future.

The principle theme to recognise is that prevention, and early detection and diagnosis of bowel cancer are our most powerful levers to reduce bowel cancer deaths. There is real potential for outcomes to further improve for late-stage patients via new treatments and approaches to functional performance pre- and post-surgery; nonetheless, at a population level, the biggest opportunities lie in earlier detection and diagnosis.

We identified a lack of evidence in some aspects of bowel cancer deaths prevention, making it difficult to estimate the opportunities for improvement. In particular, there was a lack of literature connecting improvements in public awareness/barriers to presentation and clinical outcomes, such as stage shift in diagnosis. This is consistent with findings from our previous literature review of barriers to symptomatic cancer presentation.[128] Other areas where limited literature made estimates of possible improvements difficult included behavioural risk factors, and prehabilitation. This is in keeping with previous collaborative attempts to understand bowel cancer research gaps in Wales in 2018 – where a need for increased awareness and communication between clinicians and patients, alongside interdisciplinary collaboration and trials of prevention strategies, were cited as priorities. It is interesting to note, that other identified knowledge gaps, such as how to implement an effective triage system for symptomatic patients, have to a certain extent been met in 2022.[236]

There are also some areas where a lack of data availability in Wales makes it difficult to estimate how much improvement can be made. For instance, there are no published figures on the number of patients tested/diagnosed with Lynch syndrome, or what proportion of bowel cancer diagnoses in Wales are the result of recurrence. More comprehensive data will be essential to monitor and drive improvements over time.

Summary: what could we achieve?

The opportunities we identified to reduce bowel cancer deaths in Wales are shown in Figure 4, against a summary bowel cancer pathway. For a longer summary, see Appendix A.

Our review of the available evidence suggests that in a perfect world, where most cancers are prevented by a combination of lifestyle behaviours and screening, all cancers are detected early (most by screening) and effective treatment is delivered quickly, **zero deaths from bowel cancer is a justifiable aspiration**.

Of course, in the real-world, with complex social factors, limits on healthcare resources and capacity, differing personal choices, comorbidities, and other factors, it is highly unlikely we will experience a year in Wales with zero bowel cancer deaths in the foreseeable future.

However, taking zero deaths as a north star aspiration, this review suggests that enormous reductions in bowel cancer deaths ought to be possible with the tools available to us.

Our next steps

This review, focusing on what is possible, forms an input in a larger project. Our next steps are to gather patient and carer perspectives on the challenges and opportunities to achieving the improvements outlined here; and then to seek the views of patients, healthcare, and policy professionals on a series of practicable stretch goals to reduce deaths from bowel cancer across Wales.

These stretch goals will recognise firstly that none of these opportunities exist in a vacuum. For example, work to increase public awareness of bowel cancer will likely have knock-on effects on screening participation; there is also currently no viable path to detecting more bowel cancer through screening which does not result in more colonoscopy demand. Understanding these interactions will be important to build a cogent vision of the future.

Secondly, we will recognise the context and practicalities of such opportunities. Bowel cancer pathways sit within wider NHS structures, and pressure or changes in the wider NHS will affect capacity to improve bowel cancer outcomes. Especially in light of coronavirus backlogs, we will recognise and address the serious organisational challenge this represents.

At Moondance Cancer Initiative, our findings will directly inform our partnerships, and funding strategy. We will be publishing our reports throughout 2022/23, and hope that they form a constructive contribution to conversations across Wales.

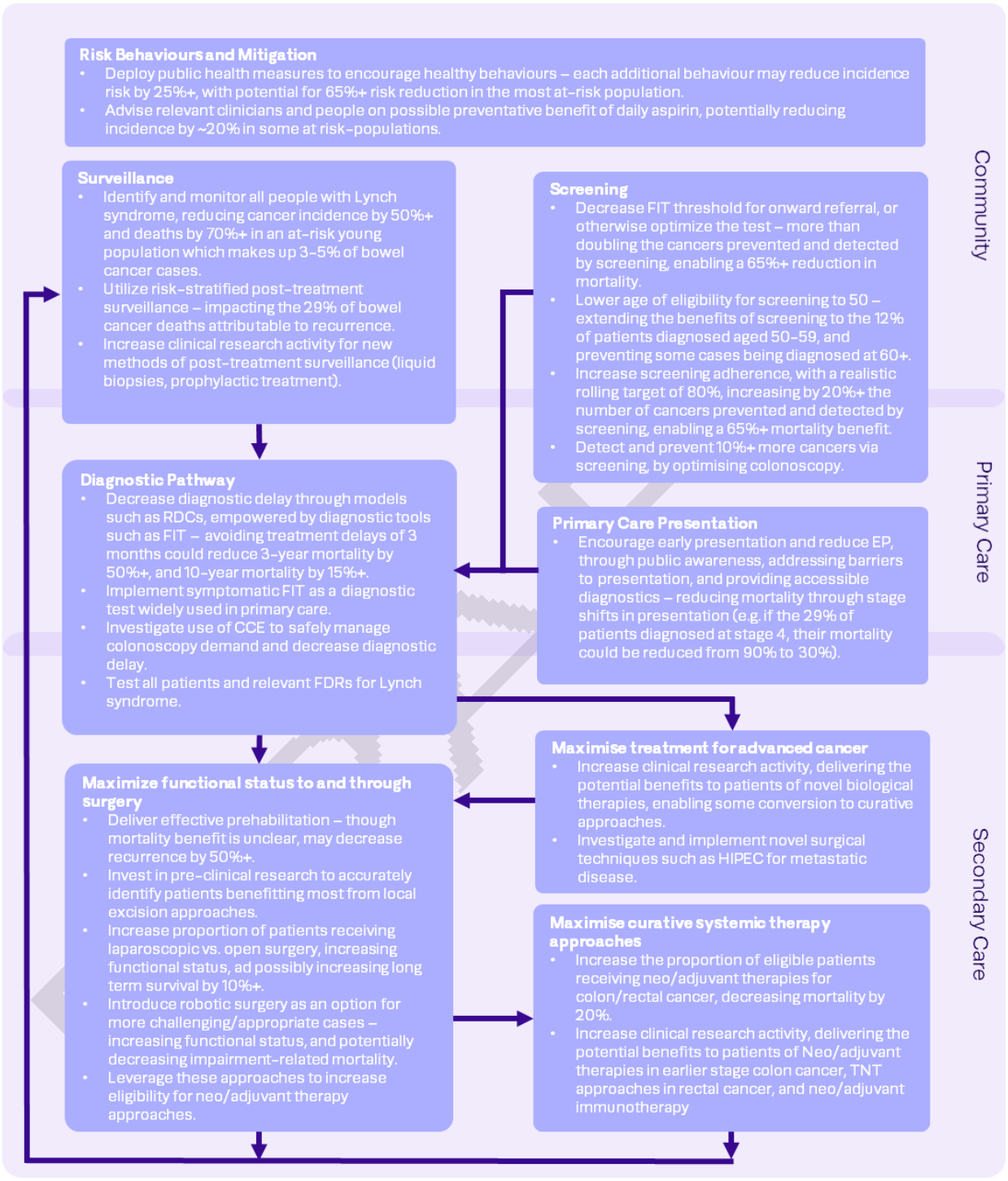

Figure 4. Opportunities to reduce bowel cancer deaths in Wales.

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Appendix A: Opportunities to reduce bowel cancer mortality

The opportunities we identified to reduce bowel cancer deaths in Wales are summarised below, in Table 3.

Opportunity	Potential Effect
Genetic surveillance	
Identify and appropriately monitor all people with lynch syndrome (and other genetic risk profiles, e.g. Lynch–like syndrome) via colonoscopy and other diagnostic tests (e.g. FIT).	Reduce incidence of bowel cancer by 50%+, and bowel cancer deaths by 70%+, in a growing at–risk young population which represents 3–5% of bowel cancer cases.
As people with lynch syndrome are identified, prescribe aspirin for prevention of bowel cancer.	Reduce incidence of bowel cancer by 40%+ in a growing at–risk young population, which represents 3–5% of bowel cancer cases.
Aspirin	
Advise relevant clinicians and people at risk of bowel cancer of the possible preventative benefit of daily aspirin.	Potentially reduce incidence of bowel cancer in some at–risk populations by ~20%.
Advise relevant clinicians and people diagnosed with bowel cancer of the possible mortality benefit of aspirin post–diagnosis – engaging the community early in case of formal recommendation as adjuvant therapy.	Potentially reduce bowel cancer mortality by 15%+ in diagnosed patients.
Public health prevention	
Deploy public health measures to encourage behaviours which reduce risk: smoking cessation, dietary/alcohol changes, exercise.	Reduce risk of bowel cancer by 25%+ for each additional behaviour adopted by members of the public. Reduce risk by up to 65%+ in the most at–risk populations.
Screening	
Decrease the FIT threshold for onward referral in screening, or otherwise optimise the test through annual application/addition of risk scores.	More than double the number of cancers prevented, and detected by screening – patients diagnosed via screening could experience 65%+ less cancer mortality.
Increase adherence to screening programmes, setting a realistic rolling target at 80%.	Increase by 20%+ the number of cancers prevented and detected by screening – enabling a 65%+ mortality reduction in screening–detected patients.
Lower the age of eligibility for bowel cancer screening to 50.	Enable the benefits of bowel screening to be extended to the 12% of bowel cancer patients diagnosed at ages 50–59 (plus those later diagnosed via symptoms aged 60+).
Early detection and diagnosis	
Encourage early presentation and reduce emergency presentation, through public awareness, addressing barriers to presentation, and providing accessible diagnostics.	If achieved, stage shift in presentation would significantly reduce mortality – e.g. the 29% of patients diagnosed at stage 4 could have their mortality rates reduced from 90% to 30% if diagnosed at stage 3.
Decrease delay from point of suspicion to first definitive treatment, through models such as RDCs, empowered by diagnostic tools such as FIT.	Avoiding treatment delays of 3 months could reduce short–term (3 year) mortality by 50%+, and long–term (10 year) mortality by 15%+.
Increase functional status to and through surgical treatment	
Deliver effective multimodal prehabilitation to those diagnosed with bowel cancer.	Reduce mortality associated with impairment/frailty (extent currently unclear), also enabling 50%+ reduction in recurrence. Increase eligibility for adjuvant therapies.
Increase the proportion of patients receiving laparoscopic (vs open) surgery.	Increase functional status through surgery, thereby increasing eligibility for adjuvant therapies. Possibly increase long–term survival after surgery by 10%+.
Introduce robotic surgery as an option for more challenging/appropriate surgical cases.	Increase functional status and eligibility for adjuvant therapies. Potentially decrease impairment–associated mortality (benefit unclear).
Maximise outcomes from systemic therapy	
Increase the proportion of eligible patients receiving adjuvant therapy for colon cancer and neoadjuvant therapy for rectal cancer.	Decrease mortality in the ~40% of stage 3 colon cancer and ~64% rectal cancer patients eligible for neo/adjuvant therapies by 20%+.
Increase clinical research activity, opening eligibility for:	Strong potential to decrease mortality in patients receiving innovative therapies, though extent remains to be proven.

• Neo/adjuvant therapies in earlier stage colon cancer. • TNT approaches in rectal cancer • Neo/adjuvant immunotherapy • Novel immunotherapies and immunotherapy combinations	
Effectively monitor patients post–treatment	
Utilise best monitoring practice and risk–stratification to appropriately monitor patients after treatment.	Decrease the ~29% of bowel cancer deaths attributable to recurrence by detecting recurrent cancer at an early stage.
Increase clinical research activity for novel methods of post–treatment monitoring: • Liquid biopsies to identify recurrence early • Prevention through low–dose medication	Potential to increase the proportion of recurrence which is detected early, and to reduce recurrence.

Table 3. Opportunities to reduce bowel cancer deaths in Wales.

MOONDANCE
CANCER INITIATIVE

TOWARDS ZERO DEATHS FROM BOWEL CANCER IN WALES

Moondance Cancer Initiative helps find solutions so that more people in Wales survive cancer. We actively support people and projects with potential to transform survival outcomes across the country, and we undertake research and insight to inform our work.

www.moondance-cancer.wales