Early Detection and Diagnosis of Cancer

A HORIZON SCAN OF INNOVATIONS FOR WALES

DRAFT

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1. About Moondance Cancer Initiative

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:

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

We're a not-for-profit company (company number 12305964), privileged to be funded by the Moondance Foundation.

2. Purpose and context of this paper

Early detection and diagnosis (ED&D) is a powerful tool in the fight against cancer. For patients with cancer diagnosed at an earlier stage, significant improvements are seen in morbidity and quality of life,[1–3] and in short and long-term survival (although these measurements are subject to lead- and length-time bias).[4–6] In addition, investment in ED&D is offset by reduction in treatment costs of earlier stage cancers,[7–10] and generally constitutes a cost-effective use of healthcare resources.[11–13]

As an organisation dedicated to enabling more people in Wales to survive cancer, helping to improve early detection and diagnosis across the country is a priority for us – especially for patients who suffer the poorest outcomes.

There is a clear commitment in Wales to ED&D, for example in the development and roll-out of rapid diagnostic centres (RDCs)[14] and optimisation of bowel screening,[15] amongst other developments.[16,17] At the same time, cancer ED&D is a rapidly evolving and exciting field. An array of innovative products,[18,19] service models,[20,21] and patient identification and screening schemes[6,22,23] are being developed in healthcare systems across the world, which offer huge potential to benefit cancer ED&D provision.

We believe these innovations, in combination with current policy motivation, mean there is a significant opportunity to transform ED&D in Wales over the next decade, radically speeding up time-to-diagnosis across all cancers – with a direct consequent impact on cancer survival.

Wales however needs a roadmap to get there.

And as an independent third-party funder, we're keen to understand what a cancer ED&D roadmap for Wales might look like, to know where we can best help. We understand that in the short-term, clinical and executive health leaders will necessarily be focused on the recovery from the pandemic.[21] Therefore, we are putting some of our own capacity into this horizon scan, with the aim of producing an outline ED&D roadmap to spark constructive debate and discussion about the way forward.

This paper presents a high-level overview of innovations relevant to cancer ED&D, examining developments in patient identification, referral, and diagnosis, and critically appraising their potential to advance cancer ED&D across Wales. It is intended as an input into a series of discussions and interviews on a potential ED&D roadmap for Wales over the summer of 2021.

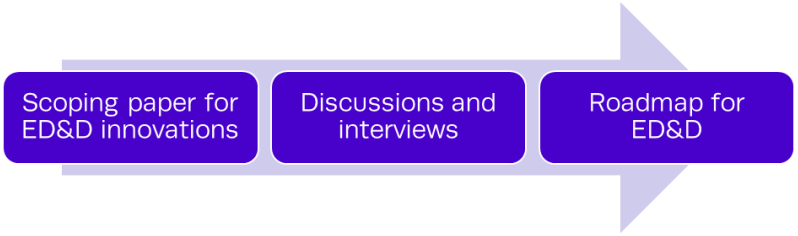

Figure 1. Structure of the MCI ED&D innovation research project

3. Context: ED&D in Wales

Our lives, and the health and social care services, are currently dominated by the Covid-19 pandemic. Even as we emerge from the pandemic itself, the anticipated knock-on effects of the extraordinary public health measures taken are beginning to reveal themselves.

With healthcare resources and personnel already stretched thin, and in combination with the estimated 3,500 'missing' cancer patients yet to appear (potentially with later than usual stage cancers), cancer services are anticipated to remain under significant strain throughout the next Senedd term.[24] At the same time, in response to a crisis which has 'deconstructed' many cancer services, a more urgent institutional motivation is emerging, to build a 'better normal' for cancer patients post-COVID, improving coordination and communication for a more efficiently functioning healthcare system – including potentially around early detection and diagnosis.[25,26]

Wales' cancer performance challenge

We should acknowledge that cancer outcomes in Wales lagged behind comparable nations before the pandemic – and that late diagnosis was an important factor. For example, as of 2018, 50% of cancers with a known stage were diagnosed at stages 3-4 in Wales,[27] compared to 45% in England.[6] The International Cancer Benchmarking Partnership (ICBP) showed that in 2014 Wales had relatively poor 1 year survival outcomes compared to countries with similar healthcare systems,[28] primarily driven by later stage at diagnosis.[29](Figure 2)

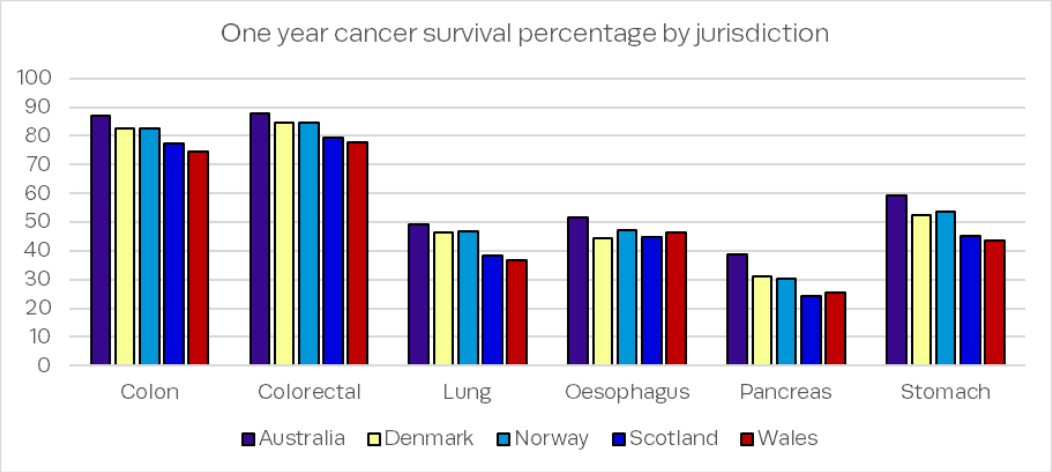

Figure 2. One year-survival rates of different cancers in countries with comparable healthcare systems to Wales in 2014, as measured in the ICBP SURVMARK-2 study.[28]

More recent data shows that the number of patients who received treatment within 62 days of cancer suspicion consistently missed the 75% target, with rates typically between 60-65% and significant disparities between health boards (see Figure 3).[30] Higher rates in the summer of 2020 are likely to be skewed due to an artefact of the dramatic reduction in patients self-referring with cancer symptoms during the COVID pandemic.[21,31] Furthermore, patients eventually arriving in care with later stage cancers are likely to cause a reduction in timely SCP rates in the short- and mid-term future.

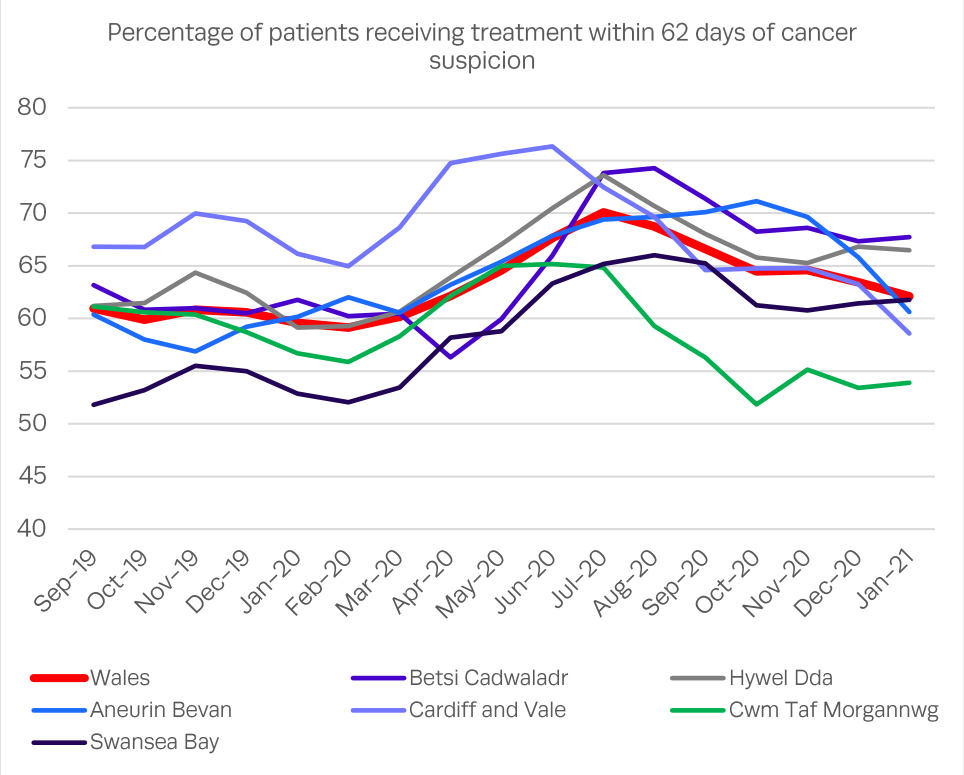

Figure 3. Percentage of patients receiving treatment with 62 days of cancer suspicion (3 month rolling average), as measured by the Welsh Government via StatsWales[30] *No data was available for the Powys health board.*

New developments in brief

The cancer performance challenge was acknowledged in the Welsh NHS 2012 and 2016 cancer delivery plans, which helped to frame and launch some key ED&D developments, including[32]:

- The single cancer pathway (SCP) - a target, and a unification of previous urgent/non-urgent diagnosis pathways, whereby every patient should receive their first definitive treatment within 62 days of the first suspicion of cancer (see Figure 1).[33] The Welsh Government aims to satisfy this target for 75% of patients.[34] The SCP is underpinned by site-specific National Optimal Pathways (NOPs)[35]
- Piloting and support to roll-out of rapid diagnostics centres (RDCs) as a cost-effective and faster pathway to diagnosis for people with vague symptoms[14]
- Ongoing improvement of screening uptake, including preparations for bowel screening optimisation (though the original plan has been scaled back in light of the Covid-19 pandemic)
- Scoping the implementation of lung health checks[32]

In March 2021, the Welsh Government replaced the cancer delivery plan with a cancer quality statement.[36] It provides the cancer services standards that Health Boards and the collaborative Wales Cancer Network are expected to meet, in the context of the National Clinical Framework. The focus is on immediate, short-term Covid-19 recovery, and the achievement of targets established in the new National Optimal Pathways.

A rolling three-year implementation plan is anticipated in the cancer quality statement. To avoid unintended path dependency, this three-year plan will also need to take into account a longer-term vision and roadmap for what ED&D could look like, and how it might be achieved.

Any roadmap for cancer ED&D must of course align with wider service improvements, recognising that cancer patients travel through core, shared NHS services and quite often have more than one health condition. A series of other diagnostics improvement programmes in Wales are therefore also critical to improving cancer ED&D in Wales, and have been established in response to serious workforce and delivery challenges, including:

- The National Endoscopy Programme, which is pushing forward schemes to standardise clinical pathways, and improve IT infrastructure[37]
- The National Pathology Programme, which is providing training and pushing for the standardization of Welsh pathology services[33]
- National Imaging Strategic Programme, which currently prioritises management of the radiology workforce, adoption and benchmarking of equipment, and standardization across Wales[38,39]

The digital transformation plan for NHS Wales is also a critical interdependency, as it sets the approach, standards and timescales for the digital health and care record, national data registry, and other digital platforms for integrated care provision.

Taking stock of diagnosis pathways and providers

In this project, we have utilised a simplified map of patient diagnostic pathways as a framework to consider the implications of potential cancer ED&D innovations. In this section, we summarise our understanding of current diagnostic pathways and providers.

The most common route by which patients are diagnosed with cancer is primary care referral.[40,41] Patients present in primary care with potential cancer symptoms (most commonly to their GP), and are referred to secondary care for diagnostics.[42] Primary care is managed within health boards in the context of the general medical services contract. Improvement is guided and supported by the Macmillan primary care cancer framework, and complemented by safety netting support, and behavioural change led interventions such as 'ThinkCancer!'.[43]

As mentioned above, rapid diagnosis centres (RDCs) present a new model bridging primary and secondary care, enabling potentially faster diagnosis for people with vague symptoms; RDCs are established in Swansea Bay and Cwm Taf Morgannwg health boards, and the Wales Cancer Network is supporting implementation across the country.[14]

Asymptomatic patients may also be referred direct to secondary care through screening programmes, which are available regularly to people at risk of three cancers: breast (for women between 50-70)[44], bowel (currently for people aged 60-74)[45], and cervical (for women aged 25-64).[46] These programmes are all managed and delivered by Public Health Wales. Planned changes to the bowel screening programme, decreasing the minimum age to 50 and increasing the sensitivity of the test have been delayed as a consequence of the pandemic.[47] People with family or individual histories of cancer may also be referred to the All Wales Medical Genomics Service (AWMGS) for genetic testing of their cancer risk, and may be screened regularly if a risk is identified.[48]

Patients already in secondary care for reasons unrelated to cancer may also be transferred into cancer services as a ward referral upon suspicious symptoms or findings.[34]

After entering secondary care with a suspected cancer, patients are triaged, investigated, diagnosed and staged on pathways dependent on the cancer site. Approximately 20-25% of cancers arrive in secondary care as emergency presentations, which is associated with later stage at diagnosis.[49] Given both demand pressures and pre-existing workforce challenges, many health boards draw upon additional NHS staff capacity (via overtime) and outsourced services contracts (such as radiology reporting) to supplement in-house diagnostic capacities.

Where a primary cancer remains undiagnosed (a 'malignancy or primary of unknown origin') the diagnosis pathway can however be much more uncertain. Later treatments are provided by health boards, with a small percentage of treatment outsourced to the English NHS or private sector for very specialist needs.

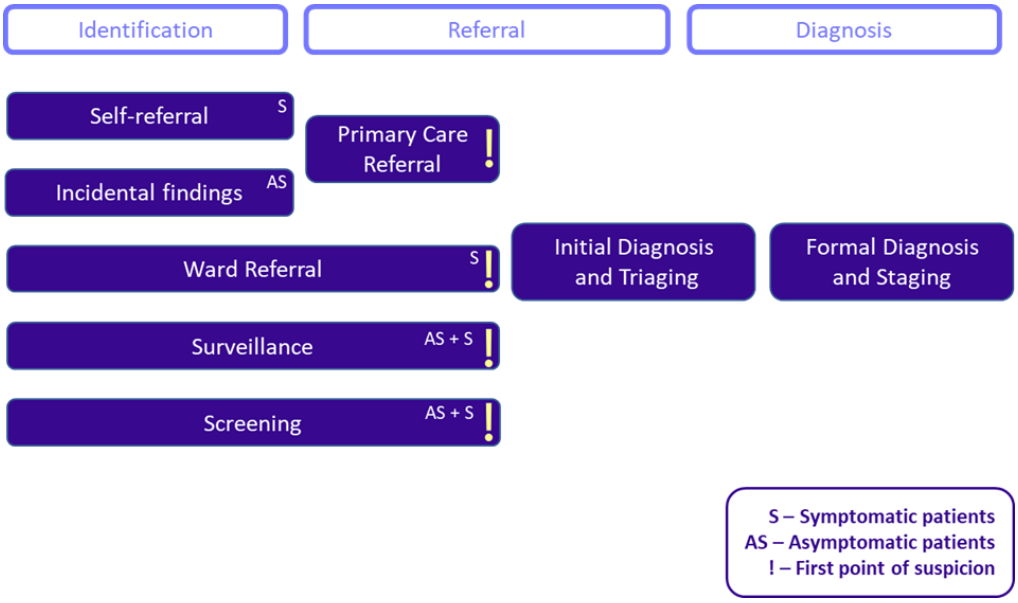

Figure 4. Patient pathways facilitating ED&D in Wales for symptomatic and asymptomatic patients, and likely locations of first point of suspicion in the SCP.

- Is this summary of simplified diagnostic pathways correct?
- Are there other key initiatives that are also important to the future of cancer ED&D?

4. Early diagnosis and detection: innovation longlist

We have critically appraised key innovations for their potential to improve cancer ED&D in Wales. We have defined improvement as:

- Fewer patients diagnosed with late-stage cancer due to earlier diagnosis - with consequential pre-cancer and early-stage cancer
- Helping to close the gap in cancer outcomes between our most and least deprived communities
- Demonstrating efficient and cost effective workforce and resource utilization
- Minimising the risk of overdiagnosis, and medicalization of patients with inconsequential disease that would not affect quality of life, morbidity, or mortality in its natural course
- Enhancing the diagnostic infrastructure to provide system- and patient-benefit diseases beyond cancer
- An innovation that could reasonably be adopted and implemented within a 3-10 year timescale.

The key innovations that have emerged from our desk review as offering particular potential to improve diagnostic outcomes are summarised below. Figure 4 below tentatively maps them to a simplified diagnostic pathway.

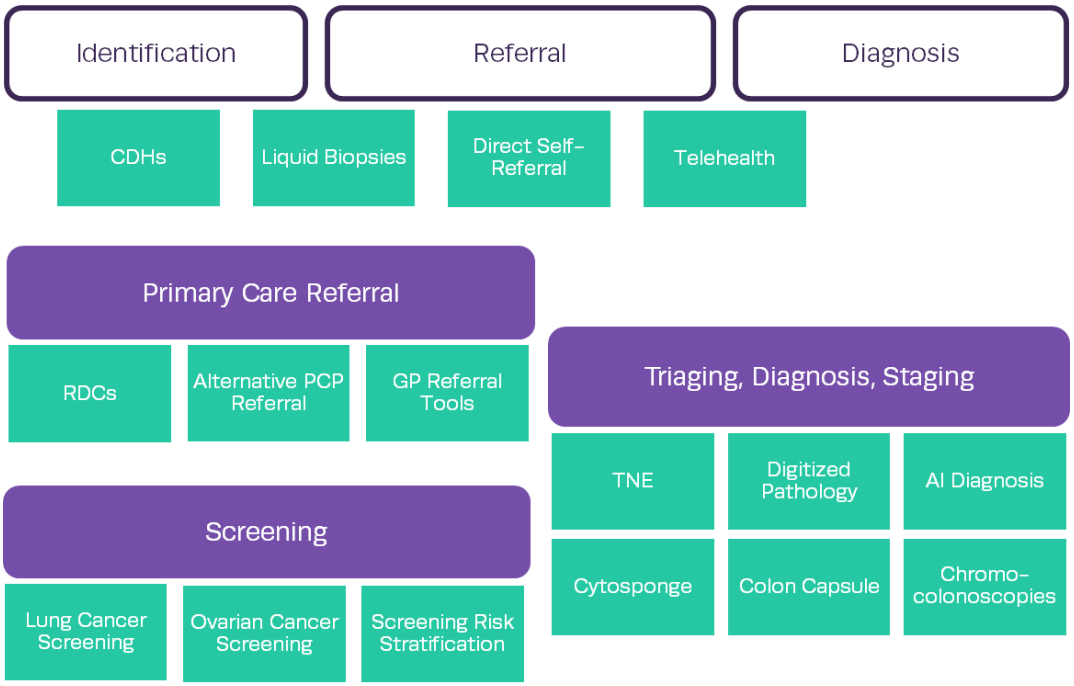

Figure 4. Innovations identified by MCI as part of the ED&D scoping paper. CDH: community diagnostic hub; RDC: rapid diagnostic centre; PCP: primary care provider; TNE: trans-nasal endoscopy.

Innovation 1 – Lung Cancer Screening

Lung cancer remains among the largest causes of cancer mortality in Wales, and late diagnosis significantly drives this, with 44.9% of patients diagnosed at stage 4.[27]

There is evidence that targeted lung cancer screening has a significant impact on stage of diagnosis and mortality. Most notably, the NELSON trial in the Netherlands, invited 7,557 participants aged 50-75 with a smoking history for low dose CT scanning for lung cancer at 1, 2, 4, and 6 years.[50] Screening procedures identified over 95% of cancers that occurred in the first two years.[50,51] Overall, 48.8% of detected cancers were stage 1-2 (compared to 23.4% in the non-screening control), and 10 years post-randomization, lung cancer mortality was decreased by 24% in men and 33% in women.[52] Other promising results were found in the similarly designed UKLS trial, where 85% of detected cancers were stage 1 or 2, and 83% of identified cancers were treated with curative-intent surgery.[53] Meta-analysis of lung screening trials found an overall 19% reduction in risk of lung cancer mortality, and 4% reduction in risk of all-cause mortality, though the latter was not a statistically significant difference.[54] Further, trials are ongoing of multimodal screening approach, using liquid biopsy to deliver more accurate diagnostic pathways, in a more-cost effective diagnostic workup.[55]

Population-level screening does bring risk of overdiagnosis. NELSON mitigated this risk by prioritizing patients with smoking history, using follow-up tests after identification of nodules, and using screening history as a risk stratification tool.[50,51] The UKLS trial used a model from GP-level data to identify patients with a 5% risk of lung cancer.[53] 2.1% and 5.7% of participants in each trial tested positive, with 0.58% and 2.1% respectively being subsequently diagnosed with lung cancer, in agreement with findings of meta-analysis that approximately half of positive screens are overdiagnosed. The overall risk of being overdiagnosed over a 10 year period in these programs is between 8.9-20%.[52,54,56] Given the lead time from detectable nodules to symptomatic cancer is often over 12 years, this overdiagnosis rate may come down. However, if this lead time is longer than a patients' life expectancy, then it effectively still represents overdiagnosis.[57] Positively, meta-analysis suggests that this overdiagnosis does not have a significant effect on mortality.[54]

These interventions are also shown to be cost-effective, with the UKLS trial showing £8,466 spent per quality-adjusted life year (QALY) gained, significantly below the lower boundary of acceptable cost-effectiveness as judged by NICE.[53,58] Other modelling has yielded figures from 21,100 EUR/QALY, and 27,600 EUR/QALY based on the NELSON study, and 15/27 screening scenarios costing below 50,000 EUR/QALY in Switzerland, with associated reductions in lung cancer mortality between 6-16%.[59,60] In addition, the use of lung cancer screening programs to leverage smoking cessation has the potential to further improve cost-effectiveness further.[60] Initial investment in setup can however be a barrier to implementation.

The Yorkshire Lung Screening Trial (YLST) affords one potential model for Wales. It provides a population-level lung screening programme for 5.2 million people. It targets at-risk communities, utilises mobile scanning units and places emphasis on changes to language such as 'Lung Health

Checks'.[61,62] In addition, 23 sites in England are rolling our targeted lung health checks, and being evaluated in cost-effectiveness terms by NHS England.[63]

- There is high–quality evidence available, suggesting in principle that this innovation should be of cost–effective benefit to patients in Wales.
- We understand that a scoping paper on Lung Health Checks has been delivered to the Wales Cancer Implementation Group, and there are early plans for an implementation pilot in 2022. [193]
- We understand that the UK National Screening Committee are currently undertaking a cost–effectiveness analysis of lung health checks, from which recommendations are expected to be deliver this year.

Innovation 2 – Ovarian Cancer Screening

Approximately 50% of patients with ovarian cancer are diagnosed at stages 3-4 in Wales, and diagnoses could be made earlier with ovarian cancer screening.[27]

Evidence for reducing the stage at diagnosis and improving mortality through ovarian screening is unclear. The most relevant example of asymptomatic ovarian cancer screening is the UKCTOCs trial with recruited 50,640 women aged 50-74 for multimodal screening of ovarian cancer. 0.7% of these women received ovarian cancer diagnosis (40% at stages 1/2/3), compared to 0.6% in the control group (26% at stages 1/2/3).[64] A statistically nonsignificant 15% reduction in mortality was observed in the 14 years post-randomization, growing mostly in years 7-14. This mortality reduction is a matter of considerable controversy: with another 4 years of follow-up yet to be reported, it may become a significant difference.[65,66] However, significant criticisms have been made of the UKCTOCS protocol, with critical features such as the exclusion of peritoneal cancer argued not to be possible.[67] Previous trials of ovarian cancer screening, with and without risk stratification retrospectively applied, have failed to demonstrate a reduction in mortality.[68,69]

Overdiagnosis is relatively rare, but not without consequence. The multimodal strategy employed in UKCTOCS applied the ROCA risk stratification tool pre-screening to mitigate overdiagnosis, which has previously been shown to have 99.9% specificity.[70] As a result no overall difference in ovarian cancer rates were found between screening/no screening groups, suggesting overdiagnosis was minimal. Conversely, as a result of the diagnostic workup, 14 false positive surgeries were performed per 10,000 patients screened.[64]

Though reported values vary, almost all studies agree that ovarian cancer screening is not cost effective at a threshold of £20,000-30,000/QALY,[58] with modelling based on the UKCTOCS trial reporting values between $585,000-763,000/QALY,[71] separate modelling in a US population at $106,000-155,000/QALY,[72] and a within-trial measure in a UK setting at £91,0000/QALY, although when testing was discounted and the model was extended out to study population life expectancy, cost-acceptability was approached.[73]

Social inequalities in cancer care could be addressed by ovarian screening, as a more deprived background is associated with a later stage of diagnosis and screening programs could help to close this gap.[74]

Ovarian cancer screening would require significant investment in resources, and whilst no examples of population-level screening are available in jurisdictions similar to Wales, the UKCTOCS trial does provide precedent of large-scale implementation.[64] Implementation of ovarian cancer screening would require significant investment in infrastructure, staffing, and patient outreach.

- The high-quality evidence currently available suggests it is unclear that ovarian cancer screening programmes would represent a benefit to either mortality or quality of life for Welsh cancer patients.
- To our knowledge, no plans are in place to establish ovarian cancer screening in Wales.

Innovation 3 – Screening Risk Stratification

Population-level screening programs are powerful tools in detecting cancer early, but are also very resource-intensive, and carry the inherent risk that screening more people leads to more overdiagnosis. In US national lung screening programmes, it is estimated that screening of the highest risk 10% of patients costs $22,000 less per life saved than screening of the lowest risk 10%.[75] In the UK, for every 10,000 women screened for breast cancer, whilst 43 deaths are prevented, 129 breast cancers are overdiagnosed, meaning they would not have affected patients in their natural course.[76]

Risk stratification algorithms seek to identify patients most at risk of cancer within populations, allowing for better selection of screening populations, and more intensive screening to be targeted to those that might benefit most, thus achieving a more favourable balance of benefits and harms and better resource utilization.

Risk stratification algorithms are well developed in breast cancer and are accurately able to distinguish high-risk patients. The BOADICEA risk algorithm includes a variety of factors such as age, lifestyle, and genetic factors[77,78] and has been able to identify a 44% share of the screening population who will develop 62% of breast cancers.[76] This includes 14.7% of the population with a 17-30% risk (requiring moderate-intensity screening), and a 1.1% of the population with a >30% risk (requiring high-intensity screening).

The literature suggests that this approach could reduce resource use and overdiagnosis. For example, one study modelled a hypothetical Dutch cohort of women at higher and lower risk of breast cancer, where reducing the screening threshold age for high-risk women and reducing the screening intensity of low-risk women led to savings of EUR 1,043-2,821 per life year gained, an increase in life years saved, and a 33% decrease in overdiagnoses.[79]

Whilst risk stratification is most developed for breast cancer,[78,80] tools with similar levels of predictive value and potential to improve service provision are being developed in colorectal cancer,[81–83] lung cancer,[75] and hepatocellular carcinoma.[84]

Considering limited direct evidence for efficacy in similar health systems, the timeframe of implementation could be extended if pilot studies and/or modelling needed to be performed to assess the likely impact of screening risk stratification in Wales. If the Welsh NHS were to subsequently adopt this innovation, it would likely be relatively fast and low-resource to implement. Surveys show that 84% of primary care providers are already using computerized risk tools for various chronic conditions based on GP-level data, and the most advanced breast cancer tool, BOADICEA, is freely accessible via the online platform CanRisk.[85]

- With medium-quality evidence available, acknowledging no top-quality record of implementation in real-world practice yet available, our appraisal suggests screening risk stratification could be a plausible way to minimize costs and overdiagnosis, and maximize benefits in screening programmes.
- Welsh screening is currently provided on a universal basis, limited only on the basis of age. The UK National Screening Committee advises all four nations on scope, approach and implementation of screening programmes, reporting to the four nations' Chief Medical Officers. Any changes would almost certainly require NSC endorsement.
- Unknowns include the availability of information required for more sophisticated risk stratification.

Innovation 4 – GP Tools for Cancer Recognition

In healthcare systems with strong gatekeeping similar to Wales, as much as 85% of cancer diagnoses come through primary care referral.[86] 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.[87] In a survey study, less than half of UK GPs could correctly identify which of a number of patient vignettes should be referred to cancer services.[88] Thus, a variety of innovative tools have been developed to educate and assist GPs in accurately assessing the risk of cancer.[89–92]

GP education tools can increase cancer referrals and diagnosis. Addition of physical risk assessment tools (printed on mouse mats, flip charts, etc.) to 165 UK GPs led to 31% and 26% increases in referrals for lung and colorectal cancers, and the detection of 57 additional cancers in a 6 month period.[93] Continuing medical education, as part of improvements to Danish cancer services, produced a significant increase in understanding of cancer risk, a doubling in urgent cancer referral rates, and a significant decrease in the number of GP contacts prior to cancer referral.[94,95] C-the signs, an online decision support tool that covers a wide spectrum of cancers, has been associated with successful cancer outcomes in UK practice.[90,96] Gateway-C education modules for recognition of lung and colon cancer have undergone a successful pilot scheme, and are currently being rolled out across Manchester.[89] Several clinical trials are underway investigating further tools in UK general practice, with the support of NHS England and NHS Improvement.[97,98]

As well as increasing cancer recognition and referral, these innovations are generally associated with easy rollout, high uptake, and efficient resource-use.[96] Earlier trials of risk assessment tools did encounter some barriers to effective implementation, such as inconsistent and time-consuming input of patient histories, and conflict between tool output and the clinician's intuition.[99] The ongoing development has enabled continual refinement and a number of GP tools for cancer recognition have in recent years been associated with high levels of GP buy-in.[85,100]

The WICKED research team at Bangor University have, through systematic review and collaborative study design with Welsh clinicians, developed the ThinkCancer platform. This combines GP education and the appointment of cancer champions in general practice.[91] A randomized controlled trial is currently underway across 30 Welsh GPs, to assess the feasibility, clinical effect, and cost-effectiveness of the ThinkCancer intervention.[43] Given the widespread nature of this study, and the fact it is adapted specifically for Welsh practice, it may represent an ideal staging post for implementation of this innovation in Wales.

- Our review has identified high–quality evidence suggesting that this innovation improves early cancer detection.
- We are aware that, on top of primary care practices participating in the ThinkCancer trial, an array of cancer recognition tools and education programmes are in use by some Welsh GPs; our understanding is that no one tool or set of tools has been specifically endorsed or integrated.

Innovation 5 – Digitization of Pathology

Alongside radiology, pathology is the major workhorse in the final diagnosis and staging of cancer. Whilst traditional pathology mostly involves the indexing and analysis of physical slides, a digitized pathology workflow involves the scanning of a digital whole slide imaging (WSI) for digital storage and analysis.[101] This approach is widely regarded as the next step in pathology, and is endorsed by the Royal College of Pathologists.[102]

Digitization of the pathology workflow is associated with an increase in throughput and analysis of pathology and a decrease in resource utilization. For example, digitization of histopathology in a multicentre hospital network in southern Spain led to a 21% increase in case output, and whilst a screening error rate of 1.5% was initially measured, this became negligible after the implementation phase.[101] Negligible scanning fail rates were also seen in a Catania hospital which switched to digital pathology as an emergency remote digital pathology workflow in response to the COVID pandemic. They found 100% major diagnostic equivalency was achieved with traditional glass analysis.[103,104] Finally, in a study of 22 pathologists across 7 Welsh hospitals from April-December 2016, concordance between digital and glass analysis was 97.1%, and sensitivity of 98.1% was demonstrated for digital diagnosis, all of which is in-line with published literature and standards for pathology. Though the study did not report turnaround time or workforce effects, a strong managerial support for efficiency was cited as essential for study implementation.[105]

Surveys show that pathologists in a nondigital setting regard 'being efficient' as the most challenging aspect of their work,[106] and digital pathology has the potential to improve this workforce pressure. In the southern Spain hospital network, one scanner could handle the entire slide volume of a central Granada laboratory. Before conversion, 3 histotechnicians had been employed full-time for slide storage, sorting, and quality checking, as compared to half the time of 1 histotechnician post-conversion. In addition, digitized images could be freely shared around the network, minimizing the need for travel.[101] Other literature has documented the use of digitized pathology for training purposes.[107] Implementing digital pathology in a Catania hospital was reported to represent an opportunity to standardize and streamline pathology workflows.[106] Finally, as pathology is not only used for cancer diagnosis, an enhanced pathology workflow will have pan-disease benefit for secondary care settings.[108]

A fully digitised pathology system offers the opportunity to share workloads across health boards and regions, and across roles and specialities - and so enabling staff to work at the top of their licence, and making the most of the whole Welsh pathology workforce. Barriers to implementation are predominantly the investment in whole-slide scanners, IT infrastructure, and training.[109] However, government funding has supported the establishment of digital pathology (and addition of AI to these systems) in the UK through institutions such as PathLAKE, the NPIC and iCAIRD, with a total funding commitment of £50m, which will provide pilots and examples of implementation, and a number of regulator approved commercial solutions for digital pathology, with digital infrastructure and training included, are available.[106,107,109,110]

- The available high–quality evidence indicates that a digitized pathology workflow would be likely to lead to faster diagnosis, with more efficient workforce requirements, and without compromising accuracy. There may however be an increased resource demand in the transition phase.
- Outside the trialed 7 hospital sites with WSI technology, we are as yet unclear on forward plans for digitized pathology across Wales.

Innovation 6 – AI and Machine Learning for Diagnosis

Analysis of pathology and radiology images by artificial intelligence (AI) has long been touted as the future of diagnostics. By training machine learning algorithms with thousands of images to produce AI systems which assist human pathologists and radiologists, it is hoped that diagnoses can be made faster, with more accuracy, and that time and resource pressures on diagnostic staff could be relieved.

Numerous AI systems have been developed with comparable or superior diagnostic value to human analysis, both in terms of cancer detection and mitigating the risk of over-diagnosis. For example, an AI system to diagnose and grade prostate cancer biopsies achieved extremely high sensitivity to malignancies, with only a very small number of false positives, and with significantly lower intra-observer variability than is usually observed with pathologists.[111,112] Similar AI has been developed for predicting lung cancer, outperforming the current gold-standard analysis technique of the British Thoracic Society,[113] for discriminating malignant breast tumours, outperforming radiologists in predictive value and producing a 5.7% reduction in false positives[114] and detecting early-stage breast cancer, where more cancers were detected than by pathologists with fewer false positivies.[115] AI analysis can also be delivered in a more disruptive fashion, such as in the development of an algorithm which can diagnose melanoma from smartphone images, with similar sensitivity and specificity to physicians.[116]

Whilst individual AI solutions have proven powerful, such approaches are generally extremely specific to their designed purpose and are not currently a panacea. Performance can drop when AI programmes are moved away from their training dataset, for instance in prostate cancer grading, where correlation with pathologists fell by 10% in the validation dataset compared to the training dataset,[111] or in breast cancer detection, where reduction in false positives was 5.7% in US women but only 1.2% in UK women.[114] AI training can be modified to mitigate this specificity,[115] but given the 'black-box' nature of AI systems, it is seldom possible to detect causes and solutions to such transferability problems when they arise.[109] As such, AI systems need to be carefully validated in their specific task before use and their most likely use in the mid-term future is as an aid to human decision making. This may lead to more efficient diagnosis, such as in the addition of AI analysis to the standard double-reader UK system for breast cancer diagnosis, which reduced the workload of the second reader by 88%, with non-inferior overall performance.[114,117] Implementation of AI analysis requires a digital workflow, and whilst this in place for radiology,[118] pathology in Wales would need to be digitized (as described in Innovation 5 above). However, conditions today are perhaps fertile for rapid digitisation, with digital diagnosis pathways seeing significant uptake and training from clinicians in light of the COVID pandemic, and several AI tools for diagnosis gaining regulatory approval.[119] Finally, as with digitized pathology, government funding is supporting the establishment of digital AI in the UK through schemes such as PathLAKE, the NPIC and iCAIRD, with a total funding commitment of £50m, which will provide pilots and examples of implementation.[109]

- Our review detected medium-quality evidence for AI-assisted diagnosis at this point in time: data from analytical validation was generally positive, but no records of clinical validation in a real-world setting were available.
- Many AI solutions offering promise in principle are currently under development, and so the evidence picture may change rapidly in coming years. We are not yet clear how large a role AI currently plays in both in-house diagnostics and outsourced reporting.

Innovation 7 – Chromocolonoscopy

White-light colonoscopy is currently the gold-standard for diagnosis and staging of colon cancers.[120] Chromocolonoscopy is a technology which involves the additional application of fluorescent dye during the colonoscopy procedure, and may increase detection of pre- and early stage cancer.

Consensus is being reached that chromocolonoscopy enables enhanced detection of pre- and early stage cancer. A clinical trial in Wales of patients who testing positive in bowel cancer screening found that chromocolonoscopy detected twice as many proximal serrated lesions (12% vs 6%), which cause approximately 20% of interval colon cancers. As a result, significantly more patients were placed on high-risk surveillance.[120] Similarly, a cap-assisted chromoendoscopy trial (CAP/CHROMO) in the US produced a significantly higher adenoma detection rate, and significantly more patients with at least 1 proximal colon adenoma.[121] Cochrane systematic review of chromocolonoscopy found it was like to detect more people with at least one neoplastic lesion,[122] and separate meta-analysis has reported that is displays a significantly higher sensitivity for detection of early-stage CRC.[123]

Concerns over time-intensiveness and cost have prevented chromocolonoscopy from becoming standard of care, but preliminary evidence suggests these problems may be small. In Welsh trials, the extra time taken for chromocolonoscopy was well within a pre-specified window of 15 minutes, with a mean difference of 6.3 minutes.[120] Similarly, the CAP/CHROMO study found only a 2 minute increase in time associated with the procedure.[121] Calculations from the Welsh study indicated an extra cost of chromocolonoscopy of £81 per procedure,[120] and whilst in a sub-population, a modelling study has suggested that a chromocolonoscopy platform results in overall less spend than white light endoscopy for colon cancer surveillance in patients with ulcerative colitis.[124] Further innovation may continue to drive down costs, such as an oral formulation of the dye, taken the day before, which lead to a significantly higher adenoma detection rate than placebo (56.3% vs 47.8%), with no significant increase in false positives.[125]

Implementation in Wales would have the advantage of the foothold provided by the Welsh trial, which 12/24 colonoscopy centres available to the bowel screening Wales program, and could provide an invaluable stepping stone to nationwide rollout.[120] Implementation in Wales would have the advantage of the foothold provided by the Welsh trial, which 12/24 colonoscopy centers available to the bowel screening Wales program, and could provide an invaluable stepping stone to nationwide rollout.[120]

- Medium-quality evidence was identified for chromocolonoscopies, with studies demonstrating an increase in pre-cancer detection. However, this work has not been underpinned by cost-effectiveness data, has not demonstrated a stage shift in cancer diagnosis in a tested population, and there is little evidence addressing the possibility of overdiagnosis with a test more sensitive to pre-cancer.
- We are aware that chromocolonoscopy is a relatively simple innovation to implement, but are unclear on whether it continued as clinical practice in the 12 trialed Welsh sites.

Innovation 8 – Rapid Diagnostic Centres

Only half of symptomatic patients who present to GPs do so with classical 'red flag' symptoms.[126] In traditional referral practice, patients presenting with low-but-not-no risk symptoms may experience significant delays before symptoms are recognized and diagnosis is performed. In Denmark, in response to this unmet need, Rapid Diagnostic Centres (RDCs) were instituted, allowing for faster testing of patients with vague symptoms, and referral on to secondary care for those with positive findings.

RDCs increase the number of cancer diagnoses and shorten diagnosis delays. An RDC in the Swansea Bay Health Board lead to mean diagnosis times of 5.9 days if at the clinic, and 40.8 if referred onwards from the clinic, compared to 84.2 days in normal clinical practice.[14] Of those attending another RDC pilot in Cwm Taf, between 7.2-12.3% received cancer diagnoses, with a mean time to diagnosis of 34 days.[127] An RDC based in Guys hospital, London, diagnosed 7.2% of attendees with cancer, with a mean time to diagnosis of 28 days, and 40% of patients received curative-intent therapy.[128,129] Success has also been seen in site-specific RDCs, for instance in a lung RDC in Canada, which was associated with a 24 days reduction to time to first treatment,[130] and an Australian same-day prostate cancer RDC, with clinically significant prostate cancer discovered in 34% of attendees.[131]

RDCs are also an efficient use of spend and resources, for cancer and pan-disease services. GPs participating in the Cwm Taf RDC pilot reported a high-speed and straightforward referral service, and a reduction in stress.[127] Modelling based on the Swansea Bay RDC indicated it ran at a cost-effectiveness of £29,732/QALY compared to a non-RDC model during its start-up phase. Further, when running at over 80% capacity (after start-up the RDC typically ran at ~95%), the RDC model was both more clinically effective and cheaper overall than non-RDC diagnosis.[14] Finally, 35.8% and 35.9% of patients seen at Guys and Cwm Taf RDCs were diagnosed with a significant non-cancer disease, proving the RDCs value to pan-disease diagnosis.[127,129]

Data suggests that RDCs help to close deprivation gaps in cancer care. The Guys RDC predominantly served patients from within the most deprived indices of London, with 74.6 of noncancer patients and 70.9% of cancer patients from London's 50% most deprived backgrounds.[129]

- High quality evidence has been published regarding the cost-effective benefit of RDCs, including their suitability to serve more deprived areas.
- The evidence identified supports the expansion of the RDC vague symptom pathway, which is currently being taken forward by the Wales Cancer Network in partnership with the Swansea Bay pilot RDC team. MCI is supporting the extension of the one-day diagnosis philosophy to site-specific pathways in Wales, with independent evaluation.

Innovation 9 – Referral from Alternative Primary Care Sites

The majority of the public interact with primary care providers other than GPs (such as dentists, opticians, pharmacies) on a regular basis. One study of 33 pharmacies found that 642 patients presented with alarm symptoms of cancer over a 6 month period.[132] Some schemes have leveraged this interaction to enable early detection of cancer, by giving these sites direct access to secondary diagnostic care.

Small-scale studies of referrals from alternative primary care sites show that they are able to refer the appropriate patients into cancer care. In a pilot of pharmacy referrals for suspected lung cancer, 55/60 were deemed appropriate referrals by secondary care,[133] a high proportion of patients referred from the South Tees Optician Referral Project (STORP) with suspected head and neck cancer were similarly appropriate,[134] and systematic review of oral cancer referral has found no significant difference in referral patterns or quality from GPs and dentists.[135]

Preliminary results from small-scale pilots indicate that these schemes can identify cancers early. Under the Cancer Research UK (CRUK) Accelerate Coordinate Evaluate (ACE) program, the STORP program lead to 17 patients referred to secondary care, of whom 1 was diagnosed and underwent curative therapy, within 8 days of cancer suspicion.[134] Despite problems of limited resourcing and buy-in, 55 and 17 patients were referred from two other pharmacy referral schemes under the ACE program.[133,136]

These pilots have also demonstrated pan-disease diagnostic benefit: STORP identified 6 patients with stroke symptoms,[134] and the pharmacy referral pilot for lung cancer found undiagnosed COPD in 14/47 patients who attended referral.[136]

Evidence suggests pharmacy-driven diagnoses may be useful in closing iniquities in cancer care. In Wales, pharmacies are more likely to be located in deprived areas,[137] and in an English prospective study, a higher number of alarm symptom presentations per pharmacy were found in higher deprivation areas.[132]

- Our review identified only low-quality evidence in support of alternative primary care referral, though some small, noncomparative studies demonstrated feasibility.
- Besides dentist referral for oral cancer, we are unaware of any Welsh provision or pilots for referral from alternative primary care sites.
- With promising small-scale results, the CRUK ACE program provides implementation examples, with learning for future pilots, which might offer potential in Wales.

Innovation 10 – Community Diagnostic Hubs

As a combined result of successful community pilots, and the overwhelming of acute healthcare provision during the COVID pandemic, Sir Mike Richards, in his independent review of diagnostics in England, recommended the implementation of community diagnostic hubs (CDHs). These have multiple forms, but generally represent entirely elective, COVID-cold diagnostic centres, positioned in the community for easy, equitable access to cancer diagnosis.[138]

The Manchester CT study demonstrates that a CDH can deliver early diagnosis in a cost-effective, equitable manner. Patients at risk of lung cancer were invited, via their GP, to attend a lung health check at a mobile unit positioned within the community, most commonly at shopping centres. 1,384 patients were screened, 3% of whom had lung cancer, 80% of which was early stage, and 65% of whom underwent surgical resection. Curative-intent therapy was offered to 89.1% of lung cancer patients. No interval cancers were detected between rounds of attendance, and in the second round, 90% attendance was recorded, with a cancer incidence of 1.6%, 79.1% of which was early stage. Over the entire program, only 0.4% of cancers were missed, 2.8% of positive patients were overdiagnosed, of whom only 4 were subjected to any invasive procedure, and no surgery was performed for benign disease. 75% of attendees were ranked in the lowest deprivation quintile in Manchester.[61,139] All these benefits were gained in a cost effective manner, with a modelled in trial cost-effectiveness of £10,069/QALY.[140]

Separation of acute and elective diagnostic procedures could lead to increased efficiency in diagnostic services in 'cold' centres as currently 85% of ultrasounds, 59% of CT scans, and 86% of MRIs are elective.[138] Other potential benefits of CDHs include a reduction in diagnostic equipment costs through bulk buying, and shorter hospital stays, through tests undertaken on the day of request.[141] These CDHs could also have pan-disease benefit, facilitating diagnosis of a variety of cardiorespiratory, musculoskeletal, or urological conditions.[142] It is hoped that such efficiencies can be used to clear the diagnostic backlog from the COVID pandemic.[143] Indeed the pandemic has enhanced the focus on this as a way of protecting services.

In light of Sir Mike Richard's report, CDHs are being rolled out across England, with the aim of roughly 3 established per million population,[138] which in combination with established CDHs, such as the successful pilot locality hubs in North West Surrey,[144] will provide numerous validation exercises of their effect, and examples of their implementation. If buy-in is achieved, changes as a result of the pandemic, such as the establishment of 'cold' community phlebotomy centres, could be leveraged as a foothold for the establishment of CDHs in Wales.[143,145]

- Whilst we identified high–quality evidence supporting the community lung CT scan, only low–quality evidence is yet available for the broader service innovation proposed by Sir Mike Richards, though this low–quality evidence plausibly supports their effectiveness.
- Cancer specific RDCs might be seen as a forerunner of CDHs; we understand two health boards have plans to develop CDHs but it is as yet unclear how these two developments will evolve.

Innovation 11 – Telehealth

With the advancement of remote working over recent years, service models have been innovated and piloted that take advantage of telecommunications, aiming to deliver cancer care with greater efficiency.

Primary care telehealth, where patients undergo a virtual consultation via video calling, is associated with greater efficiency but the effect on quality of care is currently unclear. Implementation of tele-appointments in a GP setting has been associated with an 18% drop in physical consultations, but an overall increase of 75% in total consultations.[146] Further, 75% of GP consultations during the peak strain of COVID were conducted virtually.[147] Whilst some GP education tools have been developed specifically for accurate cancer recognition via telehealth,[147] little evidence of their efficacy is available. If factors known to benefit effective ED&D, such as continuity of care,[148] could be preserved, telemedicine could plausibly be effective in this setting, but currently lacks any evaluation a real-world setting.

Nonsynchronous analysis of pathology/radiology is another form of telehealth, where images are sent remotely for efficient examination, ideally by subspecialty experts. Such systems are contracted out in Norway, Scotland, Germany, and parts of England, with a variety of private providers displaying a high degree of diagnostic accuracy.[149,150]

Telepathology/teleradiology can enable rapid and accurate diagnostic processes where implemented well. In an analysis of 124,870 cases from 62 California hospitals by just 10 radiologists, teleradiology assessments had a mean turnaround time of 12.2 minutes, with 99% delivered within an hour, and a rate of major disagreement with in-person radiologists of only 0.13%.[151] Trials of a telepathology network in Quebec found 98% total concordance with in-person pathologists, with an average turnaround time of just 20 minutes. The network also allowed for rapid pathology analysis from sites not employing a pathologist, reduced time-intensive referral between hospitals, reduced isolation of pathologists, and enabled local hospitals to retain their surgical services.[152] Remote radiology and pathology more generally can afford efficiency savings through economies of scale, and are generally regarded as a cost-effective use of resources.[153]

If telehealth, for either primary care or diagnosis, were to be considered further in Wales, accounts and recommendations on a successful transition have been published,[154] as well as example pilots such as Telemedicine Clinic (a private provider) reporting radiology for a targeted health programme in Doncaster.[155]

- We identified medium-quality evidence suggesting GP consultation is more efficient in a virtual setting, but found none on whether this affects quality of diagnosis.
- We are aware that many Welsh GPs in Wales have introduced virtual or telephone consultations in response to COVID-19; narrative 'good practice' research suggests these are likely to remain part of the mix of channels through which to access primary care – but the picture is evolving.
- We identified high-quality evidence that off-site reporting of digitized radiology/pathology leads to more workforce-efficient and faster turnaround of diagnoses, with an acceptable degree of quality in reporting. The effectiveness of the underpinning organisational or outsourcing arrangement was outside the scope of this review.
- We are aware that some radiology reporting in Wales is currently contracted out, but not of their extent. We are also aware that there are training requirements associated with off-site reporting, and that this may be difficult in the short-term given the radiology/pathology workforce challenges Wales is currently facing.

Innovation 12 – Self-Referral to Specialist Care

In Wales, when patients self-refer into the system, they must first be seen by a primary care provider. If cancer is suspected, the patient will then be referred onwards to the appropriate secondary cancer care service. A large portion of diagnostic delay has been associated with this primary care interval[156] and European countries in which primary care gatekeeping is more stringent have also been associated with worse cancer outcomes, with no measurable reduction in healthcare costs.[157]

Data on the efficacy of schemes which allow for direct self-referral into specialist care are mixed. Analysis of direct self-referral for cancer in five US states found that it was associated with slightly higher rates of curative surgery.[158] However, a self-referral scheme which was implemented for breast cancer in the US from 1991-2010, which was responsible for 50% of all breast cancer diagnoses, found no difference in stage of presentation between self-referred and healthcare-referred patients.[159] Finally, studies of countries with stronger gatekeeping and worse cancer outcomes[156,157] have not to date fully demonstrated that the requirement for a primary care referral to access specialist care is a *cause* of poorer outcomes in those countries and there is currently no evidence that complete bypassing of the gatekeeper function improves cancer outcomes. While non-exhaustive, from our review other innovations such as RDCs and GP education tools, have stronger causative evidence of delivering earlier diagnosis through reducing this interval.[14,129,148]

Some evidence suggests that direct self-referral can exacerbate healthcare inequalities. Retrospective analysis of self-referral in the US found that it was disproportionately used by white patients, patients with higher incomes, and patients with college degrees, and schemes to circumvent gatekeeping are generally associated with an increase in healthcare inequalities.[157,158]

- We were able to identify only low-quality evidence for this innovation, and with no comparative studies of direct self-referral in isolation from other factors, it is difficult to assess the likely impact of any trial in the Welsh NHS.
- Beyond private service provision, we are unaware of any direct self-referral schemes in Wales.

Innovation 13 – Liquid Biopsies

Liquid biopsies are a diverse group of technologies, characterized by molecular analysis of a liquid sample (blood, serum, urine) with the potential to improve diagnosis, prognosis, and the application of personalized medicine in cancer care. As they relate to cancer ED&D, two major categories have evolved so far: pan-cancer detection, and target-cancer screening. There are many players in this emerging market, and so here we focus on some key examples in each category.

Pan-cancer detection

The GRAIL Galleri test is a multi-target analysis of circulating DNA methylation, allowing for detection of over 50 cancer types. The GRAIL test has been analytically validated as a screening intervention, detecting cancers in asymptomatic patients. Whilst overall sensitivity to cancers was acceptable, differences in stage may limit its utility as a tool for ED&D: sensitivity for stage 1, 2, 3, and 4 cancers was 39%, 69%, 83%, and 92%, respectively. Specificity was high, with just 0.5-0.7% of false positive results. The test was able to identify the site of origin of 89% of identified cancers.[160,161]

A partnership has been agreed between GRAIL and the NHS, rolling out a pilot of the Galleri test to 140,000 asymptomatic patients aged 50-79 in England and Wales, who will receive a blood test every three years. Another 25,000 people referred from primary care will be offered the test as a means of triage. Whilst the precise design and aims of the study are not yet published, it should help to establish the feasibility and likely impact of GRAIL screening in a Welsh setting.[162162]

PinPoint is another pan-cancer test, being developed at Leeds University, which combines measurement of various regularly taken blood analytes and patient history to provide an overall risk of cancer.[163] PinPoint is currently undergoing a service evaluation in West Yorkshire and Harrogate, as a means of triaging patients referred from primary care, and is being integrated into their diagnostic workflow for the 9 most prevalent cancers.[164]

Target-cancer screening

Epi ProColon is a test for bowel cancer, by detection of circulating DNA in blood. In trials, it has displayed a sensitivity to bowel cancer of 75-81%, and a specificity of 96-99%, similar to the current performance of FIT testing.[165] Real-world studies in the US have shown slightly lower sensitivity than FIT testing, however this may be offset by greater acceptability of the blood test compared to the unpleasant process of sample collection for the FIT test.[166] For example, in one study 97% of patients refusing screening colonoscopy accepted an Epi ProColon test, compared to 37% accepting FIT testing.[165] Modelling based on reported adherence to each screening method shows that Epi ProColon may have a greater overall early detection and clinical benefit that FIT testing.[167]

Another liquid biopsy for colon cancer screening is CanSense, being developed in Swansea using Raman spectroscopy to analyse blood samples quickly and cost-effectively. It has displayed 83% sensitivity and 83% specificity for colon cancer in published testing, and could be used either as a screening or a triaging tool.[168]

- Medium-quality evidence plausibly shows that liquid biopsies could be of benefit to Welsh patients
- Given the relatively low resource-intensity and high throughput of such tests, in principle they could be used in Wales within a 3-10 year timescale. With the field developing rapidly, and new products being regularly tested and approved, bodies such as Health Technology Wales (HTW) may be well positioned to provide up-to-date appraisals of new platforms.

Innovation 14 – Cytosponge

Cytosponge is a novel diagnostic test, whereby a condensed sponge in a biodegradable capsule on a string is swallowed. The capsule degrades in the stomach, and the sponge is pulled back up, collecting tissue from the oesophagus for AI-assisted analysis, enabling detection of Barrett's oesophagus (BE), which is a key risk factor for oesophageal cancer.

Cytosponge accurately detects BE. A systematic literature review found the intervention both specific and sensitive for detection of BE.[169] A illustrative trial found 140 diagnoses of BE in the cytosponge group, compared to 13 in the control group.[170]

Triaging of patients using cytosponge can enable sensitive and cost-effective diagnosis of cancer patients. For example, cytosponge has been used to triage urgent endoscopy referrals in Cambridge, and identified a cohort with 50% cancer incidence.[171]In a real-world trial of 6,834 patients at heightened risk of oesophageal cancer, 59% of those who tested positive by cytosponge and underwent endoscopy were diagnosed with cancer. 9 cancers were identified at stage 1 and curatively treated, compared to 0 in the control arm. The number needed to test by cytosponge per cancer detected was 184.[170,172,173] Modelling of a hypothetical cohort of 50 year-old men with histories of gastroesophageal reflux disease (GERD) found that cytosponge testing reduced the incidence of symptomatic oesophageal cancer by 19%, at a cost-effectiveness of $15,724/QALY, gaining greater clinical and cost-benefit than universal endoscopy.[174] Separate economic modelling of screening of US men at 60 years of age with a history of GERD powered by results from the BEST2 trial found that a strategy of cytosponge screening followed by endoscopic confirmation was cost effective compared to no screening, at $28,791-33,307/QALY. Screening all participants with endoscopy yielded more QALYs, but not in a cost-effective fashion, from $143,041-330,361/QALY.[175]

Cytosponge is not resource intensive, is flexible to different settings, and has light training requirements. It has been used as a risk-stratification tool, identifying 35% of BE surveillance patients at a 0% risk of developing cancers, who can be excluded from endoscopy.[176] The trial in Cambridge was implemented quickly to reduce resource-utilization, in response to the COVID pandemic, and also identified a cohort where 3/8 patients were diagnosed with serious non-cancer conditions, displaying its' pan-disease benefit.[171] Finally, systematic review shows high acceptability of cytosponge amongst both healthcare providers and patients, adaptability to both primary and secondary settings, and no formal training required for its effective use.[169]

Overall, the evidence review suggests that cytosponge could be implemented in Wales with relatively few implementation barriers, potentially providing a cost-effective solution for more than one application.

- Our review identified high–quality evidence for the cost–effective use of cytosponge for initial diagnosis and triaging.
- To our knowledge, there are currently no working pilots or schemes for implementing cytosponge into Welsh practice (though Moondance Cancer Initiative is in discussions about establishing one).

Innovation 15 – Colon Capsule

Colon capsule, or PillCam, is a swallowed device, which captures and analyses images of the colon, with the potential to be used for triaging, or diagnosis of bowel cancer.

Colon capsule is more sensitive and specific than alternative non-invasive tests, but less so than colonoscopy. Meta-analysis of colon capsule trials has shown acceptably high accuracy, displaying 86% sensitivity and 88.1% specificity for pre-cancerous polyps >6mm, and 87% sensitivity and 95.3% specificity for polyps >10mm (which are more clinically significant), and no missed cancers.[177] This is in agreement with other meta-analyses, which show favourable sensitivity and specificity compared to non-invasive screening techniques, but inferior performance to colonoscopy, and the patients did not prefer colon capsule over colonoscopy.[177–179] Colonoscopy enables intervention, such as the excision of polyps, which is of course not possible with colon capsule.[180]

Colon capsule may provide a resource-light, cost-effective triaging tool or diagnostic alternative in patients ineligible for colonoscopy. A systematic literature review and economic modelling analysis in a Canadian setting found that replacing CT colonography with colon capsule in patients with an incomplete colonoscopy gave a cost-effectiveness of $26,750/LYG, as well as moderate costs in the short term for implementation.[181] Results from a study in Denmark found that using colon capsule to triage patients could reduce colonoscopies by 43%, however, this did come at the risk of patients developing interval cancers.[182] Preliminary, unpublished results from the ScotCAP study in Scotland suggests than use of colon capsule to triage patients can reduce colonoscopies by 70%, in a fashion that can reduce load on hospitals, as colon capsule is carried out in the community and over the phone.[183,184]

The data reviewed indicate that colon capsule may provide a complementary and cost-effective service to colonoscopy. Results from the ScotCAP clinical trial are due for publication shortly, but have been used to support rollout in 3 Scottish health boards and NHS England, using colon capsule as a means of triage and diagnosis.[185,186] Results from this rollout will provide data that can inform the likely impact and cost-effectiveness of colon capsule in Wales.

- High quality evidence was identified in our review, consistently reporting colon capsule as clinically valuable but less so than colonoscopy, and so as a potentially cost-effective and resource-efficient complement to existing diagnostic services.
- As far as we are aware, no plans are in place for the implementation of colon capsule in Wales.

Innovation 16 – Trans Nasal Endoscopy

Currently, endoscopy is the gold-standard test for the diagnosis of upper GI cancers. Conventionally, this is performed through the oral route with or without patient sedation. Trans Nasal Endoscopy (TNE) uses an ultrathin endoscope through the nasal passage, in a procedure which aims to be less resource-intensive and uncomfortable, whilst maintaining the same accuracy.

Ultrathin endoscope TNE generally detects pre-cancer and cancer accurately. A randomized trial of TNE found 98% sensitivity and 100% specificity for detection of BE, and 91% sensitivity and 100% specificity for detection of early cancer.[187] Another single-arm study reported 92.3-100% sensitivity for pre-cancerous lesions and specificity of 98.9%.[188] Systematic review has identified that TNE has been associated with under-diagnosis of early gastric lesions in informal findings, and that more data is required to investigate this.[189] Finally, systematic review has reported that TNE is superior to conventional endoscopy in detection of non-cancer gastro-intestinal diseases, demonstrating its' pan-disease benefit.[189] Ultrathin endoscope TNE generally detects pre-cancer and cancer accurately. A randomized trial of TNE found 98% sensitivity and 100% specificity for detection of BE, and 91% sensitivity and 100% specificity for detection of early cancer.[187] Another single-arm study reported 92.3-100% sensitivity for pre-cancerous lesions and specificity of 98.9%.[188] Systematic review has identified that TNE has been associated with under-diagnosis of early gastric lesions in informal findings, and that more data is required to investigate this.[189] Finally, systematic review has reported that TNE is superior to conventional endoscopy in detection of non-cancer gastro-intestinal diseases, demonstrating its' pan-disease benefit.[189]

TNE has been proven to be highly applicable, highly acceptable to patients, and less resource and time-intensive than conventional endoscopy. Reported completion rates of TNE vary in literature between 94-99.1% of patients,[188,190,191] with 99.2% of patients reported that they found discomfort absent or minimal.[188] Systematic review has also reported that TNE is associated with shorter procedure times and lower costs that sedated endoscopies, with two studies reporting average duration of 14.6 and 19.9 minutes.[189–191] Further, due to a good safety profile, TNE only requires one nurse to be present, as opposed to two with sedated endoscopy.[189] Use of ultrathin endoscopes can also facilitate another innovation, of peroral endoscopy, facilitated by use of pharyngeal anaesthesia. This technique had a 6% higher success rate than TNE, took on average 3.1 minutes less time, reported no complications, and found no significant difference in patient discomfort and satisfaction.[191]

Besides the short-term investment in ultrathin endoscopes, the literature agrees that TNE represents a cost- and resource-effective innovation for the diagnosis of upper GI cancers. Questions about comparators remain, with anesthetized peroral endoscopy appearing promising, but given the same equipment and similar training are required for each technique, this innovation is not at great risk of being undercut. In terms of implementation, Wales can learn from countries like Japan, where TNE is standard practice for the diagnosis of upper GI cancers, as well as hospitals in England and Scotland.[192]

- Our review captured high–quality evidence reporting that TNE is a cost–effective and resource–efficient endoscopy method, with high patient acceptability and acceptable accuracy.
- Moondance Cancer Initiative is funding the introduction of TNE for upper GI patients in Cardiff Vale and Cwn Taf Health Boards.

Reflections and next steps

In this scoping paper, we have presented the key available evidence on 16 emerging innovations in cancer early diagnosis and detection. We recognise that this is a fast-developing field – and there may be further developments with potential that arise in coming months and years.

This paper forms an input into a longer project, through which we're aiming to put together an outline cancer ED&D roadmap to reflect back to NHS Wales colleagues, and spark constructive debate and discussion about possible ways forward.

Our next steps:

- We're sharing this horizon scan paper with a sample of colleagues, to check whether we've captured everything they would expect, and to gather initial feedback
- We're aiming to host two roundtable conversations, and conduct a small sample of one-to-one interviews, with some clinical and managerial experts within the Welsh health system, to explore how these innovations could and should change cancer ED&D over the next 10 years.

These discussions will recognise that none of these innovations exist in a vacuum and that the way that they integrate towards a common vision of ED&D will be important. For example, pathology AI cannot be implemented without a digitized pathology workflow; referral from alternative primary care sites could be directed to RDCs or community diagnostic hubs; and pan-cancer liquid biopsies might one day supplant lung or ovarian cancer screening programmes.

As Moondance Cancer Initiative, these discussions and the final summary report will directly inform our partnerships and funding strategy. We hope that they will be of interest and value to colleagues across cancer services, strategy and policy too. We will publish the report on our website, and will be delighted to share it.

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