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PRECISION ONCOLOGY REPORT

EVIDENCE-ENABLED OUTCOMES RESEARCH TO INFORM PRECISION ONCOLOGY INNOVATION ADOPTION BY HEALTH SYSTEMS

Queen's University
Belfast

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Executive Summary

Innovation in the life sciences has a central role to play in preserving the health of the Northern Ireland citizen and promoting wealth generation within the Northern Ireland economy. Cancer is one of the biggest killers in Northern Ireland but represents an area of strength in the region in biomedical research and its translation for patient benefit. In this report, we highlight how a precision oncology approach, where a detailed understanding of the biology of malignancy informs the patient care pathway, is increasingly underpinning the delivery of personalised care for the cancer patient and contributing to the burgeoning biotech sector.

Four exemplars highlight the potential impact of innovation at different stages of the cancer control continuum, providing the evidence base for precision oncology commissioning and adoption in Northern Ireland.

Precision Radiotherapy
In lung cancer, research on the use of Stereotactic ABlative Radiotherapy (SABR), an innovative method that allows very precise delivery of high doses of radiotherapy to particular targets in the body, has led to the commissioning of SABR for early lung cancer and its adoption as standard-of-care in a disease which kills over 1,100 citizens in Northern Ireland each year.

Precision Prevention
The human papilloma virus (HPV) is implicated in the development of cervical cancer and is a major contributor to sexually transmitted disease. This has led to the development of a HPV vaccine which is routinely provided to adolescent girls in Northern Ireland. Research presented in this report emphasises the role of HPV in cancers which occur in both sexes such as head and neck and anal cancers, both of which are on the rise in Northern Ireland. This evidence, combined with health economic analysis demonstrating the cost effectiveness of HPV vaccination for both sexes, supports our proposal for a universal vaccination policy for adolescent girls and boys in Northern Ireland

Precision Treatment Selection
In early breast cancer, there is a need to determine which patients benefit from treatment with chemotherapy, while sparing those patients who derive no benefit, and for whom the debilitating side effects of chemotherapy can negatively impact on their Quality-Of-Life. Research presented here, in collaboration with colleagues in the Republic of Ireland, highlights the efficacy of a 21-gene signature test in stratifying breast cancer patients to receive either chemotherapy or hormonal therapy, thus ensuring the right treatment is provided to the right patient using the best available information. Health economic analysis indicates that use of this 21-gene signature test is cost effective and potentially cost saving, thus supporting our recommendation for its employment to inform treatment decision-making in early breast cancer in Northern Ireland.

Precision Partnership
Northern Ireland has a significant international reputation in colorectal cancer research. A crucial component of this recognition has been the close collaboration between academia and industry, as exemplified by the research enabled partnership between the Centre for Cancer Research and Cell Biology at Queen's University Belfast and Almac, one of Northern Ireland's leading indigenous companies and an industry leader in both the pharmaceutical and biotech/molecular diagnostics sectors. Supporting this type of academic-industry partnership is key to translating high quality discovery science into improved outcomes for cancer patients and measureable assets for the growing life sciences sector in Northern Ireland.

In order to maximise innovation adoption of precision oncology in Northern Ireland, we recommend the following:

Overarching Recommendations

1. Publication and implementation of a new cancer strategy that recognises innovation potential, setting clear targets for improved outcomes and better Quality-Of-Life for Northern Ireland citizens and patients.

2. A focus on precision oncology innovation adoption at all stages of the cancer continuum, from prevention through early diagnosis to treatment, survivorship and end-of-life care.

3. A recognition that research-enabled multistakeholder partnerships are a key component of innovation adoption.

4. A data-driven approach to accumulate and evaluate evidence to support or reject precision oncology innovations, thus ensuring a value-based perspective on innovation adoption in cancer.

5. A clear route for evidence-based outcomes focussed research to influence adoption and effective and timely commissioning of innovation in cancer care pathways and cancer services.

Specific Recommendations

1. Evidence-based outcomes research supports our recommendation for the use of Stereotactic ABlative Radiotherapy (SABR) as standard-of-care in early stage lung cancer and expansion of SABR to oligometastatic cancer in the lungs.

2. Based on the increasing incidence of Human Papilloma Virus (HPV) -related gender neutral cancers and their costs to the health system, allied to the ability of HPV Vaccination to prevent genital warts in both sexes, we recommend the introduction of universal HPV vaccination for adolescent boys and girls in Northern Ireland.

3. In light of the clinical evidence of the 21-gene signature changing clinical practice and reducing chemotherapy use in early breast cancer, allied to budget impact analysis that indicates its cost saving potential, we support the introduction of the 21-gene signature test for early breast cancer patients in Northern Ireland.

4. Recognising the potential for local cross-sectoral precision oncology partnerships to deliver health-preserving solutions for patients and new biotech assets for commercial development, we recommend the establishment of a multi-stakeholder Innovation Forum that is challenged to embed precision medicine within Northern Ireland. The priority of this multi-disciplinary team is to ensure the realisation of value based preventative, diagnostic or therapeutic interventions that benefit patients in Northern Ireland. A major secondary output of the Forum will be to contribute to growth of medical and biotech enterprise as a key economic driver within Northern Ireland.

5. Given how the data presented in this report can help influence improvements in cancer healthcare at a local level, we recommend the creation of an evidence-focussed Outcomes Research Unit, to support the proposed Innovation Forum, underpinning the accumulation and evaluation of evidence for adoption of innovations that can impact positively on cancer prevention, cancer control and Quality-Of-Life for Northern Ireland citizens.

1. Introduction

In 1996, the publication of the Campbell Report [1] highlighted significant deficiencies in cancer services in Northern Ireland. Subsequent research by the Northern Ireland Cancer Registry indicated that Northern Ireland had the poorest overall survival in the UK for the majority of cancer types. [2] Implementation of the Campbell Report's recommendations, through the establishment of a national cancer framework, underpinned by (i) a comprehensive cancer centre (The Northern Ireland Cancer Centre), (ii) a research-active national cancer registry (the Northern Ireland Cancer Registry) and (iii) an expanded research capacity (the Centre for Cancer Research and Cell Biology to translate discovery science into clinical application), led to a step change in cancer services and their delivery in Northern Ireland, such that by 2013, in diseases such as breast cancer, Northern Ireland had the best survival figures in the UK. [3, 4] The regional Northern Ireland Cancer Trials Network was also established (funded by the Northern Ireland Public Health Agency and Cancer Research UK) and this allowed access for patients to innovative phase I – IV clinical trials and other translational research studies. The impact of this cross-sectoral patient-focussed partnership (involving key stakeholders including hospital trusts, academic institutions, patients and their advocates, biotech/biopharma industry, clinicians, allied health care professionals and scientists) led to the Northern Ireland Comprehensive Cancer Programme receiving the Queen's Diamond Jubilee Award from Her Majesty Queen Elizabeth II in 2012. [5] A detailed description of this research-enabled multistakeholder partnership was recently published in *Cancer*, the Journal of the American Cancer Society. [6]

However, cancer incidence is rising in Northern Ireland. A 25% increase in men and a 22% increase in women was recorded from 2005 to 2014, largely due to an ageing population demographic. Almost 4,000 people die from cancer each year in Northern Ireland, equivalent to ~12 deaths per day. There were an estimated 55,721 prevalent cases at the end of 2014 (excluding Non Melanoma Skin Cancer (NMSC). [7] More people in Northern Ireland are now living beyond cancer, as reflected in a 5 year relative survival rate of 54% for patients diagnosed between 2004 and 2008, compared to a 38% relative survival rate for those diagnosed between 1993 and 1999). [8] Cancer survival for melanoma is the best in Europe; [8] however for most common cancers (e.g. lung, breast, colorectal, ovary), while survival rates are similar to the rest of the UK, they fall short of many countries in Europe and comparators such as Canada, and Australia. [9] Low 5 year net survival figures for cancers such as pancreatic (5.5%), lung (10.5%) and oesophageal (17.5%) highlight the extent of the challenge. [7]

Increasingly, an improved understanding of the biology of malignancy is informing our management of cancer patients. Innovative medicines such as Imatinib Mesylate (in Chronic Myeloid Leukaemia) and Transtuzumab (in her-2 positive breast cancer) have been practice changing and have heralded an era of personalised or precision oncology. [10, 11] While much of the focus has been on cancer drugs, it should be emphasised that public health interventions, prevention, early diagnosis, other cancer therapies such as radiotherapy, surgery and medical devices, improved Health Related Quality-Of-Life (HRQOL) and palliative care all contribute to a precision oncology ecosystem that promotes life-preserving health.[12] Alongside this, there is increasing recognition of the need to empower patients and involve them in decision making about research and treatment.[13, 14]

In this evolving landscape, there is a requirement to have the appropriate environment and the degree of ambition to deliver the innovation that is required to increase survival rates and further improve HRQOL for cancer patients in Northern Ireland. Nurturing the timely adoption of appropriate innovation and building in robust mechanisms for its evaluation will also enhance the burgeoning health/life sciences sector in Northern Ireland. Many aspects of the innovation-enabling infrastructure are already in place (see Panel 1 [15-22]) and this will be enhanced by the recent award by Innovate UK of the Precision Medicine Catapult to Northern Ireland. [23] However, this evolving ecosystem must be underpinned at policy/government level with a commitment to harness the tools of precision oncology for enhanced patient benefit.

Panel 1: Infrastructure enabling innovative cancer control in Northern Ireland

The **Northern Ireland Cancer Registry (NICR)**[7] captures cancer incidence, prevalence and survival data at an entire population level, underpinning service planning, cancer policy and research activities. While many European cancer registries have suboptimal data coverage, ranging from 17 to 100% (European average 50%), [15] NICR has a registry completeness of 100%. [16]

The **Northern Ireland Molecular Pathology Laboratory (NI-MPL)** [17] and the **Northern Ireland Biobank (NIB)** [18] (http://www.nibiobank.org) located within the **Centre for Cancer Research and Cell Biology (CCRCB)** are key infrastructural components of a precision oncology pipeline, allowing the collection of high quality, clinically annotated tumour samples and their molecular interrogation at a population level, thus maximising the clinical impact of discovery science to deliver new diagnostics and therapeutics. The Belfast Molecular Pathology Model [19] is recognised at national level and the recent Cancer Research UK (CRUK) Accelerator Award [20] to NI-MPL (one of only five in the UK) provides the impetus for embedding digital and molecular pathology not only in Northern Ireland but across the UK.

The **Northern Ireland Cancer Trials Network (NICTN)** has facilitated a step change in patient participation in cancer clinical trials in Northern Ireland. In the period April 2013-March 2014, 1665 patients participated in cancer clinical trials and related translational studies (over twice the recruitment target), [21] thus ensuring that the latest innovative treatments are available to Northern Irish patients. The Department of Health/CRUK funded **Experimental Cancer Medicine Centre (ECMC)** [21] focuses on driving early-phase clinical trials, thus underpinning the translation of discovery science conducted within CCRCB into new treatments for cancer patients

The **Northern Ireland Cancer Research Consumer Forum (NICRCF)** represents the patient voice for cancer research in Northern Ireland. NICRCF engages with scientists and clinicians at all stages of the cancer research process, being involved in research and clinical trial design, research grant submission, patient reported outcomes research and championing Patient and Public Involvement (PPI) in research. NICRCF are also strong advocates for cancer research in Northern Ireland

In this context, continued implementation of a modern integrated cancer strategy is key, informed by current knowledge and best international practice and enhanced by a collaborative research approach that values innovation and cross-sectoral partnership. England published its first National Cancer Plan in 2000 which was then updated in 2006. A third National Cancer Plan, *Improving Outcomes: A Strategy for Cancer* was published in 2011 and NHS England has recently launched its implementation plan for its latest cancer strategy *Achieving World-Class Cancer Outcomes: Taking The Strategy Forward*. [24] Scotland launched its new £100 million Cancer Strategy *Beating Cancer: Ambition and Action* in March 2016. [25] The most recent cancer plan for Wales *"Together for Health – Cancer Delivery Plan"* was launched in 2012 and this is being updated for publication by early 2017. However, Northern Ireland is lagging far behind, with the last cancer strategy having been published in 2008, since which time there has been a significant step change in our understanding of the heterogeneity of disease and the diversity of strategies to treat each cancer. While the review of the Cancer Services Indicator Framework is ongoing, [26] there is still a pressing need to produce an up-to-date, effective Northern Ireland cancer strategy that responds to the new cancer landscape as outlined above, allowing an increased understanding of this common disease to inform precision oncology approaches to cancer prevention, early diagnosis, effective treatments and improved quality of life for the citizens of Northern Ireland.

In this report, we present evidence to support the integration of a number of innovative precision oncology interventions into the cancer care pathway. We have chosen examples that demonstrate the potential for precision oncology to impact on different stages of the cancer journey, from prevention through cure to enhancing Health Related Quality-Of-Life (HRQOL). We highlight the need for a research-informed outcomes-focussed approach to deliver quality data in the support of innovation adoption, thus ensuring the timely and effective commissioning of value-based interventions for cancer patients in Northern Ireland. We emphasise the importance of embedding an effective evaluation function alongside the implementation of these interventions.

2. Generating the evidence base for precision oncology commissioning in Northern Ireland

2.1 Precision Radiotherapy: Delivering optimal standard-of-care for Non-Small Cell Lung Cancer

Lung Cancer is the third most common cancer in the UK, with over 45,500 new cases diagnosed per year. [27] Nearly 36,000 people died of lung cancer in the UK in 2013, making it the leading cause of cancer death. [27] The most common form of lung cancer is Non-Small Cell Lung Cancer (NSCLC) which constitutes ~80% of lung cancer cases. In Northern Ireland, over 1,100 new cases of NSCLC are reported annually, with ~900 patients dying from the disease each year. [28] While surgery is currently the standard-of-care for this disease, [29] many stage I patients (approximately 20% of all NSCLC patients) are inoperable, necessitating non-surgical approaches in their management. Conventional radiotherapy approaches involve External Beam RadioTherapy (EBRT). [30] However, 2 year Overall Survival (OS) using EBRT is <50% while 5 Year OS is ~20%, leaving significant room for improvement. [27]

Technical advances in radiotherapy have led to the development of state-of-the-art approaches such as **Stereotactic ABlative Radiotherapy (SABR)**, which allows very precise delivery of high doses of radiotherapy to particular targets in the body. In lung cancer, SABR has been shown to be highly effective, with superior 2-year OS when compared to conventional EBRT. [31]

The commissioning of SABR for early lung cancer represents a prime exemplar of the introduction of an innovative precision treatment into the Northern Ireland healthcare system and can serve as a model for how a data-driven evidence based approach can inform forward-facing planning and commissioning. Individual and meta data from a variety of international studies [31] were gathered to support the introduction of SABR for lung cancer in Northern Ireland. A pilot study was initiated in July 2013, with SABR delivered initially to one patient per month. An audit of the pilot study and the development of a comprehensive 5 year business plan (approved by the Health and Social Care Public Health Agency in May 2014) led to the introduction of the SABR Lung Programme for inoperable Stage 1 NSCLC patients in the Northern Ireland Cancer Centre. Initial follow up data were presented at the inaugural *British Institute of Radiology – UK Stereotactic Ablative Radiotherapy Consortium (BIR-UK SABR Consortium)* Annual Scientific Meeting, held in Queen's University Belfast in November 2015. [32] To date, nearly 100 patients have received SABR in Northern Ireland since its introduction in July 2013. Estimated 2 year progression free survival (PFS) rates approach 90% with significantly increased cancer control. In a recent audit, the 2-year OS rates was estimated at 68%. [33] SABR is well tolerated by the patients with reduced toxicity compared to EBRT. The more precise nature of SABR (delivered in 3-8 radiotherapy fractions) when compared to conventional EBRT (which requires 20-33 radiotherapy fractions) has led to treatment efficiencies for the Northern Ireland cancer service and shorter and fewer radiotherapy visits for the Northern Ireland cancer patient.

SABR has transformed the management of early stage lung cancer unsuitable for surgery in Northern Ireland, and is now the standard-of-care for these patients. The success of this initiative has led to the SABR Lung Implementation Team receiving the UK Cancer Team Collaboration of the Year Award at the 2016 Quality in Care Awards in London. [34] The availability of SABR in Northern Ireland has made possible local participation in the Stereotactic Ablative Radiotherapy for Oligometastatic Non-small Cell Lung Cancer (SARON) and the Conventional Care Versus Radioablation (Stereotactic Body Radiotherapy) for Extracranial Oligometastases (CORE) clinical trials, which are the key UK studies of SABR for oligometastatic disease.[35-37] Data from these trials will provide the evidence base for commissioning of SABR in metastatic lung disease. The introduction of SABR into the Northern Ireland health care system emphasises how investment in modern radiotherapy infrastructure makes it possible to provide best standard-of-care for Northern Irish patients.

2.2 Precision Prevention: Making the case for Universal Human Papilloma Virus (HPV) Vaccination

Human Papilloma Virus (HPV) infection is a significant health issue, implicated in ~5% of all cancers and a major contributor to sexually transmitted disease. [38] It is an extremely common infection within the population, with 70 - 80% of sexually active men and women contracting it at some stage during their lives. [39] There are over 100 HPV subtypes and while infection with the majority of these are short lived and clinically irrelevant, there are specific subtypes of HPV which carry a significant health burden in both men and women. Precise knowledge of which HPV subtypes are implicated in particular conditions underpins both diagnosis and potential prevention of HPV-related disease. [40, 41] HPV 6 and 11 are associated with the development of genital warts, [40] while infection with HPV subtypes 16 and 18 for example can lead to the development of malignancy. [41] From a public perspective, there is widespread awareness of the link between HPV infection and the risk of developing cervical cancer. However, what

is less well recognised is that HPV is also implicated in the development of other cancers, including cancers of the head and neck region (particularly oropharyngeal cancers), anal cancers and other genital cancers. [42-44]

Cervical Cancer is the 4th most common cancer in women, with approximately 3,000 new cases each year and ~980 deaths annually in the UK. [45] As indicated above, HPV infection is implicated in the development of the disease; HPV subtypes 16 and 18 are linked to 70% of cervical cancers, while HPV subtypes 31, 33 and 45 are linked to the majority of the remaining 30% of cases.[46] Knowledge of HPV's causative role in cervical cancer has led to the development of a HPV vaccine as a preventative public health intervention. Two vaccines are currently licenced for prevention of cervical cancer, a bivalent vaccine which is protective against the common HPV 16 and 18 subtypes and a quadrivalent vaccine which protects against both HPV 16/18 and HPV 6/11, thus acting to prevent both cervical cancer and genital warts. [47, 48] A new nonavalent vaccine has been shown to be effective against the nine most common subtypes (HPV6/11/16/18/31/33/45/52/58) and has been approved for use in the US, Canada, Australia and the EU. [49] Since September 2008, a free school-based vaccination programme has been available in the UK for 12-13 year old females (as part of the NHS national childhood vaccination programme). From September 2012, the programme has been using the quadrivalent vaccine (protecting against types 6, 11, 16 and 18); this three dose schedule was reduced to two doses in September 2014. Vaccine coverage in females in the UK is generally high, and Northern Ireland mirrors this trend, with local data indicating percentage coverage for 12-13 year old girls ranging from 81.4% - 90.8% (2 doses) (depending on the Northern Ireland Healthcare Trust) or 84.6 - 93.3% (3 doses). [50]

But as indicated above, HPV infection is also implicated in gender-neutral cancers. Over 95% of anal cancers are caused by HPV, [51] while cancers of the head and neck including oropharyngeal cancer (OPC) (which is 4 times more common in males than in females) are also attributable to HPV infection. [52] OPC incidence has been increasing rapidly – in Scotland it is the fastest growing of all cancers. [53] The significant increases in HPV-related OPC worldwide suggest that by 2020, OPC will be more common than cervical cancer. [54, 55]

Over 200,000 men in the UK are diagnosed with a HPV-related cancer and 48,000 with genital warts every year. [51] The recognition that HPV can cause cancers other than cervical cancer and its involvement in sexually transmitted disease has prompted calls for a universal vaccination policy for both girls and boys. [56-59] Australia introduced universal vaccination in February 2013, [60] while Austria became the first European country to introduce vaccination for boys in 2014. [61] Switzerland and Lichtenstein introduced vaccination for boys in 2016, [61, 62] while in Italy there is funding for vaccination in boys in 9 regions. [61] and in Germany, vaccination is recommended in the Saxony region. [63] Norway also recommend a universal vaccination programme. [64,] In Canada, of the thirteen provinces and territories, Alberta, Manitoba, Nova Scotia, Ontario, Prince Edward Island and Quebec include boys in their school-based programme [65] The USA recommends vaccination for boys [66] Targeted vaccination for high risk groups not protected by a female-only vaccination programme (e.g. for Men who have Sex with Men (MSM) have also been recommended in a number of countries including Greece [67] and the UK, [68] which has recently introduced a pilot for MSM with ~40,000 vaccines. [69]

In addition to preventing the development of malignancy and impacting positively on the sexual health of men and women, there are also the health economic benefits of universal HPV vaccination. [63, 70] In Canada, our analysis indicates that in evaluating direct healthcare costs for OPC alone, a universal vaccination strategy could save 8-28 million Canadian dollars (£4.78M - £16.71M) over the lifetime of boys receiving the HPV vaccine. [70] In the UK, we estimate that the cost of a universal vaccination strategy is approximately £20-£22M per annum. Health economic data indicate that the cost of treating genital warts in men is ~ £32M per annum; that the increased incidence of OPC have caused secondary care costs to rise from £17.2M to £30.2M per year and that the cost of treating anal cancer is £6.8M per year. In addition to direct treatment costs, there is an indirect economic impact of HPV-related disease due to the impact of treatment toxicity and disease on health and productivity.

Our preliminary data from Northern Ireland indicate that the annual costs for treating head and neck cancer approach £1.4M, while those for anal cancer total approximately £210,000 per annum. Annual treatment costs for genital warts are in the region of £950,000. In Northern Ireland in 2012, there were 11,975 boys and 11,082 girls aged 12 (the optimal age for HPV vaccination). Setting

these treatment costs for cancer and sexually transmitted disease against a conservative cost for including HPV vaccination for boys of approximately £750,000 - £900,000 per year, highlights the potential economic savings that a universal vaccination programme can deliver.

In addition to the direct costs, there is also an increased benefit to society as measured through improved productivity, increased earnings and enhanced tax revenue, due to vaccine-related reductions in mortality and morbidity. [71]

At a political level, over 100 cancer and sexual health experts, patient advocates and health policy analysts have come together to highlight the need for a universal HPV vaccination programme for boys and girls in the UK. [72, 73] Here in Northern Ireland, hosting of a HPV Round Table at Stormont Parliament Buildings has led to the formation of a HPV Alliance, bringing together all stakeholders in a united effort to "prevent the preventable", through a vaccination strategy that will protect both men and women from HPV driven disease. The recent announcement by the new Minister for Health that a targeted MSM vaccination programme will be supported in Northern Ireland [74] is to be welcomed, but the evidence that we have accumulated (as detailed above), supports the introduction of a vaccination programme for boys as well as girls in Northern Ireland. In addition, the recent announcement that vaccination rates for females in the Republic of Ireland have dropped to ~60%, with an associated significant reduction in "herd immunity", [75] confirms the need for a universal vaccination programme in Northern Ireland.

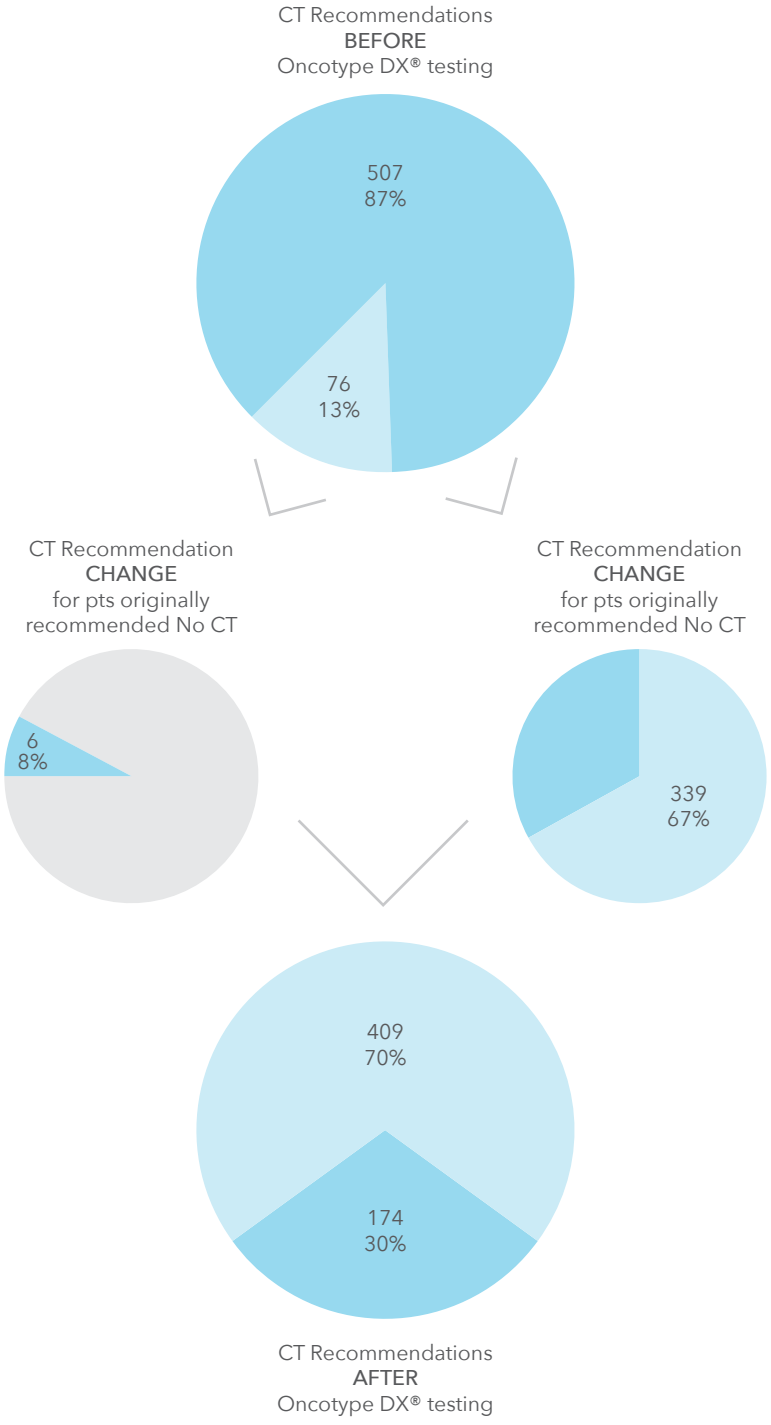
2.3 Precision Treatment Selection: A Clinical Decision Making Tool in Early Stage Breast Cancer

Breast cancer is the most frequently diagnosed malignancy in women, with > 53,500 new cases in the UK each year and almost 11,500 deaths annually. [76] In Northern Ireland, approximately 1,300 women are diagnosed with breast cancer per year and just over 300 patients die of their disease. [77] Approximately 60-70% of cases are Early Stage Breast Cancer (ESBC) and a significant proportion of these patients receive adjuvant chemotherapy. [78] However, the benefit of chemotherapy is small in many patients with ESBC (<5% improvement in 10 year disease free survival) and a significant proportion of patients experience treatment toxicities that may negatively impact on their Health Related Quality-Of-Life (HRQOL). [79] Thus, there is a clear need for an enhanced decision-making tool to select those ESBC patients who require adjuvant chemotherapy to reduce their risk of subsequent disease recurrence, while sparing those patients with a low recurrence risk the potentially debilitating side effects of chemotherapy treatment.

Our ability to dissect the biology of cancer using molecular tools is revealing new insights not only into the disease itself, but also how it responds to therapy. In breast cancer, a molecular snapshot of the tumour using gene expression profiling has identified a 21-gene signature that can measure the patient's future risk of recurrence of their cancer. [80] This 21-gene signature test (Oncotype Dx), is a quantitative predictor of the likelihood of breast cancer recurrence in women with newly diagnosed breast cancer. Patients with high breast cancer recurrence scores (RS) have an increased risk of their malignancy returning and thus are recommended to receive adjuvant chemotherapy, whereas patients with low RS have a very minimal suggested benefit from chemotherapy and can be managed by less toxic hormonal therapy, ensuring reduction in potential side effects. Introduction of the test thus allows the personalisation of care for the breast cancer patient.

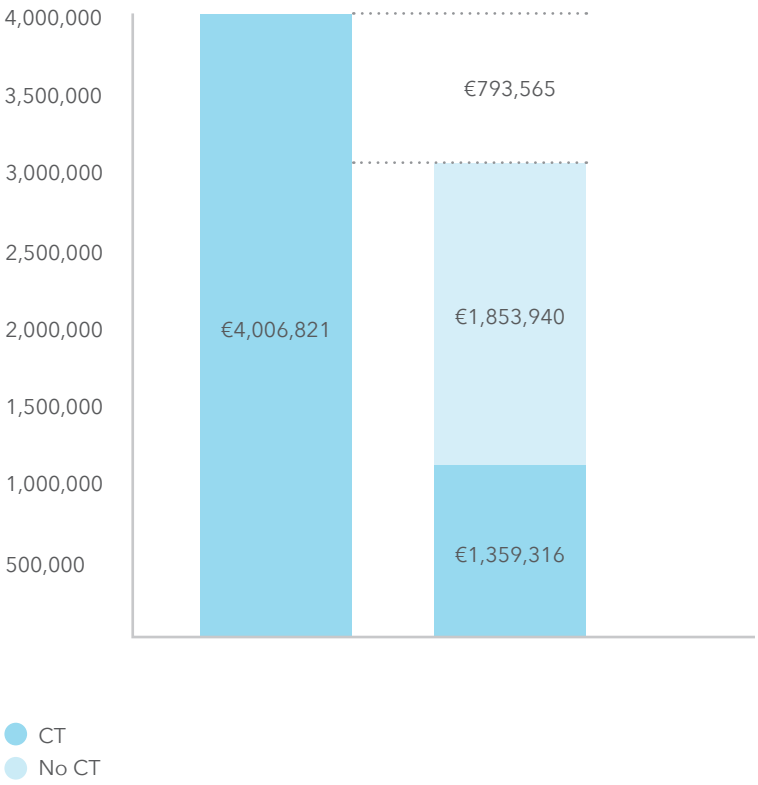
In October 2011, following extensive lobbying by patient groups, the Irish Society of Medical Oncology (ISMO) and others, [81] the Republic of Ireland became the first public health system in Europe to reimburse this test, thus making it available to Irish patients with newly diagnosed breast cancer. The impact of introducing this molecular test has been significant. Nearly 600 patients received the test between October 2011 and February 2013. Based on the results of the test, nearly 60% of the patients tested had a change in their treatment protocol (Figure 1). [82] Prior to testing, 87% of patients would have received chemotherapy. Post testing, this figure was reduced significantly, with only 30% receiving chemotherapy, while 70% receive the less aggressive hormonal therapeutic option, with a concomitant reduction in risk of developing side effects. Thus, our data indicates that this test is an effective treatment selection decision tool, ensuring that chemotherapy is recommended for those patients at highest risk of recurrence, while patients with the lowest risk of their cancer returning are spared the debilitating side effects of chemotherapy, contributing positively to a better overall HRQOL for patients with early breast cancer.

Figure 1. Economic impact of 21 gene testing on the Irish healthcare system



In addition to the clinical benefit of introducing this test, its cost effectiveness was also evaluated (Figure 2). [82] Budget impact analysis was performed, with a conservative model based on the manufacturer's list price. Total treatment expenditure before molecular testing was €4,006,821 (£3,420,476); this dropped to €1,359, 316 (£1,160,398) following the decision to change therapy based on the result of the molecular test. Given a conservative estimate (based on manufacturers list price rather than negotiated price) of the cost of molecular testing in the 16 month evaluation period of €1,853,940 (£1,582,640), this has resulted in a cost saving of €793,565 (£677,437). [82]

Figure 2. Economic impact of 21 gene testing on the Irish healthcare system



The improvement in clinical decision-making as a result of prior testing, allied to the significant cost saving outlined above, prompted our analysis to be extended to investigate the potential to introduce the 21-gene signature molecular test in Northern Ireland. Based on the overall population demographics and the projected incidence of invasive breast cancer, we estimate that approximately 150-200 breast cancer patients will be eligible for testing in Northern Ireland (Figure 3).

Figure 3. Estimated size of target patient population for 21 gene signature testing in NI

Demographic	Input Value	Patient Population
Total population	1.8 Million	–
Incidence of invasive breast cancer	0.075%	1,358
ER+	91%	1,236
HER2-	87%	1,075
'Intermediate risk' (NPI>3.4)	42.2%	454
Proportion of eligible pts expected to receive test	50%	227
pN0	70%	159

Applying a budget impact analysis similar to that employed in the Republic of Ireland study indicated that use of the 21-gene signature molecular test would lead to a total cost saving of £352,885 per year for the health service in Northern Ireland (Figure 4). This conservative estimate does not take into account the indirect costs associated with chemotherapy administration, including absenteeism from work, social welfare and childcare costs. This analysis has helped to underpin the provision of the Oncotype DX test for appropriate patients with breast cancer in Northern Ireland from 2016 onwards. Thus, precision oncology has the ability to deliver decision impact tools that ensure the best therapeutic options for individual patients in a cost effective manner, strongly supporting their integration into standard clinical practice.

Figure 4. One-year Budget Impact Estimation

A budget impact calculation was employed to determine the net budget impact (or savings) resulting from 21-gene signature testing, by comparing the cost of CT before (without) testing (CTb), with the cost of CT after (with) testing (CTa) plus the cost of the 21-gene test (T), as per below:

$(CTa + T) - (CTb)$

	Without 21-gene signature testing	With 21-gene signature testing
Tested patients	0	159
Patients receiving CT[1]	138 (87%)	48 (30%)
Cost of testing	£0	£410,220
Cost of CT2	£1,164,739	£401,634
Total costs	£1,164,739	£811,854

2.4 Precision Partnership: Enabling the Academia-Industry Intersect to deliver value-based care in Colorectal Cancer

While the exemplars outlined in Sections 2.1 – 2.3 highlight precision oncology interventions in which we have accumulated a comprehensive evidence base with locally informed supportive data that have either led to their introduction (SABR for NSCLC), their partial introduction (HPV vaccination for males) or their proposed introduction (clinical decision-making tool for early breast cancer) into the health system in Northern Ireland, our fourth example demonstrates how a research-enabled precision oncology partnership can potentially drive both improvements in healthcare and also support innovation creation within the Northern Ireland biotech ecosystem.

Colorectal (Bowel) cancer is the fourth most common cancer in the UK with over 41,000 new cases annually and nearly 16,000 people die of the disease each year, making it the 2nd most common cause of cancer death. [83] In Northern Ireland, colorectal cancer (CRC) is the 2nd most common cancer, with approximately 1,100 new cases annually and over 400 cancer deaths each year. [84] There has been a significant research focus on CRC in Northern Ireland, with a particular emphasis on how a deeper biological understanding of the disease can fuel the development of new prognostic and predictive biomarkers. [85-87] A crucial component of the translational research effort has been the close collaboration between academia and industry, exemplified by the partnership between the Centre for Cancer Research and Cell Biology in Queen's University Belfast and Almac. [88] Almac is one of Northern Ireland's leading indigenous companies. It is an industry leader in both the pharmaceutical and biotech/molecular diagnostics sectors with over 3,500 employees worldwide. The Almac-Queen's partnership receives significant support from Invest Northern Ireland.

Research between Almac Diagnostics and Queen's in CRC has led to the development of a specialised gene expression profiling platform, the proprietary Colorectal Cancer Disease Specific Array (CRC-DSA). Employing the CRC-DSA on samples from over 500 patients with Stage II Disease led to the development of a gene signature (ColDx) with prognostic potential. [85] Initial validation of this signature was performed in a multi-centre study while a just published 2nd validation study

in August 2016 [89] has highlighted the ability of this molecular test to refine patient prognosis, providing strong evidence for its introduction into clinical practice.

This research partnership has proved crucial to CCRCB and Almac Diagnostics becoming major partners in S:CORT (Stratification in COloRecTal Cancer), a UK wide Colorectal Cancer Consortium which successfully competed for a £5M Medical Research Council – Cancer Research UK funded Stratified Medicine Programme. [90, 91] S:CORT brings together all the major UK centres who are at the cutting edge of CRC research and its implementation (Oxford, Belfast, Leeds, Birmingham, Cambridge London, Aberdeen) in a unique national collaborative partnership between academia, patient advocacy groups and bio-industry. Northern Ireland is playing a major role in this Consortium, leading on three of the seven work streams. Focussing the research on clinically relevant questions with the valuable input of patient groups including Bowel Cancer UK, Beating Bowel Cancer and in particular the Northern Ireland Cancer Research Consumer Forum is underpinning a strategic approach that aims to deliver new prognostic/predictive biomarker that will inform the delivery of innovative care for CRC patients.

An example of the stratified medicine approach that is being employed in S:CORT relates to the use of the chemotherapy drug oxaliplatin. Oxaliplatin has been an effective drug in CRC, but patients who receive this drug can be prone to side effects of the treatment, particularly the development of peripheral neuropathy. [92] A detailed molecular dissection of the oxaliplatin response would underpin the development of a decision-making tool that selects for treatment those patients in whom the drug is active, while sparing non responders the neurological side effects. Such a predictive test would be practice enhancing – over 450,000 people in Europe are diagnosed with CRC each year and oxaliplatin is included in the treatment regimen of approximately one third of these patients. Currently, researchers at Queen's University Belfast and Almac Diagnostics are testing a number of prime candidates in samples from patients who participated in CRC clinical trials in the UK, including Northern Ireland.

Prostate cancer is the most commonly diagnosed cancer in men. It is a highly heterogeneous cancer with many men diagnosed with localised low grade disease that will never progress in their lifetime. Other men develop rapidly progressive, high grade prostate cancer that can spread to lymph nodes, bone and can ultimately be life-threatening. Current stratification methods are inadequate and novel methods that determine cancers that have true metastatic potential at diagnosis are urgently required. Researchers at the Centre for Cancer Research and Cell Biology were recently successful in competing for a Movember Centre of Excellence at QUB. [93]

There are a broad range of treatment options for localised prostate cancer ranging from active surveillance, to more aggressive multimodality therapy that may include a combination of radiotherapy, androgen deprivation therapy and cytotoxic chemotherapy. [94-96] Furthermore, for the first time, novel targeted therapies have recently been shown to have activity in prostate cancer. [97] The development of new methods for prostate cancer stratification would enable clinicians to avoid treatment for men with truly indolent disease and escalate treatment for men whose cancer has the highest risk of mortality.

Working with Almac Diagnostics, researchers at QUB have identified a molecular signature that indicates increased metastatic potential for patients with localised disease. Testing of this signature has indicated that it is more effective at identifying patients who will subsequently develop metastases than traditional stratification methods. The clinical utility of this approach is currently been assessed, with the intention of developing a precision medicine clinical test that underpins the decision to either give intensive treatment (to men with aggressive prostate cancer), or reduce or avoid treatment (for those men with a more indolent disease).

Congruent with the development of new diagnostic/predictive tests, we are also examining the value proposition of precision oncology. [98] Clinically meaningful outcomes need to be evaluated from health-preserving and economic perspectives, [99] thus ensuring evidence-based interpretation of the value of a diagnostic [100] or therapeutic intervention. [99, 101, 102] Additionally, the European Society of Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) [103] is a recently developed tool which can be employed to assess the effectiveness of precision oncology interventions. Establishing the cost effectiveness and the diagnostic or therapeutic value of an intervention, contributes to the evidence base for its appropriate and timely commissioning.

3. Conclusions and Recommendations

Northern Ireland has a population of 1.85M, with ~ 9,000 new patients diagnosed with cancer annually. This compact size provides the potential for cancer research and cancer services to be integrated, planned and delivered at the population level. A coordinated partnership of all the key stakeholders can underpin an integrated research-driven cancer program, delivered through a linked health and social care infrastructure, thus providing the potential for innovation to be introduced across the cancer continuum, for the benefit of patients and the wider Northern Ireland society

The four exemplars outlined above represent different stages in the translational pipeline, highlighting the potential for precision oncology implementation across the cancer continuum, from prevention, through diagnosis to therapeutic intervention. Each exemplar emphasises the skill sets that are present in Northern Ireland, from clinical, academic and industry perspectives, to underpin the delivery of a research-enabled comprehensive cancer programme that leads to improved outcomes for cancer patients, while also contributing to the growing biotech sector within the Northern Ireland economy.

Harnessing the collective strength of academia, healthcare trusts, patients and their advocates, and the biotech/biopharmaceutical industry in Northern Ireland has the potential to underpin a translational precision oncology pipeline that delivers better diagnostic, prognostic and predictive tools and more effective preventative and therapeutic interventions for cancer patients, enhances economic development and ensures more affordable and effective healthcare for the region. In order to maximise innovation adoption of precision oncology in Northern Ireland we recommend the following:

Overarching Recommendations

1. Publication and implementation of a new cancer strategy that recognises innovation potential, setting clear targets for improved outcomes and better Quality-Of-Life for Northern Ireland citizens and patients.

2. A focus on precision oncology innovation adoption at all stages of the cancer continuum, from prevention through early diagnosis to treatment, survivorship and end-of-life care.

3. A recognition that research-enabled multistakeholder partnerships are a key component of innovation adoption.

4. A data-driven approach to accumulate and evaluate evidence to support or reject precision oncology innovations, thus ensuring a value-based perspective on innovation adoption in cancer.

5. A clear route for evidence-based outcomes focussed research to influence adoption and effective and timely commissioning of innovation in cancer care pathways and cancer services.

Specific Recommendations

1. Evidence-based outcomes research supports our recommendation for the use of Stereotactic ABlative Radiotherapy (SABR) as standard-of-care in early stage lung cancer and expansion of SABR to oligometastatic cancer in the lungs.

2. Based on the increasing incidence of Human Papilloma Virus (HPV) -related gender neutral cancers and their costs to the health system, allied to the ability of HPV Vaccination to prevent genital warts in both sexes, we recommend the introduction of universal HPV vaccination for adolescent boys and girls in Northern Ireland.

3. In light of the clinical evidence of the 21-gene signature changing clinical practice and reducing chemotherapy use in early breast cancer, allied to budget impact analysis that indicates its cost saving potential, we support the introduction of the 21-gene signature test for early breast cancer patients in Northern Ireland.

4. Recognising the potential for local cross-sectoral precision oncology partnerships to deliver health-preserving solutions for patients and new biotech assets for commercial development, we recommend the establishment of a multi-stakeholder Innovation Forum that is challenged to

embed precision medicine within Northern Ireland. The priority of this multi-disciplinary team is to ensure the realisation of value based preventative, diagnostic or therapeutic interventions that benefit patients in Northern Ireland. A major secondary output of the Forum will be to contribute to growth of medical and biotech enterprise as a key economic driver within Northern Ireland.

5. Given how the data presented in this report can help influence improvements in cancer healthcare at a local level, we recommend the creation of an evidence-focussed Outcomes Research Unit, to support the proposed Innovation Forum, underpinning the accumulation and evaluation of evidence for adoption of innovations that can impact positively on cancer prevention, cancer control and Quality-Of-Life for Northern Ireland citizens.

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