



Biomarkers for detection of colorectal cancer

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1 Executive Summary

The challenge

Colorectal cancer (CRC) is the second most common cause of death from cancer in Australia, with almost 15,000 new cases diagnosed and 4,000 deaths annually. It is responsible for more than 600,000 deaths worldwide each year. Post-surgical recurrence of CRC occurs in 30 to 50 percent of cases, most often in the first 2-3 years of initial diagnosis and treatment. Current monitoring of recurrence is via a blood test for carcinoembryonic antigen (CEA), a well described marker for gastrointestinal tract diseases, especially CRC, in combination with CT scans and other clinical assessments. CEA testing has low sensitivity and is subject to false-positive results, limiting its usefulness. Detection of primaryⁱ CRC in early asymptomatic stages would reduce intensive treatment needs, associated healthcare costs¹, and risk of recurrence post-treatment, and improve survival rates. Similarly, detecting recurrentⁱⁱ CRC in early asymptomaticⁱⁱⁱ stages will reduce intensive treatment needs and associated costs, and improve survival rates.

Our response

In January 2017, Colvera™ was launched by Clinical Genomics (CG) in US markets and is now available to patients participating in post-treatment cancer surveillance in the US. Colvera™ is a blood-based test of circulating tumour DNA suitable for CRC recurrence surveillance. It detects methylated DNA from two genes, BCAT1 and IKZF1; and is twice as sensitive as the CEA assay, increasing the likelihood of detecting curable CRC recurrences, and reducing the risk of mortality. This diagnostic assay intended to aid physicians in the management of patients under routine surveillance for CRC recurrence. It is anticipated the test will become available in Australia in 2018.

Collaborative research between CSIRO, Flinders, and CG,^{iv} informed by unique skill sets and driven by commercial outcomes, aimed to find molecular markers in CRC tissue that distinguished it from normal tissue, and which could form the basis of diagnostic tests. This approach was considered an innovative way to improve the efficacy of detecting and diagnosing asymptomatic early stage CRC. From 2008, research focus shifted to identifying downregulated genes by DNA methylation in CRC tissue. This shift, which proved pivotal for research progress, is attributable to CSIRO experience, including its previous development of a prostate cancer DNA methylation biomarker. The validated assay for CRC detects the presence of circulating tumour derived hyper-methylated genes (BCAT1 and IKZF1) in the blood of CRC patients.

ⁱ In this case study primary CRC is the first case of detection and diagnosis. Treatment will normally involve surgical resection to remove the primary tumour.

ⁱⁱ Recurrent Colorectal Cancer is cancer that has returned after a period. In this case study recurrent CRC refers to CRC that has returned post-treatment.

ⁱⁱⁱ Where a condition shows no symptoms, or not recognisable symptoms.

^{iv} The time over which this project spans requires broad reference to particular contributors by name. 'Flinders' refers to collaboration with Flinders Centre for Cancer Prevention and Control, and Flinders Centre for Innovation in Cancer (both within Flinders Medical Centre). Flinders University Gastroenterology and Hepatology Department (Flinders School of Medicine) is referred to specifically and contributed to research related to commercialisation only. 'CSIRO' allows for contributions from the Preventative Health National Research Flagship – known as CSIRO Health and Biosecurity Business Unit since mid-2015.

The impacts

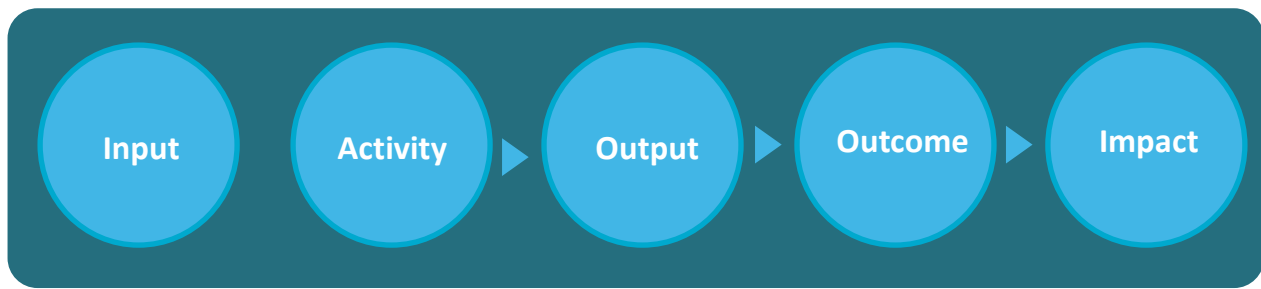
Colvera™ provides cost saving within the first year of use. Where recurrence is moved from a symptomatic to asymptomatic detection state via improved surveillance tools, an estimated \$US100,000 in downstream healthcare costs is saved. Colvera™ is, therefore, expected to reduce costs associated with detection of recurring CRC in advanced stages. Colvera™ improves health outcomes by following a proven test/treatment pathway. The assay identifies a significantly larger number of patients with recurrence than the current guideline-recommended blood test, CEA. It is therefore assumed that Colvera will result in an increased rate of curative intent therapy and improved patient survival.

While Colvera is not yet available on the Australian market, the Cost Benefit Analysis (CBA) was conducted based on its eventual uptake, and from a societal perspective of the Australian Healthcare System, including all important economic costs and benefits arising from such an intervention. As there is limited information about gains for the health system and patient outcomes over time at this stage, we have relied on limited analysis conducted across Australia and internationally. More data is recognised as needed to further substantiate the impact analysis. This analysis has been subject to sensitivity analysis and/or discretion as explicitly advised in the report. Looking at a range of impacts, our estimates suggest that the program expenditure of \$12.6 million (in real, present value terms) will lead to^v:

- Total benefits^{vi} for CRC recurrence monitoring (measured as reduced health system costs and improved patient health outcomes in Australia, in real, present value terms) between \$94.3 million and \$325.7 million over the next 10 years, depending on the assumptions made;
- A benefit cost ratio of between 7.2:1 and 30.5:1 for CSIRO.

^v CSIRO's R&D expenditure in context. This does not including expenditure born by clinical trials and implementation, etc.

^{vi} Note that these benefits do not include the potentially greater benefits if the two gene test is subsequently applied in a primary screening context following regulatory approval and royalty flows back to CSIRO from international sales.



<p>Financial</p> <ul style="list-style-type: none"> • By 2014 an estimated \$40 million was invested by all collaborators <p>CSIRO</p> <ul style="list-style-type: none"> • Purchase of original datasets from over 460 CRC cases as microchip arrays available from Gene Logic <p>CG & CSIRO</p> <ul style="list-style-type: none"> • IP/PATENTS \$501,135 <p>Government Grant</p> <ul style="list-style-type: none"> • 2007 CG & CSIRO CRADA: Commercial Ready Grant \$1.45M <p>In-kind</p> <p>CRADA (CG & CSIRO)</p> <ul style="list-style-type: none"> • 2007 CRADA: \$1M in-kind; • 2009 CRADA: \$700K in-kind; • 2009 CRADA: extension \$225K in-kind <p>Background IP</p> <p>CSIRO</p> <ul style="list-style-type: none"> • In-house technologies for screening genome-wide for differences in DNA methylation <p>Flinders</p> <ul style="list-style-type: none"> • Clinical expertise including CRC screening; specimen collection <p>CG</p> <ul style="list-style-type: none"> • Specific expertise in relation to CRC and diagnostic assay development • Commercial experience • Developing capacity for clinical trials • Laboratories in North Ryde & New Jersey 	<p>Biomarker Discovery & Validation Research</p> <p>2004-2010: Bioinformatics & Biomarker Discovery</p> <ul style="list-style-type: none"> • CSIRO, CG & Flinders • Analysis of gene expression dataset of 460 CRC cases for up and downregulated biomarker genes (Publication 1) • Identification of CRNDE among others (Publication 2) <p>2008-2011: Shift in research focus: Epigenetics & Methylated Biomarker Discovery</p> <p>CSIRO:</p> <ul style="list-style-type: none"> • Development and use of two in-house techniques for genome wide screening for differences in DNA methylation. • CSIRO, CG & Flinders • Characterisation of a panel of 66 genes demonstrating elevated DNA methylation in CRC tissue. • Differential methylation confirmed in 23 of 66 genes showing hyper-methylation in CRC tissue as a panel for clinical application (publication 5) <p>2010-2014: SHORTLISTING MARKERS & CLINICAL VALIDATION</p> <ul style="list-style-type: none"> • CSIRO, CG & Flinders • Selection of a subset of five gene targets (BCAT1, IKZF1, GRASP, IRF4 and CAHM) for CRC were selected • Clinical validation of lead candidates in blood plasma leading to an assay that detects two hyper-methylated genes (BCAT1 and IKZF1) found in colorectal cancer (Publications 6, 7, 9 & 12). 	<p>Discovery & Validation</p> <p>By 2014 Flinders, CSIRO and CG discovered and validated genes that are upregulated in CRC as well as genes downregulated and/or methylated in CRC</p> <p>Patents</p> <ul style="list-style-type: none"> • Six international patent applications for upregulated genes in CRC and downregulated methylated genes in CRC • Two international patents for in-house techniques developed by CSIRO; SuBLiME and Bisulphite-tag. <p>Publications</p> <ul style="list-style-type: none"> • 7 co-authored peer-reviewed publications in international journals 	<p>Commercialisation (CG)</p> <p>COLVERA™ blood test for monitoring recurrent CRC released on the US market December 2016</p> <p>Product uptake</p> <ul style="list-style-type: none"> • CG and Quest Diagnostic contracts increase awareness and access to test amongst partner oncologists and specialists monitoring post-treatment CRC patients • Contracts with Fortified Provider Network and Multiplan PPO facilitate a level of reimbursement through discounts offered to private health insurance partners <p>Capacity building</p> <p>Thirteen years of collaborative research experience</p> <ul style="list-style-type: none"> • Established skillset/capacity for valuable collaborative work • Collaborative projects a feasible option for future and under active discussion • Validated discovery can inform research and discovery for other cancer types 	<p>Economic impact</p> <ul style="list-style-type: none"> • Reduced economic burden on health care system. • Increase in labour productivity/ and labour force participation. • New products <p>Social impact</p> <ul style="list-style-type: none"> • Improved patient outcomes: Expected impacts through reduced mortality and improved quality of life through earlier cancer detection, both in the settings of recurrence monitoring and screening for early CRC • Innovation and human capital: Innovative epigenetics and biomarker discovery research has led to numerous licenses, patents and the eventual release of Colvera™. Through this process of innovation human capital has increased through the development and advancement of niche and valuable skills
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Figure 1: Impact pathway for discovery and commercialisation of biomarkers for Colorectal Cancer

2 Purpose and audience

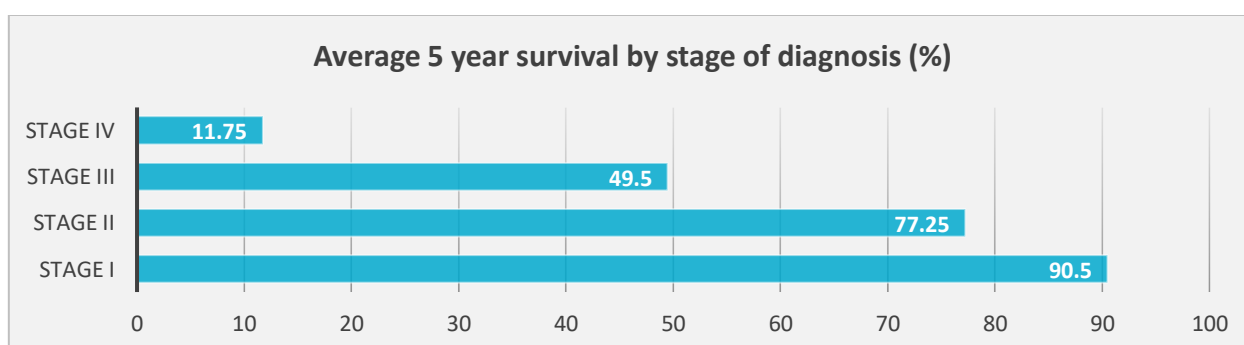
This case study can be read as a stand-alone study or alongside other evaluations to demonstrate the aggregated impact and value of CSIRO activities. The information provided is for accountability and communication purposes; and will contribute to continuing improvement. The intended audience includes members of Parliament, Government Departments, CSIRO, other researchers, and the general public.

The case study assesses the impacts arising from a new innovation known as Colvera™. CSIRO, in collaboration with Flinders and biotechnology company Clinical Genomics (CG), identified cancer-specific chemical changes (DNA methylation) at specific sites in the genome that is associated with colorectal cancer (CRC) and not found in normal colon tissue. These changes were demonstrated as detectable in the blood of patients with CRC. Clinical trials are in progress for commercialisation of a blood test for primary CRC, coordinated by CG. Colvera™ is now on market in the US as a blood test for asymptomatic recurrent CRC.

3 Background

Detecting and diagnosing primary CRC

CRC is the second most common cause of death from cancer in Australia, with almost 15,000 new cases diagnosed and 4,000 deaths annually. Worldwide it is responsible for more than 600,000 deaths annually. CRC leads to substantial financial costs to patients and the healthcare system, with expense increasing with the stage of diagnosis, subsequent treatment necessary¹, and surveillance post-treatment. Survival rates are inversely associated with the stage of primary diagnosis, which influences recurrence rates, and can be influenced by geographic location and private versus public hospital treatment. CRC mortality results from spread to, and ultimate impairment of, the function of other organs, otherwise referred to as later stage CRC. Where cancer has spread beyond the colon or rectum to either the lymph nodes or distant organs, indicated by the stage at which diagnosis occurs, survival rate post-surgery declines significantly to 72% and 14% respectively².



Source: Bowel Cancer Australia 2017

Figure 3.1: average 5 year survival by stage of diagnosis

Where screening for early stage CRC occurs, less than half (40%) of primary CRC cases are detected and diagnosed early as either Stage I or II. A similar rate (35%) is observed for Stage III and slightly less (20%) at Stage IV. Improving early diagnosis of primary CRC is therefore expected to increase opportunities for curative intent treatment and survival rate. Diagnosis of primary CRC can be inaccurate, intrusive, and culturally challenging, increasing anxiety and discomfort for patients, and reducing uptake and participation in screening and eventual diagnosis. The existing first line screening test, named Faecal Immunochemical Test (FIT), detects the presence of human blood in faecal samples. The test is not suitable for all people due to cultural and medical barriers to the required process for taking the test. Such suitability issues influence uptake particularly where the test is distributed as part of the national screening program; and participation in such programs can reduce as a result. In 2016, 37% of adults from 50-74 years old participated in the Australian Government’s National Bowel Cancer Screening Program³, which is offered for free. While it proves to be a cost effective test for screening programs, reducing advanced stage cases of CRC and saving lives, results can include false positives due to bleeding caused by other conditions.

Detecting and diagnosing recurring CRC post-treatment

Where CRC is diagnosed and treated, patients are enrolled in surveillance programs to detect any cases of recurrence post-treatment. CRC recurs in 30-50% of cases, most often within five years of treatment, with 90% presenting within two-to-three years. It is associated with a high risk of mortality, alongside economic and social costs. Early detection of recurrent asymptomatic CRC is expected to increase cure rates and to reduce associated costs. Monitoring for recurrent CRC post-surgery involves 3-5 years of surveillance. Surveillance is multi-pronged to allow for diagnostic deficiencies. Surveillance includes²:

Table 3.1: Monitoring for recurrent CRC post-surgery

<p>Office visit and CEA testing: 3-6 month intervals for first two years, then 6 month intervals for remaining three years</p>	<p>Office visits will not allow detection of asymptomatic recurrent CRC. CEA is a glycoprotein that is not specific to CRC, and immunoassays directed at CEA are relatively insensitive for the detection of recurrent CRC.</p>
<p>CT scans of chest, abdomen and pelvis: annually for five years</p>	<p>CT scans are limited in their ability to aid in the detection of micro-metastases, suffer from specificity issues, expose the patient to radiation, and are relatively expensive.</p>
<p>Colonoscopy: once in the first year following treatment</p>	<p>Colonoscopy is invasive, not without risk, and is limited to visualisation of the colon and rectum, and thereby is unable to detect the overwhelming number of recurrences because they develop outside of those organs.</p>
<p>Proctoscopy: 6-12 month intervals for 3-5 years (for rectal cancer patients who underwent resection with anastomosis 6-12 month intervals; patients with local excision 6 months intervals)</p>	

The least invasive and risk adverse method within the surveillance process is the Carcinoembryonic Antigen (CEA) test. The sensitivity and specificity of this blood test is suboptimal. Elevated plasma levels can be detected in CRC and other cancers; and are also found in smokers and people with a range of other inflammatory conditions. Improving early detection and diagnosis of primary and recurring CRC therefore relies on more accurate and less invasive detection methods, and synthesis between first line diagnostics and follow-up diagnostics.

CSIRO involvement

In the late 1990s/early 2000s information about molecular markers was becoming more specific and new methodologies for simultaneous quantification of expression levels of thousands of genes in a single experiment were becoming available. For example, microarray technology allowed unprecedented comparisons between colorectal cancer cases, normal tissue, and tissue from other colonic disease (e.g. ulcerative colitis) of gene expression levels of thousands of genes in a single experiment. Gene expression was then used as a vehicle for biomarker discovery. CG believed finding more specific molecular markers in blood, and subsequently developing them into a blood test, was an innovative way to solve the unmet clinical needs of colorectal cancer detection. CSIRO and Flinders were among the earliest research organisations to undertake extensive CRC gene expression analysis at this time. CG was well experienced in the industry, with scientific knowledge through proteomics expertise and the capacity to productise. From 2004, collaborative research between CSIRO, Flinders and CG, informed by unique skill sets and driven by commercial outcomes, commenced toward the discovery of molecular biomarkers for CRC. Research developed and evolved over time as the group remained opportunistic with respect to new technological advances and existing skill sets, driving break-through discoveries at the time in epigenetics.

From 2008, focus moved from targeting upregulated genes to identification of genes that were downregulated by DNA methylation. Further work focused on the development of DNA methylation biomarkers for detection of CRC in blood. This change in direction is attributable to CSIRO's expertise and existing in-house technologies; and proved pivotal for research progress. A range of approaches, including new methods for genome-wide analysis of DNA methylation, was used to identify and subsequently prioritise DNA regions that become methylated with high frequency in CRC toward an assay. Discovery and validation of genes that were downregulated and/or methylated in CRC led to filtering and narrowing down of gene targets in CRC to an eventual subset of the five most suitable as blood-based diagnostic markers. Clinical evaluation of these target genes led to identification of a two gene classifier model which demonstrated improved segregation of CRC from controls in blood plasma experiments. This research resulted in an optimised, sensitive assay to detect cancer-specific chemical changes in fragments of BCAT1 and IKZF1 tumour DNA found circulating in the blood.

4 Impact Pathway

Project Inputs

The research on biomarkers for detection of colorectal cancer is a collaboration between industry, government, and CSIRO. Table 4.1 demonstrates that the project has been the recipient of investment to the value of more than \$7 million from 2006-07 to 2015-16. Contributors included CG and the Department of Industry, Innovation and Science. In-kind contributions from CSIRO and CG in terms of access to infrastructure, staff time, and previously developed skills and capabilities were significant, but are difficult to quantify due to measurement constraints.

Table 4.1: Cash and in-kind support for project (\$'000, nominal)

CONTRIBUTOR / TYPE OF SUPPORT	2006-2008	2008-2009	2009-2010	2010-2011	2011-2012	2012-2013	2013-2014	2015-2016
CSIRO [#]	778	688	770	740	265	500	530	150
CG [^]	622	312	330	360	265			150
Department of Industry								150
Patents			360, 381		96, 431	44, 323		
Total								7,111

Footnotes to table

CSIRO input covers part of costs of development of Bis-tag, SuBLiME and HDCR technologies for DNA methylation analysis

[^] CG input matched by CSIRO under 2007 and 2009 CRADAs

@ Research Connection/Innovation connections – Rob Dunne (1) & Glenn Brown (2)

Activities

All collaborators had distinct expertise which allowed progress in discovery and validation over a decade. The collaboration commenced through CSIRO's Preventative Health Flagship partnership with Enterix Pty Ltd in 2004. Both parties signed a terms of agreement. The collaboration commenced with the purchase of a large gene expression microarray dataset that included approximately 460 cases. In 2006, Enterix merged with a subsidiary of Quest Diagnostics Inc., and the results of the 2004 collaboration were purchased by CG, a spin-out of the group behind Enterix, including the principal scientist. All agreements after this time including CRADAs of 2007 and 2009 were between CSIRO and CG.

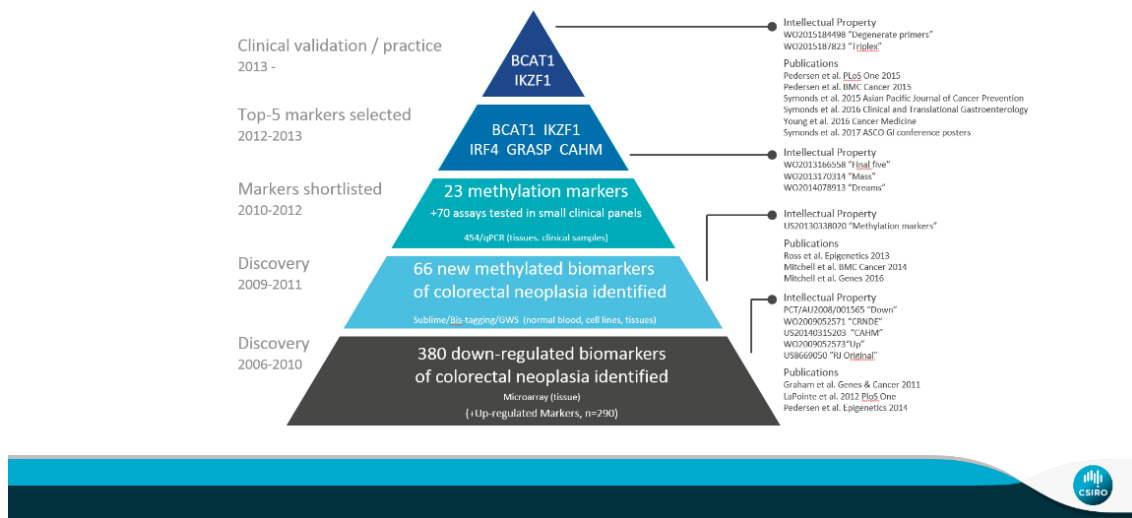
CSIRO's involvement in research continued through to 2014, at which point the technology was officially handed over to CG for commercial application. CG commenced preparation for commercialisation prior to 2014. There were three key phases in research activities prior to commercialisation:

Phase 1: 2004-2010: Bioinformatics Activity and Biomarker Discovery

Phase 2: 2009-2011: Epigenetics Activity and Methylated Biomarker Discovery

Phase 3: 2012-2014 Shortlisting markers and clinical validation

Colvera, our journey. A decade of discovery and validation



Source: Clinical Genomics slides 2017

Figure 4.1. Journey of Colvera

Phase 1, 2004-2010: Bioinformatics Activity and Biomarker Discovery

The first phase of this work utilised a large gene expression dataset of colon tissue on Affymetrix arrays. From 2004, the group performed a collaborative bioinformatics activity to find a core list of CRC biomarkers. An extensive gene expression dataset of 460 CRC cases, pre-cancerous adenomas, other colon diseases (e.g. ulcerative colitis), and control tissues were analysed to identify RNA biomarkers. A custom designed microarray targeted to leading candidate genes was used for analysis and validation of RNA markers in second case/control clinical samples. The arrays were used to identify genes that were up- and downregulated in CRC, and which might become targets for detection of protein or RNA in blood. From this lead list of candidate biomarker genes both upregulated and downregulated were validated (and patents filed).

Research in this phase paid most attention to upregulated genes in CRC as potential targets for detection of elevated levels of either protein or RNA in blood. Maintaining focus on upregulated genes for test development required obtaining good quality antibodies and an ability to detect elevated levels of secreted proteins in the blood of cancer patients. This proved resource intensive with limited results. A by-product of this phase was the identification of a novel non-coding RNA gene (CRNDE) that is highly upregulated in CRC, making it a potential blood biomarker. CRNDE was

subsequently proven as an important oncogene^{vii} regulating growth in a number of other cancers as well as CRC.

Phase 2, 2009-2011: Epigenetics activity and Methylated Biomarker Discovery

CSIRO's history and expertise with identifying regions of the genome that were downregulated as a result of methylation in cancer cells (including development of a prostate cancer DNA methylation biomarker) guided a shift in focus of the project to genes downregulated by DNA methylation. Importantly, a proof of concept using detection of aberrantly methylated DNA in the blood of CRC patients was demonstrated at that time. Collaborative research began to apply CSIRO's DNA Methylation Detection Technology to identify biomarkers for colorectal disease for the purpose of developing a diagnostic assay or test.

The research group worked through a number of approaches to develop a candidate panel of 66 DNA methylation markers in 2010. This research involved systematic analysis of DNA methylation in regulatory regions of a patented panel of 'downregulated' genes on a small set of clinical samples and colorectal cancer cell lines, and activation of expression of genes after treatment of CRC cell lines, with a DNA de-methylating agent. The two in-house technologies available from CSIRO – SuBLiME (publication 4) and Bisulphite-tag – allowed genome-wide screening for differences in DNA methylation. These methods were used to identify and subsequently prioritise DNA regions that became methylated with high frequency in CRC. The methods covered different genomic regions than those being used by other researchers; and, consequently, many of the markers identified were novel. Sequencing at individual nucleotide level of the methylation profiles across lead candidate genes uncovered optimised sites for assay development.

In 2011, a combined analysis identified 42 candidate genes for evaluation as DNA methylation markers. Differential methylation in CRC tissue was confirmed for 23 of these genes, identifying them as a panel for potential clinical application (see publication 5). The validity and potential of these markers was re-inforced through a large DNA methylation dataset that had become publically available from the international Cancer Genome Atlas project. Genes showing low levels of detectable methylation in white blood cell DNA were prioritised for further evaluation as blood-based diagnostic markers. This identified the suitability of 11 genes for blood-based diagnostic markers; six were designated as more appropriate biomarkers for stool-based assays.

Phase 3, 2010-2014: Shortlisting markers and clinical validation

Collaborative research worked on filtering biomarkers and testing in an initial set of plasma samples for CRC patients and controls. By 2012, a subset of five gene targets (BCAT1, IKZF1, GRASP, IRF4 and CAHM) for CRC were selected. Further testing of a gene two-marker combination, BCAT1 and IKZF1, in plasma obtained from a colonoscopy demonstrated the efficacy of a two-gene classifier model ("either or" rule) for improving segregation of CRC from controls, with 57 of 74

^{vii} Gene with potential to cause cancer.

cancers (77%) compared to only 11 of 144 (7.6%) controls being positive for BCAT1 and/or IKZF1 DNA methylation (see publication 7). The resulting blood test would use this two-gene classifier model to detect cancer-specific methylated DNA in fragments of BCAT1 and IKZF1 found circulating in the blood. In 2014, CG and CSIRO signed an exclusive license agreement based on their jointly discovered and patented biomarkers for colorectal cancer. The agreement allowed CG to develop, deliver, and promote a blood test for bowel cancer as an international innovation.

Outputs

R&D Discovery and Validation deliverables

CSIRO and Enterix/CG have collaborated since 2004 under specific terms. A CRADA was signed in 2007, and a further CRADA in 2009, to conduct collaborative research together. As part of the collaboration, the parties jointly own certain biomarkers for colorectal disease. From 2014, Flinders, CSIRO, and CG delivered a set of seven co-authored peer-reviewed publications in international journals leading to the current assay, and six related international patent applications (see below).

These publications and patents cover the discovery^{viii} and validation of genes that are upregulated in CRC (publications 2 & 3; patents 1 & 3), as well as genes downregulated and/or methylated in CRC (publications 3, 5, 6, 7 & 8; patents 2, 4, 5 & 6). These latter patents provide the key IP for the Colvera™ product. By the end of the discovery phase, CSIRO had optimised sensitive assays for the detection of methylated DNA sequences of target genes and transferred this technology to CG for further development and optimisation as commercial assays. Through its associated research, CSIRO also delivered new methods to screen for differential DNA methylation (bisulphite-tag, patent 7), and to enrich for methylated DNA prior to deep bisulphite genomic sequencing, SuBLiME (publication 4; patent 7).

R&D Commercialisation deliverables

The range of expertise available in the research collaboration allowed consistent market focus and rapid commercialisation of discoveries. From 2011, preparation for commercialisation commenced with technology transfer to CG. This commercial development included delivery of optimised specimen processing and automated testing to deliver an end product capable of high performance and scalability. CG's comprehension of commercial requirements and processes for carrying out product development and clinical trials, resulted in the NATA standard North Ryde Laboratories in NSW, Australia and the CLIA registered CG Pathology (CGP) lab in Bridgewater, N.J. CG, in collaboration with multiple partner organisations, delivering numerous clinical trials as required by regulatory bodies for US and Australian market entry and prospective diagnostic trials to demonstrate market advantage.

^{viii} The intention of collaboration starting from 2004 was discovery and commercialisation of biomarkers for CRC. The CSIRO was not involved in any direct commercial activities, including clinical trials and studies about market products. It is considered useful to refer to discovery and shortlisting of markers as separate from commercialisation in an effort to recognise CSIRO contributions. It is noted that discovery can occur within commercialisation activities.

Market Entry decisions

CG is leading clinical trials with partners to gain regulatory and reimbursement approval for the entry into the US and Australian markets of an early detection blood test for primary CRC screening. The aim of screening is to improve chances of detection and diagnosis of primary CRC for curative intent surgery and therapies. The required clinical trials are due for completion by the end of 2019. This requirement was recognised by CG as a delay for market entry. To avoid delay they identified a further need for improved testing for recurrent CRC as an opportunity to save lives. Furthermore, blood testing for monitoring CRC recurrence presents lower commercial and regulatory hurdles than screening for primary CRC. Importantly, the existing test for CRC recurrence monitoring, CEA, is considered to have low sensitivity and specificity, thus presenting a compelling clinical and commercial opportunity. Colvera™ was demonstrated in a clinical trial to have twice the sensitivity of CEA in head-to-head trials (publication 14).

In 2017, CG established a contract with Fortified Provider Network and Multiplan Preferred Provider Organisation (PPO) to offer a discount to private health insurance entities who are members of those PPO networks. This contract is a reasonable first step to reimbursement. CG, through an existing strategic partnership with Quest Diagnostics, arranged facilitated access and distribution of the test to and for the relevant US medical practitioners (i.e., physicians, oncologists or GPs) performing routine surveillance of patients for CRC recurrence.

Publications

(Numbers of citations, from ISI and Google Scholar shown in brackets after each publication)

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14. Young GP, Pederson SK, Mansfield S, Murray DH, Baker RT, Rabbitt P, Byrne S, Bambacas L, Hollington P, Symonds EL. 2016. A cross-sectional study comparing a blood test for methylated BCAT1 and IKZF1 tumor-derived DNA with CEA for detection of recurrent colorectal cancer. *Cancer Medicine*. Doi. 10.1002/cam4.868 (1; -)

Patents

Table 4.2 provides details of the title, registration number and status of the active Australian filed patents arising from the project.

Table 4.2: A list of patents from the project

	Title	Registration Number
1	Colorectal cancer gene expression markers, upregulated.	WO 2009052573 A1
2	Colorectal cancer gene expression markers, downregulated.	WO2009052567-A1
3	A novel gene, CRNDE a RNA biomarker	WO2009052571-A1
4	Candidate panel of 66 DNA methylation markers	WO2012034170-A1
5	DNA methylation in colorectal and breast cancer diagnosis (CAHM gene).	WO2013026104-A1
6	A subset of five gene targets for CRC	WO2013166558-A1
7	Genome-wide analysis of DNA methylation (Bisulphite tag)	WO2011017760-A1
8	Genome-wide epigenetic analysis by enriching for methylated molecules (biotin capture)	WO2011057354-A1

Outcomes

The Colvera™ assay is used for monitoring patients for recurrence following primary CRC treatment.

Colvera™ has achieved a first mover advantage in the target market of detecting recurrent CRC using a blood test. It presents a new opportunity for oncologists to potentially improve detection and treatment regimens for CRC through improved early stage disease detection accuracy, thereby potentially leading to improved patient survival. Colvera™ has multiple potential applications, including pre- and post- curative therapy testing; prognosis; and therapy monitoring. Intended as a complement to existing surveillance procedures, a positive result indicates the high likelihood of recurrence, and is intended to be followed by radiographic imaging or other diagnostics as appropriate. A negative result indicates low probability of recurrence, and regular surveillance can continue. Curative intent therapies and survival rates for CRC recurrence are expected to increase. Adoption channels include commercialisation and capacity building, such as training and further research activities.

Commercialisation

In December 2016, Colvera™ was launched by CG in the US market, and is presently available throughout the US. It is marketed as providing a better monitoring tools for colorectal cancer survivors. It is expected the test will become available in Australia in 2018.

Recurrence Monitoring

Colvera™ improves health outcomes by following a proven test/treatment pathway. The assay demonstrates an ability to improve detection of early stage asymptomatic recurrent CRC compared to the current guidelines-recommended CEA test. It is therefore likely to provide an increased rate of curative intent therapy and improved survival benefit^{ix}. Detecting recurring CRC at an asymptomatic stage may improve broader outcomes by providing doctors and patients with less-intensive improved treatment options. Patients' and carers' well-being and quality of life is expected to be positively influenced.

Primary CRC screening (potential)

Colvera's™ ability to detect primary CRC has been clinically validated in multiple prospective, blinded clinical studies covering over 4,000 patients whose status has been confirmed by colonoscopy and/or imaging. These peer reviewed, published studies indicate that Colvera™ has a higher level of specificity (88-94%) for CRC detection compared to FIT, and a similar level of sensitivity. Currently <40% of eligible Australians participate in the National Bowel Cancer Screening Program. It has been estimated that lifting the screening proportion to even 50% would result in the detection of about 200 additional cancers each year in Australia. Use of a blood-based

test such as Colvera™ as an adjunct to the screening program may improve overall screening participation by providing an alternative path for people currently not participating in stool testing for medical or personal reasons.

Expected adoption in the future

As a complementary monitoring tool within existing oncological treatment procedures and processes, uptake and adoption of Colvera™ will rely on medical practitioners being aware that the test exists, having easy access to the test, and understanding its value to a point that they feel comfortable offering or recommending it to patients as standard diagnostic for routine surveillance. Utilising existing distribution channels of Quest Diagnostics for logistical purposes and direct access to medical practitioners in the US market is therefore accepted as contributing to adoption. Arranging contracts with Fortified Provider Network and MultiPlan PPO plans will allow access to Colvera™ at a discounted price through specific health insurance providers. This approach is expected to increase the adoption of the test. As adoption of Colvera™ in the US market increases, use of the CGP laboratory will also increase.

When the product is able to satisfy regulatory requirements for Australian market entry, the NATA accredited laboratory in North Ryde is expected to be used as the site for clinical testing. Colvera™ as a blood test for early detection of primary CRC, will complete necessary clinical trials by the end of 2019, at which point all clinical trials completed to date, and those expected as complete by the end of 2019, will eventually allow introduction of an assay for detection of primary CRC. There is limited uptake of FIT for CRC screening in Australia; and existing studies have demonstrated potential efficacy of a blood test to complement or follow up the FIT for CRC screening. Adoption rates in Australia and globally will most likely depend on reimbursement opportunities and arrangements.

Capacity building

The research leading to the development of Colvera™ involved identification of sets of genes that showed significantly elevated or reduced expression in CRC relative to normal colon tissue. Changes in expression of many of these genes, including BCAT1 and IKZF1, may contribute to development of CRC. The research program also identified two previously uncharacterised long non-coding RNAs, CAHM (downregulated/methylated) and CRNDE (upregulated). The scientific impact is evidenced by the citation rates of publications, including the key biomarker paper (publication 5) and the papers describing the CRNDE and CAHM genes (publications 2 & 6). The CRNDE gene became the focus of further research within CSIRO as an OCE postdoctoral fellow project. This further work characterised the gene in depth and showed its importance in regulating key aspects of growth regulation in response to insulin and insulin-like growth factor^x. Amassing partners with distinct and unique expertise and experience in the field encouraged strategic decision making. All discoveries made through the project pushed the boundaries of their time in

^x 2 additional highly cited publications

epigenetics; and as such, this project is considered as advancing knowledge in this field with the potential of contributing to research for other cancer types. For example:

- The discovery of now patented unique non-coding RNA gene CRNDE has subsequently been shown by others to be an important driver of oncogenesis in a number of cancer types, including gliomas, gall bladder, and liver cancers.
- The project has allowed the CSIRO team to maintain high level expertise and capability in epigenetics and DNA methylation, as well as important insight into the diagnostic industry and its regulatory and commercial requirements.
- Collaborative projects are a feasible option for the future and under active discussion.
- Internally, within CSIRO, the technology and bioinformatics expertise developed through the program has led to significant involvement in the Probing Biosystems Future Science Platform. This new program is targeted to identification and characterisation of brain injury through DNA released into the blood stream post trauma.

The Colvera™ assay is used for monitoring patients for recurrence following primary CRC treatment.

Colvera™ has achieved a first mover advantage in the target market of detecting recurrent CRC using a blood test. It presents a new opportunity for oncologists to potentially improve detection and treatment regimens for CRC through improved early stage disease detection accuracy, thereby potentially leading to improved patient survival. Colvera™ has multiple potential applications, including pre- and post- curative therapy testing; prognosis; and therapy monitoring. Intended as a complement to existing surveillance procedures, a positive result indicates the high likelihood of recurrence, and is intended to be followed by radiographic imaging or other diagnostics as appropriate. A negative result indicates low probability of recurrence, and regular surveillance can continue. Curative intent therapies and survival rates for CRC recurrence are expected to increase. Adoption channels include commercialisation and capacity building, such as training and further research activities.

Impacts

Colvera™ is targeted at improving health information management which leads to a variety of impacts, most significantly reduced health system costs, improved health outcomes, and time savings. The economic and social benefits of this project to date are potential impacts due to the only recent launch of the commercial product Colvera™ as a recurrence monitoring test. CG is leading clinical trials with partners to satisfy regulatory requirement for US and Australian market entry as an early detection blood test for primary CRC screening. Using CSIRO's triple bottom line impact classification approach, Table 4.3 summarises the nature of the existing and potential impacts of the Colvera™ technology.

Table 4.3: Summary of project impacts

TYPE	CATEGORY	INDICATOR	DESCRIPTION
Economic	Productivity and efficiency	Reduced economic burden on healthcare system	Early stage detection and diagnosis can reduce associated healthcare costs ² , reduce intensive treatments and improve survival rates.
Economic	Productivity and efficiency	Increase in labour productivity and labour force participation	A more targeted and timely treatment will lead to an increase in labour productivity and labour force participation. This impact encompasses illness-related lost earnings, absenteeism, premature death and additional search and hiring costs for replacement workers.
Economic	New products	Blood test for detection of asymptomatic CRC recurrence	Colvera™ is a new blood test that can detect asymptomatic CRC in patients under surveillance post-treatment. This reaches a market niche for CRC recurrence detection a market currently dominated by one test, the CEA test
Social	Health and Wellbeing/Q quality of life	Where CRC recurrence is detected as asymptomatic, curative intent therapies will increase and intensive long-term treatment decrease.	Where CRC recurrence is detected as asymptomatic, curative intent therapies will increase and intensive long-term treatment decrease. This is expected to improve the health and wellbeing of CRC patients and carers post-treatment.
Social	Innovation and human capital	Development and advancement of niche and valuable skillsets.	Innovative epigenetics and biomarker discovery research has led to numerous licenses, patents and the eventual release of Colvera™. Through this process of innovation human capital has increased through the development and advancement of niche and valuable skills.

5 Clarifying the Impacts

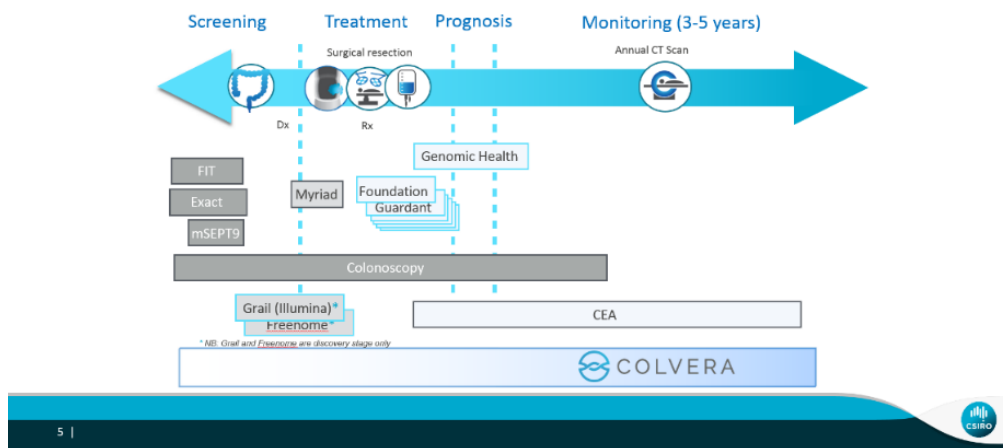
Counterfactual

CSIRO had established history and expertise in research area^{xi} which influenced the decision to re-focus work on DNA methylation markers for downregulated genes in 2008. Work towards creating new biomarkers and focusing on upregulated genes in CRC cells was proving resource intensive and difficult. If the re-focusing had not occurred, the amount of progress and eventual development of Colvera™ may not have occurred within the same timeframe.

^{xi} Including development of a prostate cancer DNA methylation biomarker.

The Competition

Colvera™ occupies a large, open market with multiple test opportunities



Source: CSIRO via Clinical Genomics 2017

Figure 5.1: Competitors operating in similar domain

There are a number of competing tests used in screening for primary CRC (e.g. FIT, Exact Science, and SEPT9) and monitoring for recurrent CRC (e.g. CEA) (see Figure 5.1). Given the data constraints and scope of this evaluation, discussion will focus on the evaluation of the effect on recurrent CRC detection. CEA, the blood test currently used in post-treatment surveillance programs, has low sensitivity, and is subject to false-positive results, limiting its usefulness in early detection. The goal of early detection of primary or recurrent CRC is to allow for surgical resection of the tumour with curative intent.^{xii} As identified in the discussions above, the CSIRO project scenario has been simplified into three broad key elements:

Without CSIRO involvement, progress, and the eventual development of Colvera™, may not have occurred within the same timeframe. The commercial value of first mover advantage is difficult to determine precisely, but given the lack of equivalent technology available at the time Colvera™ was commercialised, we estimate that it would have taken roughly 5 years for other researchers to develop technology that is similar to Colvera™ in the absence of CSIRO.

Colvera™ will be launched in the Australian market in 2018 once Australian regulatory requirements, including commercial laboratory accreditation, are met. The impacts are expected similar to those projected for the US market.

The healthcare system and patients in Australia will have access to a blood test that will increase ability to detect primary CRC in early stages.

^{xii} In Stage 4 CRC patients, neoadjuvant chemotherapy may be used to shrink the metastatic tumours sufficiently to allow for curative intent surgery. Most patients diagnosed with Stage 1, 2 or 3, and an increasing percentage of Stage 4 primary CRC are candidates for curative intent surgery. Following surgery for primary CRC, a large percentage of patients are considered to have no evidence of disease.

The counterfactual scenario describes what happens if CSIRO's Colvera™ technology is not implemented and the status quo or extension of current technology prevails. Conversely, the Counterfactual scenario includes the following two broad key elements:

- The current approach, CEA testing for CRC recurrence, would prevail, resulting in slower and less effective monitoring of CRC recurrence.
- No adoption of technology similar to Colvera™ as a benign and relatively cost-effective method of monitoring of CRC recurrence in the next 5 years.

6 Evaluating the Impacts

Cost Benefit Analysis (CBA)

Modelling approach

This section examines the impacts that Colvera™ technology has generated (economic, social, and environmental). This analysis examines two specific types of impacts: economic and non-economic. Economic impacts are considered to be impacts that have a definitive dollar value, such as an increase in productivity or a reduction in costs expended to the Australian healthcare system. Non-economic impacts are those qualitative impacts, such as improved health outcomes. We calculated Colvera™ deployment as a new technology for monitoring CRC recurrence and the counterfactual (or base) scenarios to determine the value of the entire research program's benefits (where quantification was possible). The counterfactual scenario represents the pathway where the Colvera™ technology is not implemented, and a 'status quo' or extension of current technology, CEA in this case, prevails. The benefits calculated in the analysis are the net benefits from the program, that is, they are not the difference between the 'with-' and 'without program' scenarios. The analysis is equivalent to carrying out separate analyses for the 'with' and 'without' program scenarios, and calculating the difference between them.

Due to data constraints, many of the assumptions required to value the impacts are uncertain. While reasonable and conservative assumptions have been made in the analyses, the results should be viewed with caution. This valuation provides a ball-park estimate of the potential net benefits. Therefore, there is a need for a revision of the valuation once the results of the accurate uptake/adoption become available.

Intervention modelled

Guidelines for primary CRC patients are generally consistent as recommended by both the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN). A multi-pronged surveillance regimen over five years after initial treatment for patients other than those unable to tolerate curative intent surgical or adjuvant therapy is recommended due to comorbidities. These guidelines are targeted primarily at patients with Stage 2 and 3 primary CRC; but it is also recommended that selected patients with Stage 1 colon and rectal cancer with increased risk factors be considered for surveillance following resection with curative

intent². The Colvera™ test is recommended as either a replacement for, or adjunct to, CEA, as it is twice as sensitive in detection of CRC recurrence. Colvera™ is available by physician order only and its use is limited to patients currently under surveillance for recurrent CRC. The Colvera™ pathway is consistent with, and improves upon, the use of CEA when selecting patients for accelerated imaging and further follow up. Colvera™ is likely to provide improved survival benefit compared to CEA; and to reduce the high costs associated with the detection of more advanced symptomatic recurrent CRC. A positive Colvera™ result indicates a high likelihood of recurrent CRC tumour; and should be followed up with radiographic imaging (chest, abdomen and pelvic CT scans) or other diagnostic workup as clinically appropriate. A negative Colvera™ result indicates a low probability of CRC tumour in the patient; and that no radiographic imaging outside of guideline-recommended intervals scans is warranted.

The steps in quantifying the gains from the program are as follows:

1. Estimate the benefits for CRC patients and Australian health systems in the counterfactual case (world without Colvera™ and the world with Colvera™).
2. Estimate the costs of research and implementation to adopt the technology.
3. Aggregate the costs and benefits to obtain a net benefit. All past benefit flows are compounded forward to 2016/17; and the benefits from 2016/17 are discounted back to 2016/17 at a real discount rate of 7% to convert to a present value in 2016/17.

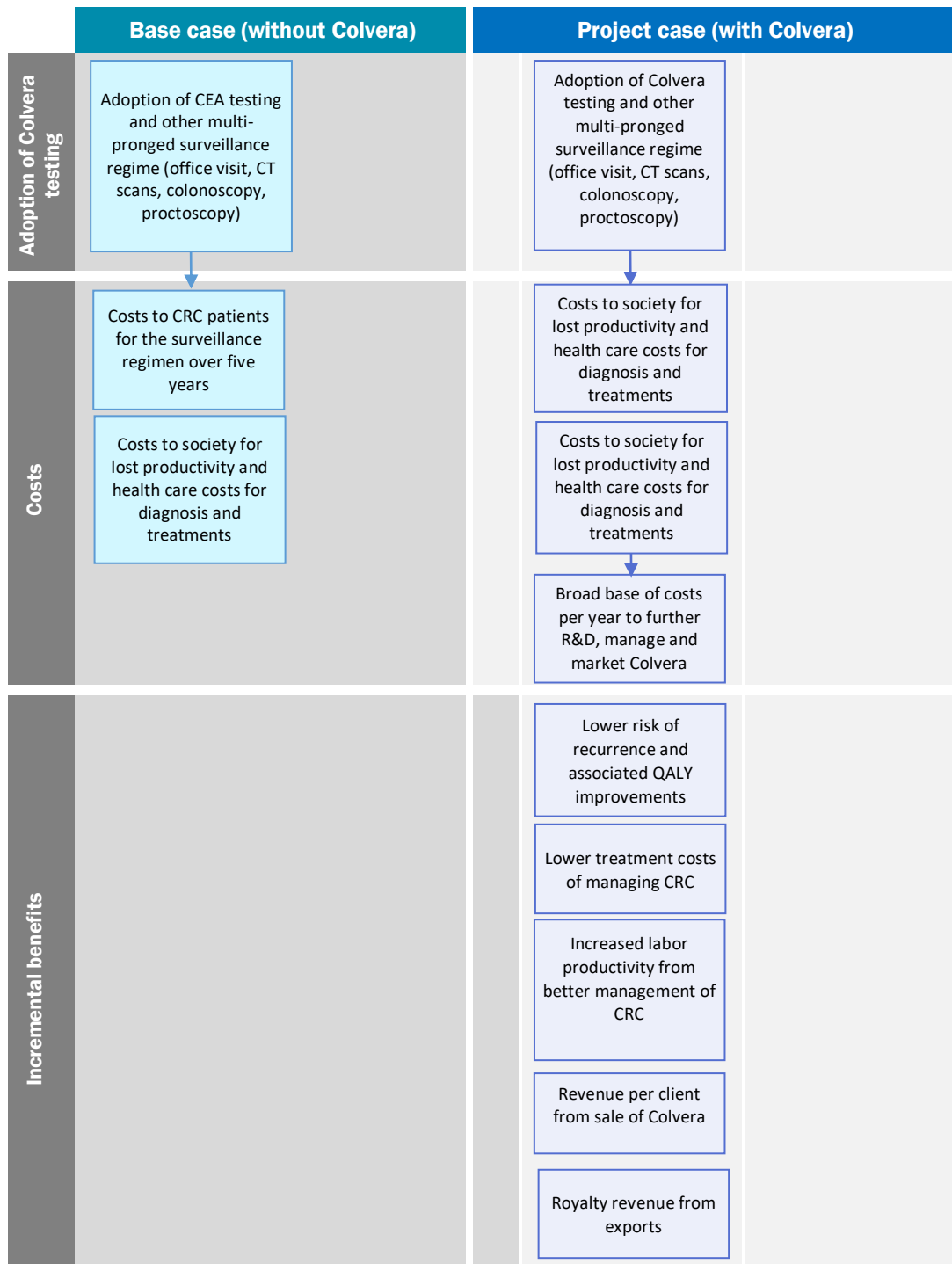


Figure 6.1: The costs and benefits associated with the adoption of Colvera testing

Perspective and stakeholders

This CBA was conducted from a societal perspective of the Australian Healthcare System, including all important economic costs and benefits arising from such an intervention. Costs and benefits to other potential stakeholders of this project will be taken into consideration, including:

- Clinical Genomics
- CSIRO
- Primary CRC patients
- Australian health care system.

Time horizon and target population

While the research program is an ongoing activity, it is necessary to define a particular period for the CBA. Given the history of the project, the analysis is based on research activity since 2006/07.

In the program, there were lags between the scientific discovery, and the realisation of benefits after adoption by government agencies and other end users. In recent years, the lag has averaged 10 years. On that basis, the benefits are only measured from 2017/18 onwards. We assume that the first year of surveillance regimen is 2017/18, giving a period of five years after initial treatment for patients until the end of 2021/22, where necessary until the end of 2026/27. In the analysis, the costs from 2006/07 are included.

Thus, the analysis involves a small component of ex-post analysis (relating to the costs in the period 2006/07-2017/18), but also a large component of ex-ante analysis, forecasting the benefits flowing from the research activities over the period to 2026/27. All input data are based on the latest data available, adjusted to reflect these start and end dates. A discount rate of 7% for both costs and benefits will be used. The starting year for costs will be dependent on the research costs record. Population coverage refers to Australia's population at the end of 2015, using Australian Bureau of Statistics (ABS) data on Australian census in 2016. The target population refers to CRC patients with primary treatments (e.g. curative intent surgical or adjuvant therapy), calculated by using the prevalence in Australia. The target population is divided into two groups based on the stage of CRC: stage 2 and 3 only according to the surveillance regimen guidelines provided.

Benefits of risk reduction and associated quality of life improvement

Clinical benefit to the patients and their families will be the enhanced quality of life due to early detection. Value of a Statistical Life (VSL) has been introduced in economic evaluation by economists to assess the benefits of risk reduction efforts. VSL is defined as the additional cost that individuals would be willing to bear for improvements in reductions in risks such as driving an automobile, smoking a cigarette, and eating a medium-rare hamburger. By convention this is usually assumed to be the life of a young adult with at least 40 years of life ahead. For many purposes, we want to know the value of a year of life because in many cases, especially in health interventions, we can save a small number of years of life rather than 40 years. Therefore, the value of a life year (VLY) is used instead of VSL. Most often VLY is taken to be the constant annual sum which, taken over a remaining life span, has a discounted value equal to the estimated VSL. The VLY may also be described as the value of a quality adjusted life year (QALY).

In Australia, a constant VLY of \$187,104 is proposed, which is independent of age. During the calculation of benefits, we have to assume the life expectancy gains for each patient from getting the new intervention, Colvera™, will have at least the identical life expectancy gains with getting the current best intervention, CEA, as no research has been conducted to measure the effectiveness of the new intervention. The mean life expectancy gain of using CEA is 0.3%⁵. Therefore, the main clinical benefit of having Colvera™ will be the extra number of patients

detected by the new intervention and the increase in their life expectancy. These assumptions will be tested in sensitivity analysis.

- CRC new cases: This number is taken from the Australian Institute of Health and Welfare (AIHW) report in 2017⁴. However, no relationship between CRC new cases and population can be discovered so far. This figure is assumed to be fixed in each year over the project period.
- CRC existing cases: Similar to the CRC new cases, this figure is also taken from AIHW report⁴, and is assumed to be constant over the project period. In addition, all existing CRC cases are assumed to be primary patients that are eligible for the modern surveillance protocols.
- Colvera™ uptake rate: The coverage of new intervention (Colvera™) that will replace the current test (CEA) is assumed to be 20%, 40%, 60%, 80% and 100% from Year 1 to 5 (2017-2020). From 2021 onward, the Colvera™ will replace all CEA as the recurrence monitoring test for CRC patients.

Based on the above assumptions, the value of ‘quality of life’ is \$5.7 million by 2026-27. The calculation for this impact is presented in Table 6.1.

Table 6.1: Impact calculation of improved health outcomes

Measure		Value	Source
With CSIRO research			
A _R	Number of CRC primary recur under surveillance	Various	AIHW 2016
B _R	Uptake rate of Colvera™	100% by year 5	Author’s assumptions
C _R	Detection rate of Colvera™	30%	ECRI Institute 2017
D _R	Positive detection rate of Colvera™		ECRI Institute 2017
	Stage 2	10.2%	
	Stage 3	20.4%	
E _R	Number of positive detection of Colvera™	$= A_R * B_R * C_R * D_R$	
Counterfactual			
C _c	Detection rate of CEA	30%	ECRI Institute 2017
D _c	Positive detection rate of CEA		ECRI Institute 2017
	Stage 2	4.8%	
	Stage 3	9.6%	
E _c	Number of positive detection of CEA	$= A_R * B_R * C_c * D_R$	
F	Life expectancy gains attributable to CRC	0.3%	Kievit 1990
G	Value of a life yea (VLY) (\$)	\$151,000	Abelson 2008
Impact	World with CSIRO research – counterfactual		
	Increase in quality of life due to early detection (\$ per annum)	$= (E_R - E_c) * F * G$	

Note: the number of positive detection are not based on full 5 year follow-up

Benefit of reduced health system costs

Reduced pressure on the healthcare system for advanced stage treatment in cases of CRC recurrence is expected. Under conservative assumptions, Colvera™ is cost saving within the first year of use. A payer’s specific difference between the costs of identification and 12 month

treatment of asymptomatic recurrences and symptomatic recurrences is a significant determinant of the value of improved surveillance methods.

Detection of additional recurrence cases moves patients to a relatively lower cost and much less significant clinical impact cohort. Each recurrence moved from a symptomatic detection state to an asymptomatic detection state via improved surveillance tools saves an estimate \$US100, 000 (\$A132, 538). Colvera™ is therefore expected to reduce the high costs associated with the detection of advanced stage recurrence. The value of reduced health system costs is \$1.7 billion by 2026/27. The calculation for this impact is presented in Table 6.2.

Table 6.2: Impact calculation for health system costs

Measure		Value	Source
With CSIRO research			
A _R	Number of CRC primary recur under surveillance	Various	AIHW 2016
B _R	Uptake rate of Colvera™	100% by year 5	Author's assumptions
C _R	Detection rate of Colvera™	30%	ECRI Institute 2017
D _R	Positive detection rate of Colvera™		ECRI Institute 2017
	Stage 2	10.2%	
	Stage 3	20.4%	
E _R	Number of positive detection of Colvera™	$= A_R * B_R * C_R * D_R$	
Counterfactual			
C _c	Detection rate of CEA	30%	ECRI Institute 2017
D _c	Positive detection rate of CEA		ECRI Institute 2017
	Stage 2	4.8%	
	Stage 3	9.6%	
E _c	Number of positive detection of CEA	$= A_R * B_R * C_c * D_R$	
F	Saving from each early detection patient	\$132,538	ECRI Institute 2017
Impact	World with CSIRO research – counterfactual		
	Saving in health system costs of burden of CRC recurrence with	$=(E_R - E_c) * F$	

Further impacts

This section provides an overview of the causal linkage from the adoption of the Colvera™ testing to generate other impacts that could not be quantified, along with examples evidencing the extent to which they have been realised to date.

Sales revenue and licensing fees

CSIRO has exclusively licenced key components of the technology to CG, in return for royalties on revenues. We are unable to quantify the benefits to CG due to commercial confidentiality issues.

Increased labour productivity and labour force participation

Adverse health impacts not only generate direct financial costs to the health system and non-financial costs of the burden of disease, but a range of additional costs to the Australian economy. Some of the additional flow-on impacts are⁷⁸:

- Productivity losses – short and long-term employment impacts and premature mortality;
- Carer costs – the value of community care services provided primarily by informal carers;
- Deadweight Loss (DWL) from transfers – taxation revenue foregone, welfare, and other government payments; and,
- Other costs – aids, equipment and modifications, transport and accommodation costs, respite and other government programs, and the bring-forward component of funerals.

In this case study, increased labour productivity and labour force participation of mature age workers⁹ are flow-on effects from having more targeted patient treatments associated with early detection from Colvera testing and reducing prevalence of CRC. A healthier workforce is generally more productive, and spends less time out of work due to CRC-related treatments and complications.

Contribution of CSIRO

The results above are modelled for both CSIRO and CG inputs, and combined impacts. This evaluation has been undertaken by CSIRO to understand the payoff from the technology, as identified above, and to identify specifically the potential net benefit and success of CSIRO. It is therefore necessary to tease out CSIRO's costs and benefits – requiring a disaggregation of the positive externalities back to either CSIRO, or to CG and other contributors.

CSIRO had an established history and expertise in the area of DNA methylation biomarkers.^{xiii} This highly influenced the decision to, and feasibility of, refocusing the biomarker pipeline work in 2008 to identifying downregulated genes by DNA methylation in CRC tissue. Development of genome-wide DNA methylation technologies, Bisulphite-tag and SuBLiME, is entirely attributable to CSIRO. This change in focus is considered to have saved time and resources compared to continuing to try and develop biomarkers with upregulated genes, and, subsequently, shifted the nature of the product developed. The resulting discoveries are attributed to all collaborators. Within the commercialisation phase (post-2014), CG led progress usually in collaboration with Flinders, but also with a range of other collaborators. CSIRO and CG were both considered necessary to achieve the ultimate objective of developing an effective monitoring method for CRC recurrence, it was appropriate to attribute benefits among the project on a cost-sharing basis. CSIRO accounted for approximately 10 per cent of total research and implementation costs. Consequently, it is assumed that roughly 10 per cent of research impacts arising from CSIRO's research can be attributed to CSIRO.

Based on the above, this case study will attribute total impacts as follows:

CSIRO – 10%

CG and others – 90%

^{xiii} Including development of a prostate cancer DNA methylation biomarker

Costs

In principle, establishing costs involved throughout the entire impact pathway is an important exercise of a CBA. This includes both the input costs incurred by CSIRO and its collaborators, as well as any usage and adoption costs borne by clients, external stakeholders, intermediaries, and end users. For Colvera™, these costs include clinical trials and implementation. CSIRO and its research partners contributed \$12.6 million respectively to research between 2006/07 and 2016/17 in real terms. Clinical trials and implementation costs are estimated to be \$48.2 million and \$282.9 million respectively. Table 6.3 summarises the adjusted costs for researching, developing and implementing the Colvera™ technology.

Table 6.3: Summary of CSIRO and industry adjusted project costs (\$m CPI adjusted, discounted at 7%)

	Present value of R&D costs (2006/07- 2016/17)	Present value of Clinical trials costs(2006/07- 2016/17)	Present value of implementation cost (2017/18 to 2026/27)
Total (\$m)	12.6	48.2	282.9
% of total cost	3.7	14	82.3

SOURCE: CSIRO

Table 6.4 summarises the present value of the increased benefits resulting from reduced health system costs and improved CRC patient outcomes in terms of QALY. Benefits ranges from \$1.67 billion ('Program in context') to \$166.5 million ('CSIRO in context'). Assuming total costs of \$343.8 million and \$12.6 million respectively, then BCRs from the research range from 4.8:1 ('Program in context') to 13.3:1 ('CSIRO in context'). Despite the conservative estimates of the potential benefits that might be delivered by CSIRO's research program, the total estimated benefits comfortably exceed the costs of research. Please note that these figures are for the Australian market only. The US and other markets will also provide economic benefit to CSIRO and Australian community at large through increased royalties.

Table 6.4: Results of Cost Benefit Analysis

Criteria	Program	CSIRO
Present value of costs (\$ m)	\$343.8	\$12.6
Present value of benefits (\$ m)	\$1,665.3	\$166.5
Net Present Value (NPV)	\$1,321.5	\$154.0
Benefit-cost Ratio (BCR)	4.8	13.3

7 Sensitivity analysis

While Colvera™ demonstrates successful attributes, the effectiveness of new testing for monitoring CRC recurrence is not certain. The overall benefits of this project depend on adoption profile and actual social and economic benefits. This adoption related to outcomes and impacts resulting from integration into surveillance monitoring for recurring CRC will take place in the future. There is, therefore, considerable uncertainty in respect of the results of the analysis due to the assumptions employed in the model, as well as the lack of generalisable data for use in the Australian region. As such, impact analysis outcomes are associated with some uncertainty. Where this data becomes available, a revision of the analysis is highly recommended, as more data is needed to substantiate this outcome. As this was not available at the time of preparing this report, consideration of this issue is based on data published in 2017².

Given these uncertainties, it would be useful to look at results under different discount, adoption, and attribution rates. Table 7.1 presents the sensitivity analyses results for selected key variables on Present Value (PV) of benefits and BCR at 7% discount rate. Overall, all scenario analysis proved that this project is generating more benefit than the cost despite assumptions and uncertainty.

Table 7.1: Sensitivity analysis results

Scenario	Assumption	Description	NPV @7% (\$m)	BCR
Scenario 1	Uptake rate change to 5%, 20%, 40%, 60% and 90% respectively	Project	\$1,007.5	3.9
		CSIRO	\$122.6	10.8
Scenario 2	LE becomes 1.4%	Project	\$1,347.3	4.9
		CSIRO	\$156.6	13.5
Scenario 3	LE becomes -0.2%	Project	\$1,309.8	4.8
		CSIRO	\$152.8	13.2
Scenario 4	VLY = \$108,000	Project	\$1,318.5	4.8
		CSIRO	\$153.7	13.2
Scenario 5	CRC recurrence rate: stage 2=10% and stage 3=25%	Project	\$951.4	3.8
		CSIRO	\$117.0	10.3
Scenario 6	CRC recurrence rate: stage 2=20% and stage 3=40%	Project	\$1,876.6	6.5
		CSIRO	\$209.5	17.7
Scenario 7	detection rate under modern surveillance protocols = 40%	Project	\$1,876.6	6.5
		CSIRO	\$209.5	17.7

Note: LE is life expectancy; VLY is value of a life year

While the parameters used in the base-case scenario seemed reasonable in light of the current situation, it is important to test the robustness of our conclusions with variations in these assumptions. The low and high alternative assumptions used in the above sensitivity analysis were brought together to estimate the benefit and cost streams under pessimistic and optimistic scenarios by combining changes across all variables jointly. The results under these different assumptions are summarised in Table 7.2. Based on this analysis, we estimate that the BCR for CSIRO is between 7.2 and 30.5.

Table 7.2: Optimistic and pessimistic scenarios results

Scenario	Variables	Description	NPV (\$m)	BCR
Optimistic scenario	Discount rate = 5%; VLY=\$187,104; LE = 1.4%; CRC recurrence rate: stage 2 = 20% and stage 3 = 40%; Detection rate under modern surveillance protocols = 40%	Project	\$3,000.8	9.2
		CSIRO	\$325.7	30.5
Pessimistic scenario	Discount rate = 10%; VLY=\$108,000 LE = -0.2%; CRC recurrence rate: stage 2 = 10% and stage 3 = 25%; Detection rate under modern surveillance protocols = 30%	Project	\$777.4	3.4
		CSIRO	\$94.3	7.2

8 Limitations and Future Directions

Overall, the base case results show that this project will bring higher future benefits than the costs to both patients and the Australian health care system. The sensitivity analysis and scenario analysis prove that this project is viable from the perspectives of patients and the Australian health care system. We are unable to quantify the benefits to the company due to commercial confidentiality issues. We believe our base case estimation is conservative because:

- The analysis is specific to the Australian health care system, but benefits will flow to Australia from international uptake/sales and royalties;
- The assumptions regarding the number of CRC primary patients in each year during our project period are made to be constant over our project period. In reality, these figures are believed to be growing due to the population growth. Taking this into consideration, the health care system and patients should have higher benefits;
- A 10-year project life has been suggested in our analyses, which is considered short in CBA terms. The merits generated from this new intervention should benefit patients over their lifetime. The net present value for the health care system and patients is expected to be higher if longer project life is considered in the base case;
- Other possible benefits have been overlooked, such as improved patient family members' quality of life, savings to caregivers' time and possible gain of productivity for patients. Those potential benefits have not been taken into account because it is difficult to measure and quantify at this stage. Where societal perspective is required in the future, those benefits should be taken into account.

Given the scope and budget for the analysis, we have relied on the ECRI Institute 2017 report and other analyses conducted in Australia⁵. As such, our analysis is limited by the constraints within these studies. Some of the key limitations include:

- Improved life expectancy value in the Colvera™ base case is taken from an analysis of CEA cost-effectiveness from 20 years ago. No reference to the analysis of effectiveness of Colvera™ is available yet, as it is a brand new intervention. This figure should be updated in our analysis once it is available.

- There is limited information about the costs for clinical trials and implementation in the past and future. This may be due to commercial confidentiality issues. The results should be updated where other relevant costs are identified in the future.
- No risk analysis has been performed in this study to investigate the possibility of getting positive benefits for both the shareholders.

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