Australian Government
Cancer Australia

Evidence Review to Inform Development of the National Framework for Genomics in Cancer Control

Statement of Acknowledgement

The authors of this evidence review would like to acknowledge the Traditional Owners of the lands on which this work was conducted and pay our respects to the ancestors and their descendants who continue cultural and spiritual connection to Country. We recognise their valuable contributions to Australian and global society.

The work for this project was conducted on the lands of multiple Traditional Owners:
Jagera and Turrbal Peoples of Meanjin (Brisbane).
Wurundjeri Woi-wurrung and Bunurong / Boon Wurrung peoples of the Kulin Nation.
The Gadigal and Wangal Peoples of the Eora Nation (Sydney).
The Ngunnawal, Ngunawal and Ngambri Peoples of the Canberra region.
The muwinina and palawa as traditional owners and continuing custodians nipaluna (Hobart).

Evidence review to inform development of the National Framework for Genomics in Cancer Control was prepared and produced by:
Cancer Australia
Locked Bag 3 Strawberry Hills NSW 2012 Australia
Freecall 1800 624 973 +61 2 9357 9400
canceraustralia.gov.au

ISBN Online: 978-1-7636672-8-0

Recommended citation:

Cancer Australia, 2024. Evidence review to inform development of the National Framework for Genomics in Cancer Control, Cancer Australia, Surry Hills, NSW

Evidence review to inform development of the National Framework for Genomics in Cancer Control can be downloaded from the Cancer Australia website: canceraustralia.gov.au

Copyright Statements

Authors

Genomics and Cancer Control

A/Prof Aideen McInerney-Leo
Emily DeBortoli
Ella McGahan
Dr Lauren Aoude
Dr Tatiane Yanes
A/Prof Julia Steinberg

Models of Care

Jennifer Berkman
Emily DeBortoli

Ethical, Legal and Social Implications

Scoping and Review of Literature

Prof Ainsley Newson
Dr Amelia Smit
Dr Akira Gokoolparasdh

Data Safety and Regulation

Prof Oliver Hofmann
Dr MJ Brion
Dr Matilda Haas
Tiffany Boughtwood

Indigenous Data Sovereignty

A/Prof Rebecca McWhirter
A/Prof Azure Hermes
Dr Lyndsay Newett

Health Economics

A/Prof Illias Goranitis
Mackenzie Bourke

Table of Contents

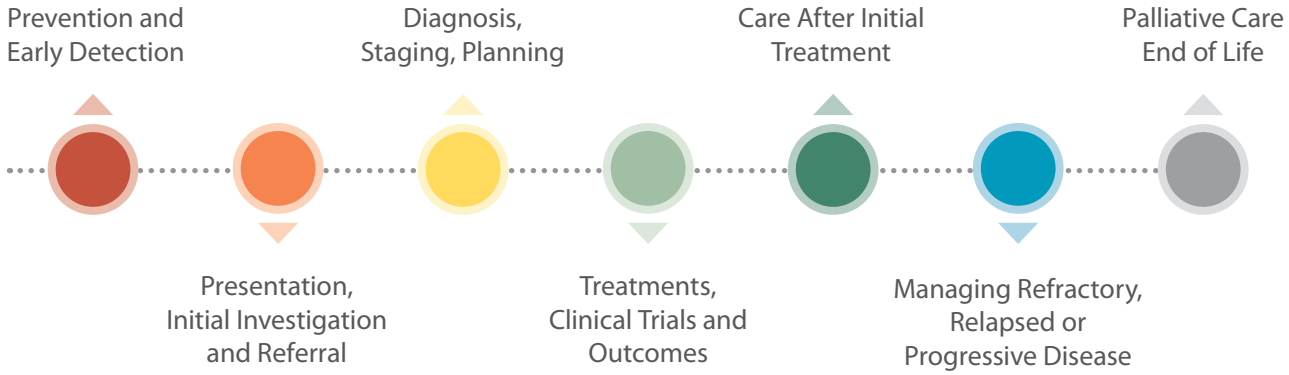
Executive Summary: The Role of Genomics in Cancer Control

Each year, >160,000 adults and >1,800 children or young adults are diagnosed with cancer in Australia. The most frequently diagnosed cancers in Australian adults are prostate cancer, breast cancer, cutaneous melanoma, colorectal and lung cancer. Leukaemia is the most common childhood cancer, followed by central nervous system tumours and lymphoma. In young Australian adults, Hodgkin lymphoma is the most common cancer followed by cutaneous melanoma. The average 5-year survival is 70% for adults, 84% in children, and 90% in young Australians.

This evidence review aims to:

1. Evaluate the current and potential impact of genomics on cancer control.
2. Summarise the ethical, legal, and social implications of cancer genomics.
3. Review models of care for providing genomic testing for prevention and treatment of cancer.
4. Explore the economic costs of cancer genomics to health systems and consumers.

Figure 1: Cancer Care Continuum



The goal of this project was to map the evidence relative to the Cancer Care Continuum (See Figure 1). To this end, five literature reviews were conducted: Cancer Genomic Testing in Adults (Narrative review); Cancer Genomic Testing in Children, Adolescents, and Young Adults (Scoping review); Mainstreaming Cancer Genomic Testing (Scoping review); Ethical, Legal and Social Implications (Scoping review); and Health Economics of Genomics Testing in Cancer (Systematic review). In addition, experts reviewed the relevant literature regarding genomically matched therapies, data management and privacy and Indigenous Data Sovereignty. The following sections summarize key findings from these reviews.

Cancer Genomic Testing in Adults

Cancer genomic variants can be classed into two broad categories: germline variants, which are present in all cells in the body, typically from conception; and somatic variants, which we accumulate in individual or groups of cells during our lifetimes. Cancer can be caused and driven by both.

Germline

Rare, pathogenic germline variants associated with hereditary cancer syndromes are identified in 10% of adults with cancer. More germline variants are detected when: a larger number of genes are screened, rare cancers are included (13-18%), in populations with a larger proportion of familial cases, and when all potentially deleterious variants are reported as opposed to just previously documented variants. Over 50% of adults with clinically actionable germline variants would not have met personal and family history criteria for genetic testing. Approximately half of adults with pathogenic germline variants are offered germline genotype-directed therapies. Some treatments are contraindicated in individuals with germline variants in specific genes e.g., radiation in TP53 carriers. After initial treatment these individuals can be offered screening or prophylactic treatment for other cancers they may be at increased risk of developing. Family members can also be offered testing for the germline variant to inform their screening and health management, both of which have been shown to reduce the risk of cancer occurrence and improve outcomes.

Common genomic variants can also increase cancer risk. The effect of each variant is small but, when aggregated to create polygenic risk scores (PGS), this can explain a significant portion of cancer risk. In Australia, PGS are already being used in clinical trials to refine breast cancer risks in individuals with high penetrance variants (e.g., BRCA1/2), and to explain risk in affected individuals who are negative for variants in high-risk genes. PGS are being increasingly utilised in research for risk refinement in other, diverse cancer types. In the near future, it is likely PGS may be used in conjunction with traditional risk factors for population risk stratification i.e., identify those at greatest risk and select optimal age to commence screening. However, several key challenges for population-wide implementation of PGS testing remain. PGS are also being used in patients with cancer to differentiate between cancer types, predict response to treatment and inform prognosis. PGS can also predict risk for subsequent malignancies. Pharmacogenomic testing may also be beneficial in predicting adverse responses to chemotherapies.

Somatic

Between 78-95% of adult cancer patients have ≥1 actionable somatic variant (informs diagnosis, prognosis and/or treatment), with advanced cancers carrying more variants than primary cancers. More variants are detected with comprehensive sequencing (whole genome, whole exome and/or large panels) combined with RNA-seq. Testing can identify individual variants as well as patterns of genomic variation, which can inform both prognosis and treatment choices.

Somatic variants can inform or refine the diagnosis in 4-10% of patients with advanced cancers and up to 51% of cancers with an unknown primary. Typically, 31-48% of adults have ≥1 molecularly matched therapy, of whom a third receive it. Few studies compared outcomes in matched therapy groups to those receiving standard treatment. Instead, progression free survival (PFS) was benchmarked relative to the PFS from the last therapy. Nonetheless, there is a growing body of evidence to show positive response rates, increased PFS and longer median overall survival in individuals receiving a matched therapy. These findings are not generalisable however as most individuals receiving matched therapies have advanced cancers, and their declining health often negatively affects their ability to pursue matched therapies. In studies which included individuals with less advanced cancers, patients with fewer prior therapies had improved survival outcomes compared to patients that received multiple prior therapies.

The genomic profile of circulating tumour DNA (ctDNA) is strongly correlated with the genomic profile of tissue samples, and ctDNA can be used to identify additional variants to capture the genomic heterogeneity of the tumour. Promising usages of ctDNA include: a prognostic biomarker, a substitute for biopsy (particularly useful

in cancers of unknown primary), and monitoring response to treatment and recurrent disease. Using ctDNA as a screening tool in the general population is currently not viable, as the false positive rate is too high. However, research is exploring the possible utility in high-risk cohorts, such as individuals with pathogenic germline variants, to enhance early detection.

More research is needed on all genomic testing in primary cancers and the sensitivity and specificity of ctDNA for as a diagnostic aid and biomarker for monitoring treatment response. Research is needed to determine whether ctDNA could be used for screening in individuals carrying germline variants in hereditary cancer genes. Longer term outcome studies are needed for evaluating response and survival in those receiving matched therapies as opposed to those receiving traditional therapies.

An emerging field of interest is cancer vaccines, which can be utilised prophylactically or therapeutically. HPV is the best characterised prophylactic application to date. Therapeutic cancer vaccines, which train the immune system to recognise and attack cancer cells, can utilise peptides, DNA, RNA, cell-based or viral technology.

Evidence conclusions:

1. **Germline pathogenic variants are identified in 10% of adults with cancer and can inform treatment and management of the patient, and screening of family members.**
2. **PGS could inform general risk estimates and refine risk for germline pathogenic variant carriers, though there are key challenges for population-wide implementation.**
3. **Pharmacogenomic testing could mitigate the risk of adverse responses to chemotherapies.**
4. **Somatic variants, which inform diagnosis, prognosis and treatments, are identified in most adult cancer patients and matched therapies improve outcomes.**
5. **Deteriorating patient condition and large numbers of prior therapies negatively predict matched therapy uptake and response. Thus, cancer genomic testing should be considered as a frontline test.**
6. **More research is needed on primary cancers and on response to matched therapies, relative to standard of care.**

Cancer Genomic Testing in Children, Adolescents and Young Adults (CAYA)

Germline

Approximately 18% CAYA with cancer are found to carry pathogenic germline variants associated with hereditary cancer syndromes. Germline variants are more common in solid tumours than blood cancers, and rare cancers are associated with the highest incidence. At least 40% of germline variants in CAYA with cancer are de novo (i.e., not inherited). The identification of germline variants can inform treatment options, as some therapies are contraindicated and many causal genes are associated with DNA repair defects, which can be targeted with immune- or targeted therapy. After initial treatment, screening for other associated malignancies can be discussed, and family members can be offered testing. Custom screening and interventions in this high-risk group is associated with better treatments and outcomes. PGS is not currently used in clinical practice in CAYA with cancers but can predict risk of a subsequent cancer (e.g., thyroid cancer) after treatment for malignancy in a young person.

Somatic

CAYA cancers are characterised more commonly by copy number variations, gene fusions and rearrangements than by single nucleotide variants and small insertions/deletions. Combining whole genome, whole exome (or large panels) and RNA-sequencing offers the greatest sensitivity in detecting variants in CAYA cancers. Central nervous system tumours would also benefit from methylation studies.

Somatic variants are more likely to inform or refine diagnosis in individuals presenting with a new primary (up to 85%) than those with advanced cancers (2-8%). Between 22-69% all CAYA cancer patients are found to have at least one somatic variant which informs prognosis and/or identifies a matched therapy. Of individuals with a targetable variant, 13-67% receive the recommended therapy, typically through a trial or compassionate access, with the majority having a gene fusion detected. The impact of receiving matched therapies on patient response and survival has been minimally studied to date. The best data was recently published by the Australian PRISM study and showed an objective response rate in 36% and improved 2-year PFS compared with those receiving standard-of-care.

Less research has been conducted on ctDNA in CAYA cancers, but preliminary evidence suggests high levels of correlation with tissue sample variants, the ability to detect ctDNA in 70% of recently diagnosed and 80% of advanced cancer patients, and the genomic profile in serial samples is consistent with treatment responses.

Research gaps include the need for larger studies on primary CAYA cancers, who have recently been enrolled in the Australian PRISM study. More research is needed to determine the extent to which matched therapies are utilised and the barriers to uptake. The is a need to compare responses and impact on survival in CAYA's receiving matched as opposed to traditional therapies. More research is needed on the potential utility of ctDNA for assisting in diagnosis and monitoring response to treatments.

Evidence conclusions:

1. **18% of CAYA cancer patients carry germline pathogenic variants, where 40% are de novo. They inform treatment and management of the patient, and screening of family members.**
2. **Somatic variants inform diagnosis in ≤85% of primary and 5% of advanced CAYA cancers.**
3. **Variants indicate a matched therapy in 22-69% of cases, but the subset of individuals receiving matched therapies varies (13-67%).**
4. **As per adult cancers, declining patient condition negatively affects matched therapy utilisation, and thus cancer genomic testing should be considered as a frontline test.**
5. **More research is needed on primary cancers and on response to matched therapies, relative to standard of care.**

Models of Care

This section of the report is divided into two sections; a scoping review on mainstreaming cancer genomic testing and an expert review on equitable access to care, particularly as it pertains to Aboriginal and Torres Strait Islanders.

Mainstreaming of cancer genomic testing to date has predominantly been facilitated by embedding genetic counsellors in oncology clinics or upskilling cancer specialists to offer testing. As genetic testing being offered by a genetic counsellor is considered standard-of-care, the impacts of that model have been less well evaluated

than the consequences of offering testing through upskilling clinicians. Both models improved access to and utilisation of genomic testing (1.2-6.7-fold increase) and reduction in the time from cancer diagnosis to test results (1.5-6 fold decrease). Genetic counsellors embedded in oncology clinics took less time to discuss and consent to testing (45-52 mins) relative to the traditional model of care (≥60 mins). Upskilled clinicians took less time again (8-10 mins). Pathogenic variants were identified in 10-22% of patients, which is consistent with clinical genetics clinics. Health economic analysis of the upskilled clinician model showed cost-effectiveness, largely due to reduced number of clinical genetics appointments. Clinicians in the upskilled model reported improved self-efficacy while patients found the model acceptable and appreciated the continuity of care.

Existing studies were limited by the fact that studies evaluated models of care for germline, not somatic genomic testing programs. No studies were identified which compared the embedded genetic counsellor and upskilled clinician models, with only a few comparing each to traditional care models. Additionally, there is a lack of research evaluating the embedded genetic counsellor model in terms of health economic benefits, clinician attitudes, patient experiences, and the impact of negative results.

An alternate model of care is the outsourcing of genetic test result disclosure to a professional genetic counselling service. Additionally, embedding a genetic counsellor in a pathology lab to address clinicians' questions can promote appropriate test ordering (stewardship model). Another intervention to optimise cancer genomic testing utilisation is the molecular tumour board (MTB). MTBs are valued by clinicians and improve their understanding and appropriate utilisation of genomic tests, increase uptake of testing and detection of clinically relevant variants and enhance genetic counselling referral.

Genomics has the potential to contribute to addressing some of the inequitable experiences and outcomes for people affected by cancer. Aboriginal and Torres Strait Islander peoples have higher age-standardised incidence and mortality rates for all cancers combined. However, there are two significant barriers currently inhibiting the extent to which Aboriginal and Torres Strait Islander peoples can benefit from genomic medicine in cancer care: inadequate diversity in reference datasets; and issues in accessing appropriate health care. The challenge of the underrepresentation in reference datasets is exacerbated by the diversity of Aboriginal and Torres Strait Islander peoples. Furthermore, given historically poor research practices, there is widespread distrust of genomics and genomic researchers, which affects the willingness of Aboriginal and Torres Strait Islander peoples to participate in research. Access to care and the cost of accessing care (e.g., travel and accommodation) explains some of the survival disparity seen in Aboriginal and Torres Strait Islander peoples. There are multiple barriers to accessing clinical genetics services including: difficulties navigating health services; limited genetic literacy; logistical factors; inadequate communication before, during and following consultations; and a lack of financial support services, culturally appropriate services and/or Aboriginal support services.

Evidence conclusions:

1. **Mainstreaming genomic testing is associated with benefits such as increased uptake of testing, reduced time from diagnosis to test result, results informing management, improved clinical confidence and high levels of patient satisfaction.**
2. **Molecular tumour boards increase the utilisation of testing, detection of germline variants, improve curation of genomic variants, enhance clinician understanding and confidence, and improve referral for genetic counselling.**
3. **Aboriginal and Torres Strait Islander peoples cannot experience health benefits from genomics until major barriers are addressed including lack of representation in genomic reference datasets and improved access to care.**

Ethical, Legal and Social Issues (ELSI) of Cancer Genomics

This chapter comprises three distinct sections: a scoping review to evaluate ELSI considerations pertinent to cancer genomics; expert review of data safety and regulatory considerations relevant to genomics; and expert review of Indigenous Data Sovereignty.

The scoping review identified eighteen ELSI themes. Of these, four particularly predominant themes were: equity of access, family considerations, legal considerations, and consent processes. Equity of access manifested in discussions of: structural barriers to testing and research, access to preventative and follow-up care, and engagement with health systems. Discussions of family considerations included that family members are generally considered to have an ethical duty to disseminate genomic information that will be relevant to other family members, but that this is not always discharged in practice. There is ongoing debate over whether health professionals also or instead have this duty. Family can also influence decision-making regarding testing, which can have both positive and concerning implications, the latter arising when there may be conflicting interests (such as the family member benefiting from the proband's test). Legal considerations include privacy and confidentiality, genetic discrimination, and the prospective duty to reclassify variants. Optimising consent processes in both clinical care and research and designing consent processes that are optimally inclusive to diverse populations, were also prevalent in the literature. Cross-cutting themes that were identified included trust and the right to know/not to know results and their implications. The research and practice gaps include a lack of literature evaluating ELSI considerations in survivors and palliative care patients. More research is needed regarding equity for people living in rural/remote areas and how to provide ethical care within culturally, linguistically and ethnically diverse communities, including First Nations Peoples. There is a need for targeted cancer-specific scholarship on legal considerations beyond privacy and discrimination.

The data safety and regulatory implications review highlighted important strategies and frameworks pertaining to the use of genomic data in healthcare e.g., the National Approach to Genomic Information Management (NAGIM), and healthcare genomics strategies by Commonwealth and the Australian states and territories. Key considerations for data management include: data quality, storage, sharing, linkage, retention and governance. The sensitive and identifiable nature of genomic data, and requirements to link it with other forms of sensitive or identifiable data requires careful considerations regarding privacy. Privacy issues include the challenges of de-identifying genomic data, the challenges with sharing data across different jurisdictions and potential for genetic discrimination. Australian Genomics has developed a National Clinical Consent form for germline testing and are planning the release of a somatic testing form, which would be highly relevant to cancer patients undergoing genomic testing. Ownership of genomic data is complex, though most stakeholders agree that patients/consumers should have rights. The practical translation of rights is more complex in terms of storage, access. and management.

Indigenous data sovereignty is a movement arising in response to the harms caused by poor data practices. Dominant data practices aggregate, homogenise and decontextualise Indigenous data, focusing on disparities and deficits. Genomics poses additional risks such as racial stereotyping, cultural undermining, using genomics to define Aboriginality and detracting from social determinants of health. In Australia, the Maiam nayri Wingara Aboriginal and Torres Strait Islander Data Sovereignty Collective has developed principles for implementing Indigenous Data Sovereignty. Collaborations with other international Indigenous data sovereignty groups, resulted in the creation of the CARE principles: Collective benefit, Authority to control, Responsibility (to communities) and Ethics. The Indigenous peoples' Rights In Data, which was released in 2023 is an important charter to guide all stakeholders wanting to engage and conduct research respectfully.

Evidence conclusions:

1. **Ethical, legal, and social issues relevant to cancer genomic testing include equity of access, family considerations, legal considerations, and consent processes.**
2. **Consent processes and legal considerations also emerged as themes in the data safety and regulation section, with genetic discrimination an important issue discussed in both reviews.**
3. **Ownership of genomic data is a complex issue legally and practically and is particularly salient for Indigenous Australians, given a history of extractive research practices.**

Health Economics of Genomic Testing in Cancer

Germline genomic testing was highly likely to be cost-effective for the prevention and early detection of breast and ovarian cancer, colorectal and endometrial cancer. Breast and ovarian cancer genomic testing was found to be more dominant (i.e., more effective and less costly), or cost-effective, compared to no screening or standard screening. Similarly, colorectal genetic screening demonstrated to be highly likely to be cost effective compared to no screening. For multi-cancer and other cancer detection the picture is more complex, especially given heterogenous testing strategies.

For diagnosis, staging and planning of cancer there was less evidence to offer clarity on the cost-effectiveness of genomic testing. Automatic germline testing in colorectal cancer patients meeting clinical and pathology criteria (reflexive testing) was shown to be cost-effective compared to no testing. Other studies showed that genomic testing was dominated by surgical resection in thyroid cancer and molecular testing dominated standard care in the diagnosis of melanoma.

Relative to either the absence of testing or standard testing, most studies evaluating the utility of genomic testing in guiding therapy showed dominance or cost-effectiveness for breast cancer, lung cancer, colorectal cancer, melanoma, and blood cancers. However, there are exceptions, e.g., 6-mercaptopurine dosing in children with leukemia. There were some positive signals that genomic testing may be cost-effective in other cancer types, including tumour agnostic therapies, but there was insufficient health economic evidence to form broad conclusions.

The use of genomic medicine managing refractory, relapsed or progressive disease and end-of-life care was demonstrated in this review to be highly likely not to be cost effective, as there are fewer potential health gains in patients with limited life remaining. To make appropriate resource allocation decision for end of life, it may be necessary to consider higher cost-effectiveness thresholds.

Clinicians perceive that although the costs of hereditary genomic testing may not be a barrier to uptake, the cost of the matched therapies could substantially increase patient out-of-pocket (OOP) costs. Higher OOP costs and/or lower incomes negatively affected the uptake of targeted therapies. When targeted therapies were not fully reimbursed, patients perceived that their use increased financial toxicity, while also expressing concern about treatment effectiveness, side-effects, and method of administration. Additional patient and public concerns included the actionability, accuracy, and privacy of results. Furthermore, patients were concerned about wait time, number of tests required and the impact of findings on relatives.

The research and practice gaps in cancer genomics economics include the need for more comprehensive studies on cost-effectiveness across various cancer types, exploration of genomic medicine's impact on financial toxicity, quality assessment of economic evaluations, understanding system capacity constraints, and incorporating patient preferences to optimize genomics application in cancer control. More papers are needed which model a treatment decision, as opposed to comparing two different treatment choices.

Evidence conclusions:

1. **Germline genomic testing is highly cost effective in the prevention and early detection of breast, ovarian, colorectal, and endometrial cancer.**
2. **Genomic testing has been shown to be cost-effective in guiding therapy for multiple cancer types.**
3. **Genomic testing may be less cost-effective in refractory, relapsed or progressive disease and end-of-life care due to decreased success in advanced disease. Higher cost-effectiveness thresholds may be considered in this cohort.**
4. **Genomic testing is less likely to be associated with financial toxicity than the costs of the resulting matched therapies.**

Introduction

Cancer is the leading cause of death and largest contributor to disease burden in Australia. Approximately 160,000 Australians will be diagnosed with cancer in 2023.[1] The most common cancers in Australia (excluding non-melanoma skin cancer) are prostate, breast, colorectal, melanoma, and lung cancer.[2] Survival rates of cancer vary depending on tumour type, however overall Australia experiences some of the highest survival rates in the world, with 70% in individuals diagnosed with cancer in 2021 surviving at least five years after diagnosis.[3] Relative survival rates are anticipated to improve due to improvements in diagnostic methods, earlier detection, and advances in treatment. Genomic testing is increasingly used in cancer risk assessment, diagnosis, prognosis, and to inform treatment choices.

Introduction to Genomics

Chromosomes are located in the centre of the cell and each person typically has 46 chromosomes, or 23 pairs, and inherited one copy of each pair from both parents. The role of chromosomes is to carry genes and therefore, as there are two copies of each chromosome, there are also two copies of each gene. Chromosomes comprise a long strand of DNA. A gene is a section of DNA which codes for a protein, and this section of DNA is further divided into subsections called exons and introns. Only the exons are transcribed into RNA, which is then translated into the amino acids which build the protein. An alteration of the DNA code which affects the quantity or quality of protein produced is called a mutation or a pathogenic variant.

A genomic variation which is present from conception is called a germline variant. These variants are inherited or can arise for the first time in an individual (de novo variant). As cells copy and divide throughout a lifetime, new genomic variations arise in individual cells or groups of cells. These are referred to as somatic variants. Somatic variants are not inherited.

Genetic analysis usually refers to evaluating the genetic code of a single gene. Genomic analysis is the analysis of multiple genes at once or the analysis of gene expression/products.

The Role of Genetics in Cancer Susceptibility

Cancer is rarely inherited, but it is always genetic. Germline and somatic mutations which occur in genes involved in cell growth, DNA repair, or tumour suppression have the potential to lead to cancer. People with a germline mutation in a cancer susceptibility gene have aberrant copy in all their cells. Therefore, if they acquire a somatic mutation in the second copy, they have a high chance of developing cancer. However, the typical cancer patient must acquire a somatic mutation in each copy of the gene in the same cell. This explains why cancers in individuals with germline mutations occur more frequently and at an earlier age than the general population.

Germline Genetic Testing

Common hereditary cancer syndromes

Germline variants associated with hereditary cancer are generally inherited in a Mendelian autosomal dominant pattern, whereby a variant in one gene copy increases an individual's susceptibility to cancer. Consequently, first-degree relatives of an affected individual have a 50% chance of carrying the same variant.

A hereditary cancer syndrome is caused by an inherited germline variant which increases an individual's risk of developing certain tumours, often at a younger age. In most common hereditary cancer syndromes, the increased cancer risk is due to a single germline variant (monogenic hereditary disease). Although each hereditary cancer syndrome displays specific clinical manifestations, common indicators can aid in their identification, such as early cancer onset, multiple tumours in the same individual, a positive family history, and an atypical sex distribution (for example, breast cancer in males). See *Table 1* for a summary of common

hereditary cancer syndromes. Criteria and referral guidelines for genetic testing for each of these conditions can be found on the Cancer Institute NSW eviQ site (https://www.eviq.org.au/cancer-genetics).

Variants identified in hereditary cancer genes must meet strict criteria to be classified as being causative. These criteria, developed by the American College of Medical Genetics and Genomics (ACMG) in collaboration with the Association for Molecular Pathology results in variants being classified as pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign or benign.[4] These classifications are aided by clinical variant databases like ClinVar,[5] which contain prior reports and classifications of specific variants. Pathogenic, likely pathogenic and VUS results are returned to patients following clinical testing. Analysis of 20 years of cancer genetic test results reveals that only 18% of VUS's will be reclassified as pathogenic/likely pathogenic, and the remainder will be reclassified as benign/likely benign.[6] From this point forward, disease causing variants will be referred to as pathogenic variants, as opposed to mutations.

Table 1: Common Hereditary Cancer Syndromes [7]

Hereditary cancer syndrome	Overview	Related genes and associated lifetime risk of cancer
Hereditary breast and ovarian cancer (HBOC) [8 9]	HBOC accounts for • 10-15% of breast/ovarian cancer cases.[10] • 25-40% of breast cancer diagnosed <35 years.[10]	• BRCA1 and BRCA2 cause 20-30% of HBOC cases.[8] • Other HBOC genes include ATM, PALB2, RAD50, FANCM, BARK1, CHEK2, and TP53.[8] • ~50-80% lifetime risk of breast cancer & 30-50% to ovarian cancer.[8] • Men - BRCA1/BRCA2 confer a 7% lifetime risk of breast cancer and 60% risk of prostate cancer.[8]
Lynch syndrome (hereditary nonpolyposis colorectal cancer) [11]	• Increased risk for colorectal, endomerial and other cancers (e.g., ovarian, bladder, gastric).[12] • Accounts for 3-5% of colorectal cancer cases and 2-3% of endometrial cancer.[12]	• Caused by variants in mismatch repair (MMR) genes, including MLH1, MSH2, MSH6, and PMS2.[12] • 57% lifetime risk of colorectal cancer and 49% chance of endometrial cancer.[12]
Li-Fraumeni syndrome (LFS) [13]	• Strong family history of multiple, early onset cancers. • Associated with sarcomas, osteosarcomas, adrenocortical carcinomas, central nervous system tumours etc.).	• Caused by variants in the TP53 gene. • Approximately, 50% of individuals with a TP53 variant will develop cancer by the age of 30 years, with a lifetime risk of up to 70% in men and ~100% in women.[14,15]

Hereditary cancer syndrome	Overview	Related genes and associated lifetime risk of cancer
Multiple endocrine neoplasia (MEN) [16,17]	• A group of syndromes (including MEN1, MEN2, and MEN4) associated with endocrine (e.g., thyroid, parathyroid, pituitary, adrenocortical etc.) and non-endocrine tumours.[18]	• Germline variants in MEN1, RET, and CDKN1B.[18,19] • Cancer risk varies according to MEN type, but can be ~ 95%.[19]
Neurofibromatosis NF) [20]	• Characterised by tumours (benign and malignant) in the nervous system, organs, skin, and bones.[21] • There are three types of NF: NF1 (96% of all cases), NF2 and schwannomatosis.[21]	• NF1 caused by NF1 gene, associated with a 60% lifetime risk of cancer. • NF2 caused by NF2 gene, almost all cases will present with a tumour by 60 years.[22] • Schwannomatosis caused by SMARCB1 and LZTR1.[23,24]
Hereditary phaeochromocytoma-paraganglioma syndromes (PPC/PGL) [25]	Neuroendocrine tumours that arise along nerve pathways. PCCs confined to adrenal glands.[26] Associated with other cancer syndromes e.g., von Hippel-Lindau syndrome, MEN.[26]	• 25% germline, remainder sporadic. • Caused by VHL, SDHD, SDHD, and SDHC. • 30-60% lifetime risk of developing pheochromocytoma or paraganglioma and ~1/3 will become malignant if not detected early.[27]

Polygenic Risk Scores

Although a minority of the population have an inherited pathogenic variant in a cancer susceptibility gene,[7] genetic variations play a role in cancer susceptibility in the general population. Based on twin studies, the heritability for most common cancer is modest to high, ranging from 15% for colorectal cancer, 31% for breast cancer, 57% for prostate cancer and 58% for melanoma.[28] Of the total heritability to cancer risk, only a proportion is attributed to polygenic factors, and not all SNP associated with cancer risk have been identified. Most people develop cancer because they have genetic variations in multiple genes which, in combination with environmental/lifestyle factors, increase their risk. These genetic variations are called single nucleotide polymorphisms (SNPs) or variations (SNVs). These variations are relatively common in the population (>1%). Although the effect of each SNP is very small, they can be combined into a single measure, known as a polygenic risk score (PRS) or polygenic score (PGS).[29] SNPs which contribute to PGS are identified by comparing the frequency in large group of affected and unaffected individuals in genome-wide association studies (GWAS) look at frequency differences for thousands of SNPs across the genome.[30] Increasingly, international consortia are being established to increase cohort sizes and subsequently improve accuracy of the GWAS.[40-42] Findings from GWAS can also found in a publicly available database called: GWAS Catalog (https://www.ebi.ac.uk/gwas/).[43]

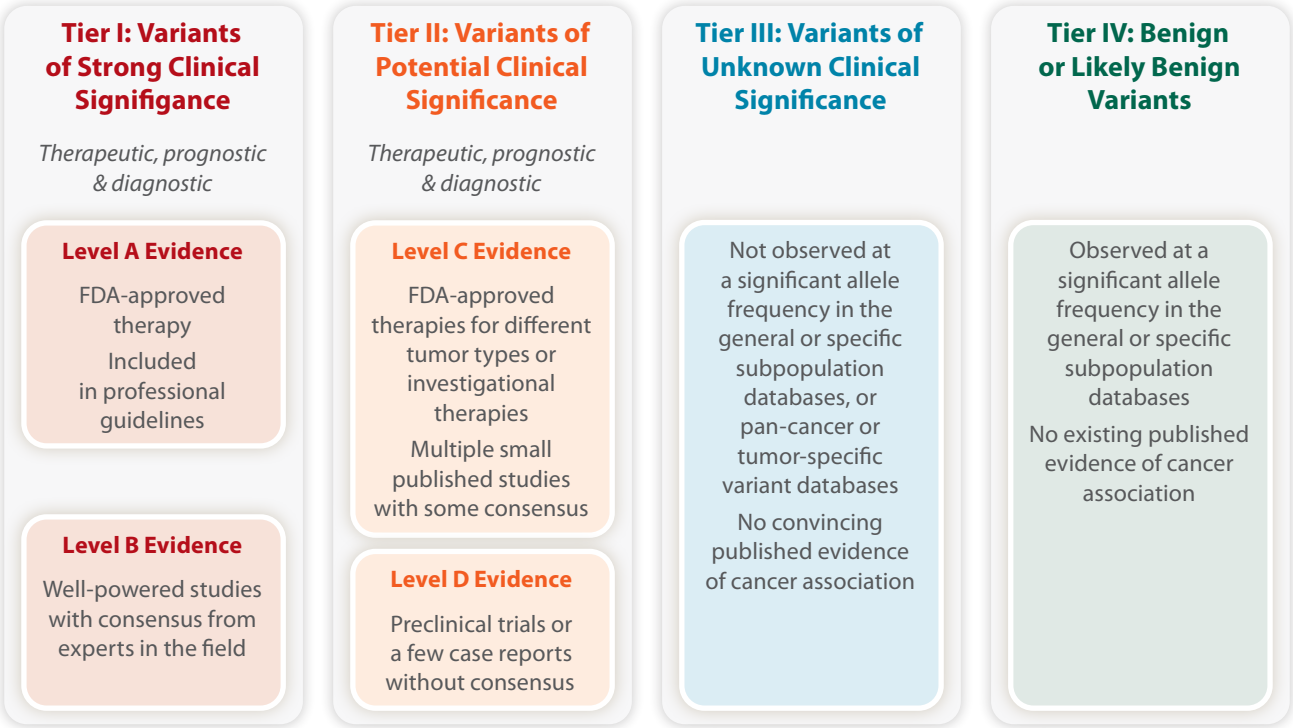
GWAS results form the basis for the development of a PGS. Thus, the validity of the PGS is directly dependent on the quality and power of the GWAS. Factors affecting the quality of the GWAS include methodological approaches, the accuracy of the diagnosis, and the populations studied. Lack of ancestry diversity in GWAS is widely recognised as a significant limitation of current data. As of 2021, around 80% of GWAS were conducted on populations of European ancestry, whereas only 16% of the global population is of European ancestry.[44,45] The lack of ancestry diversity on GWAS has resulted in a PGS that has poorer performance in non-European populations. The impact of GWAS cancer specific sub-types should also be considered e.g., ER+ versus ER- positive breast cancers.[31]

A PGS is an estimate of an individual's relative risk of having the outcome of interest, compared to the average risk in your population. Presently, there are no established protocols or best practices for developing clinically accredited PGS, and there is variability in procedures, including technology used to generate genotype, SNP selection, population used, and statistical approach used to generate the PGS. Thus, risk estimate can vary for the same condition, and potentially classify individuals at different levels of risk. Methods of constructing PGS is an active area.[32] In order to better compare emerging PGS research, a new database has been established that includes trait of interest, summary of PGS development, and population information (PGS Catalog available at: https://www.pgscatalog.org/).

Somatic Genetic Testing

Somatic variants occur in cells in the body and can arise through the natural process of aging, or they can be triggered by carcinogens like tobacco, UV or radiation exposure, viruses or chemical exposures.[33] The goal of identifying somatic variants in biopsies is to identify which variants are driving development, growth, and invasion of the cancer (i.e., driver variants). Somatic variants are classified into four tiers based on their clinical significance where Tier I is deemed to have the strongest clinical significance based on an associated therapy evaluated in well powered studies. Tier II are potentially clinically significant variants based on associations with approved therapies and limited sample sizes. Tier III is a variant of unknown clinical significance and Tier IV are considered benign (see Figure 2).[34]

Figure 2: Classification of Somatic Variants in Cancer[34]



Somatic testing is typically performed on a biopsy from the tumour/affected tissue which could be fresh-frozen or extracted from a formalin-fixed paraffin-embedded sample (FFPE). It is common for both tumour and unaffected samples to be collected and tested simultaneously to determine whether variants identified are germline or somatic. These are called matched tumour/normal samples.

Tumour cells shed their DNA into the bloodstream, creating circulating tumour DNA (ctDNA).[35] This ctDNA can serve as a proxy for tumour genomic sequencing, particularly when tumours are difficult to access for biopsy. To date, ctDNA has been predominantly used in metastatic cancers where the levels of ctDNA are higher,[35] but research is exploring utility as a biomarker of response to treatment and/or minimal residual disease.

A liquid biopsy is a genetic sample extracted from blood and can include ctDNA, circulating tumour cells, protein biomarkers and cell-free RNA.[35]

Types of Cancer Genomic Testing

There are two broad types of genomic tests. The first detects the presence or absence of specific variants in a process called genotyping. The second looks at the entire sequence of genes or regions.

Genotyping is typically performed by arrays, which use baits (two fragments of DNA which are specific for each location, one of which contains the SNP and the other of which does not). That way, for each SNP, it can be determined whether a person had none, one or two copies of the SNP. Arrays are capable of genotyping hundreds of thousands of SNPs across the genome. Arrays are also capable of detecting large copy number variants but cannot detect structural rearrangements.

Genomic sequencing is a process which shows each letter of the genetic code for a specific section of DNA or RNA. Most sequencing is performed using next generation sequencing, which means that multiple genomic regions are being sequenced simultaneously. Each sequencing fragment is known as a read. Clinical testing will require at multiple reads per nucleotide. The number of reads at any one site is referred to as the "depth of coverage".

See **Table 2** for summary of how different variant types are detected.

Whole genome sequencing

Whole genome sequencing (WGS) looks at each of the 3.055 billion letters (nucleotides) in the genetic code of the human genome. This includes the entire gene (exons and introns) as well as the regions in between genes (intragenic).[36] WGS can identify single nucleotide polymorphisms or variants(SNPs/SNVs), small insertions and deletions (indels), large deletions or duplications (copy number variants) and structural variations (areas of the genome which have been rearranged).

Whole exome sequencing

Whole exome sequencing (WES) identifies the nucleotides in the exons and the areas of introns immediately prior to and following exons. The exons comprise ~1% of the human genome.[37] Approximately, 85% of disease causing variants are believed to occur in exons.[38] As WES generates significantly less data per patient, is less expensive than WGS and has a high a *priori* chance of being able to identify disease causing variants, it has been widely used for germline testing. WES can detect SNVs and indels. It can also detect some copy number variants by looking for areas associated with changes in depth of coverage. However, WES cannot accurately report the start and end point of the deletion/duplication unless they both points occur within the exons.[39] WES cannot typically detect large structural rearrangements.

Panel testing

Panel testing typically involves sequencing the exons of a specific group of genes. Panels typically range from tens to hundreds of genes. As panels are limited to a finite selection of genes, they usually have a high depth of coverage, which means that copy number variants can be detected with greater sensitivity.[40] Again, large structural rearrangements cannot be detected with panels.

Tumour mutational burden

The tumour mutational burden (TMB) is the number of genetic variants in the DNA of cancer cells. A recent review proposed that a high TMB is defined by >10 mutations per megabase (Mb).[41] The TMB is valuable as it can predict response to immune checkpoint inhibitors across multiple cancer types. Specifically, individuals with larger TMBs (≥10 mutations/Mb) are more likely to respond to immunotherapies, such as pembrolizumab.[42]

Cancer Mutational Signatures

Cancer driver mutations can often occur in genes responsible for the DNA repair process. The breakdown of this repair process results in characteristic types of genetic variants throughout the genomes in cancer cells. These patterns are referred to as cancer mutational signatures. Mutational signatures can indicate the presence of a predisposing germline variant, clarify the diagnosis, the prognosis and facilitate treatment/management strategies. Over 30 different signatures have been described in primary cancers,[43] and these are available at the COSMIC Catalogue.[44]

RNA Sequencing

The genome comprises 20,500 genes,[36] but not all of them are needed in every cell. Only the genes which are active in each cell are transcribed. Therefore, sequencing the RNA (RNA-seq) of cancer cells can identify which genes are differentially expressed. Sequencing can be targeted to genes of interest for a specific cancer or can involve sequencing all the RNA with the tumour (transcriptome).[45] RNA sequencing can assist in identifying the underlying genetic drivers of the cancer and/or provide validation for the likely pathogenicity of identified DNA variants. RNA-seq is particularly helpful in identifying gene fusions, which are often driving cancer development and progression.[45]

Table 2: Genomic testing performed on tumour, biopsy, or liquid biopsy samples to detect cancer genomic signatures.

Genetic variation	Definition	Technology
Variants	Sequencing of one or multiple genes to detect: • Single nucleotide polymorphism (SNP) – a change in a single letter/base of genetic code. • Insertion or deletion (indels) of 1-10,000 bases.	Panel testing/ whole exome sequencing/ whole genome sequencing
	Genotyping detects the presence or absence of a specific variant. Can also detect copy number variants.	Array testing
Tumour Mutational Burden (TMB)	Density of variants in cancer cells i.e., mutations per megabase (muts/Mb). High TMB >10 muts/Mb [41]	Panel testing/whole exome sequencing/whole genome sequencing

Genetic variation	Definition	Technology
Copy Number Variants (CNV)	Sections of the genome are repeated or deleted (>1,000 bases in size)	Panel testing/whole exome sequencing/whole genome sequencing
Microsatellite Instability	Microsatellites = 1-4 bases repeated multiple times. Microsatellites expand in the absence of functional DNA repair. This expansion affects genomic stability.	Immunohistochemistry/ WGS/panel testing [46]
Methylation	Modification altering gene expression. A methylated gene is turned off. Decreased methylation (hypomethylation) Increased methylation (hypermethylation)	Sodium bisulfite conversion and sequencing, differential enzymatic cleavage of DNA, and affinity capture of methylated DNA.
Gene expression	Genetic alterations can result in abnormal gene expression, which alters protein production.	qRT-PCR, DNA microarray, RNA-Seq, FISH, and tissue microarray [47]
Gene fusion	Genomic rearrangements lead to the fusion of two genes -> an abnormal protein	Fusions usually detected using RNA based sequencing.
Circulating tumour DNA (ctDNA) aka liquid biopsy	Tumours shed short fragments of DNA into the blood stream. ctDNA levels, total number of variants and the presence of specific variants can inform treatment, prognosis and detect response.	ddPCR (droplet digital PCR) RT-PCR Testing for variants in panels of genes.

Therapies Targeting Cancer Genomic Variants

Many different types of drugs are used to treat cancer patients, such as chemotherapy, hormone therapy, targeted therapies and immunotherapies. Traditionally, the type of treatment a patient is prescribed has been determined by factors such as tissue of origin or cell type, and stage. Rapid advances in next-generation sequencing (NGS) techniques have facilitated detailed molecular tumour profiling and enabled large-scale, pan-cancer, collaborative projects such as the TCGA and ICGC.[48,49] This has facilitated the identification of genomic drivers of cancer as therapeutic targets, and the implementation of genomic testing.[50]

Over the past 25 years, there has been a rapidly growing portfolio of cancer drugs that have been developed to target specific genomic traits (biomarkers).[51] As a result, the integration of genomic medicine into cancer care has rapidly increased personalised medicine (precision oncology) options for patients. As demonstrated in the adult and paediatric evidence reviews, a substantial portion of cancer patients are found to have a somatic variant with a matched drug therapy. Some biomarkers are detected through immunohistochemistry (IHC) for protein expression or FISH for gene fusion/deletion/amplification rather than genomic sequencing.[50] The following sections will focus solely on therapies prescribed based on genomic results.

A 2024 review documented that of the 198 new oncology drugs approved since 1998, 164 (83%) were classified as molecularly targeted therapies (a cancer drug that binds to or inhibits a specific protein target). Of those 86

(52%) were classified as precision oncology therapies (a drug with maximal efficacy in a molecularly defined subset of patients) of which 80% had a genomic biomarker that could be detected by DNA-based next generation sequencing.[51]

Targeted therapies are designed to block particular molecular pathways that are required for cancer cells to grow and spread. These types of drugs are often approved for use in specific cancer types and can be used on their own (as a single agent) or in combination with other drugs. Most of these biomarker specific therapies can be grouped into two categories: small molecule inhibitors and monoclonal antibodies (mABs). In some circumstances, these precision oncology drugs are used in combination to treat specific tumour types.

Small Molecule Inhibitors

Small molecule inhibitors are a class of drug that target proteins both *within* the tumour cell and on the surface.

Tyrosine-kinase inhibitors (TKIs) are a type of small molecule inhibitor, used as an effective treatment to block cancer cells from growing and dividing. Imatinib is an example of a TKI used to treat a wide range of both solid and haematological cancer types including chronic myeloid leukaemia (CML), acute lymphoblastic leukaemia (ALL), myelodysplastic/myeloproliferative disease, dermatofibrosarcoma and gastrointestinal stromal tumours (GIST). Molecular targets include gene fusion events in genes *KIT* or *PDGFRA*.[52] There are other genomic biomarkers based on gene fusions that indicate the use of specific therapies e.g., patients with non-small cell lung cancer with somatic ALK fusions are treated with an ALK/ROS1 inhibitor (crizotinib),[53] and paediatric patients with relapsed or refractory anaplastic large cell lymphoma (sALCL) presenting with ALK fusions can be treated with crizotinib.[54]

Small molecule inhibitors can also inhibit the blood vessel growth (anti-angiogenic), crucial to the growth of cancers. Sunitinib is an anti-angiogenic used in the treatment of GIST, RCC and pancreatic neuroendocrine tumours (pNET).[55-57] It targets multiple receptor tyrosine kinases including vascular endothelial growth factor receptors (VEGF-R), platelet-derived growth factor receptors (PDGF-R) and KIT.

Mammalian target of rapamycin (mTOR) is a type of protein kinase that regulates cellular metabolism, growth, and proliferation. Many types of cancers have dysregulation of mTOR signalling which makes the cancer cells grow and develop new blood vessels. Therefore, mTOR inhibitors can be an effective treatment in some types of cancer. Everolimus is an mTOR inhibitor that targets oncogenic mutations in *TSC1/2*.[58] It is used to treat HER2-negative breast cancer, pNET, renal cell carcinoma (RCC) and subependymal giant cell astrocytoma.[59,60]

Phosphoinositide 3-kinases (PI3K) have many different cellular functions. Switching on these kinases signals cells to grow, divide and move. They can also enable the development of blood vessels and turn on other proteins such as mTOR. In some cancers PI3K is permanently switched on, which means that the cancer cells grow uncontrollably. PI3K inhibitors are a type of small molecule inhibitor used to block these pathways. Breast cancer tumours harbouring somatic *PIK3CA* mutations treated with alpelisib, in combination with fulvestrant, are associated with prolonged progression free survival.[61]

Some tumours have genomic biomarkers which are present across various cancer types, rather than specifically occurring in a select tumour types. The neurotrophic tyrosine receptor kinase (NTRK) gene fusion is one such alteration detected across a range of tumour types,[62] which is treated with a small molecule inhibitor, entrectinib.[63]

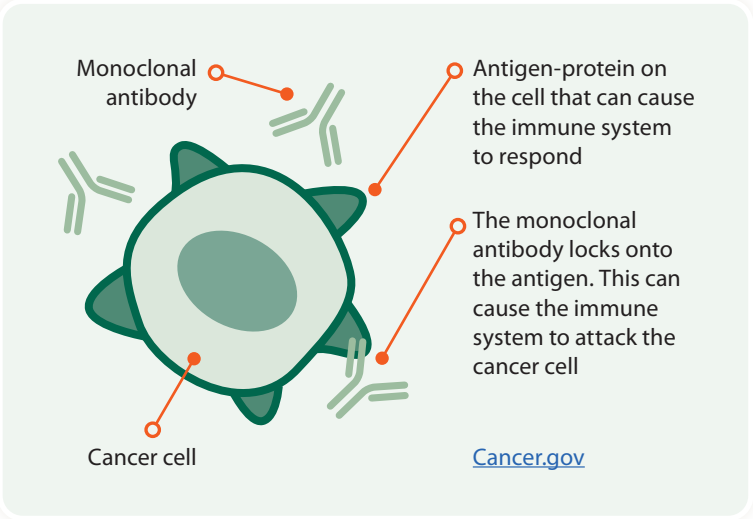
An example of **combination therapy** in melanoma care is the use of BRAF inhibitors plus MEK inhibitors (dabrafenib and trametinib) in the presence of a somatic BRAF p.V600 variant. Clinical trials have shown these drugs, both targeting different points in the mitogen-activated protein kinase (MAPK) pathway, significantly improved survival in patients with metastatic disease.[64] These drugs are now approved for use in other solid cancers harbouring these mutations e.g., anaplastic thyroid cancer, NSCLC and CRC.[65]

Some patients, carry a **germline** variant that is associated with cancer development and targeted therapies can also be used to treat patients with germline variants. In breast cancer, PARP inhibitors, such as Olaparib, can be used when a germline (or somatic) *BRCA1/2* variant is identified.[66] Olaparib has also been used in the treatment of *BRCA1/2* positive ovarian cancer and pancreatic cancer.[67,68] A clinical trial in metastatic breast cancer has shown risk of cancer progression was 42% lower in patients treated with Olaparib than with standard therapy.[66]

Monoclonal Antibodies (mABs)

Monoclonal antibodies (mABs) are a type of targeted therapy designed to interact with receptors on the *outside* surface of the cell. They can function in different ways:

- Blocking molecules that cancer cells need to grow.
- Flagging cells for destruction by the immune system.
- Delivering drugs, toxins, or radioactive particles.

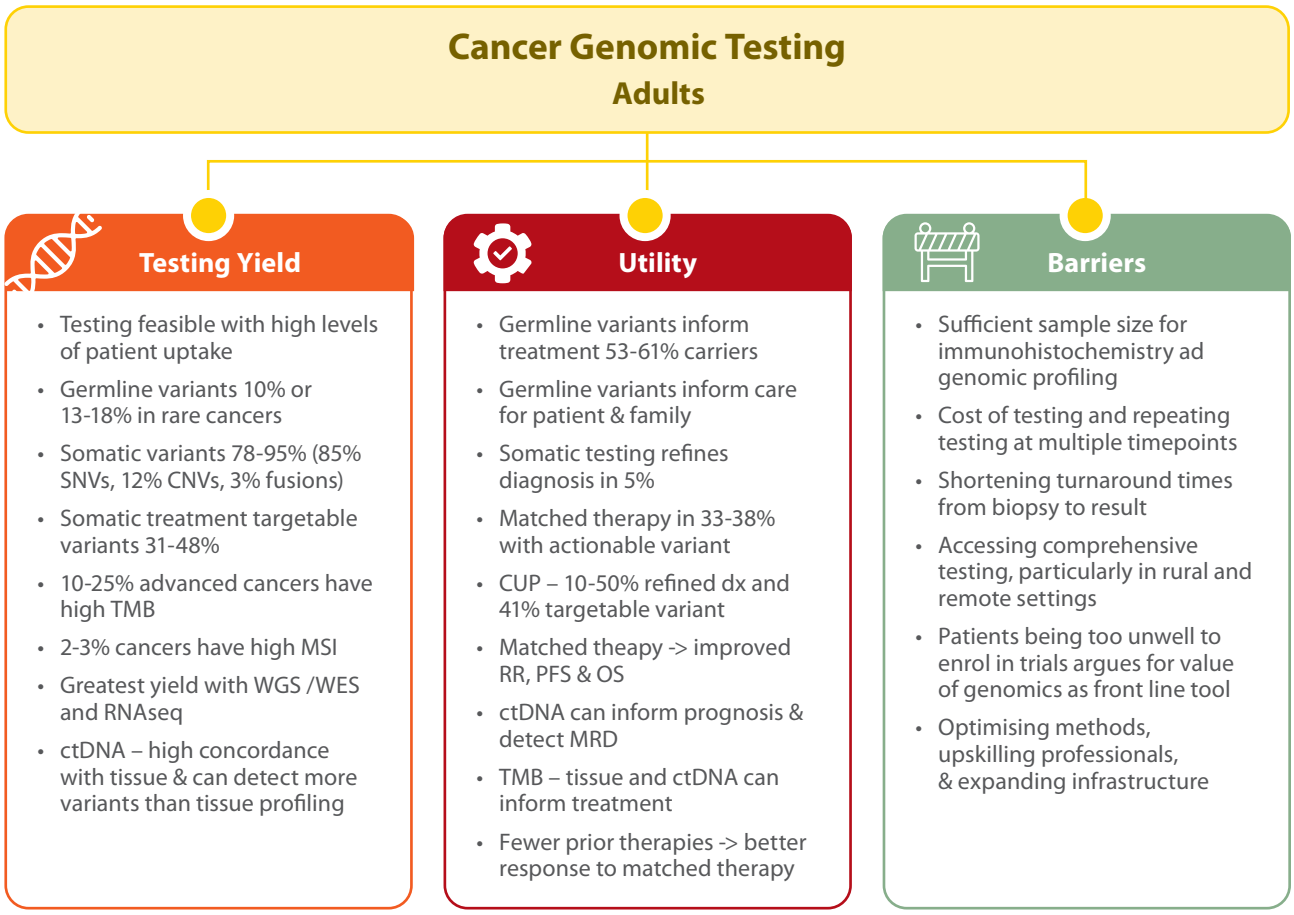


Cetuximab is a type of mAB that is used to treat a range of cancer types including head and neck squamous cell carcinoma, and colorectal cancer.[69] Cetuximab binds epidermal growth factor receptor (EGFR), which can be a driver of cancer, and is used to treat tumours that harbour genomic variations in this pathway. KRAS status is predictive of response to Cetuximab in colorectal tumours.[70]

Immunotherapies are a type of mAB that harnesses the body's immune system to target the cancer cells. These types of drugs are approved to use for a variety of cancers. There are 3 types of checkpoint inhibitors, that have been approved for use in advanced melanoma (ipilimumab, pembrolizumab and nivolumab), particularly for patients lacking a *BRAF* gene mutation. In melanoma, the use of immunotherapies dramatically improved patient outcomes. These immunotherapies can often be used in combination to treat patients, such as ipilimumab and nivolumab.[71]

More recently mABs have been approved for use all tumours with specific genomic profiles. Pembrolizumab was the first oncology drug given FDA approval for use based on a common, genomic biomarker, agnostic to tumour type.[72] Specifically, tumours that are found to have deficient mismatch repair (dMMR) or high microsatellite instability (MSI-H), such as melanoma, non-small cell lung cancer, colorectal and endometrial cancer (or other solid cancers meeting these criteria), can be treated with Pembrolizumab.[73]

Cancer Genomic Testing in Adults



CNVs: Copy number variants, TMB: Tumour mutational burden, MSI: Microsatellite instability,
CUP: Cancer unknown primary, RR: Response rate, PFS: Progression free survival, OS: Overall survival, MRD: Minimal residual disease

In 2022, over 160,000 Australian adults were diagnosed with cancer and an estimated 50,000 individuals died from cancer.[1] The most frequently diagnosed cancers are prostate, breast, cutaneous melanoma, colorectal and lung.[1] Approximately 43% of Australians are diagnosed with cancer by 85 years of age and the average 5-year survival is 70%, which is a significant improvement from 1993 figures (52%).[1] Rare and less common cancers (<12 cases per 100,000 Australians per year) account for 27% of all cancer cases, but 38% of cancer-related deaths.[1]

Germline Genomics in Adult Cancer

Germline Susceptibility – Familial Cancer Variants

Hereditary cancer syndromes are caused by germline (present from conception) variants in cancer-related genes that confer an elevated susceptibility to cancer. The majority of such known germline variants occur in high penetrance genes that exhibit an autosomal dominant pattern of inheritance, with a 50% risk of being transmitted to offspring. The most common hereditary syndromes include hereditary breast and ovarian cancer (HBOC), Lynch syndrome, Li-Fraumeni syndrome, multiple endocrine neoplasia (MEN), neurofibromatosis, and

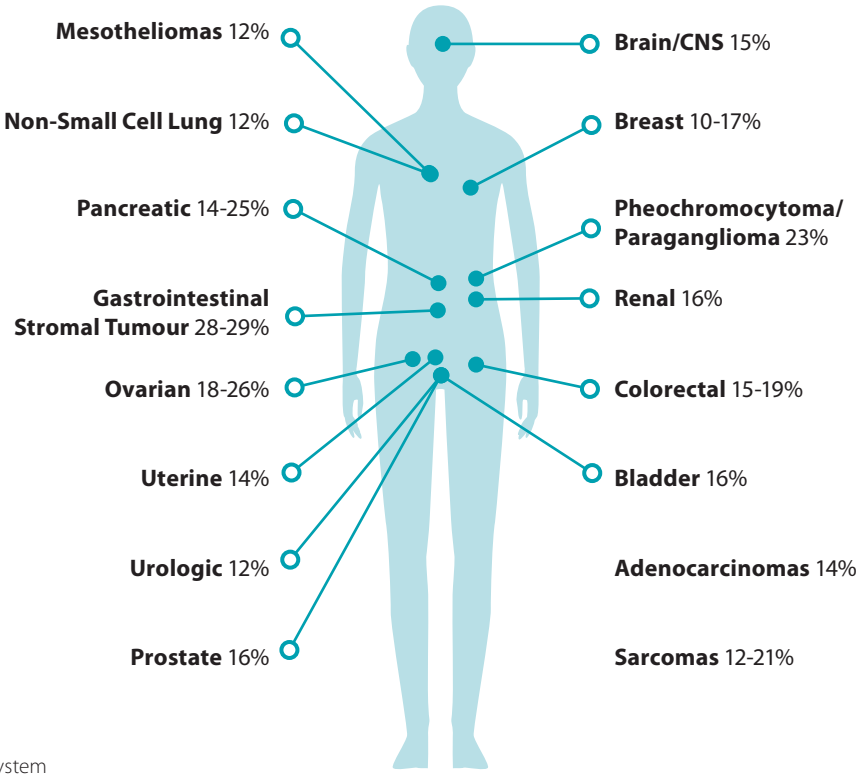
hereditary phaeochromocytoma-paraganglioma syndromes.[74] Variants in well-defined high-risk genes such as *BRCA1, BRCA2, TP53, MEN1, NF1, MLH1, MSH2, APC, RET* and *VHL* are commonly associated with these conditions and are known to significantly increase risk of cancer.[75]

The American College of Medical Genetics and Genomics (ACMG) established a framework to classify germline variants into five categories based on their pathogenicity (i.e. likelihood of causing disease): pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign.[4] Variants classified as pathogenic or likely pathogenic are considered clinically actionable and warrant disease-specific surveillance and management. For brevity, "germline variants" refer to pathogenic or likely pathogenic germline variants in the following sections.

Pathogenic germline variants are identified in 9-17% of adults with cancer, with a median of 10%.[76-85] The 2017 Memorial Sloan Kettering IMPACT study identified germline variants in hereditary cancer genes in 8% of their cohort (n=10,389).[86] More recently, two large studies (125,000 advanced cancer cases and 17,253 agnostically ascertained solid cancers) identified germline variants in cancer predisposition genes in 10.5-10.6% of individuals.[79,82]

The detection of germline variants is influenced by the cohort type and methodology employed. The inclusion of rare and advanced cancers increases the detection rate to 13-18%.[77,80,85] Similarly, cohorts enriched for familial cases report a higher detection rate (30.5%).[87] Methodology variations include; the number of genes screened (e.g., 2.5% of individuals when using a 25 gene panel[88] versus 12-17% when using 150+ gene panels[78,80]); matched tumour-normal paired samples allowing for greater discrimination in identifying germline variants,[89,90] and the time period the study was conducted (earlier studies reported 8% frequency of germline variants,[86] compared to studies from 2020 onwards, which reported 10-17%[76,78,79,81,84,85]). The increased variant detection rate over the past five years is likely attributable to the increase in the number of genes screened and the expansion in the number of variants classified as pathogenic and likely pathogenic in ClinVar, the leading international database for variant classification.[91] The cancers most likely to harbour germline variants are depicted in Figure 3 based on published data.[78,79,81,86]

Figure 3: Adult Cancers Associated with the Highest Frequency of Germline Variants.



CNS: Central Nervous System

The types of variants reported affects yield; only reporting known pathogenic variants (ClinVar)[86] versus additional review and inclusion of novel variants predicted to be deleterious;[79] the inclusion of moderate penetrance genes, which increases yields (18%);[77] reporting germline variants in cancer predisposition genes only or also the inclusion of germline variants in other actionable genes.[79]

There is growing interest in offering genetic testing for high-risk germline variants to asymptomatic individuals in the general population. A 2018 interrogation of >50,000 cases in a North American biobank found that 0.5% carried a *BRCA1/2* variant.[92] Consistently, an Australian study offering genomic testing to healthy women and found a pathogenic variant in one of 11 high-risk breast and ovarian cancer genes in 0.64% (38/5908).[93] Evaluating family history data in *BRCA1/2* variant carriers from the UK Biobank shows that 70% of individuals did not have a family history, and the cancer risk appeared to be lower in that subgroup as compared to the *BRCA1/2* carriers with a positive family history, suggesting that the nature of the variant and/or the genetic background, modifies risk.[94] The DNA Screen study will provide 10,000 Australians with genetic testing for hereditary breast and ovarian cancer, Lynch syndrome and familial hypercholesterolaemia over the next two years.[95] A comparable study in the United States found that 87% did not have a prior genetic diagnosis and 35% of these individuals had a negative personal and family history.[96]

Utility

In families with hereditary cancers, cascade testing (i.e., predictive testing in unaffected blood relatives) allows for custom screening and preventative prophylactic surgery and chemoprevention for those who also carry the predisposition, which facilitates early detection, resulting in better outcomes.[97-100] Cascade testing is thus crucial to realise the benefits of genetics for reducing cancer burden in the unaffected, high-risk individuals. Three quarters of the individuals found to carry a germline variant through cancer genomic profiling were previously unaware of their germline status.[81] Of individuals known to carry germline variants, between 53%-61% were offered germline genotype-directed therapies.[78,81]

At least 50% of individuals with cancer who were found to carry clinically actionable germline variants in cancer predisposition genes would not have met the eligibility criteria for germline testing.[77] Interestingly, in one large study, 64% of individuals with pathogenic germline variants presented with cancer types that lacked explicit hereditary cancer testing guidelines.[82]

Somatic Genomics in Adult Cancer

The goal of identifying somatic variants (i.e., variants newly arising in a tumour/affected tissue) is to detect variants driving the development, growth, and invasion of the cancer (so-called "driver variants") and identify relevant variant-matched therapies. Figure 4 illustrates the location and size of general cancer genomic trials worldwide.

Feasibility and Uptake

Somatic testing is typically performed on a biopsy from the tumour/affected tissue, which could be fresh-frozen or extracted from a formalin-fixed paraffin-embedded sample (FFPE). However, the quantity and quality of DNA attained from FFPE samples tends to be lower.[101] Nowadays, somatic testing is performed almost exclusively on FFPE samples and genomic profiling is successfully completed in 80-89% of participants, with unsuccessful cases attributed to factors such as biopsy failure, patient death, insufficient tumour material and poor quality DNA.[84,85,102]

Of note, profiling success rates are lower (39%) for cancers of unknown primary (CUP) due to inadequacy/insufficiency of samples from metastatic sites, aggressiveness of disease, and extensive testing with immunohistochemistry.[103]

Patients and clinicians held positive attitudes regarding tumour molecular profiling in most studies.[104-106] Although testing uptake is high (89%), there is some hesitation around willingness to pay for tests that are not fully publicly funded.[107] One study showed that advanced cancer patients in whom a targetable variant was identified had reduced distress, while individuals in whom an actionable variant could not be identified might benefit from support and counselling.[108]

An intervention which improves the uptake and utility of cancer genomic profiling are molecular tumour boards (MTBs). MTBs review patient results in a multidisciplinary environment that typically includes cancer specialists, genetics clinicians, pathologists, scientists, pharmacists and bioinformaticians. MTBs are highly valued by cancer clinicians,[109] improve oncologists' understanding of the strengths and limitations of genomic testing,[110] as well as their confidence and efficiency in utilising cancer genomic testing,[111,112] and promote interdisciplinary discussions.[113]

Types of Variants Detected in Adult Cancer Patients

A range of somatic variants are often found in adult cancers, including single-nucleotide variants (SNVs), small insertions or deletions of nucleotide bases (indels), large duplications or deletions (aka copy number variants (CNVs)), gene rearrangements and fusion genes. Most (85%) variants in adult cancers are SNVs or Indels, 12% CNVs and 3% gene fusions.[114] CNVs are present across a diverse range of cancer types, particularly uterine carcinosarcoma, sarcomas, oesophageal carcinomas, ovarian carcinomas, and bladder urothelial carcinomas.[115] In addition, it is possible to report on the tumour mutational burden, i.e., the density of somatic genetic variants in the DNA of cancer cells.

As per Introduction section, somatic variants are classified into four categorised based on their clinical impact: tier I, variants with strong clinical significance (level A and B evidence); tier II, variants with potential clinical significance (level C or D evidence); tier III, variants with unknown clinical significance; and tier IV, variants that are benign or likely benign.[34]

The frequency of the identified variant within a sample is considered a surrogate for tumour purity.[116]

Yield

Most large studies to date have been on advanced and/or rare cancers. Between 78-95% of adult cancer patients have ≥1 somatic variant(s) in cancer associated genes, and larger panels identify multiple variants per patient.[76,83-85,103,114,117-121] Genes with the largest number of identified variants include *TP53* (47-61%), *BRCA1* (45%) BRCA2 (29%), *KIT* (28%), *PIK3CA* (16-25%), *ATM* (23%), *KRAS* (18-24%), *APC* (12-20%), *EGFR* (20%), *CDKN2A* (7-22%) and *TERT* (16%).[83,102,109,118,119,122-127]

Actionable variants, which inform diagnosis, prognosis or treatment selection are identified in 27%-88% of samples.[76,117,118,122 83-85,109,123-126,128] The genes with the greatest numbers of actionable variants include PIK3CA, *KRAS, PTEN, TP53, ERBB2, BRCA1/2, NRAS, PR, ER, BRAF, EGFR, AKT1, RET,* and *cMET*.[84,117,118,122,125,128-130] Cancers with the greatest numbers of actionable variants are non-small cell lung cancer, oesophageal, ovarian, and cancers of unknown primary.[83] Rare cancers are associated with a higher number of actionable variants (88-93%).[76,121]

A study of <5,900 patients with refractory cancers found that 71% had resistance-conferring tumour mutations and 38% carried an actionable variant.[122] The refractory cancers most likely to be assigned to a matched therapy include cholangiopancreaticobiliary, melanoma, prostate cancer, uterine, and gastroesophageal.[122] Earlier studies identified fewer actionable somatic variants due to reduced number of: genes screened,[84] identified pathogenic variants and available trials.[129]

The addition of RNA-seq increases the detection of biomarkers,[76] e.g., miRNA, lncRNA and circRNA, which can be used to monitor disease progression and response to treatment.[45] Similarly, there is an increasing interest in detecting and monitoring gene methylation, especially in breast cancer, for the identification of therapeutic targets and for predicting response to treatment.[131,132]

Clinical Utility

Matched Therapies

Cancer genomic sequencing informed or refined diagnosis in 4.4-10.5%[76,133] of advanced patients and was particularly valuable in cancer of unknown primary (CUP) and soft-tissue sarcoma patients.[76] A study focusing on CUP reported that genomic profiling corrected or enabled a diagnosis in 51% of individuals.[85] Studies of adult cancers did not generally comment on the frequency with which identified variants informed prognosis, but instead mentioned particular variants in tissue specific cancers and patterns of aberrations (e.g., high TMB)[134] associated with a positive response to immunotherapy.[135]

Overall, 31-48% of adults have ≥1 molecular variant which has a matched therapy,[76,122,123,128,133,136] and 27-78% had a variant(s) which matched to one or more therapy.[109,114,117,118,120-124,126,128,137-140] The greatest number of actionable variants are Tier II or Tier III.[85] When restricted to Tier I and Tier II variants, 17-56% had a targetable variant.[114,120,130,141,125] Common Tier I targetable cancer included non-small cell lung cancer, breast cancer, melanoma and colorectal, while the most frequently targeted cancers [120,122] and the most common Tier I actionable drugs were based on PD-L1 immunohistochemistry (13% of patients).[140] Cancers with Tier II variants included bladder, breast, non-small cell lung cancer, pancreatic and sarcoma,[120,122] and up to 76% of recurrent/metastatic patients who had a related targetable variant received PI3K-Akt-mTOR therapies through clinical trials.[126] Therapeutic variants are more common in colorectal, gastric and pancreatic cancer (63%).[124]

On average, 33-38% (range 6%-62%) of individuals with a targetable variant received matched therapies,[76,83-85,102,109,114,117,118,122,123,125,126,128-130,137,140] with most accessed through clinical trials.[102,125,126] The main reason for not receiving matched therapy include deterioration of patient condition.[103]

In individuals with cancers of unknown primary, 91% had ≥1 actionable variant and 41% of patients had a matched therapy. A change in therapy was recommended for 64% of individuals and implemented for 16% of those with a matched therapy.[103]

It is important to note that the frequency and profile of actionable variants can vary in different ancestral populations.[142,143]

Outcomes

Studies reported response rate and compared response to non-matched therapy groups or initial response to prior therapies. Most studies focused on patients with advanced cancers generally, and intractable cancers specifically.

One study defined positive response according to the percentage of patients still taking the matched therapy 6 (37%) or 12 (20%) months later.[85] Other studies reported on the proportion of patients receiving matched therapies who had stable disease (58%),[118] partial (38%)[127] or complete response (17%),[127] while others grouped partial/complete/overall response rate (11-52%)[76,117, 120 123,125] or disease control rates (55%)[76] 6-34 months later. The two studies that compared control rates to those receiving a matched therapy had significantly higher rates than the 5%-30% of the remaining advanced disease cohort.[117,118, 123,125]

Median progression free survival (PFS) was 1.5-fold higher in matched versus unmatched therapy groups[117,125] and median overall survival (OS) ranged from 1.2 fold (8.4 months versus 7.3 months)[117] to 4.1 fold (35.1 months versus 8.5 months).[125] Individuals receiving a matched therapy had a PFS2/PFS1 ratio (ratio of progression free survival time post current treatment as compared to prior treatment) >1.3 [76,125,84,128,144] Furthermore, those receiving Tier I [125] or Tier I/II therapies [120] had better PFS and OS than those with lower evidence levels. Patients with matched therapies had significantly longer PFS than those with unmatched therapies.[121]

Two Australian studies have been reported to date. The first small study showed that 25 individuals who received matched therapy had improved survival compared to patients with unmatched therapy (n=114).[145] The MOST

Trial, as reported in a conference poster, showed that individuals with treatment refractory, advanced cancers receiving matched therapy had a longer median OS rate as compared to those receiving an unmatched therapy (16.9 months versus 10.4 months).[146]

In patients with cancers associated with a poor prognosis, (e.g., pancreatic), individuals receiving matched therapies were found to have longer median OS (2.58 years vs 1.51 years) and a longer OS (2.58 years vs 1.32 years), compared to those who received unmatched therapies.[136]

Individuals receiving matched therapies who had fewer prior therapies showed better PFS and OS than those who had received multiple therapies previously.[123,147] One small US study of individuals with advanced disease reported that the median PFS in those receiving matched therapy as a frontline therapy was 449 days.[139] This suggests that there may be benefits to implementing genomic sequencing as a frontline therapy in cancer patients.

Several molecular tumour board (MTB) studies quantified the quality of the matched therapy and those with a strong match had a longer PFS[137,147] and OS[137,146] than those with a low match score. Patients receiving MTB recommended therapy had significantly higher PFS and OS as compared to those receiving Physician Choice regimes.[123] MTBs have often been used in basket trials to assign patients to available trials based on their molecular profile.[102,148]

Evolution of Methodologies and Analytical Approaches

The most comprehensive detection of actionable variants can be achieved by using WGS/WES with RNAseq.[76,85] Initially, turnaround times were reported to vary from 19 to 21 weeks,[76,124] but more recent studies report a mean turnaround time of 5.5-7.5 weeks from enrolment to return of data to the MTB.[149,150]

The addition of RNAseq improves the detection of gene fusions, the verification of intratumoral expression of SNVs/indels, evaluations of transcriptional effects of gene amplifications and deletions and diagnostic classification of unclear disease patterns.[76]

The methylation of cancer genes can affect their expression and their role in cancer development and progression. Methylation studies are particularly valuable in the classification of brain tumours and sarcomas.[151]

Genomic Patterns within Tumour Samples

Four commonly utilised descriptors for mutation patterns within a tumour include tumour mutational burden (TMB), homologous repair defect (HRD) scores, microsatellite instability (MSI) and aberrant methylation.

Tumour Mutational Burden (TMB)

The cutoffs for TMB vary and a recent review found that ≥10 mutations per megabase was considered high.[41] Median TMB in general adult cancers is 4 and 14 in cancers of unknown primary.[83] High TMB is seen in 10-25% of individuals with aggressive, advanced and hard to treat cancers.[102,114]

The TMB is valuable as it can predict response to immune checkpoint inhibitors across multiple cancer types.[135,152] Within a cohort receiving immunotherapy, high TMB is associated with a greater response rate (58% vs 20%) and longer median PFS (12.8 months vs 3.3 months) than individuals with low (1-5 mutations per MB) to intermediate (6-19 mutations per MB) TMB.[153] TMB can also be serially evaluated to detect response to treatments.[154]

Homologous Repair Defects (HRD) Score

A HRD score is an unweighted sum of three independent DNA-based measures of genomic instability (loss of heterozygosity, telomeric allelic imbalance, and large-scale transitions).[155] High HRD scores can occur in the presence of germline and/or somatic variants and are predictive of a good response to PARP inhibitors.[156] In a cohort with advanced solid tumour malignancies including gastrointestinal (GI), genitourinary (GU), or rare cancer, HRD was observed in 75% (347/501).[157]

Microsatellite Instability (MSI)

MSI is the expansion of repeated DNA sequences through the genome. It is a recommended biomarker for at least nine cancers as it is an important predictive biomarker for response to immune checkpoint inhibitors.[158] In 2-3% of samples from general cancer cohorts, high MSI was identified,[41,102,159] which increased eligibility for immunotherapy. In one study, Lynch syndrome was subsequently diagnosed in 16% of individuals with high MSI and 2% of those with intermediate MSI, only half of whom had CRC or endometrial cancer tumours.[159]

Aberrant Methylation Patterns

Methylation is the process by which gene expression is enhanced or suppressed within cells. Hypomethylation is widespread in cancer genomes resulting in overexpression, while tumour suppressor genes are often selectively hypermethylated or turned off. Cumulatively, the aberrant methylation is thought to contribute to genomic instability. As the DNA code is not altered, this is referred to as epigenetic modification.[160] There is an increasing availability of therapies that target methylation, and hypermethylation is being explored as a biomarker.[131]

Cell-free DNA (cfDNA) and Circulating Tumour DNA (ctDNA)

cfDNA is free-floating DNA that is shed or released from cells into the bloodstream, including tumour cells. Liquid biopsy of various body fluids, such as blood, urine, and cerebrospinal fluid (CSF) can be used to detect and analyse cfDNA. In healthy individuals, the concentration of cfDNA in plasma is between 0-10ng/ml with serum concentrations of cfDNA being 10 times higher.

The proportion of cfDNA that originates from tumour cells is referred to as circulating tumour DNA (ctDNA). Overall, the percentage of ctDNA (measured as variant allele frequency [VAF]) in an individual with early-stage cancers is low (<1% of cfDNA),[161] although in patients with advanced metastatic disease, this can exceed 70%.[162] The quantity of ctDNA released by tumours depends on factors including tumour stage (increasing values with increasing stage), age of the individual (decreasing levels as age increases), sex of the individual (higher levels in those assigned male at birth), and specific tumour type.[163]

Feasibility of ctDNA assays

There were initial challenges with optimising methodology, but in a 2021 study of general cancers, 99% (n=681/687) of samples yielded sufficient ctDNA and passed quality control metrics.[164] Other studies demonstrated high sensitivity and specificity to detect SNVs, indels and fusions from ctDNA,[165,166] with higher DNA input being associated with greater detection of somatic variants.[116] One study compared the number of variants detected in tissue versus ctDNA and found high feasibility (technical success rate >99.6%) and sensitivity (86%).[165] More variants may be detected in ctDNA than tissue due to tumour heterogeneity, i.e., tumour biopsies do not always capture the complete heterogeneity.[166]

Challenges include that physiological factors alter ctDNA levels, e.g., obesity is negatively associated with ctDNA detectability.[167] Therapeutic interventions can also alter ctDNA levels, e.g., surgical resection or commencing chemotherapy can cause a decline in ctDNA, regardless of clinical response.[168] Some cancer types may secrete or shed less DNA into the circulation for unknown reasons.[169] As ctDNA fragments are short (145-165bp),[170] there

is also reduced sensitivity (18.6%) for CNVs, large rearrangements and fusions.[166] Practically, a sufficiently large blood sample (10-30mls) is required to yield enough ctDNA,[35] and there are handling and storage steps needed to mitigate the risk of ctDNA degradation in samples which are not processed promptly.[171] Other challenges to applying ctDNA in practice include cost and turnaround time.[172]

Clinical Utility of ctDNA

Compared to tissue biopsies, a liquid biopsy is minimally invasive, can be collected at multiple timepoints and is easy to process for genomic sequencing.[35] Potential applications range from profiling individuals with an unknown primary or inaccessible tumour, detecting residual disease and actionable variants in patients, to screening in the general population. Figure 5 captures the location and size of studies which evaluated ctDNA studies adults with advanced cancers worldwide.

ctDNA as Alternative to Tissue Biopsy

Carcinoma of unknown primary (CUP) account for 3-5% of all cancers and are aggressive and difficult to treat.[173] Traditionally, the molecular profile of these cancers has been determined by sequencing metastatic tissue.[173] Given that CUP is inherently metastatic, there are elevated levels of ctDNA in the bloodstream. One large study (n=442) showed that 80% of CUP patients had a variant detected on ctDNA, of which 88% had distinct genomic profiles and 99.7% had potentially actionable variants.[174]

It is difficult to provide accurate diagnosis, prognosis, and treatment choices for a cancer which cannot be biopsied. Molecular profiling of ctDNA in these patients could serve as a proxy to direct tumour profiling. Concordance between tissue and ctDNA is 61%-85% and a greater number of variants are detected in ctDNA than tissue.[175,176,177,178,169,179,180,165,164]

ctDNA for Detecting Residual Disease and Treatment Response

ctDNA can be evaluated both quantitatively and qualitatively. Quantitatively, ctDNA levels are prognostic biomarkers whereby patients with advanced solid tumours who had undetectable ctDNA had a median OS of 68.4 months versus 15.6 months for patients with detectable ctDNA. Within the cohort with detectable ctDNA, those with lower levels (below median) had longer survival than those with higher levels.[167] The presence of ctDNA after cancer therapies is evidence of minimal residual disease, and is associated with lower disease-free survival and OS.[181,182] Similarly, US and Chinese studies have shown that ctDNA content fraction was negatively associated with outcomes (stable disease, progressive disease and objective response).[183,162]

Qualitatively, the detection of more than one SNV in ctDNA is associated with poorer OS.[162] Sequencing of ctDNA can also detect variants associated with treatment resistance, as was the case in 34% of a cohort of individuals treated with different matched therapies.[184] Serial sampling can also detect cancer recurrences after prolonged periods of remission.[185] Two studies demonstrated accurate detection of microsatellite instability (MSI) relative to tissue results,[186,187] which is important given that it is a predictive biomarker for response to immune checkpoint inhibitors.[158] Similarly, blood based tumour mutational burden (bTMB) is a promising biomarker[188] and a recent study using a 324 cancer-related genes panel demonstrated high correlation between tissue TMB and blood TMB.[187,189] bTMB can predict response to immunotherapy in individuals with NSCLC.[190] Methylation patterns within ctDNA is being increasingly explored as possible biomarkers (e.g., colorectal cancer[191]).

ctDNA to Detect Actionable Variants

To date, most ctDNA studies have focused on evaluating response to treatment in individuals with advanced cancers, due to the higher ctDNA levels.[169] In 72-85% of advanced/metastatic cancers at least one alteration is detected.[162,163,166,179,192,193,194,165] Cancer type affects the yield which can range from 51% for glioblastoma, to 86-93% of non-small cell lung cancer and 93% for small cell lung cancer.[163,175,176] A larger proportion of patients (87-91%) are found to carry ctDNA variants when larger panels (70-120 genes) are used.[176,175,164] Most frequently mutated genes across all cancer types were TP53 (38-58%)[175,193,179,164] and EGFR (11-49%).[175,194]

Studies report that 36-62% of variants were actionable,[175,192,165,164,194] and one study reported that 80% of those with actionable variants received a matched therapy (including trials).[192] Actionable variants were identified in *EGFR* (26-28%), *MET* (4-6%), *KRAS* (4%), and *BRAF*(3%), most commonly treated with immunotherapy or anti-EGFR therapy.[176,180,194] ctDNA results significantly increased the proportion of patients eligible for matched therapy (7.9% vs 6% for Tier I or II variants).[178] The primary reason for not utilising personalised therapies was poor patient status.[192] Individuals with fewer prior therapies (<4) experienced greater OS.[162]

ctDNA in Cerebrospinal Fluid (CSF)

ctDNA is typically extracted from whole blood. However, in patients with suspected CNS involvement ctDNA can be successfully extracted from CSF and sequenced in 72% of cases, of whom 71% had a somatic variant. As per blood ctDNA analysis, there was high concordance with previously sequenced tumour samples and 15% had additional variants identified, which were consistent with therapy-related resistance. Of interest, 3% had variants which independently diagnosed a new primary.[116]

ctDNA as a Screening Tool

Research is increasingly exploring the viability of using ctDNA as a biomarker for early cancer detection, possibly testing for many cancers at once (often referred to as "multi-cancer early detection tests"). One of the appeals is the relative non-invasiveness of accessing a blood sample compared to other screening modalities and the possibility of early detection, which could improve prognosis.[195] However, as mentioned previously, factors other than cancer can affect the amount of ctDNA in circulation,[196] thereby increasing the risk of a false positive result.[35] Screening ctDNA for the presence of common cancer variants also presents a risk of false-positives as some cfDNA variants are found in individuals with non-malignant conditions, e.g., clonal haematopoiesis.[197] It is also possible that an actionable variant could be present but not detected, either due to the early stage of the malignancy, the fact that the variant is present at a low level in the malignancy and/or the test did not target the variant.[35] Collecting a larger blood sample reduces but does not eliminate this risk. Even for ctDNA tests using more complex algorithms e.g., aberrant methylation, sensitivity at early stage is typically low (e.g. 27.5%).[198] Finally, even if a suspicious result was detected, further clinical testing would be required to detect or rule out a cancer, given that the person is asymptomatic and the primary site would be unknown.[35] Due to the large number of false-positive results, such follow-up tests could lead to substantial health system burden, as well as psychological and physiological side-effects to individuals with false-positive results.[199]

A cohort that could possibly benefit from ctDNA as a screening tool are individuals with pathogenic variants in hereditary cancer predisposition syndrome genes. It is particularly appealing in cancers for which there is not an agreed upon screening modality, such as ovarian, pancreatic, and gastric cancers or as an adjunct to other biomarkers, e.g., CA-125 etc. Both consumers and healthcare providers are enthusiastic about the potential value of ctDNA for screening, early detection, and reducing imaging.[200,201] Longitudinal studies are needed to determine the feasibility, sensitivity and specificity of applying ctDNA as a screening tool in this high-risk population.

ctDNA in Practice Globally

The following blood tests have been approved as companion diagnostics by the FDA:[202]

- FoundationOne liquid CDx detects gene mutations in a panel of over 300 genes in ctDNA. Results are used to guide treatment decisions. Though additional services are not currently FDA-approved, this test can also report blood TMB, MSI and tumour fraction volumes.
- Guardant360 CDx evaluates a 74-gene panel in ctDNA samples in individuals with advanced solid cancers. Identified actionable biomarkers enable treatment with matched therapies.
- *The therascreen PIK3CA* RGQ PCR Kit, aids in the treatment of breast cancer. The test detects the presence of single-gene mutations in ctDNA, to identify patients eligible for trials/therapies.

- Cobas *EGFR* Mutation Test is an rt-PCR test that is available to Australian patients and ctDNA is used to determine eligibility for erlotinib treatment in patients with metastatic non-small cell lung cancer.
- Epi proColon test for the screening and detection of colorectal cancer. It is currently available in the USA, Europe, and China. The test uses methylation markers as an indicator of cancer.

Polygenic Scores (PGS)

Polygenic scores (PGS) are an emerging genetic technology used to estimate the genetic liability to complex health conditions, such as cancer. Unlike germline genetic testing for monogenic conditions (such as the familial cancer variants described above), which tests for the presence or absence of single variants, a PGS is calculated based on the combined impact of multiple common genetic variants (ranging from dozens to millions of variants depending on the approach used and condition of interest).[29] Currently, only one commercial laboratory has NATA accreditation to offer PGS testing for cancer risk in Australia[203], with testing yet to be implemented in clinical practice. However, it is anticipated that PGS will become increasingly available. Applications in cancer include population screening, refining moderate-risk and high-risk results for people with familial cancer variants, and informing prognosis and management.

Population Screening

Currently, age is the primary risk factor in determining recommendations for population screening programs. In this setting, PGS could be used, alongside other risk factors, to personalise existing population screening programs, such as more frequent and earlier screening for those at higher risk, and reduced screening for those at lower risk. Implementation of PGS can also be used to identify individuals for targeted early detection of cancers that are not part of a national population screening program, such as melanoma.[204] PGS can also be used to augment existing screening programs, e.g. to improve the positive predictive value of prostate-specific antigen levels, which are currently the basis for opportunistic early detection of prostate cancer.[205] [206] Finally, PGS can be integrated with traditional risk to generate a personalised risk score.[29]

Additionally, DNA methylation is influenced by varied exogenous and endogenous factors, including environmental risk factors and complex disease pathology, thus providing another dimension to risk assessment.[207] Early research is exploring the possibility of including methylation- based breast cancer risk scores to PGS and traditional risk factors to improve risk prediction models for population risk stratification.[208]

Familial Cancer Clinic

Risk estimates for individuals with a hereditary cancer syndrome are based on epidemiological studies. Thus, there is variability in risk and cancer development, including among individuals within families carrying the same pathogenic variant. It is well established that a PGS can modify the risk associated with a hereditary cancer syndrome, either increasing or decreasing estimated lifetime cancer risk.[29] Use of PGS can therefore inform personalised cancer risk management for individuals with a confirmed hereditary cancer syndrome, such as informing frequency of screening, and timing for risk-reducing surgery. For example, individuals carrying pathogenic variants in *BRCA1* or *BRCA2* can refine their risk from the existing broad range (BRCA1 lifetime risk ranges from 53% to 92%[209]) by including PGS information. Although these individuals will remain at high risk, PGS can adjust the age at which screening and risk-reducing surgery is recommended.[210] Furthermore, most individuals undergoing genetic testing for a hereditary cancer syndrome receive a negative result (i.e., no pathogenic variants identified). Testing for PGS can provide further information, beyond family history, regarding the genetic contribution to their cancer risk and personalise ongoing risk management.

Predicting Prognosis to Inform Therapeutic Interventions

A PGS has been demonstrated to predict prognosis and cancer aggressiveness in several settings including breast cancer [211], and prostate cancer.[212,213] Furthermore, PGS can predict risk associated with specific cancer-subtypes (e.g., ER-positive versus ER-negative breast cancer [31]). Such information can inform treatment and ongoing risk management decisions.

See Appendix Table A1.1 for applications of PGS in practice using breast cancer as an exemplar.

Pharmacogenomic Testing

Genetic variations have been identified in a number of genes (e.g., Dihydropyrimidine dehydrogenase, Thymidylate synthetase, Methylene tetrahydrofolate reductase (MTHFR), Thiopurine S-methyltransferase (TPMT), and Glutathione S-transferases) involved in the metabolism of most chemotherapy drugs.[214-216] Variations in these genes can affect therapeutic response, drug resistance and adverse effects.[214-216] However, it is unclear whether this is widely or consistently implemented in Australia.[217]

Variants in *CYP2D6*, *OPRM1* and *COMT* affect the clinical efficacy and safety of opioids like codeine, tramadol, hydrocodone, oxycodone, and methadone. In 2021, the Clinical Pharmacogenetics Implementation Consortium produced guidelines for *CYP2D6*, *OPRM1* and ¬*TPMT* variants and select opioid therapy.[218] There is currently no Medicare rebate for *CYP2D6* in Australia.[219]

See **Table 3** for summary of potential utility of genomic testing (germline and somatic) relative to the Cancer Care Continuum for adults.

Cancer Vaccines

Vaccines provide protection against a wide variety of diseases. They do this by introducing antigens which mimic an infection and train the immune system to induce an immune response. Once vaccinated, the immune system is primed to provide protection against the disease. This topic was reviewed as described in Appendix 1C.

Modern vaccinations have eradicated smallpox and brought other diseases to very low rates in the population.[220] More recently vaccinations have been used to prevent and treat different types of cancers.[221]

Cancer vaccines can be divided into two main categories:

1. Prophylactic, or preventative, cancer vaccines reduce the risk of particular types of cancers in the general population.[222] They do this by preventing or reducing infections that could lead to cancer.
2. Therapeutic cancer vaccines are used to treat existing malignancies by inducing an anti-tumour immune response to treat the cancer.[223] There are many types of therapeutic cancer vaccines in development. These technologies use a range of methods to deliver antigens including messenger RNA (mRNA), DNA, viruses or peptides (Figure 6). The technology that has shown the most promise is the mRNA vaccine. This type of vaccine has been widely used in the fight against COVID-19.

Prophylactic Cancer Vaccines

Prophylactic vaccines have been greatly successful in preventing or reducing infection caused by a range of diseases. There are currently two prophylactic vaccines that target cancer-inducing viruses.

Human papillomavirus (HPV) infections cause up to 5% of all human cancers [224] and cause almost all cervical cancer cases.[225] In Australia, HPV is detected in several other cancer types, including anal (97% cases), vaginal (78%), vulvar (15-48%), oropharyngeal (41%) and penile cancers (51%).[226]

The HPV vaccine, implemented in Australia in 2007, has not only reduced HPV infections but also the cancers that develop as a result of these infections. It is estimated that HPV vaccination has prevented 90% of cervical cancers associated with HPV infection.[227]

Chronic hepatitis B virus (HBV) infection can cause inflammation of the liver and an increased risk of developing liver cancer. Globally HBV infection accounts for approximately 33% of liver cancer deaths.[228] HBV vaccination has been shown to reduce the incidence of liver cancer which is one of the most common cancers globally.[222]

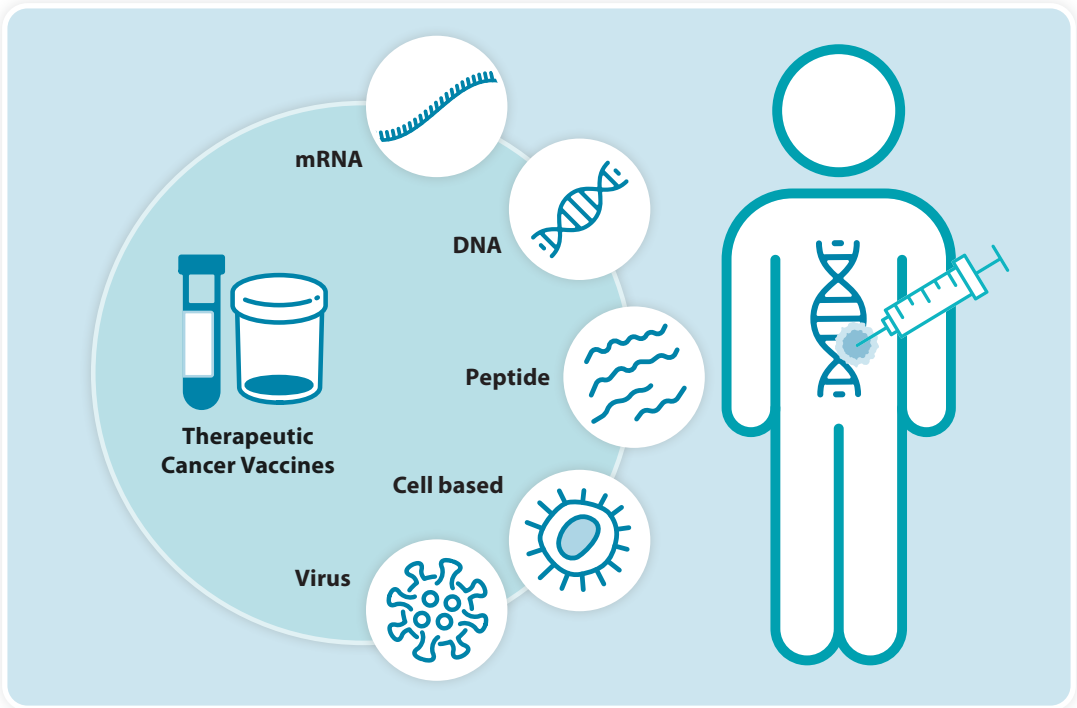
Therapeutic Cancer Vaccine Types

Therapeutic cancer vaccines train the immune system to recognise and attack cancer cells. Their ability to boost an antigen-specific immune response has shown promise as a cancer therapy.[229] There are several major types of therapeutic cancer vaccine that have been utilised: peptides, DNA, RNA, cell-based and viral (Figure 1, Table 3).[223]

Peptide vaccines are a sequence of amino acids that are designed to generate an immune response by targeting tumour-associated antigens or tumour-specific antigens.[230] The advantages of this technology include high specificity and high patient safety. Peptide vaccines have been widely trialled in cancers such as glioblastoma, prostate cancer and non-small cell lung cancer but results have shown limited patient benefit.[223] In melanoma, a trial of 50 patients, NCT02126579, showed that the peptide vaccine induced an immune response in a subset of patients.[231]

DNA-based vaccines work by delivering plasmids that contain a DNA sequence which encodes antigens, which in turn induces an immune response. Thus, the patient's immune system will recognise and target the cancer cells.[232] The advantages to using this technology include lower cost, and ease of storage and transport, as the vaccines can be maintained at ambient room temperature.[229] A trial enrolled 66 patients with ERBB2 (erb-b2 receptor tyrosine kinase 2) positive breast cancers. The DNA vaccine was administered monthly to patients with advanced stage cancers. Outcomes of the NCT00436254 trial showed safety as well as an ongoing immune response in these patients.[233] Overall, while these types of vaccinations have been able to generate an immune response in early clinical trials, these methods have had limited success achieving long -term survival benefit.[232]

Figure 6. Types of personalised therapeutic cancer vaccines used in clinical trials.
Created with BioRender.com



Antigen-presenting cell (APC) vaccines deliver mature immune cells which are able to induce an anti-tumour immune response.[223] They are created by first collecting immune cells from the patient and then adding in the immune cells before reinfusion. A phase III clinical trial, NCT00045968, treated [331] patients with glioblastoma.[234] Results from the trial show significant improvement in overall survival for both newly diagnosed patients and patients with recurrent disease.

Whole tumour cell vaccines use the patient's tumour cells as a source of immunogenic antigens. Before being administered, the cells are irradiated which stops them from being able to replicate.[235] After vaccination, in response to the antigens, immune cells such as dendritic cells are recruited to initiate the immune response. A trial in patients with mantle cell lymphoma, NCT00490529, showed that vaccination induced an anti-tumour immune response in 40% of patients.[236] Some of the limitations of whole tumour cell vaccines include high cost and manufacturing challenges.[235]

Bacillus Calmette-Guerin (BCG) is a live attenuated vaccine that was developed to prevent tuberculosis infection. In cancer treatment it is used in non-muscle invasive bladder cancer to activate the local immune system, preventing tumour cells from surviving and proliferating.[237] BCG is used as standard of care for these patients. In a separate study (NCT02779855), T-Vec, based on an oncolytic herpes simplex 1 virus, was trialled in triple negative breast cancer patients treated with a combination of neoadjuvant chemotherapy and the cancer vaccine.[238] The trial was able to increase the pathological complete responses above the rate expected for chemotherapy alone though was unable to draw conclusions regarding long-term survival outcomes.

mRNA technology is changing the way we approach cancer therapy. One of the key aspects is that these vaccines can be developed rapidly and have shown excellent safety in the clinical trials setting.[239] The first trials looking at mRNA vaccines are underway in cancers including melanoma,[240] and pancreatic cancer.[241] These cutting-edge studies have demonstrated proof-of-concept that this approach can be an effective cancer treatment and some studies have begun to move into phase 3 trials. This review focuses on mRNA vaccines.

Creation of mRNA Cancer Vaccines

mRNA vaccines are created by first taking a tumour biopsy. The tissue is sequenced and the genomic variants specific to the tumour are captured. The matching neoantigens for these variants are then predicted using bioinformatics methods. Neoantigens are tumour-specific proteins found on the surface of tumour cells. The role of the vaccine is to educate the patient's immune system to recognise and attack these cells. The personalised vaccine can encode up to 40 neoantigens specific to a patient's tumour. Genomics and bioinformatics are the key to developing these vaccines. As the interpretation of genomics data has been refined, mRNA vaccines have also become more effective with improved neoantigen calling leading to more effective personalised vaccines.[223]

One of the challenges faced by therapeutic vaccines development is that tumours evolve over time, and the genomic variants driving their tumours change. This means that they can adapt and develop mechanisms to evade the anti-tumour response that the vaccine delivers.[221] Other considerations include the high costs associated with personalised vaccines and a limited availability which restricts patient access.[242]

Emerging evidence for mRNA vaccines

A recent clinical trial, KEYNOTE-942, included 157 resected stage III/IV melanoma patients.[240] They received personalised mRNA cancer vaccine as well as an immune checkpoint inhibitor for malignant melanoma. For each person, an individualised mRNA vaccine was developed which encoded the neoantigens found on the surface of the tumour. Overall, the study found that the recurrence-free survival was longer in patients who received the combination of vaccine and immune checkpoint inhibitor compared to patients that received the inhibitor alone. This is the first personalised mRNA vaccine to reach a phase III clinical trial.[229]

A phase 1 clinical trial, NCT04161755, in 16 pancreatic ductal adenocarcinoma (PDAC) patients used a personalised mRNA vaccine.[241] For each patient, the personalised vaccine was developed after surgical resection of the PDAC tumour. The patients were then treated with anti-PD-L1 immunotherapy, chemotherapy and the mRNA vaccine. The study demonstrated that this treatment induced substantial immune response and correlated with delayed disease recurrence in 50% of patients. This has provided the preliminary evidence that will likely lead to a larger study examining the role of mRNA vaccine in surgically resectable PDAC. This is particularly exciting as PDAC typically have a high recurrence and mortality rate and cancer vaccines could provide a substantial advance in the treatment of cancers with high mortality rates.[243]

The oncogene KRAS is mutated in up to 30% of solid cancers including pancreatic cancer, colorectal cancer and non-small cell lung cancer (NSCLC).[244] There are therapeutic vaccines being investigated to target tumours harbouring these variants including mRNA vaccines and dendritic cell vaccines.[245,246] AMPLIFY-201, an mRNA trial of 25 patients with KRAS positive pancreatic ductal adenocarcinoma or colorectal tumours, has shown that the mRNA vaccine has been able to stimulate an immune response in 84% patients and demonstrated that some patients experienced longer relapse-free survival.[247] The success of this trial has given rise to testing a broader spectrum of tumours harbouring KRAS variants.

mRNA vaccines seem to be most effective when tumour burden is low, particularly in the control of residual disease and the prevention of tumour recurrence after surgery. Importantly, in the setting of early-stage disease, tumours are often slower growing and this provides time for the personalised vaccine to be made, which can take up to 4 months. Furthermore, it takes time for the patient to develop an anti-tumour immune response.

These types of vaccines have been less effective when used to treat patients with larger tumour burden or metastatic disease. However, further clinical studies are required to determine which cancer stage will benefit the most from this treatment approach. There are currently trials underway that investigate efficacy of cancer vaccines in a range of cancers and stages.

Current cancer vaccine trials in Australia

A search of the Australia and New Zealand Clinical Trials Registry (ANZCTR) failed to identify any Australian cancer vaccine trials. The search resulted in 3 studies, one study related to influenza, and the 2 others related to COVID-19. Of note, when the search was extended to include active trials, not yet recruiting, results returned one additional study that provides long-term storage of tumour biopsies for the possible production of a personalised therapeutic cancer vaccine in the future (ACTRN12615000476538).

Worldwide, there are >300 registered cancer vaccine trials, a search of the US-based clinicaltrials.gov database returned 3 studies recruiting in Australia.

- Autologous Tumour Vaccine Trial (NCT05807035) is a phase 1 trial assessing an autologous tumour vaccine for patients with advanced solid tumours. The vaccine is developed using a tumour biopsy. It aims to assess the feasibility, safety, tolerability and vaccine response in a cohort of 30 patients.
- A Study of Neoantigen mRNA Personalised Cancer in Patients With Advanced Solid Tumors (NCT05198752) is a phase 1 study in patients with advanced malignant solid tumours. This mRNA vaccine aims to enrol 30 patients to evaluate tolerability, safety, immunogenicity, and efficacy.
- A Clinical Study of the Safety and Effectiveness of an Investigational Cell Therapy Given With and Without an Investigational RNA-based Vaccine in Patients With Organ Tumors (NCT04503278) is a phase 1 study in patients with advanced solid tumours. The study is estimated to enrol 145 patients in both Australia, Netherlands, Sweden and Germany to assess safety and efficacy.

While there are few registered trials in Australia, there are several under development. In 2024, University of Queensland immunology researchers initiated the Brain Cancer Vaccine Project. With support from the Robert Connor Dawes Foundation, they have begun development of an mRNA cancer vaccine to treat paediatric brain cancer patients.[248] The collaboration brings together a multidisciplinary team to demonstrate the principles of vaccine design and delivery in these patients.

In a collaboration between WEHI and the Peter MacCallum Cancer Centre, a second Australia study, is developing a cancer vaccine focussing on patients with limited treatment options.[249] With funding from the Medical Research Future Fund, they are developing a platform to manufacture dendritic cell-based vaccines capable of treating patients that have had limited response to existing therapies, including chemotherapy.

Although many of the cancer vaccine trials to date have originated in the United States, the National Health Service (NHS) England announced the imminent commencement of their Cancer Vaccine Launch Pad (CVLP) in May 2024.[250]

Table 3. Selection of therapeutic cancer vaccine trials showing positive immune responses or improved patient survival.

Trial Name	Disease	Number patients	Technology	Trial Result	Reference
KEYNOTE-942	Melanoma	157	mRNA	Improved recurrence-free survival in patients receiving combination of vaccine and immune checkpoint inhibitor	240
NCT04161755	PDAC	16	mRNA	>50% patients had delayed disease recurrence	241
AMPLIFY-201	KRAS positive CRC and PDAC	25	mRNA	Longer relapse-free survival in patients receiving the vaccine	247
NCT00436254	ERBB2-positive breast cancer	66	DNA	ERBB2-specific type immune response demonstrated in most patients	233
NCT02126579	Melanoma	50	Peptide	Demonstrated immune response in a subset of patients	231
NCT00045968	Glioblastoma	331	Dendritic cell	Significant improvement in overall survival	234
NCT00490529	Mantel cell lymphoma	45	Whole tumour cell	Induced an immune response that was associated with improved clinical outcomes	236
NCT02779855	Triple-negative breast cancer	37	virus	Increased pathological complete response	238

Research and Practice Gaps

Additional research and data are needed:

- Large studies evaluating the frequency and utility of actionable, somatic variants in primary cancers.
- Large studies evaluating the frequency and utility of actionable findings from ctDNA (mutation patterns, methylation etc.) for primary cancers.
- The extent to which cancer genomic testing and pharmacogenomic testing is currently utilised in Australia outside of clinical trials.
- The sensitivity and specificity of ctDNA for screening and surveillance in individuals carrying pathogenic variants in hereditary cancer genes.
- Comparing response rates and longitudinal outcomes between those receiving matched therapies and those receiving standard therapies.
- PGS clinical utility, cost-effectiveness, and implementation strategies needed for effective integration across the cancer care continuum.

Table 4: Potential utility of genomic testing (germline and somatic) relative to the Cancer Care Continuum for adults

Stage	Germline/Somatic		Adults
Prevention and early detection	Germline	Familial	Predictive testing for familial cancers → screening or prophylactic surgery/chemoprevention → early detection & better outcomes.[97-100] PGS can also help with further risk stratification in germline carriers.[29,209,210]
		PGS	PGS potential role in population risk stratification, guiding onset screening,[251] increasing detection & decreasing false positive rate.[252] Early research is exploring the possible utility of adding methylation to PGS and traditional risk factors to improve risk stratification.[208]
	Somatic		N/A
Presentation, Initial Investigation and Referral	Germline	Familial	N/A
		PGS	N/A
	Somatic		ctDNA trialled for individuals presenting with some cancer symptoms but sample processing challenging, low sensitivity and primary site not always clear.[35,253]
Diagnosis, staging, planning	Germline	Familial	10% general cancer patients[79,82] and 13-18% of rare cancer patients[77,80,85] have pathogenic germline variants Greater variant yield using larger panels[78] and amongst rare cancers[77,79,81,86] Cancers with highest frequency of germline variants include gastrointestinal stromal cancer (28%) ovarian (18-26%), PCPG (23%), pancreatic (14-25%), sarcoma (12-21%), breast (10%).[78,79,81,86] 50% of adults found to carry clinically actionable germline variants would not have met eligibility criteria.[77]
		PGS	PGS predict sub-types of certain cancers[254]
	Somatic		Comprehensive genomic testing turnaround time 5.5-7.5 weeks.[149,150] 78-95% of individuals have ≥1 variant identified.[76,83-85,103,114,117-121] Rare cancers harbour variants in 88-93% of samples.[76,121] Informed/refined the diagnosis in 4-10% advanced patients[76,133] and 51% of CUP.[85]

Stage	Germline/Somatic		Adults
Treatments, Clinical Trials, and Outcomes	Germline	Familial	53%-61% of individuals with pathogenic variants were offered germline genotype-directed therapies.[78,81]
		PGX	Pharmacogenomics have the potential to identify individuals at risk of adverse events from chemotherapies.[214-216]
	Somatic		Typically, 31-48%[76,122,128,133] of individuals had ≥1 molecularly matched therapy (range 15%-62%),[123,136] 33-38% of those recommended a matched therapy received it.[76,83-85,102,109,114,117,118,122,123,125,126,128-130,137,140] Partial/complete/overall response rate to matched therapy was 11-52%.[255] PFS [117,125] and median OS [117,125] was higher in advanced cancers receiving matched therapy. Tier I [125] or Tier II therapies [120] had better PFS and OS than those with lower evidence levels. Fewer previous therapies→ better PFS and OS than those who had received multiple prior therapies.[123,147] Serial TMB can be used to detect response to therapy.[154] **MOST trial** 45% (n=1290/2852) advanced cancer cases had matched therapy. 27% (n=342/1290) received matched Tier I -Tier III therapy and had longer OS than those receiving unmatched therapies (16.9 months versus 10.4 months).[146]
Care after Initial Treatment	Germline	Familial	Adjuvant therapies can mitigate the risk of metastases for some germline carriers.[256] Discuss future cancer risks and cascade testing for 10% of those with germline variants.[257,258] Second primary could be prevented or detected earlier.[87]
	Somatic		Large research studies demonstrate that ctDNA can predict recurrences [181,182] Increasing studies exploring the use of methylation as a biomarker, especially in breast cancer.[131]

Stage	Germline/Somatic		Adults
Managing refractory, relapsed or progressive disease	Germline	Familial	PGS can predict risk of a subsequent cancer [211,212,213]
	Somatic		38% of patients with refractory or no available treatments, had an actionable variant identified and half were assigned to a treatment protocol [122] Pancreatic cancer patients with a poor prognosis who received matched therapies have longer median OS and a longer OS compared to those who received unmatched therapies.[136]
Palliative care and end of life	Germline	PGX	Variants in *CYP2D6*, *OPRM1* and *COMT* affect the clinical efficacy and safety of opioids.[218] There is no Medicare rebate for *CYP2D6* in Australia.[219]
	Somatic		N/A

PGS = Polygenic risk scores; CUP = Cancer of unknown primary; PFS = Progression Free Survival; OS = Overall survival; PGX = Pharmacogenomics; TMB = Tumour mutational burden; PCPG = Phaeochromocytoma and paraganglioma

Figure 4: Studies internationally which included germline and/or somatic genomic profiling of multiple cancer types

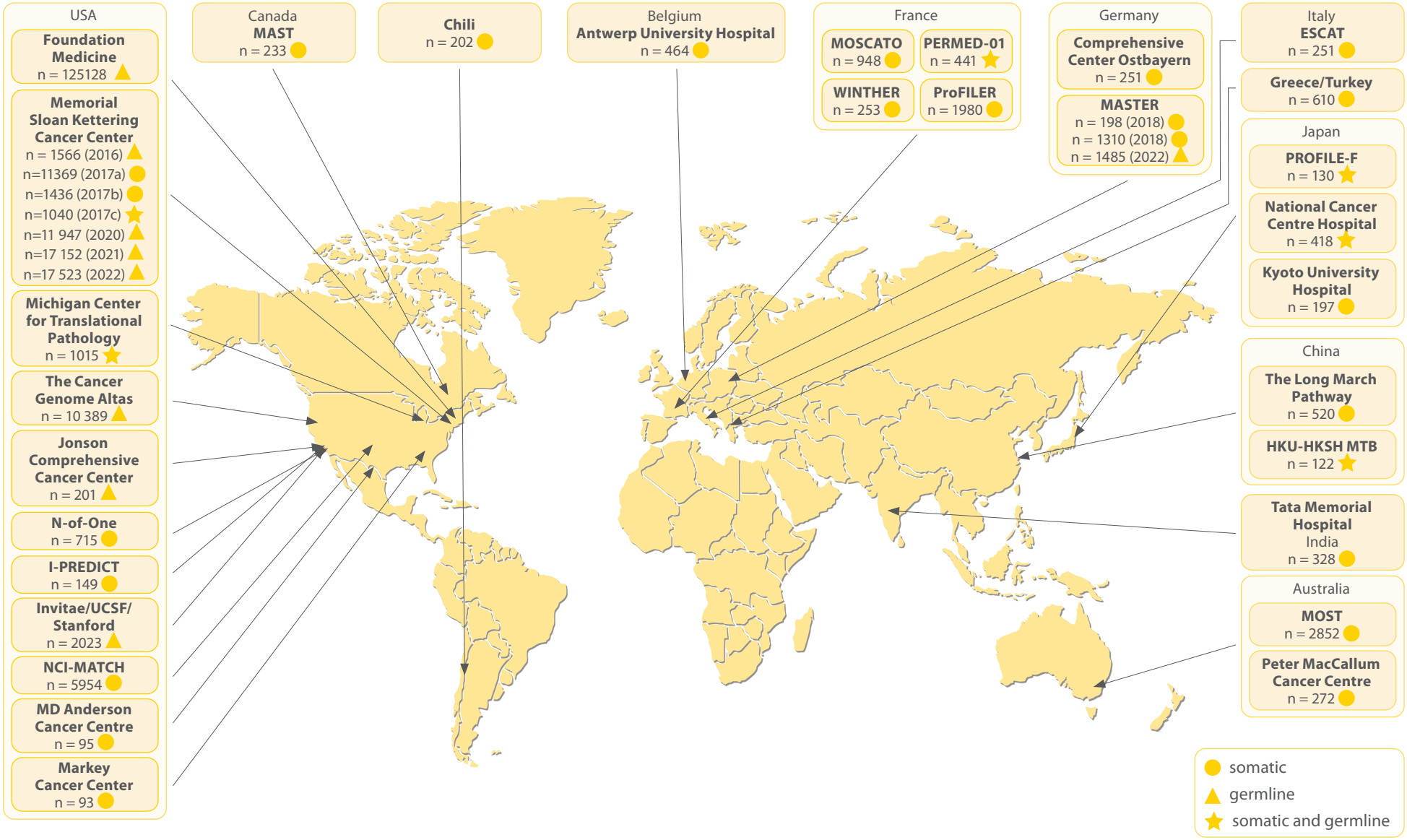
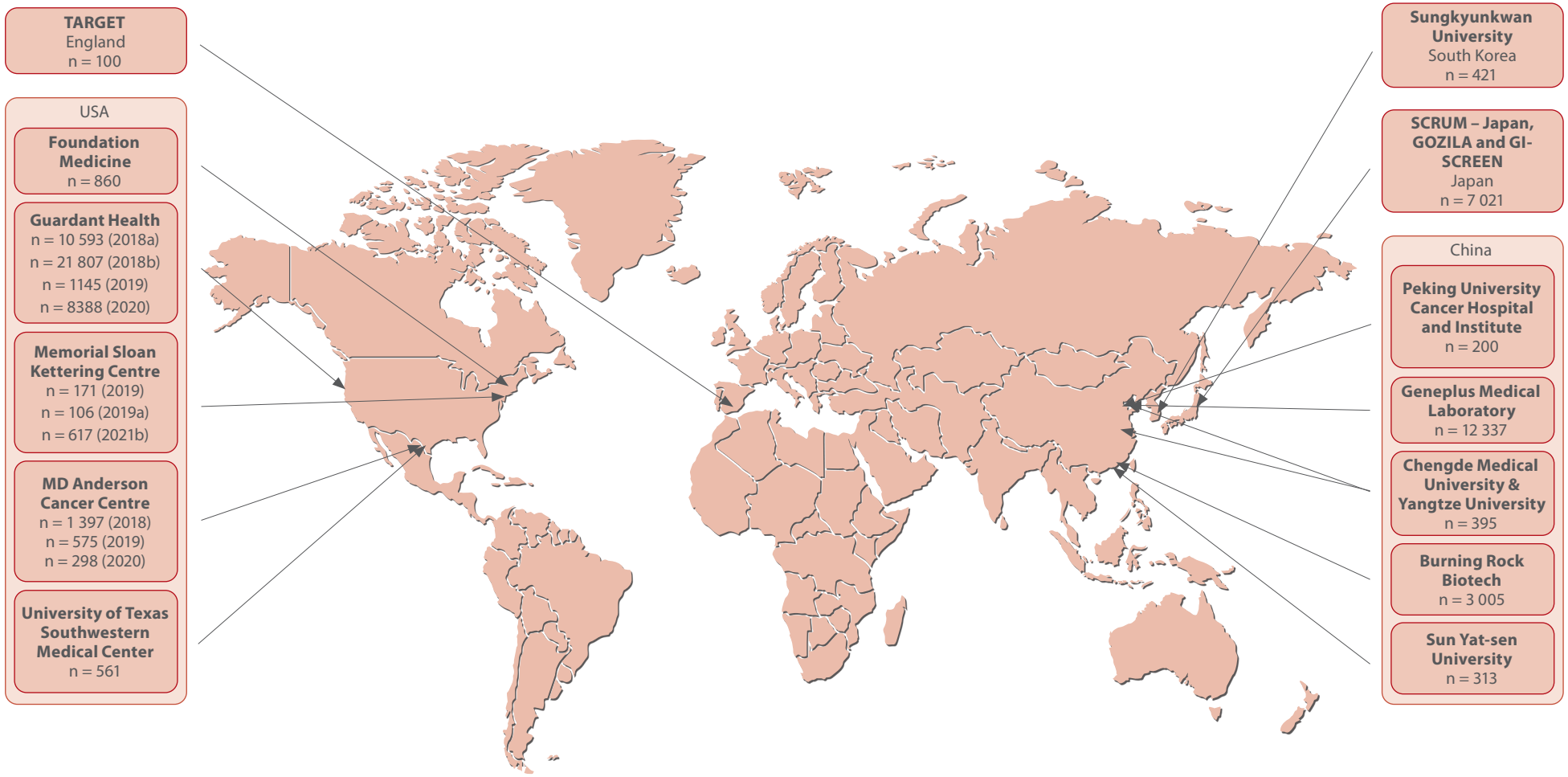
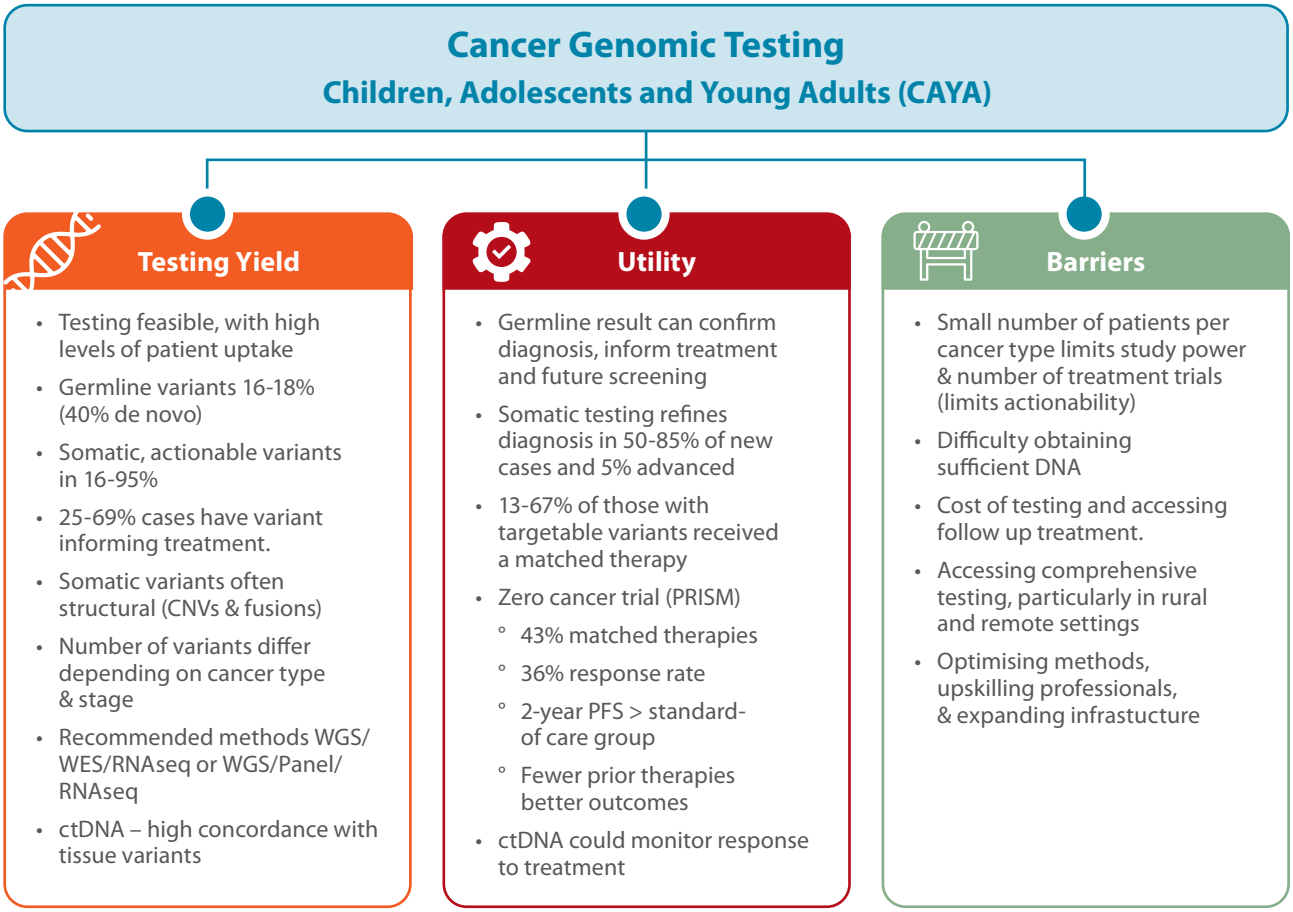


Figure 5: Studies of ctDNA in cohorts with advanced cancer



Cancer Genomic Testing in Children, Adolescents, and Young Adults (CAYA)



Cancer Epidemiology in Australian Children and Young Adults

Approximately 750 children (aged 0-14 years)[259] and 1,060 adolescents and young adults (aged 15-24 years)[260] are diagnosed with cancer in Australia annually. Children, adolescents, and young adults can present with diverse cancer types, with the majority broadly classified as leukemias, brain tumours, and non-central nervous system solid tumours.[261]

Children

Almost half (48%) of children diagnosed with cancer are aged 0-4 years and the population adjusted incidence of childhood cancers in Australia has increased by 35% between 1983 and 2014.[259] In Australia, leukemias are the most common childhood cancer, accounting for 33% of cancer diagnoses, followed by central nervous system tumours (mainly brain tumours), which account for 25%; lymphomas account for a further 10%.[259]

Cancer is the second-leading cause of death for children aged 1-14 years.[262] Five-year survival for Australian children diagnosed with cancer is 84%, and childhood cancer mortality rates have decreased by an average of 3% per year between 1998 and 2014, or a total decrease of 39%. Amongst the 101 annual cancer related deaths in childhood, 39% are attributable to central nervous system (mainly brain tumours), 22% are due to leukemias and 13% are caused by neuroblastomas.[259]

Adolescents and Young Adults

Incidence rates for all cancers combined in people aged 15–24 have been relatively steady since 1994–1998, with 315–335 cases per 1,000,000. Hodgkin lymphomas is the most common cancer in young Australian adults, followed by cutaneous melanoma.[260]

Latest survival figures for 2014-2018 show a 90% survival, which was a significant increase from 79% in 1984-1988. Between 2013-2017, 100 young Australians died of cancer each year, with males (56%) accounting for more cancer related deaths. The leading cause of cancer-related deaths in young Australian adults were bone cancer and central nervous system cancer, followed by soft tissue sarcoma, acute lymphoblastic leukaemia/lymphoma, and acute myeloid leukaemia.[260]

Genomics of Cancers in Childhood, Adolescents and Young Adults (CAYA)

Germline Susceptibility

In Australia, predictive genetic testing and screening recommendations are available for 36 paediatric syndromes associated with cancer predisposition,[263] including retinoblastoma,[264] familial adenomatous polyposis,[265] Von Hippel–Lindau disease,[266] multiple endocrine neoplasia,[267,268] Li–Fraumeni syndrome [269,270] and neurofibromatosis.[271] As per the Human Genetics Society of Australasia's Position Statement, testing in children or young people should always be offered for conditions that are likely to manifest prior to 18 years of age and there are options to treat, monitor or prevent the condition.[272] For conditions like Li-Fraumeni syndrome (caused by TP53 mutations), screening promotes early detection which is positively associated with survival,[273-276] though baseline whole-body MRI is associated with a 15-87% false positive rate.[275,276] In cancer predisposition syndromes associated with onset in adulthood, the recommendation is to postpone testing until the young person achieves capacity, thereby preserving their autonomy.[272] A review of the literature showed that although children and their families are largely supportive of predictive testing for Li-Fraumeni syndrome, some parents were concerned about the potential for genetic discrimination, and there was some hesitation amongst clinicians.[277] A recent qualitative study from the Texas KidsCanSeq (KCS) Study interviewed parents of children found to carry germline variants and found that barriers to accessing appropriate follow up care included travel time, distance and financial costs.[278] CAYA perceive that genetic testing for cancer predisposition is empowering, increases perceived control and motivates adherence to screening, without inducing distress.[279,280]

As genomic sequencing of tumours is becoming more routine, it is likely that many CAYA, and their parents, will become aware of the presence of a predisposing variant through genomic sequencing of the tumour, as opposed to family testing. In earlier studies (2015-2018), germline pathogenic variants were identified in 6-8.5% of CAYA with cancer.[281,282] More recently, (2020-2024), germline variants have been identified in 16-18% of CAYA with cancer.[257,258] Primary tumours have lower frequencies of germline variants than advanced (metastatic, recurrent or refractory) cancers.[150,258,282-286] It has been suggested that overall estimates of germline variant frequencies in some studies could be inflated by over-representation of CAYA with advanced cancers. In cohorts comprised predominantly of newly diagnosed CAYA cancers, two studies reported germline variants in 8-8.5% of cases [281,287] and one reported germline variants in 18% of cases.[258] The 8% figure was published in 2018 and as the number of pathogenic and likely pathogenic variants in ClinVar has increased significantly in the past five years,[91] this 8% figure is likely to be an underestimate. The study reporting an 8.5% germline variant frequency was published in 2023 and comprised 117 individuals analysed using whole genome sequencing in three different laboratories. The slight variations in methodologies and the limited number of genes analysed (n=50)[287] may have reduced sensitivity. Finally, a study published in 2021 used both exome and genome sequencing and reported that among 309 agnostically ascertained CAYA, 18% carried pathogenic/likely pathogenic variants in 156 cancer predisposition genes (noting only 15% of the CAYA had rare tumours).[258] Thus, the true frequency of germline variants in newly diagnosed cancers in CAYA is likely to be closer to 18%.

Frequency of germline variants differs according to cancer types, with solid tumours (22-50%)[150,258,281,282,288] having the highest rate of germline variants. Generally, central nervous system (CNS) solid tumours have lower rates of germline variants (9.5-49%, median 20%) [150,258,282,283,285-287,289] than non-CNS solid tumours (6-70% median 50%).[150,258,282-286,289] Cancer types with particularly high levels of germline variants include adrenocortical carcinoma tumours (69%), retinoblastoma (40%), brain tumours (37%), sarcomas (25-37%) and haematological malignancies (10-17%).[258,282,286 150,283]

Clinical Utility of Testing for Germline Susceptibility

The identification of germline variants can inform the diagnosis of cancer type, provide treatment options, and guide management of the current cancer and screening practices for related cancers in the patient.[258,261,282] Almost a third of parents of children found to carry a germline variant were uncertain about the significance of the result at a later date.[290] do not recall receiving results or inaccurately recall the result, possibly as a result It can also inform cancer screening in at-risk relatives, which can lead to earlier detection and better outcomes.[261] Of note, only ~40% of children and young adults found to carry a pathogenic germline variant had a positive family history.[258,282] One study performed sequencing in parents of 31 individuals with pathogenic germline variants and found that 12 (39%) were de novo.[257]

Presence of germline genetic variants can have therapeutic implications. 2-4% of all CAYA with cancer have germline variants resulting in DNA repair deficiency, indicating immune- or matched therapy.[287,77,257,258] Furthermore, germline mutations in certain DNA repair genes are associated with a large number of variants throughout the genome (High tumour mutational burden, or TMB), which is associated with response to immunotherapy.[150,258] Certain treatments are contraindicated in germline carriers e.g., radiation exposure in TP53.[261]

Somatic Genomic Variation

Feasibility and Uptake

A US study of CAYA with cancer reported that sufficient tumour tissue for WGS was available for 94% of individuals.[257] However, in this study, 95% of samples were fresh-frozen, a sample type associated with a higher DNA quality and quantity than the more commonly available formalin-fixed paraffin-embedded (FFPE) sample.[101] A small study showed comparable results from paired fresh-frozen and FFPE samples.[291] A more recent UK study, using DNA derived from FFPE only, reported that 82% passed quality control standards for a custom panel.[292]

Studies report that uptake of paediatric genomic testing was high (85-95% consent rate),[257,258,293] but families of black children were more likely to decline than families of white children (Hispanic and non-Hispanic).[258,294] Parents of paediatric cases and young adults reported feeling that the benefits of WGS/WES outweighed any potential risks.[295,296]

Types of Somatic Variants Detected in Paediatric and Young Adult Cancer Patients

Of the 142 likely driver genes identified in one CAYA cancer cohort, only 45% overlapped with those seen in adult cancers.[297] CAYA cancers are characterised less by pathogenic variants involving a single or small number of DNA bases than they are by copy number variations (CNVs) and structural rearrangements (gene fusions, chromoplexy and chromothripsis). This is in part due to the fact that blood cancers are the most common cancers in these young Australians and, even in adults, blood cancers are associated with a higher incidence of CNVs and structural rearrangements.[298] With a few exceptions, the number of single base or small somatic pathogenic variations in CAYA cancers is substantially lower than the number seen in adult cancers (0.13 versus 1.8 mutations per Mb),[261 281] though this increases with age.[281]

The presence of structural variants in CAYA cancers varies depending on cancer type (median 1 to 434 structural variants in 539 cancers).[281] CNVs, defined as an abnormal number of copies of a gene or genomic region i.e., large deletions or duplications, are common in CAYA cancers.[281] Gene fusions, which arise from chromosomal

breaks and rearrangements, are identified in 36% of CAYA cancers.[100,258,261,281] Too few or too many copies of chromosomes (aneuploidy) occurs in 30% of CAYA cancers, mostly in haematological malignancies.[258] In 11% of CAYA cancers a single event will result in hundreds or thousands of rearrangements within one and/or between two chromosomes (chromothripsis).[297] Alternatively, multiple rearrangements can occur between three or more chromosomes (chromoplexy). Both rearrangement events can give rise to gene fusions. Chromothripsis, which can also result in copy number variants, is more common in CAYAs carrying TP53 germline mutations.[281] Chromoplexy and chromothripsis can provide prognostic information while gene fusions can also guide treatment and management choices.[261]

Yield of Somatic Testing

Many pathogenic variants in early childhood cancers arise years prior to diagnosis and are either inherited or arise in early embryonic development.[282,288,299] When studying predominantly newly diagnosed CAYA cancers, 50-95% harbour diagnostic variants, 16-57% have variants which inform prognosis and 25-65% of individuals are found to carry therapeutically relevant variants.[258,287,292,300,301] Similarly, in CAYAs with relapsed, metastatic, or intractable cancers, 71-95% have an actionable (diagnostic, prognostic and/or treatment-guiding) variant and 32%-69% have therapeutically actionable variants.[150,257,292,302,303¬¬ 283 289,292,301] The mean TMB was 0.71 per megabase in paediatric CNS tumours and 0.74 per megabase in paediatric non-CNS solid tumours.[289]

Relapsed tumours harbour significantly more mutations than primary tumours.[281] Sequential sampling revealed new therapeutically targetable drivers in over a third of patients in subsequent biopsies, suggesting benefit from re-biopsy for genomic analysis at the time of relapse.[257,292] Furthermore, re-biopsy at relapse revealed that only one third retained the same therapeutic target at later timepoints.[297]

Yield of Somatic Testing is Affected by Testing Methodologies

There are different sequencing approaches used in CAYA cancers. DNA sequencing to identify variants in cancer-associated genes can be done by whole genome sequencing (WGS), whole exome sequencing (WES) and sequencing of a panel of genes, typically 70-500+ genes. Whole genome sequencing (WGS) produces a higher diagnostic yield than whole exome sequencing (WES).[258,297,304] WGS is better placed to detect activating gene fusions, small intragenic deletions, and complex copy-number abnormalities including aneuploidy, chromoplexy and chromothripsis.[257,258] These complex alterations result in diverse RNA transcriptomes. In fact, RNA analysis of malignancies in CAYAs reveals greater diversity than is seen in adult cancers.[300] RNA sequencing (RNA-seq) can improve detection of complex rearrangements in CAYA cancers, particularly blood cancers.[150] A 2018 proof-of-concept study showed that WGS, WES and transcriptome (RNA-Seq) analysis detected 98% of variants in previously tested CAYA cancer samples, while WES and RNA-Seq detected just 78% of variants.[304] A 2021 study used the same three techniques in both tumour and germline samples in 309 CAYA with predominantly newly diagnosed cancers and found that WGS enabled the detection of gene fusions, complex rearrangements and mutational signatures, which revealed the impact of pathogenic variants.[258] More recently, a prospective study utilised large cancer panels combined with WGS and RNA-seq, and argued that this comprehensive, integrated approach could save time as compared to sequential approaches.[257]

WGS may also be more effective at detecting mutational signatures (characteristic patterns of somatic mutations in cancer genomes), which can be indicative of the specific gene or pathway driving the cancer.[258] Seventeen mutational signatures have been described in CAYA cancers.[281] A study of relapsed, metastatic and/or refractory CAYA cancers found that 23% were positive for Signature 3, which is associated with defects in homologous DNA repair. Of note, individuals with germline mutations in these genes were not included in that analysis, so this figure is likely to be an underestimate.[257] This is important as defects in homologous repair can be targeted by PARP inhibitors.[305]

Finally, methylation analysis evaluates whether specific genes are "turned on" in cells. Aberrant methylation can be detected using custom arrays, which increase diagnostic yield in some CAYA cancers, particularly central nervous system cancers.[150]

Clinical Utility of Somatic Testing

Variants informing or refining diagnoses are more commonly detected in primary (17-85%)[258,287,300,306] versus relapsed cancers (2-8%).[150,257,283-286] In a substantial portion of both newly diagnosed and relapsed cancers, somatic profiling detects variants which inform prognosis (22-57%) and help identify matched therapies (22-69%).[150,257,292,302,303¬¬ 306] Fewer studies have assessed the extent to which these specific treatments were utilised and whether the outcome differed for CAYAs receiving traditional versus a personalised therapy plan. The six studies which evaluated utilisation and/or outcome on a cohort >100 CAYAs can be summarised as follows:[150,257,283-285,301]

- Five cohorts were CAYAs with relapsed, metastatic, refractory or 'high-risk' cancers, and one was a prospective cohort with solid tumours.[301]
- Matched therapies were based on both somatic and germline variants.[257,283]
- Of CAYAs found to carry a targetable variant, 13-67% received the matched therapy/therapies,[150,257,283-285,301] typically through a clinical trial (37-56%),[257,283] or compassionate (41%) access.[257] One study showed that the majority of those receiving a matched therapy had a gene fusion.[301]
- Reasons for not using matched therapies: not needing a new therapy at that time, insufficient level of evidence for matched therapy, patient was end-of-life or lack of access.[257,283-285,301,307]
- Clinical benefits included refinement of the diagnosis, which informed treatment selection and mitigated the risk of exposure to ineffective therapies and the associated side-effects.[257] Additionally, the identification of tumours with high TMB indicated possible benefit from immune checkpoint inhibitors.[257]
- Five studies had 12 month follow up data.
    - Study 1: Overall response rate was 17%, which exceeded the 4% overall response rate observed in paediatric phase I/II chemotherapy trials. When analysis was restricted to the subset who received "ready for routine use" therapies, the response rate rose to 38%. No comparisons were performed with individuals not receiving matched therapy.[283]
    - Study 2: Overall survival was 120 days post inclusion in the program, likely indicative of the poor-prognosis. No comparisons with those who did not receive a matched therapy.[285]
    - Study 3: Median progression-free survival (PFS) and overall survival was not higher in the matched therapy group as compared to those who did not receive matched therapies. However, individuals with 'highest priority' variants had a median PFS of 204 days, which was significantly longer than all other patients (median PFS was 117 days).[284]
    - Study 4: 15% (29/200) of those with recommended matched therapies received them. Of those prescribed matched therapies 24% (7/29) had a partial response or stable disease ≥ 4 months later.[301]
    - Study 5: The Australian Zero Childhood Cancer Program's precision medicine study (PRISM) study followed 384 high-risk cases for at least 18 months. 256 (67%) received precision-guided treatment (PGT) recommendations and 110 of those (43%) received recommended therapy. PGT was associated with a 36% objective response rate and improved 2-year progression free survival compared with standard of care (26% vs 12%). Treatments with greatest response included Tier 1 PGT, PGT targeting fusions, and treating individuals with less advanced disease.[308]

There is generally optimism about the potential for genomic profiling to improve treatment choices and outcomes for CAYAs. Authors of one study concluded that comprehensive somatic and germline cancer genomic analysis "conveys a breadth of clinical utility, extending beyond identifying canonical targets, which provides a rationale and urgency for its incorporation into standard clinical practice for all paediatric and AYA patients, at diagnosis and at relapse."[257] Some express concern that comprehensive genomic profiling is currently beyond the scope of most cancer clinical services.[258] Challenges included obtaining sufficient large fresh-frozen tissue for three-platform sequencing (WGS, WES/Panels and RNA-seq), as FFPE samples are less likely to produce a

sufficient quantity and quality DNA to allow for all three analyses and necessitate the choice between higher depth WES or lower coverage WGS. In addition, the infrastructure, and computational resources (including storage/management of data) needed to deliver three types of sequencing is considerable. Furthermore, the turnaround time for these tests is approximately 5-7 weeks, which can delay treatment decisions and commencement of matched therapies.[258]

Emerging Technologies

Circulating Tumour DNA (ctDNA)

Tumour cells shed their DNA into the bloodstream, creating circulating tumour DNA (ctDNA).[35] This ctDNA can serve as a proxy for tumour genomic sequencing. A 2022 review of ctDNA in CAYA cancers found potential utility regarding monitoring treatment response, disease progression and the detection of sub-clonal disease.[309] Particularly promising applications of ctDNA include cancers which are difficult to biopsy and/or the detection of minimal residual disease. Studies show high concordance between variants detected on tissue and ctDNA.[283,292,310] One study showed that 26/37 newly diagnosed paediatric patients with solid tumours had detectable ctDNA, as did 8/10 patients with metastatic solid tumours.[311] Another study did serial blood tests and showed close correlation between ctDNA variants and treatment responses,[310] indicating that ctDNA could be used for disease monitoring.

However, there is currently insufficient evidence to demonstrate that clinical application could inform prognosis and monitor treatment response. Thus, large clinical trials are required prior to determining readiness for clinical use in CAYA.[309]

Polygenic Risk Scores (PGS) – Treatment and Management Paediatric And Young Adult Cancer

Genome wide association studies have identified variants associated with cancer risk in CAYA populations and some differences are observed in populations with diverse ancestry.[312] However, there is limited research on the use of PGS for paediatric cancer care. Emerging research suggests that can predict risk for subsequent cancers and inform survivorship care.[313-315] PGS also has the potential to identify children at greater risk of developing subsequent secondary morbidities related to cancer treatment, such as pulmonary complications.[316]

Internationally, private companies are now offering PGS for embryo selection, including for cancer risk. The use of PGS for embryo selection has been strongly discouraged and is not supported by the genetics community due to the lack of validity and utility, and ethical considerations.[317-319]

Pharmacogenomic Testing

Pharmacogenomics can be used to identify CAYA at risk of adverse events from chemotherapies.[215,216] TPMT metabolizes medications that are often used to treat children with leukemia or lymphoma: azathioprine, mercaptopurine, and thioguanine. The dosage of these drugs is regularly adjusted, along with other chemotherapy to optimize response and minimize side effects. Patients with reduced TPMT and NUDT15 enzyme activity have an increased risk of mild neutropenia while those with negligible enzyme activity are at risk of life-threatening neutropenia following exposure to thiopurines.[320] This association has been well-described in relation to the treatment of blood cancers in paediatric cancer support groups for twenty years.[321] Further, by genotyping *NUDT15* a patient's treatment plan can be personalised.[320] This association has been well-described in relation to the treatment of blood cancers in paediatric cancer support groups for twenty years.[321] Genetic testing for *TPMT* is Medicare rebatable[322] but there is no rebate for *NUDT15*.[323]

Opioids are often used to manage pain in patients in palliative care. Variants in *CYP2D6*, *OPRM1* and *COMT* affect the clinical efficacy and safety of opioids like codeine, tramadol, hydrocodone, oxycodone, and methadone. In 2021, the Clinical Pharmacogenetics Implementation Consortium produced guidelines for *CYP2D6*, *OPRM1* and ¬*TPMT* variants and select opioid therapy.[218] There is currently no Medicare rebate for *CYP2D6* in Australia.[219]

Genomic Testing in Children and Young Adults Relative to The Cancer Continuum

Figure 7 summarises the size and location of paediatric cancer genomic trials internationally.
Table 5 synthesises the relevance of genomics for CAYA relative to the Cancer Care Continuum.

Insights from Australian Paediatric Cancer and Genetics Expert

Utilisation of cancer genomic testing outside of clinical trials in Australia

Multi-omic testing is part of the standard of care practice for many paediatric cancer types. Therefore, genomic testing has influenced the decision-making process (from risk stratification to disease response assessment) for decades. Moreover, multi-omics testing has been implemented up-front to inform treatment strategies in clinical practice for multiple cancer types. However, these genomic tests are very targeted, aiming to investigate very well-established specific biomarkers.

ZERO Childhood Cancer trial performs a comprehensive tumour and germline multi-omics analysis that, in addition to identifying these known biomarkers, has the potential to discover novel and emerging biomarkers that can directly impact on decision-making process.

Utilisation of cancer genomic testing for advanced and primary cancers in Australia

ZERO comprehensive platform was an exploratory testing approach in patients with rare or poor prognosis cancers to expand the possibilities of identifying therapeutical options beyond the known standard of care since 2019. Recently, since late 2023, the ZERO approach has been offered to every CAYA with a cancer diagnosis, regardless of the prognosis, to maximise options to understand the specific cancer subtype, uncover multi-omic risk stratification biomarkers, refine diagnosis and explore alternative therapeutical options.

There are multiple childhood cancer types, such as neuroblastoma or sarcomas, where genomic testing is a front-line diagnostic test embedded in the risk stratification or diagnosis standard of care pipelines. Another example of the current utility of genomic testing is in disease response assessment in Pre-B ALL, which is directly guided by a genomic test (MRD= molecular residual disease).

Pharmacogenomic testing in practice in the Australian CAYA cohort

Pharmacogenomics (PGx) testing can be highly specific or broad tests. Specific PGx markers have been used as a standard of care in Australia and overseas for the treatment of Pre-B ALL since many years ago. However, broader PGx testing, including other markers such as "sensitivity" to certain supportive care treatments, or emerging genomic PGx markers of risk of certain toxicities, has not been implemented in the clinical practice as yet. There are ongoing research initiatives to implement this in the paediatric oncology space within the next few years.

Typical turnaround time from sample collection to genomic results in Australia

Turnaround times are very test specific and may vary from a minimum 2 weeks to up to 4-6 weeks.

Research and Practice Gaps

The following gaps were identified in the literature.

- Although multiple variants with treatment implications are identified in CAYA cancers, fewer are actionable due to a lack of regulatory approvals for paediatric indications.
- There is no published data regarding whether cancer genomic sequencing for CAYA is utilised in Australia beyond the Zero Childhood Cancer Program.

- There are limited studies regarding the extent to which 'actionable' variants are actioned and the reasons as to why they have not been utilised. Notably, such information could be highly dependent on the local context (e.g., regulatory approvals), thus findings from international studies may not be immediately transferrable to Australia.
- There are limited studies on the effectiveness of genomically informed cancer therapies in improving outcomes for CAYA, and only one study comparing outcomes to a control group who did not receive a matched therapy.
- No data could be identified regarding the extent to which pharmacogenomic testing is undertaken for CAYAs prescribed opioids in Australia. As there is no Medicare rebate for any of the genes applicable to the metabolism of opioids, it may be difficult to capture this utilisation.
- There is limited data on the acceptability of cancer genomic testing to individuals of diverse geographic locations and ancestral backgrounds, and there is little research evaluating whether somatic variant types/frequencies differ according to ancestry.

Figure 7: Map Showing Location and Size of Paediatric Cancer Studies

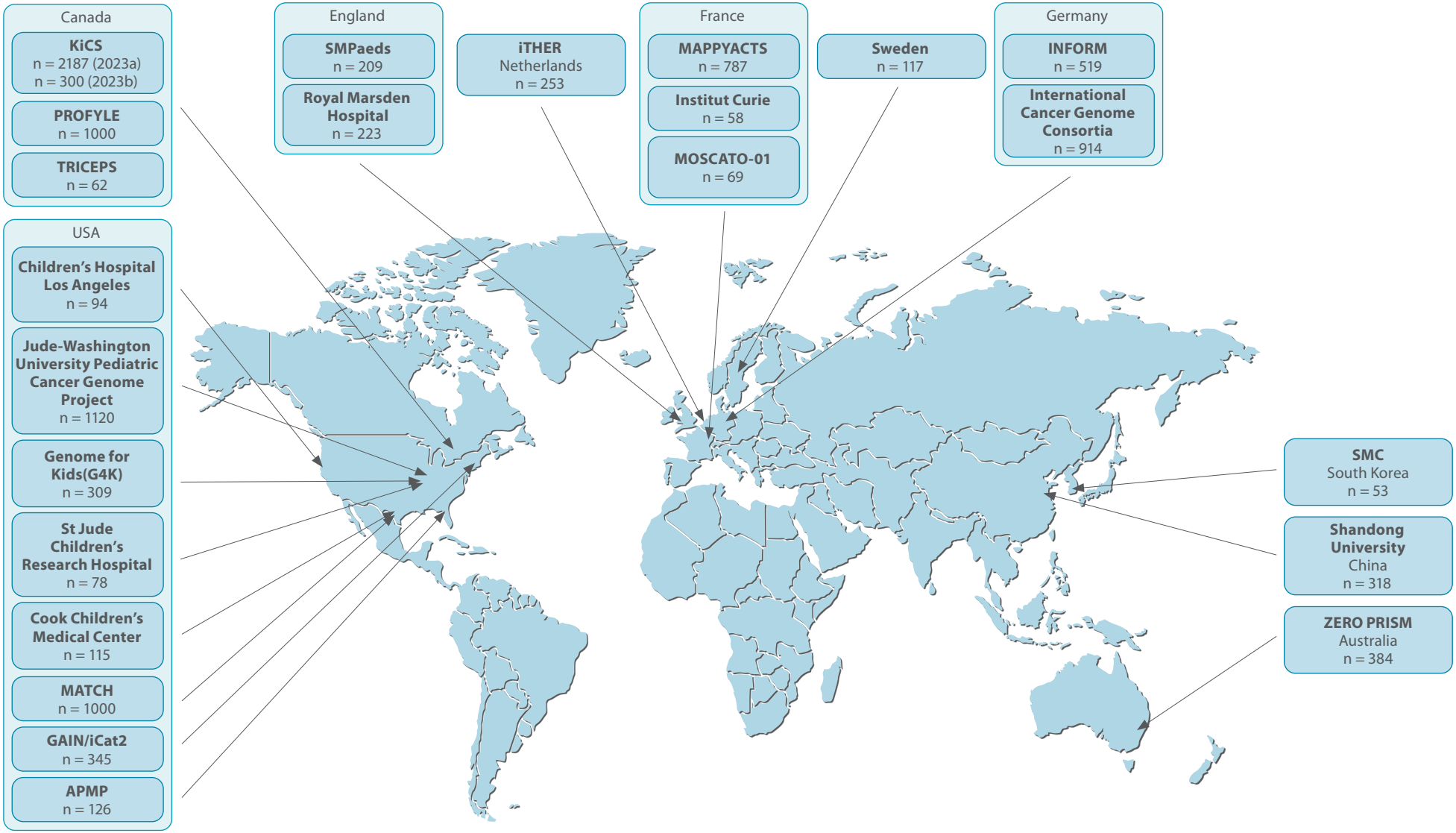


Table 5: Potential Utility of Genomic Testing Relative to The Cancer Care Continuum For Children, Adolescents, And Young Adults With Cancer

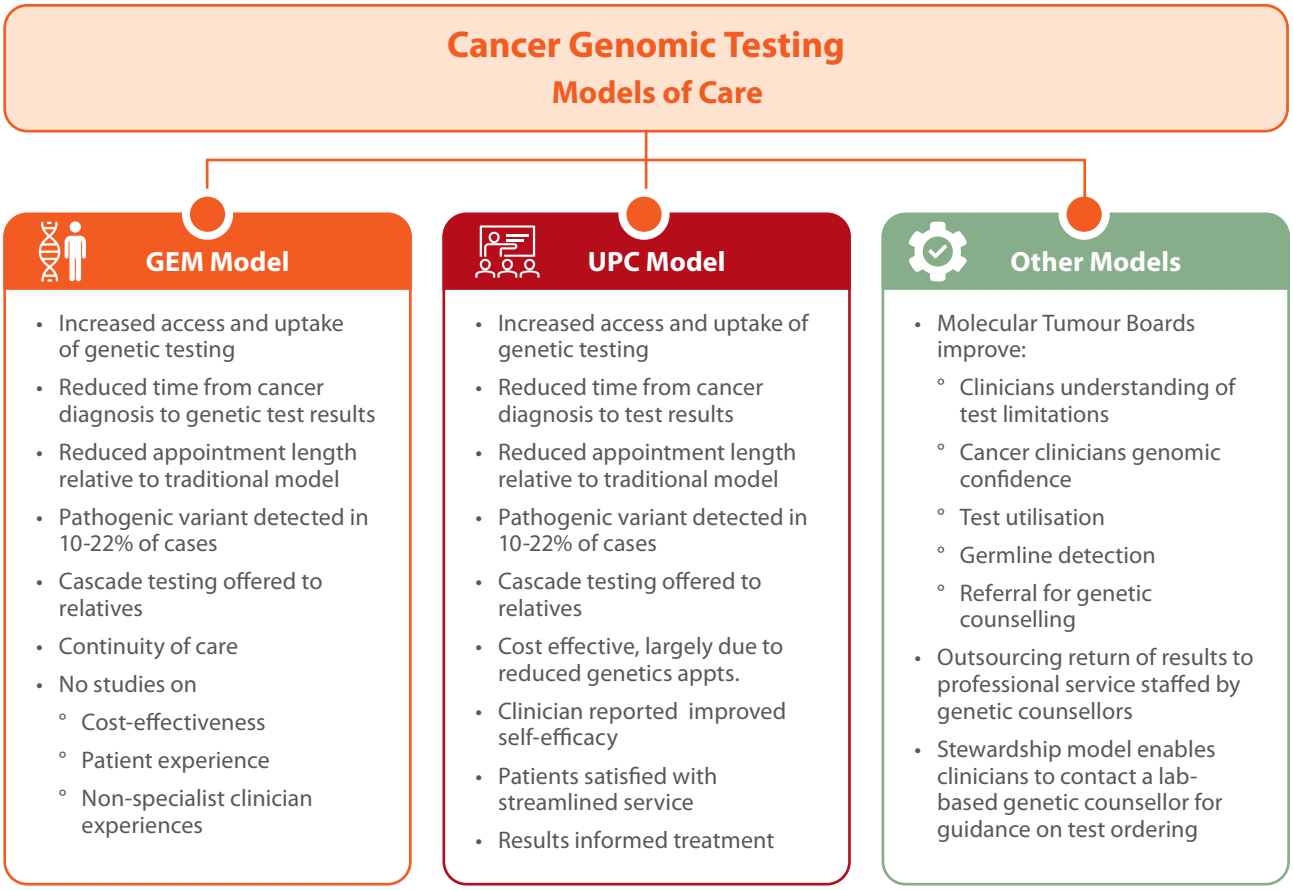
Stage	Germline/Somatic		Children/Young Adults
Prevention and early detection	Germline	Familial	Predictive testing in childhood (most commonly TP53) -> screening or surveillance -> early detection & better outcomes.[273-276] However, whole-body MRI is associated with a false positive rate of 15-87%.[275,276]
		PRS	No data on PRS usage for population screening in childhood
	Somatic		N/A
Presentation, Initial Investigation and Referral	Germline	Familial	Germline cancer predisposition improves empowerment and motivation to adhere to screening.[279,280]
		PRS	N/A
	Somatic		N/A
Diagnosis, staging, planning	Germline	Familial	16-18% of CAYA with cancer have a germline variant[150,257,258 258,285,324] Solid tumours confer the highest prevalence of germline variants (22-50%).[150,258,281,282,288] Germline variant frequencies are highest in adrenocortical carcinoma (69%)[282], retinoblastoma (40%), brain tumours (37%), sarcomas (25-37%) Approximately 40-60% of germline variants are inherited[150,257,258,282]
		PRS	N/A
	Somatic		45-95% of CAYA cancers contain an actionable variant, higher yields in advanced cancers.[150,285,287,302,324,325 289,292,301,326] Copy number variants, structural variants and gene fusions are common in CAYA cancers.[150,287,302 301] RNA-seq (for blood and bone cancers) & methylation arrays (for CNS cancers) can improve yields [150] Variant changed/refined diagnosis for 5% of advanced cancers and 17-53% of new cases [150,258,306] and clarified the prognosis in 22-63%.[257 150,258,302,306] 70% of newly diagnosed patients had detectable ctDNA.[311]

Stage	Germline/Somatic		Children/Young Adults
Treatments, Clinical Trials, and Outcomes	Germline	Familial	2-4% of CAYA have germline variants leading to DNA repair deficiency, indicating immune-or matched therapy.[287 77,257,258] High tumour mutational burden indicative of immunotherapy.[150,258] Certain treatments are contraindicated in germline carriers [261]
		PGX	Pharmacogenomics can identify CAYA at risk of adverse events from chemotherapies.[215,216]
	Somatic		Therapeutically actionable variants 22-69%.[150,257,283,285-287,292,300,302,303,306,324-326 292,301] RNA-seq increased yield.[301,324] ctDNA detects most variants identified in tumour DNA.[283,292,310] 13%-67% individuals with targetable variant received a matched therapy [150,257,283-287,302,307,324 301] Matched therapies may not be utilised due to pursuit of existing therapy and limited access.[257,283-285,307] Limited studies evaluated impact after 12 months using different outcomes, with only one benchmarking against a cohort who received no matched therapies or matched therapies with lower match scores.[283 285,284] Zero PRISM study – 384 high-risk cases – 256 (67%) received matched therapy -> 36% objective response rate and improved 2-year progression free survival compared with standard of care (26% vs 12%). Treatments with greatest response: Tier 1 matched, fusion-targeted, or less advanced disease.[308]
Care after Initial Treatment	Germline	Familial	Discuss future cancer risks and cascade testing for the 10-18%[257,258] of CAYA with germline variants. Second primary could be prevented or detected earlier.[87,273-276]
		PRS	Estimate risk for developing a subsequent thyroid cancer, secondary to treatment.[313,314]
	Somatic		Limited studies on ctDNA for monitoring response to treatment and minimal residual disease. Limited comparison to standard of care.[309]

Stage	Germline/Somatic		Children/Young Adults
Managing refractory, relapsed or progressive disease	Somatic		Relapse tumours have many more somatic variants than primary tumours.[281] 20/53 (36%) patients with relapsed or refractory cancer had actionable alterations.[327] Sequential sampling = targetable drivers are lost in 1/3, new targets identified in another 1/3, => benefit from re-biopsy at relapse.[257]
Palliative care and end of life	Germline	PGX	Pharmacogenomic testing can inform clinical efficacy and safety of opioids.[218] There is no Medicare rebate for *CYP2D6* in Australia.[219]
	Somatic		N/A

CAYA = Children, adolescents, and young adults, CNVs = Copy number variants, ctDNA = Circulating tumour DNA, PCPG = Phaeochromocytoma and paraganglioma, PRS = Polygenic risk scores; PGX = Pharmacogenomics, TMB= Tumour mutational burden

Models of Care for Cancer Genomic Testing



This chapter was divided into two sections where the first involved a scoping review to evaluate mainstreaming models of care in cancer settings. The second section involved expert review regarding equitable access to care in Aboriginal and Torres Strait Islander peoples.

Section One: Mainstreaming Cancer Genomics Testing (Scoping review)

Introduction

Genetic testing has traditionally been offered through tertiary genetics services, where patients received pre-test counselling either in-person or via telehealth and results are discussed in a subsequent appointment by a genetic counsellor or clinical geneticist.[328] Whilst this process is considered the gold standard, the increasing demands on genetics services are outweighing the capacity of the current workforce in Australia[329-331] and globally.[332] The workforce shortage combined with the increased demand for genomic testing has driven the development of alternate models-of-care (as reviewed [332]). One such model is 'mainstreaming', which involves integrating genomic testing into routine care in non-genetics specialties, either through embedding a genetic counsellor or upskilling non-genetics clinicians.[333,334] In the genetic counsellor embedded (GEM) model, a genetic counsellor practices within a specialty clinic, and assists with identifying eligible patients, providing pre-

test counselling, organising genetic testing, delivering results, and arranging testing of unaffected at-risk family members.[332] By comparison, the upskilled clinician (UPC) model empowers non-genetics clinicians' to identify eligible individuals, discuss testing options, ensure informed consent and interpret and communicate results.[332] These integrated service models serve as a 'one-stop-shop', preferred by patients in many clinical settings.[335-337]

This scoping review aimed to evaluate acceptability, feasibility, and effectiveness of mainstreaming in cancer settings for all stakeholders (patients, clinicians, and healthcare systems).

Overview of Studies

Genetic Counsellor Embedded Model

Six studies performed in either Australia, the United Kingdom (UK), or the United States of America (USA) described a GEM model in breast cancer [338] or gynaecology oncology[334,339-342] clinics. Within these studies, genetic counsellor roles included identifying eligible patients, providing pre-test genetic counselling, interpreting, and providing test results and offering psychological support. Pre-test counselling was typically offered during chemotherapy sessions or in separate appointments often on the same day as their specialist appointment.[334,338-342] One study from the USA described an integrated model of care which included a combination of embedded genetic counsellor-mediated and cancer physician-facilitated genetic testing.[339] Measured outcomes included time from cancer diagnosis to genetic test results, appointment length, testing access and uptake, pathogenic variant detection rate.

Upskilled Physician Model

Thirty-two studies across the USA, Canada, Europe and Australia described a mainstreaming model in cancer clinics where cancer physicians were upskilled to provide cancer genomic testing to inform treatment and management for ovarian,[333,338,339,343-360] breast,[343,351,353,357,361-368] prostate,[349,369] endometrial [340,370] and pancreatic cancers.[349,371,372] Most frequently, testing was ordered during a routine oncology appointment. In most settings, negative results were delivered by an upskilled cancer physician, and patients with a high-risk pathogenic variant (PV) or variant of uncertain significance (VUS) were referred to a genetics service to receive or review their results. In one clinic, a cancer specialist had sufficient training in genetics to feel confident discussing all results and their implications.[364] In all settings, patients were given the option of referral to a genetics service during their testing journey.[333,334,338,341,342,344-360,363-367,369,371,372] Like the GEM model, the UPC studies evaluated time from cancer diagnosis to genetic test results, appointment length, testing access and uptake, pathogenic variant detection rate. Furthermore, they also evaluated optimal timing of testing, impact on cascade testing, cost effectiveness, and clinician and patient attitudes and experiences.

Genetic Counsellor Embedded Model and Upskilled Clinical Model Outcomes

Time From Diagnosis to Test Result

For many newly diagnosed patients in mainstreaming models the consent and sample provision occurred immediately or within one week of their specialist appointment.[333,338,342,347,355,359,364,366] Seven studies evaluated the time lapse from diagnosis or test consent to receipt-of-result from baseline to post-mainstreaming and noted a decrease of 1.5-6-fold.[342,344,364,366,368] Recent studies report that results were returned anywhere from two weeks to two months after sample collection.[350,355,356,358,359,362,368,369]

Appointment Length

Seven studies on the UPC model reported that the time required to incorporate consent for genetic testing into standard care ranged from 8-20 minutes, which clinicians reported to be a feasible addition to routine practice.[346,347,354,355,363,369,370] An abbreviated pre-test information session was identified in three programs as a sustainable, feasible solution in busy oncology clinics.[344,367,371] Only two studies reported appointment length

for GEM models, both in the ovarian cancer setting, and highlighted a 50-70% reduction in appointment length relative to traditional genetic counselling approaches in Australian and USA settings.[334,342] Reported appointment length for the GEM model (45 - 52 minutes) [334,342] was longer than in the UPC model (8-20 mins). [346,347,354,355,363,369,370]

Testing Access and Uptake

Six studies relating to the GEM model all reported increased rates of referral for genetic counselling and testing, with four reporting referral rates of 84-97%.[334,339-341] The other two studies reported >2-fold increase in referral rate with the GEM model.[338,342] Four studies evaluated rates of genetic testing in the UPC model relative to traditional models and all reported increases in testing rates of 1.2 - 6.7-fold.[358,364,371,372] Rates of testing uptake were >90% in UPC programs.[343,346,354,361,364-366]

Pathogenic Variant (PV) Detection Rate

Detection rates of PV in most studies adopting mainstreaming (GEM and UPC models) for ovarian, breast, and pancreatic cancer ranged from 10-22%, depending on the patient cohort testing type (single gene versus panel).[333,339,340,343,347,349,355,356,358,359,362,364,366,368,371] Three studies reported lower detection rates (4-9%), attributed to inconsistencies in application of eligibility criteria [361] and a lower incidence of germline variants in endometrial and prostate cancers.[356,369,370] Conversely, other cancer types were associated with a high yield e.g., 33% of pancreatic cancer cases had a PV, although the likelihood of the variant being causal was less certain.[372] Reported VUS detection rates with the UPC model varied from 0-35% with all VUS cases being referred to genetics specialists.[349,350,352,353,355,358,359,362,364]

Additional Upskilled Clinical Model Outcomes

Timing of Genetic Testing Offering

Three studies reported that the timepoint at which testing was offered was acceptable.[344,354,360] UK nurses were concerned about potential information overload when offering ovarian cancer genomic testing at the initial appointment, but felt that it should be offered in a timely manner thereafter, and within the oncology clinic.[354] A Dutch study found that while the majority of ovarian cancer patients accepted genetic testing when offered, 50% expressed a preference for testing to occur after treatment was completed. Nonetheless, these patients were satisfied with the process overall.[344] Conversely, an English study found that ovarian cancer patients who were offered testing at initial oncology appointments following surgery were satisfied with the timing of testing.[360] The same study offered testing to breast cancer patients during neoadjuvant chemotherapy and there was high uptake and reported positivity regarding timing. Furthermore, patients were less satisfied when testing was offered following conservative breast surgery as additional surgery may be needed if a PV was identified.[360]

Cascade Testing

Most services using the UPC model routinely referred all PV carriers to clinical genetics services.[333,339,343-345,348,350,356,358,359,362,364,366,370,371] Eight UPC studies reported discussing or facilitating cascade testing within the mainstreaming model [333,343,348,356,358,359,369,370] with two identifying an average of 3.5-4 patient relatives accepting cascade testing.[333,359] Only one study compared uptake of cascade testing between models and reported that 31.6% of eligible first-degree relatives had undergone predictive testing after UPC mainstreaming testing compared with 47.3% of relatives in traditional settings.[348]

Cost Effectiveness

Five studies in Australia, the UK and the Netherlands assessed the cost effectiveness of the UPC model and found greatest benefit was due to the reduced number of clinical appointments.[333,345,362,366,369] Specifically, appointment numbers were reduced by 86-95% in breast [366], ovarian [333,362] and prostate [369] cancer settings. One

UK study extrapolated the findings from their ovarian cancer study and projected an estimated annual savings of ~£2.6M (AUD $4.97M) nationally if applied to all ovarian cancer patients.[333] Additionally, a Dutch study found that genetics-related healthcare costs decreased by 31% per patient after implementation of the UPC model of genetic testing in ovarian cancer patients.[345]

Clinician Perceptions

Attitudes

Eight studies of the UPC model from Europe, North America and Australia reported positive attitudes from clinicians involved in mainstreaming.[333,346,347,354,355,362,363,369] Three of these identified close links with genetics departments as facilitators of positive experiences.[346,362,363] Two studies hypothesized that co-designing the MGT program in collaboration with cancer physicians, further improved positive attitudes.[346,363] Oncologists in Europe and the USA reported that the process of MGT worked well and was an efficient use of their time[347,355] and specialist nurses and gynaecologists in a UK study felt confident and well supported in offering MGT.[354] An Australian evaluation of an UPC model in prostate cancer found similar results with 88% of clinicians satisfied and confident with MGT.[373]

Knowledge and Self-Efficacy

Four UPC studies in Europe reported high perceived confidence and knowledge with appropriate training and resources.[346,363,366,369] High self-efficacy was also identified in two Dutch UPC studies following training.[346,363] One study assessed clinicians' perceived knowledge and self-efficacy at baseline and six months post-training, and levels were high for both measures, though clinician knowledge increased significantly after 6 months.[346] Highlighted areas associated with lower levels of confidence included the interpretation of VUSs[369] and a lack of close working relationships with clinical genetics teams.[367] Only one GEM study attempted to evaluate clinician self-efficacy in gaining consent and delivering results but the sample size (n=11) was insufficient for statistical analysis.[20]

Training Needs

Most UPC models included the provision of training to clinicians prior to commencement of mainstreaming protocols. Only one involved the provision of materials only.[365] Training varied widely but were mostly concise and included a combinations of face-to-face sessions [359,369,370] and/or online training modules/videos. Supporting resources included printed materials such as information sheets, flipcharts, partially prefilled order forms etc.[339,343,345,347,352-355,359,362,364,369-371,374] One study appointed local 'champions' as the first point of call for genetic testing queries as longer-term sustainability strategy.[353] Three studies, which used very short (20-30 minutes) video training modules with accompanying resource packs were reported as effective programs with positive outcomes including feasibility for clinicians[33] [343,346,363] and continuity-of-care during the COVID-19 lockdown in France.[30]

Barriers

Barriers to UPC models, as identified by clinicians, included time pressure concerns,[354,369] and insufficient knowledge [356,369] and challenges with consistent medical record documentation.[339] Three studies anticipated these barriers and mitigated those risks by embedding genetic counsellors [334,339] or nurse consultants [368] to facilitate testing. Straightforward eligibility criteria and a single-step testing process e.g., ovarian cancer, were associated with high testing rates, as compared to the complex endometrial cancer testing process, which required pathological testing prior to the offer of genetic testing.[340] To address the multistep barrier for endometrial cancer, one study provided genetic testing to all affected women, though this was associated with lower test positive rate (4.3%).[370]

Facilitators

Among the reviewed studies, the inclusion of an embedded genetic counsellor or trained nurse was frequently recognised as a key facilitator of MGT.[342,363,369,375] Five UPC model studies reported additional facilitators including having a clear protocol for testing and providing supporting materials e.g., fact sheets or 'Frequently Asked Question' sheets.[333,347,355,366,369] The introduction of genetic test-based treatments increased clinician motivation and facilitated MGT.[341]

Patient Experience

Acceptability and Satisfaction

Thirteen UPC studies showed high levels of acceptability and/or patient satisfaction.[333,344,347,349,351-353,355,360,362,366,367,369] Two studies reported that more than 95% patients were satisfied with the time provided to consider genetic testing [333,344] and five studies reported that continuity-of-care positively affected patients' testing experiences.[333,362,366,369 367]

Decisional Regret and Satisfaction

Decisional regret and satisfaction was measured in five studies, all of which reported high overall satisfaction and an absence of clinically significant regret.[344,352,362,369,376] One of these which compared the UPC model to the traditional model found that decisional regret was below thresholds for clinical relevance in both groups, but the UPC group had higher levels ($p \leq 0.05$) than the traditional model.[344] Another comparative study found that decisional conflict was similar between the UPC model the traditional model.[357] Patients in an Irish UPC study reported that the decision to test was straightforward, as the benefits were seen to outweigh the risks. A recurring theme in free-text survey responses was that the time allocated for decision-making was sufficient, or exceeded what was required, though the time allocated was not reported.[352]

General and Test-Related Distress

Five UPC studies used validated scales to investigate general distress including anxiety and depression.[344,349,351,357,370] Four compared patient distress in UPC versus traditional testing models and reported low distress overall [344,351,355,357] and three reported similar outcomes in both groups.[344,355,357] The remaining study reported low levels of distress (below clinical thresholds of significance) in both groups however patients tested via the traditional model had lower general distress compared with the UPC model and higher perceived risk of hereditary cancer.[351] The remaining study in ovarian, pancreatic, and prostate cancer patients found low levels of test-related distress with testing satisfaction increasing over time. Anxiety levels on the Hospital Anxiety and Depression scale (HADS)[377] were low immediately following testing and further decreased at later timepoints regardless of result. Depression levels increased for PV-carriers over time ($p<0.05$), however levels remained within the normal range. The test specific distress scale (MICRA)[378] showed that over time (3-weeks to 3-months post-result) distress increased for PV-carriers but remained stable for non-PV carriers. However, distress levels in all groups were beneath the level of clinical concern. The MICRA subscales in this cohort showed that females had higher uncertainty scores than males for all test results with the exception of a VUS, when males had higher uncertainty scores than females.[349] Conversely an Australian UPC study, using a modified MICRA scale, found no differences in test-specific distress scores, when comparing test result type.[369]

Knowledge

Six studies evaluated patient knowledge levels following testing and showed low to moderate levels of knowledge.[344,349,351,352,367,369] Despite this, patients reported they had sufficient information to make a testing decision.[344,367] Three studies compared knowledge between UPC and traditional testing cohorts with two reporting similar levels [344,357] and one finding higher knowledge levels in patients offered testing by genetic health professionals.[351]

Management Benefits

Treatment Timing and Choice

Cancer treatment decisions were guided by genetic test results in 11 studies, which outlined changes to treatment plans following receipt of test results.[333,339,343,356,358,359,361,362,371,372,379] Specifically, in breast cancer studies, significantly more patients with a BRCA PV opted for a mastectomy as compared to a lumpectomy.[338] Furthermore, PV carriers were more likely to pursue a bilateral mastectomy, either at the time of initial surgery if results were available at that time, or as additional surgery if a PV was identified at a later timepoint.[361,362] Other treatment relevant implications for BRCA PV carriers included bilateral salpingo-oophorectomy in breast cancer patients,[343] the offer of matched therapy (PARP inhibitor) in breast,[362] pancreatic [372] and ovarian cancer patients,[333,356,358,359,371] or the removal of radiotherapy from the treatment plan in a *TP53* PV carrier.[362] Negative test results were also beneficial as they reassured patients, especially those pursuing more conservative treatments.[361]

Discussion

This review demonstrates that MGT was feasible to implement in health systems across Europe, North America and Australia, and had positive impacts on patient service and care. While the UPC model has been more broadly implemented than the GEM model, both pathways have been proven to be effective in increasing patient access to genetic testing and reducing turnaround times from cancer diagnosis to genetic test result. Patient, clinician, and health system reported outcomes of these alternate models-of-care were predominantly positive.

The six studies which evaluated the GEM model were all in the breast or ovarian cancer setting, and focused on feasibility and improvements in access, uptake and wait times for patients.[334,338-342] Models varied slightly with one program combining an embedded GC within a UPC model.[339] All programs achieved acceptable PV detection rates.[334,338-340,342] In all studies referral rates for genetic testing increased with the addition of a genetic counsellor to the oncology team. Unfortunately, the study which combined the GEM and UPC models did not compare whether genetic test utilisation differed between the genetic counsellor and upskilled clinician groups.[339] All studies reported a reduction in wait time for genetic test results following cancer diagnosis, with three studies reporting 1.5-4-fold reductions.[338,341,342] Cost-effectiveness, patient and clinician experiences were not evaluated in any of the GEM papers. Presumably, patient experience was not assessed given the extensive BRCA testing literature showing that genetic testing, when provided by a genetic counsellor, is not associated with significant distress, anxiety, cancer-related worry or decisional conflict.[380] The GEM model has been applied in other settings and evaluation of a paediatric immunology clinic model showed it was acceptable to both parents and clinicians. Consistent with cancer studies, there was improved access to testing and associated treatment benefits.[381] While the GEM model is feasible and improves access, uptake and time to results, more research is required to investigate health economics as well as patient and clinician experiences with the GEM model in the cancer setting.

The UPC model has been more extensively implemented and evaluated than the GEM model with 31 UPC-only studies across five cancer types identified in this review. Reported outcomes were positive, including cost-effectiveness, improved access, uptake of testing, reduced patient wait times and positive clinician experiences. Cost effectiveness is a significant benefit of the UPC model primarily due to the reduction in clinical genetic appointments per patient.[333,345,362,366,369] Previously, there were some reservations about genetic testing being offered by non-genetics clinicians,[382] but our review identified high levels of patient acceptability and/or satisfaction across cancer types and low levels of decisional regret and distress associated with the UPC model. While patient knowledge was lower with the UPC model in one study which compared it with the traditional pathway, patient satisfaction was similar in both cohorts [351] suggesting that informational needs were sufficiently met for diagnostic cancer genomic testing decision making. Prior to the introduction of MGT models, clinicians voiced concerns about potential barriers,[383,384] including the time commitment for consenting and knowledge

gaps, but neither of these were major barriers post-implementation.[346,347,354,355,363,369,370] While some studies compared MGT with traditional models, we did not identify any studies which directly compared the GEM and UPC models.

There are additional interventions which complement and potentially enhance the implementation of MGT; molecular tumour boards, outsourcing the return of results, and genetic stewardship within clinical laboratories. Molecular tumour boards (MTBs) review patient results in a multidisciplinary environment that typically includes cancer specialists, genetics clinicians, pathologists, scientists, pharmacists and bioinformaticians. MTBs are highly valued by cancer clinicians [109] and have been shown to improve oncologists' understanding of the strengths and limitations of genomic testing,[110] their confidence and efficiency in utilising cancer genomic testing.[111,112] Clinical benefits include improved recognition of significant germline mutations,[385] increased referral for genetic counseling,[385,386] and improvements in clinical management of patients,[109] with positive response rates.[387,388] They have been widely used in cancer clinical trials [389] and have been shown to promote interdisciplinary discussions.[113] The outsourcing of test result provision to a professional service staffed by genetic counsellors is also emerging as a desirable pathway for appropriate and timely provision of clinically actionable research results with successful initiatives in place in the USA [390,391] and more recently in Australia.[392] Additional support is also offered by genetic stewardship services which assist non-genetics clinicians with ordering genomic tests. These typically consist of genetic counsellors and/or genetic pathologists within a pathology service supporting clinicians to facilitate appropriate test ordering and interpretation, and in some settings providing pre- and post-test genetic counselling.[393,394]

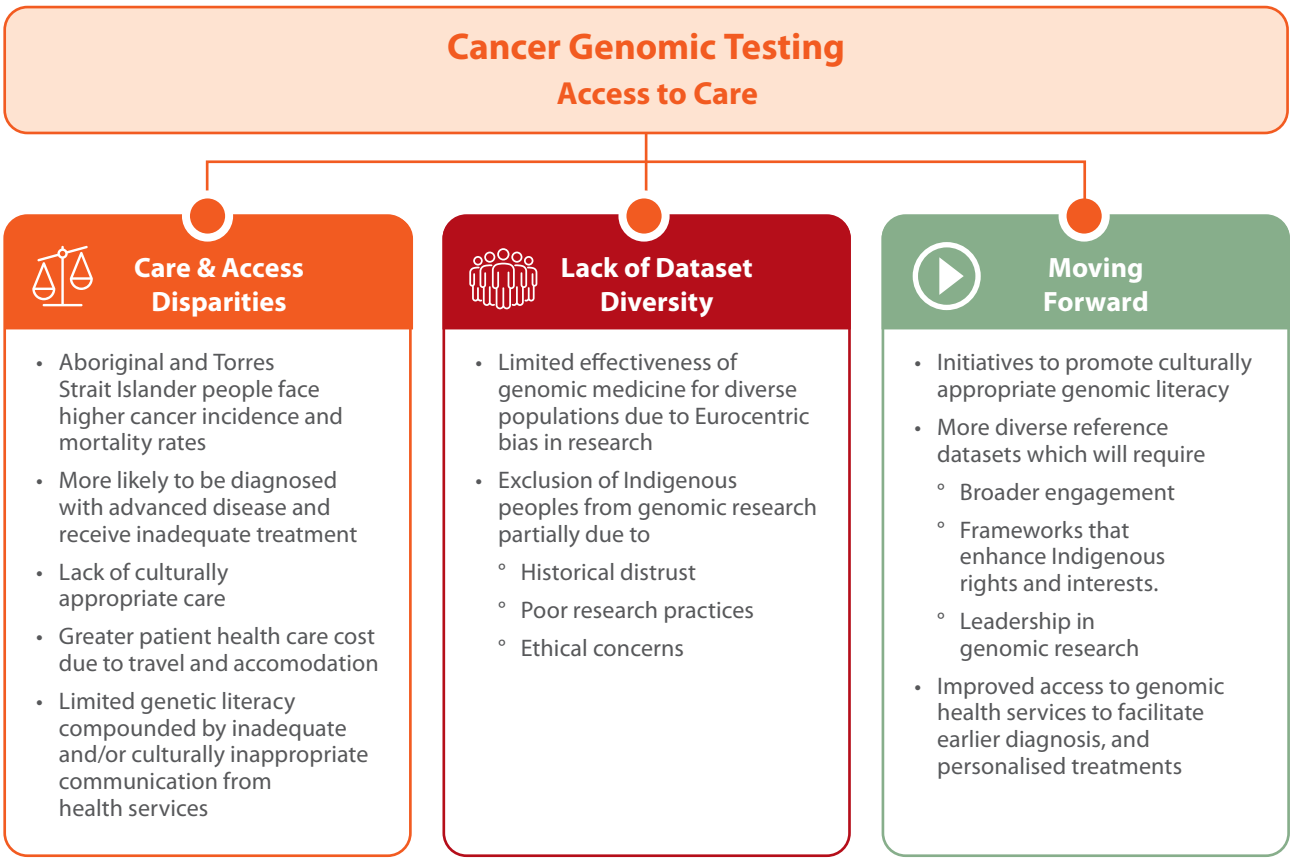
As NGS becomes more affordable and more widely adopted across cancer types, testing criteria will continue to transition from a family-based to a patient-based approach.[90] Thus, a more in-depth understanding of the patient experience of MGT is required. Mainstreaming for cancer affected patients has been found to be acceptable but there is limited understanding of the impact of receiving negative results in patients who may have had high hopes for additional treatment options based on the identification of a genetic target.[395] Furthermore, the experience of VUS carriers, including the impact of uncertainty and a potential for maintenance of hope for future treatments, is understudied.[396] Over time, there is potential for MGT to be adopted in many settings including palliative care in which significant differences in patient motivations and experiences are likely, as a focus on treatment options may not be relevant [397] and there is limited literature or policy recommendations in this area.[398]

In conclusion, our review supports the implementation of MGT in the cancer setting. MGT has been most widely studied in ovarian and breast cancer patients due to the utility of testing and high PV detection rates but is being increasingly applied across other cancer types, especially given the inclusion of cancer genomic testing in routine care. Despite gaps in the research to date, both the GEM and UPC models have been shown to be feasible, cost-effective, and to provide significant benefits to patients, including reduced waiting times, improved continuity of care and high levels of decisional satisfaction. Similarly, clinicians report positive experiences with, and attitudes towards UPC, though this was not assessed in the GEM model. As these models are more widely adopted, further research is needed to gain a more nuanced understanding of patient and clinician experiences, as well as the economic impact on the health system.

Research and Practice Gaps

- There are no studies comparing the GEM and UPC models, only a couple of studies comparing each to traditional models of care.
- There are no studies evaluating the GEM model in terms of:
    - the health economic benefits
    - Attitudes and impact on clinician colleagues
    - Patient experiences.
- More studies are needed to evaluate the impact of negative results, especially when that means the loss of a possible therapy.
- All studies have evaluated germline testing programs, and none have evaluated these models of care for somatic genomic profiling.
- More research is needed to evaluate the laboratory genetic counsellor navigators and the impacts of programs which outsource genetic result disclosure.

Section Two: Can Genomics Improve Equitable Experiences and Outcomes for People Affected by Cancer?



Genomics and Cancer Care for Aboriginal and Torres Strait Islander Peoples

Aboriginal and Torres Strait Islander people experience a high burden of cancer: compared to non-Indigenous Australians, Aboriginal and Torres Strait Islander people have higher age-standardised incidence and mortality rates for all cancers combined.[399] Aboriginal and Torres Strait Islander people have a higher incidence of cancers with a poorer prognosis, are more likely to be diagnosed with advanced disease, are less likely to receive adequate treatment, and are more likely to die from their cancer than non-Indigenous Australians.[400-402] There is an opportunity for advances in genomic medicine to contribute to reducing these disparities through the wide array of genomic applications being developed across cancer care: from earlier diagnosis using circulating tumour DNA, to screening for inherited risk factors, to personalised therapeutics.[403,404] However, there are two significant barriers currently inhibiting the extent to which Aboriginal and Torres Strait Islander people can benefit from genomic medicine in cancer care: inadequate diversity in reference datasets; and issues in accessing appropriate health care.[405-407]

Diversity in Reference Datasets

Genomic technologies in medicine rely upon reference data for effectiveness. As Bilkey et al observed, 'For equitable understanding of genomic variants, reference databases must be capable of reflecting the ethnic diversity of the relevant population/s' (Bilkey et al., 2019, p 8).[404] However, genomic research to date has disproportionately focused on populations of European ancestry, undermining the ability of clinical genomics to benefit all patients equitably.[408-410] The proportion of participants of non-European descent in genome-wide association studies increased from 4% in 2009 to 20% in 2016.[410,411] Most of this increase, however, was the result of more studies including Asian populations, and the representation of indigenous populations (including, but not limited to, Aboriginal and Torres Strait Islander peoples) actually decreased slightly over this period. This is particularly an issue for identifying gene-disease associations that are rare in European populations, and for translating research results to clinical care for diverse populations.[408]

There are multiple reasons underpinning this bias within genomic datasets, including European cohorts being in many cases easier and more affordable to access. In Australia, the ongoing effects of colonisation combined with historically poor research practices to create widespread distrust of genomics and genomic researchers, and contributed to a reduction in Aboriginal and Torres Strait Islander participation in research.[412,413] In this context, researchers were wary of initiating studies and human research ethics committees were reluctant to approve genomic research with Aboriginal and Torres Strait Islander communities, as the risks of genetic discrimination, racial stereotyping and cultural undermining were thought to outweigh the potential benefits. Thus, Aboriginal and Torres Strait Islander people were excluded from genomic research in an effort to protect them, leading to exclusion from the downstream clinical benefits.[414]

The underrepresentation of Indigenous peoples in genomics generally is accentuated when looking specifically at Aboriginal and Torres Strait Islander representation in cancer genomic research. An investigation of a vulvar cancer cluster among young Aboriginal women living in East Arnhem Land included a genomic component, although findings to date have been inconclusive.[415] For other cancers, there is an awareness that familial and genetic risk factors are likely to be important, but remain understudied in Aboriginal and Torres Strait Islander populations.[416] A pharmacogenomic study with Tiwi Islander participants identified variants important for informing treatment recommendations, including for cancer therapeutics such as thiopurines and tamoxifen.[417] Given the diversity of Aboriginal and Torres Strait Islander peoples, these findings highlight the importance of broader engagement to produce data relevant for all Indigenous Australians. Equitable inclusion in genomic research will require research practices, standards and governance frameworks that embody and enhance Indigenous rights, interests and leadership.[405,418,419]

Access to Care

In their systematic review, Dasgupta and colleagues [420] found that the survival disparity experienced by Aboriginal and Torres Strait Islander cancer patients was only partially explained by factors such as geographical location, staging at diagnosis, socioeconomic status, comorbidities and variations in treatment. They found that factors affecting access to care are likely to explain some of the remaining survival disparity, including factors such as a lack of culturally appropriate care, systemic discrimination, and issues with health literacy.[420] Further, Callander and colleagues [421] found that, while Indigenous patients spent less on healthcare co-payments than non-Indigenous patients, Indigenous patients experienced greater costs overall, particularly arising from travel and accommodation expenses for those living in rural and remote areas, as well as challenges to kinship and cultural responsibilities arising from extended treatment away from home. There is growing evidence that these types of issues with access to general cancer care are, and will increasingly become, more acute for Aboriginal and Torres Strait Islander people interacting with genomic medicine as part of their cancer care journey.

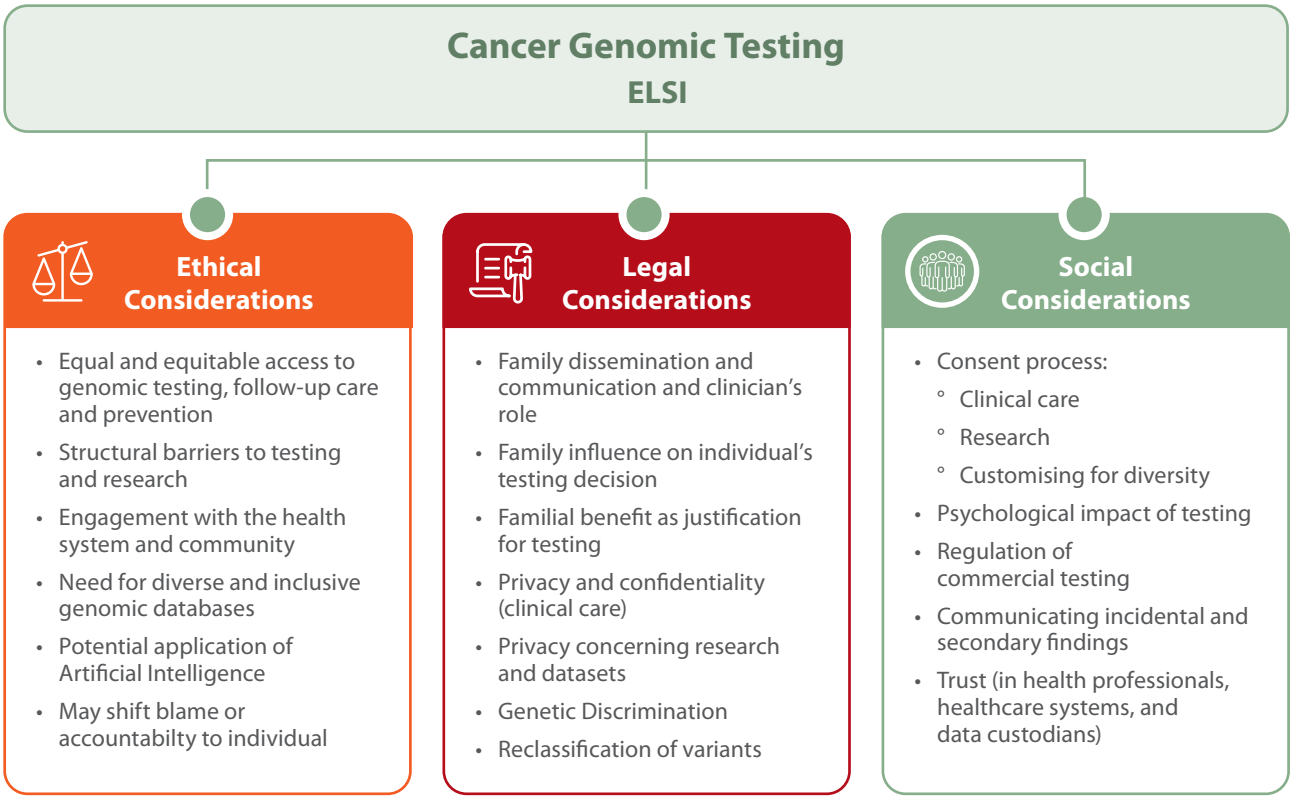
An analysis of administrative data from clinical genetic health services across the Northern Territory, Queensland and Western Australia found that Aboriginal and Torres Strait Islander people were scheduled fewer appointments than non-Indigenous Australians (58% lower for Indigenous people attending for cancer reasons)

and had lower attendance rates.[422] Underscheduling was attributed to referral bias and a lack of awareness of genetic services in primary care when compared to specialist services. A cross-sectional survey of Indigenous cancer patients in Queensland found a majority were interested in assessing their familial cancer risk with a genetic counselling service, indicating that disinterest or disengagement is not behind low attendance rates.[423]

Rather, barriers to attendance identified in a qualitative study with Aboriginal and Torres Strait Islander people who had accessed clinical genetics services in these jurisdictions included: difficulties navigating health services; limited genetic literacy; logistical factors; inadequate communication before, during and following consultations; and a lack of financial support services, culturally appropriate services and/or Aboriginal support services.[424,425] The barriers to accessing clinical genetic services identified here have also been observed in the context of rare diseases,[405] cancer genetic counselling,[426] and carrier screening.[406]

The research to date strongly indicates the need for culturally appropriate genomic literacy resources and flexible service delivery models. The Machado Joseph Disease Foundation in the Northern Territory provides an exemplar of how to deliver flexible clinical genetic services for Aboriginal families in a geographically and culturally complex setting.[427] Genetic counsellors visit communities and work in partnership with Aboriginal community workers to offer single gender, communal consultation sessions to meet client preferences. Four elements were identified as underpinning the success of this model: (1) a client led service model; (2) acceptance of a range of understandings of disease causation; (3) a focus on relationships, continuity and trust between the service and the clients; and (4) a commitment to an inclusive whole-of-family practice.[427]

What are the Ethical, Legal, and Social Considerations of Cancer Genomics?



Section One: Scoping Review of The Ethical, Legal, and Social Considerations of Cancer Genomics

Introduction

Incorporating genomics into cancer control in Australian health care needs to take place against a background of consideration of the attendant ethical, legal and social issues (ELSI) that will arise. The nature and range of ELSI in genomics in cancer control is broad and also varies with the relevant aspect of the patient journey. Additionally, a consideration of ELSI in genomic cancer control also needs to be situated against a background of several decades of global ELSI scholarship in genetics and genomics more generally, such as that brought together in the United States-based ELSI Hub.

Areas of global consensus in ELSI scholarship include the importance of gaining appropriate consent to testing,[428] ensuring results are subject to the appropriate privacy protections,[429] planning for possible psychosocial sequelae of testing,[430] of avoiding patient stigmatisation or discrimination following testing,[431] and ensuring access to ongoing care when indicated. Areas where debate continues include whether it is possible to override a person's confidentiality to warn a genetic relative about their genetic risk;[432] emerging duties to do with reanalysis and reinterpretation of genomic results,[433] and whether certain findings should be deliberately sought regardless of the initial test indication.[434] These issues are relevant to the use of genomics in cancer control too.

Debate is also ongoing regarding whether ELSI in genetics and genomics are 'exceptional', or warranting of special attention over and above issues that arise for other kinds of testing or in other areas of health care.[435] On the one hand, the increasing mainstreaming and increasing use of tests that provide risk-based information about multifactorial conditions may mean that what were traditionally considered exceptional features of genetics are dissipating. However, on the other hand, genomic information retains properties such as being predictive of future health, potentially generating findings beyond the scope of an initial test, possibly generating stigma or discrimination, and being of relevance to other family members. To this end, while the use of genomics in cancer control will give rise to ELSI that already occur in other areas of health care practice, it is also warranted to consider ELSI in this specific context.

As earlier sections of this report have described, genomics is able to be used in cancer control in many ways. These uses of genomics are set to expand as knowledge and health system capabilities advance. It is not yet known whether the ongoing use of genomics in cancer control will generate unique or new ELSI. Little is currently known regarding gaps in ELSI scholarship regarding specific aspects of the patient journey in cancer (or specific cancers), nor whether and how ELSI issues that are particularly pertinent to the Australian health system have been discussed in the ELSI literature.

To address these gaps, a scoping review of the global literature was undertaken. The aim was to identify *cancer-specific* ELSI scholarship, to synthesise the information identified and to identify gaps in both the specific issues considered (in relation to cancer genomics) and the aspects of the patient journey across the cancer care and control pathway (or the optimal steps across the cancer care continuum [436] where these issues are discussed. A consideration of ELSI in how genomics can and should be used in cancer control will help inform the framework.

Please see Appendix 4 for the scoping review methods.

Descriptive Analysis of Final Articles

A total of 1835 articles were retrieved via the database searches, of which 518 duplicates were removed (see Appendix 4 for PRISMA diagram). A total of 1317 articles underwent title and abstract screening, of which the full text of 87 were assessed for eligibility. Forty-one articles were excluded, with reasons including not being focussed substantially on ELSI or cancer genomics. Of the 46 journal articles included in this review, the first authors were predominately from the United States (n=23) and Europe (n=14), followed by the United Kingdom (n=3), Canada (n=3), Australia (n=2), and Israel (n=1), see Appendix 4 for key characteristics of final articles.

Reflective of the heterogeneity of the literature covering ELSI related to cancer genomics, we identified a wide variety of articles. The majority of papers were normative/theoretical with an ethics- and/or legal-focus. Five position statements/reports/guidelines were identified. In terms of the patient journey with respect to the cancer control and care continuum, 32 included prevention and early detection; 5 presentation, initial investigations and referrals; 24 diagnosis; 16 treatment; 3 care after initial treatment and recovery; 3 end-of-life; 2 supportive care; 7 research, and 1 managing relapse (some articles covered multiple aspects of the cancer control and care continuum, therefore the total is not 46 here).

ELSI Themes Identified Through Qualitative Analysis

Eighteen themes pertaining to ELSI were identified in the dataset. These are presented in Appendix 4 with corresponding illustrative quotes. Here, we describe the most predominant themes with reference to the relevant articles identified through the scoping review.

Equity of Access

Equity of access was a broad theme that was considered in 18 [429,437-453] of the 46 articles. It was discussed predominately within the context of prevention and early detection in the cancer care and control continuum. Within this broad theme, sub-themes were also developed to reflect observed discussion in the dataset relevant

to equity of access, including structural barriers to testing and research, access to follow-up care and prevention, impact of testing, engagement with health system and community, and who should be tested. Structural barriers to testing and research were described by 10 articles [429,438,440,443-446,449-451] and included systemic racial, socioeconomic and knowledge barriers to testing.

Some articles highlighted that access to genomic testing in cancer is not currently equitable,[438] and that populations with less access to genomics are the same communities already experiencing significant negative effects of social determinants of health.[444] Adding to this concern, is that the diversity of the human genome is not currently reflected in genomic databases and there is the potential for cancer genomics to worsen existing health disparities. With respect to the use of genomics in risk stratification, this may mean less reliable stratification for underrepresented groups.[429] The application of artificial intelligence (AI) in cancer care was also discussed with respect to disproportionately excluding or harming underrepresented populations in training datasets.[451] Several challenges to the application of AI in cancer practice were identified by Shreve et al (2022), including the requirement for diverse and inclusive datasets for training the AI models and ensuring that the predicted outcomes or clinical endpoints used for model training are not related to socioeconomic biases.[451] The importance of understanding the target population for the implementation of genomic tests and new technologies, and ensuring that the development and validation of tests reflects the target population was emphasised by multiple articles.[445,451]

Five articles explored the subtheme access to follow-up care and prevention.[429,437,438,446,447] Similar to concerns about access to testing, articles highlighted the importance of equitable access to, and the right to benefit from, relevant follow-up interventions post-testing. In relation to using genomics for risk stratification, Knoppers et al emphasise the importance of:

"… ensuring that risk-stratification achieves comparable performance across sub-populations and across human genetic diversity, ensuring that individuals in different healthcare contexts obtain equitable access to risk-stratified care, and ensuring that individuals and healthcare practitioners understand their respective responsibilities in obtaining appropriate follow-up care after their risk level has been assessed" [429]

A future-focussed topic related to access to follow-up care and prevention was epigenetic risk-predictive screening for female cancers.[437] Epigenetic markers may be incorporated into risk assessment in risk-stratified population-based cancer screening programs, and may inform cancer primary prevention interventions (such as changing lifestyle behaviours) and for monitoring responses to risk-reducing interventions.[437] This possible application raises ethical considerations that are also relevant more broadly to using genomic information in prevention and early detection, particularly with regards to the idea of personal responsibility for health (identified as a separate theme in our analysis), which may involve the shifting of blame and accountability to individuals.[437]

In the clinical setting, Morganti et al 2019 discussed the role of next-generation sequencing with respect to personalised medicine in cancer [454] and raise a concern about new therapies arising as a result of newer technologies and (genomic) information. Specifically, they are concerned that new therapies and treatments are typically expensive and therefore may not be accessible to all individuals due to their financial cost. In turn, they question whether everyone has a right to the best kind of cancer care, regardless of the financial strain that paying for the care might put on a society.

In addition to treatment options and risk stratification to guide cancer prevention and early detection, other impact(s) of testing (subtheme) may very across patient groups. In a commentary on ethical issues in reporting germline findings from paired tumour-normal genomic testing in patients with advanced cancer, Hunter et al consider the benefits and potential harms of paired whole exome sequencing of both tumour DNA and patient blood samples, which enables the identification of clinically significant germline findings as an adjunct to tumour testing that aims to identify therapeutic cancer targets and clinical trials. For patients with advanced cancer, the authors propose that any potential benefit from germline testing for their own health may be significantly reduced by their limited prognosis.[442] Given that among cancer patients, the identification of a

cancer-related variant can guide cancer risk management strategies, for advanced cancer patients this may amplify emotional distress and add to their psychological burden. But Hunter et al also highlight the potential psychological benefits of testing, which may include relief if family members can use the information to inform their cancer prevention and early detection behaviours.

Related to the idea of who benefits from being tested, is who should be tested? which was another subtheme under equity of access. In a scoping review and ethical primer on BRCA1/2 testing, Petrova et al 2022 identified concerns about equal and or equitable access to testing, including whether it should be available to all who request it or restricted to only those who appear to be high risk, and whether socioeconomic (or other) barriers would limit access.[448]

A further key recommendation for building and facilitating equity of access to testing, was engagement with the health system and community;[444,445,449] specifically in the context of research. Inclusivity, multistakeholder partnerships that inform priority-setting and determining research conditions consistent with community values and cultural needs, and improving genetic health literacy for diverse groups were some of the suggested strategies. These draw on ethical considerations including the need to avoid imposing values 'top down' on research participants, and the importance of genuine participant partnership in research.

Family Considerations

Fourteen articles[446,448,452,455-465] discussed family considerations related to cancer genomics, which were predominately focussed on high penetrance as opposed to genomic (such as polygenic) testing. These data were further coded into subthemes including family dissemination and communication, family influence on testing and familial benefit. Family dissemination and communication included considerations relating to who is responsible for communicating genetic information to extended family, including that healthcare professionals may have a responsibility to take a more active role in disclosure [458] and that doing so is legally defensible in relation to Australian Privacy Law.[461] These discussions also highlight well-established tensions between the rights of the patient versus other family members and thus conflicting arguments regarding autonomy, the right not to know, and privacy and confidentiality (which are other themes identified in this review, see Appendix 4). Three papers discussed the influence of family on cancer genomic testing,[456,457,464] which proposed that family members can dominantly influence a patient's decision making over genetic testing. For cancer patients in particular, blood relatives who are present in consultations about genetic testing can be perceived by clinicians as patients or potential patients, which may influence their engagement in the consultations.[457] With that said, however, other articles from which themes relating to autonomy were derived point out that genetic testing is inherently relational as well as individual.[457] To this end, concepts like entanglement are relevant to how family influence is approached.[456]

Legal Considerations and Genetic Discrimination

Sixteen articles[439,444-446,448,452,455,458,461-463,465-469 470] discussed legal considerations in relation to cancer genomics, which were further coded in subthemes including privacy and confidentiality (clinical care), privacy in relation to research and datasets, reclassification (law and ethics), regulation of commercial testing and genetic discrimination. Confidentiality in clinical care predominately focussed on family disclosure and traceback testing. One paper on traceback testing advocated for a framing of genetic information as part of a learning healthcare system, and its underlying ethical values of reciprocity and shared obligations.[460] Additionally (and as noted above) an Australian privacy analysis [461] argues that direct notification of at-risk relatives regarding medically actionable genetic information with index patient consent, is not a breach of Australian privacy regulations. Nevertheless, considerations of privacy in relation to research and genomic datasets demonstrated a need for ensuring privacy protections are in place, as well as there being a need for an ethically acceptable framework for all storage of data and residual samples for research.[446]

Related to legal considerations, was the subtheme of genetic discrimination.[439,445,448,455,463] In an article by Winkler and Knoppers (2022), the ethical and legal aspects of the policy debate around key topics in precision cancer medicine are discussed, including privacy and discrimination. They highlight that despite widely documented

concerns that employers or insurers could treat people unfairly in light of their genomic risk information, evidence of genetic discrimination is ambiguous. Summarising a systematic review of 33 studies by Joly et al.[471] Winkler and Knoppers note that incidences of negative impact of genetic diagnosis on access to life insurance (for Huntington's disease in particular) have been reported but there are also important evidentiary gaps and methodological challenges, including discrimination in the context of 'omics' studies, defining genetic discrimination and verifying reported incidents.[463] Winkler and Knoppers argue for balanced information about benefits and risks of genomic testing, in addition to laws and policies against illegitimate discrimination on the basis of disease risk.[463]

Consent Processes

Seventeen articles discussed consent processes in cancer genomic testing, which were further coded into subthemes including clinical care, research and designing consent for diversity.[429,439,442,445,446,449,455,460,463,469,472-478] A key attribute of consent regarding testing for hereditary cancers is the need to adapt consent models to new test methods and the implications (such as the use of molecular tumour boards).[477] Articles that proposed designing consent for diversity were predominantly focussed on the research setting, and emphasised the importance of taking into account diverse health, medical and technological literacy, the engagement of communications experts and stakeholder input, and supporting recruitment and retention of participants who reflect the diversity of the broader population.[445,469,475] There was also discussion of whether and how to return raw data to participants in cancer genomics research.[463]

Related to consent processes was the issue of Incidental, Secondary and or Unsolicited Findings (theme) with respect to mainstreaming genomic testing. Several articles highlighted potential challenges with non-genetic health professionals obtaining informed consent, particularly with regards to preparing patients for, and communicating, incidental, secondary or unsolicited findings.[448,455,472,478] However, a consensus was also evident that non-genetic health professionals could feasibly obtain informed consent, which could be enabled through appropriate collaborative services[455] and layered approaches that are integrated in information systems.[472] Bunnik et al argue that mainstream consent processes for genomic testing, which may yield results beyond the answer to the specific clinical question, should focus on briefly and effectively preparing patients and relevant family members for the clinical and psychosocial consequences of suspected germline mutations, variants of uncertain significance and unsolicited findings pertaining to other conditions.[472] They propose that when the chance of unsolicited outcomes is very low, then opt-out options may not need to be actively offered.

Trust (in health professionals, healthcare systems more broadly and data custodians) was another theme identified through this thematic analysis, which was interrelated with other themes including consent processes, data management, storage and sharing, racism and best interests of the child.

Discussion

This scoping review aimed to identify contemporary cancer-specific ELSI scholarship related to genomics. It also sought to identify gaps regarding both the specific issues that have been considered to date and the aspects of the patient journey across the cancer care and control pathway where these issues are discussed. Forty-six articles met our final search criteria. Based on a thematic analysis of the included articles' main arguments we identified eighteen ELSI themes, which predominately related to equity of access, family considerations, legal considerations (including genetic discrimination in insurance) and consent processes. A strong focus of the scholarship identified in this search was on cancer genomic testing to inform prevention, early detection, diagnosis and treatment, with limited ELSI discourse with respect to survivorship, end of life and palliative care. There was limited Australian-specific scholarship, with noteworthy gaps in the cancer genomics ELSI literature with regards to culturally, ethnically and linguistically diverse groups and Aboriginal and Torres Strait Islander Australians. Below we further discuss our findings, including gaps in the literature that we have identified and the meaning of our findings with respect to cancer genomics in personalised cancer care in Australia.

The articles identified in this search demonstrate that as genomic technologies become increasingly advanced and more broadly applied, the ELSI debate also becomes increasingly complex. The mainstreaming of cancer genomics highlights a shift in our approaches to genomic testing and has prompted evaluations such as whether the 'typical' ELSI for cancer genomics apply in broader and more community-focussed (public health) contexts too. The ethical paradigms within which genetic testing has been implemented in the clinical setting are predominately focussed on the individual and individualistic notions of patient autonomy (albeit with growing recognition of the importance of relationality, entanglement and reciprocity), whereas public health settings are more focused on disease prevention across the population.[479] Nevertheless, Lewis and Green (2021) have also argued that despite the distinct ethical frameworks that apply to clinical vs public health contexts, there are also commonalities in the ethical questions raised by high-penetrance and polygenic testing in these distinct settings, particularly with regards to secondary or incidental findings, the role of expert mediators (health professionals), potential harms of testing and the possibility of genetic discrimination.[479]

Our analysis demonstrated that the ELSI discourse that focussed on clinical contexts and high penetrance testing was typically limited to patient groups at high risk of cancer, as well as existing cancer patients and their families. In these settings, certain ELSI were well described, including privacy and confidentiality, consent processes and family considerations. In contrast, in the research context, much of the focus was on polygenic scores and the use of genomic risk information to inform population-wide interventions. The need for genuine partnership and participation with communities when designing research was also described. The ELSI regarding polygenic testing were predominately focussed on engaging diverse populations in research, possible mis-or overinterpretation of results, premature commercialisation and stigma or genetic discrimination.[439] Concerns such as obtaining informed consent were less prominent in the population health context. The current lack of standards for obtaining informed consent for genetic and genomic testing in the context of population health highlights the importance of deliberating how informed consent should be obtained for genomic testing delivered at large scale, especially to healthy individuals. This will be particularly important if genomic testing to inform risk stratification includes both polygenic and single gene variants.

Our analysis identified issues regarding genetic discrimination, such as evidentiary gaps and methodological challenges regarding discrimination in the context of 'omics' studies, defining genetic discrimination and verifying reported incidents.[431] In the Australian context, community concerns about genetic discrimination in life insurance have been reported [480] and there is ongoing research to identify evidence of genetic discrimination in Australia.[481] Although not cancer specific, the findings from the Australian genetics and life insurance moratorium-monitoring the effectiveness and response (A-GLIMMER) project and the evidence-based recommendations arising from this work will be of relevance to the use and implementation of genomics in cancer care and control.[470]

While direct-to-consumer testing was not the focus of this review, it is noteworthy that polygenic tests for cancer risk assessment are already being marketed directly to the Australian community and health professionals,[482] and thus there is a pressing need to develop guidelines and standards for the ethical and equitable translation of this information into cancer care and control. The potential inclusion of broader genomic tests within the population setting to guide risk assessment for cancer prevention and early detection also highlights a gap in the literature identified in our search pertaining to changes in our knowledge of genomic variants to inform risk assessment. While variant re-classification was an identified issue,[478] this was specific to high-penetrance variants within a targeted test setting, and there was little consideration of how changes to our knowledge of polygenic variants might be communicated or incorporated into consent processes. Models of consent (such as tiered or layered consent [472] that take into account the potential need for re-assessing and communicating risk are likely to be required. All consent approaches for the use of genomics in cancer control should also be appropriately tailored to needs and capabilities of the target group.

Our findings suggest that existing scholarship on personal responsibility and personal care for health in the cancer genomics context may require further development, particularly with regard to decision making processes regarding genomic testing as part of organised screening programs. Further considerations for incorporating genomics into cancer control efforts that were not discussed in depth in our data include how

much (and what form of) genomic information should be provided,[483] (ref) and how shared decision making should be best supported in the various settings where cancer genomic information will be generated.[484]

Our findings also indicate that there is scope for Australian-specific and cancer-specific doctrinal legal analyses of a range of scenarios, particularly legal scholarship that falls beyond a consideration of concepts like privacy and genetic discrimination. While a range of legal questions are raised in the existing Australian and international literature, detailed doctrinal legal research in response to specific scenarios and identification of any desired regulatory reform was not identified.

This scoping review demonstrated concern across the ELSI literature that current access to cancer genomic testing is inequitable and therefore access to follow-up care (including prevention and early detection interventions) may also be inequitable. Multiple strategies to mitigate the further perpetuation of access inequities that are driven by social determinants of health were proposed, which were predominately in the context of research and included: inclusivity, multistakeholder partnerships that inform priority-setting and determining research conditions consistent with community values and cultural needs and improving genetic health literacy for diverse groups. With respect to AI in cancer care and control, it will be important that underrepresented cohorts and healthcare settings are taken into account in training data sets and the development of clinical endpoints to ensure model accuracy and scalability.[451] International scholarship identified in this review emphasised the importance of deep and ongoing engagement with diverse cultures, ethnicities and health literacy levels in cancer genomics research more broadly, and with respect to tailoring meaningful consent according to patient or population subgroup characteristics. However, this search identified several gaps in ELSI scholarship that will be particularly relevant to the Australian setting, such as equity for rural/remote people, and ethical care within culturally, ethically and linguistically diverse communities; including First Nations Peoples. Evidence from other settings suggests that factors other than the economic value of genomic testing are valued by patients and research participants,[441] and determining what these are for Australians will be important to the successful and appropriate use of genomics in Australian cancer control.

This scoping review is the first of its kind to examine the vast ELSI scholarship with a specific focus on cancer genomics. The focus on cancer may have resulted in the exclusion of other ELSI that are relevant to genomics but were not captured in our search. In seeking cancer-specific ELSI scholarship, it may be implied that the authors perceive ELSI in cancer genomics as exceptional or deserving of separate attention. While all ELSI in genomics are relevant to the use of genomics across the cancer care continuum, it is also worthwhile to consider what questions and arguments have been raised about cancer genomics specifically. This review provides this analysis.

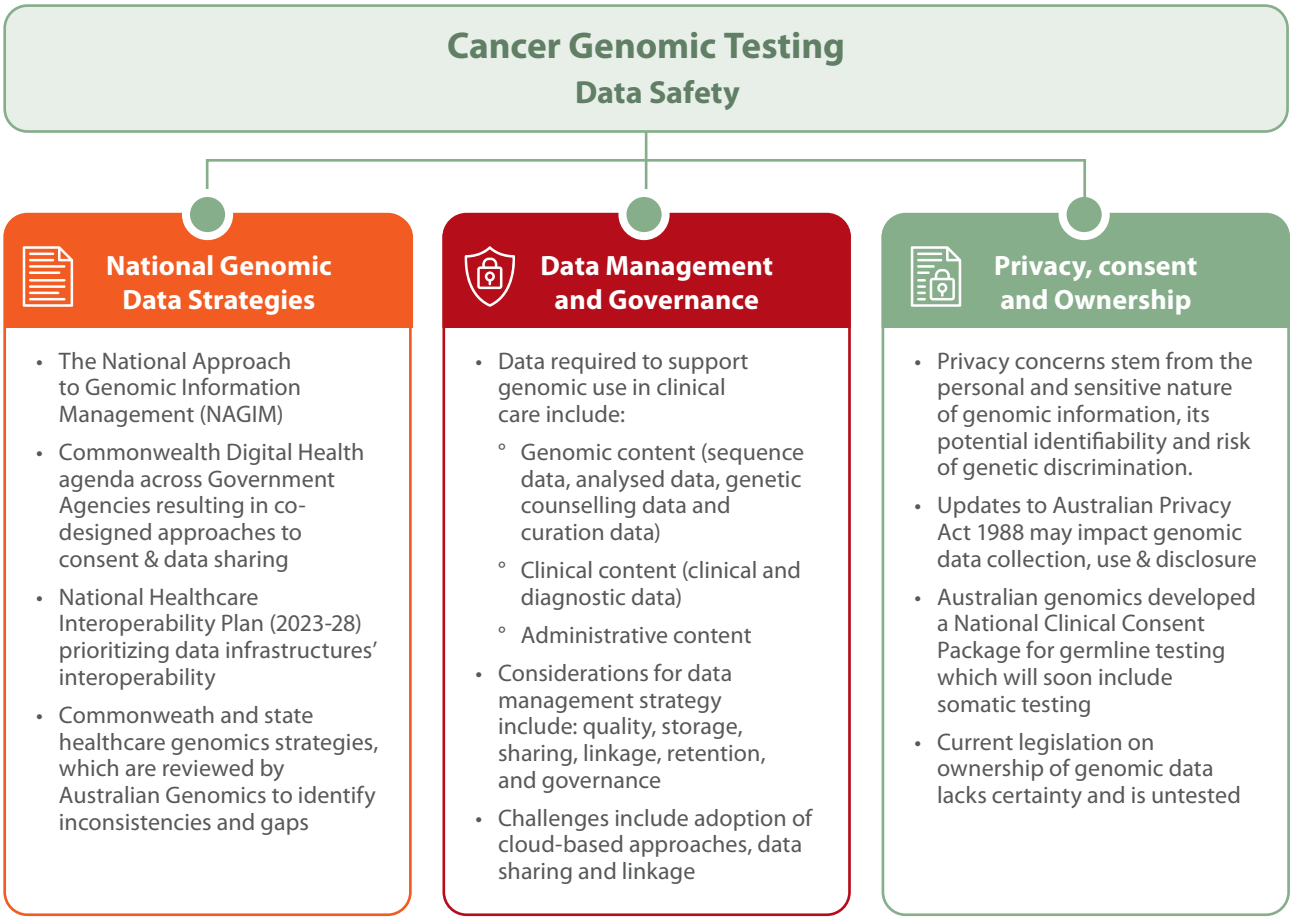
The search inclusion criteria have limited our findings to articles in English and to literature published from 2018; there may be unresolved issues from earlier years that we have not covered. Our searches may have missed material that appears only in legal databases, although we note that key medico-legal journals are indexed in databases that our search did include. The fields covered in this search are also large, and have complicated terminology across the cancer, genomics and ELSI are not always applied consistently. The ELSI of cancer genomics identified in the qualitative analysis were based on an inductive and reflexive thematic analysis approach, which the authors recognise are informed by their own analytical view of the literature. Future research could examine how the ELSI articulated in this review (that focussed specifically on cancer genomics) align with other definitions of ELSI related to genomics in other fields.[485]

In conclusion, the findings from this analysis suggest a need for a national, multidisciplinary approach to examining ELSI in cancer genomics beyond initial test indication and within the broader context of mainstreaming. In particular, we have identified gaps in the ELSI in cancer genomics literature with respect to equity for people living in rural/remote areas, and how to provide ethical care within culturally, linguistically and ethnically diverse communities; including First Nations Peoples.

Gaps in the Literature:

- The ELSI of cancer genomics literature is weighted towards the start of the patient journey on the cancer care and control continuum, with much less focus on survivorship, end of life and palliative care.
- Equity of access was a main theme, which covered international scholarship that argued a need for engagement with groups who have diverse ethnicities, health literacy and cultural backgrounds, particularly in the research settings. However, several gaps were identified that will be relevant to Australia, such as equity for people living in rural/remote areas, and how to provide ethical care within culturally, linguistically and ethnically diverse communities; including First Nations Peoples.
- There was limited deliberation about some ELSI with respect to polygenic scores, particularly regarding informed consent processes for population settings, the right not to know, and personal responsibility for health.
- There is a need for targeted cancer-specific scholarship on legal considerations beyond privacy and discrimination, and structural barriers and equity in cancer genomics in the Australian setting.

Section Two: What are the Data Safety and Regulatory Implications?



National Strategies for Genomic Data and Healthcare

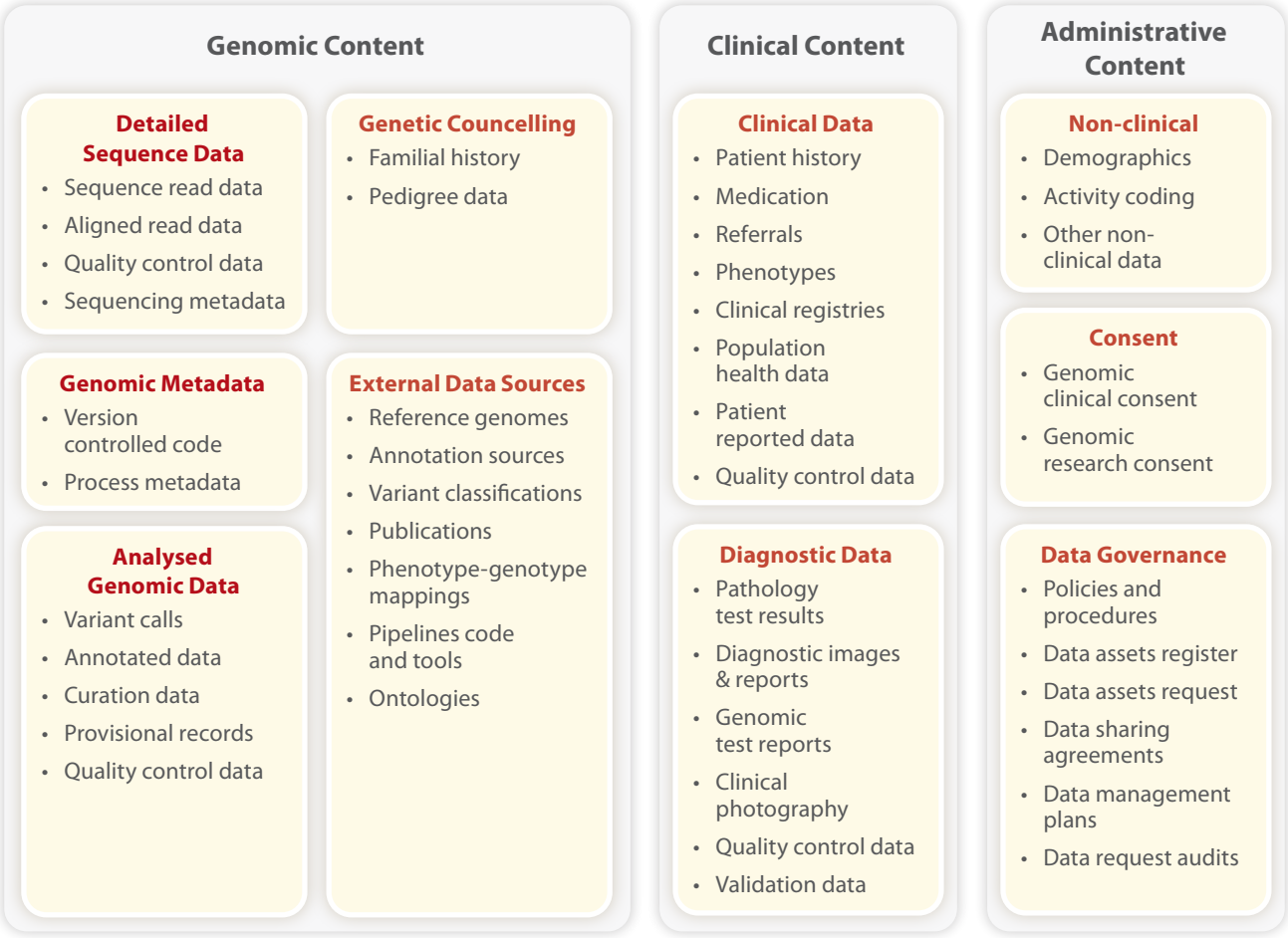
The National Cancer Framework for Genomics in Cancer can be informed by active health data policies and strategies in Australia. Relevant examples include:

- The National Approach to Genomic Information Management (NAGIM), outlining principles for managing genomic and health data, for clinical and research use.[486,487] The NAGIM Recommendations identified key architectural elements, including federated frameworks (independently governed datasets on separate infrastructures aligned to common data elements and rules), adoption of cloud, international standards and interoperable systems; as well as ethical, legal and social considerations for genomic data.
- A Commonwealth Digital Health agenda across Government Agencies that encompasses consumer choice and involvement in health system processes; modernising approaches to consent, data sharing and data use; and establishing health system standards.[488]
- The National HealthCare Interoperability Plan 2023-2028 highlighting interoperability of data infrastructures across healthcare organisations as a key priority, with a corresponding implementation strategy including standards and measuring benefits.[489]
- Healthcare genomics strategies by Commonwealth [490] and the Australian states and territories [491 492,493 494,495] (no formal strategies available for ACT, NT, or Tasmania) which also include approaches for data, privacy, and security. These strategies are being reviewed by Australian Genomics Healthcare Consistency Project,[496] which identified inconsistencies and gaps across jurisdictions.

Types of Data and General Data Management

Effective use of genomics in clinical care can include the generation and use of a range of data types, including genomic data (raw or interpreted), clinical data, and administrative data (see NAGIM Blueprint Figure 8 below). These different data types each have varying requirements and implications for management, storage, privacy, security and use. An emerging area is inclusion of patient-reported outcomes or wearables data (e.g. fitness trackers), which can provide opportunities to enhance patient-centred research and care, and promote patient empowerment.

Figure 8: Data Required to Support Genomics Utilisation in Clinical Care



Adapted from NAGIM Blueprint

In practice, many healthcare professionals in Australia already handle genetic and genomic information. The Human Genetics Society of Australasia's position statement [497] on use of genetic and genomic information in healthcare settings outlines guidance for healthcare professionals on data protection, storage, and sharing of genetic information.

Key considerations that need to be addressed as part of a data management strategy include:

- Data quality: processes for quality control, national standards, retention of metadata and supporting information.
- Data storage: cloud-based approaches are increasingly adopted for managing and using genomic data in clinical care, with the Commonwealth Department of Health and Aged Care, portfolio Agencies, and many states and territories now supporting cloud-first digital strategies [498] first strategy could align with national frameworks for scalability and interoperability of approaches, and support centralized as well as federated approaches.
    - Centralised approaches make it easier to ensure uniform data processing, updates and data linkage but requires data to be moved around (and potentially duplicated).
    - Federated stores require strict procedures on how data is processed, aligning clinical metadata and terminology, tightly coordinated upgrade paths and the development of cross-warehouse queries (e.g., if patients move between jurisdictions).
- Data sharing: in clinical settings, interpretation of a patient's information relies on comparison to data from others. In research, advances in cancer risk prediction, diagnosis, and treatment also all rely on data sharing. With the majority of genomic sequencing data likely to come from healthcare, achieving responsible clinical genomic data sharing will be vital.[499]
- Data linkage: Effective interpretation and use of genomic data to inform care requires linked non-genomic data, such as clinical outcomes and EHR records. The combination of genomic and additional sensitive data requires careful consideration of privacy.
- Data retention: long-term retention to enable re-analysis of data where appropriate, in alignment with existing NPAAC guidelines (e.g. retention of somatic testing reports for 10 years, germline testing report indefinitely, read-level genomic information for germline reports for 4 years from report date).[500] Given the large size of genomic data for cancer (e.g, WGS), infrastructure requirements and costs need to be considered for data retention.
- Data governance: consideration of ethical, legal and social issues (ELSI) around the collection and use of genomic data including consent; privacy; genetic discrimination; secondary use of data; return of findings; ownership; custodianship; sovereignty; intellectual property and provenance (NAGIM Blueprint).

Privacy, Security, and Data Sharing

Privacy is a key consideration for genomic data, which is considered personal and sensitive information and thus covered under the Australian *Privacy Act 1988*. However, there may be nuance to this, depending on identifiability of the genomic data (based on uniqueness, volume, and richness) and the 'data situation' (data, context, and relationship between them).[501]

The 'Essentially Ours' report [502] provides an extensive regulatory review of the collection and use of health-related genomic information in Australia. The report notes a complex 'patchwork of law' at the Commonwealth, State and Territory level, with different laws applying depending on the type of organisation; and uncertainties in definitions and understanding. This report also argues that the traditional regulatory frameworks focus on individual level controls (e.g. consent, data de-identification), while genomic data is inherently identifiable and shared with families and communities, thus may require different regulation.

Key Privacy Issues for Genomic Data Include

- **Challenges of de-identifying genomic data.**[503]
- **Privacy protection and genetic discrimination:** The need for privacy protection in the use of genomic data by insurance companies in developing life insurance policies and premiums - A-Glimmer study.[504]
- Limited ability to share an individual's genomic information across jurisdictional borders for clinical or research purposes, complicating and potentially delaying provision of best possible care.

The Australian *Privacy Act 1988* is currently being updated, and the proposed changes may impact how genomic data is collected, used and disclosed.

Genomic data security and privacy are also being evaluated by the Australian Government Department of Health and Aged Care. The outcomes of this consultation may impact future national security and privacy strategies for managing cancer genomic data *('Review of Genetic and Genomic Data Security Provisions' 2023, EY & DOHAC; outcomes unpublished)*.

Adoption of best-practice procedures by organisations will be key to mitigate or avoid security risks, though both technical and physical measures *(GA4GH security standards and policies e.g., GA4GH Data Privacy and Security Policy)*. Specific considerations may include de-identification of data and storage of personal identifiers; methods for encrypting data; and implications of data linkage (Blueprint). Currently, there is no nationally consistent adoption of security standards across Australia, although ISO security standards for IT infrastructure and genomics exist internationally (and are adopted by global cloud providers such as AWS, Google and Microsoft).

Processes for data sharing would depend on the data type and subject to legal agreements and privacy considerations, policies on associated outcomes (e.g. incidental findings), and infrastructure required to support secure data transfer. Alignment with public needs and trust will be crucial, with several studies examining expectations in countries including Australia.[505,506] Several international Frameworks for data sharing have been developed, e.g. the GA4GH Framework[507] and international code of conduct [508] [509] and Genomic Commons concept.[510]

In Australia, submission of anonymised or de-identified variant data to national and international databases is standard practice in clinical genomics (e.g. ClinGen, ClinVar, MatchMaker Exchange and Shariant[511]).

Emerging privacy-protecting technologies could further support data security and sharing, through e.g. "sharing without access" and "model to data" paradigms, provided such technologies are shown to be scalable, acceptable to Australian healthcare providers, and to satisfy technical, legal, financial, and political requirements.[512]

Consent

See also previous discussion in above section.

Obtaining patient consent is a key requirement of genomic testing for clinical care or research. A national approach to consent will be important for cancer genomic testing in clinical care in Australia. Australian Genomics developed the National Clinical Consent Package[513] for germline testing, with forms for somatic testing proposed for development in 2024, including considerations for dual consent (to accommodate the familial complexities of germline testing, versus somatic testing). A National Model of Consent for Clinical Genomic Testing [514] was also developed by NSW Ministry of Health on behalf of the Australian Health Minister's Advisory Council (AHMAC) Project Reference Group on Health Genomics.

These forms also capture consent to disclose genomic test results to relatives. Contacting at-risk relatives of probands **with patient consent** has been determined to not breach Australian privacy laws [461] providing the information provided at contact (e.g., in a letter) complies with regulation applicable to sensitive information. There is no legal duty to disclose results to at-risk relatives **without patient consent**, but health care

professionals may use their discretion to disclose if allowed by the applicable regulation (with a complex set of Commonwealth and state regulation, plus public/private contexts that influence this,[515] and there is no national consistency on disclosure without consent). States and territories also have different regulation around access to health information of a deceased individual. Emerging areas are dynamic consent approaches[516] and e-consent to support scalable approaches and digital readiness.[517]

As cancer genomics is mainstreamed and offered in contexts such as population health, planning for familial disclosure and cascade testing should form part of the plan for implementation.

In addition, appropriate consent in the clinical setting for sharing healthcare data is an emerging priority, with modernisation of consent and data sharing a key planned outcome of the Digital Health Blueprint;[487] and new standards for clinical genomic testing, released in 2022 by the National Pathology Accreditation Advisory Council (NPAAC)[500] require laboratories to record patient preferences for data sharing for clinical and research purposes.

Data Ownership and Sovereignty

There are complexities in achieving responsible balance between safeguarding patients' privacy and sharing genomic data for their health care and medical science.

Current legislation on ownership of genomic data lacks certainty and has not been tested in Australian courts. Existing interpretations indicate ownership likely lies with the laboratory who initially generated the genomic data.[518] This may not align with patient or public expectations, where individuals may expect or hope to be the owner of their genomic data. A growing body of literature suggests establishing individual autonomy and ownership may mitigate some of the current complexities of data governance and sharing.[519,520]

A survey of genomic professionals in Australia towards patient data ownership indicated most professionals agreed patients have the rights to data ownership.[519] However, there needs to be a clearer understanding of the nature and implications of ownership as genomic data, as it is often subject to collective ownership (e.g. with family members and/or testing laboratories). A stronger health system infrastructure will be needed for enabling patient data ownership.[519]

Data ownership is also embedded in a complex mix of rights, permissions and controls that are involved in managing and using clinical genomic data (including e.g. testing laboratory, test funder, patient, referring clinician, re-analysis providers, principal investigator, and data custodians). Moreover, Commonwealth, state and territory legislation and regulation determines how health data is managed. This includes where it can be stored and how it can be shared. Sharing genomic data across jurisdictional borders is currently very challenging. This mix of rights and complex regulation has resulted in inhibited data sharing, which can be particularly problematic in cancer care when time is valuable for therapeutic decision making, clinical trial access, and implications for family members.

In the future, challenges with cross-jurisdictional data access may be mitigated with patient consent and the adoption of My Health Record (MyHR), with improved submission of genomic test results to MyHR by health providers (which is currently highly variable).

Patient Access to Information

Currently, patient access to their genomic information is not routinely made available in Australia. Reports approved by a Molecular Tumour Board are captured by hospital EMR systems, but not consistently stored in MyHR. Patient or participant access to their genomic results will need appropriate communication and education strategies.

For both patients and research participants, there is growing support for enabling access to their own data.[521] In future, clinical labs may have an obligation to return raw data on request. While for genomic data generated in

the research setting, the National Statement [522] currently suggests that researchers have no obligation to share raw data with research participants. However, a recent study indicates individuals may have a legal right to request access to their genomic data under the *Privacy Act 1988*.[523]

International policies on returning research results to participants have been developed.[524] Harmonisation, globally, of laws and policies around return of research results will be important.[525]

Genomic Data Use for Follow-Up Cancer Care

Data retention and availability of primary tumour data will be important for assessing tumour progression. However, data is typically only kept at the testing site and unavailable as a reference for future tests conducted at other sites. This is problematic, particularly for Minimal Residual Disease (MRD) testing as it relies on information on somatic variants in the primary tumour. This often locks patients into the site that conducted the primary tumour sequencing.

The current siloed approach to clinical and cancer genomic data inhibits future data reanalysis and reduces patient options in deciding where to get their tests done. It is also a significant hurdle when patients move between states.

Data Processes and Standards, Quality Assurance and Accreditation

Cancer genomics frequently involves both clinical tests and research to obtain diagnoses or fully understand a patient's condition. In general, clinical care has more stringent data process requirements (e.g. NPAAC guidelines, NATA accreditation). Data governance processes are also impacted by the source of funding for the genomic test, which can include Australian Government (Medicare Benefits Schedule), the state and territory governments (activity-based funding), private health insurers or other NGOs, patients, and research funders (e.g. NHMRC, MRFF, ARC, universities, other funding bodies). Tests funded by Medicare/federally or the state and territory departments of health will be handled differently to research- funded testing.

Lack of national standards for cancer genomic data workflows makes it challenging to compare patient results between clinical sites, to use clinical samples in a research setting (e.g., a cohort analysis of high-risk breast cancer patients), or to compare results across research and clinically generated tests. Notably, analysis of matched tumour and germline samples involves two separate workflows, which compounds the complexity and challenges in comparability. National guidelines on resources underpinning bioinformatic workflows (e.g. reference genomes), or mandates to standardise data for exchange with other laboratories, could support data harmonisation and interoperability.

Similarly, the adoption of data standards and clinical terminologies is now a high priority for Australian healthcare/digital health strategies, see e.g. National Healthcare Interoperability Plan.[489] Implementation needed for clinical genomics including cancer genomics. Standards are needed for genomic data (including data generation and management), but also for accompanying clinical data to help curate genomic test results and prioritise findings, e.g.:

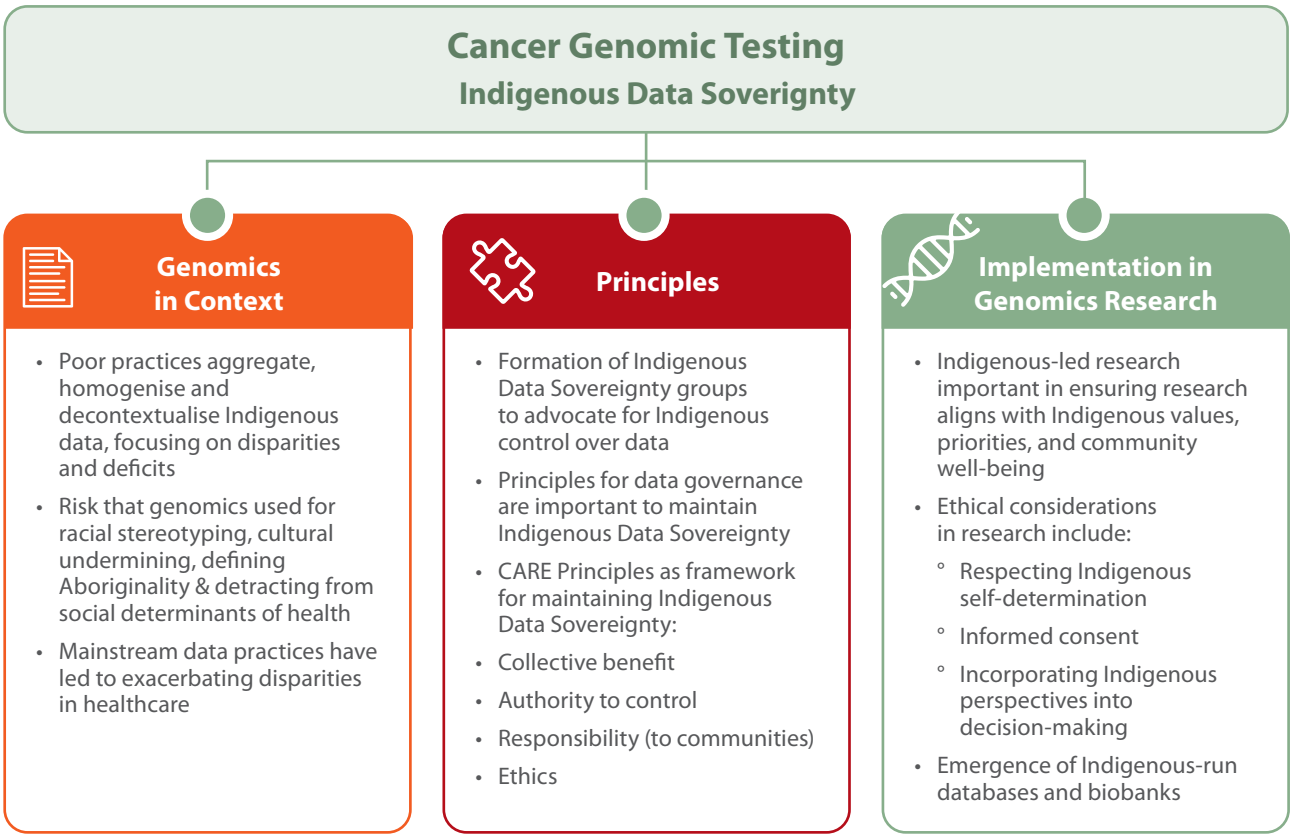
- Minimal clinical data requirements, aligning with NATA guidelines that future pathology information should be standardised. E.g. e of tumour, stage, any prior treatment history, prior cancer episodes or family history.
- Standardised clinical data capture and terminologies.

Quality assurance and accreditation are also crucial to ensure genomic test results are comparable between providers, e.g. as per the functional equivalence project [526] or ICGC-ARGO. ACMG guidelines are in place for variant interpretation – with labs following guidelines from ACMG/ClinGen ([34,527]) for germline variants and AMP for somatic changes.[34] Quality assurance processes are in place NATA accreditation or Quality Assurance Programs (QAP) available internationally (e.g., via https://www.emqn.org/); local QAP programs are limited,

particularly for comprehensive cancer panels, exomes or WGS in the cancer space. Existing QAP modules through RCPA are limited in scope and tumour-only.

Additional considerations may be required where overseas cancer screening or testing is undertaken, thus different data processes, standards, and quality assurance apply, and data may be inaccessible for re-analysis.

Section Three: What are the Implications of Indigenous Data Sovereignty



Indigenous Data Sovereignty is a movement arising in response to the harms caused by poor data practices. (Kukatai & Taylor, 2016; Walter et al., 2021). As Walter et al define it:

> Indigenous Data Sovereignty affirms the rights of Indigenous Peoples to determine the means of collection, access, analysis, interpretation, management, dissemination and re-use of data pertaining to the Indigenous Peoples from whom it has been derived, or to whom it relates. It derives from the inherent rights of self-determination as described in the United Nations Declaration on the Rights of Indigenous Peoples (UNDRIP), and includes the demand that data be used in ways that support and enhance Indigenous Peoples' collective well-being (Walter et al., 2021, p 146)in its proclamation of the right of Indigenous peoples to govern the collection, ownership, and application of data, recognises data as a cultural and economic asset. The impact of data is magnified by the emergence of Big Data and the associated impetus to open publicly held data (Open Data.)

Dominant data practices aggregate, homogenise and decontextualise Indigenous data, focusing on disparities and deficits (Walter, 2016). In the context of genomics, these broad data concerns are compounded by additional risks, including harms associated with racial stereotyping, cultural undermining, using genomics to define Aboriginality, and detracting from social and environmental determinants of disease (Garrison, Hudson, et al., 2019; McWhirter et al., 2015). These issues have combined to foster distrust of researchers and reluctance of Indigenous communities to participate in genomic research.

In response to these concerns, Indigenous Data Sovereignty groups in Aotearoa/New Zealand (Te Mana Raraunga Maori Data Sovereignty Network), Australia (Maiam nayri Wingara Aboriginal and Torres Strait Islander Data Sovereignty Collective), the United States (US Indigenous Data Sovereignty Network) and Canada

(Indigenous Data Governance Initiative) developed principles for implementing Indigenous Data Sovereignty relevant to each location (Carroll et al., 2020; Trudgett et al., 2022). Building upon this foundation, these groups came together to form the Global Indigenous Data Alliance (GIDA) and developed the CARE Principles for Indigenous Data Governance to better account for Indigenous interests, culture and collective rights in data governance (Carroll et al., 2020). The CARE Principles are intended to complement the FAIR Guiding Principles for scientific data management (Findable, Accessible, Interoperable, Reusable), and comprise the following:

- **C**ollective benefit: use of Indigenous data must contribute to collective benefit for Indigenous peoples and equitable Ta outcomes.
- **A**uthority to control: Indigenous peoples must define the governance for data derived from, or pertaining to, them and be actively involved in decision-making for Indigenous data.
- **R**esponsibility: those working with Indigenous data are responsible to the people and communities from which it was derived, for the maintenance of respectful relationships, and facilitation of self-determination and benefit-sharing.
- **E**thics: assessment of risks, benefits, benefits and future use of Indigenous data must be undertaken by Indigenous peoples and be grounded in community values and ethical frameworks (Carroll et al., 2020).

Indigenous Data Sovereignty in genomics is most fully given expression when research is Indigenous-led. However, even when not Indigenous-led, research can advance data sovereignty by integrating and protecting Indigenous peoples' rights in data, as articulated by Hudson and colleagues (Hudson et al., 2023):

- Right to self-determination: the ability to organize and control data in relation to a collective identity;
- Right to reclaim: the right to reclaim, retain, and preserve data, data labels, and data outputs that reflect Indigenous Peoples' identities, cultures, and relationships;
- Right to possess: the ability to exercise jurisdictional control over the ways that data flow/move/are queried;
- Right to use: the ability of individuals and collectives to use data for their own purposes;
- Right to consent: the expression of digital autonomy and the ability to assess risks and accept potential harms;
- Right to refuse: the right to say "no" to certain uses of data;
- Right to govern: the right to lead and collaborate in the development and implementation of protocols and in decisions about access to data;
- Right to define: the right to define lifeways of knowing and being including how they are represented in data;
- Right to privacy: the protection of collective identities and interests from undue attention, also including the possibility of requesting omission and/or erasure;
- Right to know: the ability to track the storage, use, and reuse of the data and who has had access to them;
- Right to association: the recognition of provenance and terms of attribution; and
- Right to benefit: the opportunity to benefit from the use of data and equitable benefit sharing from derivatives of data.

These rights are given effect through the operationalisation of Indigenous Data Governance, which necessitates consideration of: (1) Indigenous governance; (2) institutional ethics; (3) socio-political dynamics; (4) data management and data stewardship; and (5) overarching influences of human rights, workforce capacity, and funding (Griffiths et al., 2021).

Indigenous Data Sovereignty in Genomic Research

Implementation of Indigenous Data Sovereignty principles in genomic research is critical to ensuring that Indigenous interests are protected, group harms are avoided, and that the benefits and burdens of genomic medicine are equitably distributed. Some of these principles are in tension with mainstream moves towards open data and genomic data sharing for the acceleration of research and maximisation of public benefit (Hudson et al., 2020). Unrestricted open data, however, does not benefit all segments of the public equally. Failure to integrate Indigenous control of Indigenous data has to date resulted in extractive research practices and group harms, with little benefit to Indigenous communities.

Logistical issues also present potential barriers. What does Indigenous control of Indigenous data look like in practice? While meaningful community engagement and participation in governance may be comparatively straightforward when working with a small number of well-defined remote communities, how can that be effectively scaled up to the national level, including the diverse perspectives of more than 200 Aboriginal and Torres Strait Islander peoples, as well as those who have experienced disconnection through the ongoing effects of colonisation, Stolen Generations and other influences? Furthermore, as data travels further from the original collection relationship, to secondary research teams or industry, what mechanisms are available to give effect to Indigenous rights? These questions have not been comprehensively answered yet, but progress in being made on a number of fronts, including relating to consent, ethical review, and Indigenous-run genomic resources.

Informed Consent

Research ethics frameworks centre on consent as a key protection, and this has led to suggestions that dynamic consent, which provides options for individuals to have granular control over the use of their samples and data through an electronic interface, may facilitate Indigenous data sovereignty (Prictor et al., 2020). While this approach is a marked improvement over broad consent, it is nevertheless limited by its reliance on individuals to remain engaged with the platform over long periods of time, and would likely require additional forms of engagement to maintain the necessary trust and interest. It also inherently focuses on individuals rather than communities, and while its potential utility as a means of facilitating group discussions and interaction has been suggested, this remains untested (Prictor et al., 2020).

Ethical Review

The potential for tension between individual and communal rights, as well as the diversity of views among Indigenous peoples, are well recognised (Carroll et al., 2022; Garrison, Barton, et al., 2019; Tsosie et al., 2019)data governance and data management are becoming pressing challenges. The FAIR principles (Findable, Accessible, Interoperable, and Reusable. One way that community views are incorporated into research governance is through Indigenous representation in human research ethics review processes, either in the form of an Indigenous HREC or sub-committee supporting an HREC. In the North American context, Tsosie and colleagues argue that a tendency to overlook group risks arise when researchers focus on Western ethical and legal frameworks, and that the authority of tribal research review processes need to be respected by researchers, institutions and research ethics structures (Tsosie, Claw, et al., 2021). In Australia, the availability of Indigenous review bodies (either community or institution based) is highly variable. Investment in this area would be of benefit to genomic research, as well as more broadly.

Guidelines for ethical genomic research with Aboriginal and Torres Strait Islander people and communities represent a complementary measure to support researchers to engage with communities respectfully and to design genomic research projects in ways that are culturally appropriate, that maximise benefit and minimise risks to participants and communities. An example is *Genomic Partnerships: Guidelines for genomic research with Aboriginal and Torres Strait Islander peoples of Queensland, which were developed using a participatory action research approach to consultation, engaging with a range of stakeholders over several rounds of targeted activities* (Kaladharan et al., 2021; Pratt et al., 2019).

Indigenous-Run Genomic Resources

One of the most effective responses to these challenges has been the emergence of Indigenous-run databases and biobanks (Elsum et al., 2019; Hermes et al., 2021; Morgan et al., 2019). International examples of Indigenous-led and governed genomics resources include the Silent Genomes Project in Canada, the Aotearoa Variome in Aotearoa/New Zealand and the Native BioData Consortium in the United States (Tsosie, Yracheta, et al., 2021). In Australia, the National Centre for Indigenous Genomics exercises stewardship of historical samples and data within a governance structure that is directly informed by the principles of Indigenous Data Sovereignty (Hermes et al., 2021). The Centre's activities are underpinned by a focus on community engagements, explicit consent, and a commitment to repatriation, all overseen by an Indigenous-majority Board. These factors contribute to the trust that participants and communities put in the Centre, and to participants' experiences of moving through issues of broken trust, grief and loss towards empowerment, hope and reconnection (Hermes et al., 2021).

Indigenous Data Sovereignty in Clinical Care

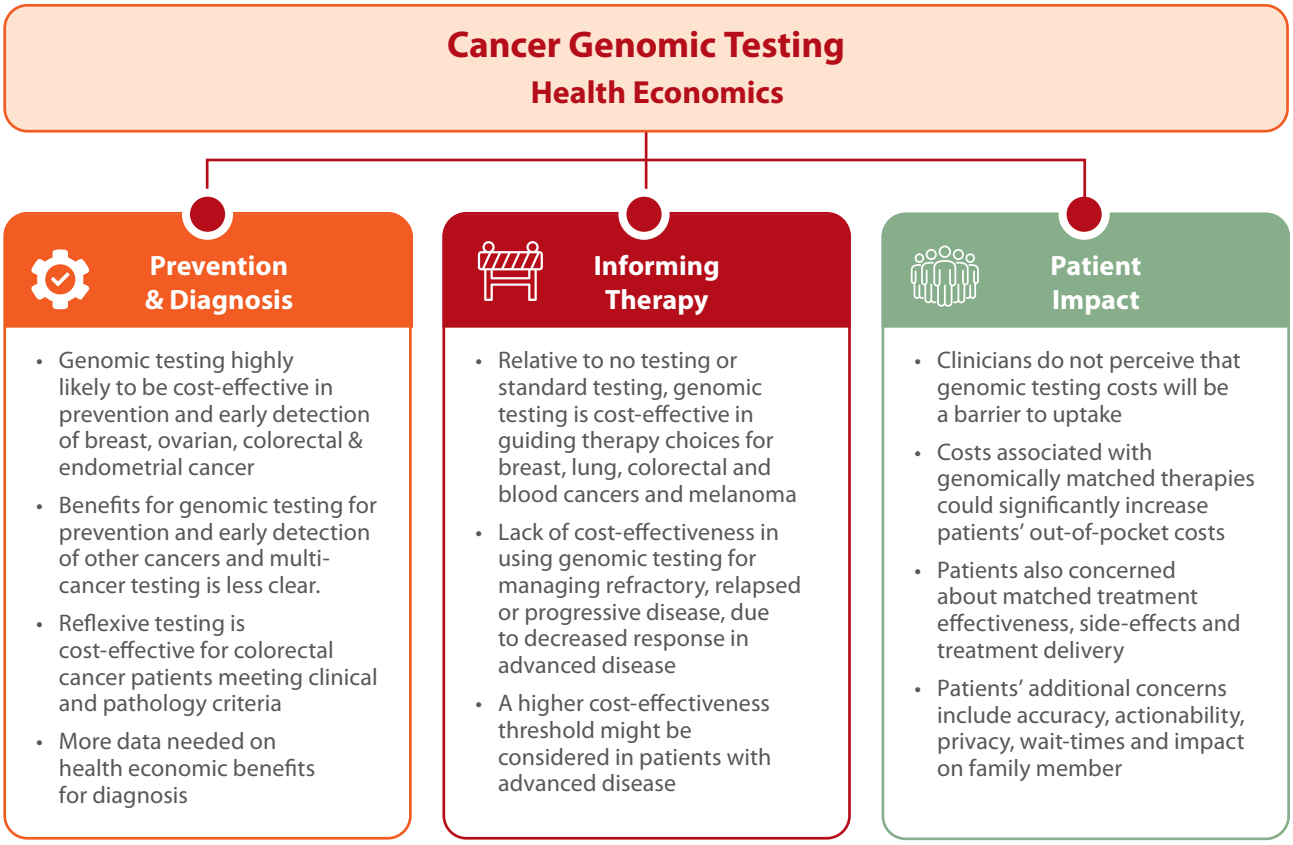
Clinical care is less directly affected than research by Indigenous Data Sovereignty, as the collection and use of genomic data in the clinical encounter is already generally undertaken with consent and for the purpose of providing clinical care for the benefit of the patient. However, where there are familial implications, the principles of Indigenous Data Sovereignty provide further impetus for the provision of culturally appropriate, client-led, flexible models of care. Models such as those employed by the Machado Joseph Disease Foundation facilitate the integration of Indigenous Data Sovereignty principles where decisions need to be made about access, use, and sharing of data beyond the proband (Elsum et al., 2020).

The provision of genomic medicine in cancer care will be improved with the inclusion of Aboriginal and Torres Strait Islander data in reference datasets. Achieving appropriate diversity in reference data will depend upon the adoption of Indigenous Data Sovereignty principles, so that the potential group harms of participation in genomic research may be managed effectively.

Indigenous Data Sovereignty has implications for clinician-researchers seeking to re-use clinical data from Aboriginal and Torres Strait Islander patients, including biological samples and genomic data, for secondary research purposes. These will be most acute for instances where waivers of consent are sought, or broad or unspecified consent for secondary research was obtained at the time of the initial clinical encounter. Where this occurs, data custodians, clinician-researchers and ethics committees will need to consider how best to give effect to the principles of Indigenous Data Sovereignty and to avoid perpetuating poor data practices and resultant harms. Ensuring there are mechanisms in place for giving effect to Indigenous data governance will require planning and investment in order to be meaningful and effective.

More generally, it would be beneficial for clinicians engaging with Aboriginal and Torres Strait Islander people affected by cancer, as well as data managers and others involved in the collection, storage, use and management of genomic samples and data, to be familiar with Indigenous Data Sovereignty principles and the issues that form its background. The awareness of these issues and the history of genomic research with Indigenous peoples might reasonably be expected to inform the provision of more culturally-appropriate data management practices and health care.

Health Economics



Introduction

Health economics combines the research methodologies from health science and economics to understand how healthcare resources are produced, allocated and consumed within a healthcare system.[528]

Genomic medicine is in a period of rapid development and affords the opportunity to improve quality of life and health outcomes for those at risk of cancer through prevention and early detection,[529] and those with cancer through targeted management.[530] However, being a relatively novel technology, genomic medicine remains expensive,[531] and healthcare resources, in any context are limited, so it is unclear whether the additional cost of genomic medicine is justified on the basis of the health and economic benefits that it generates.[531] To ensure appropriate resource allocation and the feasibility, sustainability, and scalability of genomic medicine for the management of cancer in Australia, it is essential to understand the cost-effectiveness of genomics across a variety of contexts and cancers.

When patients and families bear a cost for accessing genomic technologies, this limits uptake[532] and the opportunity to improve health outcomes, which is a concept known as 'financial toxicity'.[533] Currently little is known about how costs absorbed by patients and families impact on uptake and patient health outcomes.

To fully understand the economic value of genomics for cancer control in Australia, it is pertinent to further understand what patients and the public value about the application of genomic technologies across the cancer continuum.[534] It is likely that in practice the uptake of certain technologies, for example screening, will be different to what was established in clinical trials.[535] Preferences are inherently linked to the cost-effectiveness of health technologies and enable an accurate understanding of the Government health budget impact and the optimisation of the societal health economics outcomes.

This systematic review has three aims: A) To identify the evidence in relation to the cost-effectiveness of genomics across the cancer continuum; B) To understand how the direct costs of accessing genomics to consumers may impact utilisation and patient outcomes; and C) to identify individual preferences, priorities and values for genomic technologies.

Notes on Cost-effectiveness Results

Cost-effectiveness involves the comparative evaluation of ≥2 strategies in terms of their costs and outcomes. The recommended outcome of an economic evaluation is the quality-adjusted life-year (QALY), which is a composite measure of mortality (length of life) and morbidity (quality of life). Measuring quality of life may not always be possible and thus researchers may apply alternative outcomes, such as life-years gained (when there are longer-term outcomes that need to be captured within the evaluation) or natural units, such as number of cancer cases detected. QALYs are recommended because established thresholds have been identified to support standardised prioritisation decisions across health technologies and across clinical contexts. That being said, cost-effectiveness thresholds, which in this review are mentioned as decision-maker willingness-to-pay thresholds, are not always consistently applied and vary between countries for reasons related to health system productivity and general societal values. In Australia, the commonly used threshold of cost-effectiveness is $50,000 per QALY gained per patient. In the UK, the National Institute for Health and Care Excellence (NICE), recommends a threshold of UK£20,000-£30,000 per QALY gained. NICE also now applies a threshold of £100,000 per QALY gained for rare conditions and highly specialised technologies. The Institute for Clinical and Economic Review in the US applies a $100,000-$150,000 per QALY gained threshold. The threshold of €50,000 is also applied in many European countries.

Overview of Studies

In total, 181 articles were included for data extraction. Of these,132 (73%) related to cost-effectiveness, 14 (8%) to financial toxicity, and 35 (19%) to patient preferences.

Economic Evaluation

Prevention and early detection

Breast and ovarian cancer

The review identified 40 (31%) cost-effectiveness studies that focused on prevention and early detection of cancer, of those, the largest proportion (n=20; 50%) focused on breast and ovarian cancer. Genomic testing as a screening and prevention strategy was shown to be highly cost-effective across several testing strategies and international contexts. One of two strategies were generally applied: (A) universal population screening, whereby an entire population was screened from a certain age or (B) high-risk screening where patients newly diagnosed with breast or ovarian cancer were tested, and those who were positive for specific variants had their first (+/- second) degree relatives tested. In both strategies, those who were carriers of specific alleles had preventative strategies offered to them or were given access to additional regular screening e.g., mammography. It is important to note that there were variations in the approach taken for each study. The cost-effectiveness of population based testing approaches was shown to be dominant,[536-538] namely more effective and less costly, or cost-effective[538-554] compared to no screening or standard screening in 19 out of the 20 articles included. A study by Mital et al. (2022)[555], considered the cost-effectiveness of multiple screening strategies compared to no screening. It showed that a strategy of using polygenic risk scores (PRS) to avoid unnecessary screening in low-risk individuals was cost-effective compared to no screening. However, this strategy was also shown to be less cost-effective compared to a screening strategy using clinical history and Artificial Intelligence (AI) to prioritise screening for high-risk individuals.[555] The study by Manchanda et al. (2020)[545] considered the

cost-effectiveness of population-based testing compared to family-history based screening in the UK, USA, Netherlands (High-income), China, Brazil (middle income), and India (lower-middle income), and found that it was cost-effective in all countries except India, due to a lower decision-making willingness-to-pay (WTP) threshold per unit of outcome.

Colorectal and Endometrial cancer (Lynch syndrome)

The review identified 15 articles (38%) that considered the cost-effectiveness of screening strategies for the prevention and early detection of colorectal cancer (CRC), endometrial cancer, or a combination of both. Strategies for identifying CRC are likely to be cost-effective, however the results were slightly less clear compared to breast and ovarian cancer. Population screening was analysed in 6 studies, and it was shown to be dominant,[556] namely more effective and less costly, or cost-effective[557-560] compared to no screening or standard screening practice. A population-based screening study by Pereira et al. (2019)[561] found that polymorphism genotyping from blood samples in Portuguese adults over 40 compared to no testing was not cost-effective. Threshold analysis found that for the testing strategy to be cost-effective the population risk would need to be increased fivefold. The article advised that as their genetic test was modelled to capture variations only in the COX-2/PGE_2 pathway genes that future research should work on defining gene profiles as single-gene approaches are unlikely to be cost-effective.[562]

Multi-cancer testing

The review identified 4 articles (10%) that analysed the cost-effectiveness of genomic testing for multiple cancers (where multiple cancers was defined as ≥3), 3 pertained to adult and 1 pertained to paediatric populations. Hackshaw et al. (2021)[563] estimated the impact of the addition of a multi-cancer early detection (MCED) test to current practice screening to the population of adults aged 50-79. Results indicated that this led to a decreased (-2,176 GBP 2019) marginal cost per true cancer case detected in the UK and a slightly increased ($7,060, USD 2019) cost per marginal case detected in the US. Davidson et al. (2023)[564] considered the impact of offering reflexive testing to all patients referred to a Familial Cancer Centre (FCC) in Australia. The article considered the option for WGS as the first test rather than targeted gene or gene panel testing for specific genetic alterations. The article found that first-line NGS increased the diagnostic yield of actionable variants detected from 3.5% to 37.2% with a marginal cost per actionable variant detected of $8,744 (AUD, 2020).[564] Unfortunately, there is no accepted WTP threshold per actionable variant detected and neither of these articles presented health related outcomes or QALYs, so it is not possible to ascertain whether either intervention should be considered cost-effective. Taffazoli et al. (2022)[565] conducted a cost-benefit analysis (CBA) to evaluate the net benefit of a multi-cancer early detection test (MCED) for US adults aged 50-79, it was shown that the MCED decreased costs on average by $5,421 (USD 2021) per patient and increased QALYs by 0.13 in the screening program.[565]

Yeh et al. (2021)[566] investigated the impact of universal newborn genetic screening using targeted next generation sequencing (tNGS) for paediatric cancer predisposition syndrome in the US. The model predicted that under usual care in the cohort of 3.7million newborns, 1,803 would develop malignancy before the age 20 years. Using the tNGS strategy 13.4% of newborns were identified at risk, resulting in a 7.8% decrease in cancer death by the age of 20 across the entire cohort.[566] The incremental cost-effectiveness ratio (ICER) presented was an additional $244,860 per life-year gained (USD 2018), meaning that the intervention is unlikely to be cost-effective; however, the model showed sensitivity to the cost of genetic testing and when costs were reduced to $20 for the panel the ICER decreased to $90,430 per life-year gained (USD 2018).

Prostate cancer

The review identified 1 further article (2.5%) that analysed the cost-effectiveness of early detection and prevention for prostate cancer. Hendrix et al. (2021) [567] considered several different screening strategies that increased intensity for men at high risk and decreased intensity for men at low risk based on the germline genetic test risk score. All strategies were compared to a universal screening strategy. The analysis found that the cost-effectiveness of risk-stratified screening was uncertain and depended on the comparator being considered, it found that risk stratified screening was cost-effective compared with biennial screening starting at 55 years but not compared to when it is started at 45 years. As with all cost-effectiveness analyses, the outcomes are tightly coupled with the context within which it is taking place.

Diagnosis, staging and planning

Only 2 (1.5%) evaluations were found to fit within the diagnosis, staging and planning point of the cancer care continuum. In this review when diagnosis was used to stratify patients for treatment or guide treatment decisions it was considered under the treatment point on the continuum.

A study by Pastorino et al. (2020),[568] found that although universal testing for Lynch syndrome was cost-effective in individuals presenting with colorectal cancer, compared to no testing, it was not cost-effective when compared to age-targeted strategies. A study by Hao et al (2021) [569] found that per Lynch syndrome case identified, immunohistochemistry staining was less costly than germline or molecular sequencing, however this result is unclear, as health benefits and downstream costs were not captured, and although molecular and germline sequencing were more expensive per case identified they did capture more cases in total.

A further 6 articles considered the cost-effectiveness of reflex testing strategies, in which cases of CRC or endometrial cancer underwent genetic testing, and family members received genetic testing upon receiving positive results. All 5 articles found genetic testing to be cost-effective compared to no testing.[570-574] However the study by Stinton et al. (2021) [572] found that while germline testing was cost-effective, it was dominated by immunohistochemistry followed by methylation, which was on average more effective and less expensive. A further study by Snowsill et al. (2020) [575] considered the cost-effectiveness of a number of reflex testing approaches for women diagnosed with endometrial cancer in the UK. The authors found that the 'Manchester approach' of a four-MMR protein immunohistochemistry, followed by MLH1 testing if positive, and then NGS was the most cost-effective approach with an incremental cost-effectiveness ration (ICER) of £4,767 (GBP 2016/17) per quality-adjusted life-year (QALY) compared to a reference case of no testing.[575] QALYs are a composite measure of quality and quantity of life used to support standardised prioritisation decisions. Genetic testing for colorectal cancer is likely to be cost-effective when applied at the population level and applied reflexively, but more research considering optimal strategies for testing within specific contexts may be beneficial.

Balentine et al. (2018) [576] considered the cost-effectiveness of lobectomy vs genetic testing for patients in the US with thyroid nodules. It was demonstrated that lobectomy dominated genetic testing due to increased cost of surveillance.[576] It is worth noting that authors acknowledged uncertainty in their estimates due to utilities applied, for example the post thyroidectomy utility used in the model was 0.99,[576] which is likely to be a high estimate, particularly in the initial period.

Hornberger et al (2018) [577] evaluated the cost-effectiveness of a non-invasive molecular pathologic assay for pigmented skin lesions (PLA) compared to visual assessment followed by histopathologic assessment (VAH) for US patients. The PLA approach was shown to dominate the VAH approach with 0.016 additional QALYs gained an average per patient for an incremental per patient cost-saving of $447 (USD 2017).[577]

Treatment

Cost-effectiveness analyses of treatment formed the largest component of the review (n=78; 59%). Generally, there were two types of evaluation: those that considered the cost-effectiveness of targeted medication within a specific sub-population assuming genetic testing to have already taken place, and those that included testing to specify risk or appropriateness for medication where some patients received standard therapy and others with specific variants received targeted therapies.

Lung cancer

Lung cancer was the focus of 22 (28%) of the economic evaluations captured in this review, and the cost-effectiveness of genomic technologies in the treatment of lung cancer was uncertain. Of the 22 evaluations identified, 11 were shown to be dominant (i.e. more effective and less costly) [578] or cost-effective,[579-588] 6 were shown to have uncertain or borderline cost-effectiveness [589-594] and 5 were shown to not be cost-effective.[595-599]

In the evaluations that demonstrated cost-effectiveness two of the studies presented their outcomes in terms of life-years gained. The evaluation by Loubiere et al. (2018) [579] in France found that the knowledge of at least one biomarker led an incremental cost per life-year gained of €13,320 (EUR 2015) compared to no biomarker testing (compared to a WTP threshold of €50,000 per life-year gained).[579] The evaluation by Harvey et al. (2021)[582] found that increasing the proportion of comprehensive genomic profiling for patients with advance non-small cell lung cancer (NSCLC) from 20% to 30% led to an incremental cost per additional life-year gained of $66 (USD 2018) from a US health insurer perspective.[582] Furthermore, Cho et al. (2023)[588] demonstrated that in Spanish context, the use of liquid assay, followed by tissue molecular testing was cost-saving and led to an increase in treatments of sensitising mutations.[588] It is difficult to ascertain the cost-effectiveness from life-years alone in the absence of corresponding thresholds, however it is plausible that given the relatively low cost per life-year gained that these analyses do demonstrate cost-effectiveness, however this is even more uncertain in the Cho et al. (2023)[588] article, as changing treatments may lead to increased medical costs and changes in health outcomes. The remaining articles that demonstrated cost-effectiveness presented their outcomes in QALYs and were thus more reliably interpretable.[600] Majem et al. (2022) [585] conducted a CBA by converting QALYs into a dollar amount using a WTP threshold of €20,000 in Spain, it was found that ALK diagnosis followed by alectinib therapy compared to non-diagnosis of ALK had a cost-benefit ratio of 1.15.

The evaluations that had uncertain cost-effectiveness can be differentiated into three types. The first were those that had structural assumptions that made them unlikely to demonstrate cost-effectiveness,[589,591] for example Aguiar Jnr et al. (2019) [591] demonstrated that compared to standard use chemotherapy that anti-EGFR tyrosine kinase inhibitors (Gefitinib) led to an increased cost per LY of 33,225 BRL (BRL, no reference year), however they assumed a market penetration rate of 100%, which is extremely unlikely. The second were those that presented outcomes that made the interpretation of cost-effectiveness difficult,[592,594] for example Tan et al. (2020)[592] presented results in cost per proportion of patients who ended up on targeted therapy. The third were those that had borderline cost-effectiveness estimates,[590,593] for example Steuten et al (2019) [590] found that the use of multi-gene panel testing was cost-effective in the US context compared to single-gene testing for targeting treatment in advanced NSCLC. The evaluation estimated the incremental cost per life-year gained per patient to be $148,478 (USD 2017). While the authors claimed that the intervention was cost-effective at a WTP threshold of $150,000 per life-year gained,[590] this threshold is high compared to standardly applied WTP thresholds in the US of $50,000 - $100,000 per quality adjusted life-year,[601] and it only had 53% probability of being cost-effective at this high decision-making threshold of cost-effectiveness.[590]

The remaining cost-effectiveness studies found that genomic testing was not cost-effective in the treatment of lung cancer.[595-599] In 4 out of the 5 of these studies, the comparator considered was an alternate type of molecular testing (e.g. EGFR testing) or sequential testing scenario (e.g. RT-PCR for mutation testing followed by ALK testing if negative).[595,596,598,599] This is important, because of the evaluations that found testing guided treatment to be cost-effective, 7 out of 8 had a no testing scenario for the comparator. It is likely that cost-effectiveness in this cohort is dependent on the strategy to which it is being compared. The evaluation by Dong

et al. (2022) [597] compared tumour genomic profiling to guide first line treatment with no tumour profiling in the US context, and found it to be not cost-effective at a WTP threshold of $150,000 (ICER $310,735 USD 2019) [597], the authors claimed that the primary driver of the additional cost was the cost of targeted medication.[597]

The cost-effectiveness of the use of genetic testing to guide treatment in lung cancer remains uncertain, while it is likely that testing is preferable to no testing, further research is required to establish the optimal test and treatment pathway.

Breast cancer

The review identified 12 (15%) cost-effectiveness analyses that considered treatment in breast cancer, of these 11 focused on testing to guide treatment decisions. Genetic testing was found to be dominant [602-605] or cost-effective [606-609] in 8 of the evaluations which considered currently available genomic tests. Furthermore Trentham-Dietz et al. (2018) [610] considered a hypothetical test that could capture with 100% accuracy the prognosis for progression of ductal-carcinoma in situ (DCIS). They demonstrated that this test would dominate standard care in the USA. Wang et al. (2019) [611] presented cost-effectiveness analysis with a more nuanced interpretation, they showed that in the US using a 21-gene assay to direct chemotherapy decisions had an ICER of $62,200 per QALY gained (USD 2015), which is cost-effective against the $100,000 WTP threshold considered; however they argued that the cost-effectiveness was being driven by the high risk group, and the probability of cost-effectiveness in the low-, intermediate- and high-risk groups was 18.4%, 55.1% and 96.6% respectively. They further argued that in clinical practice the majority of patients are in the low-risk group and therefore, cost-effectiveness is uncertain. Finally, an evaluation by DeJongh et a. (2022) [612] testing-guided treatment led to a cost saving of €26,667,347 to the Dutch healthcare system, and 1,364 fewer adverse events,[612] adverse events were the only health event captured, so cost-effectiveness is uncertain.

Two studies by Ibarondo et al. (2020) [606] and Perez Ramirez et al. (2020) [603] presented findings from both the healthcare and societal perspective. In the Ibarondo et al.[606] evaluation, which was conducted in Basque Country, the incremental cost from the healthcare perspective was €1,642 (EUR 2014), when the societal perspective was taken the incremental cost changes to a saving of €849 (EUR 2014). In the Perez Ramirez et al.[548] evaluation, conducted in Spain, when the perspective was changed from healthcare to societal the cost savings increased from €13,867 to €32,678 (EUR, year not assigned), meaning that the dominance increased. The increase in cost-effectiveness in both studies was largely driven by reduced chemotherapy related absenteeism.[603,606]

One study by Sussel et al. (2022) [613] considered the cost-effectiveness of several treatment pathways for HER2 targeted treatment in the neoadjuvant treatment of high-risk HER2+ early-stage breast cancer in the US setting. It was demonstrated that targeted therapy in the neoadjuvant setting, using pertuzumab, trastuzumab, and hyaluronidase-zzxf was likely to be cost-effective, with a 70% probability of being cost-effective at a WTP threshold of $100,000 (USD 2021).

Using genomic testing to guide treatment decisions in breast cancer is highly likely to be cost-effective.

Blood cancers

The review included 8 (10%) articles that considered the cost-effectiveness of the treatment of blood cancers, 5 leukemia, 2 lymphoma and 1 multiple myeloma.

Of the evaluations that considered Leukemia only 1 by Wei et al. (2022) [614] considered the impact of genetic testing to guide treatment and found that in children in China with acute lymphoblastic leukemia that NUD15 genetic testing guided 6-mercaptopurine dosing was less costly and more effective (i.e. dominant) than standard dosing. This was also the only evaluation that considered a paediatric population. The remaining 4 articles compared different combinations of targeted therapy, immunotherapy, and chemotherapy for the management of leukemia. The evaluation by Alrawashdh et al. (2022) compared the cost-effectiveness of 9 first-line therapies in the USA to a base case of venetoclax plus obinutuzumab (targeted therapy), It was shown that the base case dominated the 4 chemoimmunotherapy agents considered [615] 4 other targeted therapies TTs were considered which were shown to improve clinical benefit however were not cost-effective with

ICERs ranging from $501,[236] per QALY gained per patient for acalabrutinib-plus-obinutuzumab to $869,300 per QALY gained (USD 2020) gained for ibrutinib-plus-rituximab. Furthermore Chatterjee et al. (2023)[616] and Slot et al. (2023)[617] demonstrated that venetoclax plus obinutuzumab was a cost-effective in Canada and Denmark respectively. Finally, Munir et al. (2023)[618] considered a comparison of two targeted therapy regimens and found that acalabrutinib monotherapy was cost-effective compared to chlorambucil + obinutuzumab in the USA with a per patient ICER of $81,960 (USD 2021) with only 59% and 73% probability of cost-effectiveness at the $100,000 and $150,000 WTP decision-making thresholds respectively.

Evaluations by Chen et al. (2018)[619] and Regier et al. (2022)[620] considered the cost-effectiveness of molecularly guided treatment to manage diffuse large B-cell lymphoma (DLBCL) from the US and Canadian context respectively compared to standard R-CHOP treatment for all. Chen et al. demonstrated that guided therapy led to an ICER of $15,015 per QALY gained (USD 2016) and was cost-effective at a WTP threshold of $50,000 per QALY.[619] Regier et al. (2022) found similar benefits however, had a lower probability of being cost-effective in the Canadian context with an ICER of $77,806 (CAD 2018) per patient and a 24.3% probability of cost-effectiveness at a WTP threshold of $50,000 per QALY gained and 53.7% probability at the $100,000 threshold.[620] Furthermore, Regier et al., considered molecularly guided therapy to improve second line therapy outcomes, at which point it was demonstrated to be more cost-effective with an ICER of $52,909 per QALY.[620]

Multiple myeloma was the focus of a single evaluation by Gaultney et al. (2018)[621] in which FISH testing risk stratification guided treatment was compared to a no testing uniform treatment strategy. Risk-stratification guided therapy was shown to be dominant in The Netherlands, Germany, the UK, France and Spain.[621]

The cost-effectiveness evidence demonstrated that targeted therapy is likely to be a cost-effective management strategy for leukemia and molecular testing guided therapy is likely to be cost-effective for the management of DLBCL. Furthermore, molecularly guided therapy may be cost-effective for managing multiple myeloma. There is some signal that molecularly guided therapy may be cost-effective in guiding 6-mercaptopurine dosing in children with leukemia.

Melanoma

The review identified 10 evaluations that considered the cost-effectiveness of the treatment of melanoma. All the articles compared immunotherapies and targeted therapies and 8 of them referred specifically to BRAF mutated melanoma,[622-629] with of the remaining evaluations considering high-risk melanoma [630] and the other considering unresectable metastatic melanoma.[631] The cost-effectiveness of these treatments within this cohort is difficult to parse. Two of the articles, Wahler et al. (2020) [628] and Mulder et al. (2021) [630] compared immunotherapy and targeted therapy against routine surveillance in Germany and The Netherlands respectively and found that both were cost-effective. Wahler et al. (2020) demonstrated that the compared to routine surveillance nivolumab had an ICER of €31,300 per QALY gained (calculated during review) and Dabrafenib + trametinib had an ICER of €37,800 per QALY gained (EUR, reference year not presented) compared to routine surveillance.[628] Mulder et al. (2021) demonstrated an ICER of €21,153 per QALY gained for nivolumab, €48,543 per QALY gained for pembrolizumab and €37,520 (EUR 2020) for dabrafenib + trametinib compared to routine surveillance. It is likely that compared to routine surveillance, both immunotherapy and targeted therapies are cost-effective, however, it is unclear which treatment option is the most cost-effective.

In 2 of the evaluations, Wu et al. (2020)[623] and Bensimon et al (2020),[622] conducted in the US, targeted therapy (dabrafenib + trametinib) was dominated by pembrolizumab. In 3 of the articles, Dabrafenib and trametinib was shown to be more effective than immunotherapy, however, it was not cost-effective by standard thresholds.[624-626] In the evaluation by Tarhini et al. (2019)[629] first line treatment with anti-PD 1 inhibitors followed by second-line BRAF and MEK inhibitors was claimed to be cost-effective compared to first line BRAF and MEK inhibitors followed by second line anti-PD1 therapy at a WTP threshold of $150,000 per QALY gained (USD 2016) with a per patient ICER of $79,124 per QALY gained.[629]

The evaluation by Charpentier et al. (2023)[631] considered immunotherapies and targeted therapies together as 'new therapies' and found them to be cost-effective compared to chemotherapies in France at a WTP

threshold of €100,000 per LY gained with an ICER of €90,184.[631] It is difficult to interpret this estimate, as no model was described and pre and post data were used, furthermore a high threshold for WTP per life-year gained was applied. The remaining evaluation considered several treatment strategies that incorporated both immunotherapies and targeted therapies. Kandel et al. (2022)[627] found that the most cost-effective strategy for BRAF mutated melanoma patients inf France was a mono-targeted therapy for first-line treatment followed by anti-PD1 therapy for second line,[627] which dominated all other strategies except anti-PD1 therapy for first line followed by bi-targeted therapy for second line, which compared to mono-targeted therapy for first-line treatment followed by anti-PD1 therapy for second line had an ICER of €180,441 per QALY gained (EUR 2019).

It is likely that immunotherapy or targeted therapies are a cost-effective treatment in the management of BRAF mutated melanoma, however the relative cost-effectiveness is uncertain and further research may be required to identify the most efficient treatment mechanism. It is likely that reducing the cost of targeted therapies would have a substantial impact on cost-effectiveness.

Colorectal cancer (CRC)

The treatment of CRC was the focus of 6 evaluations identified in the review. Of these, 2 evaluations considered the cost-effectiveness of molecular testing guided treatment. Chaudhari et al. (2022)[632] considered a 12-, 18- or 482-gene assay as well as a immunoscore assay followed by adjuvant chemotherapy for high-risk patients or no-chemotherapy for low-risk patients in the USA. They found that the immunoscore assay was the most cost-effective strategy with an ICER of $6,037 per QALY gained (USD 2014) per patient [632] compared to a no testing scenario. Fragoulakis et al. (2023) compared genotyping-guided use of capecitabine, 5-fluorouracil and irinotecan with capecitabine, 5-fluorouracil and irinotecan without genotyping in Italy and estimated the ICER at €13,418 per QALY gained (EUR 2020), which was considered cost-effective against a WTP threshold of €50,000.[633]

A further 2 evaluations demonstrated that molecular testing could improve the cost-effectiveness of medications, but did not consider molecular testing in the costs, which makes results more difficult to interpret. Harty et al. (2018)[634] demonstrated from the results of the PREPARE study that compared to the use of folfori alone, cetuximab + folfori had an ICER of £130,929 per QALY gained in the ITT population, however in the RAS mutation wild-type population this ICER decreased to £44,185 per QALY (GBP, nil reference year).[634] A similar study in Hong Kong by Lee et al. (2021)[635] showed that compared to chemotherapy + bevacizumab that chemotherapy + anti-EGFR mAB had an ICER of $106,847 per QALY gained per patient in the KRAS wild-type population compared to $76,537 (USD, nil reference year) in the pan-RAS WT left-sided tumour subgroup.[635] Furthermore, a study from the US by Jang et al. (2020)[636] compared targeted surgical and endoscopic therapies for patients with different biomarker profiles. It was found that in those with low-risk CRC endoscopic surgery was the dominant strategy, in those with the highest-risk variants laparoscopic surgery was the most effective option however was not considered cost-effective at a WTP threshold of $100,000 per QALY gained (ICER of up to $178,765 per QALY gained per patient (USD 2019)). Importantly genomically guided surgery is likely beneficial, however, as it was not compared to surgery without genomic testing cost-effectiveness is uncertain.

Finally, an evaluation by Kacew et al. (2021)[637] evaluated the use of artificial intelligence in combination next-generation sequencing using several strategies. NGS was used as the reference case and found to be the most effective, however the use of high-sensitivity AI followed by high sensitivity immunochemistry panel led to 2,929 fewer cases on appropriate treatment at a cost saving of 0.31 billion USD (nil reference year).[637] The evaluation presented outcomes in terms of number of patients who received appropriate treatment and had a time horizon of 1 year.

It appears that the use of molecular testing for the treatment of CRC may be cost-effective however there are limited evaluations that consider the comparison of those who do and do not receive genetic testing.

Renal cell carcinoma (RCC)

The review identified 4 evaluations that considered the use of genomic medicine and targeted therapies to treat renal cell carcinoma. Nazha et al. (2018)[638] compared the use of sunitinib and pazopanib (both molecule kinase inhibitors) in patients with metastatic RCC in the Canadian context and found that sunitinib improved outcomes and led to an average per patient ICER of $67,227 per QALY gained (CAD 2017). Zhu et al. (2023)[639] compared the first line use of lenvatinib + pembrolizumab or lenvatinib + everolimus against sunitinib from a US payer perspective.I It was demonstrated that compared to a WTP threshold of $150,000 per QALY gained (USD 2021), lenvatinib + pembrolizumab was cost-effective with an average per patient ICER of $131,656 per QALY but with 59% probability of being cost-effective at this threshold.[639]

The evaluation by Chen et al. (2022)[640] demonstrated that pharmacokinetically guided sunitinib, where sunitinib dose was tailored based on total trough concentration of sunitinib and its metabolites, compared to standard dose sunitinib was dominant in both a Chinese and US context.[640]

Interestingly an evaluation by Redig et al. (2019)[641] compared the cost-effectiveness of targeted therapy in two periods since its introduction (2006-2009 and 2009-2010) to the treatments regularly used prior to the introduction of targeted therapies in Swedish patients with mRCC. It was demonstrated that in the initial period when TT was first introduced the ICER was $78,656 per life-year gained per patient and in the later introduction period this had decreased to $34,132 per life-year gained (USD 2014). This suggests that cost-effectiveness may be improving.

There is signal that targeted therapies in renal cell carcinoma may be cost-effective, however there has been limited health economic analysis in this space and more research may be required.

Tumour agnostic treatments

The review identified 4 evaluations that considered the cost-effectiveness of treatments that were tumour agnostic, 2 of the evaluations considered NTRK testing. Huygens et al. (2023)[642] compared NTRK gene fusion testing for all patients with locally advanced or metastatic cancer, those who were NTRK positive received entrectinib, those who were NTRK mutation negative received usual care, this was compared to everyone receiving usual care from a societal perspective in the Netherlands. It was demonstrated that the NTRK testing strategy increased per patient QALYs by only 0.0043 and it was not considered cost-effective with an average per patient ICER of €169,957 per QALY gained (EUR 2020).[642] This was consistent with Vellekoop et al. (2023)[643] where it was demonstrated that the cost-effectiveness of NTRK testing strategies all had a negative NMB in England, Hungary and The Netherlands compared to a no testing scenario.[643]

Frangoulakis et al. (2019)[644] considered the cost-effectiveness of cancer treated with Fluoropyrimidines in two separate groups in Italy, those with and without DPYD gene mutations. The analysis showed that when the groups were compared health outcomes were better and costs were lower in those without DPYD gene mutation.[644] This may indicate the benefit of DPYD testing prior to chemotherapy, however this evaluation did not model a treatment decision, is only compared costs and outcomes in two groups. Finally, Weymann et al. (2022)[645] demonstrated in cost consequence analysis that in research participants who have had comprehensive genomic sequencing in Canada, the average annual hospital cost was $5,203 (CAD 2015) more than in the standard of care group, and there were no significant difference in outcomes.[645]

The cost-effectiveness evidence for tumour agnostic and multi tumour testing is limited, however it appears to demonstrate that treatment in this group is likely to not be cost-effective. More research may be required.

Prostate cancer

The review identified 3 evaluations that considered the cost-effectiveness of the management of prostate cancer. Two of the trials considered the cost-effectiveness of targeted therapy + androgen deprivation therapy (ADT) to ADT alone. Parmar et al. (2021)[646] demonstrated that apalutamide + ADT led to an ICER of $164,700 (CAD 2020) which exceeded WTP of $100,000 and was therefore not cost-effective in patients with metastatic castration-sensitive prostate cancer in Canada.[646] Barbier et al. (2022)[647] demonstrated that ADT + abiraterone had an ICER of €29,596 per QALY gained (EUR 2021) compared to ADT alone in patients with metastatic hormone-sensitive prostate cancer in Switzerland and was therefore cost-effective at a WTP threshold of €70,400 per QALY.[647]

Su et al. (2020)[648] demonstrated that cost-effectiveness of targeted therapy compared to standard of care treatment changed depending on the genomic population in which it is being considered. It was demonstrated that in US patients with a mutation of 1 of 3 genes BRCA1, BRCA2 and ATM the average per patient ICER was $116,903 per QALY gained, however when the population as expanded to include patients with a mutation in 1 of 15 genes BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L, Olaparib was shown to dominate standard of care therapy for patients with metastatic castration-resistant prostate cancer.[648] This analysis however did not include the cost of testing for patients who did not receive Olaparib, so is only indicative that genomic testing as a strategy for these patients may be cost-effective.

Gastrointestinal cancers

An evaluation by Banerjee al. (2020)[649] considered the cost-effectiveness of targeted gene testing directed first line imatinib followed by sunitinib compared to empirical imatinib in patients with metastatic gastrointestinal stromal tumours in the US and estimated an ICER of $92,100 per QALY gained (USD 2019), which was considered to be cost-effective with 70% probability of cost-effectiveness at the WTP threshold of $100,000 per QALY gained.[649]

Liu et al. (2022)[650] conducted a network meta-analysis and cost-effectiveness analysis of first-line immunotherapy and targeted therapy options for patients with unresectable hepatocellular carcinoma in China. It was demonstrated Sintilimab plus a bevacizumab biosimilar had the greatest impact on overall survival and camrelizumab plus rivoceranib increased progression free survival and both fell under WTP threshold of $37,653 per QALY gained (USD, year not specified) with respective ICERs of $34,959 and $22,848 perQALY gained.[650]

Krepline et al. (2021)[651] considered the cost-effectiveness of universal germline testing to guide treatment compared to selective testing based on family history in US patients with pancreatic cancer. It was demonstrated that universal testing had an incremental cost of $121,942 per life-year gained (USD 2019), and further reported that the selective testing strategy was more cost-effective at a WTP threshold of $100,000 with 59% probability of cost-effectiveness.

Gynaecological cancers

An analysis by Liu et al. (2022)[652] considered the cost-effectives of combination immunotherapy plus targeted therapy (pembrolizumab plus Lenvatinib) and chemotherapy (doxorubicin) in first-line therapy of US patients with mismatch repair-proficient advanced endometrial cancer. It was shown that combination immunotherapy and targeted therapy led to an average per patient ICER of $110,401 per QALY gained (USD 2021) which was demonstrated to be cost-effective at a WTP threshold of $150,000 with 79% probability of cost-effetiveness.[652]

Orellana et al. (2023)[653] compared the cost-effectiveness of tumour molecular testing TMT) vs no testing and 4 other different test and treat scenarios, for US patients with stage III endometrial cancer. TMT was shown to be cost saving compared to no TMT scenario, however, was shown to be not cost-effective compared to an alternative testing scenario (mismatch repair immunohistochemistry alone), against which it was not considered cost-effective at a WTP threshold of $100,000 per QALY with an ICER of $182,797 per QALY gained (USD, no year specified).

Richardson et al. (2023)[654] considered 3 potential treatment sequences of chemotherapy, immunotherapy and targeted therapy compared to prior standard of care chemotherapy and targeted therapy in US patients with advanced metastatic and recurrent cervical cancer. It was demonstrated that the combination sequences improved outcomes, however their costs were prohibitively expensive with all 3 sequences having a negative net monetary benefit compared to standard of care at a WTP threshold of $150,000 per QALY gained (USD 2022).[654]

Brain and central nervous system cancers

An evaluation by Rios et al. (2022)[655] considered the cost-effectiveness of molecular testing to determine the BRAF mutation status of paediatric patients with low-grade glioma in Canada compared to no molecular testing. It was demonstrated that even when no radiation benefit was applied that patients who received testing had benefits in terms of QALYs gained and a reduction in costs, therefore molecular testing was dominant.[655]

Ranjan et al. (2023)[656] considered the costs and outcomes of cancer stem cell assay-guided chemotherapy in US patients with unmethylated MGMT-promoter recurrent glioblastoma, they demonstrated that when patients received therapy recommended by the test they had an average life-year gain of 0.55 with an average cost of $99,221 (USD, nil year specified), when they received therapy not recommended by the test they had an average llife-year loss of 0.275 and an average cost of $57,725.[656] The article did not present an incremental analysis.

Endocrine cancers

An evaluation by Tessler et al. (2023)[657] analysed the cost-effectiveness of a molecular testing guided preventative surgery for US patients with low-risk differentiated thyroid cancer, compared to standard of care where patient undergo hemi-thyroidectomy based on clinical criteria. The results demonstrated that the risk-stratified surgery led to an increase of 1.7 QALYs per patient with an incremental cost of $327 per patient (USD, nil reference year), with an ICER of $190 per QALY gained, which was considered cost-effective at a WTP threshold of $50,000 per QALY with 100% probability of being cost-effective.

Managing refractory, relapsed or progressive disease

There were fewer evaluations identified that looked exclusively at managing refractory, relapse of progressive disease (n=9). Articles in this review that considered treatment algorithms that had multiple lines, were considered under the treatment category.

The review identified 3 articles that considered breast cancer. Saito et al. (2019)[658] examined the cost-effectiveness of BRCA1/2 mutation profiling to guide olaparib treatment in Japanese patients with HER2- or triple negative metastatic breast cancer who had previously undergone chemotherapy, compared to standard of care chemotherapy. BRCA testing guided therapy was shown to not be cost-effective at a WTP threshold of JPY 10,000,000 per QALY gained with an ICER of JPY 14,677,259 per QALY (JPY 2018).[658] Ren et al. (2023)[659] considered the comparison of two different targeted therapies, Neratinib plus capecitabine (N + C) vs lapatinib plus capecitabine (L + C) for the third-line management of Chinese patients with HER2+ metastatic breast cancer. It was shown that in 83% of simulations that N + C was dominant. Finally, Pennarun et al. (2022)[660] evaluated the cost-effectiveness of a recurrence index for distant recurrence in women with hormone receptor-positive and HER2-negative early-stage breast cancer in Taiwan using TI-DR genomic testing compared to a scenario of no testing. It was demonstrated that early treatment based on recurrence disease score was cost effective at a WTP threshold of 790,000 NTD (NTD, year not stated), with an ICER of 173,842 NTD per QALY gained compared to no testing.[660]

Renal cell carcinoma was the focus of 2 of the evaluations identified, Chandler et al. (2023)[661] and Meng et al. (2018)[662] considered the cost-effectiveness of cabozantinib vs everolimus, axitinib and nivolumab in subsequent line RCC in Japan and England respectively. In both evaluations cabozantinib was shown to be favourable in terms of health outcomes and dominated nivolumab, however in Japan it was demonstrated to be cost effective at a WTP threshold of 7.5M JPY per QALY (JPY, year not indicated) with an ICER of 5,375,559 JPY per QALY compared with evorlimus and 2,223,138 JPY per QALY vs axitinib,[661] in England it was demonstrated to

borderline cost-effective at a WTP threshold of £100,000 with an ICER of £98,967 per QALY compared with axitinib and not cost-effective with an ICER £137,450 per QALY compared with everolimus.

Cholangiocarcinoma was evaluated by 2 analyses identified in the review; both considered the cost-effectiveness of pemigatinib as a second line therapy. Chen et al. (2023)[663] considered pemigatinib vs 2 comparators, (A) oxaliplatin, L-folinic acid and fuorouracil or (B) leucovorin and fuorouracil in patients with advanced intrahepatic cholangiocarcinoma with fibroblast growth factor receptor 2 fusions in Taiwan. It was demonstrated to have an ICER of 5,814,700 NTD per QALY gained (NTD 2022) and 5,380,241 NTD per QALY for comparator A and B respectively and was therefore considered to be not cost-effective at a WTP of 3 x GDP per capita 2,928,570 NTD per QALY. Chueh et al. (2023)[664] compared pemigatinib monotherapy and mFOLFOX regimens based on FGFR2 status vs fluorouracil chemotherapy in patients advanced intrahepatic cholangiocarcinoma in Taiwan. It was shown to not be cost-effective at a WTP threshold of 2,889,684 NTD per QALY with an ICER of 3,411,098 NTD per QALY[664] and athe 47% probability of being cost-effective.[664]

An evaluation by Pandya et al. (2021) 665 compared the cost-effective of gilternitib with standard care (SC) and with best supportive palliative care (BSC) in patients with relapsed/refractory FLT3mut+ acute myeloid leukemia in the US. It was demonstrated that gilternitib was cost-effective at a WTP threshold of $150,000 (USD 2019) in 91% and 99.8% of PSA iterations vs SC and BSC respectively (ICERs of $115,192 per QALY and $107,435 per QALY).

Leung et al. (2022)[666] evaluated the incremental cost-effectiveness of 3 immune checkpoint inhibitors (pembrolizumab, nivolumab and atezolizumab) relative to docatexel for the second line treatment of patients with NSCLC in Taiwan. At a WTP threshold of 2,221,930 NTD per QALY all three therapies were shown to be cost effective with ICERs for pembrolizumab of 416,102 NTD per QALY, nivolumab 1,572,912 NTD per QALY and atezolizumab 1,580,469 NTD per QALY.

Palliative care and end of life

The review only identified 2 economic evaluation that considered the use of genomic technologies for end-of-life care in patients with cancer. Ree et al. (2022)[667] considered precision cancer medicine (PCM) genomic molecularly targeted matched off-label therapies for multiple cancer types in Norway, the analysis from the MetAction study was compared to matched cohort of BSC from published RCTs in similar populations. It was demonstrated that compared to the controls from the RECOURSE and CORRECT trials the ICER per for PCM therapy was €126,262 per QALY and €109,593 (EUR 2020) which exceeded the WTP threshold of €56,389 per QALY gained. Edwards et al. (2018)[668] considered axitinib, cabozantinib, everolimus, nivolumab, sunitinib compared to best supportive care for patients with previously treated RCC in the UK. It was demonstrated that everolimus was cost-effective at a WTP threshold of £50,000 per QALY with an ICER of £45,000 per QALY compared to BSC, the remaining treatments were unlikely to be cost-effective.[668] The article also noted that the WTP threshold of £50,000 is sometimes considered appropriate in the UK for end-of life care.[668]

There are limited economic evaluations that consider the management of relapsed and refractory and end-of-life care, so cost-effectiveness is uncertain, however it appears that medications are unlikely to be cost-effective.

The limits of cost-effectiveness in progressed disease and end of life care demonstrate the difficulties with cost-effectiveness in general in these populations, generally medications are expensive and there is a limit on the quality and quality of life that can be made.

Table 3 shows the cost-effectiveness of all aspects of the cancer care continuum for common cancer types.

Financial Toxicity

There was limited evidence that met the inclusion criteria of capturing financial toxicity, genomic technology, and cancer specifically. The review identified 14 articles that met the inclusion criteria. There was no standard methodology applied in the articles and this heterogeneity leads to some uncertainty in conclusions.

Of the articles included 2 sought the perspective of clinicians.[669,670] Lin et al (2022)[669] reported that in a US context the out-of-pocked (OOP) cost for NGS panel test for hereditary cancer was relatively low and patients paid less than $250 per test,[669] however they found that when genetic testing required genetic counselling, the cost of genetic counselling was unlikely to be covered by an insurance company and this was shown to be a barrier to patients receiving genetic tests.[669] Weldon et al. (2022)[670] conducted a survey of genetic counsellors in the US and found that the counsellors perceived that only 16% of their patients would be unwilling to pay for genetic testing and therefore believed that OOP costs were not a major barrier to hereditary cancer testing.[670]

Gogebakan et al. (2021)[671] analysed the impact of novel systemic therapies on first year out-of-pocket (OOP) costs for US patients with melanoma, over two time periods, 2004 to 2010 and 2011 to 2015. It was demonstrated that the general trend for first-year OOP costs per person was decreasing from $9,248 in 2004 to $8,487 (USD, no specified year) in 2011.[671] While the trend is decreasing, this still represents a substantial burden for a patient to share. Ngan et al (2022)[672] considered the cost of breast cancer treatment from the perspective of the patient in Vietnam, it was reported that in Vietnam targeted therapy (Trastuzumab and Pertuzumab) is optional and based on perceived need and patient ability to pay, and was reportedly 10 times more expensive than total cost of diagnosis and all other treatments,[672] the estimated OOP cost per patient of targeted therapies was estimated to be 558.6 million (VND 2020).[672] Shen et al. (2022)[673] presented the OOP costs borne for EGFR mutation testing and targeted treatment by US patients with metastatic lung adenocarcinoma. It was demonstrated that EGFR testing cost patients $1,767 (USD 2016), a month of erlotinib cost $594 and a month of aftinb cost $605.[673] Importantly there was still equal numbers of patients receiving targeted therapy with an without EGFR testing demonstrating the testing was being underutilised.[674]

The review identified 4 further articles that used different quantitative techniques to estimate the impacts of cost and incomes on uptake of novel therapies. Grant et al. (2023)[675] considered the income of patients who were and were not offered OOP funded genomic testing in the US. It was demonstrated that the likelihood of being offered an OOP funded genomic test increased by 42% for each increasing quintile of the income distribution.[675] Meaning that those with lower incomes were less likely to be offered, or to conduct an OOP genomic test.[675] Caram et al. (2020)[676] considered the adherence and OOP costs for patients prescribed oral targeted therapies in the US using a retrospective cohort. It was found that the median cost for targeted therapies was $706 (range $0 – 3505) (USD nil reference year) and the multivariable adjusted adherence rate for those with and without low-income subsidy was 69% and 76% respectively (P<0.01),[676] indicating that having lower income may be a driver of targeted therapy non-adherence.[676] Wang et al. (2022)[677] developed a logistic regression analysis to analyse the predictors of high OOP costs for individuals with CRC in China. It was demonstrated that compared to no testing genetic testing had an odds-ratio of 1.26 (95%CI 1.1-1.45), and compared to not using targeted treatment, targeted treatment had an OR of 2.12 (95%CI 1.79 - 2.51)[677] meaning that those who had genetic testing had a 26% increase in their odds of having high medical expenses and those that had targeted treatment had a 112% increase in their odds of having high medical expenses.[677] Finally Li et al. (2018)[678] utilised an natural experiment from the Medicare system in the US to demonstrate that elderly patients with metastatic RCC who did not receive subsidies for targeted therapies and therefore had considerable OOP costs, were 51% less likely to initiate targeted therapy than patients who did receive subsidies.[678]

The remaining articles were all patient surveys that directly considered patient perceptions of financial toxicity. Sasaki et al. (2022)[679] considered the influence of financial burden on whether patients had chosen to discontinue or change cancer treatment. The proportion of patients on targeted therapy did not appear to be a driver of why patients discontinued treatment, however the analysis appears to only have considered molecular treatments that were insured.[679] Knapp et al. (2022)[680] considered the OOP cost of breast cancer care in Nigeria and the risk of catastrophic health expenditure (CHE) defined as a loss of annual household income of greater than 10% and 25%. The mean OOP cost for diagnosis and management was $2,049 (USD 2019), and only one patient included in this analysis underwent targeted therapy, with a cost of $6,568.[680] Based on the mean value 85.7% or participants experienced a 25% CHE, therefore it is likely that more widespread use of targeted therapy would increase financial toxicity. Liu et al. (2022)[681] Considered the financial toxicity of females with breast cancer in China, it was demonstrated that a history of targeted therapy increased likelihood of financial

toxicity.[681] Keilson et al. (2022)[682] considered the financial toxicity in clinical trials and personalised medicine for patients with cholangiocarcinoma, it was demonstrated that Comprehensive Score for Financial Toxicity (COST) questionnaire scores were lower for patients not receiving targeted therapy compared to those who were (24.67 vs 28.89, p=0.01) respectively, p=0.05),[682] indicating that targeted therapies may be driving financial toxicity. Finally, Jiang et al. (2022)[683] demonstrated that receiving targeted therapy was a significant predictor of financial toxicity in patients with nasopharyngeal carcinoma undergoing radiotherapy in China.[683]

There were no papers that explicitly modelled the financial toxicity of genomic technologies in the management of cancer in Australia. Financial toxicity is highly context dependent, it is conditional on factors such as national and private insurance, local patient incomes, government benefits, sick leave and many more.[533] The evidence identified in this review, perhaps obviously, indicates that targeted therapy is likely to be associated with significant OOP costs when not reimbursed, and when this cost is absorbed by patients it is highly likely to drive financial toxicity. Although the cost of genetic testing is unlikely to be a driver of financial toxicity on its own,[669,670] when it leads to targeted therapy it may be.[678,681]

Patient and public preferences for genomic technology in the management of cancer

The review identified 35 articles that considered the preferences of patients, patient families and the public regarding the use of genomic testing and targeted therapy in the management of cancer. The articles fit roughly into three categories, preferences for genetic testing (n=19; 54%), return of results (n=9; 26%) and for treatment (n=7; 20%).

Preferences for genetic testing

The public was surveyed in 8 (22%) of the articles identified in the review and were asked their preferences for genetic screening for early detection. It was demonstrated across the 7 studies that the public preferences for genetic testing were most influenced by the cost of testing,[684-689] testing accuracy,[689-691] actionability of results,[686,689-691] type of sample taken (i.e. buccal vs blood),[684] the ability to test for multiple cancers,[689,690] the type of clinician taking the sample,[684,685] and the privacy of genetic information.[689] As an example, Venning et al. (2022)[689] demonstrated that the Australian public had a marginal willingness to pay (mWTP) of $176 (AUD) to move from a test with 60% accuracy to 90% accuracy, and a mWTP of $145 to move to a multicancer test from a pancreatic cancer test.[689] WTP in other contexts was lower, Guo et al. (2022)[687] reported that 64% of Women in Southeast Texas would pay up to $25 (USD) for genetic testing and 29% would pay in the range of $25-$500,[687] and Hardy et al. (2022)[686] demonstrated that in an Ashkenazi Jewish population in the US, the interest in BRCA1/2 carrier screening was high, however 60.2% of participants reported that they would not be willing to spend over $50 (USD) on testing.[686]

Preferences of parents, clinicians and general community members were considered in 2 (6%) articles that evaluated preferences for genomic medicine in paediatrics. Abreu Lourenco et al. (2021)[692] considered the choice to participate (parents/community members) or recommend (clinicians) genomic medicine for children with cancer in Australia. In all groups, the most highly weighted components were survival benefit and quality of life, however interestingly there were differences between clinicians and the community preferences, for example clinicians were more responsive to survival outcomes and parents were more heavily influenced by quality of life.[692] McCarthy et al. (2020)[693] using qualitative methods highlighted factors that were important to parents regarding genetic testing, effects on function, actionability, cost, whether biopsy was needed, and recommendation of clinician.[692]

Patient preferences for genetic testing were explored in 9 (26%) analyses. The factors that patients considered most important were actionability of results,[694-699] cost,[697,698] wait time,[698,699] number of tests required,[698,699] privacy of results [696] and impact of findings on relatives.[700] It is difficult to compare WTP estimates across these articles as they pertain to different cancers and occur in different contexts. Weyman et al. (2018)[699] demonstrated that American adults with CRC would be willing to pay between $400 and $1,541 (USD) for massively parallel

sequencing with high yield and fast turnaround times. Mayer et al. (2019)[700] demonstrated that in a population of German men who had received radical prostatectomy, 81% of patients would pay up to €500 for a test and 19% would pay between €500-€2,000.[700] Butow et al. (2022)[695] demonstrated that Australian cancer patients and first-degree relatives would be willing to spend $1,000 for a test that returned actionable results on 20% and 30% of tests respectively.[695] Clasan et al. (2022)[696] showed that German cancer patients would be willing to pay an additional €1,081 to improve clinical outcomes from 60% to 80%.[696] Davidson et al. (2019)[697] demonstrated that women with epithelial ovarian cancer in the US were willing to pay an additional $150 (USD) for 5% increase in the ability of a test to capture deleterious mutations.[564] Two articles conducted WTP for patients in lower-middle income countries. Aizuddin et al. (2021)[559] demonstrated that only 22.3% of patients with cancer and their family members in Myanmar were willing to undergo genetic testing if there were any OOP costs.[559] Adejumo et al. (2023),[701] found that 71.1% proportion of Nigerian cancer patients and their first-degree relatives were willing to pay for cancer genetic testing, and 53.3% were willing to pay between N10,000 and N30,000 (convert).[701]

Finally, Veldwijk et al. (2019)[702] compared the preferences for genetic testing in CRC of patients (those who had attended clinical appointment after confirmed faecal blood) and the general public (Dutch adults aged 55-65). It was shown that those in the patient population valued survival higher than those in the general population, whereas the general population, who still valued overall survival the highest, was more concerned with frequency of colonoscopies and risk of being genetically disposed than the patient population.[702]

Preferences for return of results

The review identified 9 (26%) articles that investigated the preferences of patients and the public for return of results from genetic testing, 5 of the articles considered the preferences of patients for what could be considered incidental findings. Godino et al. (2021)[703] surveyed Italian patients undergoing genetic testing for cancer regarding preferences for receiving results that were not pertinent to their cancer diagnosis. It was found that 70% of participants wished to receive incidental findings.[703] The main factors for wanting results were awareness of risk, inform relatives and the hope for preventative measures in the future,[703] the primary driver for not wanting results was fear of negative impact on QoL.[703] Radecki Breitkopf et al. (2018)[704] considered the return of genetic results to first-degree relatives if they were to die, 94% of participants were in favour of sharing their genetic testing results with their relatives.[704] Mighton et al. (2021)[705] considered patient preferences for being recontacted with updated genomic results in Canada. Participants were strongly in favour of receiving future results and showed a WTP of $1,075 (CAD) to be recontacted by a provider, patients also placed weight on costs and accuracy of results.[705] Shickh [706] et al. (2023) demonstrated that among adult cancer patients in Canada, 97% were interested in receiving secondary findings from genomic tests, with the largest proportion interested in actionable results.[706] Best et al. (2022)[707] showed that 93% of cancer patients and 91% of first-degree relatives surveyed in Australia, believed that people would be interested in receiving clinically actionable germline results, however they noted the importance of balancing potential risks with benefits.[707]

The impact of psychological profile and clinical history on desire for return of results was considered in 3 (9%) of the articles. It was demonstrated that low tolerance of uncertainty,[708] cancer recurrence worry,[709] genetic risk worry,[709,710] health information orientation,[709,710] future orientation,[709] and knowledge of genomic sequencing [709,710] were all predictive of a preference for actionable findings. Furthermore, parental status was predictive of a preference towards carrier information.[710] Clinical history associated with a preference for actionable findings were prior genetic testing, BRCA mutation status and family history of breast cancer.[709]

Finally, Matsen et al. (2019) [711] surveyed young breast cancer patients in the US and demonstrated that when receiving genomic results most patients preferred a collaborative (45%) or active (45%) role in the decision making process, whereby they were a key decision maker in their care going forward.[711]

Preferences for targeted treatment

The review identified 7 (20%) articles that considered patient preferences for targeted therapies in the management of cancer. The factors that were considered the most important when considering

the treatment of cancer were, treatment effectiveness,[712-717] side-effects,[712-718] cost,[713,715,718] and drug administration method.[712,714,717,718]

Avoiding side-effects is obviously preferable to not and the included articles considered trade-offs between multiple side-effects. Mansfield et al. (2019)[714] demonstrated that melanoma patients had a far greater preference for avoiding fever, colitis and hormone gland problems than avoiding extreme sun sensitivity.[714] Stenehjem et al. (2019)[713] showed that patients and providers were willing to pay $50 and $55 (USD) respectively to reduce the probability of immunotargeted therapy-related side effects by 1%.[713] Interestingly, Wong et al. (2020)[718] showed that in patients with mCRC avoiding a severe skin rash was weighted more highly than change from 8 to 16 weeks progression free survival.[718] Nazari et al. (2021) showed that in Iranian women with breast cancer patients, it was most preferable to avoid neutropenia (preference weight 1.214), followed by stomatosis (0.727 then arthralgia (0.672).[715] Mansfield et al. (2023) [716] surveyed women with advanced breast cancer in Japan, the US and UK and it was found that the most highly weighted preferences for side effects were a 15% risk reduction for heart failure , followed by 15% risk reduction for serious lung damage and infections, avoiding the possibility of severe liver function problems, avoiding severe nausea and vomiting, and avoiding severe diarrhea.[716] Finally, in Amaador et al. (2023)[717] demonstrated that patients in the Netherlands with Waldenström's Macroglobulinemia would only accept a treatment with a side-effect of atrial fibrillation of neuropathy if it meant a 7.2% increase in treatment efficacy.[717]

Unfortunately, only one of the DCEs presented considered the willingness-to-pay for targeted therapies. Stenehjam et al. (2019)[713] used the results of their DCE combined with efficacy and safety results from literature to ascertain a WTP for combination nivolumab plus ipilimumab as well as BRAF/MEK inhibitors for US patients with melanoma, and clinicians. For combination nivolumab plus ipilimumab patients and providers were estimated to be willing to pay a monthly cost of $2,357 and $2,484 respectively, for BRAF/MEK inhibitors the WTP estimates were $1,648 and $1,350 respectively.

Discussion

This systematic review aimed to understand and synthesise the state of the literature regarding genomic medicine, cancer, and health economics. The review identified 181 articles with the majority (n=132; 73%) focusing on cost-effectiveness, and the remaining articles focusing on patient preferences (n=35; 19%) and financial toxicity (n=14; 8%).

Optimal decision making in healthcare is a process and not a destination, it requires careful consideration of the decision context, the current state of care, capacity of the system and the current state of the health and economics literature.[719] This review demonstrates the cost-effectiveness of a variety of genomic technologies throughout the cancer care continuum.

Prevention and early detection

This review demonstrated that the use of genomic testing was highly likely to be cost-effective for the prevention and early detection of cancer for breast and ovarian cancer and for CRC and endometrial cancer (Lynch syndrome). For breast and ovarian cancer 19 out of the 20 articles identified in the review demonstrated genomic testing to be dominant,[536-538] namely more effective and less costly, or cost-effective [538-554] compared to no screening or standard screening. A similar pattern was shown for CRC where genetic screening was shown to be highly likely to be cost effective [556-560] compared to no screening. For multi-cancer detection the picture

is slightly less clear, and the testing strategies considered were more heterogenous than for the other cancers. Prostate cancer was considered in 1 article and again the cost-effectiveness was unclear and depended on the comparator chosen.[567]

Diagnosis, Staging and Planning

For diagnosis, staging and planning of cancer there was insufficient evidence (2 articles) to offer clarity on the cost-effectiveness of genomic testing, 1 evaluation demonstrated that genomic testing was dominated by surgical resection in thyroid cancer [576] and the other demonstrated that molecular testing dominated standard care in the diagnosis of melanoma.[577] Furthermore, reflexive genomic testing, where testing was automatically performed on colorectal patients meeting clinical and histological criteria, was shown to be cost-effective compared to no testing or standard testing in all the studies included.[570-574]

Treatment

When considering treatment two main types of articles were identified, those that used genomic testing to guide treatments and therefore included the cost of testing, and those that considered the cost-effectiveness of a drug in a specific molecular population, and therefore did not include the cost of testing. For the treatment of lung cancer, the use of genomic testing to guide therapy was shown to be dominant (i.e. more effective and less costly)[578] or cost-effective,[579-588] in 11 articles, uncertain in 6,[589-594] and not cost-effective in 5.[595-599] Those that were uncertain were largely due to structural issues and difficulty with interpretability of findings, for those that were not cost-effective, 4 out of 5 compared genomic testing to a different genetic test, or genetic test sequence. Those that were cost-effective 5 out of 6 were compared to a no-testing or standard testing scenario. Meaning that gnomically guided treatment for CRC is highly likely to be cost-effective compared to no testing, however the ideal testing strategy may require more research.

When considering treatment for breast cancer the use of genomic testing to guide therapy was likely to be cost-effective, of the 11 articles that considered molecular testing-guided treatment 9 were shown to be dominant [602-605,611] or cost-effective.[606-609] One article also demonstrated that neoadjuvant pertuzumab, trastuzumab, and hyaluronidase-zzxf was likely to be cost-effective for the management of HER2+ breast cancer in a US setting compared to standard care.[613] However, this was a single study caution should be exercised in drawing conclusions.

For blood cancers, targeted therapy is likely to be cost-effective for the management of leukemia [615-618] and molecular testing-guided therapy is likely to be cost-effective for the management of DLBCL.[619,620] It is less certain but, molecular guided treatment may be cost-effective for the management of myeloma,[621] and molecularly guided therapy appears to not be cost-effective in guiding 6-mercaptopurine dosing in children with leukemia.[614]

The use of targerted therapy in melanoma is likely to be cost-effective compared to no therapy,[622-629] however, the relative cost-effectiveness of targetted agents is uncertain, and therfore more research may be required.

For patients with CRC there is some signal that molecular testing-guided treatment may be cost-effective compared to a no testing scenario,[632,633] however some of the evidence compared the cost-effectiveness of two therapies in two different populations, and did not model a treatment decision.[634,635] Therefore, more research that considered the cost of patients going through testing before receiving specific therapies is necessary to form stronger conclusions.

For renal cell carcinoma and for tumour agnostic therapies there was insufficient health economic evidence to form broad conclusions. There was some signal that the use of targeted therapy in RCC may be cost-effective [638-641] and there was some signal that the use of targeted therapy in tumour agnostic patients was not cost-effective.[642-645]

For the remaining cancer types identified in this review there was limited evidence to form conclusions regarding the cost-effectiveness, however there was some signal that genomic medicine may be cost-effective for the treatment of prostate,[646-648] gastrointestinal,[649-651] brain and central nervous system [655,656] and endocrine [657] cancers. There is also some signal that genomic medicine may not be cost-effective for the treatment gynaecological [652-654] cancer.

Refractory, relapsed or progressive disease

The use of genomic medicine managing refractory, relapsed or progressive disease and end of life care, was demonstrated in this review to be highly likely not to be cost effective.[658-668] In general, treatment tends to become less cost-effective later in life, due to the limited potential health gains and medical care required.[720,721] It is therefore perhaps unsurprising that genomic technologies were not shown to be cost-effective for patients with limited life remaining. In order to make appropriate resource allocation decision for end of life, it may be necessary to consider higher cost-effectiveness thresholds.[721]

See Table 6 for a summary of evidence regarding cost-effectiveness of genomic testing relative to the Cancer Care Continuum.

Financial toxicity

The review only identified 14 articles that met the inclusion criteria for financial toxicity, genomics, and cancer and no articles explicitly considered the impact of genomic technologies on financial toxicity in Australia. However, the review paints a reasonably complete picture of the relative impact of genomic medicine on financial toxicity in cancer. Financial toxicity has been established to be an issue in the management of cancer generally.[533] It appears that from a clinician perspective that costs of hereditary genomic testing may not be a barrier to uptake.[669,670] However, when it comes to the treatment of cancer, in systems where targeted therapies are not reimbursed, their inclusion in treatment can substantially increase OOP costs for patients.[671-674] When OOP costs were demonstrated to be higher, or incomes were demonstrated to be lower, the proportion of patients on targeted therapies was shown to decrease.[675-678] Finally, when patients were surveyed in environments where targeted therapies were not fully reimbursed, the use of targeted therapy was demonstrated to increase financial toxicity.[680-683]

The findings of the financial toxicity articles were consistent with patient and public preferences for genomic medicine that were identified in this review. The review identified 35 articles that considered patients preferences, they included preferences for genetic testing (n=19; 54%), return of results (n=9; 26%) and for treatment (n=7; 20%). Across all studies the cost of the test [684-689,697,698] or treatment [713,715,718] was demonstrated to be of high importance. For both the public and patients the actionability of the results [686,689-691,694-699] and the privacy of results [689,696] were demonstrated to be important drivers. For the public there was additional emphasis on accuracy of the tests,[689-691] the type of sample taken (i.e. buccal vs blood),[684] the ability to test for multiple cancers,[689,690] and the type of clinician taking the sample.[684,685] For patients there was additional emphasis on wait time,[698,699] number of tests required,[698,699] and the impact of findings on relatives.[700] For patients considering targeted therapies the most important consideration was treatment effectiveness,[712-717] side-effects,[712-718] cost,[713,715,718] and drug administration method.[712,714,717,718] In terms of side-effects these were independent to the type of cancer and the type of treatment.

Incidental Findings

Finally, 9 articles considered patient preferences for the return of incidental findings, i.e., not related to their primary diagnosis. It was demonstrated that patients were in favour of receiving incidental results.[703-707] The primary driver of wishing to receive incidental findings were awareness of risk, inform relatives and the hope for preventative measures in the future.[703] Finally, 3 articles considered the psychological characteristics that were predictive of wanting the return of results low tolerance of uncertainty,[708] cancer recurrence worry,[709] genetic risk worry,[709,710] health information orientation,[709,710] future orientation,[709] and knowledge of genomic sequencing [709,710] were predictive of a preference for actionable findings and parental status was predictive of a preference for carrier information.[710] Clinical history associated a preference for actionable findings were prior genetic testing, BRCA mutation status and family history of breast cancer.[709]

In conclusion this systematic review demonstrates that genomic medicine is likely to be cost-effective across several cancer types and points on the cancer care continuum. Although there is limited evidence for OOP costs and financial toxicity of genomic medicine, it is likely that if it is not reimbursed it will very likely increase financial toxicity for patients with cancer and their families. Patients and the general population generally have a preference for testing that is low cost, accurate, actionable and private, and patients have a preference for treatment that is efficacious, cheap and low demand.

Research and Practice Gaps

- While there is a substantial amount of cost-effectiveness literature for certain cancers, there is limited amount for others. Future research should focus on understanding the cost-effectiveness of screening and treating other cancers, particularly those with preventable end-stage disease.
- Little is known about the relative impact of genomic medicine on financial toxicity. Studies that directly compare the financial toxicity of cancer care that involves genomic medicine and cancer care may be beneficial.
- There is significant need for a quality assessment of the economic evaluations included in the review. Due to the magnitude of the review and short time-frame this was not possible. Model inputs and analytical assumptions can often significantly impact on cost-effectiveness results. For example, the uptake of genomic testing may not be perfect and assumptions on the level of uptake may drive cost-effectiveness and budget impact.
- Population testing also has non-marginal impacts to the government budget and may be limited due to systemic limitations with capacity and other financial (or non-financial) constraints. Further research is needed to understand and incorporate system capacity and constraints into economic evaluations and consider equity issues.

Finally, the economic value of genomics in cancer control depends on patient preferences and priorities. Further work is needed to understand how preferences for genomics in cancer control may drive economic value and how preferences can be used to optimise the application of genomics for cancer control as well as the societal health and economic outcomes. While no studies incorporated directly patient preferences in economic evaluations, more studies are needed to explicitly link aspects of genomics in cancer control included in this review (i.e., cost-effectiveness, preferences, financial toxicity).

Table 6: Evidence of cost-effectiveness for common cancers relative to the Cancer Care Continuum

	Prevention and Early detection	Diagnosis, staging and planning	Treatment	Managing refractory, relapse of progressive disease	Palliative care
Breast cancer					
Lung cancer					
CRC					
Multicancer					
Prostate cancer					
Thyroid cancer					
Melanoma					
Blood cancer					
RCC					
Gastrointestinal cancer					
Gynaecological cancer					
Brain and central nervous system cancer					

Highly likely to be cost effective	
Some evidence of cost-effectiveness	
Insufficient evidence	
Some evidence of lack of cost-effectiveness	
Highly likely not-cost-effective	

References

1. Australian Institute of Health and Welfare. Cancer data in Australia. In:2023.
2. Cancer Australia. Facts and Figures: Cancer statistics in Australia. In:2023.
3. Australian Institute of Health and Welfare. Cancer in Australia 2021. In:2021.
4. Richards S. *Genet Med*. 2015;17(5):405-424.
5. Landrum MJ. *Hum Mutat*. 2018;39(11):1623-1630.
6. Esterling L. *JCO Precis Oncol*. 2020;4.
7. Rahner N. *Dtsch Arztebl Int*. 2008;105(41):706-714.
8. da Costa ESCS. *BMC Med Genomics*. 2020;13(1):21.
9. Mainor CB. *Curr Breast Cancer Rep*. 2020;12(2):66-74.
10. Ponti G. *Crit Rev Clin Lab Sci*. 2023:1-11.
11. Edwards P. *Frontline Gastroenterol*. 2022;13(e1):e80-e87.
12. Gallon R. *Cancers (Basel)*. 2021;13(3).
13. Consul N. *AJR Am J Roentgenol*. 2021;216(1):252-263.
14. Frebourg T. *Eur J Hum Genet*. 2020;28(10):1379-1386.
15. Barnett M. *Clin Genet*. 2022;101(2):161-182.
16. Pieterman CRC. *Clin Endocrinol (Oxf)*. 2022;97(4):409-423.
17. Al-Salameh A. *Nat Rev Endocrinol*. 2021;17(4):207-224.
18. Hu X. *Annals of translational medicine*. 2021;9(11):944.
19. McDonnell JE. *Intern Med J*. 2019;49(8):954-961.
20. Karaconji T. *Asia Pac J Ophthalmol (Phila)*. 2019;8(1):62-72.
21. Tamura R. *Int J Mol Sci*. 2021;22(11).
22. Coy S. *Acta Neuropathol*. 2020;139(4):643-665.
23. Schraepen C. *Br J Neurosurg*. 2022;36(2):171-174.
24. Pennington Z. Schwannomatosis: Review of Diagnosis and Management. In: Guedes F, Zager EL, Garozzo D, Rasulic L, Socolovsky M, eds. *Diagnostic Assessment and Treatment of Peripheral Nerve Tumors*. .2021:371-382.
25. Muth A. *J Intern Med*. 2019;285(2):187-204.
26. Favier J. *Nat Rev Endocrinol*. 2015;11(2):101-111.
27. Lenders JWM. *J Hypertens*. 2020;38(8):1443-1456.
28. Mucci LA. *JAMA*. 2016;315(1):68-76.
29. Yanes T. *Hum Mol Genet*. 2020;29(R2):R165-R176.
30. Uffelmann E. *Scientific reports*. 2023;13(1):4219.
31. Yanes T. *Breast Cancer Res*. 2020;22(1):21.
32. Wand H. *Nature*. 2021;591(7849):211-219.
33. Van Horebeek L. *Trends Genet*. 2019;35(12):935-947.
34. Li MM. *J Mol Diagn*. 2017;19(1):4-23.
35. Dang DK. *J Clin Invest*. 2022;132(12).
36. Nurk S. *Science*. 2022;376(6588):44-53.
37. Teer JK. *Hum Mol Genet*. 2010;19(R2):R145-151.
38. Cooper DN. The nature and mechanisms of human gene mutation. In: Scriver C, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*. 7th ed. New York: McGraw-Hill; 1995:259-291.

39. Tilemis FN. *Genes* (Basel). 2023;14(7).
40. Singh AK. *BMC Med Genomics*. 2021;14(1):214.
41. Kang YJ. *Scientific reports*. 2022;12(1):20495.
42. Fusco MJ. *JAMA Oncol*. 2021;7(2):316.
43. Van Hoeck A. *BMC Cancer*. 2019;19(1):457.
44. COSMIC. Mutational Signatures (v3.3 - June 2022). 2022; https://cancer.sanger.ac.uk/signatures/.
45. Hong M. *J Hematol Oncol*. 2020;13(1):166.
46. Baudrin LG. *Front Oncol*. 2018;8:621.
47. Narrandes S. *J Cancer*. 2018;9(13):2249-2265.
48. Cancer Genome Atlas Research N. *Nat Genet*. 2013;45(10):1113-1120.
49. Consortium ITP-CAoWG. *Nature*. 2020;578(7793):82-93.
50. Casolino R. *CA Cancer J Clin*. 2024.
51. Suehnholz SP. *Cancer discovery*. 2023.
52. Khosroyani HM. *Drugs*. 2023;83(1):55-73.
53. Solomon BJ. *N Engl J Med*. 2014;371(23):2167-2177.
54. Merino M. *Pediatr Blood Cancer*. 2022;69(8):e29602.
55. Motzer RJ. *Oncologist*. 2017;22(1):41-52.
56. Demetri GD. *Lancet*. 2006;368(9544):1329-1338.
57. Raymond E. *N Engl J Med*. 2011;364(6):501-513.
58. Huynh H. *Mol Cancer Ther*. 2015;14(5):1224-1235.
59. Ryan CW. *Lancet*. 2023;402(10407):1043-1051.
60. Raphael J. *Target Oncol*. 2020;15(6):723-732.
61. Andre F. *N Engl J Med*. 2019;380(20):1929-1940.
62. Stransky N. *Nat Commun*. 2014;5:4846.
63. Marcus L. *Clin Cancer Res*. 2021;27(4):928-932.
64. Robert C. *N Engl J Med*. 2015;372(1):30-39.
65. Chakravarty D. *J Clin Oncol*. 2022;40(11):1231-1258.
66. Robson M. *N Engl J Med*. 2017;377(6):523-533.
67. Golan T. *N Engl J Med*. 2019;381(4):317-327.
68. Moore K. *N Engl J Med*. 2018;379(26):2495-2505.
69. Wong SF. *Clin Ther*. 2005;27(6):684-694.
70. Lievre A. *Cancer Res*. 2006;66(8):3992-3995.
71. Hodi FS. *Lancet Oncol*. 2016;17(11):1558-1568.
72. Ayers M. *Clin Cancer Res*. 2019;25(5):1564-1573.
73. Marcus L. *Clin Cancer Res*. 2019;25(13):3753-3758.
74. Garutti M. *Genes (Basel)*. 2023;14(5).
75. Ercoskun P. *Mol Syndromol*. 2022;13(2):123-131.
76. Horak P. *Cancer discovery*. 2021;11(11):2780-2795.
77. Mandelker D. *JAMA*. 2017;318(9):825-835.
78. Stadler ZK. *J Clin Oncol*. 2021;39(24):2698-2709.
79. Ceyhan-Birsoy O. *Genome Med*. 2022;14(1):92.
80. Schrader KA. *JAMA* Oncol. 2016;2(1):104-111.

81. Jahn A. *Ann Oncol*. 2022;33(11):1186-1199.
82. Tung N. *NPJ Precis Oncol*. 2023;7(1):76.
83. Aoyagi Y. *PLoS ONE*. 2022;17(3).
84. Bertucci F. *Genome Med*. 2021;13(1):87.
85. Cobain EF. *Jama Oncology*. 2021;7(4):525-533.
86. Huang KL. *Cell*. 2018;173(2):355-370 e314.
87. Lincoln SE. *JAMA Netw Open*. 2020;3(10):e2019452.
88. Ladekarl M. *Acta Oncol*. 2023;62(3):261-271.
89. Koboldt DC. *Genome Med*. 2020;12(1):91.
90. Liu YL. *J Natl Compr Canc Netw*. 2021;19(7):871-878.
91. Sharo AG. *Genome Med*. 2023;15(1):51.
92. Manickam K. *JAMA Netw Open*. 2018;1(5):e182140.
93. Rowley SM. *Genet Med*. 2019;21(4):913-922.
94. Jackson L. *EClinicalMedicine*. 2023;64:102159.
95. Lacaze PA. *Med J Aust*. 2022;216(6):278-280.
96. Buchanan AH. *Genet Med*. 2020;22(11):1874-1882.
97. Ludwig KK. *Am J Surg*. 2016;212(4):660-669.
98. Li X. *Clin Cancer Res*. 2016;22(15):3971-3981.
99. Collins IM. *Med J Aust*. 2013;199(10):680-683.
100. Lindor NM. *JAMA*. 2006;296(12):1507-1517.
101. Talaulikar D. *J Clin Pathol*. 2008;61(1):119-123.
102. Teuwen LA. *Diagnostics (Basel)*. 2023;13(9).
103. Huey RW. *J Natl Cancer Inst*. 2023;115(8):994-997.
104. Best MC. *BMC Cancer*. 2019;19(1):753.
105. Davies G. *Transl Oncol*. 2020;13(9):100799.
106. Shirdarreh M. *Oncologist*. 2021;26(8):e1359-e1371.
107. Butow P. *JAMA Netw Open*. 2020;3(5):e204721.
108. Butow PN. *Patient Educ Couns*. 2022;105(7):2206-2216.
109. Behel V. *JCO Glob Oncol*. 2022;8:e2200030.
110. Hirshfield KM. *Oncologist*. 2016;21(11):1315-1325.
111. Schwaederle M. *Oncologist*. 2014;19(6):631-636.
112. McGowan ML. *BMC Med Genomics*. 2016;9(1):71.
113. Azzollini J. *Front Oncol*. 2022;12:857515.
114. Ozdogan M. *BMC Med Genomics*. 2021;14(1):105.
115. Harbers L. *Front Oncol*. 2021;11:700568.
116. Bale TA. *J Mol Diagn*. 2021;23(6):742-752.
117. Tsimberidou AM. *J Hematol Oncol*. 2019;12(1):145.
118. Hoefflin R. *JCO Precis Oncol*. 2018;2.
119. Groisberg R. *Mol Cancer Ther*. 2018;17(7):1595-1601.
120. Jiao XD. *Front Oncol*. 2023;13:860711.
121. Kato S. *Oncologist*. 2018;23(2):171-178.
122. Flaherty KT. *J Clin Oncol*. 2020;38(33):3883-3894.

123. Kato S. *Nat Commun*. 2020;11(1):4965.
124. Kondo T. *Cancer Sci*. 2021;112(1):296-304.
125. Repetto M. *Eur J Cancer*. 2023;183:79-89.
126. Tredan O. *Ann Oncol*. 2019;30(5):757-765.
127. Slosberg ED. *Oncotarget*. 2018;9(30):21383-21395.
128. Massard C. *Cancer discovery*. 2017;7(6):586-595.
129. Zehir A. *Nat Med*. 2017;23(6):703-713.
130. Cordova-Delgado M. *J Pers Med*. 2022;12(2).
131. Brown LJ. *Cancers (Basel)*. 2022;14(3).
132. Kim A. *Epigenomes*. 2023;7(1).
133. Gounder MM. *Nat Commun*. 2022;13(1):3406.
134. Zhang L. *Oral Oncol*. 2020;110:104943.
135. Cao D. *Oncoimmunology*. 2019;8(9):e1629258.
136. Pishvaian MJ. *Lancet Oncol*. 2020;21(4):508-518.
137. Sicklick JK. *Nat Med*. 2019;25(5):744-750.
138. Le Tourneau C. *Lancet Oncol*. 2015;16(13):1324-1334.
139. Miller RW. *JCO Precis Oncol*. 2022;6:e2100524.
140. Scheiter A. *Br J Cancer*. 2023;128(6):1134-1147.
141. Green MF. *JCO Precis Oncol*. 2021;5.
142. Jiagge E. *Cancer Cell*. 2023;41(11):1963-1971 e1963.
143. Weigelt B. *Cancer discovery*. 2023;13(11):2356-2369.
144. Gambardella V. *Br J Cancer*. 2021;125(9):1261-1269.
145. O'Haire S. *Target Oncol*. 2022;17(5):539-548.
146. Lin FPY. *Developmental Therapeutics—Molecularly Targeted Agents and Tumor Biology*. 2022.
147. Rodon J. *Nat Med*. 2019;25(5):751-758.
148. Garralda E. *Mol Oncol*. 2019;13(3):549-557.
149. Luchini C. *Trends Cancer*. 2020;6(9):738-744.
150. Wong M. *Nat Med*. 2020;26(11):1742-1753.
151. Koelsche C. *Genes Chromosomes Cancer*. 2022;61(6):346-355.
152. Samstein RM. *Nat Genet*. 2019;51(2):202-206.
153. Goodman AM. *Mol Cancer Ther*. 2017;16(11):2598-2608.
154. Klempner SJ. *Oncologist*. 2020;25(1):e147-e159.
155. How JA. *Cancers (Basel)*. 2021;13(5).
156. Chopra N. *Nat Commun*. 2020;11(1):2662.
157. Ahn MJ. *Hum Genet*. 2012;131(3):365-372.
158. Le DT. *Science*. 2017;357(6349):409-413.
159. Latham A. *J Clin Oncol*. 2019;37(4):286-295.
160. Paska AV. *Biochem Med (Zagreb)*. 2015;25(2):161-176.
161. Bettegowda C. *Sci Transl Med*. 2014;6(224):224ra224.
162. Pairawan S. *Clin Cancer Res*. 2020;26(8):1924-1931.
163. Zill OA. *Clin Cancer Res*. 2018;24(15):3528-3538.
164. Rose Brannon A. *Nat Commun*. 2021;12(1):3770.

165. Odegaard JI. *Clin Cancer Res*. 2018;24(15):3539-3549.
166. Wang M. *Mol Diagn Ther*. 2022;26(3):309-322.
167. Hsiehchen D. *Cancer Biol Ther*. 2021;22(7-9):455-464.
168. Sanz-Garcia E. *Sci Adv*. 2022;8(4):eabi8618.
169. Zhang Y. *Nat Commun*. 2021;12(1):11.
170. Underhill HR. *PLoS Genet*. 2016;12(7):e1006162.
171. Risberg B. *J Mol Diagn*. 2018;20(6):883-892.
172. Hasenleithner SO. *Mol Cancer*. 2022;21(1):81.
173. Laprovitera N. *Cancers (Basel)*. 2021;13(3).
174. Kato S. *Cancer Res*. 2017;77(16):4238-4246.
175. Cai J. *Front Oncol*. 2021;11:751106.
176. Mack PC. *Cancer*. 2020;126(14):3219-3228.
177. Rothwell DG. *Nat Med*. 2019;25(5):738-743.
178. Nakamura Y. *Nat Med*. 2020;26(12):1859-1864.
179. Clark TA. *J Mol Diagn*. 2018;20(5):686-702.
180. Park S. *Cancer*. 2021;127(16):3019-3028.
181. Radovich M. *JAMA Oncol*. 2020;6(9):1410-1415.
182. Kim ST. *Nat Med*. 2018;24(9):1449-1458.
183. Li J. *J Transl Med*. 2020;18(1):293.
184. Bayle A. *Mol Cancer*. 2023;22(1):176.
185. Lipsyc-Sharf M. *J Clin Oncol*. 2022;40(22):2408-2419.
186. Willis J. *Clin Cancer Res*. 2019;25(23):7035-7045.
187. Razavi P. *Nat Med*. 2019;25(12):1928-1937.
188. Wang Z. *JAMA Oncol*. 2019;5(5):696-702.
189. He J. *J Immunother Cancer*. 2023;11(11).
190. Gandara DR. *Nat Med*. 2018;24(9):1441-1448.
191. Nassar FJ. *Clin Epigenetics*. 2021;13(1):111.
192. Sanchez NS. *JCO Precis Oncol*. 2019;3.
193. Zhang M. *J Mol Med (Berl)*. 2021;99(9):1311-1321.
194. Strickler JH. *Cancer discovery*. 2018;8(2):164-173.
195. Campos-Carrillo A. *Pharmacol Ther*. 2020;207:107458.
196. Velders M. *Clin Biochem*. 2014;47(6):471-474.
197. Steensma DP. *Blood*. 2015;126(1):9-16.
198. Klein EA. *Ann Oncol*. 2021;32(9):1167-1177.
199. Turnbull C. *Lancet*. 2024.
200. Adi-Wauran E. *Eur J Hum Genet*. 2023.
201. Shickh S. *Oncologist*. 2022;27(5):e393-e401.
202. Kim H. *Cancer Res Treat*. 2023;55(2):351-366.
203. National Association of Testing Authorities. Genetic Technologies Limited. 2024; https://nata.com.au/accredited-organisation/genetype-pty-ltd-20432-24460/?highlight=Polygenic. Accessed 23.01.24.
204. Cust AE. *J Invest Dermatol*. 2018;138(12):2617-2624.
205. Li-Sheng Chen S. *J Urol*. 2019;201(3):486-495.

206. Seibert TM. *BMJ*. 2018;360:j5757.
207. Yousefi PD. *Nat Rev Genet*. 2022;23(6):369-383.
208. Kresovich JK. *Mol Oncol*. 2022;16(1):42-53.
209. Gallagher S. *JAMA Netw Open*. 2020;3(7):e208501.
210. Kuchenbaecker KB. *J Natl Cancer Inst*. 2017;109(7).
211. Shieh Y. *NPJ Precis Oncol*. 2023;7(1):42.
212. Klein RJ. *NPJ Precis Oncol*. 2022;6(1):25.
213. Song SH. *Scientific reports*. 2023;13(1):798.
214. Miteva-Marcheva NN. *Biomark Res*. 2020;8:32.
215. Al-Mahayri ZN. *Frontiers in pharmacology*. 2020;11:445.
216. Al-Mahayri ZN. *Expert Opin Drug Metab Toxicol*. 2021;17(7):785-801.
217. White C. *Med J Aust*. 2022;217(10):510-513.
218. Crews KR. *Clin Pharmacol Ther*. 2021;110(4):888-896.
219. Australian Clinical Labs. Pharmacogenetics in Oncology. 2023; https://www.clinicallabs.com.au/cancer-services/pharmacogenetics/.
220. Shchelkunova GA. *Acta Naturae*. 2017;9(4):4-12.
221. Sayour EJ. *Nat Rev Clin Oncol*. 2024.
222. Crews DW. *Front Oncol*. 2021;11:626463.
223. Janes ME. *Bioeng Transl Med*. 2024;9(1):e10588.
224. Crusz SM. *Womens Health (Lond)*. 2020;16:1745506520961709.
225. Yang A. *J Biomed Sci*. 2016;23(1):75.
226. Bruni L, Albero G, Serrano B, Mena M, Collado JJ, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. ICO/IARC nformation Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in Australia. Summary Report 10 March 2023. [Accessed 26 July 2024]
227. Patel C. *Euro Surveill*. 2018;23(41).
228. Akinyemiju T. *JAMA Oncol*. 2017;3(12):1683-1691.
229. Fan T. *Signal Transduct Target Ther*. 2023;8(1):450.
230. Abd-Aziz N. *J Oncol*. 2022;2022:9749363.
231. Patel SP. *J Immunother Cancer*. 2021;9(8).
232. Pandya A. *Med Oncol*. 2023;40(7):200.
233. Disis MLN. *JAMA Oncol*. 2023;9(1):71-78.
234. Liau LM. *JAMA Oncol*. 2023;9(1):112-121.
235. Pérez-Baños A. *British Journal of Cancer*. 2023;129(4):572-585.
236. Frank MJ. *J Exp Med*. 2020;217(9).
237. Liu J. *Hum Vaccin*. 2009;5(2):70-78.
238. Soliman H. *Nat Med*. 2023;29(2):450-457.
239. Yao R. *Hum Vaccin Immunother*. 2024;20(1):2307187.
240. Weber JS. *Lancet*. 2024;403(10427):632-644.
241. Rojas LA. *Nature*. 2023;618(7963):144-150.
242. Alexandrov LB. *Nature*. 2013;500(7463):415-421.
243. *Nature Medicine*. 2023;29(6):1287-1287.
244. Fernandez-Medarde A. *Genes Cancer*. 2011;2(3):344-358.
245. Krishnan T. *Mol Diagn Ther*. 2022;26(1):39-49.

246. Zhang Y. *Expert Rev Vaccines*. 2020;19(2):163-173.
247. Pant S. *Nat Med*. 2024;30(2):531-542.
248. https://rcdfoundation.org/brain-cancer-vaccine-project/
249. https://www.wehi.edu.au/news/funding-boost-advances-research-cancer-vaccine/
250. NHS Cancer Vaccine Launch Pad. www.england.nhs.uk/cancer/nhs-cancer-vaccine-launch-pad
251. Lall K. *BMC Cancer*. 2019;19(1):557.
252. Sud A. *NPJ Precis Oncol*. 2021;5(1):40.
253. Carr DJ. *JAMA internal medicine*. 2023;183(10):1144-1151.
254. Mavaddat N. *Am J Hum Genet*. 2019;104(1):21-34.
255. Hainsworth JD. *J Clin Oncol*. 2018;36(6):536-542.
256. Tutt ANJ. *N Engl J Med*. 2021;384(25):2394-2405.
257. Villani A. *Nat Cancer*. 2023;4(2):203-221.
258. Newman S. *Cancer discovery*. 2021;11(12):3008-3027.
259. Cancer Council Queensland. 2023.
260. Australian Institute of Health and Welfare. Cancer in adolescents and young adults in Australia 2023. In:2023.
261. Sweet-Cordero EA. *Science*. 2019;363(6432):1170-1175.
262. Australian Institute of Health and Welfare. Australia's Children. https://www.aihw.gov.au/reports/children-youth/australias-children/contents/health/infant-child-deaths. Accessed 19.01.24.
263. eviQ. Paediatric syndromes with cancer predisposition. In: NSW CI, ed2023.
264. eviQ. RB1 (non-retinoblastoma cancer risk) – risk management. In: NSW CI, ed2023.
265. eviQ. APC (Familial adenomatous polyposis) – risk management. In: NSW CI, ed2023.
266. eviQ. VHL (von Hippel-Lindau) disease – risk management. In:2023.
267. eviQ. Facts for people and families with Multiple Endocrine Neoplasia type 1. In: NSW CI, ed2023.
268. eviQ. Facts for people and families with Multiple Endocrine Neoplasia type 2. In: NSW CI, ed2023.
269. Kratz CP. *Clin Cancer Res*. 2017;23(11):e38-e45.
270. eviQ. TP53 (Li-Fraumeni) – risk management (child). In: NSW CI, ed: NSW Government; 2023.
271. eviQ. NF1 (Neurofibromatosis type 1) – risk management. In: NSW CI, ed2023.
272. Vears DF. *Twin Res Hum Genet*. 2020;23(3):184-189.
273. Villani A. *Lancet Oncol*. 2016;17(9):1295-1305.
274. Villani A. *Lancet Oncol*. 2011;12(6):559-567.
275. Ruijs MWG. *JAMA Oncol*. 2017;3(12):1733-1734.
276. Ballinger ML. *JAMA Oncol*. 2017;3(12):1634-1639.
277. Warby M. *Clin Genet*. 2019;95(1):140-150.
278. Vuocolo B. *J Genet Couns*. 2024.
279. Stump TK. *J Genet Couns*. 2018;27(4):955-967.
280. Alderfer MA. *J Genet Couns*. 2017;26(5):1106-1115.
281. Grobner SN. *Nature*. 2018;555(7696):321-327.
282. Zhang J. *N Engl J Med*. 2015;373(24):2336-2346.
283. Berlanga P. *Cancer discovery*. 2022;12(5):1266-1281.
284. van Tilburg CM. *Cancer discovery*. 2021;11(11):2764-2779.
285. Langenberg KPS. *Eur J Cancer*. 2022;175:311-325.

286. Harttrampf AC. *Clin Cancer Res*. 2017;23(20):6101-6112.
287. Wadensten E. *JCO Precis Oncol*. 2023;7:e2300039.
288. Akhavanfard S. *Nat Commun*. 2020;11(1):2206.
289. Gong J. *J Cancer Res Clin Oncol*. 2023;149(11):8791-8802.
290. McGill BC. *Cancer*. 2023;129(22):3620-3632.
291. Izquierdo E. *Oncotarget*. 2017;8(67):112036-112050.
292. George SL. *Eur J Cancer*. 2019;121:224-235.
293. Brozou T. *Eur J Pediatr*. 2018;177(1):53-60.
294. Howard Sharp KM. *JCO Precis Oncol*. 2020;4:202-211.
295. Oberg JA. *JCO Precis Oncol*. 2018;2.
296. Sedig LK. *Pediatr Blood Cancer*. 2022;69(9):e29791.
297. Ma X. *Nature*. 2018;555(7696):371-376.
298. Mirzaei G. *Mutat Res*. 2022;824:111773.
299. Vladoiu MC. *Nature*. 2019;572(7767):67-73.
300. Comitani F. *Nat Med*. 2023;29(3):656-666.
301. Church AJ. *Nat Med*. 2022;28(8):1581-1589.
302. Summers RJ. *JCO Precis Oncol*. 2022;6:e2100451.
303. Parsons DW. *J Clin Oncol*. 2022;40(20):2224-2234.
304. Rusch M. *Nat Commun*. 2018;9(1):3962.
305. Rose M. *Front Cell Dev Biol*. 2020;8:564601.
306. Trotman J. *Br J Cancer*. 2022;127(1):137-144.
307. Pincez T. *Pediatr Blood Cancer*. 2017;64(6).
308. Lau LMS. *Preprint*. 2024.
309. Doculara L. *Front Mol Biosci*. 2022;9:885597.
310. Stankunaite R. *Eur J Cancer*. 2022;162:209-220.
311. Christodoulou E. *NPJ Precis Oncol*. 2023;7(1):21.
312. Plon SE. *Annu Rev Genomics Hum Genet*. 2019;20:241-263.
313. Song N. *Cancer Epidemiol Biomarkers Prev*. 2021;30(11):2096-2104.
314. Im C. *J Clin Oncol*. 2023;41(27):4381-4393.
315. Ballinger ML. *Lancet Oncol*. 2016;17(9):1261-1271.
316. Im C. *Cancer Res*. 2022;82(16):2940-2950.
317. Young MA. *Twin Res Hum Genet*. 2023;26(1):40-48.
318. Wand H. *J Genet Couns*. 2023;32(3):558-575.
319. Abu-El-Haija A. *Genet Med*. 2023;25(5):100803.
320. Relling MV. *Clin Pharmacol Ther*. 2019;105(5):1095-1105.
321. American Childhood Cancer Organization. Genetics and Anti-Leukemia Therapy: The TMPT Story. 2003; https://www.acco.org/genetics-and-anti-leukemia-therapy-the-tpmt-story/. Accessed 23rd September 2023.
322. Medicare Benefits Schedule. Medicare Benefits Schedule - Item 73327. In: Care DoHaA, ed2023.
323. Sonic Genetics. TPMT and NUDT15 genetic testing. 2023; https://www.sonicgenetics.com.au/our-tests/doctor-resources/tpmt-and-nudt15-genetic-testing/. Accessed 23rd September 2023.
324. Khater F. *JAMA Netw Open*. 2019;2(4):e192906.

325. Liu A. *Hematol Rep*. 2023;15(2):244-255.
326. Grover SA. *Cancer Res*. 2023;83(7):4509.
327. Lee JW. *PLoS ONE*. 2019;14(11):e0224227.
328. DeMarco TA. Practical aspects of delivering hereditary cancer risk counseling. Paper presented at: Seminars in oncology2007.
329. Barlow-Stewart K DK, Fleischer R, Shalhoub C, Williams R. *The NSW Genetic Counselling Workforce: Background Information Paper: an Evidence Check rapid review*. 2015.
330. *Statewide Genetic Health Queensland Service Plan*. 2017.
331. Nisselle A. *J Genet Couns*. 2019;28(2):367-377.
332. McCuaig JM. *Cancers (Basel)*. 2018;10(11).
333. George A. *Scientific reports*. 2016;6:29506.
334. Kentwell M. *Gynecol Oncol*. 2017;145(1):130-136.
335. Buckley L. *Curr Oncol Rep*. 2018;20(10):83.
336. Hegarty J. ES, Jones M.M., Odisigo C., O'Flaherty S.J., Chakraborty S., O'Reilly D., & Saab M.M. *The unmet need in cancer genetic services: conducting an environmental scan of the cancer genetics services in an Irish context underpinned by a mixed methods approach* Report prepared for the Irish Cancer Society, Ireland. 2021 2021.
337. Kansal A. *Genes (Basel)*. 2022;13(10).
338. Pederson HJ. *Breast Cancer Res Treat*. 2018;169(1):43-46.
339. Bednar EM. *Gynecol Oncol*. 2017;146(2):399-404.
340. Bednar EM. *Gynecol Oncol*. 2019;152(2):328-333.
341. Rana HQ. *Gynecol Oncol*. 2021;160(2):457-463.
342. Senter L. *Gynecol Oncol*. 2017;147(1):110-114.
343. Benusiglio PR. *Eur J Med Genet*. 2020;63(12):104098.
344. Bokkers K. *Hered Cancer Clin Pract*. 2022;20(1):33.
345. Bokkers K. *Gynecol Oncol*. 2022;167(1):115-122.
346. Bokkers K. *Fam Cancer*. 2022;21(3):295-304.
347. Colombo N. *J Clin Oncol*. 2018;36(13):1300-1307.
348. Flaum N. Eur *J Hum Genet*. 2020;28(11):1541-1547.
349. Hamilton JG. *Genet Med*. 2021;23(11):2105-2113.
350. Ip E. *Asia Pac J Clin Oncol*. 2022;18(5):e414-e419.
351. McCuaig JM. *Curr Oncol*. 2021;28(2):1459-1471.
352. McLeavy L. *Int J Gynecol Cancer*. 2020;30(2):221-226.
353. McVeigh TP. *Fam Cancer*. 2023;22(2):135-149.
354. Percival N. *Br J Nurs*. 2016;25(12):690-694.
355. Powell CB. *Gynecol Oncol*. 2020;159(1):221-228.
356. Rahman B. *J Med Genet*. 2019;56(3):195-198.
357. Richardson M. *Cancers (Basel)*. 2020;12(2).
358. Rumford M. *Scientific reports*. 2020;10(1):3390.
359. Srinivasa S. *Aust N Z J Obstet Gynaecol*. 2023.
360. Wright S. *J Genet Couns*. 2018;27(6):1459-1472.
361. Ain Q. *Breast*. 2023;67:30-35.
362. Beard C. *Eur J Hum Genet*. 2021;29(5):872-880.

363. Bokkers K. *Ann Surg Oncol*. 2023;30(6):3248-3258.
364. Chai TS. *Fam Cancer*. 2023.
365. Grindedal EM. *Fam Cancer*. 2020;19(2):133-142.
366. Kemp Z. *JAMA Netw Open*. 2019;2(5):e194428.
367. Stromsvik N. *Hered Cancer Clin Pract*. 2022;20(1):6.
368. Scott N. *Br J Nurs*. 2020;29(10):S6-S13.
369. Scheinberg T. *JCO Oncol Pract*. 2021;17(2):e204-e216.
370. Ryan NA. *J Clin Med*. 2020;9(6).
371. Ramsey ML. *Fam Cancer*. 2023;22(1):91-97.
372. Walker EJ. *Oncologist*. 2021;26(11):e1982-e1991.
373. Scheinberg T. *Asia Pac J Clin Oncol*. 2021;17(3):163-177.
374. Vlaming M. *BMC Cancer*. 2022;22(1):1365.
375. O'Shea R. *Front Oncol*. 2023;13:1140135.
376. Hamilton JG. *Hastings Cent Rep*. 2019;49 Suppl 1(Suppl 1):S44-S52.
377. Zigmond AS. *Acta Psychiatr Scand*. 1983;67(6):361-370.
378. Cella D. *Health Psychology*. 2002;21:564-572.
379. Czekalski MA. *JCO Precis Oncol*. 2022;6:e2100409.
380. Madlensky L. *J Genet Couns*. 2017;26(3):361-378.
381. Yanes T. *Eur J Hum Genet*. 2023;31(10):1125-1132.
382. Bensend TA. *J Genet Couns*. 2014;23(1):48-63.
383. Hallowell N. *Fam Cancer*. 2019;18(3):293-301.
384. Lee YQ. *J Genet Couns*. 2022;31(5):1080-1089.
385. Worst BC. *Eur J Cancer*. 2016;65:91-101.
386. Cheng HH. *Prostate*. 2016;76(14):1303-1311.
387. Larson KL. *JCO Precis Oncol*. 2021;5.
388. van der Velden DL. *Ann Oncol*. 2017;28(12):3070-3075.
389. Basse C. *ESMO Open*. 2018;3(3):e000339.
390. Darnell AJ. *Am J Hum Genet*. 2016;98(3):435-441.
391. Schwartz MLB. *Am J Hum Genet*. 2018;103(3):328-337.
392. Willis AM. *Eur J Hum Genet*. 2022;30(3):363-366.
393. Kieke MC. *J Genet Couns*. 2021;30(4):1203-1210.
394. Thomas M. *Dela J Public Health*. 2021;7(5):20-23.
395. Roberts JS. *Cancer Med*. 2019;8(1):227-237.
396. Medendorp NM. *Patient Educ Couns*. 2020;103(9):1692-1708.
397. White S. *Eur J Hum Genet*. 2024;32(1):109-116.
398. White S. *Public Health Genomics*. 2022.
399. Brands J. Development of a National Aboriginal and Torres Strait Islander Cancer Framework: A Shared Process to Guide Effective Policy and Practice. *Int J Environ Res Public Health*. 2018;15(5).
400. Condon J. *Cancer Forum*. 2013;37(1):27-30.
401. Cunningham J. *The Lancet Oncology*. 2008;9(6):585-595.
402. Peng Y. *Cancer Causes Control*. 2021;32(11):1315-1320.
403. Belcher A. *Aust N Z J Public Health*. 2019;43(3):204-206.
404. Bilkey GA. *Frontiers in Public Health*. 2019;7.

405. D'Angelo CS. *Frontiers in Pediatrics*. 2020;8.
406. Easteal S. *The American Journal of Human Genetics*. 2020;107(2):175-182.
407. O'Shea R. *Med J Aust*. 2022;217(11):559-563.
408. Landry LG. *Health Aff (Millwood)*. 2018;37(5):780-785.
409. Popejoy AB. *Nature*. 2016;538(7624):161-164.
410. Popejoy AB. *Hum Mutat*. 2018;39(11):1713-1720.
411. Mills MC. *Communications Biology*. 2019;2(1):9.
412. Dodson M. *J Med Ethics*. 1999;25(2):204.
413. McWhirter R. *Monash Bioethics Review*. 2015;33(2):203-209.
414. McWhirter R. *The American Journal of Bioethics*. 2023;23(6):100-102.
415. McWhirter RE. *Gynecol Oncol*. 2014;133(3):421-426.
416. Tapia KA. *Asian Pac J Cancer Prev*. 2017;18(4):873-884.
417. Samarasinghe SR. *Frontiers in pharmacology*. 2023;14.
418. Fox K. Rewriting Human History and Empowering Indigenous Communities with Genome Editing Tools. Genes. 2020;11(1).
419. Henare KL. *The Lancet Oncology*. 2019;20(6):e327-e335.
420. Dasgupta P. *Frontiers in Oncology*. 2022;12.
421. Callander E. *Asia Pac J Clin Oncol*. 2019;15(6):309-315.
422. Luke J. *Nat Commun*. 2022;13(1):4966.
423. Bernardes CM. *Aust N Z J Public Health*. 2014;38(4):344-348.
424. Dalach P. *International journal for equity in health*. 2021;20(1):103.
425. Kelaher M. *Better Indigenous Genetic (BIG) Health Services project [Policy Brief]*. 2020.
426. Gonzalez T. *J Genet Couns*. 2020;29(4):542-552.
427. Elsum I. *PLoS ONE*. 2020;15(10):e0239765.
428. Rego S. *Cold Spring Harbor perspectives in medicine*. 2020;10(8).
429. Knoppers BM. *Hum Mol Genet*. 2021;30(R2):R156-R160.
430. Wade CH. *Hastings Cent Rep*. 2019;49 Suppl 1:S88-S96.
431. Joly Y. *Trends Genet*. 2021;37(11):951-954.
432. Lucassen A. *Hum Genet*. 2022;141(5):1053-1058.
433. Watts G. *J Med Ethics*. 2023;49(12):808-814.
434. De Wert G. Opportunistic Genomic Screening: Ethical Exploration. In: Tibben A, Biesecker B, eds. *Clinical Genome Sequencing*.: Academic Press; 2019:203-224.
435. Garrison NA. *Am J Bioeth*. 2019;19(1):51-63.
436. Cancer Australia. *The Australian Cancer Plan*. 2023.
437. Bolt I. *J Med Ethics*. 2021;47(12).
438. Caffrey RG. *J Genet Couns*. 2022;31(3):584-589.
439. Chapman CR. *JOURNAL OF COMMUNITY GENETICS*. 2022.
440. Chavez-Yenter D. *J Genet Couns*. 2021;30(3):911-918.
441. Darling KW. *NEW GENETICS AND SOCIETY*. 2022;41(3):254-283.
442. Hunter CL. *JOURNAL OF CLINICAL ONCOLOGY*. 2023;41(11):1982-+.
443. James JE. *PLoS One*. 2021;16(10):e0258571.
444. Khoury MJ. *Genet Med*. 2022;24(8):1630-1639.
445. Kolarcik CL. *AMERICAN JOURNAL OF PATHOLOGY*. 2022;192(9):1218-1229.

446. Lévesque E. *Public Health Genomics*. 2018;21(1-2):37-44.
447. Morgan G. *Adv Exp Med Biol*. 2019;1168:91-101.
448. Petrova D. *Breast*. 2022;61:66-76.
449. Rebbeck TR. *JAMA HEALTH FORUM*. 2022;3(4).
450. Senier L. *Int J Environ Res Public Health*. 2019;16(20).
451. Shreve JT. *Am Soc Clin Oncol Educ Book*. 2022;42:1-10.
452. Smith-Uffen M. *PATIENT EDUCATION AND COUNSELING*. 2021;104(6):1325-1334.
453. Tellier L. *Genes (Basel)*. 2021;12(8).
454. Morganti S. *Adv Exp Med Biol*. 2019;1168:9-30.
455. Charron M. *Crit Rev Oncol Hematol*. 2022;178:103797.
456. Dimond R. *Soc Sci Med*. 2022;298:114857.
457. Gilbar R. *Bioethics*. 2018;32(6):378-387.
458. Grill K. *JOURNAL OF MEDICAL ETHICS*. 2021;47(12).
459. Hirsch S. *NEURO-ONCOLOGY PRACTICE*. 2021;8(5):526-538.
460. Martucci J. *JOURNAL OF LAW MEDICINE & ETHICS*. 2022;50(4):818-832.
461. Tiller JM. *Eur J Hum Genet*. 2023:1-11.
462. Wagner JK. *JOURNAL OF LAW AND THE BIOSCIENCES*. 2022;9(2).
463. Winkler EC. *SEMINARS IN CANCER BIOLOGY*. 2022;84:263-270.
464. Zimmermann BM. *Bioethics*. 2021;35(2):199-206.
465. *Obstet Gynecol*. 2020;135(4):e189-e192.
466. Hammer MJ. *Semin Oncol Nurs*. 2019;35(1):93-106.
467. Koch VG. *Fordham Law Rev*. 2022;91(3):795-841.
468. Offit K. *J Clin Oncol*. 2023;41(1):11-21.
469. Zhang TR. *J Med Ethics*. 2023.
470. Tiller J. *The A-GLIMMER (Australian Genetics & Life Insurance Moratorium: Monitoring the Effectiveness and Response)*

Project: Final Stakeholder Report Monash University;2023.

471. Joly Y. *BMC Med*. 2013;11:25.
472. Bunnik EM. *Eur J Cancer*. 2021;148:405-410.
473. Ehmann F. *Br J Clin Pharmacol*. 2020;86(8):1454-1464.
474. Horton RH. *J Med Ethics*. 2023.
475. Kraft SA. *Am J Med Genet C Semin Med Genet*. 2018;178(1):75-80.
476. Pujol P. *Eur J Hum Genet*. 2018;26(12):1732-1742.
477. Stoeklé HC. *Sci Eng Ethics*. 2018;24(1):307-322.
478. Vos S. *J Pathol*. 2018;246(4):405-414.
479. Lewis ACF. *Genome Med*. 2021;13(1):14.
480. Tiller J. *Eur J Hum Genet*. 2023;(under review).
481. Tiller J. *BMC Med Ethics*. 2021;22(1):63.
482. Genetype. 2023; https://genetype.com/for-individuals/multi-risk-test-au/. Accessed 1st February 2024.
483. Dive L. *Am J Bioeth*. 2023;23(7):34-42.
484. Gallagher JH. *PEC Innov*. 2023;2:100127.
485. Ascencio-Carbajal T. *BMC Med Ethics*. 2021;22(1):156.

486. Australian Genomics. *National Approach to Genomic Information Management (NAGIM) Implementation Recommendations*. 2023.
487. Australian genomics. *Blueprint for a national approach to genomic information management* 2020.
488. Australian Government. *The Digital Health Blueprint and Action Plan 2023–2033*. 2023.
489. Australian Government. *Connecting Australian Healthcare – National Healthcare Interoperability Plan 2023-2028*. 2023.
490. Australian Government. *National Health Genomics Policy Framework*. 2017.
491. NSW Government. *NSW Health Genomics Strategy*. 2021.
492. South Australia Government. *Clinical Genomics Plan 2022*. 2022.
493. Queensland Government. *Statewide Genetic Health Queensland Service Plan*. 2017.
494. Government of Western Australia. *WA Health Genomics 2021-2023*. 2020.
495. Victorian Government. *Genetic and genomic healthcare for Victoria 2021*. 2017.
496. Australian Genomics. Achieve consistency between health systems – clinical and laboratory delivery. 2023; https://www.australiangenomics.org.au/projects/achieve-consistency-between-health-systems-clinical-and-laboratory-delivery/.
497. Ayres S. *Twin Res Hum Genet*. 2021;24(6):377-384.
498. Australian Government. Digital Transformation Agency. 2023.
499. Birney E. Genomics in healthcare: GA4GH looks to 2022. In: Cold Spring Harbor Laboratory; 2017.
500. Australian Commission on Safety and Quality in Health Care. *Requirements for the retention of laboratory records and diagnostic material*. 2022.
501. Paltiel M. *Int Data Priv Law*. 2023;13(1):47-62.
502. McWhirter R. 2021.
503. phg foundation. *The GDPR and genomic data* 2017.
504. Tiller J. *Med J Aust*. 2021;214(4):157-159 e151.
505. Milne R. *Genome Med*. 2021;13(1):92.
506. Middleton A. *Eur J Hum Genet*. 2020;28(4):424-434.
507. Knoppers BM. *Hugo J*. 2014;8(1):3.
508. Global Alliance for Genomics and Health. Regulatory & Ethics Work Stream (REWS). 2023; https://www.ga4gh.org/work_stream/regulatory-ethics/.
509. Sugano S. *The HUGO Journal*. 2014;8(1):1.
510. Contreras JL. *Annual Review of Genomics and Human Genetics*. 2018;19(1):429-453.
511. Tudini E. *Am J Hum Genet*. 2022;109(11):1960-1973.
512. Joly Y. *Cell*. 2016;167(5):1150-1154.
513. Australian Genomics. National clinical consent forms. 2023; https://www.australiangenomics.org.au/tools-and-resources/national-clinical-consent-forms/.
514. NSW Government. *National Model of Consent for Clinical Genomic Testing*. 2021.
515. Tiller J. *Eur J Hum Genet*. 2020;28(1):108-113.
516. Haas MA. *Eur J Hum Genet*. 2024;32(1):61-68.
517. Chen C. *AMIA Jt Summits Transl Sci Proc*. 2020;2020:80-88.
518. Australian Genomics Health Alliance. *Genomic Data & Privacy Law*. 2018.
519. Malakar Y. *Eur J Hum Genet*. 2023.
520. Malakar Y. *European Journal of Human Genetics*. 2023.
521. Thorogood A. *Hum Genomics*. 2018;12(1):7.

522. National Health and Medical Research Council. *National Statement on Ethical Conduct in Human Research (2007) - Updated 2018*. 2018.
523. Nielsen JL. *Med J Aust*. 2022;216(11):550-552.
524. Lewis ACF. *Genome Med*. 2021;13(1):115.
525. Thorogood A. *Eur J Hum Genet*. 2019;27(4):535-546.
526. Regier AA. *Nat Commun*. 2018;9(1):4038.
527. Resource CG. Sequence Variant Interpretation. 2023; https://clinicalgenome.org/working-groups/sequence-variant-interpretation/.
528. Drummond MF. *Methods for the economic evaluation of health care programmes*. Oxford university press; 2015.
529. Manickam K. *JAMA Network Open*. 2018;1(5):e182140-e182140.
530. Kelsey R. *Nature Cancer*. 2022;3(12):1441-1441.
531. Christofyllakis K. *Mol Clin Oncol*. 2022;16(1):21.
532. Weymann D. *Cancer medicine*. 2021;10(15):5131-5140.
533. Tran G. *Annals of translational medicine*. 2018;6(9):166.
534. Jiang S. *Pharmacoeconomics*. 2023;41(1):43-57.
535. Wilding S. *Social Science & Medicine*. 2020;265:113496.
536. Patel S. *Am J Obstet Gynecol*. 2018;218(4):431.e431-431.e412.
537. Wong JZY. *BMC Health Serv Res*. 2021;21(1):379.
538. Manchanda R. *J Natl Cancer Inst*. 2018;110(7):714-725.
539. Guzauskas GF. *JAMA Network Open*. 2020;3(10):e2022874-e2022874.
540. Muller D. *The European journal of health economics : HEPAC : health economics in prevention and care*. 2019;20(5):739-750.
541. Hurry M. *Int J Technol Assess Health Care*. 2020;36(2):104-112.
542. Michaan N. *Cancer prevention research (Philadelphia, Pa)*. 2021;14(4):455-462.
543. Lourencao M. *Frontiers in Oncology*. 2022;12((Lourencao, Oliveira) School of Economics, Business Administration and Accounting at Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Brazil(Lourencao, Galvao, Antoniazzi, Grasel, Mauad, Reis, Palmero) Molecular Oncology Research Center, Barretos):951310.
544. Oh M. *Expert Rev Pharmacoecon Outcomes Res*. 2023;23(3):309-316.
545. Manchanda R. *Cancers*. 2020;12(7):1-38.
546. Michaelson-Cohen R. *Cancers*. 2022;14(24):6113.
547. Ramos MCdA. *Rev Saude Publica*. 2018;52(0135043, t5x):94.
548. Moya-Alarcon C. *Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico*. 2019;21(8):1076-1084.
549. Kwon JS. *Gynecol Oncol*. 2019;152(3):459-464.
550. Hoskins P. *Gynecol Oncol*. 2019;153(1):87-91.
551. Lim KK. *Appl Health Econ Health Policy*. 2018;16(3):395-406.
552. Kemp Z. *JAMA network open*. 2019;2(5):e194428.
553. Simoes Correa-Galendi J. *Appl Health Econ Health Policy*. 2021;19(1):97-109.
554. Sun L. *Cancers*. 2022;14(7):1839.
555. Mital S. *BMC Cancer*. 2022;22(1):501.
556. Thomas C. *Cancer prevention research (Philadelphia, Pa)*. 2021;14(8):811-822.
557. Cenin DR. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2020;29(1):10-21.

558. Biltaji E. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2021;30(6):1106-1113.
559. Aizuddin AN. *Int J Environ Res Public Health*. 2021;18(16).
560. van den Puttelaar R. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2023;21(13):3415-3423.e3429.
561. Pereira C. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*. 2019;51(12):1731-1737.
562. Beresford L. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2022;25(7):1133-1140.
563. Hackshaw A. *Br J Cancer*. 2021;125(10):1432-1442.
564. Davidson AL. *Genome Med*. 2023;15(1):74.
565. Tafazzoli A. *Pharmacoeconomics*. 2022;40(11):1107-1117.
566. Yeh JM. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2021;23(7):1366-1371.
567. Hendrix N. *Am J Epidemiol*. 2021;190(10):2064-2074.
568. Pastorino R. *PLoS ONE*. 2020;15(7):e0235038.
569. Hao J. *Journal of Personalized Medicine*. 2021;11(12):1284.
570. Azardoost H. *International Journal of Cancer Management*. 2021;14(4):1-7.
571. Snowsill TM. *PLoS ONE*. 2019;14(8):e0221419.
572. Stinton C. *Health technology assessment (Winchester, England)*. 2021;25(42):1-216.
573. Salikhanov I. *J Med Genet*. 2022;59(9):924-930.
574. Kang Y-J. *The Medical journal of Australia*. 2020;212(2):72-81.
575. Snowsill TM. *Journal of Clinical Medicine*. 2020;9(6):1664.
576. Balentine CJ. *Surgery*. 2018;163(1):88-96.
577. Hornberger J. *JAMA dermatology*. 2018;154(9):1025-1031.
578. Ezeife DA. *Therapeutic Advances in Medical Oncology*. 2022;14((Ezeife) Department of Oncology, Tom Baker Cancer Center, 1331 29 St NW, Toronto, ON T2N 4N2, Canada(Spackman) University of Calgary, Calgary, AB, Canada(Juergens) Juravinski Cancer Center, McMaster University, Hamilton, ON, Canada(Laskin, Melosky, Shokoo).
579. Loubiere S. *The European respiratory journal*. 2018;51(3).
580. You JHS. *PLoS ONE*. 2021;16(3):e0247860.
581. Nadal E. *BMC Cancer*. 2021;21(1):689.
582. Harvey MJ. *JCO precision oncology*. 2021;5(101705370):1611-1624.
583. Rojo F. *BMC Cancer*. 2022;22(1):292.
584. Wolff HB. *JCO precision oncology*. 2022;6(101705370):e2200201.
585. Majem M. *Global and Regional Health Technology Assessment*. 2022;9((Majem) Hospital de la Santa Creu i Sant Pau, Barcelona, Spain(Alvarez) Hospital Gregorio Maranon, Madrid, Spain(Ortega) Hospital Universitario de Jaen, Jaen, Spain(de Alda, Gordo, Garcia) Roche Farma, Madrid, Spain(Ivanova-Markova, Gonzalez-Dominguez, Sa):82-90.
586. Arriola E. *JCO precision oncology*. 2023;7(101705370):e2200546.
587. de Alava E. *Expert Rev Pharmacoecon Outcomes Res*. 2022;22(6):1033-1042.
588. Cho SM. *Annals of laboratory medicine*. 2023;43(6):605-613.
589. Lu S. *PLoS ONE*. 2018;13(10):e0205827.
590. Steuten L. *JCO clinical cancer informatics*. 2019;3(101708809):1-10.

591. Aguiar Junior P. *Sao Paulo medical journal = Revista paulista de medicina*. 2019;137(6):505-511.
592. Tan AC. *Lung cancer (Amsterdam, Netherlands)*. 2020;139(b3u, 8800805):207-215.
593. Englmeier F. *J Cancer Res Clin Oncol*. 2023;149(4):1495-1511.
594. Hofmarcher T. *Frontiers in Medicine*. 2023;10((Hofmarcher, Malmberg, Lindgren) IHE-The Swedish Institute for Health Economics, Lund, Sweden(Lindgren) Karolinska Institutet, Solna, Sweden):1119506.
595. Schluckebier L. *BMC Cancer*. 2020;20(1):875.
596. Simons MJHG. *Pharmacoeconomics*. 2021;39(12):1429-1442.
597. Dong OM. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2022;25(4):582-594.
598. Zou D. *The Journal of molecular diagnostics* : JMD. 2022;24(8):901-914.
599. Simons MJHG. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2023;26(1):71-80.
600. Whitehead SJ. *British Medical Bulletin*. 2010;96(1):5-21.
601. Menzel PT. *AMA Journal of Ethics*. 2021;23(8):601-606.
602. Jongbloed EM. *Breast Cancer: Targets and Therapy*. 2023;15((Jongbloed, Martens, Wilting, Jager) Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands(Blommestein, van Schoubroeck, Groot) Erasmus School of Health Policy and Management, Erasmus University, Rotterdam, Netherlands):147-161.
603. Perez Ramirez S. *Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico*. 2020;22(5):717-724.
604. Rojas L. *Cost Effectiveness and Resource Allocation*. 2023;21(1):42.
605. Curtit E. *Frontiers in Oncology*. 2023;13((Curtit) University of Franche-Comte, University Hospital of Besancon J. Minjoz, INSERM, EFS UMR 1098, Besancon, France(Bellanger) UMR CNRS6051, Ecole des Hautes Etudes en Sante Publique, School of Public Health (EHESP), University of Rennes, Rennes, Fran):1191943.
606. Ibarrondo O. *Gac Sanit*. 2020;34(1):61-68.
607. Ozmen V. *Meme Sagligi Dergisi / Journal of Breast Health*. 2019;15(3):183-190.
608. Wei X. *Pharmacogenomics*. 2020;21(1):43-53.
609. Wei X. *Clin Drug Investig*. 2020;40(1):25-32.
610. Trentham-Dietz A. *Breast Cancer Res Treat*. 2018;168(1):229-239.
611. Wang S-Y. *Journal of the National Comprehensive Cancer Network : JNCCN*. 2019;17(1):39-46.
612. De Jongh FE. *International Journal of Breast Cancer*. 2022;2022((De Jongh) Breast Cancer Center South Holland South, Ikazia Ziekenhuis Rotterdam, Montessoriweg 1, Rotterdam 3083 AN, Netherlands(Efe, Spoorendonk) OPEN Health, Marten Meesweg 107, Rotterdam 3068 AV, Netherlands(Herrmann) Exact Sciences Deutschland GmbH):5909724.
613. Sussell JA. *Adv Ther*. 2022;39(3):1375-1392.
614. Wei X. *Int J Hematol*. 2022;115(2):278-286.
615. Alrawashdh N. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2022;25(10):1685-1695.
616. Chatterjee A. *PharmacoEconomics - Open*. 2023;7(2):199-216.
617. Slot M. *Blood advances*. 2023;7(15):4186-4196.
618. Munir T. *Expert Rev Pharmacoecon Outcomes Res*. 2023;23(5):579-589.
619. Chen Q. *Leuk Lymphoma*. 2018;59(7):1700-1709.
620. Regier DA. *Cancers*. 2022;14(4):908.
621. Gaultney JG. *Pharmacogenomics*. 2018;19(3):213-226.

622. Bensimon AG. *Clin Drug Investig*. 2020;40(7):629-643.
623. Wu B. *JAMA dermatology*. 2020;156(11):1177-1184.
624. Mojtahed SA. *Ann Surg Oncol*. 2021;28(13):9039-9047.
625. Gil-Rojas Y. *Value in health regional issues*. 2021;26(101592642):182-190.
626. Li SN. *BMC Health Serv Res*. 2023;23(1):49.
627. Kandel M. *Current oncology (Toronto, Ont)*. 2022;29(12):9255-9270.
628. Wahler S. *Health Economics Review*. 2022;12(1):8.
629. Tarhini A. *Immunotherapy*. 2019;11(4):283-295.
630. Mulder EEAP. *ESMO open*. 2021;6(6):100303.
631. Charpentier C. *European journal of dermatology : EJD*. 2023;33(2):81-86.
632. Chaudhari VS. *Annals of translational medicine*. 2022;10(23):1260.
633. Fragoulakis V. *Pharmacol Res*. 2023;197(phc, 8907422):106949.
634. Harty G. *Appl Health Econ Health Policy*. 2018;16(4):515-525.
635. Lee SF. *Frontiers in Oncology*. 2021;11((Lee, Chiang) Department of Clinical Oncology, Tuen Mun Hospital, New Territories West Cluster, Hong Kong, Hong Kong(Choi, Chan, Lam, Lee, Chiang) Department of Clinical Oncology, University of Hong Kong, Hong Kong, Hong Kong(Lam, Lee, Chiang) Clinical On):651299.
636. Jang SR. *JAMA Network Open*. 2020;3(3):e1919963-e1919963.
637. Kacew AJ. *Frontiers in Oncology*. 2021;11((Kacew) Pritzker School of Medicine, University of Chicago, Chicago, IL, United States(Strohbehn, Laiteerapong, Pearson) Department of Medicine, University of Chicago, Chicago, IL, United States(Saulsberry) Department of Public Health Sciences, University):630953.
638. Nazha S. *Current oncology (Toronto, Ont)*. 2018;25(6):e576-e584.
639. Zhu Y. *Clin Genitourin Cancer*. 2023;21(3):417.e411-417.e410.
640. Chen T. *Therapeutic Advances in Medical Oncology*. 2022;14((Chen, Chen, Guo, He) College of Pharmacy, Fujian Medical University, Fuzhou, China(Chen) Department of Pharmaceutical and Health Economics, School of Pharmacy, University of Southern California, Los Angeles, CA, United States(Zheng) Department of Urology).
641. Redig J. *Cancer Management and Research*. 2019;11((Redig, Dalen, Akerborg) ICON, Stockholm, Sweden(Harmenberg) Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden(Lindskog) Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden(Ljungberg) Department of):1289-1297.
642. Huygens S. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2023;26(2):193-203.
643. Vellekoop H. *Personalized medicine*. 2023;20(4):321-338.
644. Fragoulakis V. *Am J Hum Genet*. 2019;104(6):1158-1168.
645. Weymann D. *Journal of community genetics*. 2022;13(5):523-538.
646. Parmar A. *Can Urol Assoc J*. 2021;16(3).
647. Barbier MC. *PLoS ONE*. 2022;17(11):e0277282.
648. Su D. *Frontiers in pharmacology*. 2020;11((Su) Department of Pharmacy, Hospital of University of Science and Technology of China, Hefei, Anhui 230001, China(Wu) Department of Pharmacy Medical Decision and Economic Group, Ren Ji Hospital, South Campus, School of Medicine, Shanghai Jiaotong Univers):610601.
649. Banerjee S. *JAMA network open*. 2020;3(9):e2013565.
650. Liu K. *Frontiers in immunology*. 2022;13(101560960):1103055.
651. Krepline AN. *Surgery*. 2021;169(3):629-635.
652. Liu K. *Gynecol Oncol*. 2022;166(3):582-588.
653. Orellana TJ. *Gynecol Oncol*. 2023;173(fxc, 0365304):81-87.

654. Richardson MT. *Cancer control : journal of the Moffitt Cancer Center*. 2023;30(dlg, 9438457):10732748231182795.
655. Rios JD. *BMC Pediatr*. 2022;22(1):13.
656. Ranjan T. *Neuro-Oncology Advances*. 2023;5(1):vdad055.
657. Tessler I. *Cancers*. 2023;15(3):786.
658. Saito S. *Personalized medicine*. 2019;16(6):439-448.
659. Ren L. *Frontiers in Oncology*. 2023;13((Ren, Ren, Yang) Fourth Clinical Medical College of Zhejiang Chinese Medical University, Zhejiang, Hangzhou, China(Zheng) Second Clinical Medical College of Zhejiang Chinese Medical University, Zhejiang, Hangzhou, China(Xu) Department of Clinical Pharmaco):1221969.
660. Pennarun N. *Cancer Management and Research*. 2022;14((Pennarun, Huang) Amwise Diagnostics Pte. Ltd, Singapore(Chiu) Department of Medical Operation, Amwise Diagnostics Pte. Ltd, Singapore(Chang) Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei):761-773.
661. Chandler C. *Journal of medical economics*. 2023;26(1):1009-1018.
662. Meng J. *ClinicoEconomics and Outcomes Research*. 2018;10((Meng, Lister, Casciano) Analytica Laser, London, United Kingdom(Vataire, Dinet) Ipsen Pharma, Boulogne-Billancourt, France):243-250.
663. Chen Z-R. *Cost Effectiveness & Resource Allocation*. 2023;21(1):1-10.
664. Chueh C-H. *Pharmacoeconomics*. 2023;41(3):307-319.
665. Pandya BJ. *Journal of managed care & specialty pharmacy*. 2021;27(10):1469-1481.
666. Leung JH. *Future oncology (London, England)*. 2022;18(7):859-870.
667. Ree AH. *Acta oncologica (Stockholm, Sweden)*. 2022;61(8):955-962.
668. Edwards SJ. *Health technology assessment (Winchester, England)*. 2018;22(6):1-278.
669. Lin GA. *J Genet Couns*. 2022;31(1):130-139.
670. Weldon CB. *J Genet Couns*. 2022;31(6):1394-1403.
671. Gogebakan KC. *Cancer*. 2021;127(16):2926-2933.
672. Ngan TT. *BMC Public Health*. 2022;22(1):61.
673. Shen C. *BMC Health Serv Res*. 2022;22(1):470.
674. Shen L. *Journal of medical economics*. 2020;23(5):456-463.
675. Grant P. *Clin Genet*. 2023;103(4):424-433.
676. Caram MEV. *Cancer*. 2020;126(23):5050-5059.
677. Wang H. *Annals of translational medicine*. 2022;10(6):356.
678. Li P. *Cancer medicine*. 2018;7(1):75-86.
679. Sasaki T. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2022;30(6):5115-5123.
680. Knapp GC. *The Pan African medical journal*. 2022;41(101517926):272.
681. Liu M. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2022;30(10):8231-8240.
682. Keilson JM. *Ann Surg Oncol*. 2022;29(SUPPL 2):S398.
683. Jiang H. *Frontiers in Oncology*. 2022;12((Jiang, Jiang, Hu, Yang) School of Medicine, University of Electronic Science and Technology of China, Chengdu, China(Mou, Liu, Zeng) School of Nursing, Chengdu Medical College, Chengdu, China(Lyu, Zheng, Jiang) Department of Head and Neck Radiotherapy, S):1011052.
684. Wong XY. *Patient Preference and Adherence*. 2018;12((Wong, Wee) Department of Pharmacy, Faculty of Science, National University of Singapore, Singapore, Singapore(Groothuis-Oudshoorn, van Til, Ijzerman) Department of Health Technology and Services Research, Faculty of Behavioural, Management and Social Sci):1837-1852.

685. Roberts MC. *Frontiers in genetics*. 2022;13((Roberts) Division of Pharmaceutical Outcomes and Policy, UNC Eshelman School of Pharmacy, Chapel Hill, NC, United States(Foss, Powell, Weck, Milko) Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States(Hender):886640.
686. Hardy MW. *Journal of community genetics*. 2022;13(3):281-292.
687. Guo F. *Journal of cancer education : the official journal of the American Association for Cancer Education*. 2022;37(2):362-369.
688. Blouin-Bougie J. *BMJ open*. 2018;8(2):e016662.
689. Venning B. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2022;24(10):2144-2154.
690. Gelhorn H. *The patient*. 2023;16(1):43-56.
691. Regier DA. *Pharmacoeconomics*. 2020;38(1):57-68.
692. De Abreu Lourenco R. *Pediatr Blood Cancer*. 2021;68(8):e29101.
693. McCarthy MC. *The patient*. 2020;13(3):347-361.
694. Costa S. *The patient*. 2021;14(2):187-196.
695. Butow P. *J Genet Couns*. 2022;31(1):96-108.
696. Clasen K. *Personalized medicine*. 2022;19(2):103-112.
697. Davidson BA. *Gynecologic Oncology Research and Practice*. 2019;6(1):1.
698. Fifer S. *Journal of Personalized Medicine*. 2022;12(6):879.
699. Weymann D. *European journal of human genetics : EJHG*. 2018;26(9):1257-1265.
700. Mayer M. *Familial cancer*. 2019;18(2):221-230.
701. Adejumo PO. *JCO global oncology*. 2023;9(101760170):e2100140.
702. Veldwijk J. *Patient Preference and Adherence*. 2019;13((Veldwijk) Erasmus School of Health Policy and Management, Erasmus University, Rotterdam, Netherlands(Veldwijk, Kihlbom, Langenskiold) Centre for Research Ethics & Bioethics, Uppsala University, Uppsala, Sweden(Veldwijk, De Wit, Lambooij) Centre for Nutri):273-282.
703. Godino L. *J Genet Couns*. 2021;30(3):665-675.
704. Radecki Breitkopf C. *Journal of empirical research on human research ethics : JERHRE*. 2018;13(3):295-304.
705. Mighton C. *Hum Genet*. 2021;140(12):1695-1708.
706. Shickh S. *Hum Genet*. 2023;142(4):553-562.
707. Best MC. *European journal of human genetics : EJHG*. 2022;30(8):930-937.
708. Meiser B. *Am J Med Genet A*. 2022;188(3):725-734.
709. Kaphingst KA. *Translational behavioral medicine*. 2018;8(1):71-79.
710. Guo S. *J Genet Couns*. 2020;29(1):131-134.
711. Matsen CB. *Patient Educ Couns*. 2019;102(1):155-161.
712. de Freitas HM. *Adv Ther*. 2019;36(2):318-332.
713. Stenehjem DD. *Melanoma Res*. 2019;29(6):626-634.
714. Mansfield C. *Future oncology (London, England)*. 2019;15(11):1255-1268.
715. Nazari A. *Value in health regional issues*. 2021;25(101592642):7-14.
716. Mansfield C. *Breast cancer (Tokyo, Japan)*. 2023;30(1):23-35.
717. Amaador K. *Cancer medicine*. 2023;12(3):3376-3386.
718. Wong XY. *Curr Med Res Opin*. 2020;36(10):1677-1686.
719. Orton L. *PLoS One*. 2011;6(7):e21704.
720. Luta X. *BMC Palliative Care*. 2021;20(1):89.
721. Reckers-Droog V. *Social Science & Medicine*. 2021;279:113987.

722. Ferrari R. *Medical Writing*. 2015;24(4):230-235.
723. Vachon CM. *J Natl Cancer Inst*. 2015;107(5).
724. Mavaddat N. *J Natl Cancer Inst*. 2015;107(5).
725. Lee A. *Genet Med*. 2019;21(8):1708-1718.
726. Hurson AN. *Int J Epidemiol*. 2022;50(6):1897-1911.
727. eviQ. Cancer Genetics Protocols. 2023; https://www.eviq.org.au/cancer-genetics.
728. Lakeman IMM. *J Med Genet*. 2019;56(9):581-589.
729. Arksey H. *International Journal of Social Research Methodology*. 2005;8(1):19-32.
730. M P. *JBI Manual for Evidence Synthesis*. 2020:pp. 406-451.
731. Tricco AC. *Annals of internal medicine*. 2018;169(7):467-473.
732. Knoppers BM. *JOURNAL OF PERSONALIZED MEDICINE*. 2021;11(8).
733. Gustavsson E. *BMC MEDICAL ETHICS*. 2020;21(1).
734. Tiller J. *BIOTECH*. 2023;12(2).
735. Fritzsche MC. *Frontiers in genetics*. 2023;14.
736. Bester J. *Pediatrics*. 2018;141(4).
737. Tempini N. *Soc Sci Med*. 2021;272:113760.
738. Rubin LR. *Ethical analysis of PGD for BRCA: attending to more than risks and benefits*. London: Routledge; 2014.
739. McKenzie JE. *Cochrane handbook for systematic reviews of interventions*. 2019:33-65.
740. Schwarze K. *Genet Med*. 2018;20(10):1122-1130.
741. Santos Gonzalez F. *Genet Med*. 2023;25(6):100829.
742. Kohler JN. *Eur J Hum Genet*. 2017;25(6):662-668.
743. Fahr P. *Pharmacoeconomics*. 2020;38(2):143-158.
744. Johnson K. *Genet Med*. 2022;24(2):262-288.
745. Callahan KP. *JAMA Network Open*. 2022;5(8):e2225980-e2225980.
746. Miller EG. *JAMA Network Open*. 2023;6(5):e2310367-e2310367.
747. Mohan G. *JAMA Oncol*. 2020;6(9):1434-1444.
748. Ehsan AN. *JAMA Network Open*. 2023;6(2):e2255388-e2255388.
749. Al-Aqeel S. *Health Econ Rev*. 2023;13(1):17.
750. Bailey C. *Pharmacoeconomics*. 2022;40(7):663-698.

Appendices

Appendix 1A: Genomics in Adult Cancer Section Methods

We initially attempted to conduct a systematic literature search pertaining to genomic profiling across multiple adult cancer types. However due to the variability in terms associated with this topic and the resulting large volume of records, this approach proved to unsuitable. To address these challenges, we opted for a more tailored approach by conducting a narrative synthesis of the literature. This method allowed us to provide a broad overview of the current applications of genomic profiling in the adult cancer setting.[722]

Eligibility Criteria

We aimed to capture records that explored genomic profiling in the adult general cancer setting. Eligible articles were published in English between 2017 and 2024. We omitted papers that focused on one cancer type (e.g., colorectal cancer) and studies with a small cohort size (<100 patients profiled) to ensure that the reported values were representative. Only articles reporting original data and review articles were included. Such choices were based on capturing a current overview of the subject area and highlighting gaps in the literature.

Search Strategy

PubMed, Web of Science and Google scholar databases were utilized to identify initial key large studies determined by the review team (AML, ED, and EM) to be relevant using combinations of the following key search terms: cancer, genomic profiling, germline, somatic, ctDNA, and specific methodology (e.g., microsatellite instability, tumour mutational burden, homologous repair defect scores, and methylation defects). These key papers were then used to identify additional terms and to explore alternative search strategies. The references and citations for all included articles were reviewed to identify other large studies on cancer genomics. Seminal research was included even if it predated the 2017 date. Finally, additional articles were also identified by field experts.

Selection of Studies and Data Extraction

To assess eligibility for inclusion in the study, the titles and abstracts of articles were screened. Records were deemed relevant if they met the inclusion criteria. The full texts of the selected articles were then reviewed in tandem by authors AML, ED and EM. Any inconsistencies were addressed and resolved through discussion among the review team. Following the filtering of studies, selected articles were charted in Microsoft Excel, which included bibliographic details, study type, country, participant characteristics, key findings, and clinical outcome measures.

Data Analysis

We inductively mapped the studies key findings and outcomes and conducted a narrative synthesis.

Results

77 records were included. The majority were from the United States (n=35, 45%). It is estimated that approximately 300 records were screened for eligibility. Of the included articles 66 (86%) were original articles and the remainder were review articles (n=15, 19%). 41 articles (53%) pertained to germline or somatic, and 21 (27%) were relevant to ctDNA.

Appendix 1B: Potential Polygenic Risk Score Applications

Table A1.1 Potential applications for PGS in breast cancer

Context	Application	Considerations
Population screening	Used as part of integrated risk assessment that include PGS, family history of cancer, other non-genetic risk factors such as breast density, hormonal factors, lifestyle (e.g. diet, exercise and alcohol consumption).[723-725] Integrated risk models, with PGS have been shown to improve risk classification and identify people at increased risk who may benefit from earlier and more frequent screening, and those who can delay screening.[726] Ongoing risk management can be based on existing guidelines for breast cancer risk management.[727]	• Acceptance of reduced screening among people at lower risk. • Development of processes to implement integrated risk on population level including risk calculation, education of primary healthcare providers, and communication of results to the public. • It is not possible to estimate PGS based on close relatives' results. Therefore, individual PGS testing is needed. • Currently limited evidence of clinical utility and cost benefit.
Refining risk to monogenic risk	Used as part of an integrated risk assessment to refine risk for people with confirmed breast and ovarian cancer hereditary syndrome and those with negative results from genetic testing.[725] **For those with a high-risk condition** (e.g. *BRCA1*, *BRCA2*), inclusion of PGS information is unlikely to reduce risk estimates below high-risk (i.e. lifetime risk to age 80 for PGS and *BRCA1* ranges from 53% to 92%).[209] Although these individuals will remain at high-risk, an age effect of PGS is seen with individuals reaching threshold for screening and risk-reducing surgery at different ages based PGS percentile. Thus, integration of PGS can inform risk management decision making.[210] **For those with moderate-risk condition** (e.g. CHEK2) integration of PGS can result in changes to risk categories. The estimated lifetime risks to age 80 years for PGS and *CHEK2* ranges from 7% to 71%. Thus, a person can be classified from population to high risk based on their PGS result.[209]	• Acceptance of personalised risk and risk variance within families. • Acceptance of delayed risk-reducing surgery and screening for those with lower risk due to PGS result. • Upskilling genetic healthcare professionals on use of PGS and integrated risk who have reported low confidence and knowledge using this information in clinical practice. • Requires discussion of both monogenic and polygenic inheritance. • Currently limited evidence of clinical utility and cost benefit.

Context	Application	Considerations
	For those with negative results from genetic testing a PGS can be calculated to estimate the genetic contribution to the familial risk.[728] Risk estimates to age 80 years for people in this group ranges from 3% to 62%.	
Predicting prognosis to inform therapeutic interventions	Used to aid complex treatment and risk management decision making potentially leading to improved patient outcomes. PGS has been shown to differentiate risk based on breast cancer sub-type, namely estrogen receptor (ER). However, PGS is a more accurate predictor of ER- positive disease than ER-negative.[31] This information may inform decisions on uptake of chemoprevention with Tamoxifen, which is a well establish risk-reducing strategy for ER-positive disease.[31] PGS has also been shown to predict risk of contralateral disease, which can aid treatment decisions for people with a personal history of breast cancer (e.g. bilateral mastectomy vs conservative surgery). Lastly, PGS is also associated with more favourable prognosis including more likely to be diagnosed during routine screening, ER-positive disease, smaller tumour size and less diagnosed with distant.[31]	

Appendix 1C: Methods for Cancer Vaccine Section

An umbrella review was performed to identify the different applications and impact of cancer vaccines. A PubMed search was performed using key search terms: 'prophylactic cancer vaccine', 'therapeutic cancer vaccines' AND 'clinical trials'. The references and citations for all included articles were reviewed to include other relevant reviews, and title/abstract and full text screening of articles in English were performed. The search was limited to studies from 2020 onwards. An additional search used similar key search terms but aim to identify any original cancer vaccine research studies conducted in Australia.

The ANZCTR database was reviewed to identify active Australian cancer vaccine trials (Description of intervention "Vaccine" AND Condition Category "Cancer" AND Condition Code "Any Cancer" AND Recruitment "Australia". Additionally, ClinicalTrials.gov was searched to identify any additional Australian studies registered with that database (Condition/Disease = Cancer AND Intervention/Treatment = Vaccine AND Location = Australia AND STUDY Status = Recruiting and not yet recruiting studies).

Results

Search of PubMed identified 81 papers, of which 27 met the criteria for review. International trials which documented cancer vaccine efficacy were noted and captured in Table 3.

Appendix 2: Genomics in Paediatric Cancer Section Methods

We conducted a scoping review guided by the methodology described by the Jonna Briggs Institute,[729] to map and describe the current application of genomic testing in the paediatric cancer care.

Eligibility Criteria

Using the Population, Concept, and Context criteria [730] we aimed to capture records that that explored the use of genomic testing in the paediatric cancer setting and clinical patient outcomes. Eligible articles were published in English between 2017 and 2024. We excluded papers that focused on singular conditions (e.g., sarcoma) as we aimed to explore the broader paediatric cancer context. Due their small sample sizes and observational nature, case reports were excluded. Such choices were based on capturing a current overview of the subject area and highlighting gaps in the literature.

Search Strategy

Relevant records were identified through searching PubMed, which was filtered by title and abstract to ensure that the records captured were relevant. Articles were restricted to those written in English. A date limit of 2017-2024 was applied to ensure that relevant articles were captured. A combination of search terms and Boolean operators "OR", "AND" and "NOT" were used to address four key search areas and eliminate irrelevant records (see Table A2.1). The references and citations for all included articles were reviewed to identify relevant studies. Seminal research was included even if it predated the 2017 date. Finally, additional records were also identified by field experts. The search was last conducted on January 24, 2024. Search results were imported into Covidence, for screening and data extraction.

Selection of Studies and Data Extraction

To assess eligibility for inclusion in the study, the titles and abstracts of all identified articles were screened. Records were deemed relevant if they met the inclusion criteria or required further reading to determine eligibility. The full texts of the selected articles were then reviewed in tandem by authors AML and ED. Any inconsistencies were addressed and resolved through discussion among the review team. Following the filtering of studies, selected articles were charted in Microsoft Excel, which included bibliographic details, study type, country, participant characteristics, key findings, and clinical outcome measures.

Data Analysis

We inductively mapped the studies key findings and outcomes and conducted a narrative synthesis.

Results

48 records were included (see Figure A2.1). The majority of original articles were from the United States (n=10, 33.3%). Original articles accounted for 30 (62.5%) and reviews comprised the remainder (n=18, 37.5%).

A total of 437 records were identified from the initial database search and from reference and citation searches of included articles and field experts. Figure A2.1 depicts a PRISMA flowchart of the database and citation searchers. The title and abstracts of 436 records were then screened as there were no duplicate records identified. A total of 380 records were excluded at this stage as they did not meet the inclusion criteria. The remaining 56 records underwent full text screening, and a further 11 were excluded as were not relevant to the inclusion criteria or the results were considered outdated. This left a total of 48 eligible records for data extraction.

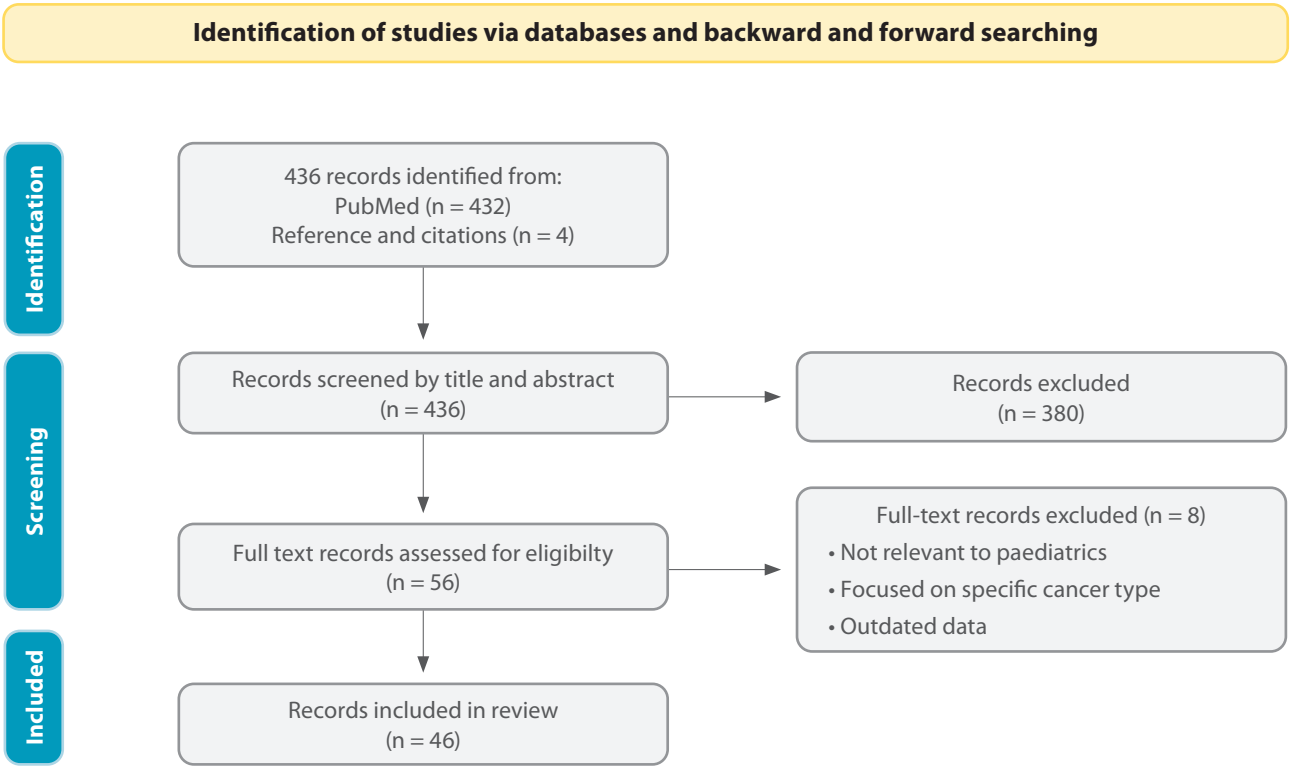


Figure A2.1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Table A2.1: Search terms

Search area	Search terms	Number of records captured
Context	Cancer OR Oncology OR Carcinoma OR Solid tumo*r OR Solid cancers OR Neoplasm OR Malignancy AND	1,169,139
Field area	Genomic OR Genetic OR Germline OR Somatic OR Hereditary cancer OR Mutation OR Alteration OR Variant OR Variation OR Pathogenic AND	1,056,955
Population	P*ediatric OR Child* OR Kid* OR Young adult OR Adolescen*	698,615
Subject specific	Personalised OR Landscape OR Targetable or Targeted sequencing OR Precision medicine OR Precision Oncology OR Actionable OR Therapeutic OR WES OR WGS OR RNA seq* OR Molecular screening OR Molecular profiling	728,249

Appendix 3: Methods and Summary Data on Models of Care

This scoping review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist for Scoping Reviews.[731] Relevant records were identified through a search of PubMed. Articles were restricted to English, the date range applied was 1 January 2013 to 1 September 2023 and only articles published in English were included. A combination of search terms and Boolean operators "OR", "AND", and "NOT" were used to address three key search areas (see Table A3.1). Articles identified from reference and citation searches of included articles were also included. Search results were imported into Covidence by ED for independent screening and data extraction by JB and AML.

Inclusion and Exclusion Criteria

We included original research articles describing the trial or implementation of a mainstream genetic testing (MGT) pathway in oncology settings. Exploratory studies, opinion pieces, and reviews were excluded.

Results

A total of 146 studies were identified from the initial PubMed search. Figure A3.1 depicts a PRISMA flowchart of the database and citation searches and a summary of included articles are detailed in Table A3.2. Following title and abstract screening 100 articles were excluded as they did not meet the inclusion criteria. The remaining 46 records underwent full text screening and a further 19 were excluded as they did not detail outcomes of MGT in cancer settings. A review of references or papers which cited the 27 remaining relevant articles identified 10 additional eligible studies. Thus, 37 articles were included in the review.

Table A3.1: Search terms to identify mainstreaming papers

Search area	Search terms
What	Cancer OR
	"Cancer* AND tumo*" OR
	Malignan* AND
Setting	Famil* OR
	Inherit* OR
	Hereditary OR
	Predispos* OR
	Genetic* OR
	Genom* OR
	Human Genetics[Mesh] OR
	Neoplastic Syndromes, Hereditary[Mesh] OR
	"Neoplasms/genetics"[Mesh] AND
Model-of-care	Mainstream* OR
	Embed* OR
	"Model of care" OR
	Upskill*

Excluded: *paraffin*

Figure A3.1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

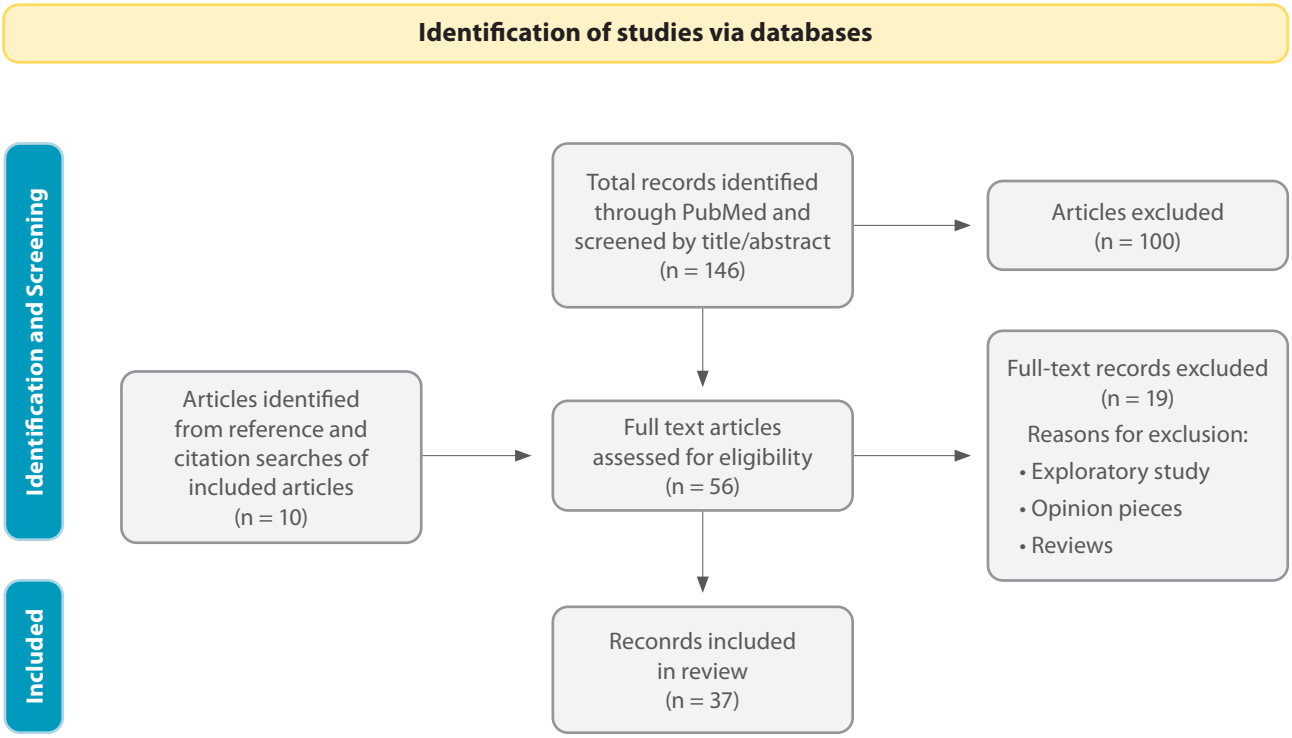


Table A3.2: Summary of articles

Model	Reference	Participants	Setting	Country	Study design	Outcomes assessed	Key findings
GEM	Bednar et al 2019	n = 241, high grade OC (n=57) and EC (n=184) patients	MGT/IHC in a hospital gyne-oncology clinic	USA	Retrospective	GC recommendation GT rates Wait times	84% HGOC patients recommended for GC, 81% completed GT. PV detection rate 20%. For EC patients, 81% recommended to have Lynch gene IHC. ↓ Wait times from diagnosis to GT.
	Kentwell et al 2017	n = 64, OC patients.	Familial cancer centre	Australia	Retrospective (Pre-post comparison)	PV detection rate, GC referral rate, time from diagnosis to GT result, appointment length.	PV detection rate was 17%, referral rate >90%, Time to results <5 months, ↓ Appointment length (120 to 54 min). MGT acceptable to HCPs.
	Pederson et al 2018	BC patients. n = 471 (2012); n = 440 (2014)	Breast clinic	USA	Retrospective cohort study (Pre-post comparison)	GC referral rate and test uptake, time from diagnosis to GT result, appointment length, PV detection rate.	Patients 49% more likely to be referred to genetics, 66% more likely to complete GT, 74% (4-fold) reduction in wait times and 69% more likely to have GT results prior to surgery. PV detection rates 9% in 2012 and 6.6% in 2014 (expected rates).
	Rana et al 2021	n = 358, OC patients	Medical and gyne-oncology practice	USA	Prospective cohort study (Pre-post comparison)	Compare cancer care pre- and post-implementation of GEM model	88–92% referred for GC. Pre GEM 66% completed GC and 61% tested. Post-GEM >80% completed GC and GT. Time to GC ↓ from 107 to 40 (2.67 fold) days.
	Senter at el 2017	n = 737, OC patients. (n=401 pre-GEM, n=336 post-GEM)	Gyne-oncology clinic. Pre GEM vs post GEM.	USA	Retrospective (Pre-post comparison)	GC referral rates, Time from referral to test	↑ Referral rate for GC (from 21 to 44%), ↑ GC appts scheduled for referred patients from 38% to 84%, ↓ Time from referral to result - 2.5 to 1.7 months (1.5-fold).
GEM + UPC	Bednar et al 2017	n = 1636, high grade OC patients	BRCA MGT in hospital gyne-oncology clinic	USA	Retrospective (Pre-post comparison)	GC recommendation and GT rates	↑ HGOC patients referred for GC/GT (from 12% to 87%). 85% completed GT and PV detection rate 18%. 46% had GT with embedded GC or cancer specialist, others tested externally.

Model	Reference	Participants	Setting	Country	Study design	Outcomes assessed	Key findings
UPC	Ain et al 2023	n = 474, female BC patients	BRCA MGT ordered by breast clinicians	UK	Prospective; surgical data retrospective	Surgical decision-making following MGT.	64% received results before surgery. 88% PV carriers = bilateral mastectomy. 98% non-carriers = unilateral surgery. PV identified post-surgery -> 39% returned for further surgery.
	Beard et al 2021	n = 230, female BC patients n=72 clinicians	5-gene panel MGT in surgical and oncology clinics. Supported by FCC	Australia	Retrospective	Outcomes of MGT for breast cancer patients at surgical and oncology clinics	PV detection rate 15%. Treatment modified in 89% PV carriers. 52% of patients managed in clinic. 20% referred to FCC. 90% reduction in FCC appointments over two years.
	Benusiglio et al 2020	n = 234, BC and OC patients	BRCA ordered by gynaecologists and oncologists	France (3 hospitals)	Retrospective	Feasibility of MGT in France. PV detection rates including during COVID lockdown.	MGT feasible. 12.1% of patients had a PV. Continuity of care maintained during lockdown.
	Bokkers, Bleiker et al 2022	n = 196, epithelial OC patients	BRCA MGT in gynecology department vs TGT	Netherlands	Prospective longitudinal, MGT; retrospective, TGT	PROMs. Used validated scales.	Genetics knowledge, decisional conflict, depression, anxiety, and distress were comparable in the two groups. MGT is acceptable to patients.
	Bokkers, Zweemer et al 2022	n = 20, gynaecology HCPs	MGT in gynecology departments	Netherlands (4 hospitals)	Prospective longitudinal study (pre to 6 months post-training)	HCP attitudes, perceived knowledge, and self-efficacy. Feasibility of MGT.	HCPs had a positive attitude, high perceived knowledge and high self-efficacy. ↑Knowledge after 6 months. 60% of HCPs could discuss GT in 5-10 min, 40% in 10-20min. 92% could order GT in ≤10min.
	Bokkers, Frederix et al 2022	n = 196, epithelial OC patients	MGT in gynecology departments	Netherlands (4 hospitals)	Prospective observational study.	Acceptability and feasibility of MGT for EOC patients.	GT offered to 70% EOC compared with 56% prior to MGT. MGT reduces genetics-related healthcare costs by 31% per patient.

Model	Reference	Participants	Setting	Country	Study design	Outcomes assessed	Key findings
UPC	Bokkers et al 2023	n = 70, surgeons, oncologists and breast care nurses	MGT after online training	Netherlands (11 hospitals)	Prospective, longitudinal study (pre to 6 months post-training)	Clinician attitudes, knowledge, & self-efficacy; feasibility of MGT.	Attitudes, knowledge, and self-efficacy of HCPs high at baseline and 6 mo after training. ↑Perceived knowledge of implications of GT after 6 months. Time for pre-test GC <15min for 89%.
	Chai et al 2023	n = 406, BC patients	Academic breast surgeon's practice	USA	Retrospective comparative study	Impact of MGT on timing and uptake of testing	↓Time to test initiation from 7 months to same day post-MGT. Pre-MGT 71.4% patients consented to GT vs 88.1% post-MGT.
	Colombo et al 2020	n = 700, OC patients	26 oncology clinics in USA (n = 11), Italy (n = 8), and Spain (n = 7).	USA, Spain, Italy	International, multicenter, prospective, observational study	Feasibility of BRCA MGT in OC patients. TAT, patient and HCP satisfaction. Used validated scales.	Median TAT 9.1 weeks. >99% patients satisfied with pre and post-test GC. 93.7% pleased to have had GT at oncology appt. >80% oncologists agree MGT is an efficient use of their time. Time to discuss test ~20min. PV rate 13.8%.
	Flaum et al 2020	n = 1081, epithelial OC patients	MGT in gynae-oncology clinics in 3 hospitals vs TGT.	UK	Retrospective comparative study	Changes in GT and BRCA PV detection rates across 12 years (pre- and post-MGT).	resource requirements GT uptake 2.5-fold. ↑PV detection rate from 17.2% to 18.5%. Uptake of cascade testing in FDR lower compared to traditional model uptake (31.6% compared to 47.3%).
	George et al 2016	n = 207, OC patients	Oncology clinic at one hospital. UK.	UK	Prospective	Availability, utility and equity of access to BRCA testing for OC patients.	GT result informed management of 79%. Positive patient and HCP feedback. Compared with traditional GT pathway, ↓Time (4-fold) & resource requirements (13-fold)
	Grindedal et al 2020	n = 361, BC patients	Oncology clinics in 2 hospitals.	Norway	Retrospective observational	Rate GT is offered to patients	75% of eligible patients offered GT (63% at regional hospital, 90% at metro hospital). 95% completed GT.
	Hamilton et al 2021	n = 1054, OC, PaC and PrC patients	Oncology department at cancer centre	USA	Prospective single-arm study	Evaluated patient experiences of MGT.	High acceptability, high GT decisional satisfaction. Outcomes depended on GT result: temporary ↑ in depression for non-carriers; small ↓ in GT distress for PV carriers.
	Ip et al 2022	n = 289, OC patients	Genetics service-supported MGT	Australia (5 hospitals)	Retrospective over 5-year period.	Number of patients undertaking GT/year.	Baseline = 44% of GT via MGT, compared with 76% post. PV detected 13.7% of MGT patients vs 20.3% in genetics service.

Model	Reference	Participants	Setting	Country	Study design	Outcomes assessed	Key findings
UPC	Kemp et al 2019	n = 1184, BC patients.	Oncology clinic at a metropolitan hospital.	UK	Quality improvement study	PV detection rates, quality-adjusted life-years (QALYs), cost-effectiveness ratios, patient and HCP acceptability	9.9% patients had a PV. >50% PV carriers did not meet traditional FH-based criteria. GT was cost-effective with cost-effectiveness ratios of US$1225 or $1330 per discounted QALYs. High patient and HCP acceptability.
	McCuaig et al 2021	n = 276, BC and OC patients	Oncology clinic and familial cancer clinic.	Canada	Pragmatic, prospective survey	PROMs in TGT vs MGT models. Used validated scales.	TGT cohort had higher knowledge and experience scores and more concerns about hereditary predisposition. MGT cohort more concerns about general emotions.
	McLeavy et al 2020	n = 170, OC patients	Oncology clinic at a metropolitan hospital.	UK	Retrospective questionnaire	Patient experience of MGT. Used validated scales.	PV detection rate 13.5%. Main motivations for genetic testing: improved medical management, providing relatives with genetic information. No adverse effects of result disclosure post-MGT.
	McVeigh et al 2023	n = 101, BC and OC patients.	3 tertiary oncology centres.	Ireland	Prospective, survey	Diagnostic yield, TAT, referral rates, patient and clinician feedback.	PV detection rate 12%. Satisfaction surveys indicated that the pathway was acceptable to patients and clinicians.
	Percival et al 2016	n = 108, OC patients	Hospital medical oncology clinic.	UK	Descriptive, survey	Access to GT. Doctor- vs nurse-led GT. HCP confidence	No difference in reported patient satisfaction between nurse or a doctor-led GT. All patients accepted GT. No significant issues raised in pre-test counselling. Nurses felt well supported.
	Powell et al 2020	n = 40, OC patients; n = 6, oncologist	MGT in 2 gyne-oncology hubs vs 3 hubs using TGT model	USA	Prospective pilot study	Patient and oncologist satisfaction. Used validated scales.	Uptake of GT 100% MGT vs 67.3% TGT model. Median time from Dx to result 52.5 days MGT vs 78.5 days TGT. PV detection 22.5% MGT vs 10.3% TGT. HCP satisfaction high. Patient satisfaction high in both cohorts.
	Rahman et al 2019	n = 122, OC patients	Tertiary oncology centre	UK	Retrospective review	PV detection rate, GC referral rate, impact on treatment choice.	MGT feasible for BRCA testing in OC patients. 14.8% had BRCA PV. 30% had no FH. 33% of PV carriers had change to treatment.

Model	Reference	Participants	Setting	Country	Study design	Outcomes assessed	Key findings
UPC	Ramsay et al 2023	n = 245, PaC patients	Oncology clinics offering 86-gene panel test.	USA	Retrospective cohort study	PV detection rate, GC referral rate, impact on treatment options.	6.5-fold increase in rate of GT for PC pts with MGT. 13.9% had PV with 6.9% in high/mod risk gene. 2% had option for matched therapy. 64.7% referred for GC with minimal impact on genetics service workload.
	Richardson et al 2020	BC and OC patients. n = 400 (GT); n= 148 (surveys)	Oncology clinic panel MGT vs TGT model.	Canada	Observational study	Wait times and PROMs for MGT vs TGT model, HCP experience. Used validated scales.	Wait time from referral to results 191 days MGT vs 403 days TGT model. Pt uncertainty, distress, knowledge and experience were similar between both models. HCPs had positive attitudes towards MGT.
	Rumford et al 2020	n = 255, OC patients	BRCA MGT in gyne-oncology clinic vs TGT model.	UK	Prospective cohort study, compared to retrospective data.	Uptake of GT	Uptake of GT increased with MGT vs TGT (65% vs 14%). TAT decreased from 148.2 to 20.6 days. PV detection rate 13.3% and 41.1% of these had change to treatment plan.
	Ryan et al 2020	EC patients. n = 300 (GT); n = 175 (surveys)	Gynae-oncology service offering Lynch GT.	UK	Prospective, survey	Impact of MGT in EC pts. Used validated scales.	Average time for consent was ~7.5 min. Anxiety levels not affected by familial cancer history and were lower if GT offered during follow up vs at time of surgery. 4.3% PV detection rate.
	Scheinberg et al 2021	PrC patients. n = 63 (GT), n = 9 (surveys); HCP, n = 50 (surveys)	Medical oncology clinics at 3 sites offering 16-gene panel GT.	Australia	Multicenter, prospective study	HCP and patient satisfaction with MGT model. PV detection rates, model efficiency.	High patient satisfaction (100%) with MGT approach. 88% HCPs confident and satisfied with MGT model and preferred inclusion of CNC. MGT efficient requiring 87% fewer GC consultations than TGT model.
	Scott et al 2020	n = 290, BC patients	Hospital Breast Institute. Nurse-led MGT vs TGT model.	UK	Retrospective	Wait time, PV detection rate.	PV detection rate average 14.5%. Mean wait time from referral to results 7-9 months pre-MGT vs 35.8 days post-MGT.
	Srinivasa et al 2023	n = 119, OC patients.	Gynae-oncology clinic offering BRCA GT.	Australia	Retrospective review	PV detection rate, TAT, impact on treatment, cascade testing	10.1% BRCA PV detection rate overall. Treatment changed for 83%. Median TAT 44.5 days. 88% reduction in potential GC appointments. Cascade testing in 75% of PV families, mean ~3 relatives per family.

Model	Reference	Participants	Setting	Country	Study design	Outcomes assessed	Key findings
UPC	Strømsvik et al 2022	n = 22, BC patients	BC pts at one metro and one regional hospital	Norway	Qualitative	BC patients' experience of MGT	100% patients agreed standardised GT process important in diagnosis and treatment. 27% had to initiate test request. Information needs varied, trust in clinician facilitated communication.
	Walker et al 2021	n = 22, PaC patients	Medical oncology clinic offering multi-gene panel MGT.	USA	Retrospective review	Rates of offered GC and confirmed GT pre- vs post-MGT	GC offered to 94%; 71% completed GT vs 19% in TGT model. Patient attrition from referral to GT appt decreased from 36% (TGT) to 3% (MGT).PV detection rate increased from 20% (TGT) to 33% (MGT).
	Wright et al 2018	OC patients, MGT (n = 8); BC patients, TGT (n = 18)	Oncology clinic MGT (TFGT) vs TGT model.	UK	Retrospective, qualitative interviews	Patient experience of TFGT, motivations for GT, views models.	Patients happy to have TFGT early in cancer care, either pathway. Patients offered TFGT after surgery questioned timing. Treatment role conflated with role in prevention for family members.

Abbreviations: MGT, mainstream genomic testing; GT, Genetic testing; GEM, GC embedded model; UPC, Upskilled clinician model; TGT, Traditional genetic testing model; TFGT, Treatment-focused genetic testing; GC, Genetic counselling; HCP, Health care professional; OC, Ovarian cancer; BC, Breast cancer; EC, Endometrial cancer; PaC, Pancreatic cancer; PrC, Prostate cancer; PV, Pathogenic variant; TAT, Turn-around time; PROMs, Patient reported outcome measures ; IHC, Immuno-histochemistry.

Appendix 4: Ethical, Legal, and Social Implications Scoping Review Methods

Given the diverse terminology and methodological approaches across ELSI research and literature a comprehensive scoping review was conducted by adapting methods used in both umbrella and scoping reviews. This allowed for the most relevant literature to be captured.

Literature searches were conducted in July 2023 in PubMed and Web of Science, with further targeted searches within relevant bioethics, cancer- and genetics-related journals conducted in November 2023 via Web of Science. These databases were selected as they cover topic areas of relevance to the review (i.e. bioethics, ELSI, cancer, genomics and genetics).

The search strategies were developed in an iterative process and in consultation with two librarians at the University of Sydney. The search strategies included terms focussed on the key concepts relevant to our research question and objectives including keywords related to cancer, bioethics, genomics and genetics, and ELSI. Searches were limited to title, abstract, keywords and/or subject headings. Searches were undertaken by AKS with support from the librarians. Articles retrieved from the searches were imported into a web-based literature reviews application (Covidence).

Eligibility Criteria

The following criteria were applied in order to assess articles: (a) written in English language, (b) articles that were either reviews, bioethical analyses, policies, guidelines, position statements, substantive, (c) published in 2018 or onwards, and (d) pertaining to research in humans. We excluded articles that were (a) primary research articles unless they contained a substantial bioethics or sociological/ethical component, (b) published prior to 2018, (c) not in English or (d) focused on biological genetic processes with no or little consideration of ELSI.

Selection of Studies

Covidence was used to facilitate independent screening of all articles by two independent reviewers. One reviewer (AG) screened all titles and abstracts, and a second reviewer (AJN or AKS) independently screened all titles and abstracts. The resultant full text articles were all independently double screened by AG and either AJN or AKS. During regular team meetings, consensus was reached for any screening conflicts through group discussions.

Data Collection

For the selected articles, a data extraction form was developed to capture all information relevant to the research question, including the patient journey across the cancer control and care continuum. Data were extracted using Covidence by two authors independently (AG and either AKS or AJN) and were then exported into Microsoft Excel where any discrepancies between the data extracted were resolved through team discussion. Descriptive data collected via the data extraction form included: article title, journal, type of study, main argument or idea, key findings, study design (if articles included empirical data), relevance to the research question, and relevance to the patient journey. The patient journey matched the optimal care pathways across steps along the cancer control and care continuum as per the Australian Cancer Plan, which included: prevention and early detection; presentation, initial investigations and referrals; diagnosis, staging and treatment planning; treatment, care after initial treatment and recovery; managing recurrent, residual or metastatic disease; and end-of-life care. Survivorship and research were included as additional categories.

Data Synthesis and the Approach to Data Analysis

Synthesis of the categorical descriptive data extracted from the final articles was conducted using frequency counts (e.g. number of articles related to prevention and early detection). The qualitative data extracted from the final articles (the main argument or idea, and key findings) were synthesised using thematic analysis to inductively identify themes relating to ELSI. Using NVivo (a collaborative qualitative analysis software), AG and AKS familiarised themselves with the data and independently generated codes from the data. AG, AKS and AJN met regularly to consolidate a coding framework and to discuss the themes being generated by the authors from the data. A final set of themes was developed by AG and AKS and reviewed by AJN. A narrative summary to describe the final articles and the ELSI themes generated by the authors was undertaken by AKS, which was reviewed by AG and AJN. Any disagreements were resolved through discussion.

Search terms

Search terms for PubMed:

((cancer[Title/Abstract]) OR (oncology[Title/Abstract]) OR (neoplasms[Title/Abstract])) AND ((bioethics[Title/Abstract]) OR (ethic*[Title/Abstract]) OR (regulatory[Title/Abstract]) OR (ELSI[Title/Abstract]) OR (legal[Title/Abstract]) OR (social[Title/Abstract])) AND ((genetics[Title/Abstract]) OR (genomics[Title/Abstract])) – LIMITS: 2018-present, English.

Search terms for Web of Science:

(TS=(Cancer) OR TS=(Neoplasms) OR TS=(Oncology)) AND (TS=(bioethics) OR TS=(ethics) OR TS=(ethical) OR TS=(ELSI) OR TS=(legal) OR TS=(regulatory) OR TS=(social)) AND (TS=(genetics) OR TS=(genomics)) – LIMITS: 2018-present, English.

Targeted journal searches conducted via Web of Science:

Bioethics-focussed journals and search terms:

- Nature Reviews Genetics
- Genome Medicine
- American Journal of Human Genetics
- Genetics in Medicine
- European Journal of Human Genetics
- Annual Review of Genomics and Human Genetics
- npj Genomic Medicine
- Journal of Medical Genetics
- Heredity
- Journal of Genetic Counselling

(TS=(cancer) OR TS=(neoplasm*) OR TS=(Oncology)) AND (TS=(bioethics) OR TS=(ethics) OR TS=(ethical) OR TS=(ELSI) OR TS=(legal) OR TS=(social)) - LIMITS: 2018-present, English

Cancer-focussed journals and search terms:

- CA: A Cancer Journal for Clinicians
- Nature Reviews Clinical Genetics
- Nature Reviews Cancer
- Lancet Oncology

- Annals of Oncology
- Journal of Clinical Oncology
- JAMA Oncology
- Nature Cancer
- Trends in Cancer
- Cancer Communications
- Familial Cancer

(TS=(bioethics) OR TS=(ethics) OR TS=(ethical) OR TS=(ELSI) OR TS=(legal) OR TS=(social)) AND (TS=(gene*) OR TS=(genom*)) - LIMITS: 2018-present, English

Genetics-focussed journals and search terms:

- Nature Reviews Genetics
- Genome Medicine
- American Journal of Human Genetics
- Genetics in Medicine
- European Journal of Human Genetics
- Annual Review of Genomics and Human Genetics
- npj Genomic Medicine
- Journal of Medical Genetics
- Heredity
- Journal of Genetic Counselling

(TS=(cancer) OR TS=(neoplasm*) OR TS=(Oncology)) AND (TS=(bioethics) OR TS=(ethics) OR TS=(ethical) OR TS=(ELSI) OR TS=(legal) OR TS=(social)) - LIMITS: 2018-present, English

Figure A4.1: PRISMA diagram

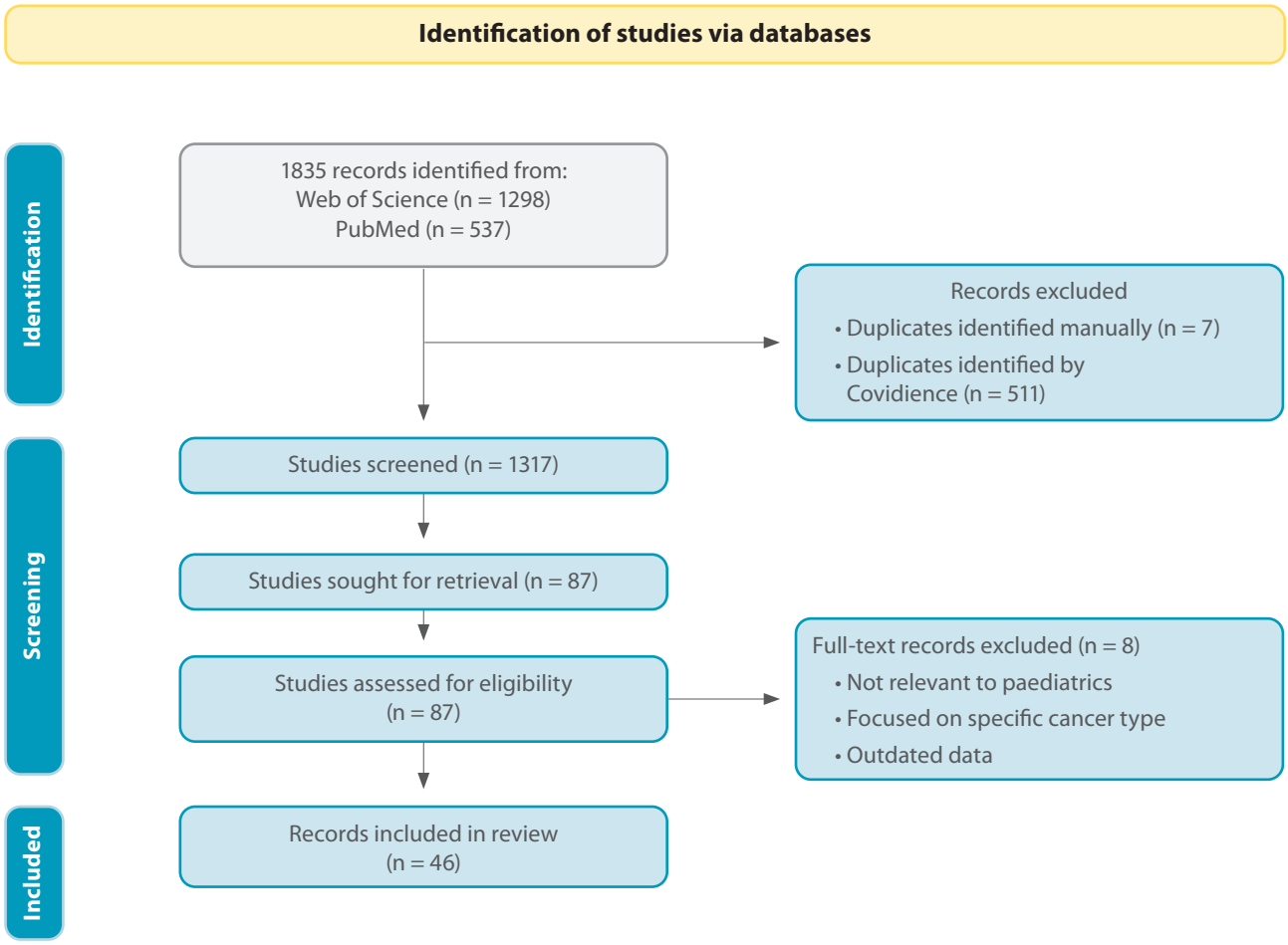


Table A4.1: Descriptive data from 46 final articles in the scoping review

Author	Country	Title	Journal	Type of paper	Empirical data (Y/N)	Relevance to patient journey	Main argument/idea
American College of Obstetricians and Gynecologists, Committee on Genetics 2020	United States	Legal considerations in genetic screening and testing: three case studies: ACOG Committee opinion, number 805	Obstretrics & Gynecology	Normative / theoretical (legal-focused)	Yes	Prevention & early Detection; Diagnosis	The authors discuss legal issues that may arise for obstetrician-gynaecologists when performing genetic testing. Health information should be available to patients and not withheld. Guidance from an ethics committee can be sought out when deciding whether to reveal genetic information to or withhold it from family members who may be at risk.
Bester et al. 2018	United States	Please test my child for a cancer gene, but don't tell her	Pediatrics	Normative / theoretical (ethics-focused)	No	Prevention & early Detection; Diagnosis	The authors address the ethical concerns around genetic testing for cancer predisposition syndromes with childhood-onset malignancies, focusing on whether it is permissible to test the child without their knowledge. The authors discuss the impact of withholding information on future trust in the health care system, the importance of psychological support in pre-test care, upholding parental autonomy and when there is ethical tension, keeping 'the door open' and offering a second opinion may be useful.
Bolt et al. 2021	The Netherlands	Prevention in the age of personal responsibility: epigenetic risk-predictive screening for female cancers as a case study	Journal of Medical Ethics	Normative / theoretical (ethics-focused)	No	Prevention & early Detection	The authors address ethical concerns related to personal responsibility raised by epigenetic risk-predictive tests in cancer population screening. If someone is responsible on grounds of a negative and/or prospective account of responsibility, there may be moral and practical reasons to abstain from moral sanctions. Implementation of epigenetic risk-predictive tests in population-based screening can only be morally acceptable by taking seriously people's varying health literacy, and social and economic situations.

* Country is denoted by the institutional affiliation of the paper's first author.

Author	Country	Title	Journal	Type of paper	Empirical data (Y/N)	Relevance to patient journey	Main argument/idea
Bunnik et al. 2021	The Netherlands	Mainstreaming informed consent for genomic sequencing: A call for action	European Journal of Cancer	Normative / theoretical (ethics-focused)	No	Treatment; Care after initial treatment	Mainstreamed informed consent practices should focus on preparing patients for all possible findings and the layered approach to consent should be considered whereby key information is discussed with the patient, and then subsequent layers comprising additional information are provided on request.
Caffrey 2022	United States	Advocating for equitable management of hereditary cancer syndromes	Journal of Genetic Counseling	Normative / theoretical (ethics-focused)	No	Prevention & early Detection	Genetics professionals who offer genetic testing for hereditary cancers should also think about the downstream impacts, especially equitable access to preventive interventions. This need is based on the concepts of equity and justice. Cancer genetic counsellors can advocate for health equity by collaborating with other disciplines to coordinate care, lobbying state, and national representatives to pass legislation promoting health equity, providing thorough pre-test genetic counselling, and developing a management clinic that helps to ensure follow-up.
Chapman 2022	United States	Ethical, legal, and social implications of genetic risk prediction for multifactorial disease: a narrative review identifying concerns about interpretation and use of polygenic scores	Journal of Community Genetics	Normative / theoretical (ethics- and legal-focused); Mixed approach	No	Prevention & early Detection	Multiple ELSI concerns related to genetic risk prediction were identified through a systematic review. Potential risks of polygenic risk scores include the potential for mis- or overinterpretation, stigma and discrimination, premature commercialization, and inequitable access to benefits. To minimise these harms, there is a need to diversify research, safeguard and share data responsibly, accurately communicate the meaning and limitations of polygenic risk, and develop appropriate guidelines, standards, and regulations.

Author	Country	Title	Journal	Type of paper	Empirical data (Y/N)	Relevance to patient journey	Main argument/idea
Charron et al. 2022	Canada	Integrating hereditary breast and ovarian cancer genetic counselling and testing into mainstream clinical practice: Legal and ethical challenges	Critical Reviews in Oncology / Hematology	Normative / theoretical (ethics- and legal-focused); Mixed approach	No	Prevention & early Detection; Diagnosis	The authors identified legal and ethical issues surrounding the integration of genetic services in general practice. The key issues related to obtaining informed consent, lack of adherence to best-practice guidelines, health professional education, psychosocial impacts of genetic testing, continuity of care, complexity of genetic test results, confidentiality, risks from post-test clinical mismanagement.
Chavez-Yenter et al. 2021	United States	State of recent literature on communication about cancer genetic testing among Latinx populations	Journal of Genetic Counselling	Review - empirical ELSI	Yes	Prevention & early Detection	There needs to be more engagement and partnerships with relevant patient and community groups, to help with aspects such as language and messaging. This may enhance participation in research.
Darling et al. 2022	United States	"Doing good" in US cancer genomics? Valuation practices across the boundaries of research and care in rural community oncology	New Genetics and Society	Normative / theoretical (ethics-focused); Primary research; Mixed approach	Yes	Treatment	The authors explored the valuation practices of "doing good" within genomic science and care. Minimising economic considerations allows clinicians and stakeholders to feel like they are not participating in the marketing of genomics.
Dimond et al. 2022	United Kingdom	Genetic testing and family entanglements	Social Science and Medicine	Primary research	Yes	Diagnosis	The authors highlight the importance of viewing an individual within their social context. The concept of entanglement is used to acknowledge the influence of the family system on how the individual makes meaning of genetic information.

Author	Country	Title	Journal	Type of paper	Empirical data (Y/N)	Relevance to patient journey	Main argument/idea
Ehmann et al. 2020	The Netherlands	Commentary on ICH guideline on genomic sampling and data management-enabling opportunities in drug development and patient treatment	British Journal of Clinical Pharmacology	Position Statement / Report / Guidelines	No	Research and clinical trials	The ICH E18 Guidance encourages the implementation of sampling during clinical trials to enable genomic research. When handling and processing samples and data, the confidentiality and privacy of the individual study participant needs to be maintained. The authors recommend anonymisation, international frameworks for data sharing with external organisations, the development of a globally accepted informed consent for exploratory research and return of clinically relevant findings.
Fritzsche et al. 2023	Germany	Ethical layering in AI-driven polygenic risk scores - New complexities, new challenges	Frontiers in Genetics	Normative / theoretical (ethics-focused)	No	Prevention & early Detection; Presentation Initial investigation and referral; Treatment	A proactive approach needs to be taken to embed ethics in research for polygenic risk scores driven by artificial intelligence. Potential ethical implications of AI driven PRS include (1) complexity regarding fairness and justice, (2) challenges in building trust, communication and education, (3) privacy and autonomy challenges and (4) regulatory uncertainties and further challenges.
Gilbar & Barnoy 2018	Israel	Companions or patients? The impact of family presence in genetic consultations for inherited breast cancer: Relational autonomy in practice	Bioethics	Primary research	Yes	Presentation Initial investigation and referral; Diagnosis; Treatment	In the context of genetic testing, the conventional approach to autonomy is challenged, and a relational approach is applied whereby decisions are made in a social context and the views of the patient's family are considered. The authors propose that clinicians move between relational and individualistic approaches to autonomy, and therefore relying solely on an individualistic approach should be reconsidered.

Author	Country	Title	Journal	Type of paper	Empirical data (Y/N)	Relevance to patient journey	Main argument/idea
Grill & Rosén 2021	Sweden	Healthcare professionals' responsibility for informing relatives at risk of hereditary disease	Journal of Medical Ethics	Normative / theoretical (ethics-focused)	No	Prevention & early Detection; Diagnosis	When moving from targeted genetic testing in cancer to expanded (panel-based) tests, ethical considerations lie in tension with cost-effectiveness analyses. Larger panels increase the chance that an incidental/additional finding, or an uncertain finding, will be made. There are also risks of overdiagnosis or overtreatment, but also possible underdiagnosis or false reassurance. These considerations demand a broader analysis of the place of genetic information in determining valuable health care, as well as the place and definition of patient autonomy within this.
Gustavsson et al. 2020	Sweden	Genetic testing for breast cancer risk, from BRCA1/2 to a seven gene panel: an ethical analysis	BMC Medical Ethics	Normative / theoretical (ethics-focused)	No	Prevention & early Detection; Diagnosis	Results from genetic tests for hereditary cancer have implications for relatives' risk. Targeted prevention is not accessible to relatives unless they know they are at risk. Whose duty is it to make this information available to relatives, and how should this be balanced with other considerations such as patient confidentiality and the right not to know? Rather than apportioning this duty only to patients, health professionals have a general responsibility towards a patient's relatives. They should strive to meet this responsibility within the practical reality of their practice. This goes beyond merely advising patients that they should disclose this information to their relatives.
Hammer 2019	United States	Beyond the helix: ethical, legal, and social implications in genomics	Seminars in Oncology Nursing	Review - empirical ELSI	Yes	Prevention & early Detection; Diagnosis	The authors emphasise the need to adhere to key ethical tenets, namely autonomy, beneficence, non-maleficence and justice. technology is integrated into cancer care. A range of considerations are made on the policies and protocols for how to conduct research studies, interpret the data, and disclose findings to patients.

Author	Country	Title	Journal	Type of paper	Empirical data (Y/N)	Relevance to patient journey	Main argument/idea
Hirsch et al. 2021	Germany	Cancer predisposition in pediatric neuro-oncology-practical approaches and ethical considerations	Neuro-Oncology Practice	Review - empirical ELSI	No	Prevention & early Detection; Diagnosis	Ethical challenges will arise in pediatrics from the widespread use of new diagnostic techniques to identify a tumour predisposition. Guiding principles recommend that any decision has to be made in the best interest of the child and any possible harms must be avoided. The child's current needs and interests should be considered, but also the child's future interests.
Horton et al. 2023	United Kingdom	Discussion of off-target and tentative genomic findings may sometimes be necessary to allow evaluation of their clinical significance	Journal of Medical Ethics	Primary research	Yes	Presentation Initial investigation and referral; Diagnosis	There needs to be a greater focus on the ethical challenges that scientists and clinicians face in the construction of genomic results. Public conversations around genomics need to adapt to prepare future patients for potentially uncertain and unexpected outcomes from clinical genomic tests.
Hunter & Helft 2023	United States	Yes, we can, but should we? Ethical considerations in reporting germline findings from paired tumor-normal genomic testing in patients with advanced cancer	Journal of Clinical Oncology	Normative / theoretical (ethics-focused)	No	Managing refractory, relapsed or progressive disease; End of Life	The identification of a clinically significant germline finding can alter the risk-benefit ratio leading to more informed decisions regarding cancer risk management. However, for patients with advanced cancer, this potential benefit is significantly reduced by their limited prognosis. Discussions about the benefits and risks of genetic testing need to be personalised, informed by the patient's prognosis and align with their values and preferences.
James & Joseph 2022	United States	"It's personalized, but it's still bucket based": the promise of personalized medicine vs. the reality of genomic risk stratification in a breast cancer screening trial	New Genetics and Society	Normative / theoretical (ethics-focused) and Primary research	Yes	Prevention & early Detection; Research and clinical trials; Diagnosis	The inherent tension between the ideals of personalised medicine and the implementation of risk-stratified care on a population scale needs to be addressed, particularly with respect to risk classification and the use of social classifications of self-identified race and ethnicity.

Author	Country	Title	Journal	Type of paper	Empirical data (Y/N)	Relevance to patient journey	Main argument/idea
James et al. 2021	United States	The limits of personalization in precision medicine: Polygenic risk scores and racial categorization in a precision breast cancer screening trial	PLOS One	Normative / theoretical (ethics-focused); Mixed approach	Yes	Prevention & early Detection	There are potential harms of practicing genomic medicine using under-theorized and ambiguous categories of race, ethnicity, and ancestry.
Khoury et al. 2022	United States	Health equity in the implementation of genomics and precision medicine: A public health imperative	Genetics in Medicine	Review - empirical ELSI; Position Statement / Report / Guidelines	No	Prevention & early Detection; Diagnosis; Treatment	A public health agenda is needed to address disparities in implementation of genomics and precision medicine. Public health actions can be centred on policy and evidence development, population-specific needs and outcomes assessment, and assurance of delivery of effective and ethical interventions.
Knoppers et al. 2021	Canada	Of screening, stratification, and scores	Journal of Personalised Medicine	Normative / theoretical (ethics- and legal-focused)	No	Prevention & early Detection	The authors highlight key ethical issues in the provision of risk-stratified cancer care including equitable access, the need for human genetic diversity in risk-scoring algorithms and establishing follow-up plans for alerting patients when risk-scores are updated.
Koch 2022	United States	Medical harm without negligence	Fordham Law Review	Normative / theoretical (ethics-focused)	No	Prevention & early Detection	The authors explore the legal issues surrounding gene reclassification. The potential harms of taking medical action based on uncertain information is often unrecognised. When a patient is harmed by variant reclassification, there is a lack of legal recourse and common-law negligence can fall short.
Kolarcik et al. 2022	United States	Returning individual research results to vulnerable individuals	The American Journal of Pathology	Review, Normative / theoretical (ethics-focused)	No	Research and clinical trials	Participation of vulnerable individuals in research is critical to ensure the development of effective treatments for these groups and to better understand and mitigate health disparities. The decision to offer independent research results to participants raises issues of beneficence and justice that go beyond those of simple research participation.

Author	Country	Title	Journal	Type of paper	Empirical data (Y/N)	Relevance to patient journey	Main argument/idea
Kraft & Doerr 2018	United States	Engaging populations underrepresented in research through novel approaches to consent	American Journal of Medical Genetics	Mixed approach	No	Prevention & early Detection; Presentation Initial investigation and referral	Adapting study materials to be more accessible and meaningful is essential to promote diversity in research participation. This can be achieved using communications experts, stakeholder input, bilingual team members, culturally competent practice, audio and visual aids, accommodating to participants irrespective of their geographical location.
Lévesque et al. 2018	Canada	Ethical, legal, and regulatory issues for the implementation of omics-based risk prediction of women's cancer: points to consider	Public Health Genomics	Review - empirical ELSI; Position Statement / Report / Guidelines	No	Prevention & early Detection	The most relevant issues to be considered for the implementation of genetic risk prediction in clinical practice include: (A) health services planning, (B) information and invitation, (C) consent and data/sample collection, (D) risk calculation and communication of results, and (E) storage of data and residual samples.
Martucci et al. 2022	United States	An examination of the ethical and legal limits in implementing "traceback testing" for deceased patients	Journal of Law Medicine & Ethics	Normative / theoretical (legal-focused)	No	End of Life	The value of traceback testing and its potential benefits are not fully recognised within the confines of traditional legal and ethical frameworks. The authors propose the use of the learning health care system approach, a more integrated ethical framework that emphases the reciprocal obligation through which clinicians, researchers and patients share responsibilities.
Mehta & Kuo 2021	United States	To test or not to test: genetic cancer predisposition testing in paediatric patients with cancer	Journal of Medical Ethics	Normative / theoretical (ethics-focused)	No	Prevention & early Detection; Diagnosis	Ethical issues affecting the decision-making process for genetic cancer predisposition syndrome testing in children with cancer are discussed. Virtue ethics is applied in order to envision the best characters of the patient, parents and healthcare providers and make a decision that will achieve the best outcome for survival.
Morgan 2019	Sweden	Issues and ethical considerations in pharmaco-oncogenomics	Advances in Experimental Medicine and Biology	Mixed approach	No	Prevention & early Detection; Presentation Initial investigation and referral; Diagnosis; Treatment	New technologies and personalised oncology will indisputably improve health outcomes and will demand a more in-depth level of education and collaboration between cancer specialists, patients and researchers.

Author	Country	Title	Journal	Type of paper	Empirical data (Y/N)	Relevance to patient journey	Main argument/idea
Offit et al. 2023	United States	Regulation of laboratory-developed tests in preventive oncology: emerging needs and opportunities	American Society of Clinical Oncology	Normative / theoretical (legal-focused)	No	Prevention & early Detection; Diagnosis; Treatment	There has been a rapid increase in cancer-related genetic testing initiated by the consumer and a lack of regulation and uncertainty about the accuracy of tests. Regulatory oversight is needed for diagnostic genetic tests marketed to consumers to ensure that the tests are safe and effectively used.
Petrova et al. 2022	Spain	BRCA1/2 testing for genetic susceptibility to cancer after 25 years: A scoping review and a primer on ethical implications	The Breast	Normative / theoretical (ethics-focused); Review - empirical ELSI	Yes	Prevention & early Detection; Diagnosis	The authors generated a conceptual map of key ethical challenges related to the BRCA1/2 gene discovery, the test distribution for clinical use, the choice to undergo testing, receiving and disclosing test results, reproductive decision making, and culture-specific ethics. Multidisciplinary ethical discussion is necessary to guide individual decision making, medical guidelines, and societal practices.
Pujol et al. 2018	France	Guidelines for reporting secondary findings of genome sequencing in cancer genes: the SFMPP recommendations	European Journal of Human Genetics	Position Statement / Report / Guidelines	No	Diagnosis; Treatment; Care after initial treatment; Supportive care	Managing secondary findings associated with cancer-related genes has become an emerging concern for clinicians and laboratories because of the extensive use of gene panels and large-scale genomic analysis at somatic and germline levels. The recommendations provide a first step toward standardized guidelines in France and Europe for secondary findings related to cancer-predisposing genes.
Rebbeck et al. 2022	United States	A framework for promoting diversity, equity, and inclusion in genetics and genomics research	JAMA Health Forum	Normative / theoretical (ethics-focused)	No	Research and clinical trials	The authors put forward a framework for equity and inclusion in genomics research. Their framework focuses on participant engagement that promotes a mutual partnership between communities and researchers. The framework can guide our understanding of the health system, cultural, social, policy, community, and individual contexts in which engagement and genomics research are being done.

Author	Country	Title	Journal	Type of paper	Empirical data (Y/N)	Relevance to patient journey	Main argument/idea
Senier et al. 2019	United States	Blending insights from implementation science and the social sciences to mitigate inequities in screening for hereditary cancer syndromes	International Journal of Environmental Research and Public Health	Normative / theoretical (ethics-focused)	No	Prevention & early Detection; Diagnosis; Treatment	The authors argue for a more disciplined use of theory in designing, implementing, and evaluating screening programs that will integrate genomic applications. Conceptual frameworks that guide implementation science could also be integrated with insights from the social and behavioural sciences, in particular they argue for the engagement and recruitment with more diverse partners in implementation and dissemination.
Shreve et al. 2022	United States	Artificial intelligence in oncology: Current capabilities, future opportunities, and ethical considerations	American Society of Clinical Oncology	Normative / theoretical (ethics-focused)	No	Diagnosis; Treatment	Artificial intelligence models applied in the oncology setting generate unique ethical considerations. There is an inherent bias that comes from training the models with data sets that disproportionately exclude underrepresented persons.
Smith-Uffen et al. 2021	Australia	Motivations and barriers to pursue cancer genomic testing: A systematic review	Patient Education and Counselling	Review - empirical ELSI	No	Prevention & early Detection; Diagnosis; Treatment; Supportive care	Consumers are interested in cancer genomic testing. Motivations included ability to predict cancer risk, inform disease management, benefit families, and understand cancer. Barriers included concerns about cost, privacy/confidentiality, clinical utility, and psychological harm.
Stoeklé et al. 2018	France	Molecular tumor boards: Ethical issues in the new era of data medicine	Science & Engineering Ethics	Position Statement / Report / Guidelines	No	Prevention & early Detection; Diagnosis; Treatment; Care after initial treatment; Research and clinical trials	Molecular tumour boards (MTB) play a role in coordinating the flow of biological samples, genetic data and information between patients, clinicians and more recently researchers. As the role and responsibility of MTBs in data sharing continues to grow, we need to reconsider the form and content of informed consent documents.
Tellier et al. 2021	United States	Embryo screening for polygenic disease risk: recent advances and ethical considerations	Genes	Normative / theoretical (ethics-focused); Review - empirical ELSI	No	Prevention & early Detection	New technologies including polygenic risk scores, precision genotyping of embryos, and genomic indices that can predict overall health will benefit an order of magnitude more patients compared to monogenic screening. Determining the health score of an embryo might affect parent-child relationships and lead to potential parental anxiety.

Author	Country	Title	Journal	Type of paper	Empirical data (Y/N)	Relevance to patient journey	Main argument/idea
Tempini & Leonelli 2021	United Kingdom	Actionable data for precision oncology: Framing trustworthy evidence for exploratory research and clinical diagnostics	Social Science & Medicine	Normative / theoretical (ethics-focused); Primary research	Yes	Diagnosis; Treatment; Research	There needs to be an understanding of actionability and trust in data that depends on the goals and resources within the situation of inquiry, and the social epistemology of standards.
Tiller et al. 2023	Australia	Privacy implications of contacting the at-risk relatives of patients with medically actionable genetic predisposition, with patient consent: A hypothetical Australian case study	BioTech	Normative / theoretical (legal-focused)	Yes	Prevention & early Detection	The authors assessed the application of Australian privacy regulations on cascade testing using a hypothetical case study. The authors found that collecting relatives' contact details, and using those details with patient consent, to notify relatives of possible genetic risk, does not breach Australian privacy law, providing that healthcare professionals adhere to regulatory requirements.
Vos et al. 2018	The Netherlands	Ethical considerations for modern molecular pathology	Journal of Pathology	Normative / theoretical (ethics-focused)	No	Diagnosis; Treatment	Pathologists need to take responsibility for the adequate use of molecular analyses and be fully aware and capable of dealing with the diverse, complex, and challenging aspects of tumour DNA sequencing.
Wagner et al. 2022	United States	Exploring access to genomic risk information and the contours of the HIPAA public health exception	Journal of Law and the Biosciences	Normative / theoretical (legal-focused)	Yes	Prevention & early Detection; Diagnosis; End of Life	The HIPAA Privacy rule is currently not a viable approach for traceback programs aiming to inform at-risk relatives and offer testing. Healthcare systems interested in pursuing a traceback program guided by HIPAA PHE, would also need to perform extensive due diligence to understand if the state reportable conditions and information privacy laws allows for disclosures of genetic risk information.
Winkler & Knoppers 2022	Germany	Ethical challenges of precision cancer medicine	Seminars in Cancer Biology	Normative / theoretical (ethics-focused)	No	Prevention & early Detection; Diagnosis; Treatment; Research and clinical trials	The authors argue that research participants need to be able to access personal information such as raw sequencing data and know what happens with their personal data. The authors question the level of consent required for participants to access their genomic data and for the data to be shared with third-party researchers.

Author	Country	Title	Journal	Type of paper	Empirical data (Y/N)	Relevance to patient journey	Main argument/idea
Zhang 2023	United States	Ethics of 'Counting me in': framing the implications of direct-to-patient genomics research	Journal of Medical Ethics	Normative / theoretical (ethics-focused)	No	Prevention & early Detection	Large-scale participatory research projects using a top-down approach have raised many ethical issues that are not addressed by the current legal and regulatory frameworks. This type of research model promotes a sense of personal and social duty for the participant towards the advancement of generalisable knowledge about health and disease in society. The authors question whether these values should be imposed onto the research participant.
Zimmermann et al. 2021	Switzerland	Autonomy and social influence in predictive genetic testing decision-making: A qualitative interview study	Bioethics	Normative / theoretical (ethics-focused)	Yes	Prevention & early Detection; Treatment	Relational and individualistic reasons influence decision-making. Aspects of social influence include responsibility towards relatives, healthcare professionals' influence, individualistic decisions and social relationships. Individuals should be able to determine how much their social environment influences their decision about predictive genetic testing.

Table A4.2: Themes identified from the 46 articles included in the scoping review and illustrative quotes

ELSI themes and subthemes	Illustrative quotes
1. Equity of access	
1.1. Structural barriers to testing and research	"Participation of vulnerable individuals in research is critical to ensure the development of effective treatments for these groups and to better understand and mitigate health disparities." [445] "…it is important to recognize that even though many of the populations with less access to genomics are the same communities with significant negative effects of social determinants of health, genomics will not address disparities that are primarily caused by social determinants." [444] "Health disparities in access to personalised risk stratification levels could arise across different ancestral groups due to a lack of access to rich genomic data concerning such ancestry groups that are often underrepresented in population health databases or large-scale genetic database." [732]
1.2. Access to follow-up care and prevention	"Providers who offer genetic testing for hereditary cancer have an ethical responsibility to ensure that patients identified as having a hereditary risk for developing cancer receive the appropriate, recommended screening and prevention measures, to prevent harm and provide equitable access to resources." [438]
1.3. Impact of testing	"Several articles note the connection between the potential for misunderstanding PGS and possible downstream negative consequences…" [439]
1.4. Engagement with health system and community	"Achieving health equity in genomics and precision medicine will depend on strong collaborations with community leaders, patient organizations, professional organizations, academia, health care systems, health care payers, industry, and charitable foundations. " [444] "With a more robust understanding of the heterogeneity within the Latinx population, researchers, genetics providers and counselors, and policymakers can improve utilization of CGT [cancer genetic testing] and therein health outcomes to advance health equity." [440]
1.5. Minimising costs to patients	"De-economizing the cancer genomics initiative [should take place] by minimizing economic considerations and removing costs to patients was critical to making clinicians and stakeholders feel like they were not simply participating in the marketing of genomics or a market-driven effort to maximize profit." [441] "The discussion in this paper strongly suggests that health economic analysis cannot reasonably be the only basis upon which decisions about what test to implement are made. Decisions based upon such a ground alone could significantly risk ignoring the relevant ethical differences among the different types of testing." [733]
1.6. Bias	"To prevent or minimize bias from being introduced into AI algorithms and CDSS, it is imperative that training data sets and clinical endpoints are inclusive of the underrepresented cohorts and health care settings they are intended to serve…" [451]
1.7. Who should be tested	"concerns about equal and/or equitable access to testing have also been raised, such as whether it should be available to all who request it or restricted to only those who appear to be high-risk." [448]

ELSI themes and subthemes	Illustrative quotes
2. Family considerations	
2.1. Family dissemination and communication	"…communicating genetic information to extended family is ethically complex and that it is still a matter of debate with whom the responsibility lies: the index patient or the genetic counsellor." [448] "when [health care professionals] learn that a particular individual … is at substantial risk of having a hereditary [and preventable] condition…, then [healthcare professionals] have a moral duty to make this information available to her. …[T]his duty is conditional on available resources as well as on balancing against other moral duties." [458]
2.2. Family influence on testing	"the role of family is central for understanding the personal experience of genetic disease and genetic testing." [456] "family presence has an impact on the patient's decisions to undergo genetic testing and preventative operations when she is diagnosed as a carrier." [457]
2.3. Familial benefit	"Certainly, for the patient's family, identification of a clinically significant PV [pathogenic variant] allows for more accurate risk assessment and medical care." [442]
3. 3. Legal considerations	
3.1. Privacy and confidentiality – clinical care	"Direct notification of a patient, at-risk relatives regarding medically actionable genetic information, with patient consent, is not a breach of Australian privacy regulations, providing it is conducted in accordance with the applicable principles set out." [734]
3.2. Privacy – research datasets	"The first area of concern is ensuring privacy protections in the setting of shared large-scale genomic databases. Genetic information is of potential interest to numerous parties, including for-profit organisations and law enforcement agencies." [469]
3.3. Reclassification (law and ethics)	"…individuals can experience both physical and psychosocial harms due to the reclassification of genetic variants, even in the absence of negligence." [467]
3.4. Regulation of commercial testing	"Scholars have long expressed concerns about premature commercialization and potential conflicts of interest… Despite the uncertain clinical value of PGS at the present time […] PGS are increasingly becoming available through direct-to-consumer (DTC) testing companies…" [439]
3.5. Genetic discrimination	"[those who receive positive BRCA results become a] 'cancer previvor' ... [S]hould this information become known to third parties … one can become subject to genetic discrimination … Although various countries have specific legislation and regulations to protect against discrimination … they may only provide an "illusion of protection" due to limited effectiveness in practice." [448] "While some advocate that PGS should be treated like other non-genetic laboratory tests and biomarkers […], others worry that genetic information in the context of multifactorial disease may elicit stigma or discrimination. This potential is particularly acute in certain therapeutic areas, such as mental health, as biogenetic explanations and the de-emphasis of social determinants may be associated with lower social acceptance for individuals with mental health disorders." [439]

ELSI themes and subthemes	Illustrative quotes
4. Consent processes	
4.1. Clinical care	"With the capacity of genomic testing to create difficult-to-anticipate situations, however granular the consent process there may yet be unanswered questions, and it is important to recognise the ethical challenge this presents for scientists and clinicians charged with creating 'results' from a person's genetic code." [474] "The personalized discussion of possible benefits and burdens in the context of the clinical situation (age, cancer type) of patients with advanced cancer, informed by their prognosis, and aligning with their stated values and preferences is in keeping with the ethical principle of acting in the patient's best interests." [442] "There is, therefore, a need to reconsider the form and content of informed consent (IC) documents at all academic medical centers and to introduce dynamic and electronic informed consent." [477]
4.2. Research	"…consent should be obtained to use samples beyond the time that the study is closed." [473] "Providing consent to receive [individual] research results involves qualitatively different decisions for a research participant than the initial decision to participate in research. Institutionally vulnerable individuals are at risk because their lives are controlled by others who may have different priorities than they do." [445]
4.3. Designing consent for diversity	"While researchers can work to ensure that all necessary information is presented clearly, it is much more difficult to gauge comprehension when understanding depends on the motor and reading skill, English proficiency and medical and technological literacy of patients" [469] "Deliberate design efforts focused on creating informed consent processes that actively engage with prospective participants in a meaningful way are essential tools to realizing greater diversity in genomic datasets…. [This] also has the potential to build trust by literally meeting prospective participants where they are." [475]
4.4. Polygenic scores	"Concerns about informed consent, which dominate the ethics literature for genetic testing for monogenic disorders, were not as prominent in the context of genetic risk prediction for multifactorial disease. Although reasons for this are unclear, it could be because PGS are only emerging in clinical and direct-to-consumer settings, are perceived as less specifically actionable than monogenic tests (e.g., they do not provide clarity on disease mechanism), and/or have less significance for family members." [439]
4.5. Advanced cancer patients	"In the setting of advanced cancer, returning germline results raises unique issues. Most significantly, the patient may die before the report's availability. Identification of a surrogate is important to establish during pretest discussions. The surrogate ought to be aware of the testing, understand the patient's decision for proceeding, and be willing to undertake the responsibility of sharing the result with relevant family members. This could well add to the burdens and emotions surrounding the family member's death." [442]
5. Embedding ethics in the application of polygenic scores	"…autonomy was a significant focus in the literature, as it relates to accurate understanding of PGS. Indeed, apart from the issue that PGS will not be equally accurate across different population groups and therefore may have the unintended effect of contributing to health inequities, the major concern about PGS emerging from this review relates to possible misinterpretation, misrepresentation, or misuse." [439] "If we fail to address these challenges, the danger is that not only will advances in AI and/or the applications of PRSs outstrip our ability to understand or regulate them, but that the potential for overreliance and indeed misapplication or misuse from an ethical and social standpoint may create further and insurmountable complexities in the future." [735]

ELSI themes and subthemes	Illustrative quotes
6. Autonomy	"in genetics, a relational approach to autonomy is applied. Decisions are made in a social context, where the relatives, views are heard and taken into account. The findings suggest that the conventional bioethical approach to autonomy, which perceives the decision, making unit as comprising a clinician and an individual patient, is challenged in genetics." [457] "Relational and individualistic reasons play a role in predictive genetic testing decision-making, which affects the conception of autonomous decision-making. While the principlist and relational conceptions of autonomy are competing concepts in the theoretical debate, they are two sides of the same coin when using them as lenses of analysis for predictive genetic testing decision-making. Still, we showed that those declining genetic testing based on individualistic reasons might face implicit or explicit social pressure and that some tested individuals might persuade family members to test out of a sense of duty. However, individuals should be able to freely decide how much their social environment influences their decision for or against predictive genetic testing." [464]
7. Right not to know	"In the case of cascade screening in traceback testing, the family members, right to know remains in tension with the privacy and autonomy rights of the patient. For this reason, the patient, consent has remained essential for ethically and legally sharing genetic risk information with family members." [460] "On one hand, the right to privacy of the index patient may be in conflict with the right to know of the affected family members. On the other hand, the direct disclosure of genetic information to the family members may also violate their right to privacy and not to know." [448]
8. Best interests of the child	"The child's current needs and interests should be considered, but also the child's future interests (e.g., access to surveillance for adult-onset tumours, the child's autonomy, and the right not-to-know, i.e., the child's right to an open future). This may also affect the interests of other family members involved, especially the interests of the child's parents should also be considered. It may at least be conceivable that a potentially life-saving diagnosis of a cancer predisposition in a parent is indeed in the interest of the child." [459] "The integrity of trusting relationships is an important value. One should carefully think about the effect that withholding information may have on this child's future relationships with health care professionals, her parents, and on her future decision-making." [736]
9. Trust	"These trustworthiness-seeking data management practices sit squarely at the heart of cancer genomics." [737] "The relationship to patients must be managed respectfully and constructively, of course, and so confidentiality and trust should be given a high priority when they are at stake." [458]
10. Avoiding harm	"Oversight and support mechanisms should be implemented to ensure the quality of genetic healthcare services is maintained when allowing non-genetic health professionals to undertake some key genetic tasks." [455] "Not all medical tests … [and]results, are created equal. Ambiguous and changing genetic test results can exacerbate uncertainty … and, in some cases, lead to misguided and contraindicated medical interventions. ... In short, more information does not always mean more certainty in medical decision-making." [467]
11. Managing community expectations	"[There is a] need for scientists, clinicians and society to become comfortable in the "messy zone" of genomic data, and the importance of working to develop societal perceptions of genomic testing in line with technical realities." [474]
12. Screening principles and ethics	"the traditional ethical problems with screening (such as overtreatment) is more problematic with regard to the [expanded] panel" [733] "Another challenge inherent in implementing population health screening programmes is establishing the subsequent benefit, harm balance thereof." [732]

ELSI themes and subthemes	Illustrative quotes
13. Personal responsibility for health	"…there is a tension between the broader societal shift to personal responsibility of individuals for their own health and one of the distinguishing features of epigenetics, namely the effects of environmental factors on epigenetic processes. Who ought to be held responsible for the detrimental effects on a person's health caused by environmental pollution or unhealthy work-conditions?" [437]
14. Racism	"Our research highlights the potential harms of practicing genomic medicine using under-theorized and ambiguous categories of race, ethnicity, and ancestry." [443] "It is important to note that although a focused population health approach to genomics might broaden access to genomic innovations, a public health approach including community engagement will be needed to address issues of trust, many of which are rooted in long-standing community experiences with structural racism." [444]
15. Impacts on future childbearing	"[I]ronically, the availability of an additional choice of PGD [i.e., PGT-M] can put constraints on previvors' choices regarding reproduction, because once an option becomes available that eliminates the increased cancer risk, the other options (e.g., a natural pregnancy) seem less justifiable" (Petrova et al 2022, synthesising Rubin & de Melo Martin, 2014). [448,738]
16. Data storage and sharing	"In the long term, the adoption of concerted national and international institutions dedicated to the clinical implementation of personalised medicine and to the creation of common platforms for data storage, harmonisation and interpretation are necessary… Barriers to such data-sharing include non-harmonized or unclear data protection laws and data localization requirements, which can preclude the creation of large representative datasets. Legal doctrines including collection limitation and data minimization, purpose limitation, and strict interpretations of consent requirements and anonymization requirements, all common to data protection law, can impede the collection of rich datasets and the efficient sharing thereof." [732] "The actionability of cancer genomics data thus rests on a nested architecture of dynamic, yet standardised, procedures of data management, in which multiple organisations committed to demonstrating trustworthiness intervene in a sequence of operations of data management and interpretation. Beyond the trust in standard procedures, little else is firm in this chain of custody. These trustworthiness-seeking data management practices sit squarely at the heart of cancer genomics, making it possible to bear an increasing amount and diversity of data upon each other, while the chance for individual researchers to directly scrutinize sources is decreased." [737]
17.Role of health professionals: genetics and non-genetics specialists	"Most concerns regarding non-genetic health professionals undertaking genetic tasks relate to the ethical principle of non-maleficence, which is interested primarily in preventing harm which could result from nongenetic professionals using sub-optimal practices when delivering genetic health services. We agree with the position of these authors that oversight and support mechanisms should be implemented to ensure the quality of genetic healthcare services is maintained when allowing nongenetic health professionals to undertake some key genetic tasks." [455]
18.Incidental, secondary and/or unsolicited findings	"We argue that when patients undergo genomic sequencing as part of their cancer care, they should know at a minimum that doing so may entail learning about a suspected germline mutation, or, less likely, VUS (variants of uncertain significance) or other unsolicited findings, which may be hereditary, and for which they may need to be referred to a clinical geneticist for follow-up." [472] "When it comes to individual cases, the presence of VUS (variants of uncertain significance) and SF (secondary findings) only adds to the already high complexity of the genetic and statistical information patients and counselors need to discuss. As a result, ensuring informed patient decision making only becomes more difficult, especially having in mind that a substantial proportion of the general population has low numeracy and health literacy skills, both essential for understanding cancer risk and risk reduction information. We should not forget that deliberations would also be replete with emotions, especially among families in which multiple members have been affected by cancer, 'and thus fear and terror of developing cancer are beyond what most people would experience.'" [448]

Appendix 5: Health Economics Section Methods

We conducted a systematic literature review in line with Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) Guidelines.[739]

Overview

The aim of the systematic review was to identify articles that included information regarding 1) genomic testing/ technology and 2.1) economic evaluation or 2.2) financial toxicity or 2.3 patient preferences and 3) cancer. The primary aim of this review was to gather and synthesise the available evidence pertaining to health economics, genomics, and cancer to better understand the current state of the literature.

Search strategy

The search strategy was developed in collaboration with a biosciences research librarian at the University of Melbourne. The search terms were developed to include all concepts that related to genomic medicine [740-746] and cancer [747,748] in line with published systematic reviews in the literature. The health economics component of the review had three subcomponents, for which search terms were also developed in line with systematic reviews in the literature, they were economic evaluation,[740,743,744,747,748] financial toxicity [748] and patient preferences.[749,750] The search strategies were developed to for 4 data bases Medline and Embase via the Ovid platform, and Cumulated Index to Nursing and Allied Health (CINAHL) and EconLit via the EBSCOhost platform. The final search was run using medical subject headings and free text that was limited to title and abstract. The final search combined search terms using Boolean operators. Search results were limited human studies published in English after the 1st of January 2018.

Study Selection

The final search was conducted on the 12th of December 2023. All search results were downloaded and imported into Covidence systematic review software. Duplicates were removed and 3 reviewers were responsible for title and abstract screening. A single reviewer (MB) conducted all title and abstract screening with 10% of articles being reviewed by a second reviewer (RP) and 10% of articles being reviewed by a third reviewer (FSG) to ensure consistency and low discrepancy. The same process was used for the full text and data extraction process whereby a single reviewer (MB) completed the process in its entirety and quality assurance checks were completed by 2 reviewers (RP & FSG). Inclusion criteria was any full original research article that included all three of the key subjects, cancer, genomics, and health economics (economic evaluation, financial toxicity or patient preferences). Review articles were excluded.

Data extraction

A data extraction template was developed using Covidence research software. It contained a generic starting template which gave general background about the article which finished with a question regarding the type of health economic study that was being conducted. For each other health economics subtypes economic evaluation, financial toxicity or patient preferences, the reviewer was directed to complete the corresponding data extraction template. The data collected included type of cancer, point on the cancer continuum, germline or somatic testing, type of health economic evaluation. For economic evaluation data included perspective, country, type of evaluation, model type, model structure cost, outcomes cost-effectiveness estimates, time horizon, intervention, comparator, utility source WTP threshold applied, probability of cost-effectiveness, conclusions, and whether equity, system capacity and patient preferences were included. For financial toxicity it included OOP costs, impact on health outcomes, impact of private health outcomes and elasticity estimates. For patient preferences it included sample size, statistical analysis used, marginal rate of substitution, marginal WTP, total WTP.

Data analysis

All extracted data was organised into the appropriate health economic subtype. Economic evaluation was organised into the points on the cancer continuum and then further broken down into types of cancer, data were then narratively reviewed and synthesised. Financial toxicity data was subdivided according to the methodology applied and analysed narratively. Patient preference data was broken down according to whether it considered preferences for getting tested, preferences for receiving results or preferences for treatment.

Glossary

Term	Description
Cancer mutational signatures	Characteristic patterns of genetic variants found throughout the genomes of cancer cells, arising from disruptions in DNA repair processes
Chromosomes	Located in the centre of the cell. Each person typically has 46 chromosomes, with one copy inherited from each parent. The role of chromosomes is to carry genes.
Copy Number Variants (CNVs)	Sections of the genome are repeated or deleted (>1,000 bases in size)
Circulating tumour DNA (ctDNA)	DNA shed by tumour cells into the bloodstream which can serve as a proxy for tumour genomic sequencing
Depth of coverage	The number of times that a given nucleotide in the genome has been read using genomic sequencing
DNA	Composed of nucleotides, DNA carries the genetic information essential for the growth and functioning of organisms
Driver variants	Variants/mutations which drive the development, growth, and invasion of a cancer
ELSI	Ethical, legal and social issues
Gene	Section of DNA that codes for a protein. Can be further divided into subsections called exons (coding region) and introns (non-coding region)
Gene expression	The process in which information coded in genes is turned into a function e.g. synthesizing proteins. Genetic alterations can result in abnormal expression
Gene fusion	Genomic rearrangements lead to the fusion of two genes and subsequently abnormal protein production
Genome-wide association studies (GWAS)	Identifies single nucleotide polymorphisms (SNPs) responsible for certain genetic traits across the genome by comparing the frequency in large groups of affected and unaffected individuals
Genomic sequencing	Sequencing process that shows each letter of the genetic code for a specific section of DNA or RNA, mostly performed using next generation sequencing
Genotyping	The process of determining the DNA sequence, referred to as the genotype, to detect the presence or absence of specific variants
Germline variant	A genomic variation that is present from conception and is inherited or can arise for the first time in an individual (de novo variant)
Hereditary cancer syndrome	Caused by an inherited germline variant which increases an individual's risk of developing certain tumours, often at a younger age

Term	Description
ICER	Incremental cost-effectiveness ratio (the difference in costs divided by the difference in outcomes)
LY	Life-year
Liquid biopsy	A genetic sample extracted from blood that can include ctDNA, circulating tumour cells, protein biomarkers and cell-free RNA
Matched tumour	Both tumour and unaffected samples (e.g. blood or saliva) are collected and tested simultaneously to determine whether variants are germline or somatic
Microsatellite Instability	Microsatellites are short sets of repeated DNA that are not present in the corresponding germline DNA, which can contribute to genetic instability in cells
Next generation sequencing (NGS)	Technique used for DNA and RNA sequencing and consequently the detection of genetic variants
OOP	Out-of-pocket costs
Panel testing	Involves sequencing the exons of a specific group of genes, ranging from tens to hundreds of genes
Pathogenic variant/ mutation	An alteration of the DNA code that affects the quantity or quality of protein produced and can increase the risk of particular types of disease
Polygenic risk score (PRS)	A numerical assessment to summarise an individual's genetic susceptibility to a particular trait or disease (such as cancer), based on many genetic markers across the genome
QALY	Quality-adjusted life-year (measure of disease burden including both the quality and quantity of life lived)
RNA	A molecule that is translated into the amino acids that build proteins
RNA sequencing	Technique that quantifies the RNA in a sample and can assist in identifying which genes are turned on, or expressed, in a cell
Single nucleotide polymorphism (SNP)	A common genetic variation that occurs in the population. In combination with environmental/lifestyle factors, some SNPs increase the chance of developing certain conditions (e.g., cancer)
Somatic variant	New genomic variations that arise in individual cells or groups of cells and are not inherited
The tumour mutation burden (TMB)	The number (or rate) of somatic variants in the DNA of cancer cells
Variant of uncertain significance (VUS)	A genetic variant whose role in disease is not yet understood or determined
Whole exome sequencing (WES)	Identifies nucleotide variants in the exons and the areas of introns immediately prior to and following exons
Whole genome sequencing (WGS)	Identifies nucleotide variants in the exons and introns (entire gene), as well as structural variations (areas of the genome which that have been rearranged)
WTP	Willingness-to-pay