

WHITE PAPER

Realising the full potential of genomics to personalise healthcare

Future directions for health technology
assessment in Australia

March 2022

Prepared by HTANALYSTS

AIDH

InGeNA Precision Medicine Workforce Competency Framework
March 2022

ISBN 978-0-6454659-0-7

Australasian Institute of Digital Health
ABN: 80 097 598 742
ACN: 097 598 742
Level 1, 85 Buckhurst Street
South Melbourne VIC 3205
Australia
+61 3 9326 3311
info@digitalhealth.org.au
www.digitalhealth.org.au

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Foreword

Healthcare is being transformed by rapid advances in technology which are increasingly enabling the personalisation of healthcare. In particular, genomic technologies are enabling a more targeted approach to managing an individual's health by providing insights into the molecular basis of their disease. The potential benefits and promise of this rapidly evolving approach to healthcare has led to Commonwealth and State / Territory Government investment to support research into genomics together with initiatives to support the integration of genomics into clinical practice.

However, genomics is complex and evolving rapidly. Therefore, successful integration into clinical practice will require effective collaboration between the different stakeholders in the genomics value chain, including Government, pathologists, healthcare professionals, consumers and suppliers of genomic technologies. It was this recognition, and the need for better understanding the needs of consumers, that led a group of forward-thinking genomic technology suppliers to unite as InGeNA - the Industry Genomics Network Alliance - in 2020.

Equitable and affordable access to precision medicine is central to harnessing the true potential of genomics and as such, it forms one of InGeNA's strategic pillars with priority given to addressing barriers to such access. There was a view by InGeNA members that equitable access to genomic testing could be improved if health technology assessment (HTA) processes could be improved. This view aligns with numerous submissions to the *Parliamentary Inquiry into approval processes for new drugs and novel medical technologies (the Parliamentary Inquiry)*.

In early 2021, Health Technology (HT) Analysts were commissioned to develop a white paper identifying current HTA challenges and potential solutions for genomic tests, particularly large panel tests. The findings of this white paper are the result of an extensive 6-month process informed by published literature and broad stakeholder consultation conducted in an ever-changing policy environment with the commencement of the National Medicines Policy (NMP) Review and the Medicines Australia – Government Strategic Agreement (*the Strategic Agreement*).

The recommendations made to InGeNA in this white paper include those which relate to the information needs of HTA advisory committees, processes leading up to and after HTA advisory committee consideration and evidentiary requirements.

At the time of writing this Foreword, the recommendations made in the *Parliamentary Inquiry's* final report "The New Frontier – Delivering Better Health for All Australians" is awaiting a response by Government. Notably, the report includes various recommendations which relate to genomics, including establishing a national genomics testing program jointly funded by different levels of Government to provide equitable access to genomic testing nationwide.

InGeNA believes that the recommendation made in this white paper strongly align with many of the recommendations of the *Parliamentary Inquiry* but also offer specific suggestions about what can be actioned and how. Notably, aligned with the concept that integration of genomics requires a collaborative approach across stakeholders in the value chain, the recommendations outlined in this white paper offer tangible actions for policy-makers, industry and consumers.

As InGeNA, for 2022, we will focus on how we will progress and build on the recommendations in this report and collaborate with other stakeholders nationally and internationally. This will be particularly important to ensure that we remain aligned and co-ordinated in a fluid policy environment and can continue to support the growing momentum behind genomics and precision medicine.

As Chair of InGeNA, I would like to thank MTPConnect whose generous support enabled this white paper to be developed. I would also like to thank the numerous participants at the workshops who donated their time to inform this process and the consumer members of InGeNA who have actively engaged, participated and informed this process. Lastly, I would also like to thank the members of InGeNA's Access and Equity Working Group who have helped to develop, drive and in a myriad of other ways support this project.

It is my sincere hope that this white paper can inform not only the genomics-related initiatives outlined in the *Parliamentary Inquiry* but also those outlined in the *Strategic Agreement* and the NMP Review and that InGeNA's work can take us a step closer to enabling all Australians to have affordable access to the benefits of precision medicine.

David Bunker
InGeNA Chair

This report was commissioned by InGeNA and prepared by HTANALYSTS. The information for this report was sourced from published literature and from stakeholder interviews. Given the intent of the report, which was built recommendations based on feedback obtained through workshops and stakeholder consultations, opinions may be reported without supporting evidence. The intention was to accurately reflect the outcomes of the consultations and the emerging themes. Where opinions conflicted, the report attempts to present the different perspectives, where possible. Where information has been obtained from third-party sources, this is referenced.

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Executive Summary

Background

Industry Genomics Networks Alliance (InGeNA) facilitates collaboration between industry players, as well as with consumers, academia, and government to help inform and develop policy to make Australia a world leader in genetic and genomic technologies in healthcare.

In Australia, Health Technology Assessment (HTA) is used by decision makers to evaluate new genetic and genomic technologies. HTA involves a range of processes and mechanisms that use scientific evidence to assess the quality, safety, efficacy, effectiveness, and cost-effectiveness of health services. Genetic and genomic technologies are typically evaluated by the Medical Services Advisory Committee (MSAC) for the purposes of federal funding. Besides MSAC, genetic and genomic technologies may also be evaluated by other payors, such as the state and territory governments or private health insurers. The focus of this report is the MSAC HTA pathway as the predominant access pathway for new genetic and genomic technologies in Australia.

InGeNA believes that the challenges in the HTA processes for genetic and genomic technologies are having a negative impact on equitable, affordable, and timely patient access to healthcare across Australia. Where and how patients access genetic and genomic technologies in the clinical setting is variable, as are the costs incurred by patients. With the predicted increase in use of these technologies in the coming years and the speed with which new technologies are being developed and moving from the research to clinical setting, the current access and affordability issues are likely to grow if left unaddressed. Additionally, the rapid development of genetic and genomic technologies blurs the delineation between research and the clinical setting, challenging existing HTA pathways.

Acknowledging this challenge, InGeNA commissioned HTANALYSTS to identify HTA issues and potential solutions for genetic and genomic technologies, with a view to these solutions being included in HTA guidelines and having a broader impact on shaping policy and legislation. In addition, the proposed solutions could potentially broaden the understanding of the current lack of universal funding for genetic and genomic technologies in many conditions and the impact on patients and the broader society.

Consultations

This whitepaper included input from over 60 stakeholders. The consultation process involved background research including a literature review. This formed the pre-read materials for stakeholders prior to attending a series of workshops. The workshops were held with key stakeholder groups to identify perceived issues as well as develop or refine solutions. Following consultations, the draft recommendations were independently reviewed by the Reimbursement Expert Advisory Panel (REAP) before HTANALYSTS developed the final recommendations in the form of a preliminary roadmap.

A variety of perspectives was obtained through the workshops, however several core issues were identified. The identified issues primarily related to the overall MSAC process and were not necessarily specific to genetic and genomic technology applications. The report aims to reflect the outcomes of the consultations and the emerging themes as presented by the different stakeholders. While the consultations identified consistent themes regarding the HTA challenges and proposed solutions, between the stakeholders, there were subtle nuances. For example, the Department of Health and MSAC stakeholders focused on challenges related to germline applications (e.g. cascade testing) while industry stakeholders focused primarily on challenges around co-dependent applications (e.g. test and drug combinations).

Workshop summary

WORKSHOPS	1	Industry representatives - Defining critical issues
	2	Industry representatives - Developing solutions
	3	Academic & clinicians – Group 1 - Revisiting issues & refining solutions
	4	Patients & patient representatives - Refining solutions & defining impact
	5	Academics & clinicians – Group 2 - Revisiting issues & refining solutions
	6	Government & MSAC representatives - Revisiting issues & refining solutions
	7	Consumer, evidence & engagement unit (Government) - Revisiting issues & refining solutions
	8	MSAC chair - Revisiting issues & refining solutions

From the consultations the following method was adopted:

1. Report challenges raised by stakeholders and assess for impact; consolidate into themes.
2. Report proposed solutions as presented by stakeholders and assess for feasibility; consolidate into themes.
3. Connect challenges and solutions to ensure key challenges are addressed.
4. Gather feedback from the Reimbursement Expert Advisory Committee (REAP).
5. Develop recommendations and preliminary roadmap.

A summary of consolidated challenges and solutions as well as the recommendations and preliminary roadmap is provided on the following pages.

Challenges identified by stakeholders

The impact of these challenges on HTA processes (e.g. delays in access, lack of alignment and lack of consultation) was assessed.

		What is the impact?
1	Length & efficiency The MSAC process is long and complex for genomic applications, which does not match the evolution of clinical practice	Delays in access due to application complexity
2	Stakeholder alignment There is misalignment between key stakeholders on the critical HTA challenges and potential solutions for genomics	Difficult to progress reform without alignment on challenges
3	Evidentiary requirements MSAC evidentiary requirements are difficult to meet and the HTA process struggles to cope with some genomics applications (e.g. large panel applications)	Delays in access as unable to meet evidentiary requirements
4	Low transparency There is a lack of transparency around MSAC decision making and ongoing reforms in the MSAC process	Difficulty to progress reform without alignment on current initiatives
5	Patient participation Lack of opportunities for patients and patient representatives to be educated, engage and be equally represented across disease areas in the HTA process	Inadequate consultation with patients
6	Value definition MSAC adopts a narrow definition of value which inhibits the adoption of new genomic technologies	Delays in access as value cannot be demonstrated
7	Incremental change A paradigm shift in clinical practice is required to harness the benefits of genomics, whereas MSAC deals with incremental change	Delays in access due to application complexity
8	Funding programs Both federal and state governments are responsible for funding genomics and have different pathways creating ambiguity and opportunities for funding delays	Delays in access due to different funding pathways
9	MSAC legislation There is no requirement for the government to act on MSAC recommendations	Delays in access due to recommendations not progressing

Consolidated solutions identified by stakeholders

The solutions identified during the workshops were refined and consolidated to provide InGeNA with a targeted set of solutions. Stakeholders were asked to provide input on the structure, feasibility, and relative impact of the proposed solutions. Solutions were developed further to identify specific activities to form a preliminary roadmap that maximised efficiency. This included prioritising short-term feasible projects with maximum impact and collaboration where possible.

	Information needs of the HTA advisory committees	How to implement the solution?
1	<ul style="list-style-type: none"> Develop a framework to evaluate large gene panels Establish a managed entry framework Have industry representation on MSAC 	Collaboration with Medicines Australia (MA)
	<ul style="list-style-type: none"> Develop a framework to value increased knowledge in comparison to other areas of value 	Living guidance and collaborations with MA
	<ul style="list-style-type: none"> Increase collaboration between federal and state evaluation processes Establish a national policy to guide decisions on access to genomic testing and the ethical issues raised by genomic information 	Long term structural reform
	Processes before and after the HTA advisory committee consideration	
	<ul style="list-style-type: none"> Increase alignment between applicants addressing somatic and germline variants 	Education to address alignment on issues
	<ul style="list-style-type: none"> Have greater industry/stakeholder collaboration on applications 	Collaboration
2	<ul style="list-style-type: none"> Carry out horizon scanning Increase patient and patient representative engagement 	Collaboration with MA
	<ul style="list-style-type: none"> Increase transparency around ongoing reform/guidelines updates and an opportunity for stakeholders to be part of the conversation Improve and update the MSAC website 	Collaboration with the Department of Health
	<ul style="list-style-type: none"> Improve guidance based on latest MSAC decision making (without having to review through public summary documents [PSDs]) 	Living guidance
	<ul style="list-style-type: none"> Future proof applications 	Living guidance, education to address alignment on issues and promoting better collaboration
	Evidentiary requirements	
	<ul style="list-style-type: none"> Improve the linkage between research and MBS Clarify federal vs state funding by expanding the National Health Reform Agreement to include genomics or leveraging experience with the Jurisdictional Blood Committee (JBC) Develop a central data repository for genomic information Establish legislation to compel the government to act on MSAC decision making 	Long term structural reform
<ul style="list-style-type: none"> Develop mechanisms to allow for special pricing arrangements 	Collaboration with MA	
3		

Recommendations and preliminary roadmap

In establishing a program of reform, it is recommended that InGeNA prioritise high-impact solutions that can be actioned unilaterally. Secondly, many of the issues and potential solutions have broad applicability beyond genetic and genomic technologies. Therefore, there may be overlap of InGeNA's interests with that of other stakeholders who also deem the MSAC process as a rate limiting step to access innovative treatments. Finally, it is critical to consider and address fundamental structural challenges such as funding.

Short term

- Better defining the problem**
Commission a report to characterise historical and current MSAC process metrics

By working to better define the problem through quantitative metrics, this solution will increase **stakeholder alignment**. In addition, as solutions are implemented, this data can be used to increase **transparency** around progress to improve the **length and efficiency of the MSAC process**.

- Education to address alignment on issues**
Conduct targeted education with industry and non-industry stakeholders focusing on potential issues across somatic and germline MSAC applications as well as practical solutions

This solution is a fundamental building block as it will improve **stakeholder alignment** and help address other solutions by allowing stakeholders to clearly articulate issues and solutions during reform discussions and ensure any reform initiatives do not adversely impact one category of applications over the other (somatic vs germline).

- More specific guidance based on latest MSAC decision making to increase the probability of approval for genomics applications**
Establish 'living guidance' which compiles best practices and MSAC interpretation from PSDs, allowing future applications to leverage this guidance to enhance the probability of success

Applicants will be able to leverage MSAC precedents, decision-making and interpretation to enhance the probability of successful outcomes. This would address the **length and efficiency of the MSAC process** and **stakeholder alignment**. Applicants will be able to better meet MSAC **evidentiary requirements** and **value definitions**.

- Establishing priority MSAC applications that can be undertaken collaboratively**
Create a program of work to update MBS items aligned with current practice, particularly with regard to panel testing in oncology

This could **improve the length and efficiency of the MSAC process** by potentially reducing the number and complexity of co-dependent applications being evaluated by MSAC – providing benefit to multiple stakeholders. The **evidentiary requirements** for submissions would be reduced as the testing algorithm would be simplified through the consolidation of sequential single variant testing into a common panel.

Long term

To achieve long-term reform, structural issues such as funding should be addressed in a step-wise manner. While the feasibility of solutions identified during consultations vary, it is **recommended a roadmap is established to address the issues** below:

- Clarifying and aligning federal vs state funding and evaluation processes
- Legislation or an agreement to compel the Government to act on MSAC decision making
- A national policy to guide decisions on access to genomic testing and the ethical issues raised by genomic information

A roadmap should include consultation with InGeNA members and other stakeholders and a detailed timeline of activities.

Collaborations

- Medicines Australia**
Work closely with MA on projects established in the 2021 Deed of Agreement to ensure the genomics perspective is represented

The HTA review within the new Strategic Agreement is a watershed moment which could potentially address many issues such as **length and efficiency of the MSAC process, evidentiary requirements, value definition and transparency**. The review could also address broader issues such as **funding programs** and **MSAC legislation**. In addition, the reforms to consumer engagement should be harmonised across the PBAC and MSAC process which would increase **patient engagement**.

- Department of Health**
Establish a forum for an ongoing dialogue with the Department of Health. A working group could also provide a forum to discuss issues and increase accountability

Greater alignment with the Department of Health will address the issue of **transparency**, which was noted on multiple occasions during consultations. In addition, establishing a working group would also provide a forum to work towards addressing other issues such as **evidentiary requirements** and **value definitions** as well as increasing accountability.

- Promoting better collaboration for genomics applications**
Promote collaborations between industry and non-industry stakeholders and establish a framework for industry collaborations. This should include historical examples and best practice methods to ensure independence is maintained

By promoting collaboration on future MSAC applications several issues are addressed. This includes reducing the **length of the MSAC process and improving efficiency**. In addition, **patient participation** can be enhanced, and **stakeholder alignment** improved.

Abbreviations

aCGH	Array comparative genomic chain reaction (PCR)
ACM	Advisory Committee on Medicines
ADEC	Australian Drug Evaluation Committee
BRCA1	Breast cancer 1
BRCA2	Breast cancer 2
CALR	Carcinogenic mutated form of the calreticulin gene
CF	Cystic fibrosis
CUC	Clinical Utility Card
DNA	Deoxyribonucleic acid
ESC	Economic Sub-Committee
FISH	Fluorescence in situ hybridisation
FXS	Fragile X syndrome
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
InGeNA	Industry Genomics Network Alliance
ISH	in situ hybridisation
JBC	Jurisdictional Blood Committee
LHNs	Local Health Networks
MBS	Medicare Benefits Schedule
MEA	Managed Entry Agreements
MLPA	Multiplex ligation-dependent probe amplification
MPN	Myeloproliferative neoplasms
MPS	Massively parallel sequencing
MRFF	The Medical Research Future fund
MSAC	Medical Services Advisory Committee
NGS	Next-generation sequencing
NHRA	National Health Funding Agreement
NIPT	Non-Invasive Prenatal Testing
PASC	The PICO Advisory Sub-Committee
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCR	Polymerase chain reaction
PICO	Population, Intervention, Comparator and Outcome
PVI	Patient Voice Initiative
RANZCOG	The Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RCPA	Royal College of Pathologists of Australasia
REAP	Reimbursement Expert Advisory Panel
RhD	Rhesus D
SMA	Spinal muscular atrophy
SNP	Single nucleotide polymorphism
SoC	Standard of care
SPA	Special Pricing Arrangements

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Whitepaper Introduction

InGeNA facilitates collaboration between industry players, as well as with consumers, academia, and government, to help inform and develop policy and make Australia a world leader in genetic and genomic technologies in healthcare.

In Australia, Health Technology Assessment (HTA) is used to evaluate new genetic and genomic technologies. HTA involves a range of processes and mechanisms that use scientific evidence to assess the quality, safety, efficacy, effectiveness, and cost-effectiveness of health services. Genetic and genomic technologies are typically evaluated by the Medical Services Advisory Committee (MSAC). Genetic and genomic technologies may also be evaluated by other stakeholders, such as state and territory governments or private health insurers. The focus of this report is the MSAC HTA pathway as the predominant access pathway for new genetic and genomic technologies in Australia.

InGeNA believes that challenges in HTA for genetic and genomic technologies are having a negative impact on equitable, affordable, and timely patient access to healthcare across Australia. Where and how patients access genetic and genomic technologies in the clinical setting is variable, as are the costs incurred by patients. With the predicted increase in clinical use of genetic and genomic technologies in coming years and the speed with which new technologies are being developed and moving from the research to clinical setting, the current access and affordability challenges are likely to grow if left unaddressed. Additionally, the rapid development of genetic and genomic technologies blurs the delineation between research and the clinical setting, challenging existing HTA pathways.

Numerous published articles outline the challenges associated with the current HTA methodology for genetic and genomic technologies (1, 2). Far fewer though have identified solutions with a level of granularity that would be useful for the industry in providing the clarity it needs for lodging submissions through a HTA process such as MSAC. While MSAC has amended its guidelines for genetic and genomic technologies (3), the broad industry view is that these amendments are still unclear and insufficient to provide the clarity required. Additionally, the administrative processes associated with applications for genetic and genomic tests will also pose challenges for the current MSAC processes, and more pragmatic solutions may need to be adopted.

InGeNA commissioned HTANALYSTS to identify HTA challenges and potential actionable solutions. The proposed solutions may broaden the understanding of the current lack of universal funding for genetic and genomic technologies in many conditions and the impact on patients and the broader society.

Consultation Process

This section provides an overview of the consultation process, including preliminary work and consultation workshops

The process to develop this paper was extensive and included background research and a literature review to inform the consultation process and several consultations with stakeholder groups (see *Overview of Consultation Process*). Following the consultation process, draft recommendations were independently reviewed by the Reimbursement Expert Advisory Panel (REAP) before final recommendations were developed by HTANALYSTS to form a preliminary roadmap.

Importantly, the scope of challenges and solutions included all types of genetic and genomic applications (e.g. diagnosis, prognosis or co-dependent companion diagnostics).

Preliminary work

A systematic literature review was undertaken by a member company of InGeNA which identified several HTA methodology and process challenges and solutions in the evaluation of new genetic and genomic technologies.

A literature search was conducted for articles from database inception to 21 April 2021. Studies were included if they met pre-specified inclusion criteria to identify any articles that explore HTA challenges and solutions around genomic technologies for diagnosis and/or part of personalised medicine.

The search identified 422 publications, of which 34 fulfilled the inclusion criteria. A total of 47 studies were analysed including 13 additional studies that were identified through convenience searching and a review of the study bibliographies.

Challenges identified from the literature were categorised into seven themes:

1. HTA process
2. PICO
3. Data and evidence base
4. Defining value of health technologies
5. Economic analysis
6. Pricing and budgetary impact
7. Other considerations in reimbursement decision-making

The review then outlined potential solutions addressing each of the issues. These challenges and solutions identified in the review formed part of the foundation for the subsequent consultation process.

Further validating these findings, a recent local review of MSAC's experience in assessing genetic and genomic technologies for heritable conditions identified similar themes (1). Ten applications were included in the review covering a range of testing purposes and types of technologies. Methodological and policy challenges faced during the assessments resulted in high levels of uncertainty regarding the appropriate testing population, and lack of evidence on the positive and negative impacts of testing. The review also highlighted uncertainty around the appropriate place of testing in clinical care pathways and the clinical utility of technologies leading to uncertainty in the cost-effectiveness and budgetary impact of genetic and genomic technologies. Despite these challenges, nine of the ten applications were recommended, demonstrating that in some circumstances, MSAC has a willingness to accept a lower evidence threshold. This may be related to the high unmet clinical need and low budget impact due to the low prevalence of the conditions.

In recognising the importance of consumer and societal input for HTA, Norris, Belcher (1) proposed that HTA agencies around the world, including Australia, should consider the following:

- Co-designing HTA processes incorporating consumer and societal preferences
- Including consumer and societal preferences in evaluations for the health and non-health outcomes of genetic and genomic technologies
- Incorporating the co-production of health-related utility that occurs when family members experience positive health outcomes
- Engaging clinicians as referrers while ensuring equity of access.

Overview of consultation process

The consultation process included eight workshops with more than 60 stakeholders representing the pharmaceutical and medical device industry, government, academia, clinical practice, consumers, and consumer representatives (Figure 1).

The results of the literature review conducted as preliminary work were used to develop pre-read materials on challenges and solutions identified in the literature. The pre-read was used to build a consensus among industry regarding the core challenges and potential solutions. These challenges and solutions were then refined through consultations with non-industry stakeholders including government, academic and clinicians to ensure the challenges were representative of all relevant stakeholders and to ascertain the feasibility of addressing the challenges identified. Patient representatives were also consulted to validate the patient impact of existing proposals, as well as build on them based on their unique perspectives. Further refinement then occurred once more with government, academia, and clinicians.

Workshops were also held with MSAC members and representatives of the Department of Health to validate solutions and identify if any reforms are under way already.

A variety of perspectives was obtained through the workshops, at times also in conflict; however, several common core challenges were identified (see *Consolidated challenges*). The identified challenges primarily related to the overall MSAC process and were not necessarily specific to genetic and genomic technologies. While the consultations identified consistent themes regarding the HTA challenges and proposed solutions between the stakeholders, there were subtle nuances. For example, the Department of Health and MSAC stakeholders focused on challenges related to germline applications (e.g. cascade testing) while industry stakeholders focused primarily on challenges around co-dependent applications (e.g. test and drug combinations).



Figure 1. Focus and purpose of workshops

Background

This section introduces the role of genetics and genomics in health and disease, as well as the technologies used to test for variants

Definitions

Genetics and genomics both play a fundamental role in health and disease. Genetics refers to the study of genes and the way that certain traits or conditions are inherited from one generation to another. Genomics is a more recent term that describes the study of all genes within an individual (the genome). Genomics can encompass the scientific study of complex diseases that are typically caused by a combination of genetic and environmental factors as opposed to individual genes (e.g. heart disease, asthma, diabetes and cancer). Genomics offers new possibilities for therapies and treatments for some complex diseases, as well as new diagnostic methods (4). Genetic and genomic technologies can have a variety of applications including:

- Screening
- Diagnosis
- Prognostic testing
- Monitoring
- Companion diagnostics – for access to innovative therapies

Genetic and genomic technologies have opened multiple new possibilities for patient care. HTA frameworks, which are guided by specific patient characteristics and comparators, may be challenging to define for genetic and genomic technologies.

Germline vs somatic

Genes and chromosomes can change in either somatic or germinal tissue, and these changes are called somatic variants and germline variants, respectively. Somatic or acquired genomic variants are the most common drivers of cancer, occurring from damage to genes in an individual cell. From a HTA perspective, somatic variants are categorised into four tiers based on clinical significance: (5)

- Tier I – variants of strong clinical significance
- Tier II – variants of potential clinical significance
- Tier III – variants of unknown clinical significance
- Tier IV – benign or likely benign variants.

In contrast, a germline variant occurs in a reproductive cell (i.e. a sperm or egg cell) inherited directly from a parent at the time of conception. This means that the variant can pass from generation to generation. As the embryo develops the germline variant is replicated into every cell in the body. From a HTA perspective, germline (heritable) variants are categorised using five classes: (6)

- Class 1 – benign
- Class 2 – likely benign
- Class 3 – variant of unknown significance
- Class 4 – likely pathogenic
- Class 5 – pathogenic.

When a condition is heritable, outcomes of testing the initial person or patient (the index case or proband) may impact other family members, their diagnosis and potential clinical management. Therefore, cascade testing of first- and/or second-degree biological family members, or reproductive partners, may be considered.

Somatic and germline variants have different challenges for HTA frameworks. Testing for heritable conditions often includes cascade testing of family members and reproductive partners.

Testing technology

Testing for genetic or genomic alterations can be performed using several pathology methods and technologies. Typically, anatomical pathologists observe tumours' histology under a microscope. Subsequently, molecular pathology tests can identify genetic or genomic alterations or the presence of specific proteins. Conventional pathology techniques for genetic and genomic testing include in situ hybridisation (ISH), fluorescence in situ hybridisation (FISH), immunohistochemistry (IHC), mass spectrometry, polymerase chain reaction (PCR), single nucleotide polymorphism (SNP) microarrays, array comparative genomic hybridisation (aCGH), and multiplex ligation-dependent probe amplification (MLPA). Some techniques are best suited to identifying small target sections of deoxyribonucleic acid (DNA) (e.g. PCR, Sanger sequencing), others detect specific proteins (e.g. mass spectrometry, IHC), and still others are used to investigate larger sections of the genome (e.g. SNP microarray, aCGH).

Massively parallel sequencing (MPS) technology, commonly known as next-generation sequencing (NGS), is a high-throughput method of sequencing many sections of genetic material simultaneously. NGS technology has advanced significantly since the early 2000s and the costs continue to decline. NGS is capable of analysing genes, exomes, genomes, transcriptomes (RNA), and DNA methylation. (7)

For the purposes of HTA, the scale of the gene analysis is split into classifications: (3)

- monogenic testing – limited variant testing or whole gene testing
- small gene panel – assaying 2 to ≤ 10 genes
- medium gene panel – assaying 11 to ≤ 200 genes
- large gene panel – assaying >200 genes, but remaining sub-exome
- non-targeted – whole exome sequencing or whole genome sequencing.

NGS technology can be used for small, medium, and large gene panels, which presents challenges for HTA as multiple patient populations, comparators and pathways can be included.

Disruption

It took over a decade to sequence the human genome at a cost of \$2.7bn (8). Since that time, the cost to sequence human genes has reduced to somewhere between a few hundred dollars (for a small panel of variants) and a few thousand dollars (for sequencing a whole genome), and the time to complete an analysis has reduced to between hours and days (9).

The mass affordability of sequencing has enabled a paradigm shift in drug discovery and clinical care by offering the potential for precise and personalised approaches to treatment. In addition, genetic and genomic testing has shifted focus from patients with risk factors (such as family history or medical symptoms) to sequencing proactively to identify risk factors.

Genomics has now become an essential component of pathogen surveillance and infection management, as demonstrated during the COVID-19 pandemic. In addition, genomics is extensively utilised in cancer care and rare diseases, and stakeholder feedback has indicated that the Medicare Benefits Schedule (MBS) has not kept pace with clinical practice. This results in patients undertaking a 'testing odyssey' which involves a series of single-gene or targeted tests, rather than a comprehensive panel test which covers all known variants (9). In addition, stakeholder feedback canvassed the use of genomics as standard practice in many other areas such as monogenic congenital disorders or in the development of genetically modified treatments such as Chimeric antigen receptor T-cells (CAR-T).

Rapid developments in genetic and genomic technologies have transformed clinical care. However, funding in the Australian health system has struggled to keep pace.

Funding for genetic and genomic technologies in Australia

This section provides an overview of Federal and state government funding for genetic and genomic technologies, as well as current federal government spending on genetic and genomic technologies via the MBS.

State vs Federal

Pathology is funded through a mix of federal funding from the MBS and state and territory funding through hospitals (Figure 2). In some cases, state and territory governments allocate funding to Local Health Networks (LHNs), which then distribute funding accordingly to hospitals within their networks. Hospitals have a fixed budget allocation for pathology. A 2017 genetic and genomic technology survey by the Royal College of Pathologists of Australia estimated that almost half (49%) of genetic and genomic technologies were funded by the MBS (10). The remaining technologies are paid for by the states and territories or other stakeholders (e.g. life insurers or industry funding).

According to pathologists, laboratories typically charge hospitals for genetic and genomic technologies on a fee-for-service basis. Federal Medicare funding is also fee-for-service according to the MBS item schedule fee. Despite the lower relative cost of testing compared to treatments, pathologists report that pathology has typically been underfunded compared to pharmaceuticals. Stakeholder feedback highlights the important role of pathology in ensuring targeted use of pharmaceuticals in patients likely to garner the most benefit. As Medicare covers all Australian citizens, if genetic and genomic technologies are not listed on the MBS, there can be inconsistent funding at a state and territory level. This leads to inequitable access and some patients may need to pay out of pocket fees.

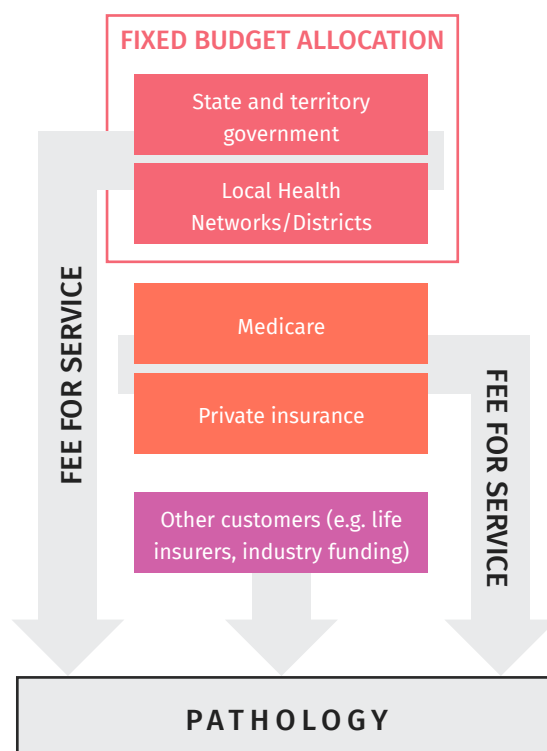


Figure 2. Pathology funding structure

The complex funding arrangements for genetic and genomic technologies can lead to ambiguity resulting in funding delays between states/territories and the Federal Government. This means that technologies can be evaluated at multiple levels including national, state/territory and hospital. Further, there could be delays in evaluating and implementing new technologies if there is a lack of agreement as to who pays.

Medicare spending on genetic and genomic technologies

MBS spending on genetic and genomic technologies increased by 24% between 2012 and 2016, with \$43.5 million spent in 2016 (inclusive of both cancer and non-cancer technologies). However, Medicare's funding and coverage is limited compared to the number of genetic and genomic technologies available to patients in Australia: there are over 80 genetic/genomic technologies (46 of which are cancer-related) listed on the MBS, while there are approximately 1,700 types of tests being performed by laboratories across Australia. (11)

In the last four years, the majority (75%) of MBS spending on genetic and genomic technologies was diagnostic. (Figure 3)

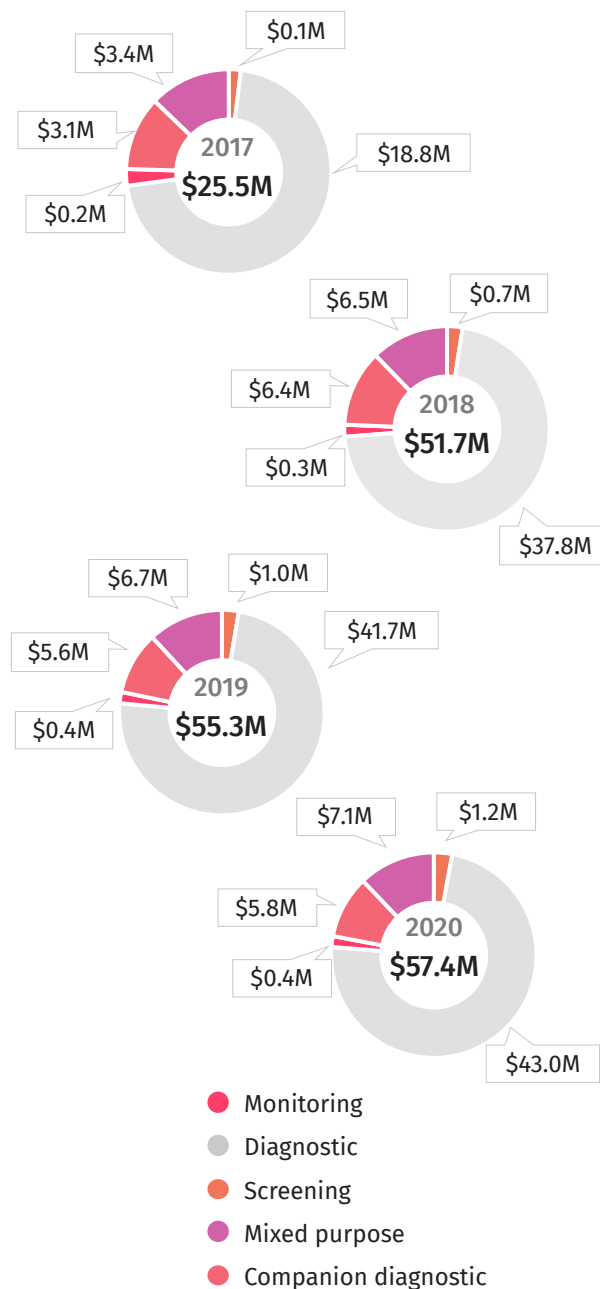


Figure 3. Overview of MBS spending on genetic and genomic technologies

Source: MBS Item Reports

Overview of current HTA methodology and processes

This section covers Australian HTA pathways and focuses on the MSAC process as the key HTA process used to evaluate new genetic and genomic technologies at a national level.

Australian HTA pathways

Due to the complex funding arrangements, there are various pathways to fund genetic and genomic technologies in Australia (12). State-based evaluations are often ad hoc and inconsistent, including individual business cases evaluated by individual hospitals, and state-wide procurement processes. At the federal level the MSAC makes recommendations to the Minister for Health regarding new MBS items or amendments to existing MBS items (3).

Although HTA evaluations can take place at a state/territory and Federal level in Australia, the focus of this report is the MSAC HTA pathway as the predominant access pathway for genetic and genomic technologies.

Role and function of the MSAC

MSAC is a non-statutory committee established by the Australian Minister for Health in 1998. MSAC's role is to provide recommendations regarding funding of health technologies other than medicines. MSAC provides advice to the Minister for Health, the Health Council, Jurisdictional Blood Committee/National Blood Authority, and other committees as required. The technologies evaluated by MSAC include (but are not limited to) new and existing medical services, other programs (blood products or screening programs), highly specialised therapies delivered as state-based services, and services involving prostheses (13).

MSAC's recommendations are based on the strength of evidence about the comparative safety, comparative effectiveness, cost-effectiveness, and overall budgetary impact of the proposed health technology. MSAC's recommendations encompass (3):

- whether public funding should be supported for the technology and, if so, the circumstances under which public funding should be supported
- the proposed MBS item descriptor and fee for the service where funding through the MBS is supported
- other matters related to the public funding of health services referred by the Minister for Health.

The advice provided by MSAC can result in new MBS items or amendments to existing MBS items and may inform funding decisions for programs such as the National Blood Agreement or National Blood Authority Immunoglobulin Governance Program (3).

The Federal Government is not obliged to accept or implement the advice MSAC provides. If the Federal Government accepts MSAC advice, there is no agreed timeframe to implement recommendations. When considered together with the potential for cost re-allocation, there can be considerable delays between an MSAC recommendation and an MBS listing for genetic and genomic technologies.

The MSAC process

As highlighted above, genetic and genomic technologies can be used for several purposes including diagnosis, screening, prognosis, monitoring and for access to targeted therapies. Therefore, the types of genetic and genomic applications considered by MSAC are broad and include:

1. Investigative applications covering diagnosis, screening, prognosis and monitoring.
2. Co-dependent applications covering linked genetic/genomic technologies and targeted drugs.

In both cases, applicants may request testing for one or more genetic variants, which may be present in one or more

patient populations. Applications for NGS-based panel testing of multiple genetic variants are increasingly being assessed by MSAC.

There are several key steps in the MSAC process (Figure 4). As mentioned above, in the case of genetic and genomic applications there can be multiple populations (including patients with the disease/condition and healthy people who may later develop the disease/condition) which makes it challenging to build an accurate PICO (Patient, Intervention, Comparator and Outcome) and to evaluate the application. In applications for targeted cancer therapies, a variant is usually included with a specific cancer type and a specific therapy. However, with the introduction and speed at which tumour-agnostic therapies are being developed and moving from the research to clinical setting, it is likely that the number of applications that include multiple cancer types and thus multiple patient populations will increase. Furthermore, applications for oncology testing may include testing for somatic and/or germline variants (e.g. BRCA 1 or BRCA 2).

For genetic diseases, such as Fragile X or Alport syndrome, applications tend to focus on identifying affected individuals. However, once a variant is identified in a patient, cascade testing of biological relatives or reproductive partners (for family planning) is often recommended. Cascade testing presents ethical issues, such as obtaining consent from the patient, and their relatives, the risk of psychological distress, confronting preferences to not be tested and breaching confidentiality.

The MSAC process is challenging for genetic and genomic technologies, as the PICO is complex to define. This is due to the inclusion of multiple patient populations, comparators, and pathways. In addition, cascade testing is often recommended to family members and reproductive partners – which increases the complexity of the application.

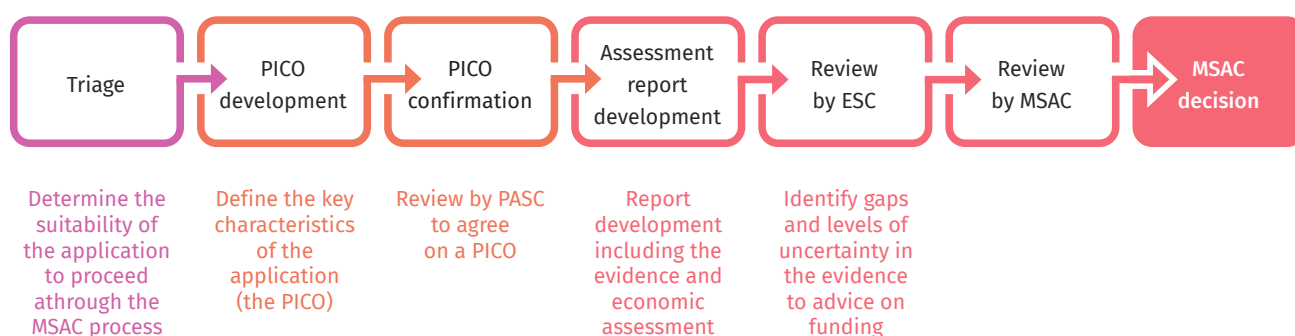


Figure 4. Overview of the MSAC process

MSAC funding mechanisms compared to the PBAC

The MBS is a list of the medical services for which the federal government provides a rebate, to provide patients with financial assistance towards the costs of the medical services. Pathology tests are included in Category 6 of the MBS within the Pathology Services Table (14). In contrast the Pharmaceutical Benefits Scheme (PBS) includes a list of medicines available for which the federal government will provide a subsidy, covering the majority of the cost. Most pathology services in Australia are bulk-billed, with Medicare paying the rebate directly to the provider. This has important implications for pricing and HTA.

The Health Insurance Act (1973) defines a provider as someone who renders a pathology service (15). Under this definition, companies that supply pathology technologies are often not eligible to receive an MBS fee and therefore companies cannot easily enter Special Pricing Arrangements (SPAs) to facilitate commercial pricing arrangements¹, as happens on the PBS. This means there is no mechanism to list proprietary products on the MBS (16) and remains a challenge for genetic and genomic technologies, such as proprietary test kits. This structure also makes it more challenging to administer conditional listing arrangements such as Managed Entry Agreements (MEA), and currently the

¹ Common commercial pricing arrangements include differential pricing in the public compared to the lower (effective) price that is paid by the Federal Government.

MSAC has no MEA framework².

As the MBS lists services in the Pathology Services Table which are brand agnostic, the HTA evaluation can include multiple competing technologies. Although this provides several challenges from an assessment perspective, it also opens the door to collaboration on applications (discussed below).

Most pathology services are bulk-billed, and pathology technology companies do not directly receive MBS fees. Therefore, there is no mechanism available for commercial pricing arrangements¹ and using MEAs, similar to the PBS, on the MBS.

Public consultation

Public consultation during MSAC applications is typically conducted after the triage assessment. Informal public consultation can occur at the same time point and continue throughout the MSAC process. As discussed below, there are several reforms under way to improve patient engagement in the MSAC process (see *Consumer engagement*).

Although public consultation does occur during MSAC applications, patient feedback obtained as part of this whitepaper indicated engagement in the process is not easy or transparent.

Relevant regulatory reform

The success of precision medicine is reliant upon having accurate tests to detect specific variants that are associated with an improved outcome with a particular medicine. In the in vitro diagnostic (IVD) medical device sector such a test is commonly referred to as a companion diagnostic. An IVD companion diagnostic can be developed from a range of technology and includes IHC tests to NGS-based tests. With NGS, IVD companion diagnostic status may be conferred only to a subset of variants within a much broader panel that detects a wide range of variants. The Changes to Therapeutic Goods (Medical Devices) Regulations 2002 (the Medical Devices Regulations) regarding the definition of 'IVD companion diagnostic' came into effect on 1 February 2020 (17). The changes include a Unique Product Identifier (UPI) and a requirement to submit separate applications for each IVD companion diagnostic, including laboratory developed 'in-house' tests. In addition, it is a requirement that the Instructions for Use (IFU) stipulates how the IVD is intended for use with the corresponding medicine or biological. An IVD manufacturer cannot make claims in the IFU that the IVD is intended for use as a companion diagnostic unless the corresponding medicine or biological has been approved for use in Australia, or there are concurrent applications for approval of both the IVD companion diagnostics and the corresponding medicine or biological.

The recent regulatory reform may add additional barriers to co-dependent applications through MSAC as tests will need to specify co-dependency relationships as part of a regulatory approval.

MSAC reforms

Guidelines

A recent review looked at the MSAC guidelines, including the Therapeutic Guidelines (version 2.0, March 2016) and the Investigative Guidelines (version 3.0, July 2017), and a range of challenges raised by stakeholders (3). There is now only one set of technical guidelines – which combines guidance for therapeutic and investigative applications. The revised guidelines provide guidance for newer technologies, including genetic testing for heritable diseases and other screening tests, incorporating information that used to be in the Clinical Utility Card (CUC) Proforma³. There is also an exemplar/facilitated approach for investigative/diagnostic genetic tests which is an alternative approach intended to simplify the assessment of gene-related investigative technologies. The principles of the exemplar/facilitated approach involve describing similarities between technologies for which there is adequate evidence to inform a decision and

² An MEA allows coverage at a price justified by the existing evidence, pending submission of more conclusive evidence.
³ The CUC Proforma was a template specific to applications for heritable variants that increase the risk of a disease.

technologies that have less established evidence. For example, with a gene panel, one or several genes that have evidence to support clinical utility could be used as exemplars for other genes on the panel with less or no evidence.

The revised guidelines now include a framework for evaluating the broader benefits associated with investigative technologies, including non-health outcomes, health outcomes that affect others, or health outcomes that may be difficult to quantify (such as quality of life related to knowing a diagnosis). In particular, additional guidance has been provided in relation to the value of knowing. Some examples include (3):

- ending the patient's diagnostic odyssey
- reproductive planning
- long-term planning (e.g. education, career, housing, finances)
- increased/decreased sense of control
- psychological (positive or negative) impact on index patient⁴ (or proband)
- stigmatisation or discrimination
- access to the National Disability Insurance Scheme
- greater understanding of future health care needs
- the ability to connect with others in the same situation.

Although the revised guidelines represent an important step forward, stakeholder feedback suggested additional and more regular revisions of the guidelines need to be made to ensure they are fit for purpose for future technologies. Some stakeholders commented that the ethical and policy issues around genomics are complex and can impact on HTA and reimbursement decisions. This needs to be recognised together with the fact that MSAC has been tackling some of these issues in the course of making genomics-related recommendations.

Consumer engagement

In 2019 the Consumer, Evidence and Engagement unit was established within the Department of Health to allow the development of structured engagement with consumer and patient groups. The Consumer, Evidence and Engagement unit was consulted during the development of this report. Recently, there has been an update to the MSAC website with a section on 'engaging with MSAC' for consumers and consumer advocacy groups, detailing when and how people can get involved in the MSAC process, what happens to their comments and a summary of the overall MSAC process. Several well attended consumer webinars on the MSAC process, guidelines and how consumers and consumer advocates can contribute to the value of knowing, have taken place. Consultation for this whitepaper also revealed several reforms that are under way to improve consumer engagement within the MSAC process:

- Redeveloped MSAC website – the presentation of current content will be updated, and new content included. A consumer 'consultation hub' will be launched on the MSAC website which pulls together all consultations being held across the PBAC and MSAC so consumers can view all open consultations in one place.
- HTA support unit to oversee and coordinate consultations from July 2021 – Targeted consultations will be coordinated by the HTA support unit with assistance from the Consumer, Evidence and Engagement unit. The HTA support unit will liaise with consumers and consumer advocacy groups and additional support is offered for those that are unfamiliar with the process.
- Consumer symposiums – The HTA consumer consultative committee that provides strategic advice to the Office of HTA in relation to consumer matters is hosting a symposium for consumers and consumer advocacy groups. A key session is being held around genomics and gene and cell therapies discussing specific challenges on genomic testing and MSAC applications, how consumers can be involved, how consumers can collaborate with industry and issues that may arise with implementation of genetic and genomic technologies. As part of the symposium, pre-recorded sessions explaining the MSAC process, how consumers can provide comments and detailing information that is helpful to provide to a committee, will be available online for consumers and consumer advocacy groups to access at their leisure.
- Patient voice initiative (PVI) – The consumer, evidence and engagement unit are providing input into the PVI website which covers the MSAC process.

⁴ An individual in a family who is affected with a heritable disease or condition and has a relevant known pathogenic germline variant.

The MBS review

The Australian Government established the MBS Review Taskforce in mid-2015 to review all items on the MBS (>5,700). This was the most comprehensive review of Medicare since its inception in 1984, and resulted in more than 1,400 recommendations to strengthen, modernise, and protect the MBS. A key recommendation in the final report was to continuously review MBS items to maintain the MBS as a contemporary, fair, and high value system to support the delivery of health care for Australians.

Medicines Australia Strategic Agreement

While developing this whitepaper, Medicines Australia signed a Strategic Agreement for 2022-27 with the federal government (18). The agreement includes an ambitious reform agenda with direct implications to HTA for genetic and genomic technologies via the MSAC pathway. Specifically, the review includes:

- An independent review of Australia's HTA system to keep pace with advancements in medical technologies and achieve faster access to new medicines for patients. The review will run from July 2022 – June 2023, with recommendations to be implemented by July 2024. The review will cover issues including but not limited to:
 - selection of comparators
 - methods for rare diseases, new and emerging technologies
 - methods for all new medicines and vaccines
 - use of real-world evidence
 - managing uncertainty
 - international work sharing.
- An Enhanced Consumer Engagement Process will be established and co-designed with consumers from July 2022.
- An early review of the discount rate (to be implemented by July 2022).
- A Horizon Scanning Forum, to be run annually by Medicines Australia from 2022.
- An industry representative will be appointed to the MSAC.

Inquiry into approval processes for new drugs and novel medical technologies in Australia

- Another important report released during the development of this whitepaper was the outcome from the Inquiry into approval processes for new drugs and novel medical technologies in Australia – by the House of Representatives Standing Committee on Health, Aged Care and Sport (19). The inquiry received over 200 submissions and held extensive public hearings. Key recommendations related to genetic and genomic technologies include:
 - Establish a Centre for Precision Medicine and Rare Diseases within the Department of Health.
 - Building on the Medical Research Fund Genomics Mission, the Australian Government and state and territory governments should establish a jointly funded national genomics testing program to provide equitable access to genomic testing nationwide. As part of the program, governments should ensure the provision of genomics counselling for all patients.
 - Increase efforts to educate and engage with patients, clinicians, industry and the public and develop education campaigns on all aspects of the regulatory and reimbursement system.

There is a considerable amount of ongoing reform related to the MSAC process; however, transparency and engagement have been highlighted by industry and patient representative stakeholders as a key issue. There are multiple opportunities for InGeNA to advocate for genetic and genomic technologies in the reform process and to collaborate with other bodies, such as Medicines Australia.

Previous MSAC recommendations for genetic and genomic technologies

This section provides an overview of genetic and genomic MSAC applications to highlight the diversity of applications and challenges that can arise during the evaluation process.

To highlight the diversity of genetic and genomic MSAC applications, a summary of recent applications was compiled (see Table 1). Selected applications cover many purposes including testing for access to targeted drugs, testing for heritable disease (+ cascade testing), prenatal testing, prognostic testing and screening. Overall, the applications highlight numerous challenges, such as lack of concordance between testing methods, how to value a diagnosis with no treatment, lack of applicable evidence to support change in management following a test and uncertainty in the utilisation of tests. In addition, the applications also highlight the evolution in MSAC decision-making regarding the value of diagnostic knowledge and ethical issues associated with applications. This highlights the potential need for a repository of information regarding MSAC decision-making, to inform future applications (see *Consultation outcomes – solutions*).

In addition to the applications in Table 1, Application 1634 was also identified as a relevant example of the implications of panel testing for access to targeted medicines. Specifically, Application 1634 is for comprehensive genomic profiling (CGP) of non-squamous non-small cell lung cancer (NSCLC) tumour tissue specimens using NGS assays, which has a PICO developed but has not yet progressed to MSAC. Although panel testing is already present on the MBS this application would establish a precedent by allowing clinicians to run a single panel and determine appropriate treatments for patients with NSCLC (a practice that already occurs in Australian clinical practice but is not subsidised on the MBS). Once established, adding new variants should be more efficient as uncertainty around test timing and methodology is removed, and the application also provides a template for other tumour-specific panels (such as breast and colorectal) and later a tumour-agnostic panel.

However, Application 1634 also raises several issues that will require consideration to allow broader access to panel testing for co-dependent drugs. This includes the timing of test panels, the clinical consequences of discordant results between the panel and other test methodologies and the lack of Therapeutic Goods Administration (TGA) approved NGS assays.

Table 1. Summary of recent MSAC recommendations

Type Application # # of deferrals Year	PICO	Challenges	Solution
<p>Co-dependency 1440.1 Two deferrals Recommended in 2018 (20)</p>	<ul style="list-style-type: none"> Population: Treatment naïve NSCLC patients with locally advanced or metastatic NSCLC for access to pembrolizumab Intervention: IHC testing Comparator: SoC, no test and treatment with platinum-based doublet chemotherapy Outcome: Analytic and clinical validity, clinical utility, safety 	<ul style="list-style-type: none"> PD-L1 was considered an imperfect biomarker, potentially excluding patients who may benefit from pembrolizumab Failure to recognise the prognostic effect associated with PD-L1 status Insufficient evidence of analytical validity and clinical validity and clinical utility Insufficient evidence to establish concordance between the different antibodies and assays/platforms 	<ul style="list-style-type: none"> The PD-L1 inhibitor, nivolumab was recommended in the second line setting so patients who test negative (correct or not) will still have access to a nivolumab in second line The RCPA developed a quality assurance program to determine quality and reproducibility of PD-L1 tests Additional evidence and information on observer overall percent agreement to establish concordance was provided
<p>Germline testing (and cascade testing) 1600 I No deferrals Recommended in 2021 (21)</p>	<ul style="list-style-type: none"> Population: Genetic testing for heritable kidney disease other than Alport syndrome in affected individuals, cascade testing in biological relatives, testing to enable reproductive decision-making (for recessively inherited variants: cascade testing for reproductive partners and potentially affected foetuses), and data reanalysis Intervention: Whole genome sequencing and analysis Comparator: No genetic testing Outcomes: Analytic and clinical validity, clinical utility, safety 	<ul style="list-style-type: none"> Failure to recognise the benefits beyond ascertaining a genetic diagnosis of affected individuals Insufficient evidence for diagnostic yield across the genetic tests and how well the genotype predicted the phenotype No evidence to support change in the course of disease following early genetic diagnosis ICERs failed to capture the clinical benefit (other than diagnosis), focusing on the lifetime costs of disease 	<ul style="list-style-type: none"> Consumer feedback and support via public consultation was vital in communicating that the value of knowing is empowering, and genomic testing can provide clinical utility of certainty in diagnosis, prognosis, shorten the diagnostic odyssey and lead to better clinical management including results from cascade testing with avoided monitoring Low financial impact to the MBS and low risk of leakage

Type Application # # of deferrals Year	PICO	Challenges	Solution
<p>Prenatal testing 1574 No deferrals Recommended in 2020 (22)</p>	<ul style="list-style-type: none"> Population: (1) RhD negative pregnant women and (2) RhD negative non-alloimmunised pregnant women for the detection of RhD foetal DNA circulating in maternal blood Intervention: NIPT to determine RhD genotype Comparator: No testing for pregnant women who are non-alloimmunised Outcome: Analytic and clinical validity, clinical utility, safety 	<ul style="list-style-type: none"> Population 1 was not evaluated because the test used a difference process with different costs compared to Population 2 Inferior effectiveness due to false negative results, resulting in a small increase in the risk of alloimmunisation due to the lost opportunity to receive routine anti-D immune globulin prophylaxis and other possible adverse events 	<ul style="list-style-type: none"> Population 1 is a small population and was supported by the RANZCOG as it was already being provided by Australian Red Cross LifeBlood Recommended an external quality assurance and evaluation program to monitor false negatives
<p>Prognostic 1532 One deferral Recommended in 2020 (23)</p>	<ul style="list-style-type: none"> Population: Patients with myeloproliferative neoplasm Intervention: Expansion of myeloproliferative neoplasms (MPN) genetic testing under MBS item number 73325 by adding the CALR and the population of patients with PMF Comparator: Genetic testing with current MBS item 73325 Outcome: Analytic and clinical validity, clinical utility, safety 	<ul style="list-style-type: none"> ALR variant testing is not needed in patients with polycythaemia vera; lack of clarity in the testing algorithm for MPNs and the need for multiple iterations of the item to cover real testing costs. With respect to the testing costs, it was noted that all three genes cannot be assessed for \$100. This was because CALR variants are very heterogeneous, and analysis of this gene requires different methodology than testing for the common JAK2 V617F variant Failure to recognise the clinical utility of testing to determine subtypes of MPN and the potential impact on prognosis and treatment 	<ul style="list-style-type: none"> Stepwise testing algorithm (i.e. initial JAK2 V617F triage testing) MSAC considered that if additional genes are added in the future for NGS panels and requires a higher fee, a separate application should be made

Type Application # # of deferrals Year	PICO	Challenges	Solution
Screening 1573 I No deferrals Recommended in 2020 (24)	<ul style="list-style-type: none"> Population: Reproductive carrier testing in women who are planning or in early stages of pregnancy and in their reproductive partners (as needed) for the monogenic conditions of CF, SMA and FXS Intervention: Reproductive carrier testing Comparator: No reproductive carrier testing Outcome: Analytic and clinical validity, clinical utility, safety 	<ul style="list-style-type: none"> Ethical issues that need to be considered during decision-making, including the impact on human rights Uncertainty in clinical validity for how well pathological variants detected in the genotype of carriers predict disease severity in offspring. Included studies were mostly non-comparative Uncertainty in clinical utility or failure to recognise the broader value of knowing Uncertainty in utilisation and uptake of test 	<ul style="list-style-type: none"> The proposed test is more effective than no testing based on sufficient indirect evidence. MSAC accepted that although it is hard to measure, there was the intrinsic value for couples and women being empowered to control their reproductive options based on the knowledge provided by tests MSAC reviewed submission estimates and there was insufficient evidence that the financial estimates were in error by more than 10 or 20%
Screening and co-dependency 1634 I N/A Not yet assessed (25)	<ul style="list-style-type: none"> Population: Patients with non-squamous (or histology not specified) NSCLC Intervention: Comprehensive genomic profiling using a NGS assay to simultaneously test for relevant variants in the following genes: EGFR, ALK and ROS1 Comparator: Testing for activating variants in the EGFR gene, ALK IHC, ROS1 IHC, with subsequent ALK FISH or ROS1 FISH as appropriate Outcome: Analytic and clinical validity, clinical utility, safety 	<ul style="list-style-type: none"> First oncology panel test with co-dependency to be assessed by MSAC Intervention is proposed to be 'treatment agnostic' meaning the results may be used to identify patients eligible to access to targeted treatment listed on the PBS for the treatment of NSCLC 	N/A

Abbreviations: ALK, anaplastic lymphoma kinase; CALR, carcinogenic mutated form of the calreticulin gene; CF, cystic fibrosis; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridisation; FXS, fragile X syndrome; ICER, incremental cost-effectiveness ratio; IHC, immunohistochemistry; MBS, Medicare Benefits Scheme; MPNs, myeloproliferative neoplasms; MSAC, Medical Services Advisory Committee; N/A, not applicable; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PBS, Pharmaceutical Benefits Scheme; PD-L1, programmed death-ligand 1; RANZCOG, Royal Australian and New Zealand College of Obstetricians and Gynaecologists; RCPA, Royal College of Pathologists of Australia; RhD, rhesus D; ROS1, c-ros oncogene 1; SMA, spinal muscular atrophy; SoC, standard of care

Consultation outcomes – challenges

This section provides an overview of challenges identified during the consultation process and the consolidated summary of high-impact challenges to which solutions were identified.

Overview of challenges identified from the literature and consultations

The literature review and workshop process identified and validated challenges within eight categories.

PICO

A critical part of the MSAC HTA process is the development of the PICO. For new genetic and genomic technologies, defining a target population and comparator can be difficult given that some technologies have small populations and/or numerous populations depending on its application and the type of conditions/diseases it targets. The definition of the genetic and genomic technologies can also vary significantly given the breadth of possible applications (i.e. screening, diagnosis, treatment and/or prognosis). Stakeholders also mentioned the challenge of an outdated reference standard⁵ as adding complexity to applications. With complex applications, many patient support groups do not have adequate funding to contract a consultant to assist them with an application.

Data and evidence

Feedback suggested that there is a perception that current decision-making throughout the MSAC HTA process relies too heavily on high standards of evidence (such as randomised controlled trials) which is often not available for genetic and genomic technologies. Often evidence is limited, particularly regarding aspects such as how clinical practice changes as a result of a test and the value of knowledge to test recipients. This results in a lack of consistency and transparency around evidentiary requirements and expectations in the MSAC HTA process. Despite the fact that feedback from the Department indicates RCT evidence forms the basis of only a minority of successful applications, industry and clinical stakeholders reported a different perception, which in itself could represent a communication and transparency issue within the process.

As previously mentioned, gaps in evidence cannot be addressed through a MEA (as occurs with PBAC submissions), as MSAC lacks a MEA framework. Stakeholders also mentioned a lack of guidance on the methodology required to evaluate large gene panels, and the Department of Health agreed with this issue, noting ongoing work to update the HTA methodology for large gene panels.

Economic analysis and quantifying value

As the economic analysis typically relies on the clinical evidence, feedback from stakeholders suggested economic model assumptions were over scrutinised, rather than adopting a pragmatic perspective. However, other stakeholders maintained this is not the case for many successful applications. Stakeholders also suggested the current MSAC HTA processes focuses on a narrower definition of value, failing to capture the full value of genetic and genomic technologies. However, many stakeholders did not have experience with the new MSAC guidelines, which do include broader guidance on value (see *MSAC reforms*). The inability to include the broader health utility metrics (e.g. value in a quantifiable manner) in economic evaluations often means genetic and genomic technologies are not deemed cost-effective when compared with the standard of care. In contrast, the Department of Health and MSAC stakeholders warned about expanding the definition of value as health outcomes for genetic and genomic applications may be valued less or the threshold for cost-effectiveness may be lowered. In addition, some stakeholders highlighted how changes to value assessments are also complicated by the fact society does not have a clear and unambiguous position on the matter, but rather a wide range of views on the value of genomic information.

⁵ The reference standard is a test or series of tests that are used to determine the presence or absence of the target condition or clinical information of interest.

Pricing mechanisms

Stakeholders highlighted a lack of value-based payment models, such as coverage with evidence development for new technologies through the MSAC process. Given the challenges relating to data and evidence, this often results in lower reimbursement rather than the opportunity to prove utility in the real-world (via a mechanism such as pay-for-performance), as MSAC lacks a MEA framework and item codes are not brand specific. However, the Department of Health noted MSACs previous experience with interim funding (26). This raised issues, such as generic item numbers and multiple providers, which made it challenging to assess the performance of individual technologies. In addition, the split funding for genetic and genomic technologies between state and Federal Governments raises challenges with implementation. Similarly, the lack of SPA's was mentioned by stakeholders as potentially limiting reimbursement opportunities for genetic and genomic technologies (see *MSAC compared to the PBAC*).

Budgetary challenges

To contain leakage and reduce resource use, decision makers and payers ensure the use of new technologies is limited to the most appropriate patient groups. This is further compounded by the difficulties in tracking the utilisation of genetic and genomic technologies with the use of generic MBS item numbers. The distribution of costs between the state and Federal Governments was identified as a major challenge by stakeholders as it can slow down the HTA evaluation process and can lengthen the time between recommendation and implementation. This is often due to limited clarity on post-MSAC processes and a lack of defined timelines. Further, the lack of risk-share agreements on the MBS limits the ability of the federal government to manage risk.

Process mechanics

Although not specific to genetic and genomics, stakeholders characterised the MSAC pathway as a lengthy and complex process. Furthermore, stakeholders commented on a lack of transparency and consistency around the acceptance of evidentiary standards and decision-making across genetic and genomic technology MSAC applications. Patients and patient representatives and medical professionals knowledgeable on the MSAC process stressed the disappointing lack of early and continual consultation throughout the entire application process. Stakeholders suggested patient and patient representatives should always be consulted through a variety of mechanisms and not just limited to written consultation. Multiple challenges stemmed from a lack of a forum for ongoing engagement between MSAC and stakeholder groups and a conversation around broader issues. Specifically, industry and academic stakeholders highlighted a lack of reform in the MSAC process whereas Government and MSAC stakeholders mentioned several areas of ongoing reform. Finally, due to differences in priorities between stakeholder groups, i.e. industry's focus on issues around somatic variants for co-dependent applications compared to clinicians, patients and Department of Health's focus on issues surrounding germline variants, there is a lack of alignment between stakeholders on the key HTA challenges for genetic and genomic applications needing to be addressed.

Other considerations

Data standards and governance, data access and privacy and data infrastructure that facilitates interoperability of genetic and genomic information between already available data repositories within states and linked to patient outcomes data is needed. Specifically, data standards and governance including legislation and policies on data access and privacy need to be updated to incorporate generation, collection, storage, usage and sharing of genetic and genomic data as well as issues such as dynamic consent. Without these updates, the availability of useful real-world data is limited. Stakeholders also mentioned a lack of future proofing of applications (i.e. to ensure multiple applications are not needed for the same test) and the MSAC website is currently not up to date with the most recent decision-making regarding genetic and genomic technologies. Consultations also raised broader challenges, such as an agreement for the Federal Government to fund MSAC recommendations within a timely manner and issues related to legislation. Specifically, MSAC is bound by legislation outlining that MBS funding cannot be used for access to a clinical trial. Finally, the need for a national policy to guide decisions on access to genetic and genomic technologies, as well as the ethical issues raised by genetic and genomic information were also points raised through the consultation process.

Consolidated list of challenges

The HTA challenges identified during the consultation process were reviewed and consolidated into nine key themes (Figure 5). The impact of these challenges on HTA processes (e.g. delays in access, lack of alignment and lack of consultation) was assessed.



Figure 5. Overview of consolidated challenges

Consultation outcomes – solutions

This section provides an overview of the solutions developed during consultations and how these were connected to the key challenges identified above.

Consolidated solutions

Solutions to the consolidated list of challenges were developed in a stepwise manner starting with initial suggestions from industry and refined by non-industry stakeholders including the Department of Health and MSAC stakeholders throughout the workshop process. Stakeholders were invited to provide input on the feasibility and relative impact of the proposed solutions. These perspectives formed a key input into the final list of solutions.

The consolidated set of solutions were structured into three key categories based on recommendations from the Department of Health:

1. Information needs of the HTA advisory committees
2. Processes before and after the HTA advisory committee consideration
3. Funding programs which the HTA advisory committees provide advice in relation to.

This categorisation ensures that solutions were targeted to all stages of the HTA process.

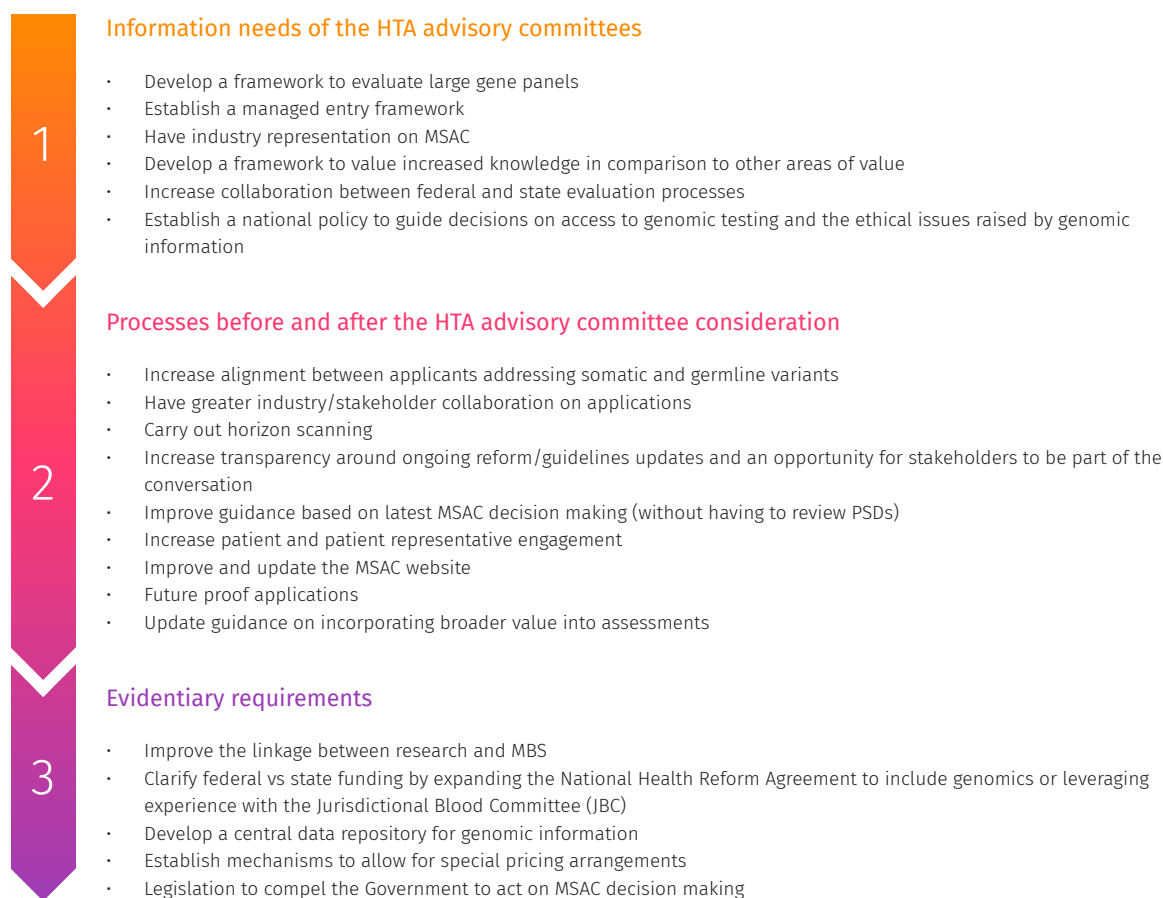


Figure 6. Overview of consolidated solutions

Connecting challenges and solutions

The list of consolidated challenges (Figure 5) and solutions (Figure 6) were combined to illustrate how each of the key challenges raised in consultations were addressed by the proposed solutions (Table 2). All challenges were addressed by the proposed solutions.

Table 2. Connecting solutions with the challenges

Length and Efficiency 1	Industry representation on MSAC	Horizon scanning	Greater Industry and stakeholder collaborations	Future proofing applications	Guidance based on latest MSAC decision-making	Educate stakeholders and increase alignment
Stakeholder alignment 2	Industry representation on MSAC	A national policy to guide decisions	Applicants' alignment on addressing somatic and germline variants	Horizon scanning	Educate stakeholders and increase alignment	--
Evidentiary requirements 3	Industry representation on MSAC	Establish a managed entry framework	Greater Industry and stakeholder collaborations	Guidance based on latest MSAC decision-making	Educate stakeholders and increase alignment	--
Transparency 4	Industry representation on MSAC	More transparency on ongoing reforms	Educate stakeholders and increase alignment	An improved and updated MSAC website	--	--
Patient participation 5	A national policy to guide decisions	Educate stakeholders and increase alignment	An improved and updated MSAC website	--	--	--
Value definition 6	Industry representation on MSAC	A national policy to guide decisions	Framework to value increased knowledge	Updated guidance on incorporating broader value into assessments	Educate stakeholders and increase alignment	Guidance based on latest MSAC decision-making
Incremental change 7	A framework to evaluate large gene panels	Increased collaboration of federal and state evaluation processes	Clarifying federal vs state funding	Future proofing applications	Educate stakeholders and increase alignment	Central data repository for genomic information
Funding programs 8	Educate stakeholders and increase alignment	Future proofing applications	Clarifying federal vs state funding	--	--	--
MSAC legislation 9	Legislation to compel the government to act on MSAC decision-making	Government commitment to implement MSAC recommendations	--	--	--	--

Feedback from the Reimbursement Expert Advisory Panel (REAP)

This section outlines feedback received from the REAP during the project.

The REAP is comprised of 21 Australian reimbursement experts — including previous PBAC, ESC, DUSC, MSAC and ADEC/ACM members, previous Departmental pricing, evaluation and secretariat personnel, consumer representatives, hospital and government specialists, economic modellers and reimbursement submission experts. The REAP reviewed the key challenges and draft solutions proposed by HTANALYSTS, and the full report is in the public domain.

The REAP advised that InGeNA should demonstrate the need for reform. This includes:

- demonstrating a problem exists (use a single therapeutic area if necessary) i.e. evidence that patients are missing potential benefit(s)
- identifying the most important specific source(s)/reasons for the problem
- proposing a limited number of solutions which will address the source

The REAP also recommended focusing on challenges which will have the most direct effect on patient access to genetic and genomic technologies, including:

1. MSAC process length and efficiency
2. Patient participation
3. Evidentiary requirements

Based on the REAPs review, the following solutions were considered quick wins and major projects, respectively.

Quick wins:

1. Specific guidance based on latest MSAC decision-making
2. Separate somatic versus germline issues in applications
3. Education of stakeholders including patients to increase genuine participation in process

Major Projects:

1. Develop a framework to evaluate large gene panels
2. Develop a Managed Entry for genetic and genomics
3. Future proof MSAC applications
4. Pursue a federal government commitment to implement MSAC recommendations within a defined period
5. Develop a national policy on access and ethical issues with genetic and genomic technologies
6. Develop a central data repository for genetic and genomic information

Connecting solutions with activities

Once the solutions had been refined, HTANALYSTS connected solutions with potential activities that formed the basis of a roadmap. The activities were selected by HTANALYSTS to maximise efficiency, including prioritising short-term feasible projects with maximum impact, and collaborating with other groups where possible.

	Information needs of the HTA advisory committees	How to implement the solution?
1	<ul style="list-style-type: none"> Develop a framework to evaluate large gene panels Establish a managed entry framework Have industry representation on MSAC 	Collaboration with Medicines Australia (MA)
	<ul style="list-style-type: none"> Develop a framework to value increased knowledge in comparison to other areas of value 	Living guidance and collaborations with MA
	<ul style="list-style-type: none"> Increase collaboration between federal and state evaluation processes Establish a national policy to guide decisions on access to genomic testing and the ethical issues raised by genomic information 	Long term structural reform
2	<ul style="list-style-type: none"> Increase alignment between applicants addressing somatic and germline variants 	Education to address alignment on issues
	<ul style="list-style-type: none"> Have greater industry/stakeholder collaboration on applications 	Collaboration
	<ul style="list-style-type: none"> Carry out horizon scanning Increase patient and patient representative engagement 	Collaboration with MA
	<ul style="list-style-type: none"> Increase transparency around ongoing reform/guidelines updates and an opportunity for stakeholders to be part of the conversation Improve and update the MSAC website 	Collaboration with the Department of Health
	<ul style="list-style-type: none"> Improve guidance based on latest MSAC decision making (without having to review through public summary documents [PSDs]) 	Living guidance
	<ul style="list-style-type: none"> Future proof applications 	Living guidance, education to address alignment on issues and promoting better collaboration
3	<ul style="list-style-type: none"> Improve the linkage between research and MBS Clarify federal vs state funding by expanding the National Health Reform Agreement to include genomics or leveraging experience with the Jurisdictional Blood Committee (JBC) Develop a central data repository for genomic information Establish legislation to compel the government to act on MSAC decision making 	Long term structural reform
	<ul style="list-style-type: none"> Develop mechanisms to allow for special pricing arrangements 	Collaboration with MA

Recommendations and preliminary roadmap

This section uses the solutions and activities generated above to build a preliminary roadmap for InGeNA.

Considering outcomes from the consultation and feedback from the REAP and in establishing a program of reform, it is recommended that InGeNA prioritise high-impact solutions that can be actioned unilaterally. Secondly, many of the challenges and potential solutions have broad applicability beyond genetic and genomic technologies. Therefore, there may be overlap of InGeNA's interests with that of other stakeholders who also deem the MSAC process as a rate limiting step to access innovative treatments. Finally, it is critical to consider and address fundamental structural issues such as funding.

To progress these solutions, it is recommended that InGeNA consider three tranches of work, including:

1. Short-term wins
2. Collaborations
3. Long-term structural reform

Short-term wins

Consultations established several short-term projects which can be undertaken unilaterally by InGeNA, including:

1. Better defining the problem
2. Education to address alignment on challenges
3. More specific guidance based on latest MSAC decision-making to increase the probability of approval for genetic and genomics applications
4. Establishing priority MSAC applications that can be undertaken collaboratively

These can be addressed in a stepwise manner:

1. Better defining the problem

As highlighted by the REAP, for reform to be successful, it is critical to establish the need for reform. The consultations highlighted many perceived challenges with the MSAC process, but few were specific to genetic and genomic applications. In addition, although many stakeholders spoke about challenges with the length and efficiency of the MSAC process related to genetic and genomics applications, there was little quantitative data to support this. To increase understanding around challenges specific to genetic and genomic applications through MSAC, InGeNA should commission a report to characterise historical and current process metrics, such as:

- The number of genetic/genomic applications by therapeutic area by year
- Application outcomes (approval / deferral / rejection) by submission number (1st, 2nd, 3rd etc.) by year
- For successful outcomes:
 - Average number of submissions to positive MSAC recommendation
 - Time from MSAC recommendation to MBS listing (for those applications that are relevant to the MBS only)

The report could be completed regularly and provide an environmental scan of reimbursement outcomes for genetic and genomic technologies.

In addition, a report could help clarifying situations where conflicting views were expressed by different stakeholders. This would represent a step forward in identifying objective issues as opposed to perceptions and miscommunications, better directing the efforts to design actionable solutions to ultimately improve the access to genetic and genomic technologies in Australia.

What will this solve?

By working to better define the problem through quantitative metrics, this solution will increase **stakeholder alignment**. In addition, as solutions are implemented, this data can be used to increase **transparency** around the **progress of applications** to improve the **length and efficiency of the MSAC process**.

2. Education to address alignment on challenges

A clear outcome from the consultations undertaken for this report was the lack of alignment between stakeholders on the key challenges related to HTA of genetic and genomic technologies. In general, pharmaceutical stakeholders were focused on applications for somatic variants to provide access to targeted medicines (co-dependent applications). In contrast, other stakeholders such as some clinical experts, patient organisations and the Department of Health were more focused on applications for germline variants. As previously mentioned, many of the challenges identified through consultations were not specific to genetic or genomic applications.

To increase awareness and alignment, it is recommended that InGeNA conduct targeted education with industry and non-industry stakeholders focusing on potential challenges across somatic and germline MSAC applications, as well as practical solutions (leveraging other recommended work).

What will this solve?

An education initiative will improve **stakeholder alignment** which was a key challenge identified during consultations. This solution is a fundamental building block to addressing **other solutions** as it will allow stakeholders to clearly articulate challenges and solutions during reform discussions and ensure any reform initiatives do not adversely impact one category of applications over the other (somatic vs germline).

3. More specific guidance based on latest MSAC decision-making to increase probability of approval for genetic and genomic applications

Although the MSAC guidelines have recently been updated, there are considerable insights in published public summary documents (PSDs) which can be used to enhance the probability of successful applications. This includes MSACs interpretation of many challenges such as star performer genes⁶ and non-health outcomes, as well as ethical and equity considerations. An example is Application 1476 which established a new MBS item for genetic testing using NGS for childhood syndromes. As testing may have identified disorders with no treatment, an issue addressed in this application was how to value a diagnosis that has no immediate clinical utility. In evaluating 1476 MSAC accepted that positive test results can lead to benefits, such as educational or disability support services, and that the information obtained may become 'actionable' in the future when new treatments become available (27). Similarly, this application and others, such as 1492 and 1533 highlighted the value of 'reproductive confidence' as a measure of test impact, as people taking the test are able to make informed family planning decisions (28, 29). Other information that can be used to inform future applications includes legal issues, cascade testing and pathways of care.

Overall, it is suggested that InGeNA establish a 'living guidance' which compiles best practices and MSAC interpretation from PSDs to inform future genetic and genomic applications.

What will this solve?

By creating living guidance, applicants would be able to leverage MSAC precedents and decision-making to enhance the probability of successful outcomes. This would address several challenges such as length and efficiency of the MSAC process (by reducing resubmissions) and stakeholder alignment (by highlighting key challenges in different application categories). In addition, applicants will be able to better meet MSAC evidentiary requirements and value definitions by leveraging previous decision-making and interpretation.

⁶ The actionable gene(s) for which the strongest clinical utility and/or cost-effectiveness argument is likely to apply for an affected individual.

4. Establishing priority MSAC applications that can be undertaken collaboratively

A key feature of the MSAC process is the ability of multiple parties to collaborate on applications, however, a framework is crucial to guide industry collaborations. To update MBS items to ensure they align with current practice, particularly with regard to panel testing in oncology to determine appropriate treatments, a program of work is needed. An example of an application which provides benefits across industry is Application 1634 by Roche Diagnostics (summarised above), which will establish a NSCLC panel test. In doing so, this application will establish a precedent by combining multiple existing MBS items such as EGFR, ALK and ROS1 variants in one panel, which can be used to determine appropriate therapies, such as tyrosine kinase inhibitors or anaplastic lymphoma kinase inhibitors.

To continue this work, it is recommended InGeNA gauge interest from industry and non-industry stakeholders in establishing similar panels in other areas, such as colorectal, breast cancer or blood cancers to determine access to reimbursed targeted drugs. Collaboration of industry stakeholders could be guided through a framework established by InGeNA (see below). Once further precedents are established, work could shift to establishing a tumour-agnostic panel, which would facilitate the arrival of an increasing number of tumour-agnostic therapies and allow for testing of common biomarkers (such as NTRK fusions) which are present in multiple cancer types.

What will this solve?

In theory, once panels are established on the MBS for access to targeted therapies, only minor changes would be required to amend the descriptor for further biomarkers and targeted therapies as they are approved for use. This could **improve the length and efficiency of the MSAC process** by potentially reducing the number and complexity of co-dependent applications being evaluated by MSAC – providing benefit to multiple stakeholders. This is further highlighted in Application 1634 which documents at least 16 targeted therapies in development for NSCLC alone, which could be added to an established panel. Once approved, the **evidentiary requirements** for submissions would be reduced as the testing algorithm would be simplified through the consolidation of sequential single variant testing into a common panel.

Collaborations

The consultations undertaken for this report identified three priority areas for collaboration, including:

1. Medicines Australia
2. Department of Health
3. Promoting better collaboration for genetic and genomic applications

They are addressed stepwise below:

1. Medicines Australia

Genetic and genomic technologies are increasingly used to identify patients for treatment with targeted medicines. In addition, the MSAC pathway is used for new innovative medicines, such as cell and gene therapies. An immediate priority for InGeNA should be to establish a relationship with Medicines Australia due to combined interests and mutual benefits when considering HTA reform. InGeNA should seek to work closely with Medicines Australia (18) on the following projects established in the 2021 Deed of Agreement to ensure the genetic and genomics perspective is represented:

- Independent HTA review.
- An Enhanced Consumer Engagement Process will be established and co-designed with consumers from July 2022.
- An early review of the Discount Rate (to be implemented by July 2022).
- A Horizon Scanning Forum, to be run annually by Medicines Australia from 2022.
- An industry representative will be appointed to the MSAC.

It is noted that the terms of reference for the HTA review are yet to be established and the review will consider methods

for evaluating new and emerging technologies and the suitability of existing funding pathways. Although it is not clear if MSAC is in scope, this work could include changes to conditional listing arrangements (such as managed entry) which may also have applicability to genetic and genomic technologies and the MSAC process.

InGeNA should ensure the MSAC process is included in the HTA review and seek to broaden the proposed terms of reference to cover large gene panels (as described above), as this is a key roadblock in the HTA process for both targeted medicines and for hereditary diseases. In addition, the proposed horizon scanning forum should be broad enough to capture genetic and genomic technologies and InGeNA should ensure the proposed industry representative for MSAC has genetic and genomics expertise (or are educated in the key challenges).

Lastly InGeNA should ensure proposed reforms for consumer engagement include consideration of genetic and genomic applications, which often have a broader range of stakeholders.

What will this solve?

Alignment with Medicines Australia has the potential to progress multiple solutions simultaneously. The HTA review within the new Strategic Agreement is a watershed moment which could potentially address many challenges such as length and efficiency of the MSAC process, evidentiary requirements, value definition and transparency. The review could also address broader issues such as funding programs and MSAC legislation. In addition, the reforms to consumer engagement should be harmonised across the PBAC and MSAC process which would increase patient engagement.

2. Department of Health

It is recommended that InGeNA establish a forum for an ongoing dialogue with the Department of Health. This could be modelled on the Access to Medicines Working Group which is a collaboration between Medicines Australia and the Department of Health to consider issues regarding timely and appropriate access to new medicines for the PBS. Consultations revealed that the Department of Health is progressing reform in several areas that were highlighted as issues by industry and non-industry stakeholders, such as the MSAC website, patient engagement and HTA methods for large gene panels. There may be an opportunity for industry members, patients and patient representative groups to co-design the MSAC website to ensure that the process is transparent and can support all stakeholders equally.

What will this solve?

Greater alignment with the Department of Health will address the challenge of transparency, which was noted on multiple occasions during consultations. In addition, establishing a working group would also provide a forum to work towards addressing other challenges such as evidentiary requirements and value definition as well as increasing accountability.

3. Promoting better collaboration for genetic and genomic applications

In contrast to the PBS, the MBS includes generic non-branded listings. Therefore, a new MBS item is often of benefit to multiple parties, including several companies, as well as the clinical service provider. Historically MSAC applications have frequently included multiple applicants, highlighting the feasibility of collaboration (30, 31).

Consultations highlighted that the MBS is not keeping up to date with the progress of genetic and genomic technologies. This is particularly true of panel testing where the MBS lacks any items related to panel testing for somatic variants in cancer (to provide access to targeted medicines), despite this being an established part of clinical practice. Consultations also highlighted a reluctance from industry to enter collaborations due to competition law, despite the existence of numerous historical precedents (30, 31).

To move forward InGeNA should establish a framework for industry collaborations. This should include historical examples and governance to ensure independence is maintained. InGeNA should also seek to promote collaboration

with non-industry stakeholders, such as clinical societies or patient organisations, and InGeNA should consider its own role in future MSAC applications, potentially as a lead organisation.

What will this solve?

By promoting collaboration on future MSAC applications several challenges are addressed. This includes reducing the length of the MSAC process and improving efficiency. In addition, patient participation can be enhanced, and stakeholder alignment improved.

Long-term structural reform

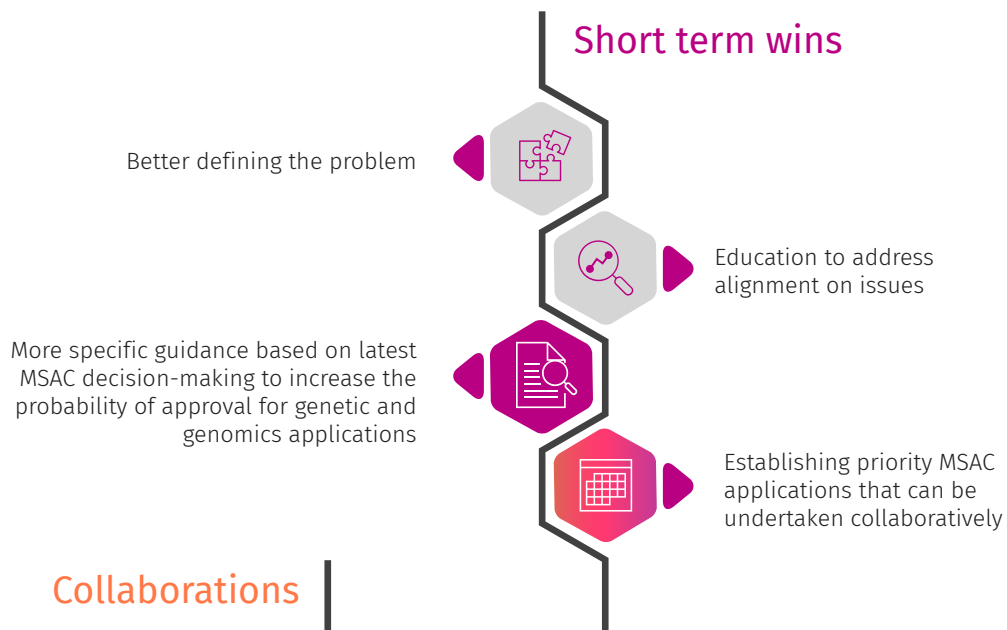
It is acknowledged that many challenges and potential solutions in consultations require deep structural reforms or legislation and require extensive input from the federal government. The prime example is funding, which for genetic and genomic technologies is estimated to be split 50/50 between the states and the federal government and remains a roadblock to greater uptake of new technologies. To achieve long-term reform a structural issue, such as funding, should be addressed in a stepwise manner. Consultations revealed that a possible avenue would be to expand the National Health Funding Agreement (NHRA), which was used to fund cell and gene therapies.

The list of structural issues that need to be addressed include:

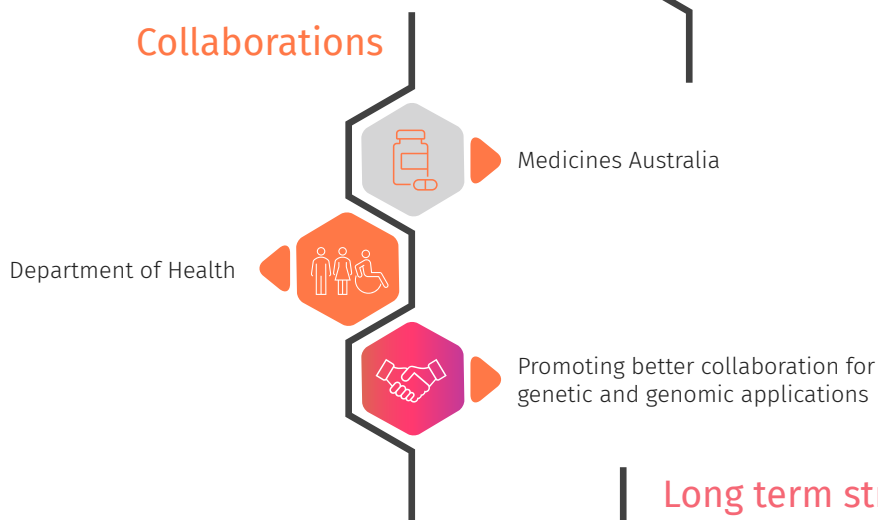
- Clarifying and aligning federal versus state funding and evaluation processes
- Legislation or an agreement to compel the federal government to act on MSAC decision-making
- A national policy to guide decisions on access to genetic and genomic technologies and the ethical issues raised by genetic and genomic information
- Investigating a mechanism to link research funding through schemes such as the MRFF to HTA decision-making
- A central data repository for genomic information

It is recommended a roadmap is established to address the first three issues, as these will have the greatest impact on achieving faster access and long-term sustainable reform. This would include consultation with InGeNA members and other stakeholders and a detailed timeline of activities.

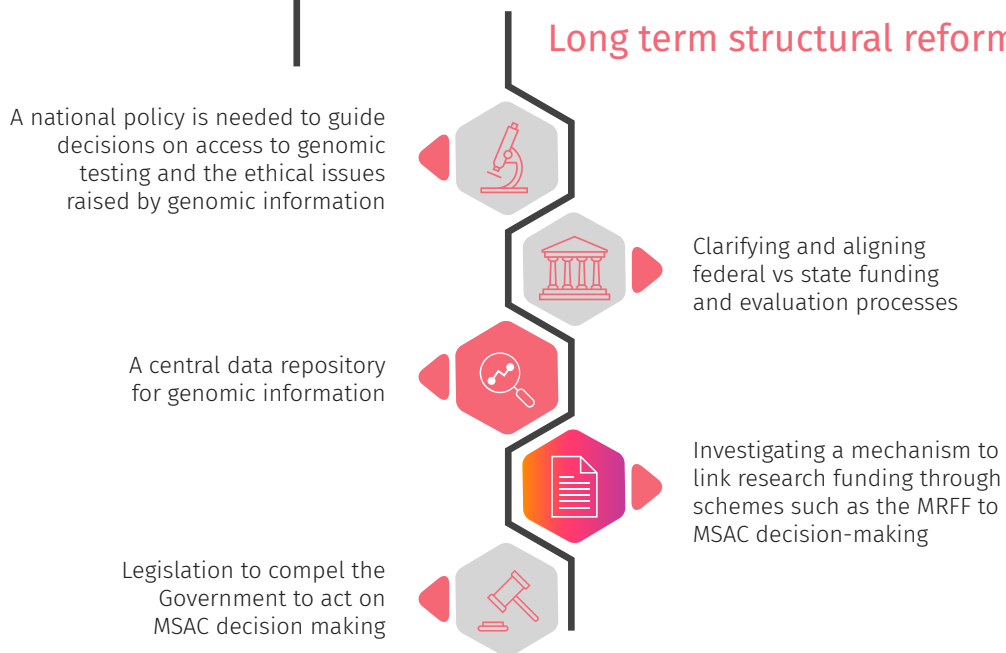
Short term wins



Collaborations



Long term structural reform



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