MSAC Application 1810

Genomic testing for the diagnosis of inborn errors of immunity (IEI)

Applicant: The Royal College of Pathologists of Australasia

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1. PICO Genomic testing in people with suspected of inborn errors of immunity (IEI): PICO Set 1.

Component	Description
Population	People presenting with symptoms suggestive of an inborn error of immunity (IEI) *(testing may also include the parents for the purposes of determining phase of the identified variants and/or whether de novo or not, known as "trio testing")*
Prior tests	Current targeted diagnostic tests based on traditional immunological and phenotype-driven diagnostic processes used to inform differential diagnoses include: • Immunology tests for the quantitation of immunoglobulins (IgG, IgA, IgM and potentially IgD and IgE) • Immunology tests for the characterisation of 3 or more leucocyte surface antigens by immunofluorescence or immuno-enzyme techniques to assess lymphoid or myeloid cell populations • Chromosome analyses by genome-wide micro-array (in those with intellectual disability or other congenital multi-systemic disorder)
Intervention	Genomic testing for the diagnosis of IEI, comprising 1. Whole exome sequencing (WES) or whole genome sequencing (WGS) and curation of the IEI gene panel for the singleton/index case; or 2. Trio WES/WGS testing of the affected individual and their parents and curation of IEI gene panel (and immunophenotyping of the parents where required); or 3. Single gene testing for a specific IEI phenotype where clinical presentation strongly suggests a particular gene affected
Comparator/s	No genomic testing (i.e. prior tests alone)
Reference standard	Not applicable
Outcomes	Test performance: • Concordance of different forms of genomic testing • Proportion of individuals who receive a clinically informative result • Proportion of individuals who receive a new/refined diagnosis or prognosis • Proportion of individuals who receive a targeted therapy or other therapy change (different to what they would have received based on clinical diagnosis)

Component	Description
	• Proportion of individuals with variants that have family utility (variants identified that allow cascade testing), or reproductive utility (variants that would inform reproductive planning) Change in patient management: • Investigations/monitoring/treatments received (including any targeted treatments or avoiding those contraindicated) Safety: • Adverse events (AEs) related to genomic testing • AEs from change in patient management (such as avoiding harms from unnecessary invasive investigations) Economic and Financial Implications: • Incremental cost per additional clinically informative result gained • Cost associated with change in treatment • Cost to the Australian healthcare system • Incremental cost of diagnostic, treatment, familial implications from additional clinically informative results Other relevant considerations: • Value of knowing (benefits and harms) • Ethical considerations (equity of access, considerations regarding consent)
Assessment question	What is the safety, effectiveness and cost-effectiveness and financial impact of genomic testing versus no genomic testing in people with signs/symptoms suggestive of IEI (± their parents for trio testing)?

Table 2. PICO for cascade testing of biological relatives of people diagnosed with IEI: PICO set 2

Component	Description
Population	"At risk" biological relatives of an individual with an IEI.
Prior tests	The diagnosis of IEI in the proband/index case (genetic confirmation of IEI for the intervention arm, clinical diagnosis suggestive of IEI for the comparator arm)
Intervention	Targeted genomic testing for the familial variant causative of the IEI identified in the proband (cascade testing)
Comparator	No genomic testing in relatives of the index case. This may or may not involve monitoring, depending on the specific IEI diagnosed in the proband/index case and the age of the relative.

Component	Description
Outcomes	Uptake of cascade testing Test outcomes: • Number of additional relatives with IEI detected as genotype-positive for an IEI rather than from monitoring alone • Number of relatives identified as carriers for an IEI for informing reproduction options • Number of relatives not requiring monitoring Linked evidence of change in management: • Time to diagnosis/treatment in those with an IEI Safety: adverse events from the genomic test, test results, investigations, treatments Incremental cost per additional clinically informative result gained Value of knowing (e.g. psychological benefits/harms from being diagnosed or ruled out as having IEI or being a carrier of IEI, impact on reproductive decision-making)
Assessment question	What is the comparative safety, effectiveness, cost-effectiveness and financial impact of cascade targeted genomic testing of 'at risk' biological relatives of people diagnosed with IEI who have at least one pathogenic (P)/likely pathogenic (LP) variant identified compared to no cascade targeted genomic testing, or clinical cascade testing/monitoring of biological relatives of someone clinically diagnosed with an IEI?

Table 3. PICO for partner testing of people diagnosed with, or carriers of, an IEI: PICO Set 3

Component	Description
Population	Reproductive partners of either: • proband with an IEI with 2 P/LP variants identified for an autosomal recessive condition • biological relatives of probands who have been identified as cases or carriers of an autosomal recessive IEI (≥1 P/LP variant)
Prior tests	Genomic testing for the diagnosis of/carrier status of IEI in the proband/relative
Intervention	Genomic testing of the same gene in which their reproductive partner harbours ≥1 P/LP variant (preconception carrier testing)
Comparator	No sequencing of the gene implicated in the IEI
Outcomes	Diagnostic yield of P/LP variants associated with IEI (may be derived from general population)

Component	Description
	Uptake of partner testing Value of knowing for informed reproductive decision-making At-risk couples identified, or couples whose risk status is identified Number of couples provided with information for reproductive decisions Cost per at-risk couple identified Cost per couple provided with information
Assessment questions	What is the value of knowing from partner genomic testing vs no partner genomic testing of someone with at least one variant associated with an autosomal recessive IEI? (proportion reassured and proportion provided with information for reproductive planning) What is financial impact of partner genomic testing to determine carrier status in partners of people with at least one P/LP variant identified for an autosomal recessive condition?

Table 4. PICO for reanalysis of Next-Generation Sequencing (NGS) data: PICO Set 4

Component	Description
Population	Individuals with a strong suspicion of IEI on immunophenotyping and/or functional assay despite uninformative or uncertain WES or WGS result on the initial genomic test after at least 2 years.
Prior tests	Next generation sequencing (NGS) for WES or WGS
Intervention	Re-analysis of NGS data after at least 2 years from the initial analysis of the primary test
Comparator	No reanalysis of NGS data
Outcomes	Diagnostic yield of new P/LP variants Change in patient management
Assessment questions	What is the diagnostic yield of incremental P/LP variants identified from reanalysis of NGS data after at least 2 years? In what proportion of cases of those suspected of IEI does reanalysis of NGS data result in any change of management? What is the cost per new variant identified, and financial impact associated with re-analysis of NGS data of people with a strong suspicion of IEI?

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of genomic testing for the diagnosis of IEIs was received from The Royal College of Pathologists (RCPA) by the Department of Health, Disability and Ageing.

PICO criteria (PICO set 1: diagnostic testing)

Population

The Population 1 of interest are people presenting with symptoms suggestive of inborn errors of immunity (IEI), or those with signs of IEI (identified through newborn bloodspot screening [NBS]). IEIs are a heterogeneous group of genetically encoded disorders of the immune system. They are associated with many single-gene variants (at least 485 identified to date) that result in the loss of expression, loss of function, or gain in function of the encoded protein (Chinn & Orange 2020). IEIs were previously commonly termed primary immunodeficiency (PID). Variants can be dominantly or recessively inherited, autosomal, or X-linked, and with complete or incomplete penetrance of the clinical phenotype (Bousfiha et al. 2022). Most individual IEIs are considered to be rare; there are difficulties associated with deriving prevalence estimates because of underdiagnosis, underreporting, and potentially death prior to a diagnosis (Ballow & Leiding 2022). Taken together, and with advancement of diagnostic technologies for diagnosing suspected IEIs, prevalence rates are estimated to range between 1:1,000 to 1:5,000 (Ballow & Leiding 2022), representing a significant global burden of disease. Prevalence also varies with ethnicity, and increases have been observed with consanguinity (Kobrynski, Powell & Bowen 2014).

PASC noted that the application documents referred to genomic testing for the diagnosis of primary immunodeficiency (PID), but that more recently, the preferred term has been inborn errors of immunity (IEI). PASC advised that the term 'inborn error of immunity' or 'IEI' should be used in preference to 'PID'.

Children and adults can be affected by IEIs. Initial clinical symptoms often present in childhood in patients with increased susceptibility to infection, autoimmunity, autoinflammatory diseases, allergy, bone marrow failure, and/or malignancy (Bousfiha et al. 2022). IEIs are caused by germline variants in single genes that alter both the adaptive immune response (B- and T-lymphocytes) and the innate immune response (phagocytic cells, complement system, cytokines and their receptors). As such, the immunodeficiency caused by these variants results from intrinsic defects in cells of the immune system, including T and B lymphocytes, phagocytes, and the complement system.

Typically, patients with IEIs associated with B-cell defects are more vulnerable to infections caused by bacteria, such as pneumonia, otitis media and sinusitis. Patients with IEIs associated with T-cell defects experience increased susceptibility to fungal and viral infections due to the loss of T-cell help for B-cell function, and a higher risk of developing malignancies. There are wide variations across both B-cell and T-cell defects giving rise to IEIs; many T-cell defects impact on B-cell function which increases patients' susceptibility to invasive bacterial infections. Conversely, some patients with B-cell defects experience severe infections including abscesses, meningitis or sepsis from common pathogens. In addition to increased risks of infection by opportunistic pathogens, other characteristics of innate immunity

deficiencies are characterised by failure to thrive, and some inflammatory or autoimmune disorders (Justiz Vaillant & Qurie 2024).

The International Union of Immunological Societies (IUIS) Expert Committee currently lists 10 phenotypic classifications that are associated with significant morbidity (Tangye et al. 2022) and have overlapping sub-classifications of IEIs that compromise the immune system.

1. Combined immunodeficiencies (B and T lymphocyte cell function affected)
    - Severe combined immunodeficiency (SCID) is the most serious of these disorders. Since May 2024, SCID has been screened for through the NBS programs throughout Australia. SCID requires urgent commencement of treatment and a haematopoietic stem cell transplant (HSCT) for survival.
2. Combined immunodeficiencies with syndromic features.
3. Predominantly antibody deficiencies (B lymphocyte)
    - Common variable immunodeficiency (CVID) is the most common form of antibody deficiency and usually presents with recurrent chest and sinus infections. Symptoms can start at any age, although most cases are diagnosed in adults.
    - X-linked agammaglobulinaemia is an antibody deficiency that is usually diagnosed in male infants. Common symptoms include frequent pus producing infections of the ears, lungs, sinuses and bones, chronic diarrhoea and poor growth.
4. Diseases of immune dysregulation - includes a broad group of disorders that occur when the body's immune system is not being controlled normally and may react against its own cells. People with immune dysregulation can have fever, damage to organs or blood cells, and increased risk of infection. Examples of immune dysregulation include immuno-dysregulation polyendocrinopathy enteropathy x-linked syndrome (IPEX), Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED), autoimmune lymphoproliferative syndrome (ALPS) and autoinflammatory disorders.
5. Congenital phagocytic cell deficiencies (deficiencies in neutrophils and macrophages – associated with severe infections)
    - X-linked chronic granulomatous disease (CGD) is the most serious form of phagocytic cell deficiency. In CGD neutrophils can't capture and kill germs. People with CGD have frequent and severe infections of the skin, lungs, and bones. They can also develop chronic inflammation, including inflammatory bowel disease (IBD).
6. Defects in intrinsic and innate immunity including predisposition to mycobacterial disease, viral infection and invasive fungal disease.
7. Autoinflammatory disorders.
8. Complement deficiencies – some can increase the risk of autoimmune disease, whilst others result in severe infections such as meningitis or septicaemia.
    - Hereditary angioedema (HAE) is a different sort of a complement disorder, that is due to C1 esterase inhibitor deficiency. In people with HAE, the small blood vessels leak fluid into the tissues, causing non-itchy swellings known as angioedema. People with HAE can have unpredictable and sometimes severe swellings throughout life that may be life-threatening (ASCIA 2024).
9. Bone marrow failure.
10. Phenocopies of inborn errors of immunity (Tangye et al. 2022).

A study in France reported IEIs are rarely investigated when children are admitted to paediatric intensive care units with community-onset severe bacterial infections (Flatrès et al. 2021), despite the necessity of early diagnoses of IEIs for the delivery of treatment to prevent associated morbidity and mortality (Devonshire & Makhija 2019). Worldwide, IEI mortality rates range between 34.5% of patients in Tunisia, to 2.1% in Germany (Lougaris et al. 2020). Most mortality data are derived from registries; rates of mortality differ according to rates of diagnosis and the initiation of appropriate treatment. Delayed diagnoses of IEIs were associated with increased morbidities, including potentially irreversible complications of recurrent infections such as bronchiectasis. In addition, older age at diagnosis was associated with higher mortality compared to an age-matched general population (Joshi et al. 2009).

Patients with a suspected IEI should be referred to a clinical immunologist for evaluation. Upon referral, investigations would include blood tests to quantitate immune system including immunoglobulin levels, lymphocyte subpopulations (T, B, and NK cells) and complement proteins. Immune function tests may also be conducted, including assessments of T cell proliferation, antibody responses to vaccination, neutrophil migration and oxidative burst (killing), and complement function. In addition, imaging studies of may also be performed to investigate lymphoproliferation (e.g. enlarged spleen and/or lymph nodes), evidence of infections, or complications of chronic disease such as bronchiectasis or chronic sinusitis. Clinical history and investigations would be used to exclude secondary causes of immunodeficiency (e.g. haematological malignancy, immunosuppressive treatment, HIV infection, or protein-losing states).

The most severe IEI is severe combined immunodeficiency (SCID). Infants with SCID require bone marrow transplantation (BMT), ideally within the first three months of life. Without this treatment which can be curative, most affected children will die within the first two years of life (Goebel et al. 2024). The most common cause of SCID is a gene defect on the X chromosome which accounts for more than 50% of cases and affects males, although there are several other genetic causes of SCID with autosomal recessive inheritance. Newborn screening for SCID has now been introduced in all Australian states, which detects the characteristic T-cell deficiency in newborns that characterises SCID. Newborns with a positive SCID newborn screen undergo further laboratory testing performed to confirm the diagnosis of SCID. Genetic testing is then required to identify the molecular defect causing SCID, and to determine optimal approaches for curative bone marrow transplant and to inform genetic counselling for future pregnancies. Although many cases of classic SCID detected by newborn screening can be cured with BMT, other cases of SCID caused by thymic disorders are not remedied by BMT. Genetic testing early in life to identify alternative causes of severe T-cell deficiency can enable appropriate treatment, and avoid risks associated with inappropriate treatment or BMT (Ballow & Leiding 2022). However, given that SCID is detected via NBS, this condition will be excluded from the assessment for the benefit of testing in PICO set 1.

Most patients with suspected IEI are investigated in outpatient settings, often after presentation in hospital with recurrent, severe and/or opportunistic infections. There are often delays in the diagnoses of IEIs because of a broad range of clinical phenotypes of IEI and a lack of recognition of a potential IEI by non-immunologists. Management of IEIs are dependent on confirmation of the underlying molecular defect, and the clinical phenotype (Quinn et al. 2022).

Most IEIs are associated with susceptibility to infections; hence, antimicrobial prophylaxis for bacterial, fungal and/or viral infections is prescribed according to the underlying immune defect. Patients with antibody deficiencies commence immunoglobulin replacement therapy soon after diagnosis to prevent further bacterial infections, and complications such as bronchiectasis. Other patients with IEIs associated with immune dysregulation and autoimmunity may require immunosuppressive therapies to manage

these complications, and antimicrobial therapies to manage their risk of infections (Quinn et al. 2022). Targeted therapies addressing specific molecular defects that are implicated in IEIs are now increasingly available, including medications already licensed for other indications that have been repurposed to treat specific IEIs (Sogkas et al. 2022).

Early diagnosis of IEIs is important because delayed treatment can lead to complications of a life-threatening nature (Sogkas et al. 2022). The warning signs or indicators of IEI are summarised in Table 5: these were developed to raise awareness amongst non-immunology specialists to consider the possibility of an IEI. These indicators do not represent diagnostic criteria; rather they are patient presentations which could necessitate further investigations for IEI (ASCIA 2024).

Table 5. Warning signs of primary immunodeficiency/inborn errors of immunity

	Paediatric	**Adult**
1	4 or more ear infections within 1-year	2 or more ear infections within 1 year
2	2 or more serious sinus infections within 1 year	2 or more sinus infections in 1 year in the absence of allergies
3	2 or more pneumonias within 1 year	1 pneumonia per year for more than 1-year
4	Recurrent deep skin or organ abscesses	Recurrent deep skin or organ abscesses
5	2 or more deep-seated infections such as sepsis, meningitis, or cellulitis	Infection with normally harmless tuberculosis-like bacteria
6	Persistent thrush in the mouth, skin or elsewhere after age 1-year	Persistent thrush or fungal infection
7	2 or more months on antibiotics with little effect	Repeat viral infections (colds, herpes, warts, condyloma)
8	Requirement for intravenous antibiotics to clear infections	Requirement for intravenous antibiotics to clear infections
9	Failure to gain weight, grow normally, or experience of chronic diarrhoea	Chronic diarrhoea with weight loss
10	Family history of PID/IEI	Family history of PID/IEI

Source: (ASCIA 2025)
PID=primary immunodeficiency; IEI=Inborn errors of immunity.

Parents of the affected patient may also be tested as part of trio testing, for segregation purposes. This helps establish phase of variants, and whether they are *de novo*, and which variant is inherited from which parent, confirming compound heterozygosity. When performed for the purposes of establishing the genetic cause of IEI in the proband, it is proposed that this testing would be assessed as part of the diagnostic testing.

PASC noted that the proposed population in the pre-PASC PICO confirmation included those with symptoms suggestive of an IEI, or those with signs of an IEI (identified through NBS, including those that screen positive for severe combined immunodeficiency [SCID]).

PASC considered whether neonates identified through NBS programs should be included in the population or not. Those identified through NBS would undergo the same investigations as those suspected of having an IEI due to symptoms. However, the majority of cases identified through NBS would have their subsequent investigations performed through the public health system (by the states/territories), rather than using the proposed MBS items. Although a small number of cases would undergo investigations in the private health system (using the proposed MBS items if available), PASC considered that for these patients, the appropriate comparator would be genomic testing (paid for by the states/territories) rather than no genomic testing. The safety and effectiveness of the genomic testing would therefore not need to be assessed in those identified with signs of an IEI identified through NBS (as the intervention and comparator would be the same). This population could therefore be excluded from the assessment of safety and effectiveness for PICO set 1 (although would be relevant to consider in the financial analysis and for downstream testing of relatives under PICO set 2).

Prior tests

Patients referred to a clinical immunologist with signs or symptoms suggestive of an IEI as outlined in Table 5 would undergo a detailed clinical history, physical examination, and series of routine investigations with additional investigations undertaken based on the clinical presentation. These would include, but are not limited to complete blood counts, peripheral blood smear, serum immunoglobulins, flow cytometry-based phenotypic screening and testing for secondary causes such as human immunodeficiency virus (HIV). Some of these tests may require samples to be sent to highly specialised immunology laboratories (often interstate), may require advanced notice for the laboratory to prepare the necessary reagents to perform the test, and/or be poorly remunerated or not funded by existing item numbers due to the esoteric nature and infrequent use of these tests. A phenotypic diagnosis of IEI may be made such as a common variable immunodeficiency, which has heterogeneous clinical manifestations between individuals and is caused by a range of different molecular defects. However, these diagnostic tests may not show abnormal findings in some IEIs.

Genetic testing would then be recommended, after appropriate counselling and obtaining the informed consent of the patient. Immune cell-specific functional assays should be conducted in parallel to genotyping. These tests require blood, saliva or a buccal sample from which DNA is extracted for genomic analysis.

The principal MBS services used to diagnose IEIs in the absence of genomic testing are listed in Table 6 below.

There will be some patients for whom functional assays may either improve or decrease the likelihood of a diagnosis; however, only a limited number of these assays possess definitive diagnostic utility. These assays are frequently restricted to highly specialised research facilities or a small subset of diagnostic laboratories, and their applicability may be constrained by logistical limitations, particularly with respect to the viability of shipped specimens.

Table 6. Immunological and phenotype-driven tests for standard investigations for IEIs

Item number (Group)	Description and fee
73802 (Group P9 - Simple Basic Pathology Tests)	One test: Leucocyte count, erythrocyte sedimentation rate, examination of blood film (including differential leucocyte count), haemoglobin, haematocrit or erythrocyte count **Fee:** $4.55 **Benefit:** 75% = $3.45 85% = $3.90

Item number (Group)	Description and fee
71066 (Group P4 – Immunology)	One test: Quantitation of total immunoglobulin A by any method in serum, urine or other body fluid **Fee:** $14.90 **Benefit:** 75% = $11.20 85% = $12.70
71068 (Group P4 – Immunology)	One test: Quantitation of total immunoglobulin G by any method in serum, urine or other body fluid **Fee:** $14.90 **Benefit:** 75% = $11.20 85% = $12.70
71072 (Group P4 – Immunology)	One test: Quantitation of total immunoglobulin M by any method in serum, urine or other body fluid **Fee:** $14.90 **Benefit:** 75% = $11.20 85% = $12.70
71074 (Group P4 – Immunology)	One test: Quantitation of total immunoglobulin D by any method in serum, urine or other body fluid **Fee:** $14.90 **Benefit:** 75% = $11.20 85% = $12.70
71081 (Group P4 – Immunology)	Quantitation of total haemolytic complement **Fee:** $41.50 **Benefit:** 75% = $31.15 85% = $35.30
71127 (Group P4 – Immunology)	Functional tests for lymphocytes - quantitation other than by microscopy of: (a) proliferation induced by 1 or more mitogens; or (b) proliferation induced by 1 or more antigens; or (c) estimation of 1 or more mixed lymphocyte reactions, including a test described in item 65066 or 65070 (if performed), 1 of this item to a maximum of 2 in a 12 month period **Fee:** $180.60 **Benefit:** 75% = $135.45 85% = $153.55
71133 (Group P4 – Immunology)	Investigation of recurrent infection by qualitative assessment for the presence of defects in oxidative pathways in neutrophils by the nitroblue tetrazolium (NBT) reduction test **Fee:** $10.65 **Benefit:** 75% = $8.00 85% = $9.10
71134 (Group P4 – Immunology)	Investigation of recurrent infection by quantitative assessment of oxidative pathways by flow cytometric techniques, including a test described in 71133 (if performed) **Fee:** $106.55 **Benefit:** 75% = $79.95 85% = $90.60
71135 (Group P4 – Immunology)	Quantitation of neutrophil function, comprising at least 2 of the following: (a) chemotaxis; (b) phagocytosis; (c) oxidative metabolism; (d) bactericidal activity;

Item number (Group)	Description and fee
	including any test described in items 65066, 65070, 71133 or 71134 (if performed), 1 of this item to a maximum of 2 in a 12 month period **Fee:** $212.95 **Benefit:** 75% = $159.75 85% = $181.05
71139 (Group P4 – Immunology)	One test: Characterisation of 3 or more leucocyte surface antigens by immunofluorescence or immunoenzyme techniques to assess lymphoid or myeloid cell populations, including a total lymphocyte count or total leucocyte count by any method, on 1 or more specimens of blood, CSF or serous fluid **Fee:** $106.55 **Benefit:** 75% = $79.95 85% = $90.60
73292 (Group P7 – Genetics)	One or more test: Analysis of chromosomes by genome-wide micro-array including targeted assessment of specific regions for constitutional genetic abnormalities in diagnostic studies of a person with developmental delay, intellectual disability, autism, or at least two congenital abnormalities (including a service in items 73287, 73289 or 73291, if performed). **Fee:** $589.90 **Benefit:** 75% = $442.45 85% = $501.45

PASC noted that one of the proposed prior tests included in the PICO set was microarray testing under MBS item 73292. PASC queried whether microarray testing was clinically relevant for all patients suspected of having an IEI. PASC advised that more justification for the use of microarray was required. In the application it was suggested that patients with an intellectual disability or other congenital multi-systemic presentation be referred to clinical genetics before genotyping, as these syndromes may not be covered by the IEI gene panel. Therefore, the microarray item may potentially be used in a subset of patients suspected of an IEI, who also meet the criteria for MBS 73292.

PASC noted a range of immunoglobulins are to be tested. The applicant's pre-PASC response clarified that IgE would be tested more commonly than IgD. IgD is sometimes tested if mevalonate kinase deficiency (MVK) is suspected but it has poor specificity and sensitivity for this condition. More recent literature suggests IgD is not a useful test; however, some clinicians do use this test occasionally, particularly in the context of autoinflammatory conditions.

Intervention

Genetic testing to identify molecular defects is regarded as essential for the diagnosis and management of patients with suspected IEIs. Knowledge of the specific genetic diagnosis informs clinical decision-making. Massively parallel exome sequencing, or depending on availability, whole genome sequencing (WGS) is commonly used to expedite an IEI diagnosis and reduce the number of non-diagnostic results (Chinn & Orange 2020). Other techniques that can be used include high-throughput sequencing using gene panels.

The types of genomic tests used for diagnosing IEIs are outlined in Table 7. Patients suspected of having an IEI would require testing with the proposed next-generation sequencing (NGS), such as whole exome sequencing or whole genome sequencing (Item AAAA or BBBB), unless there is a high clinical suspicion of a single-gene disorder (in which case single gene testing by Sanger sequencing may be preferred).

Table 7. Types of genomic sequencing approaches used for the diagnosis of IEIs

Test Type	Function of the Test	When the test is utilised
Single gene testing (such as by Sanger sequencing)	Sequences a single gene	When there is a high clinical suspicion of a particular genotype, based on the phenotype. This is faster to perform than larger panels, less likely to result in incidental findings, and cheaper.
Targeted Gene Panels	Sequences a specific predefined set of genes known to cause IEIs	When symptoms suggest a particular IEI (e.g., SCID, X-linked agammaglobulinemia [XLA])
Whole Exome Sequencing (WES)	Sequences all the protein-coding regions of the genome (approximately 1–2% of DNA)	Used when the diagnosis is unclear or multiple genes may be involved
Whole Genome Sequencing (WGS)	Sequences the entire genome, including non-coding regions	Used when the diagnosis is unclear or multiple genes may be involved Or when intragenic copy numbers are common source of disease
Copy Number Variant (CNV) Analysis	Detects smaller intra-genic and large deletions or duplications in DNA	Often included in WGS pipelines and some targeted gene panels. If WES used, then microarray may be used to perform CNV for large deletions
Functional Immune Testing	Measures immune cell function and protein levels	Complements genomic testing to confirm diagnosis and guide treatment

The analyses of the genomic tests are performed by the National Association of Testing Authorities (NATA)-accredited diagnostic laboratories; such laboratories are required to undergo a joint NATA/RCPA accreditation process aligned with ISO 15189 standards, with specific approval granted for conducting genetic testing. This accreditation encompasses all technical stages, including sample reception and handling, sequencing procedures, data analysis workflows, result interpretation, and the generation of clinically compliant reports. There is no requirement for laboratories to use reagents, equipment, or analysis pipelines from any particular manufacturer. Any variants identified would be reported in alignment with established guidelines such as the American College of Medical Genetics and Genomics criteria by a pathologist with the required scope of practice for genomic testing supervision.

The results of genomic testing are interpreted alongside previous laboratory and imaging investigations, clinical progress of the patient, and the patient's response to treatment to determine the clinical relevance of any genetic variants identified. In addition, the results of any family studies may be used to determine the inheritance pattern for some IEIs. The reporting pathologist would contribute to the multidisciplinary team involved in patient management by assisting with the interpretation of the genomic testing results.

The absence of genetic causes for an IEI cannot be used to exclude an IEI (although it may decrease the likelihood).

Note: An in-house in vitro diagnostic (IVD) is required to be regulated but not to be listed on the Australian Register of Therapeutic Goods (ARTG). Testing using an IVD would be delivered only by Approved Pathology Practitioners in NATA Accredited Pathology Laboratories by referral in line with other tests in the MBS Pathology Services Table.

PASC confirmed that the intervention is genomic testing for diagnosing IEIs. However, the pre-PASC PICO confirmation did not include single gene testing for those with symptoms of an IEI.

PASC noted there is a subset of patients in whom one or two pathogenic variants in a particular gene can be strongly suspected based on the patient's phenotype, or some other reason. The applicant-stated examples include males with clinical and laboratory phenotype of X-linked agammaglobulinemia (XLA), males with a non-genetic diagnosis of CGD, known familial pathogenic variants, CD40 ligand deficiency, and leukocyte adhesion deficiency type 1 (LAD1). PASC noted that in these cases, some laboratories currently conduct single gene testing as a first-line investigation, potentially obviating the need for WES/WGS. PASC noted that Sanger sequencing of a single gene can be both cheaper and quicker than WES/WGS, and considered that it should be included as an option. PASC advised that the intervention for PICO set 1 is either WES/WGS (singleton or trio testing) or single gene testing (with the possibility of subsequent WES/WGS if no pathogenic/likely pathogenic variants identified on single gene testing).

PASC considered that one of the main concerns with the intervention is determining the virtual panel of evidenced-based genes proven to be associated with IEI to be curated after genomic sequencing has been completed. MBS funding does not support research testing, and the genes whose variants are being curated must have proven gene-disease validity. PanelApp has a Severe Combined Immunodeficiency panel (although those with SCID would likely be detected through NBS and need not be considered in the assessment of safety/effectiveness). In the application, the International Union of Immunological Societies (IUIS) Expert Committee phenotypic classification register was provided as an example of a standards-based approach to genotyping that could be undertaken. However, the applicant advised that IUIS register is largely used for research rather than clinical practice, and recommended the use of PanelApp, as it is based on phenotypes and more frequently curated and updated than the IUIS register. Based on this advice, PASC supported the use of PanelApp as a reference source of gene-disease validity but acknowledged that the evidence is evolving. PASC considered that PanelApp may be mentioned in the explanatory notes of the proposed MBS items, but that the types or number of genes to be tested should not be included (as this will differ depending on the phenotype and may change over time). PASC noted the applicant's proposed practice note (PN).7.13 provided a balance of requiring a recognised test directory to be used, without being specific.

Expected utilisation of genomic testing

Individual IEIs are rare and vary with different IEIs; e.g., the national prevalence rate in Australia for SCID is approximately 1 in 60,000 to 1 in 69,000 live births. However, IEIs collectively incur significant health burdens. The prevalence of IEIs can vary by ethnicity and occurs more frequently in populations where consanguinity is common.

The application stated that international IEI registries report prevalence rates for symptomatic individuals ranging from 1 in 8,500 to 1 in 100,000. In Australia, registry data from 2018 showed there were 1,876 registered patients with IEIs in a population of 24.6 million, which represents a rate of 7.6 per 100,000; there was no information on specific IEIs or if the patients received a genetic diagnosis. An earlier dataset of Australian and New Zealand patients in 2007 showed a lower prevalence of 4.86 per 100,000, with most cases comprising antibody deficiencies (77.4%), with common variable immunodeficiency (CVID), accounting for 38.4% of all patients. Other categories included cellular and humoral immunodeficiencies (8.9%), complement deficiencies (5.9%), phagocyte disorders (3.2%), and miscellaneous IEIs (4.6%). Only 18.4% of these patients had received a genetic diagnosis. The Australian data from 2007 showed an estimated prevalence was 5.6 per 100,000, though South Australia reported a higher rate of 12.4 per 100,000 which may reflect increased clinical awareness of IEIs than a difference in prevalence. It is widely acknowledged that IEIs remain under-diagnosed and under-reported.

A substantial number of patients experience extensive diagnostic odysseys that have concomitant detrimental impacts on health status and quality of life and extensive use of the health system prior to achieving a diagnosis of an IEI. A recent study by Nikzad et al. (2025) reported that only 28% (108 of 383 children) aged 0-5 years who had experienced serious infections received a diagnosis of IEI; these children subsequently reported improved health status than children who were not diagnosed. In addition, the mean number of clinicians seen by patients was 3 ± 2.4 (range: 0–11) during the process of attaining a diagnosis, which represents a significant burden on the health system.(Nikzad et al. 2025)

Given the above, deriving an estimate of the incidence/prevalence of IEI in the Australian population is challenging. The number of tests being conducted currently may be used as an estimate of the potential size of the testing population. According to the applicant, approximately 300 children per year are currently tested for IEIs in New South Wales (NSW); some 20 patients undergo testing for suspected SCID per year, with genetic variants being identified in approximately 95% of these children. An extrapolation of these figures to the Australian population results in an estimate of 959 tests in year 1 (90% tested with NGS, and 10% tested with Sanger sequencing). Sanger sequencing would be used to confirm a known variant or for testing a specific gene and is often used to validate results from other tests. The estimated yield of approximately 15% in local practice is similar to rates reported in Germany by Sogkas et al. (2022).

Comparator(s)

The comparator is no genomic testing to diagnose IEIs. In the absence of genomic testing, differential diagnoses of IEI are based on traditional immunological and phenotype-driven diagnostic processes. The comparator would not be substituted in the event of public funding of genomic testing; the prior tests would continue to be used as preliminary tests prior to genomic testing (i.e. see 'prior tests' for more description of the comparator). There would also be no re-analysis of the test results for PICO set 4.

PASC confirmed that the comparator was 'no genetic testing', meaning that prior tests alone would be used.

PASC noted that cases detected through newborn bloodspot screening (NBS) would be referred for genetic testing through an independent process. The comparator for this subgroup, therefore, would also be genetic testing (i.e. the same as the intervention). This means that the clinical utility of genomic testing in those detected by NBS does not need to be assessed (as genomic testing would occur in both the intervention and comparator arms). However, the assessment of the financial implications to the Commonwealth health budget will need to consider the impact of these patients being tested.

Reference standard

There was no reference standard stated in the application. Genomic testing using NGS methods for WES/WGS is assumed to be the most accurate method of identifying variants for IEI.

PASC noted that the pre-PASC PICO confirmation proposed the reference standard to be WGS of both the affected individual and their parents. PASC advised that there was no reference standard. The accuracy of testing depends on both the variant detection and curation.

Outcomes

It is assumed that a pragmatic abbreviated linked evidence approach will be taken in the assessment report (see assessment framework section).

The current targeted diagnostic tests provide differential diagnoses of certain IEIs. By comparison, given the clinical, phenotypic and genetic heterogeneity of IEIs, genomic testing enables the concurrent analysis of numerous potentially causative variants to deliver a definitive diagnosis. Therefore, the clinical claim is that genomic testing is superior to no genomic testing in relation to diagnostic precision and provides downstream benefits for both clinical management and improved outcomes.

Genomic testing for early diagnosis in cases of suspected IEI may improve patient outcomes by:

1. Enabling earlier and precise treatment selection, including targeted therapies based on the underlying genetic defect (such as immunoglobulin replacement, stem cell transplantation, or gene therapy) and eligibility for relevant clinical trials.
2. Reducing the risk of cumulative organ damage, recurrent infections, and autoimmune complications because of timely diagnosis and prompt initiation of treatment.
3. Informing treatment decisions by identifying contraindications to immunosuppressive or biologic therapies that could worsen outcomes for people with some of IEIs.
4. Enabling early identification of patients at high risk of severe complications, such as malignancy or immune dysregulation to enable proactive monitoring and management.
5. Concluding diagnostic odysseys for patients, potentially improving psychological wellbeing by providing clarity, reducing parental guilt, and providing families with disease-specific support networks.
6. Offering prognostic information to manage long-term care planning, including discussions around curative treatments, supportive care, or palliative approaches where appropriate.
7. Supporting genetic counselling and facilitating cascade testing to identify at-risk family members and to inform reproductive decision-making.

Preliminary evidence presented in the application suggests the detection and diagnosis of specific IEIs by genotyping may lead to the initiation of appropriate, targeted and effective treatment, and consequently improved prognoses for patients. Treatments for IEIs can include provision of nutritional supplements, treatment with antibiotic, antifungal, or antiviral medication, immunoglobulin therapy, immunosuppression, transplantation, thymic transplantation, gene therapy, treatment with biologics/monoclonals and small molecule inhibitors, and cytokine therapy.

Outcomes related to the value of knowing a diagnosis of an IEI would also include the ability to gain information for reproductive decision-making, and reductions in diagnostic odysseys.

Currently, genomic testing for IEIs is primarily reimbursed via research funding or self-funding by patients or their families. A range of outcomes to be evaluated regarding the cost effectiveness of genomic testing include the incremental costs per additional clinically informative result obtained, of diagnostics, treatment (including changes of treatment) from additionally clinically informative results and costs associated with familial implications of test results. The total costs to the Australian government also require assessment.

The pre-PASC PICO confirmation included a broad range of outcomes including health outcomes. PASC queried the practicality and likelihood of there being a sufficient evidence-base to assess all the proposed outcomes in the pre-PASC PICO confirmation (given that IEIs encompass a large heterogenous group of clinical conditions, associated with over 400 genes).

The applicant suggested that there were published articles looking at the use of WGS in IEI, demonstrating changes in health outcomes or management. There was also anecdotal clinical experience reported by a paediatric immunologist that having a diagnosis allows transplantation or targeted therapies, which can be life changing. For example, activated phosphoinositide 3-kinase δ syndromes 1 and 2 (APDS1 and APDS2) are combined immunodeficiency disorders with targeted therapies available (small molecule inhibitors). The applicant suggested there would be health outcomes data from trials of these therapies. In patients with an LRBA deficiency, hematopoietic stem cell transplantation (HSCT) is an option in severe cases, and genetic testing plus earlier intervention may facilitate better outcomes. The applicant stated that in those with SCID, there are a number of potential genetic causes, and the conditioning that would be used for HSCT differ depending on the genetic cause. Targeting the type of conditioning for HSCT has a large influence on the rate of complications.

PASC advised that although there was good evidence on the clinical utility for SCID, the effectiveness in this population will not be included in the assessment (as genetic testing is already occurring subsequent to NBS).

PASC advised that for IEIs, there are too many different conditions and heterogeneity for exemplars to be informative. Instead, PASC considered that there is precedence from MSAC 1684 and MSAC 1675 for the assessment of large gene panels to report on the proportion of patients who have a change in diagnosis, change in prognosis, identified for targeted therapy, or other therapy (i.e. without any measure of the impact on health outcomes).

There is also precedence from MSAC 1684 and MSAC 1675 that the accuracy of testing (analytical validity) need not be assessed, which is consistent with PASC's advice that there is no reference standard available.

PASC considered that outcomes to be assessed include the proportion of individuals who receive a clinically informative result that impacts on the confirmation of diagnosis (including a refinement or change in diagnosis), prognostic utility, predictive utility for therapy (including changes in therapy), family utility (including the proportion of family members who are diagnosed via cascade testing), and reproductive utility.

PASC noted that assessing the impact of genetic testing on quality of life (allowing the assessment of incremental cost per quality adjusted life year gained) would be very difficult. PASC advised that the broader demonstration of clinical utility should be more qualitative than quantitative (i.e. providing examples of the types of benefits available, rather than quantifying the average benefit across all patients tested, or by type of IEI). This is consistent with the preferred assessment approach for large gene panels of the MSAC Executive and MSAC and supported for MSAC applications 1585 and 1675. PASC recommended removal of outcomes relating to quality of life, morbidity and mortality due to these precedents.

PASC considered that the pragmatic assessment would not need to include the following outcomes: time to diagnosis between phenotype onset and diagnosis (as the population has already received a clinical diagnosis), time to monitoring/treatments (from phenotype onset),incremental costs per early diagnosis, numbers of patients commencing earlier appropriate therapy, numbers of patients reducing ineffective therapies for incorrectly diagnosed conditions, and the costs of molecular system testing compared to health system savings enabled via reduced hospitalisations and ICU admissions.

PICO criteria (PICO set 2: cascade testing)

Population

The population of interest for PICO set 2 is biological relatives of people with molecular confirmation of their IEI diagnosis (referred to as the proband/index case) who are at risk of IEI through having inherited the familial IEI genotype including women at risk of harbouring an X-linked L/P variant. This could include the parents of the proband for determining their carrier status (to allow further cascade testing), although the parents may already have been tested for segregation purposes (determining the phase of the identified variants).

PASC noted targeted parental testing is primarily intended for phase analysis where the index case has autosomal recessive IED and may be most relevant to PICO Set 1 for refinement of the diagnosis in the index case.

PASC clarified that the intended purpose of cascade testing is to identify additional family members who are at risk of having the disease themselves (i.e. to detect additional cases). Although cascade testing may identify carriers, and this information may be useful for reproductive planning, this is secondary to the purpose of identifying those at risk, who would benefit from early intervention.

Intervention

The proposed intervention for PICO Set 2 would be targeted genomic testing for the familial variant(s) identified in the proband. The item CCCC is intended for targeted genotyping in the proposed cascade testing population (see Proposal for public funding). The use of targeted gene testing for a specific variant or two for Population 2 would be more focused than the genomic testing used for the population in PICO set 1. If molecular testing confirms the same IEI genotype identified in the biological relative, then they would undergo monitoring and/or treatment as required.

The proposed fee is method-agnostic to capture a range of potential testing modalities depending on the IEI indication.

The prior tests for this population would be the genomic testing for diagnosis and molecular confirmation of IEI diagnosis in the proband in the intervention arm of studies, and the achievement of a clinical diagnosis suggestive of an IEI in the proband in the comparator arm.

PASC confirmed the intervention for PICO Set 2 was targeted genomic testing based on the variant(s) identified in the proband.

Estimates of cascade testing

If it is assumed that parents are already tested together with the proband as part of trio testing, the uptake of the proposed cascade testing item is assumed to predominantly be siblings. The application assumed one sibling would be tested per proband.

Cascade test items for family members on the MBS are reported by the applicant to be underutilised (e.g. MBS item 73353), which may mean the estimate of family members to be tested may be lower than this derived estimate.

It is possible that family members of those with an IEI or XLA diagnosed through NBS would use an MBS item for cascade testing, so estimates should incorporate relatives of probands identified in this manner.

Comparator

As for PICO Set 1, the proposed comparator is no genomic testing. In the absence of genomic testing, some family members would undergo no clinical testing, whereas others may undergo testing for signs of IEI, or monitoring for signs/symptoms.

PASC advised that further information is required regarding the level and type of monitoring for biological relatives of an index case diagnosed with an IEI (in the absence of genomic testing) currently. PASC stated it was unclear from the PICO what tests would be performed, the role of clinical vigilance vs testing for monitoring, and at what age monitoring would cease. This information will need to be presented in the assessment report. The applicant stated that the monitoring of family members is very diverse, depending on the nature of the condition (such as the age of onset). PASC noted the applicant's pre-PASC advice that monitoring would be on a case-by-case basis. Initial assessment of relatives (such as those of patients with CVID or ALPS) may include functional screening, but if results are normal and no genetic diagnosis is available, routine monitoring would be uncommon. The applicant advised that management would typically involve a lower threshold for review, with ongoing monitoring guided by evolving symptoms and the specific IEI involved.

Outcomes

For biological relatives of probands diagnosed via genomic testing for an IEI, the results of targeted genomic testing will be that they have the IEI (either one P/LP autosomal dominant variant or two P/LP autosomal recessive variants or a male with an X-linked disorder), or are a carrier for a genetic variant associated with the IEI of interest (have one P/LP autosomal recessive variants or a female carrying an X-linked disorder) or are neither affected or a carrier (no P/LP variants). For those diagnosed with an IEI, the benefit of cascade testing would be earlier diagnosis (potentially prior to symptom onset). For carriers, a principal benefit of cascade testing would be to inform further reproductive decision-making. Carriers and those without any P/LP variants would also be the benefit of being ruled out from requiring monitoring.

The principal outcome of interest for this population will be:

- the numbers or proportion of relatives with IEIs diagnosed via genotype determination compared to those diagnosed after symptom onset without the use of cascade testing,
- changes in treatment, and
- achievement of benefits via early treatment for the IEI.

Other outcomes of interest in this population would be the health impact of any earlier diagnosis, monitoring and treatment, those related to the value of knowing, uptake of cascade testing, and the safety of testing/monitoring for specific IEIs. There may also be financial impacts of increases in cascade genomic testing, including the incremental costs per additional clinically informative result gained.

PASC advised the outcomes for PICO set 2 would be the number of additional relatives with IEIs diagnosed due to having the same genotype as the proband (diagnostic yield) who may benefit from early treatment, the number of relatives reassured and ruled out from requiring monitoring (due to being genotype negative), number of relatives identified as a carrier for an autosomal recessive condition, changes in treatment, reproductive implications, and benefits of early treatment.

PASC advised that there are implications for those identified as carriers of a variant implicated in an IEI regarding reproductive risk. Many of these are asymptomatic. They are, therefore, different to the population in PICO set 1, who are symptomatic individuals.

Other outcomes to be evaluated include the number of relatives withdrawn from monitoring following a negative genotype test, and safety outcomes including adverse events from the test, test results and preventive treatments in unaffected individuals. Outcomes related to value of knowing will also be assessed.

PICO criteria (PICO set 3: carrier testing of potential reproductive partners)

Population

The population of interest for PICO set 3 is the potential reproductive partners of probands with an autosomal recessive IEI, and biological relatives of probands who have been diagnosed as carriers of a familial variant for an autosomal recessive IEI condition.

PASC confirmed the population was reproductive partners of an individual who has an autosomal recessive IEI or biological relative who is a carrier of one familial autosomal recessive IEI variant.

Intervention

The proposed intervention would be preconception carrier screening by targeted genomic screening of the same gene in which their reproductive partner has bi or mono-allelic P/LP variant(s).

PASC confirmed that the genomic test for this population will be sequencing of the gene implicated in the IEI their partner has or carries.

Estimates of carrier testing

As most patients with suspected IEIs are children, rates of testing of reproductive partners are likely to be limited within the next five years.

Comparator

The comparator would be no genomic testing via gene sequencing of potential reproductive partners.

PASC confirmed the comparator is no genomic testing of potential reproductive partners.

Outcomes

The diagnostic yield of P/LP variants in genes associated with IEI would be assumed to be the same in reproductive partners as in the general population.

As for the outcomes for PICO set 2, a proposed benefit of targeted genomic testing would be in value of knowing to inform future reproductive decision-making. Other outcomes of interest for this population would include uptake of such partner testing to determine carrier status, and the financial impact of targeted genomic screening for this population in terms of costs per couple identified to be at risk of having an affected pregnancy.

PASC advised that the diagnostic yield for population carrier frequency may be able to be determined from gnomAD, although the database is not specific to the Australian context. This would provide an estimate of the proportion of couples identified as being at risk of having an affected child, who may be able to receive information for reproductive decision-making.

PASC noted the addition of outcomes relating to the uptake of PGD in the event that a potential reproductive partner returns a positive test for the gene implicated in their partner's carrier status or diagnosed IEI could be included.

Following the meeting, the department advised that a more pragmatic approach, consistent with previous applications (e.g. MSAC 1675 and 1680) would be to instead assess the following outcomes:

- *At-risk couples identified, or couples whose risk status is identified*
- *Number of couples provided with information for reproductive decisions*
- *Cost per at-risk couple identified*
- *Cost per couple provided with information*

PASC agreed with this approach.

PICO criteria (PICO set 4: reanalysis)

Population

The population of interest for PICO set 4 are people with a strong suspicion of an IEI for whom previous WES or WGS genomic tests have been inconclusive or uninformative, and/or for people in whom a variant of unknown significance (VUS) has been identified. These variants are not considered to be clinically actionable and the detection of these would not be used to alter a patient's medical management or treatment plan. Patients suspected of having an IEI for whom a NGS test was uninformative may require the proposed reanalysis item number for the characterisation of previously unreported gene variants related to the clinical phenotype. This test should take place two years following the initial genomic test.

PASC confirmed the population is individuals with a strong suspicion of IEI on immunophenotyping and/or functional assay despite uninformative or uncertain result on initial test after at least 2 years.

Intervention

The proposed intervention for this population would be a re-analysis of NGS data obtained as described for PICO set 1 after an interval of at least two years for the characterisation of previously unreported gene variants related to clinical phenotypes.

PASC noted the applicant's pre-PASC response supported the removal of a 48-month minimum interval in favour of a maximum of 3 tests per lifetime per patient, in line with similar pre-analysis items on the MBS (73428). The applicant's pre-PASC response explained that the minimum of 48 months may not be appropriate depending on the speed at which research in this area identifies new variants of interest, particularly given the possibility of the application of artificial intelligence systems to interrogate large-scale genomic datasets in the future.

PASC advised that the reanalysis should take place at least 2 years after the initial genomic test.

PASC advised that there is insufficient evidence to support the use of 2 versus 3 re-analysis opportunities per lifetime and advised the proposed restriction should remain as 2 per lifetime.

Estimates of reanalysis

The number of patients suitable for reanalysis will depend on the proportion who are found to have a VUS, or where additional clinical features suggest testing should be undertaken for different variants. This will need to be estimated during the assessment report.

PASC noted the applicant's pre-PASC response suggested that the use of currently existing re-analysis items is low.

Comparator

The proposed comparator would be no reanalysis of data from NGS.

PASC confirmed the comparator is no re-analysis.

Outcomes

The principal outcome of interest would be the diagnostic yield of new P/LP variants from reanalyses of NGS data after at least 2 years. In addition, as for PICO set 1, other outcomes of interest would include changes in patient management from the findings of such tests, and the financial impacts of the reanalyses.

PASC confirmed the outcomes for PICO set 4.

Assessment framework (for investigative technologies)

PASC considered an abbreviated assessment framework, stopping at change in management, would be an appropriate use of a pragmatic approach, similar to MSAC applications 1675, 1585, and 1684.

PICO set 1: Diagnostic testing

The application made a claim of clinical superiority of genomic testing; the overall claim for the genomic testing for IEIs as an add-on test to current targeted diagnostic tests, is that it leads to superior health outcomes compared to no genomic testing (i.e. current targeted diagnostic tests alone). The applicant stated that although the results of current targeted diagnostic tests inform the probability of differential diagnoses, genomic testing enables the simultaneous analysis of multiple causative variants to provide a definitive diagnosis.

For this application, evidence is required that the information from genomic testing will alter decision-making and/or clinical management.

The framework used in MSAC's reformed approach for linked assessment of genomic tests (from MSAC 1675) is shown in Figure 1. Italicised questions would not necessarily need to be addressed if a reformed assessment approach is used (noting question 3 may alternatively be assessed in a qualitative rather than quantitative manner).

1. Test performance: What is the diagnostic yield of genomic testing? (i.e. what proportion of individuals receive a new or refined diagnosis (including prognostic yield and predictive yield)?

2. How does the genomic test results impact the clinical management of the individual? (What proportion of individuals have a change in management?)

3. *[Does the change in the clinical management improve health outcomes (morbidity, mortality, QoL)?] - NB: not required to be assessed quantitively.*

4. Are there other benefits regarding "value of knowing" for patients with a confirmed IEI diagnosis due to genomic testing? (i.e. benefits to the individual or their family outside of the impact on their healthcare)

5. What are the adverse events associated with genomic testing for detection of IEIs, when compared to the current practice of no genomic testing and the use of current targeted diagnostic tests to make differential diagnoses?

6. Are there harms that arise from the knowledge of IEI status (outside of the impact on their healthcare, i.e. psychological harm)?

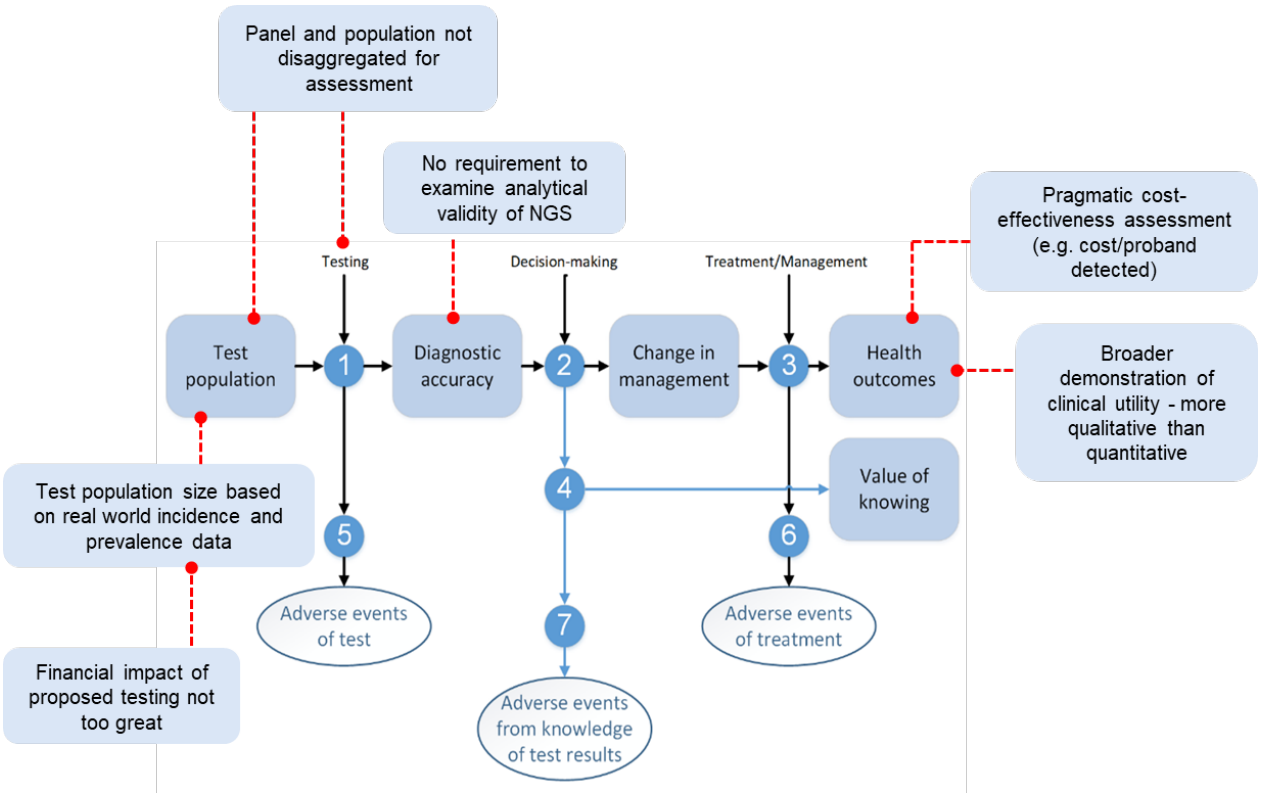

Figure 1. MSAC's reformed assessment framework for linked assessment of genomic tests PICO set 1.

PICO set 2: Cascade testing

For the assessment framework for PICO set 2, the following questions would be part of the assessment:

1. What is the incremental diagnostic yield of genomic cascade testing (detection of cases)?

   What proportion of relatives are provided reassurance from genomic testing, and ruled out from requiring monitoring?

What proportion of relatives are identified as a carrier for an autosomal recessive condition?

2. What impact does genomic testing on the monitoring/treatment of relatives? (those test positive, negative, or without genomic test information)

   How much earlier does genomic cascade testing identify cases, compared to no genomic testing?

3. Is there a value of knowing of either a positive or negative genomic test result (knowledge of being a case, a carrier or having no variants, compared to not knowing)?

4. *What changes in reproductive planning occur as a consequence of genomic testing?*

5. What are the adverse events associated with cascade genomic testing for cases or carriers of IEIs, when compared to the current practice of no genomic testing?

6. What are the adverse events associated with the monitoring and treatment of individuals diagnosed with IEIs via genomic testing or without genomic testing?

The assessment framework is outlined in Figure 2 below.

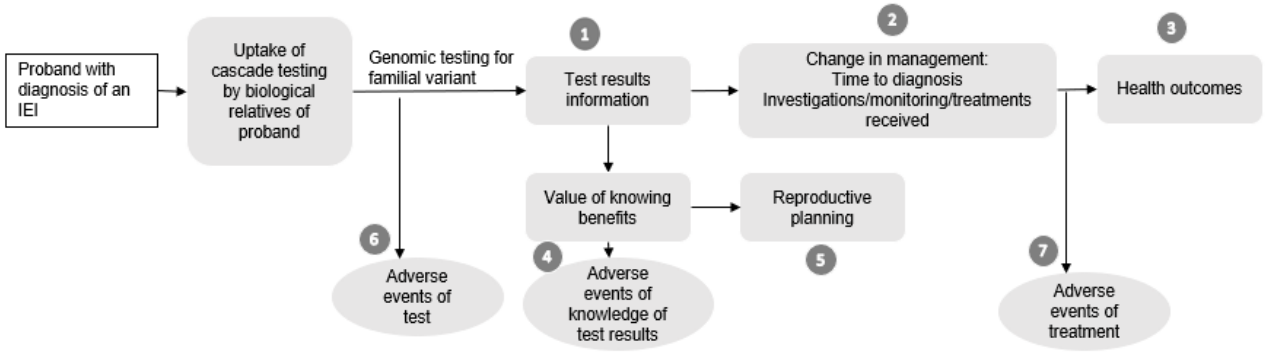

Figure 2. The proposed assessment framework showing the links from the biological relatives to outcomes for PICO set 2.

Figure notes: 1: linked evidence to health outcomes; 2: linked evidence value of knowing harms and or benefits.

IEI = inborn error of immunity

PICO set 3: Reproductive partner testing

For PICO set 3, the proposed assessment framework, outlined in Figure 3, should address the following questions:

1. What is the uptake rate of reproductive testing for potential reproductive partners of probands with an IEI or relatives with confirmed carrier status for a variant implicated in an IEI?

2. Is there evidence of changes in management regarding reproductive planning for this population?

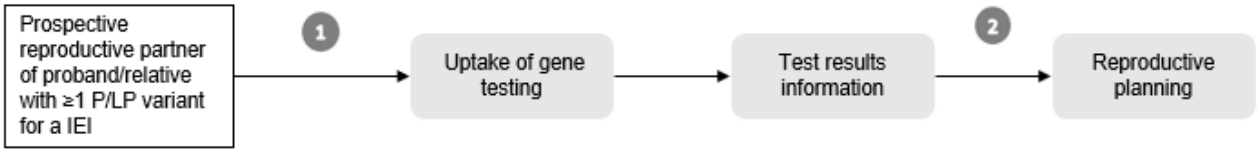

Figure 3. The proposed assessment framework showing the links for potential reproductive partners to outcomes for PICO set 3.

Figure notes: 1: linked evidence to uptake of testing; 2: linked evidence to reproductive planning outcomes

IEI = inborn error of immunity; P/LP = pathogenic/likely pathogenic

Clinical management algorithms

Current management algorithm

The current clinical management algorithm is shown in Figure 4, which shows the tests and investigations currently in use in the identified population. Presently, patients are referred to a clinical immunologist if they have a clinical history with signs or symptoms suggestive of primary immunodeficiency as outlined in Table 5. Infants with a positive NBS screen finding for SCID or XLA would also be referred to specialist immunology services. Patients would undergo a detailed clinical history, physical examination, and series of routine investigations with additional investigations undertaken based on the clinical presentation. These would include, but are not limited to; complete blood counts, and tests of peripheral blood smears and serum immunoglobulins, flow cytometry-based phenotypic screening and testing for secondary causes such as human immunodeficiency virus (HIV). A phenotypic diagnosis of IEI may be made based on observable characteristics, and clinical features including currently targeted diagnostic tests. Based on the differential diagnoses, patents would be treated as indicated.

Family members may or may not be recommended to undergo clinical testing for the diagnosed IEI or monitoring to determine whether they become affected. In the absence of genetic testing, at-risk family members cannot be ruled out, until they are beyond the age by which symptom development would be expected. In the absence of genetic testing, no reproductive partner testing would occur. Any children born may be monitored for whether they develop an IEI (Figure 4). The current algorithm for potential reproductive partners (PICO set 3) is outlined in Figure 5.

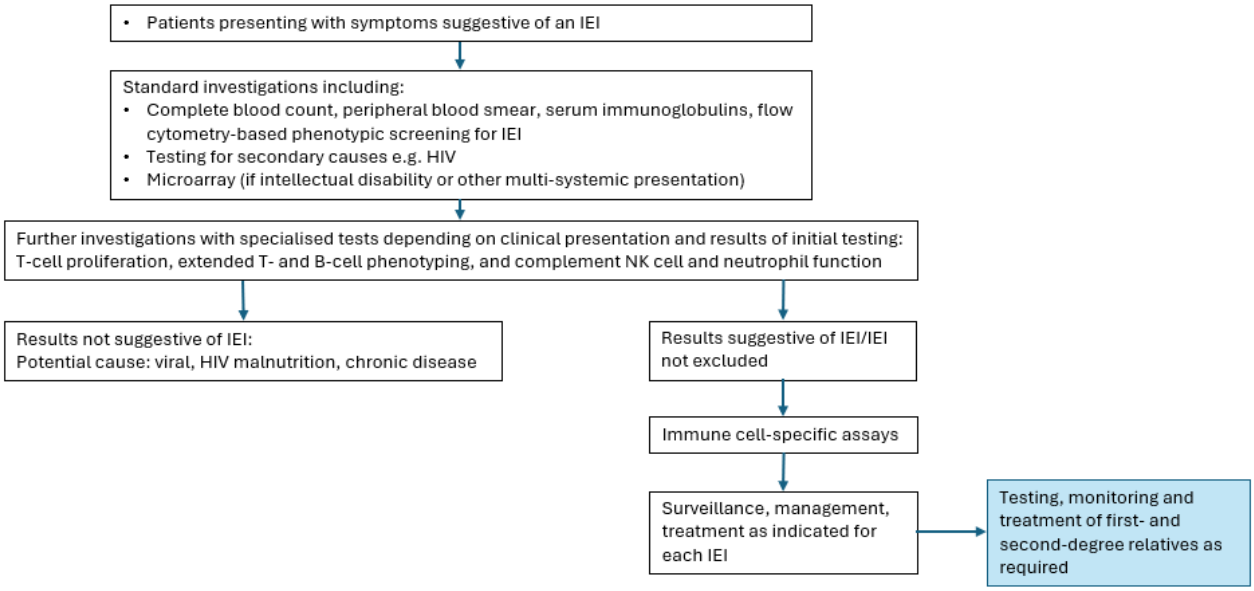

Figure 4. The current management algorithm for people with suspected IEIs (PICO sets 1, 2 and 4)

HIV = human immunodeficiency virus; IgA= immunoglobulin A; IgE = immunoglobulin E; IgG = immunoglobulin G; IgM = immunoglobulin M; NBS= Newborn screening; IEI = Inborn error of immunity

NB. In the population we have included newborns with a positive finding from a newborn screening test for an IEI as this has implications for the relatives of the index case.

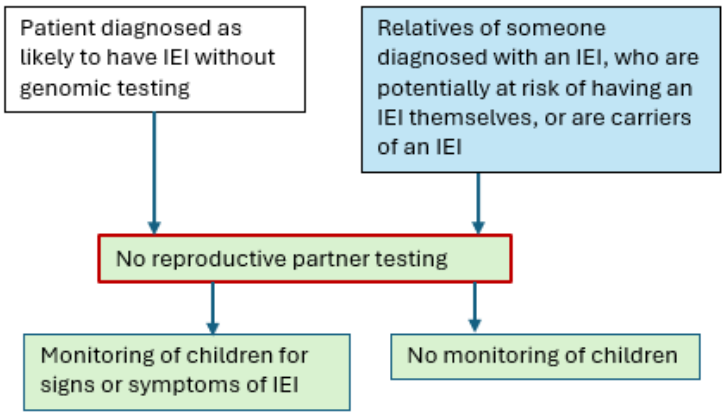

Figure 5. The current management algorithm for potential reproductive partners of individuals clinically diagnosed with or potentially carriers of an IEI (PICO set 3).

IEI = Inborn error of immunity

Proposed clinical algorithms

The proposed clinical algorithm in Figure 6 outlines the diagnostic process including genomic testing for people with suspected IEI. This is the same as the current algorithm up to and including the completion of the prior tests. After this point, for patients with a suspected IEI, the clinician would decide if genomic testing is required to identify the molecular defect to achieve a precise diagnosis. The purpose of genomic testing is to expedite diagnosis and reduce the number of inconclusive results. Although targeted gene panels may be used, massively parallel exome sequencing or WGS, depending on availability, are more commonly performed to expedite diagnosis and reduce the number of inconclusive results. In specific circumstances, exome sequencing may miss relevant variants; in these cases, chromosome microarray or WGS is conducted to identify specific variants of concern. The management outcomes upon identification of the molecular defect via genomic testing are determined by the nature of the identified IEI; appropriate, targeted and effective treatment and improved prognoses can be achieved through the early detection of IEI by genome testing.

PASC advised that the identification of a VUS in a potential reproductive partner would not make them eligible for a reanalysis of the genomic test results.

PASC advised that for PICO sets 1 and 4, the originally proposed clinical management algorithm should not include a 'no genetic testing' pathway. PASC noted that if a causative P/LP is not identified, the diagnosis is unlikely to change (as a lack of informative variant does not mean that the person does not have an IEI). PASC noted that there are different types of outcomes that could be captured in the algorithm – diagnostic implications, treatment implications, family implications and reproductive implications.

Cascade testing and genetic counselling should be offered to relatives of those testing positive or who are found to be carriers. This algorithm is outlined in Figure 7. In cases where someone is carrying at least one P/LP variant associated with an autosomal recessive condition and wishing to have children, their potential reproductive partner may also be tested.

PASC noted that there would be reproductive implications for carriers detected in PICO set 2. This subgroup, however, would not require monitoring. For clinical cases detected, there would be both diagnostic/monitoring implications, and reproductive implications.

The algorithm for the management of potential reproductive partners is outlined in Figure 8.

PASC noted that for PICO set 3, the current and proposed clinical management algorithms should not include the health outcomes for conceived children.

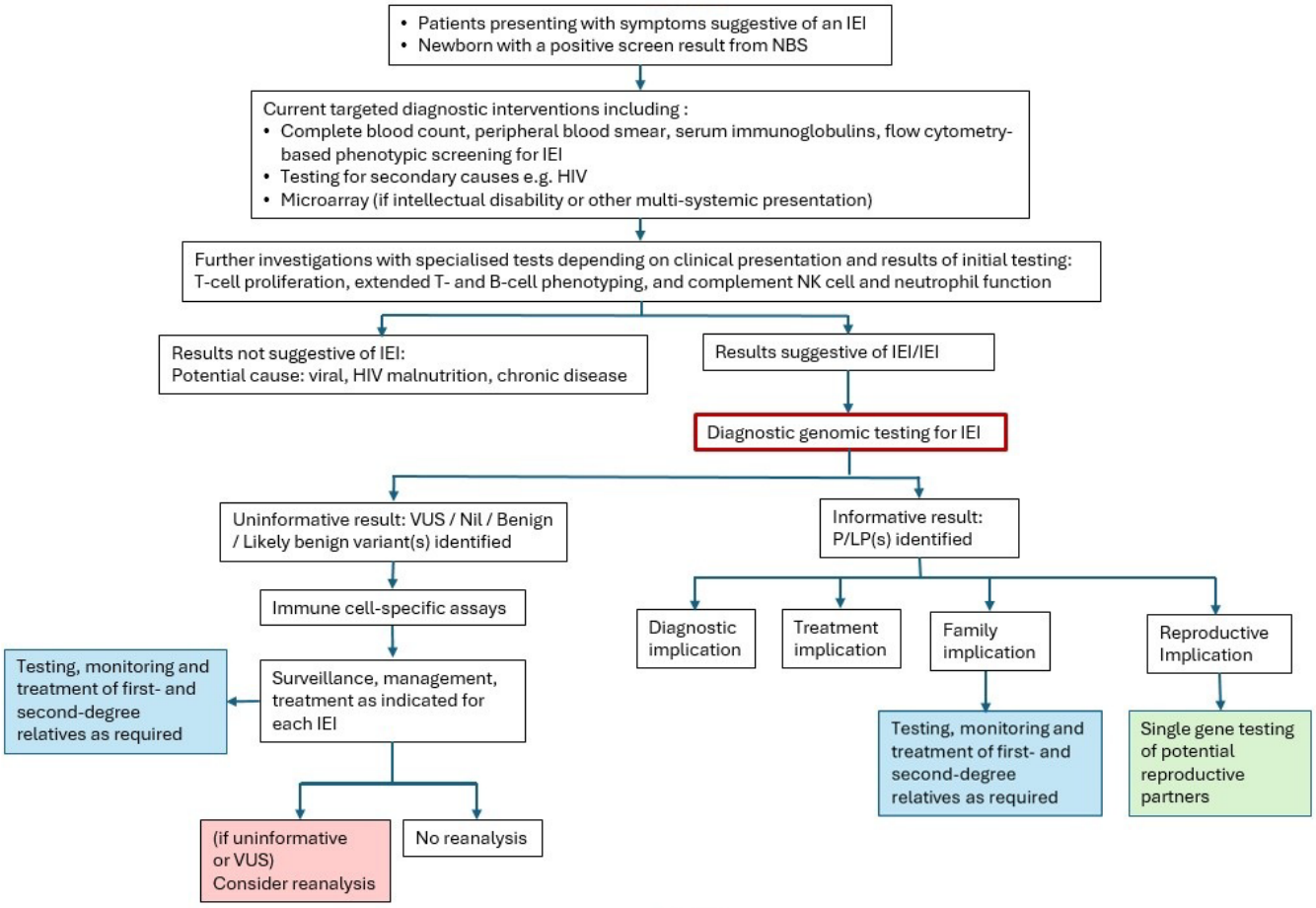

Figure 6. The proposed management algorithm for people with suspected IEI (PICO sets 1 and 4)

HIV = human immunodeficiency virus; IgA immunoglobulin A; IgE = immunoglobulin E; IgG = immunoglobulin G; IgM = immunoglobulin M; NBS= Newborn bloodspot screening; NGS = next generation sequencing; NK = non-killer; IEI = Primary immunodeficiency; P/LP = pathogenic/likely pathogenic; VUS = variant of uncertain significance; NB: Those detected through NBS are shown in this algorithm, as the downstream implications of cascade testing of family members may occur

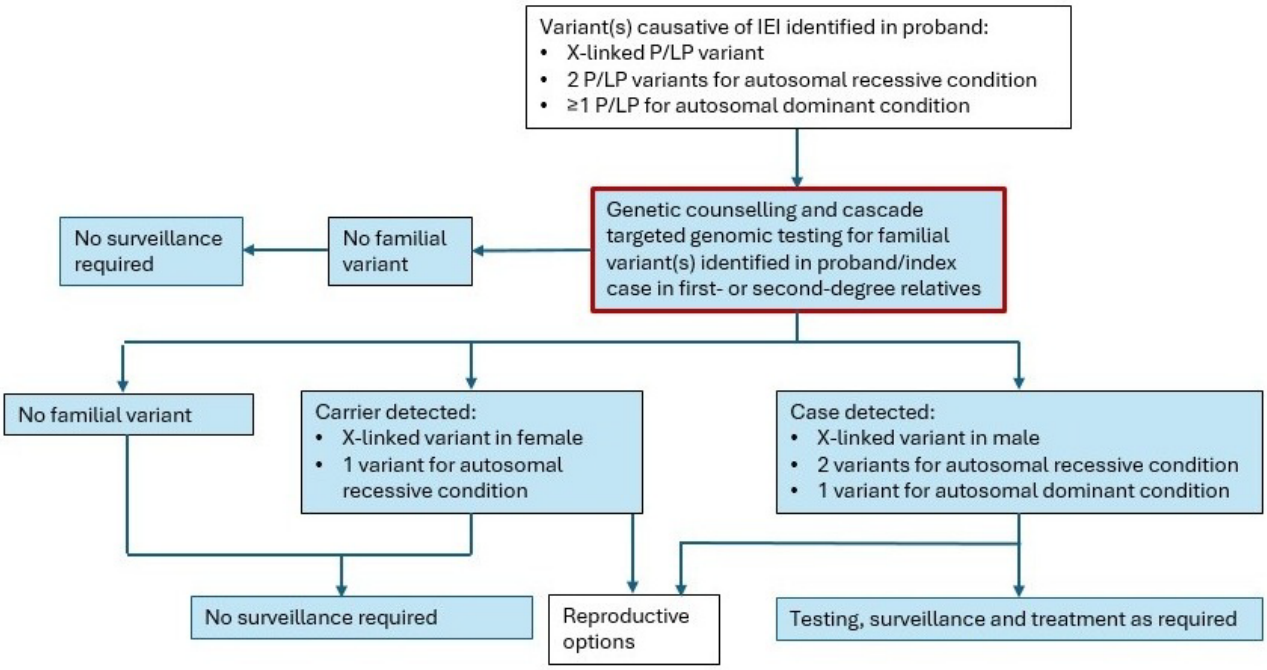

Figure 7. The proposed management algorithm for cascade testing of biological relatives of probands diagnosed with an IEI (PICO set 2)

IEI = Primary immunodeficiency; P/LP = pathogenic/likely pathogenic

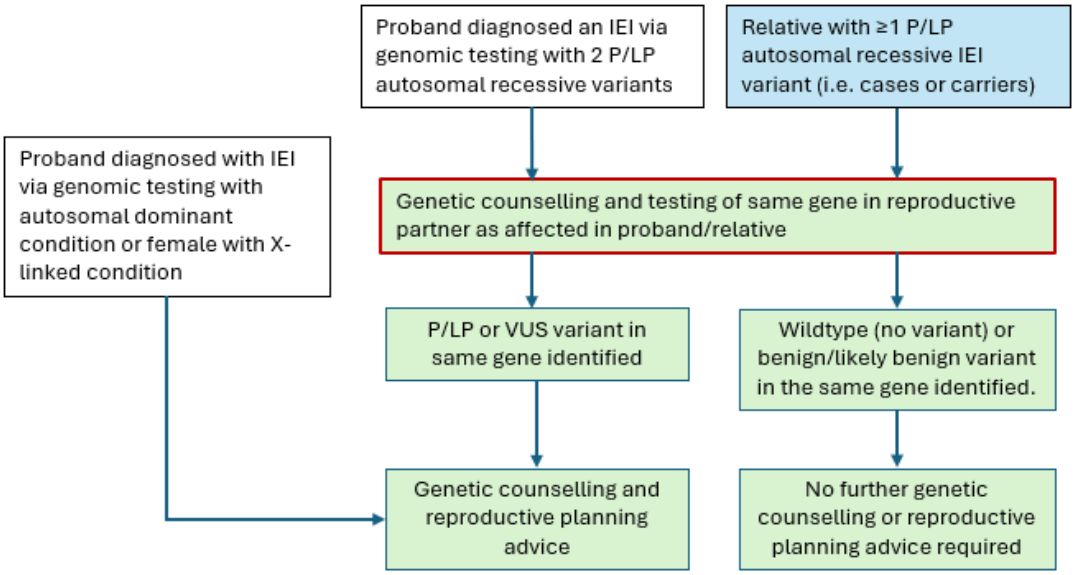

Figure 8. The proposed management algorithm for potential reproductive partners of individuals diagnosed with, or carriers of, an IEI (PICO set 3)

IEI = Primary immunodeficiency; PGD = Pre-implantation genetic diagnosis; P/LP = pathogenic/likely pathogenic; VUS = variant of uncertain significance

Proposed economic evaluation

The clinical claim outlined by the applicant is that the use of the proposed technology results in superior health outcomes compared to the comparator/standard practice.

For PICO set 1, the application made a claim of superiority of genomic testing, compared to the use of current targeted diagnostic tests to achieve a differential diagnosis of IEI.

MSAC's reformed approach for the assessment of genomic tests (including large gene panels) is to avoid disaggregating the panel and population and express the cost-effectiveness in terms of 'cost per proband detected'. This approach was supported for MSAC 1585 and MSAC 1675.

No claims were made regarding testing in populations other than for those with symptoms suggestive of IEI.

PASC noted that a CUA may not be informative, as IEIs include a broad range of different disorders, and determining the average health benefit of genomic testing would be very difficult with the limited evidence base. PASC therefore advised that a CEA using a truncated approach would be appropriate for this assessment. This would be based on the incremental cost per additional identified proband for PICO set 1, incremental cost per additional case and carrier detected for PICO set 2, and incremental cost per informative result on reanalysis (PICO set 4).

The costs to be evaluated for PICO set 1 include the incremental costs per additional clinically informative result obtained, of diagnostics, treatment (including changes of treatment) from additionally clinically informative results and costs associated with familial implications of test results.

Table 8. Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain[a]	Noninferior[b]	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

[b] An adequate assessment of 'non-inferiority' is the preferred basis for demonstrating equivalence

Proposal for public funding

The applicant has proposed public funding of genomic testing for IEIs through the MBS. Currently, there is no specific MBS item number to cover the cost of this procedure. Genomic testing is performed across Australia but is primarily reimbursed via research funding or self-funding by patients. If genetic testing is performed subsequent to a positive NBS, it would be covered by the states/territories.

Testing would be delivered only by approved practising pathologists with appropriate scopes of practice in NATA-accredited laboratories by referral only by registered medical practitioners in alignment with other tests in the MBS pathology table.

Proposed MBS items AAAA, CCCC, DDDD, and EEEE below were drafted by the applicants, and include amendments from the HTA group, PASC and the policy area of the department. The descriptor and fee of proposed item AAAA was based on MBS 73358 (WES or WGS for monogenic disorders). Proposed item BBBB was drafted by the assessment group based on MBS 73359 to allow for simultaneous trio testing (rather than requiring parents to be tested as part of cascade testing subsequent to a P/LP variant being identified in the proband), with edits from PASC and the department.

Three different items are proposed for those suspected of having an IEI based on phenotyping (Table 9, Table 10, Table 11).

PASC advised that an MBS item for single gene testing should be included for use in the subset of patients in whom a single pathogenic variant can be strongly suspected based on the patient's phenotype, or some other reason.

PASC advised that the items for patients suspected of having an IEI (i.e. items AAAA, BBBB and CCCC) should be restricted to "requested by a specialist or consultant physician practising as an immunologist" with clinical geneticists removed. PASC noted that the applicant had made a pre-PASC request for the addition of a prenatal testing item, similar to items created for heritable kidney disease (MBS 73406).

Table 9. Proposed MBS item for singleton WES/WGS diagnostic genomic testing for IEI, updated to reflect PASC and department advice

Category 6 - PATHOLOGY SERVICES Group P7 - Genetics
MBS item AAAA Characterisation, via whole exome or genome sequencing and analysis, of germline gene variants that cause inborn errors of immunity if the service is: (a) requested by a specialist or consultant physician practising as an immunologist; and (b) for a patient with a strong suspicion of inborn errors of immunity based on immunophenotyping; and (c) not performed in conjunction with a service to which item BBBB applies Applicable only once per lifetime
Fee: $2,100.00 Benefit = 75% = $1,575.00 85% = $1,995.50*

*85% benefit reflects the 1 November 2025 Greatest Permissible Gap (GPG) of $104.50

PASC advised that trio testing (including the parents) should only be performed when the immunophenotype of the parents is known.

Table 10. Proposed MBS item for trio WES/WGS diagnostic genomic testing for IEI, updated to reflect PASC and department advice

Category 6 - PATHOLOGY SERVICES Group P7 - Genetics
MBS item BBBB Characterisation, via whole exome or genome sequencing and analysis, of germline gene variants that cause inborn errors of immunity, if the service: (a) is requested by a specialist or consultant physician practising as an immunologist; and (b) is for a patient with a strong suspicion of inborn errors of immunity based on immunophenotyping; and (c) includes the request stating that singleton testing is inappropriate; and (d) is performed using a sample from the patient and a sample from each of the patient's biological parents whose immunophenotype is known; and (e) is not performed in conjunction with a service to which item AAAA applies. Applicable once per lifetime
Fee: $2,900.00 Benefit = 75% = $2,175.00 85% = $2,795.50*

*85% benefit reflects the 1 November 2025 Greatest Permissible Gap (GPG) of $104.50

Proposed explanatory notes to item AAAA and BBBB:

- When determining the genes to be assessed, the list of genes with an evidence-based association with an IEI phenotype should be based on a recognised test directory.
- Patients with an intellectual disability or other multi-systemic presentation are to be reviewed by a clinical geneticist before sequencing, as these syndromes may not be covered by the standard IEI gene panel.
- Patients with a strong suspicion of a specific inborn errors of immunity phenotype where a limited number of specific gene variants are highly associated with the clinical presentation and investigations, targeted gene testing under item CCCC should be considered before whole exome or genome sequencing.

Informed consent and genetic counselling for genetic tests (proposed for all items: AAAA, BBBB, CCCC, DDDD and EEEE):

Prior to ordering these tests, the ordering practitioner should ensure the patient (or approximate proxy) has given written informed consent. Testing should only be performed after genetic counselling. Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner or clinical genetic service on referral. Further counselling may be necessary upon receipt of the test results. Patients who are found to harbour a likely pathogenic or pathogenic variant should be referred for post-test genetic counselling as there may be implications for other family members. Appropriate genetic counselling should be provided to the patient through a clinical genetic service.

Two items for single variant/single gene testing are proposed. The item CCCC outlined below is intended for targeted genotyping in affected individuals, where there is a strong clinical suspicion of variants in a particular gene/a particular variant being present. Item DDDD is intended to identify known pathogenic germline gene variants in siblings or aunts/uncles (or a parent if not performed as part of trio testing), and allow for reproductive partner testing.

The proposed fee for both item CCCC and DDDD is method-agnostic to capture a range of potential testing modalities depending on the IEI indication. Notably, Sanger sequencing would be less expensive than the proposed fee in practice, and other tests will be more costly. The proposed fee has been benchmarked against similar items for targeted genotyping (e.g. MBS Item 73434).

Table 11. Proposed MBS item for single gene diagnostic testing for IEI, updated to reflect PASC and department advice

Category 6 - PATHOLOGY SERVICES Group P7 - Genetics
MBS item CCCC Characterisation of one or more pathogenic gene variants known to cause inborn errors of immunity, if the service is: (a) requested by a specialist or consultant physician practising as an immunologist; and (b) for a person: i. with a strong suspicion of inborn errors of immunity where a limited number of specific gene variant(s) is highly associated with the clinical presentation and investigations, and ii. who has not previously received a service to which item AAAA or BBBB applies Applicable once per lifetime.
Fee: $400.00 **Benefit: 75%** = $300.00 **85%** = $340.00

The intended purposes of item DDDD are to identify known pathogenic germline gene variants in siblings or aunts/uncles (or a parent if not performed as part of trio testing), and allow for reproductive partner testing.

Table 12. Proposed MBS item for cascade and reproductive partner testing, updated to reflect PASC and department advice

Category 6 - PATHOLOGY SERVICES Group P7 - Genetics
MBS item DDDD Characterisation of one or more pathogenic or likely pathogenic gene variants in the same gene known to cause inborn errors of immunity, if the service is: (a) requested by a specialist or consultant physician practicing as an immunologist or clinical geneticist; and (b) for a person (the person tested) who is either: i. a biological relative of a patient with an identified pathogenic or likely pathogenic germline gene variant/s known to cause inborn errors of immunity (confirmed by laboratory findings); or ii. a reproductive partner of a person with an identified recessive pathogenic or likely pathogenic germline gene variant known to cause inborn errors of immunity (confirmed via laboratory findings); and (c) the person tested has not previously received a service to which item AAAA, BBBB or CCCC applies. Applicable once per lifetime
Fee: $400.00 Benefit**: 75%** = $300.00 85**%** = $340.00

A re-analysis item number (EEEE) is also proposed for characterisation of previously unreported gene variants related to the clinical phenotype. This test would be for patients in whom IEI is suspected but for whom the NGS test was uninformative. Typically, this test would be conducted 4-5 years after the initial NGS test. The proposed fee has been benchmarked against existing MBS items for re-analysis of WES or WGS data (73428), and services advertised by Victorian Clinical Genetics Services, with no out-of-pocket fees (Victorian Clinical Genetics Services 2025). The minimal interval proposed is two years from the initial genome test.

PASC advised that reassessment should be undertaken at the request of the treating clinician, to prevent automatic reanalysis that may not be clinically justified, necessary and/or without patient consent.

PASC advised the minimal interval proposed for the reanalysis item for the population in PICO set 4 is 2 years from the initial genome test.

Table 13. Proposed MBS item for reanalysis of NGS data in patients suspected of having IEI, updated to reflect PASC and department advice

Category 6 - PATHOLOGY SERVICES Group P7 - Genetics
MBS item EEEE Re-analysis of whole exome or genome data obtained in performing a service to which item AAAA or BBBB applies, for characterisation of previously unreported germline gene variants related to the clinical phenotype, if the service is: (a) requested by a specialist or consultant physician practicing as an immunologist or clinical geneticist; and (b) for a patient with a strong suspicion of inborn errors of immunity; and (c) performed at least 24 months after a service to which item AAAA or BBBB applies. Applicable twice per lifetime As with existing item 73428, PN.7.7 is also applicable to proposed item EEEE
Fee: $500.00 Benefit**: 75%** = $375.00 85**%** = $425.00

Summary of public consultation input

PASC noted and welcomed consultation input from 5 organisations and 1 individual health professional. The organisations that submitted input were:

- Advocacy and Support for People with Primary Immune Deficiency (AusPIPS)
- Public Pathology Australia (PPA)
- Australasian Society of Clinical Immunology and Allergy (ASCIA)
- Rare Voices Australia (RVA)
- Australian Pathology (AP)

Consultation input was supportive of public funding for genomic testing for the diagnosis of IEI. PPA raised concerns that the proposed fees for some of the items do not cover the cost for testing.

Consumer Experience

Input from consumer and advocacy organisations such as RVA and AusPIPS, highlighted the profound impact of delayed diagnosis and the 'diagnostic odyssey' experienced by individuals with IEI and their families. Many described repeated investigations, uncertainty, and emotional distress prior to receiving a definitive diagnosis.

The burden of lifelong treatment, frequent hospitalisation, and limited access to specialised care outside metropolitan centres was emphasised. Input stated that families face practical and psychosocial challenges, including the need for regular immunoglobulin therapy and ongoing specialist reviews. The diagnostic journey can be long and emotionally taxing, with delayed diagnosis contributing to significant morbidity and early mortality in these patients.

Consumers also stressed the value of early and accurate diagnosis in improving health outcomes, as well as the importance of informed reproductive decision-making and access to genetic counselling for families.

Benefits and Disadvantages

Consultation input consistently indicated that public funding for genomic testing would bring significant benefits for individuals with suspected IEI. Earlier and more accurate diagnosis was seen as a key advantage, enabling timely intervention and improved patient management. Input emphasised that molecular diagnosis not only streamlines care pathways and reduces unnecessary investigations but also supports informed reproductive decision-making and access to targeted therapies. The ability to facilitate cascade testing for family members at risk was also highlighted as an important benefit, contributing to better health outcomes for families.

Individual health professional input stated that multiple international studies have shown that genomic testing has consistently increased diagnostic yields by 20-58%, with results directly changing clinical management and treatment decisions, which are well substantiated and achievable in the Australian context.

However, some disadvantages were identified, primarily relating to the potential for inequities in access. Consultation input expressed concern that patients in rural and remote areas, as well as those from culturally diverse backgrounds, may face barriers to accessing genomic testing and associated counselling.

Organisations also raised issues regarding the unviability of the MBS rebates demonstrating correlation with service delivery costs, specialist involvement and multidisciplinary support. This could reduce equity of access and restrict the benefits of genomic testing to only certain patient groups. Input stressed the need for policy frameworks and service delivery models that ensure equitable access to genomic testing across all communities.

Individual health professional input included a requirement for access to clear communication and genetic counselling, and investment in variant curation, data reanalysis, secure data analysis and functional testing capabilities to support delivery of validated genomic results with certainty.

Population, Comparator (current management), and Delivery

The consultation input was consistently supportive of the proposed population for genomic testing, agreeing that individuals with suspected IEI would benefit from improved diagnostic accuracy and early intervention.

Consultation input agreed with the comparator of standard immunology and phenotype-driven diagnosis without genomic testing accurately reflects current Australian practice for investigating IEI. Patients typically undergo MBS-funded tests e.g. immunoglobulin quantitation, full blood count, lymphocyte subset analysis and functional immune assays. These investigations remain essential first line tools for IEI diagnosis and are consistent with national and international guidelines.

Input highlighted that people in rural and remote areas, including First Nations communities, often face diagnostic delays due to limited immunology services, and lack of culturally safe, coordinated pathways for diagnosis. The potential for genomics to improve service delivery was noted, provided it is accompanied by telehealth-enabled specialist consultation, outreach sample collection, and culturally safe counselling pathways.

MBS Item Descriptor and Fee

The consultation input was generally supportive of the proposed MBS item for genomic testing for IEI. Health professional and organisational feedback agreed that the service descriptor accurately reflects the clinical context and requirements for testing.

PPA commented that although the proposed MBS item fee for item AAAAA is appropriate and reflective of service delivery costs for this method of testing, the proposed MBS item fees for both item BBBBB and CCCCC are highly understated and not financially viable to recover costs when comparing to the cost of delivery of similar services.

PASC acknowledged that positive and supportive feedback was received from 5 organisations and one individual with specialist knowledge.

PASC noted that the applicants agreed with public consultation that the fees for targeted testing and re-analysis are very low, and that many laboratories will struggle to provide the service at the nominated price. PASC noted that the proposed fees have been benchmarked against existing items. PASC noted the concerns regarding the fees, and advised it is a broader issue than MSAC 1810.

PASC queried whether there were concerns with access for patients in rural and remote communities, if patients need to access immunologists in order to be eligible for testing. The applicant explained that patients may see immunologists via telehealth. The collection of DNA is able to be performed locally, so there should not be problems with patients from rural/remote areas accessing the proposed testing.

However, the applicant stated that it is advantageous to have a face-to-face appointment at some point, and that there are some specialist tests that may only be available in cities. PASC noted that telehealth ameliorates the potential access issues to the proposed genomic testing.

Next steps

PASC noted that this application will progress as a department contracted assessment report (DCAR).

Applicant Comments on Ratified PICO

The RCPA appreciates PASC's careful consideration of this complex application. Regarding trio testing, in our clinical experience parental immunophenotyping is generally not practical or necessary prior to testing in routine care; in IEI genomics, parental samples are primarily used to support variant interpretation and segregation (e.g., de novo assessment, phasing for autosomal recessive conditions). The parental "phenotype" is typically captured through targeted clinical history (affected/unaffected and pertinent symptoms). Where additional parental immunology investigations are helpful, these are best undertaken selectively after trio results are available, rather than as a precondition for access; we suggest the importance of providing relevant parental clinical information could be reinforced in a practice note, rather than specified as a requirement in the item descriptor.

References

ASCIA 2024, *Primary Immunodeficiencies (Inborn Errors of Immunity) - Frequently asked questions*, Australasian Society of Clinical Immunology and Allergy, viewed 24th September 2024, <https://www.allergy.org.au/patients/immunodeficiencies/primary-immunodeficiency>.

ASCIA 2025, *Primary Immunodeficiencies (Inborn Errors of Immunity) - Frequently asked questions*, viewed October 1st, 2025, <https://www.allergy.org.au/patients/immunodeficiencies/primary-immunodeficiency>.

Ballow, M & Leiding, JW 2022, 'Precision Medicine in the Treatment of Primary Immune Deficiency Patients With Disorders of Immune Dysregulation', *Clin Rev Allergy Immunol*, vol. 63, no. 1, Aug, pp. 1-8 10.1007/s12016-021-08871-4.

Bousfiha, A, Moundir, A, Tangye, SG, Picard, C, Jeddane, L, Al-Herz, W, Rundles, CC, Franco, JL, Holland, SM, Klein, C, Morio, T, Oksenhendler, E, Puel, A, Puck, J, Seppänen, MRJ, Somech, R, Su, HC, Sullivan, KE, Torgerson, TR & Meyts, I 2022, 'The 2022 Update of IUIS Phenotypical Classification for Human Inborn Errors of Immunity', *J Clin Immunol*, vol. 42, no. 7, Oct, pp. 1508-1520 10.1007/s10875-022-01352-z.

Chinn, IK & Orange, JS 2020, 'A 2020 update on the use of genetic testing for patients with primary immunodeficiency', *Expert Rev Clin Immunol*, vol. 16, no. 9, Sep, pp. 897-909 10.1080/1744666x.2020.1814145.

Devonshire, AL & Makhija, M 2019, 'Approach to primary immunodeficiency', *Allergy Asthma Proc*, vol. 40, no. 6, Nov 1, pp. 465-469 10.2500/aap.2019.40.4273.

Flatrès, C, Roué, JM, Picard, C, Carausu, L, Thomas, C, Pellier, I, Millot, F, Gandemer, V, Chantreuil, J, Lorton, F, Gras Le Guen, C & Launay, E 2021, 'Investigation of primary immune deficiency after severe bacterial infection in children: A population-based study in western France', *Arch Pediatr*, vol. 28, no. 5, Jul, pp. 398-404 10.1016/j.arcped.2021.03.009.

Goebel, GA, de Assis, CS, Cunha, LAO, Minafra, FG & Pinto, JA 2024, 'Survival After Hematopoietic Stem Cell Transplantation in Severe Combined Immunodeficiency (SCID): A Worldwide Review of the Prognostic Variables', *Clin Rev Allergy Immunol*, vol. 66, no. 2, Apr, pp. 192-209 10.1007/s12016-024-08993-5.

Joshi, AY, Iyer, VN, Hagan, JB, St Sauver, JL & Boyce, TG 2009, 'Incidence and temporal trends of primary immunodeficiency: a population-based cohort study', *Mayo Clin Proc*, vol. 84, no. 1, pp. 16-22 10.4065/84.1.16.

Justiz Vaillant, AA & Qurie, A 2024, 'Immunodeficiency', in *StatPearls*, StatPearls Publishing

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Kobrynski, L, Powell, RW & Bowen, S 2014, 'Prevalence and morbidity of primary immunodeficiency diseases, United States 2001-2007', *J Clin Immunol*, vol. 34, no. 8, Nov, pp. 954-961 10.1007/s10875-014-0102-8.

Lougaris, V, Pession, A, Baronio, M, Soresina, A, Rondelli, R, Gazzurelli, L, Benvenuto, A, Martino, S, Gattorno, M, Biondi, A, Zecca, M, Marinoni, M, Fabio, G, Aiuti, A, Marseglia, G, Putti, MC, Agostini, C, Lunardi, C, Tommasini, A, Bertolini, P, Gambineri, E, Consolini, R, Matucci, A, Azzari, C, Danieli, MG, Paganelli, R, Duse, M, Cancrini, C, Moschese, V, Chessa, L, Spadaro, G, Civino, A, Vacca, A, Cardinale, F, Martire, B, Carpino, L, Trizzino, A, Russo, G, Cossu, F, Badolato, R, Pietrogrande, MC, Quinti, I, Rossi, P,

Ugazio, A, Pignata, C & Plebani, A 2020, 'The Italian Registry for Primary Immunodeficiencies (Italian Primary Immunodeficiency Network; IPINet): Twenty Years of Experience (1999-2019)', *J Clin Immunol*, vol. 40, no. 7, Oct, pp. 1026-1037 10.1007/s10875-020-00844-0.

Nikzad, S, Johnson, R, Scalchunes, C & Rider, NL 2025, 'Quantifying the Diagnostic Odyssey Burden Among Persons with Inborn Errors of Immunity', *J Clin Immunol*, vol. 45, no. 1, Jan 2, p. 61 10.1007/s10875-024-01855-x.

Quinn, J, Modell, V, Johnson, B, Poll, S, Aradhya, S, Orange, JS & Modell, F 2022, 'Global Expansion of Jeffrey's Insights: Jeffrey Modell Foundation's Genetic Sequencing Program for Primary Immunodeficiency', *Front Immunol*, vol. 13, p. 906540 10.3389/fimmu.2022.906540.

Sogkas, G, Dubrowinskaja, N, Schütz, K, Steinbrück, L, Götting, J, Schwerk, N, Baumann, U, Grimbacher, B, Witte, T, Schmidt, RE & Atschekzei, F 2022, 'Diagnostic Yield and Therapeutic Consequences of Targeted Next-Generation Sequencing in Sporadic Primary Immunodeficiency', *Int Arch Allergy Immunol*, vol. 183, no. 3, pp. 337-349 10.1159/000519199.

Tangye, SG, Al-Herz, W, Bousfiha, A, Cunningham-Rundles, C, Franco, JL, Holland, SM, Klein, C, Morio, T, Oksenhendler, E, Picard, C, Puel, A, Puck, J, Seppänen, MRJ, Somech, R, Su, HC, Sullivan, KE, Torgerson, TR & Meyts, I 2022, 'Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee', *J Clin Immunol*, vol. 42, no. 7, Oct, pp. 1473-1507 10.1007/s10875-022-01289-3.

Victorian Clinical Genetics Services 2025, *Exome sequencing*, viewed 10 July 2025, <https://www.vcgs.org.au/tests/exome-sequencing/>.