MSAC Application 1810

Genomic Testing for the diagnosis of Primary Immunodeficiency (PID)

PICO Set

Population

Describe the population in which the proposed health technology is intended to be used:

Primary immunodeficiencies (PIDs) are a heterogeneous group of genetically encoded disorders of the immune system associated with 485 single-gene variants that result in the loss of expression, loss of function, or gain in function of the encoded protein.[1-3] PIDs have more recently been termed inborn errors of immunity (IEI) in the literature, but for historic consistency and ease of recognition, the term PIDs will be used in this application. Variants can be dominantly or recessively inherited, autosomal, or X-linked, and with complete or incomplete penetrance of the clinical phenotype.[4] Individually most PIDs are considered rare with true prevalence estimates hindered by underdiagnosis, underreporting, and potentially death before diagnosis. However, when taken as a group and with the advent of molecular techniques now diagnosing clinically suspected PIDs, prevalence rates are estimated to be more common, ranging from 1:1,000 to 1:5,000.[3] Prevalence also varies with ethnicity and increases with consanguinity.[5]

Although PIDs affect both adults and children, they more commonly present with first clinical manifestations during childhood and are associated with significant morbidity and mortality.[4] PIDs result from variants that compromise the adaptive immune response (B and T lymphocytes) and the innate immune response (phagocytic cells, complement system, cytokines and their receptors). Typically, PIDs associated with B-cell defects are characterised by susceptibility to infections caused by bacteria, such as pneumonia, otitis media and sinusitis, whereas those associated with T-cell defects are susceptible to fungal and viral infections, as well as malignancies. However, there is wide phenotypic variability amongst B-cell and T-cell defects e.g. many T-cell defects impact on B cell function and so predispose to invasive bacterial infections, and some patients with B-cell defects suffer severe viral infections including encephalitis. As well as susceptibility to infection by opportunistic pathogens, deficiencies of the innate immunity are characterised by failure to thrive, and certain inflammatory or autoimmune disorders such as lupus-like syndromes.[6]

The International Union of Immunological Societies (IUIS) Expert Committee currently lists 10 phenotypic classifications (with overlapping sub-classifications of PIDs that affect the immune system in different ways and are associated with significant morbidity:[7]

1. Combined immunodeficiencies (B and T lymphocyte cell function affected)
   - **Severe combined immunodeficiency** (SCID) is the most serious of these disorders. SCID is **usually** diagnosed within the first year of life and requires urgent commencement of treatment and a haematopoietic stem cell transplant (HSCT) to survive.
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

immunodysregulation polyendocrinopathy enteropathy x-linked syndrome (IPEX), 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.[8]
9. Bone marrow failure
10. Phenocopies of inborn errors of immunity.[7]

A 2021 study in France noted that PID is rarely investigated after children are admitted to hospital (paediatric intensive care unit) with community-onset severe bacterial infections,[9] despite the need for early PID diagnosis to deliver prompt treatment and intervention to prevent associated morbidity and mortality.[10] Most mortality data are obtained through registries and rates of mortality differ according to rates of diagnosis and subsequent appropriate treatment. The recent study by Lougaris et al (2020) noted that worldwide PID mortality rates ranged from 34.5% of patients in Tunisia, to 2.1% in Germany.[11]

A 2009 retrospective cohort study from Minnesota, USA, found that a delayed diagnosis of PID was associated with increased morbidity, including potentially irreversible complications of recurrent infections such as bronchiectasis, and that older age at diagnosis was associated with mortality compared to an age-matched general population.[12]

When a patient is found to carry a genetic variant causative of PID, targeted genotyping is recommended in several populations captured in proposed item CCCCC. These populations are also captured within the scope of the current application, but have not been separated in separate PICO sets due to overlap between the indications. These include:

1. Biological relatives who may also carry the same pathogenic variant, allowing for early diagnosis, monitoring, and intervention.
2. Parents of an individual with a detected mutation, to assist in evaluating pathogenicity.
3. Reproductive partner testing, particularly for autosomal recessive or X-linked conditions, to assess the risk of passing the condition to future children and to inform reproductive decision-making.

Specify any characteristics of patients with, or suspected of having, the medical condition, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian healthcare system in the lead up to being considered eligible for the technology:

PIDs are caused by germline variants in single genes and may present in patients with an increased susceptibility to infection, autoimmunity, autoinflammatory diseases, allergy, bone marrow failure, and/or malignancy. Taken individually, PIDs are rare; however, when considered as an aggregated group, the number of individuals with a PID represents a significant burden of disease. Variants result in altered gene products, such as abolishing (null) or reducing (hypomorphic) protein expression, modifying the protein (gain- or loss-of-function), or acquiring novel functions (neomorphic).[13]

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. As B-cells produce antibodies, patients with a B-cell deficiency are susceptible to pneumonia, otitis, and other infections caused by extracellular bacteria. As T-cells differentiate into helper, cytotoxic, or regulatory T cells, patients with a T-cell deficiency are susceptible to fungal and viral infection, as well as having a susceptibility to developing tumours, bacterial infections due to the loss of T-cell help for B-cell function, and immune dysregulation including autoimmune and lymphoproliferative disease. Deficiencies in phagocytic cells, the complement system and cytokines disrupt the body's innate immunity system that plays a key role in the early immune response to infections and helping B and T lymphocytes to function, resulting in infection caused by rare and opportunistic pathogens, and/or increased susceptibility to severe infections such as abscesses, meningitis or sepsis due to common pathogens. Defects of innate immunity can result in a failure to thrive and some inflammatory or autoimmune disorders.[6]

The mechanism of PID disease will depend on the nature of the variant and its mode of inheritance, with PIDs variously following X-linked, autosomal dominant and autosomal recessive inheritance patterns.[13]

The most severe PID is severe combined immunodeficiency (SCID). Babies with SCID require urgent bone marrow transplantation, a potentially curative procedure, optimally within the first 3 months of life, without which most affected children will die within the first 2 years of life. The most common cause of SCID, accounting for more than 50% of cases, is due a gene defect on the X chromosome and therefore affects males, however 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 severe T cell deficiency in newborns that characterises SCID but does not provide a genetic diagnosis. Babies with a positive SCID newborn screen have further laboratory testing performed to confirm the diagnosis of SCID. Genetic testing is then required to identify the molecular defect causing SCID in that patient, optimal approaches to curative bone marrow transplant may need to be varied dependent on the genetic cause and the results inform genetic counselling for future pregnancies. While most causes of severe T cell deficiency detected by newborn screening is due to classic SCID that can be cured with bone marrow transplant (BMT) there are some causes (e.g. thymic disorders) that are not corrected by BMT. Identifying these alternative causes of severe T-cell deficiency by early genetic testing avoids the risk of bone marrow transplant, whilst enabling appropriate alternative treatment, such as thymic transplant.

The majority of patients with suspected PID are investigated as an outpatient, potentially after presenting to hospital with recurrent, severe and/or opportunistic infections. Patients with suspected primary immunodeficiency should be referred to a clinical immunologist for evaluation,

however there is often a delay in recognition of potential PID amongst non-immunologists due to the broad range of potential clinical phenotypes of PID.

Depending on the nature of the clinical presentation, investigations would include blood tests to quantitate various components of the immune system including immunoglobulin levels, lymphocyte subpopulations (T, B and NK cells) and complement proteins. Laboratory testing of immune function may also be performed, including assessment of T cell proliferation, antibody responses to vaccination, neutrophil migration and oxidative burst (killing), and complement function. Imaging may also be performed to assess for 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 also be used to exclude secondary causes of immunodeficiency (e.g. haematological malignancy, immunosuppressive treatment, HIV infection, protein losing states).

Management of PID is directed by the underlying molecular defect, where it has been confirmed, and the clinical phenotype. Bone marrow transplantation is essential for management of SCID, unless it is due to a thymic disorder.

Most PIDs are associated with susceptibility to infections and antimicrobial prophylaxis against bacterial, fungal and/or viral infections is prescribed where relevant according to the underlying immune defect. For patients with antibody deficiencies, immunoglobulin replacement therapy is instituted as soon as possible after diagnosis to prevent further bacterial infections and complications such as bronchiectasis. Many PIDs are also associated with immune dysregulation and autoimmunity, and patients may require immunosuppressive therapies to manage these complications while at the same time taking antimicrobial therapies to manage their risk of infections. Targeted therapies addressing the specific molecular defect that cause certain PIDs are now increasingly available, including medications already licensed for other indications that have been repurposed to treat PID.

Early diagnosis of PID/IEI disorders is important as delayed treatment can result in complications that may be life threatening.

Table *1* summarises the 10 warning signs of PID, noting that these were developed to raise awareness amongst non-immunology specialists to consider the possibility of PID and do not represent diagnostic criteria.

Table 1 Warning signs of primary immunodeficiency/inborn errors of immunity disorders[8]

	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	Two 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 one	Persistent thrush or fungal infection on skin or elsewhere
7	2 or more months on antibiotics with little effect	Repeat viral infections (colds, herpes, warts, condyloma)
8	Need for intravenous antibiotics to clear infections	Need for intravenous antibiotics to clear infections
9	Failure to gain weight, grow normally, or chronic diarrhoea	Chronic diarrhoea with weight loss
10	Family history of PID/IEI	Family history of PID/IEI

Provide a rationale for the specifics of the eligible population:

See responses above.

Are there any prerequisite tests?

Yes, see **Table 2** in the Comparator section for more detail.

Are the prerequisite tests MBS funded?

Yes

Provide details to fund the prerequisite tests:

Not applicable

Intervention

Name of the proposed health technology:

Genomic testing for the diagnosis of PID

Describe the key components and clinical steps involved in delivering the proposed health technology:

Genetic testing is essential for the diagnosis and clinical management of patients with phenotypic or suspected PIDs, with identification of the molecular defect needed for diagnostic confirmation. Knowledge of the specific genetic diagnosis facilitates prognostication and informs clinical decision-making. Although other techniques such as high-throughput sequencing using gene panels can be used, massively parallel exome sequencing or WGS (depending on availability) are more commonly used to expedite PID diagnosis and reduce the number of non-diagnostic results.[1]

Patients referred to a clinical immunologist with signs/symptoms suggestive of primary immunodeficiency (e.g. based on the 10 Warning Signs described in

Table *1*) would undergo a detailed clinical history, physical examination, and series of routine investigations with additional investigations directed according to the clinical presentation.

Depending on the results of the initial investigations, further specialised testing may be performed; this testing may only be available via send away testing to highly specialised immunology laboratories (often interstate), require advanced notice for the laboratory to prepare the necessary reagents to perform the test, and/or be poorly remunerated or unfunded by existing item numbers due to the esoteric nature and infrequent use of these tests.

Based on the clinical history, examination and investigation findings (including imaging and pathology), a phenotypic diagnosis of PID may be made (e.g. common variable immunodeficiency, a condition which still has heterogeneous clinical manifestations between individuals and is caused by a range of different molecular defects). Despite strong clinical features suggestive of a PID, routinely available diagnostic tests may not be abnormal in types of PIDs which are subsequently genetically proven.

Genetic testing would then be recommended, after appropriate counselling and obtaining the informed consent of the patient. Genetic testing requires a blood, saliva or buccal sample from which DNA is extracted for genomic analysis.

Genetic testing is performed by a NATA-accredited diagnostic laboratory in accordance with NPAAC guidelines. Any variants identified would be analysed and reported in accordance with established guidelines e.g. American College of Medical Genetics and Genomics criteria for interpretation of genomic testing by a pathologist with the required scope of practice for supervision of genomic testing.

The results of genomic testing are then interpreted in conjunction with the other laboratory and imaging investigations, clinical progress of the patient (including response to any treatments initiated) and in some cases the results of a family study to determine the inheritance pattern to determine the clinical relevance of any genetic variants identified. The reporting pathologist would be available to contribute to a multidisciplinary team meeting to assist with the interpretation of the genetic testing results.

Patients presenting with symptoms suggestive of primary immunodeficiency consistent with the 10 warning signs and symptoms described in

Table *1* would undergo a series of standard investigations. If results of these tests are suggestive of a PID, immune cell-specific functional assays should be conducted in parallel to genotyping. Genotyping requires the collection of a sample (usually blood, saliva or buccal/cheek swab) that is referred to a pathology laboratory, where DNA is extracted for genetic analysis (NGS panel testing). The results of these genomic tests are then interpreted with the rest of the pathological data of the patient to categorise the patient.

Identify how the proposed technology achieves the intended patient outcomes:

Genomic testing in cases of suspected PID improves patient outcomes by:

1. Enabling earlier, more 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 by facilitating timely diagnosis and intervention.
3. Avoiding unnecessary and invasive investigations by establishing a clear genetic cause for immune dysfunction.
4. Informing treatment decisions by identifying contraindications to specific immunosuppressive or biologic therapies that could worsen outcomes in certain genetic forms of PID.
5. Allowing early identification of patients at increased risk of severe complications, such as malignancy or immune dysregulation, enabling proactive monitoring and management.
6. Ending the diagnostic odyssey, potentially improving psychological wellbeing by providing clarity, reducing parental guilt, and connecting families with disease-specific support networks.
7. Offering prognostic information to help guide long-term care planning, including discussions around curative therapies, supportive care, or palliative approaches where appropriate.
8. Supporting genetic counselling and enabling cascade testing to identify at-risk family members and inform reproductive decision-making.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

No

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

Not applicable

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):

Yes

Provide details and explain:

Patients would require testing with the proposed NGS (e.g. WES, WGS) item (AAAA) and targeted single-gene testing (CCCC) once per lifetime; however, a reanalysis item number (BBBB) is proposed for characterisation of previously unreported gene variants related to the clinical

phenotype, in a patient with a strong suspicion of primary immunodeficiency in whom the NGS test was uninformative. This would usually only be necessary 4-5 years after the initial NGS test.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

Testing will be provided by Approved Practising Pathologists in line with other tests on the MBS Pathology Table.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:
Not applicable

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:
Patients should be referred by or in consultation with a specialist clinical immunologist.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?
Yes

Provide details and explain:

The National Association of Testing Authorities (NATA) and the Royal College of Pathologists Australasia (RCPA) oversee the regulation of pathology testing for clinical purposes. Laboratories require accreditation by a joint NATA/RCPA process to ISO 15189 and are specifically accredited to provide genetic testing. This accreditation process covers the technical aspects of the sample reception and processing, laboratory sequencing, analysis pipelines, curation (or interpretation) of results and production of the report to a clinical standard. There are no requirements for the use of a specific manufacturer's reagents, equipment or analysis pipelines.

Testing would be delivered only by Approved Practising Pathologists with appropriate scope of practice in NATA Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered Medical Practitioners (non-pathologists) in line with other tests in the MBS Pathology Table.

Note: A non-commercial IVD is required to be regulated but not to be listed on the ARTG: testing using an IVD would be delivered only by Approved Practising Pathologists in NATA Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral in line with other tests in the MBS Pathology Table.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

- ☐ Consulting rooms
- ☐ Day surgery centre
- ☐ Emergency Department
- ☐ Inpatient private hospital
- ☐ Inpatient public hospital
- ☒ Laboratory
- ☐ Outpatient clinic
- ☐ Patient's home
- ☐ Point of care testing

☐ Residential aged care facility
☐ Other (please specify)

Is the proposed health technology intended to be entirely rendered inside Australia?

Yes

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e., how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian healthcare system). This includes identifying healthcare resources that are needed to be delivered at the same time as the comparator service:

The comparator is no genomic testing. In the absence of genomic testing, a differential diagnosis of PID will be based on a traditional immunological and phenotype-driven diagnostic process.

List any existing MBS item numbers that are relevant for the nominated comparators:

Table 2 lists the main MBS services used to inform a differential diagnosis of PID in the absence of genomic testing. For the purposes of the PICO, these are effectively prior tests, not comparators.

Table 2 MBS items for standard investigations for PID

Item number (Group)	Description and fee
73802 (Group P9 - Simple Basic Pathology Tests)	Leucocyte count, erythrocyte sedimentation rate, examination of blood film (including differential leucocyte count), haemoglobin, haematocrit or erythrocyte count - 1 test **Fee:** $4.55 **Benefit:** 75% = $3.45 85% = $3.90
71066 (Group P4 – Immunology)	Quantitation of total immunoglobulin A by any method in serum, urine or other body fluid - 1 test **Fee:** $14.90 **Benefit:** 75% = $11.20 85% = $12.70
71068 (Group P4 – Immunology)	Quantitation of total immunoglobulin G by any method in serum, urine or other body fluid - 1 test **Fee:** $14.90 **Benefit:** 75% = $11.20 85% = $12.70
71072 (Group P4 – Immunology)	Quantitation of total immunoglobulin M by any method in serum, urine or other body fluid - 1 test **Fee:** $14.90 **Benefit:** 75% = $11.20 85% = $12.70
71074 (Group P4 – Immunology)	Quantitation of total immunoglobulin D by any method in serum, urine or other body fluid - 1 test **Fee:** $14.90 **Benefit:** 75% = $11.20 85% = $12.70
71139 (Group P4 – Immunology)	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 P6 – Pathology Services)	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) - 1 or more tests. **Fee:** $589.90 **Benefit:** 75% = $442.45 85% = $501.45

Provide a rationale for why this is a comparator:

In the absence of genomic testing, a differential diagnosis of PID will be made based on a traditional immunological and phenotype-driven diagnostic process. While traditional processes remain essential for initial screening and understanding immune function, they are increasingly being supplemented or replaced by genomic testing due to its higher diagnostic yield, especially in complex or unexplained cases.

For some patients, functional assays will increase or decrease the probability of a diagnosis but very few are definitively diagnostic, and many are only offered by highly specialised research laboratories or limited numbers of diagnostic labs, and may not be suitable for shipped samples.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

None (used with the comparator)

Outline and explain the extent to which the current comparator is expected to be substituted:

Not applicable

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

- Health benefits
- Health harms
- Resources
- Value of knowing

Outcome description – include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

Safety outcomes:

- Adverse events (AEs) related to PID testing
- AEs from the change in patient management
- AEs from treatment (if given)

Clinical effectiveness outcomes:

- Direct evidence:
    - Change in patient health outcomes: mortality, morbidity, quality of life
- Indirect evidence
    - Clinical utility: change in patient management/treatment resulting change in patient outcomes: mortality, morbidity, quality of life: comparing patients who received PID testing versus those who did not receive PID testing
    - Clinical validity: prognostic value: assessment of diagnostic/test accuracy: sensitivity, specificity, number of false positives, number of false negatives, number of inconclusive results

Value of knowing:

- Informed reproductive decision-making
- Reduced diagnostic odyssey

Cost-effectiveness outcomes:

- Cost per patient with a PID variant identified.
- Cost per patient avoiding ineffective therapies
- Cost per patient commencing appropriate therapy
- Cost per quality-adjusted life year (QALY) gained.

Health system resources:

- Cost of molecular testing vs. health system savings (reduced hospitalisations and ICU admissions etc)
- Total Australian Government healthcare cost.

Proposed MBS items

How is the technology/service funded at present? (e.g., research funding; State-based funding; self-funded by patients; no funding or payments):

Genomic testing for PID is primarily reimbursed through research funding,[14] or self-funding by patients.

Provide at least one proposed item with their descriptor and associated costs, for each Population/Intervention:

MBS item number	AAAAA
Category number	6
Category description	Pathology services
Proposed item descriptor	Characterisation, via whole exome or genome sequencing and analysis, of germline gene variants in a patient with a strong suspicion of primary immunodeficiency disease / inborn errors of immunity, if the characterisation is requested by or in consultation with an immunologist or clinical geneticist Applicable only once per lifetime
Proposed MBS fee	**Fee:** $2,100 **Benefit**: **75%** = $1,575.00 **85%** = $1,997.60
Indicate the overall cost per patient of providing the proposed health technology	$2,100
Please specify any anticipated out of pocket expenses	Nil

Provide any further details and explain	As the list of target genes for genotyping will evolve over time, we suggest a practice note be included that recommends a standards-based approach to genotyping be undertaken, e.g. PN.7.13, using the International Union of Immunological Societies (IUIS) Expert Committee phenotypic classification register.[7] A practice note should be included, specifying patients with an intellectual disability or other multi-systemic presentation be referred to clinical genetics before genotyping, as these syndromes may not covered by the gene panel. A practice note should be included, specifying that patients who receive a molecular diagnosis receive genetic counselling by either the treating immunologist, genetic counselling service, or a clinical geneticists on referral, to discuss implications for relatives (where relevant). The proposed fee has been benchmarked against existing MBS items (73358).

MBS item number	BBBBB
Category number	6
Category description	Pathology services
Proposed item descriptor	Re-analysis of next generation sequencing data obtained as described under item AAAA, after an interval of not less than 48 months, for characterisation of previously unreported gene variants related to the clinical phenotype, in a patient with a strong suspicion of primary immunodeficiency / inborn errors of immunity, as requested by a consultant physician practicing as an immunologist or clinical geneticist Applicable twice per lifetime
Proposed MBS fee	**Fee:** $500.00 **Benefit: 75%** = $375.00 **85%** = $425.00
Indicate the overall cost per patient of providing the proposed health technology	$500
Please specify any anticipated out of pocket expenses	Nil
Provide any further details and explain	The proposed fee has been benchmarked against existing MBS items for re-analysis of WES or WGS data (73428), and services advertised by VCGS, with no out-of-pocket fees.[15] The IUIS phenotype classification register noted in item AAAA is updated regularly and it (or a similar standards-based approach) should be used to inform the genes included in the re-analysis. This should be nominated in a practice note. As with existing item 73428, PN.7.7 is also appliable to proposed item BBBB.

MBS item number	CCCCC
Category number	6
Category description	Pathology services
Proposed item descriptor	Characterisation of one or more gene variants known to be causative or likely causative of primary immunodeficiency disease / inborn errors of immunity, for any of the following: (a) a person with suspected primary immunodeficiency where a suspected specific gene variant is highly associated with the clinical presentation and investigations (b) a reproductive partner of a person with a recessive pathogenic or likely pathogenic germline gene variant associated with a primary immunodeficiency (confirmed via laboratory findings) (c) a biological relative of a patient with a germline gene variant known to be causative or likely causative of primary immunodeficiency disease (confirmed by laboratory findings) Applicable only once per lifetime
Proposed MBS fee	**Fee:** $400.00 **Benefit: 75%** = $300.00 **85%** = $340.00
Indicate the overall cost per patient of providing the proposed health technology	$400
Please specify any anticipated out of pocket expenses	Nil
Provide any further details and explain	PN.0.23 (genetic counselling) is applicable to item CCCC. As noted in the item descriptor, this item is intended for targeted genotyping in several eligible populations. The proposed fee is deliberately method agnostic to capture a range of potential testing modalities depending on the indication, noting that some (e.g. sanger sequencing) will be cheaper than the proposed fee in practice, and others will be more costly. The proposed fee has been benchmarked against similar items for targeted genotyping (e.g. MBS Item 73434). Indication C has two primary intended purposes: 1) to aid in the determination of pathogenicity in variants identified in the proband via confirmation of the mutation in birth parents, and 2) to identify known pathogenic germline gene variants in siblings.

Algorithms

PREPARATION FOR USING THE HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

See previous responses in the Intervention section.

Is there any expectation that the clinical management algorithm before the health technology is used will change due to the introduction of the proposed health technology?

No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

Not applicable

USE OF THE HEALTH TECHNOLOGY

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

Genomic testing may involve additional appointments with a clinical geneticist or genetics counsellor, depending on the level of experience of the treating immunologist with genomic testing, and indication for the test (i.e. in a proband suspected of PID, in a parent to confirm the pathogenicity of the identified variant in the proband, in a biological relative).

Explain what other healthcare resources are used in conjunction with the comparator health technology:

None in addition to standard PID work-up as described above, the comparator is no genomic test.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

See response above.

CLINICAL MANAGEMENT AFTER THE USE OF HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the proposed health technology:

See previous responses in the Intervention section.

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the comparator health technology:

See previous responses in the Intervention section.

Describe and explain any differences in the healthcare resources used after the proposed health technology vs. the comparator health technology:

Appropriate, targeted and effective treatment and improved prognoses can be achieved through the early detection of PID by genotyping. Treatment will vary depending on diagnosis but may include immunoglobulin therapy, treatment with antibiotics, antifungals or antivirals, nutritional supplements, immunosuppression, transplantation, thymic transplantation, gene therapy, biologics/monoclonals and small molecule inhibitors, and cytokine therapy, the choice of many of which will be highly dependent on a genetic diagnosis.[6] In addition, a genetic diagnosis of PID in a proband enables targeted cascade screening of family members to identify others at risk, allowing for early diagnosis and management. It also informs reproductive planning by clarifying inheritance patterns and guiding discussions on reproductive options. These would involve consultation with a clinical geneticist and/or genetic counsellor.

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

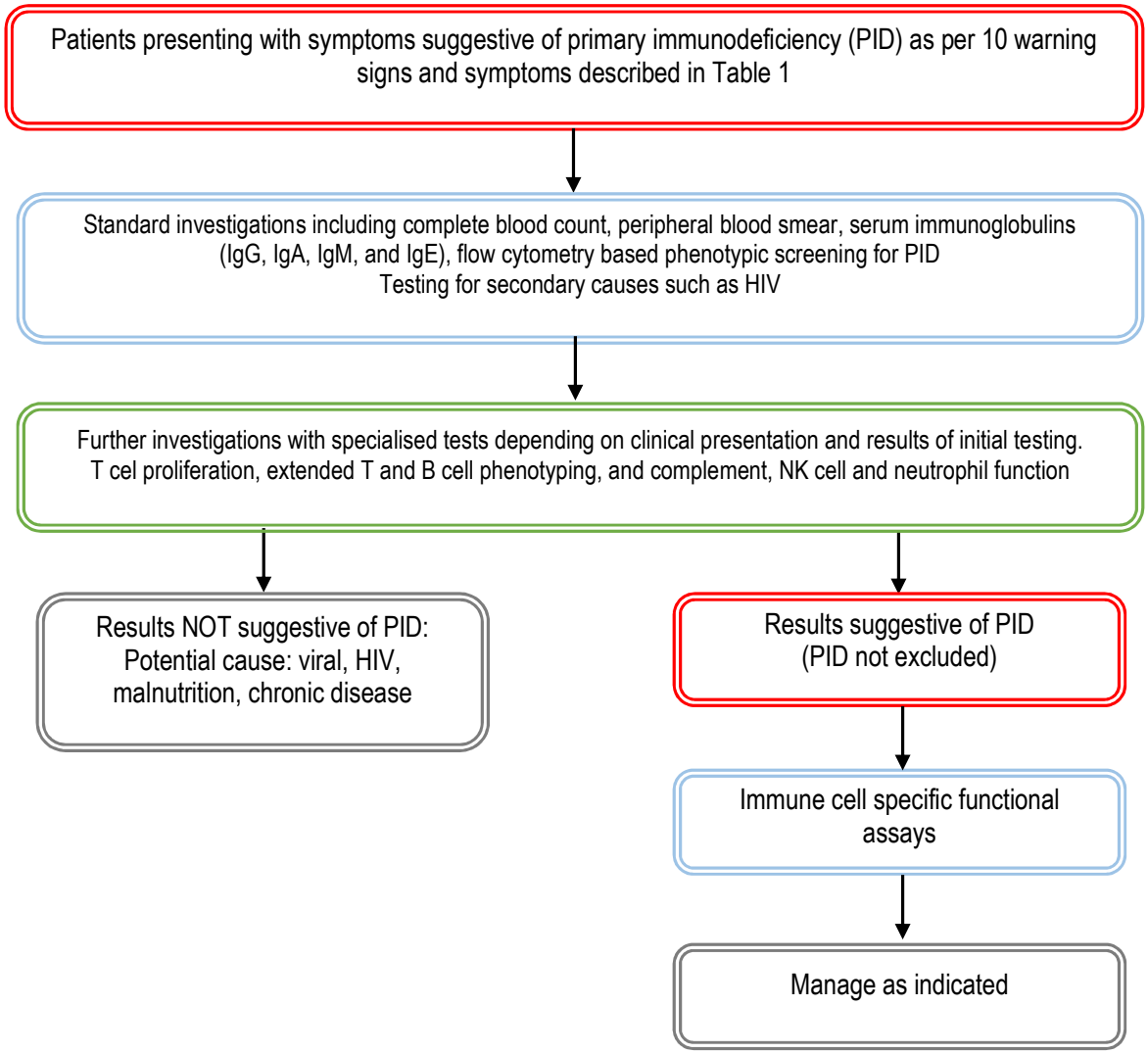

Figure 1 Clinical algorithm for investigating suspected primary immunodeficiency without genotyping

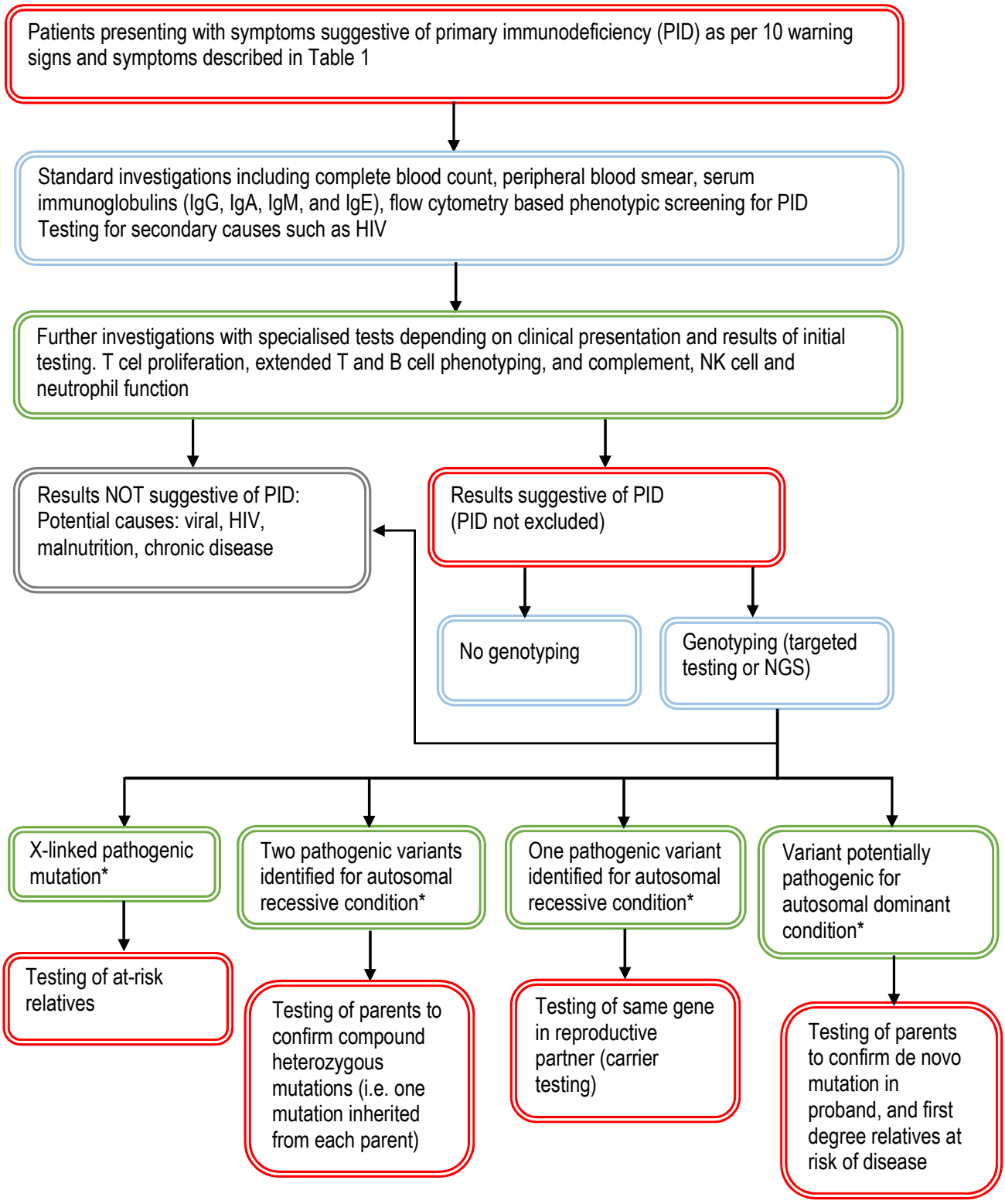

Figure 2 Clinical algorithm for investigating suspected primary immunodeficiency with genotyping

Notes: * the green cells nominate indications for testing of family members (item CCCCC). In all cases, a pathogenic variant has been identified in the proband (blue cell above), who will be managed as indicated depending on the diagnosis. Treatments are not represented in the flowchart for simplicity.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

Superior

Please state what the overall claim is, and provide a rationale:

As described in

Figure 2, patients suspected of having a PID would undergo standard diagnostic tests and immune cell-specific functional assays if deficiencies were noted (T or B lymphocytes, natural killer cells etc). Given the clinical, phenotypic and genetic heterogeneity of PID, standard tests inform the probability of certain diagnoses (i.e. a differential diagnosis), but only genotyping enables the concurrent analysis of numerous causative variants to deliver a definitive diagnosis. Therefore, the clinical claim is that genetic testing is superior to no genetic testing in relation to diagnostic precision, and therefore downstream impacts on clinical management and improved clinical outcomes.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

A requestor might seek to use genomic testing for PID instead of relying solely on standard investigations (i.e. no genomic testing) to enable:

1. **Faster diagnosis:** A significant number of patients experience an extensive diagnostic odyssey, with a concomitant decrease in health status and quality of life, as well as extensive use of the health system *before* establishing a diagnosis. The recent study by Nikzad et al. (2025) reported that only 108 (28%) of 383 children (self-reported PID) aged 0-5 years who had experienced serious infections received a diagnosis of PID and consequently reported better health status than those who were not diagnosed. In addition, patients saw a mean number of 3 ± 2.4 (range: 0–11) clinicians whilst seeking a diagnosis, representing a significant burden on the health system.[16]
2. **Improved diagnostic precision:** Genomic testing can identify the exact genetic cause of the immune deficiency, providing a definitive diagnosis that standard investigations (such as immunophenotyping or functional assays) often cannot achieve on their own.[17]
3. **Personalised management:** Knowing the precise genetic variant can guide more targeted treatment decisions, predict disease progression, identify eligibility for therapies like stem

cell transplantation, and support family planning through carrier testing or prenatal diagnosis.[2]

Identify how the proposed technology achieves the intended patient outcomes:

See previous question.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management? Yes

A change in health outcome? Yes

Other benefits? Yes

Please provide a rationale, and information on other benefits if relevant:

In addition to impacts on clinical management and health outcomes, genomic testing for PID:

1. **Enables family planning and cascade testing:** Identifying the genetic cause for PID allows for testing of family members to assess carrier status, guide reproductive decisions, and enable early diagnosis and intervention in at-risk relatives.
2. **Reduces the diagnostic odyssey:** As discussed above, a molecular diagnosis can help avoid repeated, invasive, or costly investigations by providing an explanation for the clinical presentation.[16]
3. **Enables access to clinical trials:** Given the heterogeneity and specificity of patients with PID, clinical trials may offer the only available treatment option. A genetic diagnosis may make patients eligible for enrolment in clinical trials, including novel targeted therapies or gene therapy.

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

More costly

Provide a brief rationale for the claim:

Genomic testing is an adjunct to existing clinical investigations for suspected PID, so represents an additional cost rather than a cost-offset. Downstream consequences of more accurate diagnosis due to genomic testing may result in downstream cost savings, but this will need to be borne out in the financial modelling conducted for the DCAR.

If your application is in relation to a specific radiopharmaceutical(s) or a set of radiopharmaceuticals, identify whether your clinical claim is dependent on the evidence base of the radiopharmaceutical(s) for which MBS funding is being requested. If your clinical claim is dependent on the evidence base of another radiopharmaceutical product(s), a claim of clinical noninferiority between the radiopharmaceutical products is also required.

Not applicable.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement',

#	Study design	Title	Abstract	Link	Date
1.	Clinical practice guideline[18]	European Society for Immunodeficiencies (ESID) and European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA) Complement Guideline: Deficiencies, Diagnosis, and Management	Current management strategies for complement disorders associated with infection include education, family testing, vaccinations, antibiotics and emergency planning.	PMID 32064578	May 2020
2.	Systematic review and meta-analysis[17] Diagnostic yield	Diagnostic yield of next-generation sequencing in suspect primary immunodeficiencies diseases: a systematic review and meta-analysis	A meta-analysis of 29 studies involving 5,847 patients showed that NGS achieved a 42% diagnostic yield in suspected PID cases, rising to 58% in those with a family history. NGS improves early diagnosis, guides treatment, and identified key genes, including some not on current reference lists.	PMID 38890201	Jun 2024

#	Study design	Title	Abstract	Link	Date
3.	Case series[2] Diagnostic yield Change in management International, multicentre	Global Expansion of Jeffrey's Insights: Jeffrey Modell Foundation's Genetic Sequencing Program for Primary Immunodeficiency	Patients with suspected PID who lack a genetic diagnosis often face long diagnostic delays, leading to inappropriate management and treatment. NGS helps overcome this by providing faster, accurate diagnoses. In a study of 1,398 patients, NGS identified a molecular diagnosis in 20.3%, leading to changes in clinical diagnosis (39%), disease management (38%), treatment (35%), and genetic counselling (53%).	PMID 35757720	Jun 2022
4.	Case series[19] Diagnostic yield Germany	Diagnostic Yield and Therapeutic Consequences of Targeted Next-Generation Sequencing in Sporadic Primary Immunodeficiency	Diagnostic yield and the clinical consequences of targeted NGS (tNGS) in a cohort of 294 PID patients, primarily consisting of cases with sporadic primary antibody deficiency. tNGS identified a definite or predicted pathogenic variant in 15.3% of patients. The highest diagnostic rate was observed among patients with combined immunodeficiency or immune dysregulation, for whom genetic diagnosis may affect therapeutic decision-making.	PMID 34619682	Oct 2021
5.	Case series[20] Diagnostic yield Cost USA	Efficacy and economics of targeted panel versus whole-exome sequencing in 878 patients with suspected primary immunodeficiency	In 878 patients with suspected primary immunodeficiency, targeted gene panel testing achieved a 56% diagnostic yield, increasing to 58% with additional whole exome sequencing (WES). A WES-only approach yielded 45% and could save $300–$950 per patient. Overall, 56% received molecular diagnoses across 152 monogenic disorders, including 16 novel conditions.	PMID 32888943	Feb 2021

#	Study design	Title	Abstract	Link	Date
6.	Case series[21] Diagnostic yield Change in management India	Primary Immunodeficiencies in India: Molecular Diagnosis and the Role of Next-Generation Sequencing	Mutation analysis in 229 patients with suspected PID identified pathogenic variants in 97 patients involving 42 genes. Autosomal recessive and X-linked recessive inheritance were seen in 51.6% and 23.7% of patients. Targeted NGS is an effective diagnostic strategy for PIDs in countries with limited diagnostic resources. Molecular diagnosis of PID helps in genetic counselling and to make therapeutic decisions including the need for a stem cell transplantation.	PMID 33225392	Feb 2021
7.	Case series[22] Diagnostic yield Change in management South Africa	Clinical Utility of Whole Exome Sequencing and Targeted Panels for the Identification of Inborn Errors of Immunity in a Resource-Constrained Setting	WES or NGS was performed in 80 patients with suspected IEI and 107 family members recruited over an 8 year period. Overall, a molecular diagnosis was achieved in 30% (24/80) of patients. Clinical management was significantly altered in 67% of patients following molecular results. All 24 families with a molecular diagnosis received more accurate genetic counselling and family cascade testing.	PMID 34093558	May 2021
8.	Case series[23] Diagnostic yield Change in management Israel	Whole exome sequencing (WES) approach for diagnosing primary immunodeficiencies (PIDs) in a highly consanguineous community	WES was performed on 106 patients with suspected PID in a highly consanguineous population, achieving a likely genetic diagnosis in 70% of cases. Diagnostic yield was higher in younger patients, those with consanguinity, a family history of PID, or syndromic presentations. Importantly, WES results led to changes in clinical management in 39% of patients.	PMID 32135276	May 2020

#	Study design	Title	Abstract	Link	Date
9.	Case series[24] Diagnostic yield Japan	Whole-Exome Sequencing-Based Approach for Germline Mutations in Patients with Inborn Errors of Immunity	WES for candidate genes was performed in 136 patients with suspected inborn errors of immunity (IEI) who tested negative by conventional screening methods. Disease-causing pathogenic mutations were identified in 36 (26.5%) of the patients which were found in known IEI causing genes. Although the overall diagnostic rate was not high and was not apparently correlated with the clinical subcategories and severity, earlier onset with longer duration of disease was found to be associated with positive WES results, especially in paediatric cases.	PMID 32506361	Jul 2020
10.	Case series[25] Diagnostic yield United Kingdom	Whole-genome sequencing of a sporadic primary immunodeficiency cohort	Whole-genome sequencing of 1,318 PID patients identified disease-causing mutations in 10.3%, including noncoding regulatory deletions. This cohort-based approach improves diagnostic yield and deepens understanding of immune pathways influencing primary immunodeficiencies.	PMID 32499645	Jul 2020
11.	Case series[26] Diagnostic yield Spain	Expanding the clinical and genetic spectra of primary immunodeficiency-related disorders with clinical exome sequencing (CES): expected and unexpected findings	Exome sequencing in 61 suspected PID patients yielded diagnoses in 42%, with a 12% increase after expanding from a limited gene panel to over 4,000 genes. Limited CES coverage explains many undiagnosed cases; broader WES/WGS improves yield but some patients remain without a genetic diagnosis.	PMID 31681265	Oct 2019

#	Study design	Title	Abstract	Link	Date
12.	Case series[27] Diagnostic yield Change in management Netherlands	Exome sequencing in routine diagnostics: a generic test for 254 patients with primary immunodeficiencies	Exome sequencing of 254 suspected PID patients identified pathogenic variants in 28% (72 patients), including 10 from exome-wide analysis. In 34% of diagnosed cases, findings directly informed novel treatment options, demonstrating the clinical value of comprehensive genetic testing in primary immunodeficiency.	PMID 31203817	Jun 2019
13.	Case series[28] Diagnostic yield Change in management United Kingdom	Clinical efficacy of a next-generation sequencing gene panel for primary immunodeficiency diagnostics	Twenty-seven participants were recruited, and underwent testing with an NGS panel of 242 PID genes. A total of 15 reportable variants were identified in 48% (13/27) of the participants. The panel results had implications for treatment in 37% (10/27) of participants.	PMID 29077208	Mar 2018
14.	Case series[29] Diagnostic yield Kuwait	Comprehensive genetic results for primary immunodeficiency disorders in a highly consanguineous population	264 patients from Kuwait PID Registry with clinical PID diagnosis. 206 patients underwent genetic testing (78%) with an overall diagnostic yield of 70% (184 patients) (FISH and Sanger sequencing were 30 and 99, respectively, while 44 and 11 patients were diagnosed by WES and WGS).	PMID 30697212	Jan 2019
15.	Case series[30] Diagnostic yield China	Targeted next-generation sequencing for genetic diagnosis of 160 patients with primary immunodeficiency in south China	In 160 paediatric PID patients, targeted NGS of 269 genes identified causative variants in 43.8%. Autoinflammatory diseases were most common (20%), followed by immune dysregulation (17.5%) and combined immunodeficiencies (16.2%). X-linked inheritance accounted for 45.7% of diagnosed cases, highlighting genetic diversity in paediatric PID.	PMID 30152884	Dec 2018

#	Study design	Title	Abstract	Link	Date
16.	Case series [31] Diagnostic yield Change in management International, multicentre	Primary immunodeficiency diseases: genomic approaches delineate heterogeneous Mendelian disorders	A total of 278 families with PID from 22 countries were consecutively recruited and underwent WES. A likely molecular diagnosis was achieved in 110 (40%) unrelated probands. Clinical diagnosis was revised in about half (60/110) and management was directly altered in nearly a quarter (26/110) of families based on molecular findings.	PMID 27577878	Jan 2017
17.	Case-control[32] Diagnostic yield Saudi Arabia	Unbiased targeted next-generation sequencing molecular approach for primary immunodeficiency diseases	In 261 suspected PID patients, targeted NGS detected known mutations in 96% of positive controls (117/122) and identified new genetic diagnoses in 25% of unsolved cases (35/139), many with atypical presentations of known PIDs, supporting NGS as a powerful diagnostic tool.	PMID 26915675	Jun 2016

Abbreviations: **CES**, clinical exome sequencing; **FISH**, fluorescence in situ hybridisation; **IEI**, inborn errors of immunity; **NGS**, next-generation sequencing; **PID**, primary immunodeficiency disease; **WES**, whole exome sequencing; **WGS**, whole genome sequencing.

Yet-to-be-published research that may have results available in the near future

#	Design	Title	Description	Link	Date
1.	Case series Diagnostic yield Switzerland	Towards Identification of New Inborn Errors of Immunity by Whole Exome/Genome Sequencing ClinicalTrials.gov ID NCT03414528	Analysis of DNA samples of patients with molecularly undetermined PID by whole exome/genome sequencing. Estimated enrolment 300 patients. Primary outcome identification of genetic defects (diagnostic yield).	NCT03414528	Estimated completion August 2025 (Note: status may be unreliable as last update was in 2018)
2.	Case series Diagnostic yield France	Systematic Screening for Primary Immunodeficiencies in Patients Admitted for Severe Infection in Paediatric Intensive Care Unit ClinicalTrials.gov ID NCT04990908	This study aims to determine the incidence of PID in children with severe infections, regardless of cause. Estimated enrolment 100 patients. Primary outcome identification of genetic defects (diagnostic yield).	NCT04990908	Estimated completion September 2026

Abbreviations: **PID**, primary immunodeficiency disease.

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