MSAC application 1810

Genomic testing for the diagnosis of primary immunodeficiency (PID)

Application for MBS eligible service or health technology

HPP Application number:
HPP200289

Application title:
Genomic testing for the diagnosis of primary immunodeficiency (PID)

Submitting organisation:
THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

Submitting organisation ABN:
52000173231

Application description

Succinct description of the medical condition/s:
Primary immunodeficiencies (PIDs), also known as inborn errors of immunity (IEI), are genetic disorders that weaken the immune system. Caused by variants in over 450 genes, PIDs can be inherited in a dominant or recessive pattern, may be autosomal or X-linked, and can show complete or incomplete penetrance. They are more commonly diagnosed in children and are more prevalent in populations with higher rates of consanguinity. PIDs result from genetic defects that affect either the adaptive immune system (B and T lymphocytes) or the innate immune system (phagocytes, complement proteins, cytokines, and their receptors), leading to increased risk of bacterial, viral, fungal, and opportunistic infections, as well as autoimmune conditions and some cancers.

Succinct description of the service or health technology:
Genetic testing is essential for the diagnosis and management of patients with suspected PIDs, as identifying the molecular defect is necessary for diagnostic confirmation. Knowing the specific genetic cause of PID helps guide prognosis and informs clinical decision-making around appropriate treatments. While targeted gene panels may be used, massively parallel exome sequencing or whole genome sequencing (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 and/or sanger sequencing is conducted to identify specific variants of concern.

Application contact details

Are you the applicant, or are you a consultant or lobbyist acting on behalf of the applicant?

Applicant

Are you applying on behalf of an organisation, or as an individual?

Organisation

Applicant organisation name:

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

Application details

Does the implementation of your service or health technology rely on a new listing on the Pharmaceutical Benefits Scheme (PBS) and/or the Prescribed List?

No

Is the application for a new service or health technology, or an amendment to an existing listed service or health technology?

New

What is the type of service or health technology?

Investigative

Please select the type of investigative health technology:

Molecular diagnostic tests

Please select the type of molecular diagnostics health technology:

Whole exome/genome sequencing

PICO sets

Application PICO sets:

Patients presenting with symptoms suggestive of primary immunodeficiency (PID)

State the purpose(s) of the health technology for this PICO set and provide a rationale:

Purpose category:

Diagnosis / sub-classification

Purpose description:

To establish a diagnosis or disease (sub)classification in symptomatic or affected patients

What additional purpose(s) could the health technology be used for, other than the purposes listed above for this PICO set?

Purpose category:

Value of knowing

Purpose description:

Tests may also provide additional non-health value to patients or to their family members and carers, and discussion of these outcomes could supplement an assessment of the clinical utility of the technology

Rationale:

Identifying the genetic cause for PID allows for testing of family members to assess carrier status, guide reproductive decisions.

A molecular diagnosis can help avoid repeated, invasive, or costly investigations by providing an explanation for the clinical presentation

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. 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.

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. 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.

Select the most applicable Medical condition terminology (SNOMED CT):

Immunodeficiency disorder

Intervention

Name of the proposed health technology:

Genomic testing for the diagnosis of PID

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 health care system). This includes identifying health care 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 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.

Outcomes

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

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. 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.

Proposed MBS items

Proposed item:

AAAAA

Category number:

Category 6: Pathology Services

Category description:

Group P7: Genetics

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:

$2,100.00

Indicate the overall cost per patient of providing the proposed health technology:

$2,100.00

Please specify any anticipated out of pocket expenses:

$0.00

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).

Proposed item:

BBBBB

Category number:

Category 6: Pathology Services

Category description:

Group P7: Genetics

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:

$500.00

Indicate the overall cost per patient of providing the proposed health technology:

$500.00

Please specify any anticipated out of pocket expenses:

$0.00

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.
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.

Proposed item:

CCCCC

Category number:

Category 6: Pathology Services

Category description:

Group P7: Genetics

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:

$400.00

Indicate the overall cost per patient of providing the proposed health technology:

$400.00

Please specify any anticipated out of pocket expenses:

$0.00

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.

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

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

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:

Patients suspected of having a PID typically undergo standard diagnostic tests and immune cell-specific functional assays if deficiencies are 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 downstream impacts on clinical management and improved clinical outcomes.

Estimated utilisation

Estimate the prevalence and/or incidence of the proposed population:

Although individual IEI are rare, IEIs as a group are not, and they represent a significant health burden. The prevalence of some PIDs varies with ethnicity, and is increased in the offspring of consanguineous parents. Globally, PID registries in different countries report PID prevalence rates ranging from 1:8,500 to 1:100,000 for symptomatic patients. A recent study reported that the incidence of IEIs in the USA was 6 per 10,000 people. Australian registry data obtained in 2018 indicated that there was a total of 1,876 registered patients in a population of 24.6 million people, translating to a rate of 7.6 per 100,000 individuals, with no information on the type of PID or whether these patients had received a genetic diagnosis. Combined Australia and New Zealand data obtained in 2007 revealed a lower rate of 4.86 per 100,000 individuals, with the majority diagnosed with predominantly antibody deficiencies (77.4%, noting that CVID was the most frequent diagnosis at 38.4% of all patients), followed by immunodeficiencies affecting cellular and humoral immunity (8.9%), complement deficiencies (5.9%), congenital defects of phagocyte number or function (3.2%) and other PIDs (4.6%). Only 18.4 per cent of these patients received a genetic diagnosis. When only Australian data was considered, the prevalence of PID was estimated to be 5.6 per 100,000; however, South Australia reported a rate of 12.4 per 100,000, which may reflect greater clinical awareness of PIDs rather than a real difference in prevalence, noting that it is generally accepted that PID is under-diagnosed and under-reported.

Provide the percentage uptake of the proposed health technology by the proposed population:

Year 1 estimated uptake (%):
100

Year 2 estimated uptake (%):
100

Year 3 estimated uptake (%):
100

Year 4 estimated uptake (%):
100

Estimate the number of patients who will utilise the proposed technology for the first full year:

863 NGS (item AAAAA); 431 familial tests + 95 sanger sequencing of probands (item CCCCC)

Optionally, provide details:

As stated above, estimating the incidence/prevalence of PID in the Australian population is difficult. However, the number of tests currently being conducted may be used as an estimate of the potential size of the testing population. New South Wales is currently testing approximately 20 patients with suspected SCID per year (noting that a genetic variant is identified in approximately 95% of these children). When all other suspected PIDs are included, NSW tests approximately 300 children per year. These numbers have been extrapolated to Australia as a whole based on relative population size of 959 in year 1 (90% tested with NGS, 10% tested with sanger sequencing). With an estimated yield of ~15% in local practice (similar to rates reported in Germany, Sogkas 2022), testing an average of 3 family members (2 parents to determine pathogenicity in the proband, plus one sibling) per proband with an informative positive result will result in 431 family members tested per year. In practice, cascade testing items on the MBS are often underutilised (e.g. MBS item 73353), so the actual number is likely to be lower. As most patients with suspected PID are children, rates of testing of reproductive partners is likely to be negligible within the next five years.

Will the technology be needed more than once per patient?

No, once only

Consultation

List all entities that are relevant to the proposed service / health technology. The list can include professional bodies / organisations who provide, request, may be impacted by the service/health technology; sponsor(s) and / or manufacturer(s) who produce similar products; patient and consumer advocacy organisations or individuals relevant to the proposed service/health technology.

Entity who provides the health technology/service:

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

THE HUMAN GENETICS SOCIETY OF AUSTRALASIA LIMITED

PATHOLOGY AUSTRALIA LIMITED

PUBLIC PATHOLOGY AUSTRALIA

Entity who requests the health technology/service:

AUSTRALASIAN SOCIETY OF CLINICAL IMMUNOLOGY AND ALLERGY LIMITED

Entity who may be impacted by the health technology/service:

THE ROYAL AUSTRALASIAN COLLEGE OF PHYSICIANS

Patient and consumer advocacy organisations relevant to the proposed service/health technology:

AUSPIPS INC.

HAE AUSTRALASIA LTD

The Immune Deficiency Foundation of Australia Limited

Rare Voices Australia Ltd

Regulatory information

Would the proposed health technology involve the use of a medical device, in-vitro diagnostic test, radioactive tracer or any other type of therapeutic good?

Yes

Has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

No

Is the therapeutic good classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

Class III

Is the intended purpose in this application the same as the intended purpose of the ARTG listing(s)?

No

Is the therapeutic good to be used in the service exempt from the regulatory requirements of the Therapeutic Goods Act 1989?

No

Is the therapeutic good classified by the TGA as for Research Use Only (RUO)?

No