



Australian Government

Department of Health

RATIFIED PICO

Application 1476:

Genetic testing for childhood syndromes

Background

Whole exome analysis (WEA) is a new test that is not available to Australian children under the Medicare Benefits Schedule (MBS). This application is requesting a MBS listing for next generation WEA in patients (<18 years) with undiagnosed suspected syndromic genetic disorder, with targeted cascade testing for relatives. Analysis would be restricted to known causative genes, and prioritised by phenotype. Children presenting with syndromic genetic disorders face difficulties in accessing accurate diagnosis, with more than 1,000 possible underlying genetic disorders. The applicant confirmed that, for this application, whole genome sequencing (WGS) and whole exome sequencing (WES) represent different approaches to WEA. The applicant has stated there is no published literature measuring diagnostic utility or health economic impact of WGS in children with suspected syndromes, whereas WEA using data generated by WGS is expected to yield at least equivalent diagnostic utility to the childhood syndromes cohort presented in *Stark et al (2016)*. There is some published evidence comparing variant detection across the exome in WGS and WES, suggesting there is a 5% increase in detection of variants using WGS. It is reasonable to expect this would apply to children with suspected syndromes (Meynert, A.M., Ansari, M., FitzPatrick, D.R. & Taylor, M.S. - Variant detection sensitivity and biases in whole genome and exome sequencing. *BMC Bioinformatics* 2014, 15:247).

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

Table 1: Initial testing for the diagnosis of childhood syndromes

| Component | Description |
|---|--|
| Patients | Children (<18 years) with undiagnosed suspected syndromic genetic disorder, including at least 2 of the following: <ul style="list-style-type: none">- Single or multiple congenital abnormalities AND/OR- Dysmorphic facial features AND/OR- Intellectual disability |
| Prior tests (for investigative medical services only) | Detailed previous medical and family history. Micro-array testing with uninformative result; Multi-disciplinary team review to exclude those who exhibit features likely to be caused by a known single gene/simple genetic defect amenable to straightforward testing, and those whose features suggest a non-monogenic disorder. |
| Intervention | Testing for germline gene variants using whole exome analysis (WEA) |
| Comparator | Standard of care (which may involve a variety of genetic testing services, including sequential single-gene testing) <i>(Microarray testing is not a comparator – it is in addition to WEA for WES-based testing)</i> |
| Outcomes | <ul style="list-style-type: none">- Analytic validity- Clinical efficacy (diagnostic yield, time to definitive diagnosis, change in clinical management)- Safety- Health resource changes- Quality of life |

Table 2: Re-interrogation analysis for patients who did not have a definite diagnosis at initial testing

| Component | Description |
|--------------|---|
| Patients | Patients with initial negative results are to receive data re-interrogation 18 months later, as additional genes are discovered and added to the analysis list (with potential for further re-analyses as required) |
| Prior tests | Initial WEA testing with negative result conducted 18 months ago |
| Intervention | Re-analysis of sequencing data (not before 18 months) for patients without a definitive diagnosis as new genes are discovered and added to the list. |
| Comparator | No re-analysis and standard care |
| Outcomes | As for the genetic testing |

Abbreviations: WEA = whole exome analysis

Table 3: Cascade testing of family members

| Component | Description |
|--------------|---|
| Patients | First-degree family members of children where a definite pathogenic variant or potentially causative variant has been identified |
| Prior tests | Detailed previous medical and family history |
| Intervention | Sanger sequencing or a suitable alternative approach using an assay specific for the variant that has been identified |
| Comparator | Cascade testing in families after diagnosis by standard/current methods (likely to be diagnostic in around 14% of cases), which may include current (limited) genetic testing |
| Outcomes | Clinical efficacy (diagnosis yield, time to definitive diagnosis, restoration of reproductive confidence); and Health resource costs |

[*PICO or PPICO rationale for therapeutic and investigative medical services only*](#)

Population

Monogenic syndromes in children

Monogenic syndromes are a clinically and genetically heterogeneous group of disorders, typically with onset during infancy or early childhood. Individual syndromes usually have a constellation of features including, but not limited to, facial dysmorphism, congenital malformations, single or multi-organ functional anomalies, and variable degrees of intellectual disability.

Each particular genetic syndrome will have specific clinical features, depending on which organ systems are affected by the abnormal genes. The genetic basis of these conditions is highly heterogeneous, with a large number of genes (>1000) implicated in genetic syndromes of childhood, making molecular diagnosis of these conditions complex.

Patient population

Three populations are proposed:

Population 1

Initial testing of the proband for children (<18 years) with undiagnosed suspected syndromic genetic disorder, including at least 2 of the following:

- single or multiple congenital abnormalities AND/OR
- dysmorphic facial features AND/OR

- intellectual disability.

The applicant proposes a definition of intellectual disability based on age of the patient:

- An IQ<70 if the patient is old enough for a formal IQ assessment
- In younger individuals, a clinical assessment by a paediatric specialist that the child has at least moderate developmental delay
- In infants less than one year old, evidence of neurological impairment, such as delayed early developmental milestones, hypotonia and poor feeding.

Patients should be reviewed by an expert multi-disciplinary team to exclude patients who exhibit features likely to be caused by a known single gene/simple genetic defect for which other testing is available.

Population 2

Children with initial negative results who would benefit from data re-analysis of the initial whole exome, 18 months after receiving an initial negative result. Data re-interrogation is only of benefit if advances in genetic knowledge have led to new genes for monogenic conditions are discovered and added to the analysis list.

The applicant indicated there is evidence of effectiveness of re-analysis of WEA, but they are not aware of any studies that compare re-analysis of data versus repeat sequencing.

The applicant suggested that, if re-analysis is supported, the allowance be capped at two.

Population 3

Cascade testing for first-degree family members of children would be offered, but only for the specific causative genetic abnormality identified in the proband (i.e. not WEA).

Rationale

Patients with childhood syndromes may present with a number of different clinical features, due to the heterogeneous nature of monogenic syndromes that present in early childhood. Patients may present quite early (i.e. after birth) - or may even be recognised in utero as a consequence of prenatal ultrasound or other imaging studies - with specific or nonspecific features, or symptoms may manifest later in childhood, following a period of apparently normal development. The symptoms may be severe, and patients may be presented (usually by parents/guardians) directly to hospital emergency departments, and become inpatients, or they may be stable and referred from the community for assessment by a paediatrician or specialist clinic.

Where a clinical diagnosis can be made, but the molecular cause is genetically heterogeneous, or in cases where features overlap several known conditions, repeated genetic tests may be requested (with the most likely candidate gene being first screened, followed by sequential testing of other candidates over a period of time). In some cases, this lack of molecular diagnosis can result in an incorrect clinical diagnosis persisting, with inaccurate information provided in regard to recurrence risks and missed opportunities in specific therapies or disease surveillance.

Firstly, the proposed service should be indicated for detection of genetic variants in patients with a phenotype suspected to be due to a mendelian (single-gene) disorder, after exclusion of those who exhibit features likely to be caused by a known single gene/simple genetic defect amenable to straightforward testing, and those whose features suggest a non-monogenic disorder.

Secondly, a multidisciplinary team must approve eligibility of a patient for initial testing for childhood syndrome via the proposed service. The applicant indicated that the pre-test expert review panel appraisal (required for approval of whole exome analysis test) should include at least the following:

- Clinical geneticist with experience in interpretation of genomic test results, and who is not directly involved in the patient's care;
- Laboratory geneticist (a genetic pathologist or senior laboratory scientist with a fellowship of the Human Genetics Society of Australasia and/or Fellowship of the Faculty of Science (Royal College of Pathologists of Australia) from a laboratory with Next Generation Sequencing (NGS) expertise, accredited by the National Association of Testing Authorities (NATA);
- Other medical subspecialists (neurologist; metabolic physician) may be co-opted on a needs basis; and
- Genetic counsellor involvement on a needs basis.

For periodic re-analysis of the initial exome data, the applicant specified that re-analysis could occur at an interval not less than 18 months, as clinically indicated, and be capped at two.

The applicant argued that new disease genes are being identified on a regular basis and periodic re-analysis of original NGS could reveal the causative gene without the need to have to undertake a new round of NGS.

For cascade testing of family members, the strategy for selecting family members to undergo the sequencing and analysis will be influenced by the expected inheritance patterns (i.e. dominant or recessive) and whether other family members with and without similar features are available for phenotyping and genetic testing [1].

PASC considered that the average number of cascade tests per identified disorder should be capped at two. The applicant stated that, on average, the number of cascade tests was two per index case, but they believe there should not be a cap on number of cascade tests; they should just be limited to first degree relatives. Such testing may include siblings (including those under the age of 18 years), where such information would be important to help gather support for pathogenicity of the variant. However, PASC was concerned that, without a cap, it will be difficult to estimate impact (given a first degree relative could be tested every time there was a new syndrome-gene link, regardless of likely relevance). The issue of capping needs to be explored during the assessment phase.

Impact on family

The proposed service could provide a formal genetic diagnosis, with this ensuring children have timely access to treatments and symptom management pathways to alter the impact of the disease and avoid harmful treatments.

However, many patients may still not achieve a definitive diagnosis and the proposed service may possibly identify incidental findings (this is minimised if analysis is limited to known causative genes as proposed). This may cause concern for the patient and their families. Thus, consideration should be given to careful selection, testing and provision of genetic counselling.

Cascade testing would ensure families, who receive a definitive diagnosis, can access relevant support, plan for the future, make informed decisions about reproduction and access reproductive technologies, and has the potential to restore reproductive confidence in families.

Identification of the causative variant may provide accurate estimates of recurrent risk and facilitate preconception intervention or prenatal diagnosis for the affected patient or affected or at-risk relatives [1].

Estimates of the size of the testing population:

It may be difficult to estimate the number of patients likely to be eligible for initial testing of childhood syndromes (using whole exome analysis), due to the clinically and genetically heterogeneous nature of this group of disorders.

The applicant has estimated 200 new patients per year would be seen across Victoria. The applicant has also estimated that 500 patients (already being seen by Victorian clinical genetics services) would become eligible under the proposed population. The applicant has estimated an expected national prevalence of 2,000 patients. This does not factor in the population eligible for re-analysis (subsequent to not receiving a definitive diagnosis), which is estimated for up to 50% of the patient cohort, nor does it consider the volume of cascade testing in first-degree relatives.

Prior test (investigative services only - if prior tests are to be included)

For initial testing of proband, the applicant requested that patients receive genome-wide copy number assessment (i.e. microarray testing or equivalent technology) with an uninformative or non-diagnostic result before referral for the proposed service. After clinical assessment, if a monogenic syndrome is suspected and a genome-wide copy number assessment has been returned with uninformative or non-diagnostic findings, then whole exome analysis (WEA) would be considered as a diagnostic test for childhood syndromes.

The applicant specified that genome-wide copy number assessment by micro-array currently diagnoses between 10-20% of children presenting with the clinical features of the proposed population.

The applicant indicates that single/multi-gene testing achieved a diagnosis in 13% of their childhood syndromes infant cohort, compared with 58% diagnosis rate by WEA, hence a significant proportion of patients would require further testing beyond single/multi gene approaches. They suggest that the earlier in the diagnostic process that WEA is performed, the more clinically useful and cost-effective it becomes, rather than being used as a test of last resort.

Intervention

There are three interventions proposed for three different populations:

1. Whole exome analysis (WEA) for germline gene variants in children (<18 years) with undiagnosed suspected syndromic genetic disorder, including at least 2 of the following:
 - Single or multiple congenital abnormalities AND/OR
 - Dysmorphic facial features AND/OR
 - Intellectual disability.

Patients would be referred for testing by a clinical geneticist after a multidisciplinary team review (including a relevant paediatric sub-specialist). PASC noted that patients would have a prior microarray assay to exclude copy number changes.

2. Re-analysis of sequencing data (not before 18 months) for patients without a definitive diagnosis (estimated to be 50% of patients) as new genes are discovered and added to the

list, capped at two re-analyses.

3. Cascade testing for relatives (where definitive diagnosis has been made in the proband by WEA) using Sanger sequencing or suitable alternative approach.

Whole exome analysis

Exome sequencing consists of DNA sequencing that targets exons of all genes in the genome [1]. The exome is the component of the genome that predominantly encodes protein; these segments are referred to as exons and can include non-coding exons. The exome makes up about 1% of the genome, primarily exons of genes that code for proteins. To date, the exome is the component most likely to include interpretable mutations that result in clinical phenotypes. Whole exome sequencing (WES) is a next-generation sequencing strategy that isolates the majority of the protein-coding portion of the genome [1]. WES involves determination of DNA sequence of most of these protein-encoding exons, and may include some DNA regions that encode RNA molecules that are not involved in protein synthesis [4].

The applicant specified that the proposed whole exome analysis (WEA) service refers to analysis being performed only on the exonic regions of the genome, as this area of the DNA currently has the greatest evidence for clinical utility. They further specify that only genes known to be causative in monogenic syndromic disorders would be analysed, minimising the chance of incidental findings.

The applicant requests WEA to be delivered as one-off diagnostic test accessed through clinical geneticists, after multidisciplinary patient review. The multidisciplinary team must formally document approval regarding the patient's suitability for genetic testing. The applicant specified that the core personnel of the multidisciplinary team would include at least a clinical geneticist, a senior laboratory scientist/genetic pathologist and other medical subspecialists (on an as needed basis).

Pre-requisites for genetic testing for childhood syndromes

The applicant specified that a complete phenotypic assessment of a child with suspected syndromic disorder currently requires a variety of investigations being carried out which may include: urine, blood and CSF biochemical studies, imaging of brain and/or other organs, muscle and/or liver biopsies for histological and functional studies, molecular karyotype analysis by microarray, and/or specific candidate gene testing based on the clinical phenotype. It is proposed by the applicant that many of these investigations would not be routinely required if WEA were available. PASC noted that, if a monogenic disorder is suspected, an uninformative microarray assay would be required before WEA (to exclude copy number changes – not detected by WEA).

Patients should also undergo a thorough family history to assess whether there are similar or related phenotypes in other family members, as well as to evaluate and assess the inheritance pattern [1].

Genetic counselling

Patients and their families should have access to pre-test genetic counselling to ensure they have understood the implications, indications, and limitations of the test.

Patients and their families should be encouraged to maintain realistic expectations for finding the causative variant and understand that a positive result will not necessarily change treatment or improve the prognosis. Further, they should be advised that incidental findings unrelated to the reason for testing may be found and reported [1].

Patients' parents/guardians will need to sign an informed consent form including consent to who has access to the results given the implications for their relatives. Consultation may take place in private

practice or in the public domain. After the test, if a positive finding is made, further formal genetic counselling will be required (e.g. discussion of the results, reproductive options, risks to relatives and their screening).

It is important that patients and their families have access to genetic counselling prior to testing and once diagnosis has been confirmed. For first-degree and second-degree family members, it may be important to also provide genetic counselling as they may themselves be at risk of passing onto their future offspring. Pre-test genetic counselling should be provided by genetic counsellors and/or a clinical geneticist [3].

Delivery of the intervention

A paediatrician will often first see patients with symptoms as inpatients or in a clinic by referral from a community general practitioner. After an initial clinical assessment, the paediatrician is likely to refer the patient to one or more specialists depending on the clinical presentation of the child: clinical genetics, neurology and/or metabolic medicine.

After a clinical assessment, if a monogenic syndrome is suspected and a microarray has been returned with a non-diagnostic finding, WEA would be considered as a diagnostic test.

The patient would be approved by the multi-disciplinary team as suitable to receive WEA. Clinical geneticists will have the appropriate formal qualifications as genetic specialists to make the request for WEA and to provide guidance for the multi-disciplinary patient review meeting.

Once the request for WEA is made, the patient would be required to provide a sample or consent to the access of a stored sample for use in the test. DNA would be extracted from peripheral blood, and exome analysis would be performed. The applicant stated that, in some instances, other tissues or buccal swabs may be used (if laboratories have validated the use of alternative samples).

Initial analysis of the exome would include a targeted analysis of the candidate genes, as selected by the expert review panel approving the test. The laboratory would prioritise the analysis of any variations in these genes. Where there is no clear causative variant, the analysis of the full mendeliome may occur. The applicant agreed that the term 'mendeliome' is not in common use and its reference should be replaced by 'analysis being limited to variants in genes currently known to cause monogenic disorders'. Where a potential causative variant is found in either set of genes that cannot be ascribed definitive pathogenic status, a laboratory-driven multidisciplinary team review would occur.

The applicant specified that the multidisciplinary team in charge of the analysis should be comprised of laboratory geneticists/ genetic pathologists, and clinical geneticists with genomics expertise with appropriate input from a bioinformatician. Causation is determined by assessment of pathogenicity of individual variants based on internationally agreed criteria and correlation with patient clinical features.

The whole exome data would undergo detailed bioinformatics analysis, prioritised based on a list of genes where there is evidence of association with the phenotype under investigation. This gene list will be developed in consultation with clinical geneticists or other subspecialists.

Bioinformatics analysis

The applicant informed that gene lists are determined by the laboratory providing the testing. These lists are developed in conjunction with the requesting multidisciplinary team. For a gene to be included on these lists, pathogenic mutations in the gene must have been reported in peer-reviewed

literature (for at least two unrelated individuals with concordant clinical features), or in the case of a single patient or family, pathogenicity has been confirmed using a robust suite of functional studies, with veracity scrutinised through peer-reviewed literature.

Regulatory requirements

The applicant stated the proposed service could be provided in public hospital inpatient settings and outpatient clinics/consulting rooms. The applicant argued that some patients (such as neonatal patients born in private hospitals) may present as an inpatient private hospital patient.

The applicant specified that the National Association of Testing Authorities (NATA) and Royal College of Pathologists of Australasia (RCPA) would oversee regulation of whole exome sequencing and whole genome analysis for clinical purposes. Laboratories would need accreditation by a joint NATA/RCPA process (to ISO 15189), and be specifically accredited to provide genetic testing via massively parallel sequencing, with full whole exome analysis studies. This accreditation process covers technical aspects of the laboratory sequencing, analysis pipelines, curation (or interpretation) of results, and production of the report to a clinical standard. This allows any accredited laboratory to provide equivalent WEA services to a minimum standard. There are no requirements for use of specific manufacturer reagents, equipment or analysis pipelines.

An appropriately qualified laboratory geneticist would be responsible for overseeing WEA in the laboratory, and providing the clinical report that includes interpretation of results. The applicant stated that some laboratories may have the ability to sequence and capture all regions of the genome. The applicant does not intend to limit laboratories to performing exome sequencing only, and the decision to use more expensive technology to perform the same proposed service would not be expected to receive a higher reimbursement.

Currently, there are three diagnostic laboratories in Australia accredited to deliver equivalent services of WEA for diagnostic purposes. Other diagnostic laboratories are expected to become accredited to deliver equivalent services in the future.

Impact on clinical management

The outcome of the initial diagnostic testing by WEA could optimise medical management. Patients who receive a definitive diagnosis may have their management plan altered by either starting an additional treatment or have modifications to existing treatment regimens [2]. Patients may also receive additional surveillance for known complications of their condition or be discharged from surveillance based on an erroneous clinical diagnosis.

For relatives of patients diagnosed by WEA who receive cascade testing, a diagnosis may identify them as being at high risk of recurrence in future pregnancies [2]. This may also lead to further management initiated in these family members on the basis of the exome result.

Periodic re-analysis of the initial exome data

The applicant requested that provision should be made for future re-analysis of the initial whole exome data (in patients for whom a genetic diagnosis was not established with the initial WEA), as new disease genes associated with the phenotype in question are identified. Frequency of these is suggested at 18-20 month intervals. PASC noted that re-analysis would not occur before 18 months. In the instance that the result from initial WEA testing was negative, subsequent improvements in knowledge may lead to recognition that a previously uninterpretable variant (in a negative clinical diagnostic test result) is in fact pathogenic [1]. As new disease genes are identified, the genes lists will be expanded, allowing subsequent re-analysis of the initial whole exome data.

PASC noted the maximum number of rounds of re-analysis (that could occur) had not been stated. The applicant confirmed this is currently unknown, and acknowledged this is still in a gene discovery phase, that will plateau in time. PASC queried the utility gain of re-analysis, and the applicant confirmed re-analysis increases diagnosis by 10%, while recognising a limit is needed.

PASC noted the applicant did not initially support repeat sequencing WEA for population two (because it cannot currently be justified on cost-effectiveness grounds). The applicant suggested that (if repeat re-analysis is supported) the number of repeat re-analyses be capped at two. The applicant is unaware of any comparative evidence for re-analysis of data, versus a repeat of WEA test.

Cascade testing of first-degree relatives

The applicant is also requesting a separate MBS item number for cascade testing of first-degree relatives. The applicant noted that a Sanger sequencing or a suitable alternative approach will be taken using an assay specific for the variant that has been identified through WEA.

Clinical usefulness

A definitive molecular diagnosis will facilitate informed prognosis, disease management, recurrence risk counselling; and genetic testing of at-risk family members [4].

Early and accurate diagnosis at birth or in children with childhood syndromes may open a window of opportunity for early intervention. It is particularly valuable to identify additional associated features of clinical syndromes before they become symptomatic, to prevent or ameliorate the manifestations and to minimize the diagnostic evaluation of new symptoms [3].

For family members, cascade testing would provide clarification of reproductive risks. It would also determine the carrier status of parents for a presumed autosomal recessive, autosomal dominant or X-linked disorder; determine whether other first degree relatives are affected; exclude parental mosaicism for disorders that are presumed to be de novo mutations; and provide additional evidence for pathogenicity.

Identifying the variant that is the cause of a previously undiagnosed syndrome may lead to a specific treatment or management strategy that dramatically changes the clinical outcome [1]. In some cases, the results of the clinical diagnostic testing might not change clinical management, treatment or prognosis, but it may end the diagnostic odyssey and thus avoid an expensive, potentially invasive clinical diagnostic pathway[1]. The applicants are proposing that WES should be used as a first-line sequencing test for infants in order to considerably shorten and simplify the diagnostic process by enabling diagnostic testing to occur at a much earlier point and eliminating sequential testing of candidate genes.

Comparator

Comparator for whole exome analysis (population 1)

The applicant stated there is no direct comparator to the whole exome analysis diagnostic test proposed for initial testing of the proband. The applicant proposed ongoing periodic clinical review and further testing as the nominated comparator against initial WEA; i.e. standard of care. The variety of genetic testing services may include sequential single-gene testing, as well as multigene panel testing.

The applicant described current standard of care for children with suspected syndromes as regular reviews by multiple sub-specialists for diagnostic purposes.

Comparator for re-analysis (population 2)

The comparator for re-analysis is no re-analysis and standard care with ongoing reviews and further testing as clinically indicated. The applicant noted that where a definite diagnosis cannot be made, patients would be reviewed periodically in the hope that further phenotypic features would emerge over time to enable a diagnosis, or with new knowledge a genetic diagnosis becomes apparent. For some childhood syndromes, clear phenotypic features may develop relatively quickly (i.e. by 18 months of age; e.g. Kabuki syndrome). For other, the diagnostic clinical features may only manifest in late childhood to early adolescence. Such an individual would be liable to multiple rounds of testing until a genetic diagnosis is established. Thus, ongoing review by clinical genetics services would be required for the amount of time that it takes for definitive features to manifest in patients with suspected monogenic syndromes. With ongoing clinical reviews, there may also be provision of further testing, such as: tissue biopsies for histology and functional studies; brain and other imaging; repeated rounds of blood, urine or CSF collections for biochemical screening; electrophysiological studies; molecular karyotype (microarray analysis) and single gene testing.

Comparator for cascade testing (population 3)

The applicant suggested the appropriate comparator for cascade testing in first-degree family members (of a proband diagnosed via WEA) should be assessment of families via cascade testing where diagnosis was made through standard means.

Reference standard

PASC noted there is no clear reference standard. Sanger sequencing for multiple single genes appears to be an unrealistic standard; WGS is an immature standard and not demonstrated as superior. The applicant stated WGS provides 5% increase in detection of variants over WES, but is considerably more expensive. The applicant added that the published reference states the cost of whole exome analysis is approximately 30-40% of whole genome analysis (McRae JF, Clayton S, Fitzgerald TW *et al*: Prevalence and architecture of *de novo* mutations in developmental disorders. *Nature* 2017; **542**: 433–438). This statement reflects the difference in underlying technology to generate the data, and the added complexity of analysing a genome compared to an exome. The cost of exome analysis regardless of underlying technology (WGS or WES) is identical - it is the cost of generating the data that differs (currently ~\$1250 for WES, compared to ~\$1950 for WGS for generation of data only).

Outcomes

The following efficacy and safety outcomes are relevant to populations 1 and 2:

Analytic validity:

- Sensitivity
- Reproducibility

Clinical efficacy:

- Diagnostic yield
- Time to definitive diagnosis
- Change in clinical management – provision of effective treatment to delay onset or halt progression of disorder, ineffective treatments ceased, modifications of current treatment regimens; Improved surveillance of known complications of disorder, discharge from surveillance (for incorrect clinical diagnoses)

Safety outcomes:

- Avoidance of adverse events due to invasive interventions such as tissue biopsies, MRI scans; most of which would require a general anaesthetic in the paediatric population
- Possible harm associated with incidental findings (limited by restricting gene analysis)

Quality of life measured with: Carroll and Downs and the HUI23 utility measures for children and AQL8D for parents

Social and economic impacts:

- Relationship, family finances, future planning

Health care resources:

Testing

- The additional cost of performing WEA testing
- The cost of re-analysis (multiple times) if initially non-diagnostic
- The cost of cascade testing for first-degree family members
- The potential reduced utilisation and cost of testing (i.e. reduced the number of genetic tests performed compared to WEA only)
- Cost per definitive diagnosis made

Treatment

- The cost of treating the identified disorder including ongoing patient monitoring, e.g. physician visits
- The cost of genetic counselling
- The potential reduced utilisation of any therapeutic options resulting from altered, improved and targeted clinical management

The following efficacy and safety outcomes are relevant for population 3:

Clinical efficacy:

- Diagnostic yield
- Time to definitive diagnosis
- Restoration of reproductive confidence

Healthcare resources:

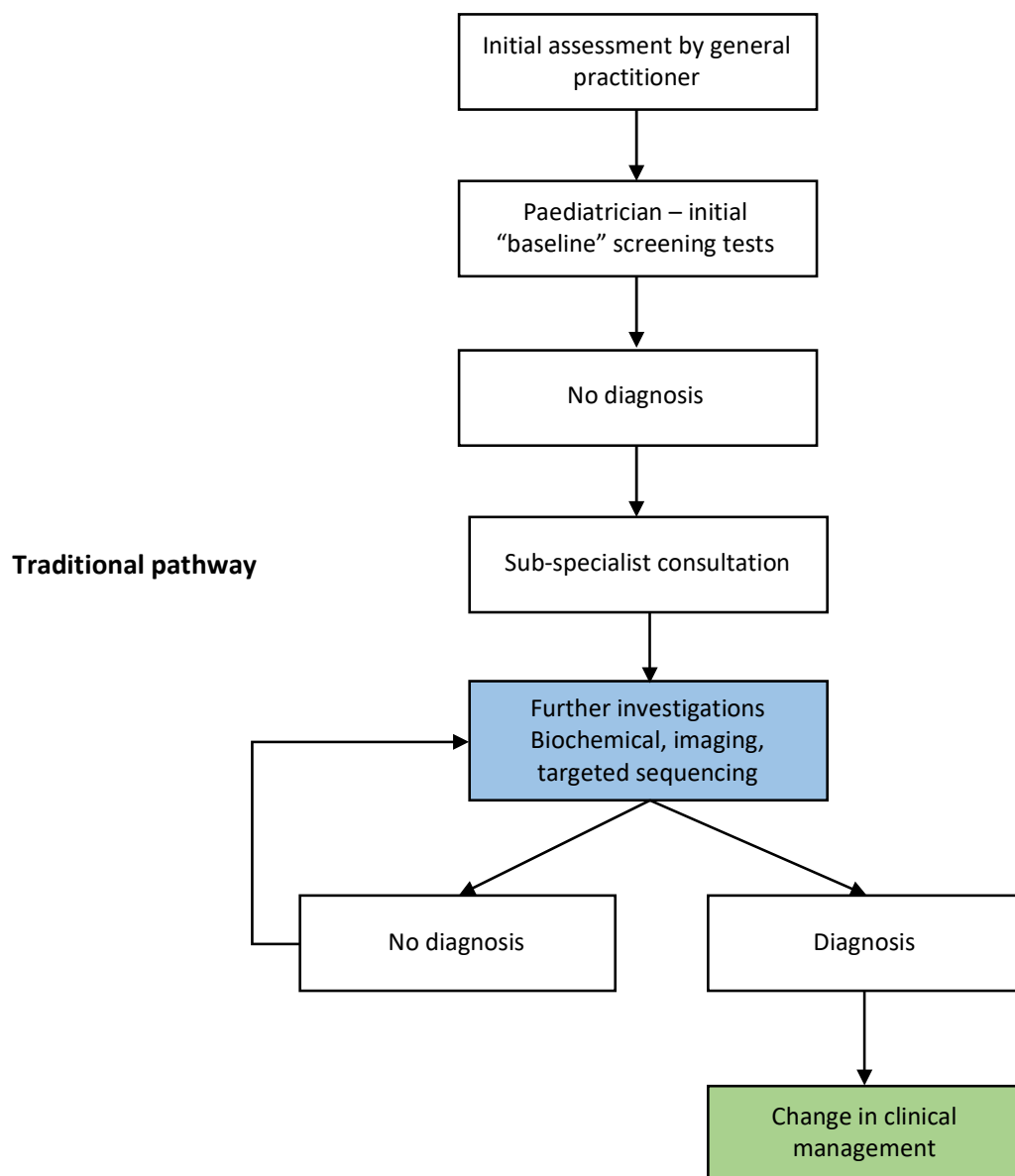
- Cost of cascade testing family members

[Current clinical management algorithm for identified population](#)

Currently, there is no single, standardised genetic test for childhood syndromes. The first treatment option for patients with childhood syndromes consists of standard care, which may involve a number of genetic tests.

The current clinical management algorithm is presented in Figure 1.

Figure 1: Current clinical algorithm for the diagnosis of childhood syndrome

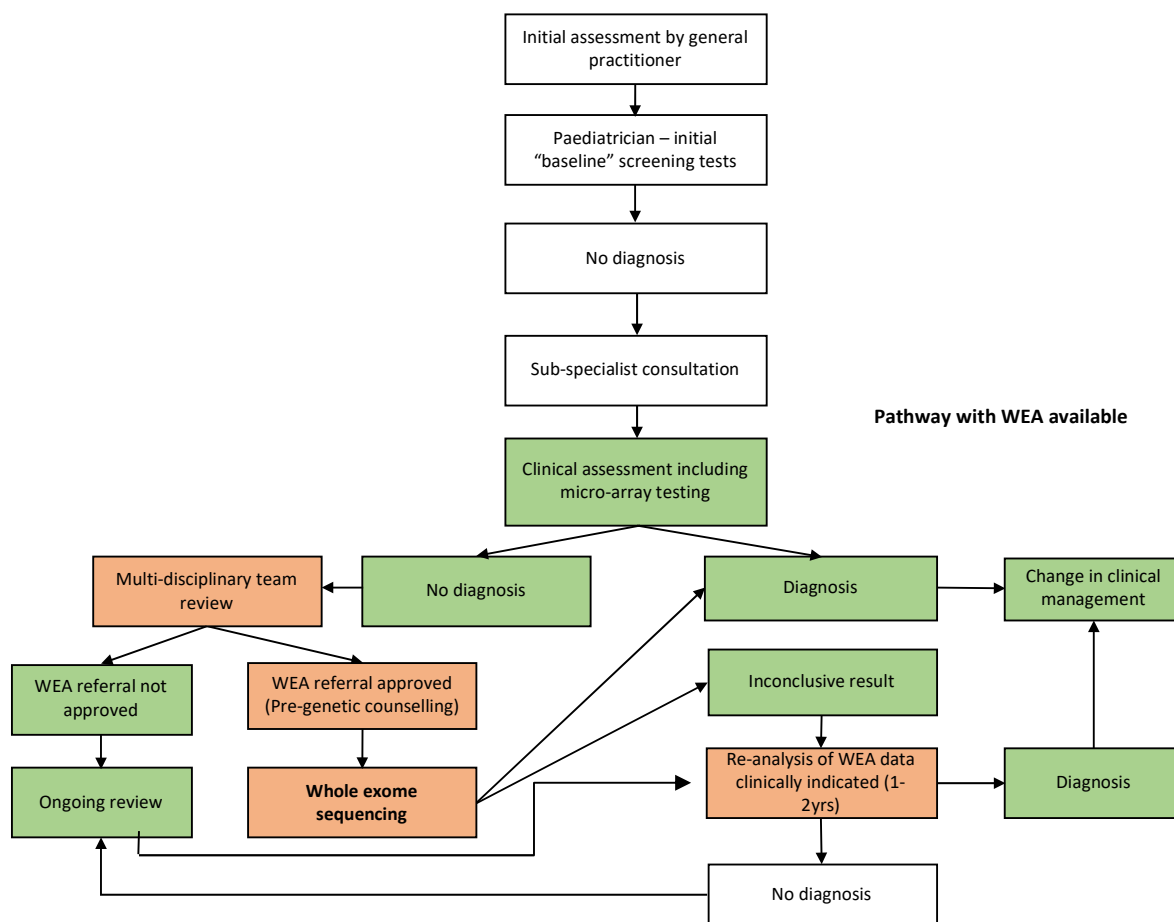


Proposed clinical management algorithm for identified population

Should WEA testing become MBS-funded, it is expected that patients who receive a specific genetic diagnosis would have an altered management plan that consisted of a more targeted treatment plan (with informative genetic counselling). For many, this would end the diagnostic odyssey and allow symptomatic treatment.

The proposed clinical algorithm, with WEA testing available, is presented in Figure 2.

Figure 2: Proposed clinical algorithm for the diagnosis of childhood syndrome



PASC noted (in the standard care pathway) that 14% of cases will have a diagnosis.

PASC noted (in the proposed pathway) that 58% of cases will have a diagnosis, following WEA. PASC queried whether a multidisciplinary team (MDT) is required for each re-analysis, noting the applicant’s response that the clinical geneticist would determine (on a case-by-case basis) if the MDT would need to be re-consulted.

PASC suggested including the feedback loop for re-analysis in the proposed pathway.

Proposed economic evaluation

The clinical claim proposed by the applicant is that genetic testing via WEA in patients suspected of childhood syndromes is superior to standard care.

The applicant stated the overall claim is ‘superiority’, for which a cost-effectiveness analysis could be conducted.

PASC considered there are challenges identifying incremental value of the proposed intervention and the following questions need to be answered:

- Population one: What is the clinical utility and cost effectiveness of whole exome analysis (WEA) for monogenic syndromic childhood disorders [as an early component of the diagnostic algorithm] as opposed to standard care?
- Population two: What is the clinical utility and cost effectiveness of re-analysis of whole exome data for monogenic syndromic childhood disorders (after non-diagnostic initial result at least 18 months prior) compared to standard follow-up care?
- Population three: What is the clinical utility and cost effectiveness of cascade testing of first degree relatives of patients diagnosed with a monogenic childhood syndrome via WEA, compared to testing following diagnosis made by standard means?

The applicants have agreed to provide further information on clinical utility and cost-effectiveness for all three populations (proposed MBS items), compared to standard diagnostic care.

PASC advised that current funding of genetic testing via State-based clinical genetic testing services had not been considered, and data should be sought on the current average cost of achieving a diagnosis via whatever means. The applicant has agreed to provide (at the assessment stage) further information on the cost of achieving diagnosis through standard means within the childhood syndromes cohort, including a break-down of State versus Federal costs.

PASC deliberated on the most suitable funding mechanism for genetic tests (in order to: minimise out-of-pocket costs for patients; maintain downward pressure on private and public pricing; and maintain affordability for hospitals/governments). PASC considered whether the extra resources needed for the proposed intervention should be funded through the MBS, or via a pooled-funding arrangement. Currently, most testing occurs in the public system, but this varies between States. PASC noted an RCPA survey that demonstrates patient out-of-pocket expenses for genetic testing ranges from 2% in one State, to 50% in another. PASC expressed concern that MBS funding might encourage the lower charging States to increase their out-of-pocket costs for patients.

The applicant commented that a large number of patients are in situations where no funding is available for WEA, and at least MBS rebates would increase equity and affordable access across States/Territories. The applicant advised that the Department of Health has commissioned the Royal College of Pathologists of Australasia to identify genetic and genomic tests currently being performed in each State/Territory, including current expenditure and cost. Results may not be available in the shorter term.

[Proposed MBS item descriptors](#)

The applicant proposed MBS item descriptors for: provision of WEA for affected individuals; re-analysis of WEA; and cascade testing of family members. The items would be listed in the Genetics section of the Pathology Services Table. PASC suggested (and the applicant agreed) that the term 'mendeliome' is not in common use and its reference should be removed from this application: it means [all] genes previously linked to single gene disorders – which is not the same as whole exome. The applicant suggested alternative wording: 'analysis limited to variants in genes currently known to cause monogenic disorders'.

PASC suggested four separate MBS item descriptors as follows:

MBS item number: AAAAA

Characterisation of germline variants via whole exome analysis, from a phenotypically driven gene list where analysis is limited to variants in genes currently known to cause monogenic disorders, requested by a clinical geneticist following multidisciplinary review and non-informative microarray testing for copy number alteration, in a patient (<18 years old) with a strong suspicion of a monogenic syndrome based on the following criteria:

Onset of clinical features prenatally, in infancy or childhood, and a minimum of two of the following features:

- Dysmorphic facial appearance, and/or
- Single or multiple congenital anomalies, and/or
- Intellectual disability.

MBS Fee: \$2,400.00

Benefit: 75% = \$1,800.00 85% = \$2,040.00

MBS item number: BBBB1

Re-analysis of whole exome data obtained under item AAAAA, at an interval of not less than 18 months, for characterisation of new germline gene variants related to the clinical phenotype, in a patient (<18 years old) with a strong suspicion of a monogenic syndrome, where re-analysis identifies new variants requiring curation.

MBS Fee: \$650.00

Benefit: 75% = \$487.50 85% = \$552.50

MBS item number: BBBB2

Re-analysis of whole exome data obtained under item AAAAA, at an interval of not less than 18 months, for characterisation of new germline gene variants related to the clinical phenotype, in a patient (<18 years old) with a strong suspicion of a monogenic syndrome, where the re-analysis is negative.

MBS Fee: \$350.00

Benefit: 75% = \$262.50 85% = \$297.50

MBS item number: CCCCC

Request by a specialist for the detection of a single gene variant, in a first degree relative of a patient with a known monogenic syndrome where previous genetic testing performed under item AAAAA or BBBB1 has identified the causative variant.

MBS Fee: \$400.00

Benefit: 75% = \$300.00 85% = \$340.00

Proposed relevant explanatory notes: Testing must be performed in laboratories that have received National Association of Testing Authorities (NATA) accreditation.

Other issues

PASC noted the shortage of genetic counselling services and the impact this may have in delaying treatment options. PASC noted increases in workforce demand (caused by MBS changes) can be raised/escalated by jurisdictions through COAG processes.

PASC agreed equity of access is an issue, and genetic testing is a very resource-intensive and complicated process. PASC commented that funding via the MBS would not guarantee an absence of out-of-pocket expenses, and may in fact worsen cost implications for patients in some States (decreasing access to the service). PASC advised that wider discussion is required about whether funding these services through the MBS is the most efficient funding mechanism, compared to alternative funding models. PASC advised that MSAC may make recommendations for public funding that are broader/alternative to the MBS.

References

1. Biesecker, L.G. and Green, R. C., *Diagnostic clinical genome and exome sequencing*. The New England Journal of Medicine, 2014. **370**: p.2418-2425.
2. Stark, Z., et al., *A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders*. Genetics in medicine, 2016. **18**(11): p. 1090-1096.
3. Iglesias, A., et al., *The usefulness of whole-exome sequencing in routine clinical practice*. Genetics in medicine, 2014. **16**: p.922-931.
4. Hamilton, A., et al., *Concordance between whole-exome sequencing and clinical Sanger sequencing: implications for patient care*. Molecular genetics and genomic medicine, 2016. **4**(5): p.504-512.