MSAC Application 1793

Diagnostic genomic testing for fetal anomalies

# PICO Confirmation

Applicant: PreGen National Implementation Consortium

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

Table 1 PICO for whole genome/exome sequencing for fetal anomalies: PICO set 1

| Component | Description |
| --- | --- |
| Population | Fetuses with a structural anomaly likely to have a single gene germline aetiology, detected on ultrasound  ± both biological parents (if available). |
| Prior tests | Fetal ultrasound for morphology with or without biometry  Chorionic villus sampling (CVS) or amniocentesis  Where relevant, maternal viral serology or assay, fetal MRI  Perinatologist +/- neonatologist specialist review |
| Intervention | Whole genome sequencing (WGS) only, or whole exome sequencing (WES) in addition to genome-wide microarray (GWMA) testing. This can include:   * Trio testing on a deoxyribonucleic acid (DNA) fetal sample from amniocentesis (typically after 16 weeks gestation) or CVS (11-14 weeks gestation), AND a sample from both biological parents; or * Fetal testing of the DNA sample obtained from amniocentesis or CVS only (when one or both biological parents are unavailable for testing)   Testing the fetal tissue is proposed in the following ways:   * + A combination of GWMA testing and WES (done in parallel), or   + WGS only (no GWMA testing) |
| Comparator | GWMA only |
| Reference standard | WGS interpreted with reference to a large genetic database of monogenic conditions e.g., ClinGen, OMIM, OrphaNet, PanelApp |
| Outcomes | Test information according to each test methodology and time-point   * Incremental diagnostic yield of monogenic conditions * Summary of additional diagnoses identified in the test population and their inheritance pattern * Proportion of diagnoses identified that are de novo * Incremental proportion of fetuses where prognosis is informed * Incremental proportion of fetuses where therapeutic intervention is informed * Time to diagnosis * Test turnaround times (TAT) * Rate of (i) fetal and (ii) parental incidental or secondary findings   Impact on clinical management   * Change in pregnancy management * Change in termination of pregnancy (TOP) rate * Change in treatment of the fetus when an informative genomic test diagnosis is made (earlier treatment, access to more personalised treatment) * Avoidance of unnecessary investigations and treatment after birth (e.g. the proportion of cases who would be testing for monogenic conditions under MBS 73358)   Health/pregnancy outcomes   * Quality of life of the parents * Rate of stillbirth / neonatal death * Miscarriage rates * Live births * Psychological impact from receiving a genetic test result or not (e.g. impact of finding an informative genomic result, or variant of uncertain significance (VUS), or no informative genomic test result, or impact of making a pregnancy management decision with, or in the absence of, an informative result)   Safety   * Physical harm from obtaining a sample for testing * Impact of fetal or parental incidental or secondary findings   Family utility   * Change in future reproductive decisions (e.g. preimplantation genetic testing or early diagnosis in future pregnancy) * Value of knowing (e.g. possibility for increased social support) * (Early) access to support programs/funding due to a diagnosis (e.g. National Disability Insurance Scheme, NDIS)   Cost-effectiveness   * Cost per incremental monogenic diagnosis provided   Other relevant considerations   * Acceptability of testing * Increased need for genetic counselling (e.g. after testing parents, after finding VUS) * Ethics of expanding genetic testing to WGS/WES in a prenatal setting * Avoidance of postnatal diagnostic odyssey due to earlier genetic diagnosis |
| Assessment questions | What is the comparative safety, effectiveness and cost-effectiveness of WES or WGS (in addition to or as a replacement to GWMA) versus GWMA alone in pregnancies where a structural FA likely to have a single gene germline aetiology has been found on ultrasound? |

Table 2 PICO for reanalysis of whole genome/exome sequencing data for fetal anomalies: PICO set 2

| Component | Description |
| --- | --- |
| Population | Child or fetus who had a fetal anomaly detected on ultrasound and was tested with WES/WGS prenatally (either with or without a diagnostic result) |
| Prior tests | WES/WGS |
| Intervention | Reanalysis of WES/WGS data |
| Comparator/s | No reanalysis of WES/WGS data |
| Outcomes | Test information   * Rate of repeat data analysis after WGS/WES * Yield of new diagnoses * Yield of new variant classification   Impact on clinical management   * Change in treatment * Avoidance of unnecessary investigations and treatment after birth   Safety   * Impact of fetal or parental incidental or secondary findings   Health outcomes   * Quality of life of the parents * Psychological impact from reanalysis or no reanalysis (e.g. impact of finding an informative genomic result, or variant of uncertain significance (VUS), or no informative genomic test result   Family utility   * Change in future reproductive decisions (e.g. preimplantation genetic testing or early diagnosis in future pregnancy) * Value of knowing (e.g. possibility for increased social support) * (Early) access to support programs/funding due to a diagnosis (e.g. National Disability Insurance Scheme, NDIS)   Cost-effectiveness   * Cost per incremental monogenic diagnosis provided * Cost per reclassification of variant pathogenicity   Other relevant considerations   * Acceptability of retaining sample/ genetic results in database for reanalysis |
| Assessment questions | What is the comparative safety, effectiveness and cost-effectiveness of reanalysis of the WES or WGS result versus no reanalysis, in a child (or fetus) who had a fetal anomaly detected on ultrasound and was tested with WES/WGS prenatally (either with or without a diagnostic result)? |

Table 3 PICO for cascade testing in close relatives of people with a pathogenic variant identified through whole genome/exome sequencing (after detecting a fetal anomaly): PICO set 3

| Component | Description | |
| --- | --- | --- |
| Population | For intervention: Biological first or second degree relatives of a proband with a familial monogenic disorder which was detected as a result of WES/WGS in a prenatal setting (through either trio testing or testing of fetal DNA) (either primary analysis or reanalysis of data) | For comparator: Biological first or second degree relatives of a proband who had a fetal anomaly detected on ultrasound, who did not undergo WES/WGS prenatally, and was diagnosed through other means to have a familial monogenic condition |
| Prior tests | For intervention: WGS/WES in fetus ± parents | For comparator: GWMA or diagnostic genetic testing in the proband |
| Intervention | Cascade variant-specific testing to determine the presence of (a) known familial pathogenic variant(s) | |
| Comparator/s | 1. No cascade genetic test 2. Cascade testing after fetus diagnosed with pathogenic/likely pathogenic variant by GWMA 3. Delayed cascade testing after child is diagnosed postnatally | |
| Reference standard | N/A | |
| Outcomes | Test information   * Uptake of cascade testing * Diagnostic yield   Impact on change in management   * Couples changing their reproductive decisions (e.g. in vitro fertilisation (IVF), preimplantation genetic diagnosis (PGD), donated oocytes or sperm) * Possible earlier detection and treatment of the condition (in cases where the prenatal test had an incidental finding for a (late-onset) condition)   Health outcomes   * Psychological impact of receiving a genetic test result or not (e.g. impact of finding a known germline pathogenic variant)   Safety   * Adverse events from obtaining a sample for testing   Cost-effectiveness   * Cost per pathogenic variant detected | |
| Assessment questions | What is the comparative safety, effectiveness and cost-effectiveness of variant-specific cascade testing in:  biological relatives of an individual with a familial monogenic condition which was detected as a result of WES/WGS in a prenatal setting (through either trio testing or testing of fetal DNA) versus   1. no cascade genetic testing or 2. cascade genetic testing after an individual is identified through GWMA or 3. delayed cascade genetic testing in biological relatives of an individual with a familial monogenic condition which was detected due to diagnostic testing postnatally? | |

## Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of diagnostic genomic testing for fetal anomalies was received from Neuroscience Research Australia by the Department of Health and Aged Care.

The application requested MBS listings for:

* Trio testing (of the fetus and both parents) using whole exome sequencing (WES)/ whole genome sequencing (WGS)
* WES/WGS of fetal deoxyribonucleic acid (DNA) (when biological parents are unavailable for testing)
* Reanalysis of WES/WGS data

Furthermore, during the Pre-PASC meeting the decision was made to also include:

* Cascade testing of biological relatives for a familial germline pathogenic or likely pathogenic (P/LP) variant after a monogenic condition is detected in the proband[[1]](#footnote-2)

The application states that genomic testing for fetal anomalies results in superior health outcomes compared to the comparator/standard practice.

## PICO criteria

### Population

#### PICO set 1: Affected individuals/cases[[2]](#footnote-3) (± parents)

The proposed intervention would be offered to pregnant women where a fetal anomaly (FA) has been found through fetal imaging (i.e. ultrasound and/or magnetic resonance imaging (MRI)), and where a single gene germline aetiology is suspected. DNA samples would be collected from (1) the fetus (through amniocentesis or chorionic villus sampling (CVS)), and (2) the fetus’ biological parents (if both biological parents are available for testing).

FAs could include significant brain, cardiac, renal or gastrointestinal anomalies, evidence of skeletal dysplasia, increased nuchal translucency in first trimester (>5mm), hydrops fetalis, ambiguous genitalia, fetal growth restrictions, or other significant anomalies. The application did not limit the population to a certain type of fetal anomaly. Severe FAs could result in fetal or neonatal death, or could lead to disease with severe morbidity and/or increased mortality. A brief description of common fetal anomalies diagnosed via ultrasound is shown in Table 4.

Table 4 Example fetal anomalies that can be diagnosed by ultrasound (Fiolna & McEwan 2023)

| Fetal anomaly | Description | Associated conditions |
| --- | --- | --- |
| Ventriculomegaly | A condition where the cerebral ventricular system is enlarged, due to cerebrospinal fluid (CSF) blockage, or poor growth of the cerebral cortex.  It is often diagnosed during an ultrasound in the second trimester. | Chromosomal abnormalities (e.g. T21, T18 or T13)  Structural brain abnormality  CMV, toxoplasmosis infection |
| Anencephaly | A condition where the upper part of the neural tube fails to close during early fetal development, leading to the incomplete formation of brain hemispheres (i.e. missing large parts of the brain). | Multifactorial aetiology  (linked to low folate intake) |
| Spina bifida | A neural tube defect which occurs when the neural tube fails to close properly during early fetal development. | T18  (linked to low folate intake, diabetes mellitus, and/or obesity) |
| Congenital diaphragmatic hernia | A rare (1 in 4000 births) birth defect that occurs when the diaphragm does not develop or close properly. This results in herniation of abdominal organs in the chest cavity. | T18, T13, rare single gene disorders  Cardiac and craniofacial defects |
| Gastroschisis | An abdominal wall defect (1 in 3000 births). An opening in the abdominal wall (usually to the right of the umbilical cord insertion) which causes the intestines (and in some cases other organs) to be outside of the body. | Usually isolated |
| Exomphalos | An abdominal wall defect (1 in 2000 births). Herniation of the abdominal organs due to a midline defect within the umbilical ring. | T13, T18  Beckwith-Wiedermann syndrome  Cardiac abnormalities |
| Congenital heart defects | Structural birth defects involving the heart. Some common types include atrial septal defect, ventricular septal defect, tetralogy of Fallot, transposition of the great arteries, and hypoplastic left heart syndrome. | T21, T13, T18  22q11 deletion (DiGeorge syndrome) |
| Hydronephrosis | The most common urinary tract abnormality (1 in 500 births), also called renal pelvis dilatation. It occurs when one or both kidneys become swollen due to buildup of urine. | Other renal abnormalities |
| Renal agenesis | The absence of a kidney. This can be unilateral (one in 2000 births), or bilateral (1 in 5000 births). The diagnosis is often suspected at the second trimester ultrasound. | Could be inherited (familial cause) however most cases are sporadic |
| Skeletal dysplasia | An umbrella term characterised by abnormal growth and development of bone and cartilage (1 in 4000 births) | Single gene disorders |
| Talipes | Lower extremity malformation (also known as ‘club foot’). Occurs in 1 in 1000 births. | T13, T18  Spina bifida  Oligohydramnios/uterine crowding  Neuromuscular disorders |

CMV = cytomegalovirus; CSF = cerebrospinal fluid; T13 = Trisomy 13 (i.e. Patau syndrome); T18 = trisomy 18 (Edwards syndrome), T21 = trisomy 21 (i.e. Downs syndrome)

It has been estimated that approximately 2-5% of pregnancies will have a detected fetal anomaly on ultrasound (Wou et al. 2018). There were 286,998 registered births in 2023, which was a decrease of 4.6% from 2022[[3]](#footnote-4). It is difficult to estimate the number of pregnancies terminated due to FAs. The reported number of surgical abortions in 2017-2018 (for any reason) was 67,546 (13.2 per 1000 women) (Keogh, Gurrin & Moore 2021).   
Based solely on the number of births in Australia, it is estimated that 5,740 – 14,350 (2-5%) pregnancies would have an FA on ultrasound. It was reported that around 3% of babies born in 2017 in Australia had a congenital anomaly. This equates to around 8,400 babies born. Congenital anomaly is defined as a wide range of atypical bodily structures or functions that are present at or before birth, e.g. neural tube defects, heart defects, cleft lip/palate, or chromosomal abnormalities such as Down syndrome (Australian Institute of Health and Welfare (AIHW) 2024).

*PASC noted that there were two different methods used to estimate the size of the population, either based on epidemiology (the proportion pregnancies affected by fetal anomalies, applied to the Australian birth rate), or by assessing the use of MBS items for amniocentesis or CVS (required to get samples for GWMA/WES/WGS). PASC noted that the two methods resulted in considerably different utilisation estimates ranging from approximately 300-1,000 patients/year using the MBS item usage based method and approximately 2,296-5,740 patients/year using the epidemiological method (both methods assuming a test uptake of 50% as proposed in the application for the first year). PASC noted that the application (using the MBS item usage based method) estimated that 495 patients will utilise the proposed testing in the first year. PASC noted that using MBS item statistics would likely underestimate the entire population eligible for WES/WGS, as the MBS statistics data do not capture the number of patients who would currently be tested using GWMA in the public health system, some pregnancies may be terminated, and not all patients choose to undergo testing.*

If an FA is found on ultrasound, the patient would be referred to a specialist obstetrician or a clinical geneticist, who would refer the patient for further imaging (to understand the extent of the anomaly if not already performed) and where indicated, genetic testing and counselling. If the parents decide to undergo genetic testing, chorionic villus sampling (CVS) or amniocentesis will be done to collect fetal DNA. Currently GWMA would be done to diagnose the fetal anomaly.

The PreGen study provides funded genomic testing in three laboratories in Australia for families who have fetal anomalies identified through ultrasound in pregnancy. Some of the exclusion criteria for this study include (but are not limited to); (1) the process of termination of pregnancy (TOP) has begun or the family decided to have a TOP no matter what is reported on genomic testing; (2) Likely non-genetic or undiscoverable aetiologies including teratogenesis, viral infections, and poorly controlled maternal diabetes; (3) Recognised syndromes/ malformation complexes with no known gene associations (Pentalogy of Cantrell/ limb body wall complex/ cloacal anomalies/ field defects); (4) Apparently isolated anatomical cardiovascular defect with low diagnostic rates on prenatal genomic testing (such as ASD, VSD, PDA); and (5) Isolated mild unilateral or bilateral ventriculomegaly without other cerebral malformations[[4]](#footnote-5).

*The applicant comments on the pre-PASC PICO confirmation requested removal of the requirement for testing to occur only in cases where a decision has not yet been made to proceed to termination of pregnancy. PASC supported the omission of this restriction.*

#### PICO set 2: Population for reanalysis

Reanalysis of the WES/WGS data may be done if additional clinical factors/signs are found, which may suggest a[n additional] diagnosis, or if more information on possibly pathogenic/likely pathogenic variants becomes available (allowing for a specific diagnosis). In the proposed item descriptor, the application proposed that reanalysis should be available once during pregnancy, and once after birth. Reanalysis would be available for the same population as the initial test (i.e. irrespective of the initial test result).

*PASC noted that there were no estimates for the likely use of reanalysis (PICO set 2) or cascade testing (PICO set 3) included in the PICO confirmation. PASC requested that the applicants provide estimates for the likely re-analysis rate and cascade testing rate.*

*PASC suggested that a possible means of estimating the potential reanalysis rate was to use the rate of non-diagnostic results after the initial WGS or WES plus GWMA (i.e. approximately 65% of those tested based on PreGen March 2025 update[[5]](#footnote-6)), as well as considering the proportion of cases where additional clinical features suggested a[n additional] diagnosis after the 2nd trimester ultrasound, and the proportion of cases where additional clinical features suggested a[n additional] diagnosis after birth.*

#### PICO set 3: Biological relatives at risk of having a child with the same syndrome/anomaly

When a specific monogenic condition is diagnosed following diagnostic genomic testing for fetal anomalies, at-risk biological relatives could be eligible for cascade testing for the familial pathogenic/likely pathogenic variant. This includes:

* adults (e.g. aunts and uncles) for the purposes of reproductive decision making/family planning purposes. This also includes the biological parent of the fetus if singleton prenatal WES/WGS was done due to the other biological parent being unavailable for testing.
* Siblings who may be less severely affected or unaffected (however may be carriers)
* The fetus in a subsequent pregnancy

Note, if the means of detecting the proband is incorporated into the description of the population for PICO set 3, then the population description for those who receive cascade testing after the intervention (i.e. family members of a proband detected through prenatal WES/WGS) will differ from the population description for those who receive the comparator (i.e. family members of a proband detected without WES/WGS).

*PASC requested estimates of the number of at-risk relatives per proband, and the proportion of eligible relatives who accept genetic testing. PASC noted that as of the March 2025 update of the PreGen study, 58% of variants identified were de novo, and 42% were inherited. PASC suggested the use of cascade testing be estimated by (PICO 1 population) x (diagnostic yield for prenatal genomic testing for monogenic condition) x 0.42 x (average number of at-risk relatives per proband) x (proportion of eligible relatives accepting genetic testing).*

### Intervention

#### PICO set 1: Prenatal testing

The proposed intervention is whole exome sequencing (WES) in combination with genome-wide microarray (GWMA), or whole genome sequencing (WGS), in those pregnancies where a fetal anomaly is detected.

One of the proposed item descriptors is for trio testing. Trio testing is an approach where the DNA of the fetus/child and both parents are sequenced and compared, to identify likely pathogenic variants. Segregation analysis plays an important role in trio testing, as it helps to identify whether a variant found in the child is inherited from the parents or whether it is a de novo variant.

WGS is the process of determining the entire DNA sequence of an organism’s genome. This includes both coding and non-coding regions[[6]](#footnote-7). Next-generation sequencing (NGS), originally referred to as massive parallel sequencing (MPS), refers to the field of genomics where large amounts of DNA or RNA are sequenced at once (unlike traditional Sanger sequencing, which sequences one DNA fragment at a time) (Bagger et al. 2024). NGS allows for high-throughput WGS by generating large amounts of data. The costs of NGS have significantly decreased over the last few years, due to advancements in second-generation chips and developments in chemistry.

Where WGS refers to sequencing the entirety of the genetic information, which includes around three billion base pairs, WES only focuses on an estimated 1% of the genome (around 30 million base pairs coding for proteins) (Reilly et al. 2023). WES is the process of sequencing only the protein-coding regions for the genome (i.e. the exons). NGS can also be used to do WES. WES is not designed for copy number variant (CNV) detection and may not be as sensitive for this as other methods like GWMA or WGS.

WES is therefore proposed to be used parallel to GWMA. Conversely, WGS would replace the use of GWMA due to it showing equivalent accuracy for finding aneuploidy and copy number changes. It is expected that in the future, (once availability is broader, and costs are reduced) WGS will become the genetic test of choice.

WES/WGS require a sample of fetal DNA, typically collected through CVS or amniocentesis. When WES/WGS is done on the parents of the fetus, a blood sample would be taken for testing. In Australia, WGS and WES are available in laboratories accredited by the National Association of Testing Authorities (NATA) in conjunction with the Royal College of Pathologists of Australasia (RCPA), with ISO 15189 standards. They also must implement a robust quality management system (QMS) to ensure consistent and reliable results[[7]](#footnote-8).

Test results are interpreted in the context of the fetus’ clinical presentation and family history. A report is then generated summarising the findings. Genomic databases like ClinGen, OrphaNet, OMIM and PanelApp can enhance the interpretation of WES/WGS results by providing an up-to-date resource for identifying relevant genes and gene variants. As of March 2025, PanelApp Australia reports a fetal anomalies panel comprising 1454 genes with a known genotype-phenotype relationship relevant to this application.

*In the application, it was proposed that for those with fetal anomalies detected on first trimester ultrasound, the intervention would be GWMA followed by WGS/WES if no anomalies are found on GWMA. PASC noted that in the applicant response to the pre-PASC PICO confirmation, the request was to remove GWMA as a pre-requisite test. PASC confirmed that the intervention should be changed to be either WGS alone, or WES plus GWMA (done in parallel, without GWMA being used as a triage test). Concurrent WES and GWMA or earlier WGS would result in some cases being diagnosed earlier, that could allow the use of less-invasive methods of TOP to be performed, if needed. Furthermore, the applicant noted that 3-5% of fetuses may have more than one monogenic condition, and therefore testing using both GWMA and WES would increase the probability of diagnosing multiple monogenic conditions. PASC noted that GWMA plus WES would enable combined copy number variant (CNV) and sequence variant detection, with a diagnostic rate of approximately 35-40%. PASC noted that WGS is not widely available outside of a research setting, although noted from the applicant that it is expected to be the preferred method in the future. WGS may detect both CNV and sequence variants with a diagnostic rate of approximately 40%.*

*PASC noted that the analysis of WES/WGS data would be restricted to a large virtual panel of genes known to be associated with FAs (e.g. PanelApp Australia has a Fetal Anomalies virtual panel with 1454 diagnostic grade genes [V.1.321]), and that this would reduce the likelihood of incidental findings being detected, and allows improved variant curation efficiency, reducing turnaround time (TAT).*

#### PICO set 2: Reanalysis

In the context of genetic testing, reanalysis refers to the practice of reevaluating and reinterpreting previously obtained genetic sequencing data. WES/WGS data may need to be reanalysed due to:

* New discoveries in genomic knowledge. Discoveries regarding the pathogenicity of variants and their associations with different diseases lead to a need to reanalyse previously sequenced data.
* Clinical relevance. If the individual’s clinical condition changes or shows new symptoms, or new family history data suggest a genetic condition, reanalysis of the WES/WGS data may be done to find a genetic cause that was missed in the initial analysis.
* Advances in analysis tools. Improved bioinformatics tools, analysis techniques and algorithms could increase accuracy and sensitivity of detecting variants.
* Family planning. Individuals could decide to reanalyse the data when they are planning to have biological children, to determine whether they are at risk of passing on any serious genetic conditions.

The American College of Medical Genetics and Genomics (ACMG) states that for fetal WES/WGS with non-diagnostic results, reanalysis could be considered if a new phenotype develops after birth, if a subsequent pregnancy is planned, or if a significant amount of time has passed since the testing was performed (12 months, or at the discretion of the laboratory). They discuss that every laboratory should have a defined policy and protocol regarding reanalysis and the release of an updated report (Monaghan et al. 2020).

In stakeholder discussions held for MSAC 1476 (Genetic testing for childhood syndromes), it was noted that the pace of innovation meant that a WES would be reliable for reanalysis for 5 years (beyond which, the sequencing should be performed again).

Best et al. (2024) investigated clinical practice in laboratories in Australia, and found that no laboratories had formal and specific guidelines or policies regarding reanalysis. Reanalysis of sequencing data was mainly done based on individual clinical requests. Four of seven (57%) laboratories reported that they had performed reanalysis due to new discoveries or advances in analysis tools, or rectifying errors (initiated by the laboratory itself). Regarding who was able to request reanalysis of data; all laboratories indicated they accepted requests by the original referring clinician or other clinicians involved in the patient’s care. Some of the laboratories also accepted requests by genetic pathologists or researchers (Best et al. 2024).

Reanalysis is currently a heavily manual process, however automation of this process is widely anticipated (Best et al. 2024). Automation of the WES/WGS data reanalysis would lead to improved equity in diagnostic (and possible health) outcomes. Currently, reanalysis of sequencing data is underutilised in Australia (Best et al. 2024). Individual practice is highly inconsistent regarding the initiation, timing and process of reanalysis. Even though automation of reanalysis could lower a number of barriers (e.g. workforce capacity, process issues), a number of challenges still exist regarding automating the reanalysis process (e.g. unknown consent process, how to update clinical information, lack of trust in the automatic pipeline, unknown laboratory workforce implications and skills shortage, limitations in clinical workforce capacity and implications when informing the patient of the results, ensuring the report is received by the clinician who can action it, lack of a national process for recontacting patient/families) (Fehlberg, Stark & Best 2024).

When a variant is reclassified, EuroGentest have suggested that the laboratory is responsible for reissuing the diagnostic report and for recontacting the patient (Vears et al. 2018).

*PASC noted that a reanalysis would be prompted in pregnancy when a new phenotype is identified or when the original phenotype progresses. PASC noted that a reanalysis would be prompted after birth (either live births or still births and products) if a new phenotype is identified (that was not identified through ultrasound analysis).*

*PASC queried how long the reselection of new virtual panels, reanalysis and reporting would be expected to take, and queried whether there was sufficient time available during the pregnancy to undertake a reanalysis for a specimen collected after the 2nd trimester ultrasound (18-22 weeks) followed by the initial WES/WGS analysis (4 weeks).*

#### PICO set 3: Cascade testing

##### Biological relatives at risk of having a child with the same syndrome/anomaly

Variant-specific cascade testing may be undertaken to identify individuals with the specific genetic variant that has already been identified in a family member using diagnostic genomic testing for fetal anomalies. Once a specific pathogenic/likely pathogenic variant has been identified (e.g. through trio testing), at-risk biological relatives could be tested specifically for that variant. The methods used would be chosen based on what type of variant was identified in the proband.

Cascade testing could be done when the pathogenic/likely pathogenic variant is determined to be hereditary, and when the family member is considered to be at risk to have a child with the same syndrome/anomaly. This could help the family member make informed decisions and plan for the future.

In rare cases, WGS/WES may have found a familial pathogenic/likely pathogenic variant unrelated to the FA (i.e. an incidental finding) which could lead to a condition that may manifest later in life (e.g. BRCA1, Lynch syndrome). The National Pathology Accreditation Advisory Council (NPAAC) state that incidental findings must only be reported if consent from the parents has been received to receive incidental findings, and that the laboratory must use techniques aimed at minimising the likelihood of identifying incidental findings[[8]](#footnote-9). If an incidental finding is identified and reported, cascade testing could also be done in at-risk biological relatives to allow for early detection and treatment of these conditions.

*PASC noted that the intervention for PICO set 3 was cascade testing of family members for the specific likely pathogenic/pathogenic variants identified through PICO set 1 or 2. PASC noted applicant’s advice that incidental findings would only be reported in rare cases, and that laboratories have clear guidelines on when this should occur (such as if incidental findings would alter the management of the child in the first months of neonatal life). As such, no cascade testing after the identification of incidental findings would be expected to occur.*

##### Subsequent pregnancies

Families who underwent WGS/WES for fetal anomalies and where a germline pathogenic/likely pathogenic variant was found could choose to do a variant-specific test in subsequent pregnancies, to determine whether their subsequent child is affected or is carrying the pathogenic/likely pathogenic variant.

### Comparator(s)

#### PICO set 1: Comparator to WES/WGS in affected individuals/cases (± parents)

The proposed comparator is GWMA only (no WES/WGS). *PASC agreed that the comparator is GWMA.*

Currently, a routine first trimester fetal anatomy scan is done at 11-14 weeks' gestation. This is followed by a routine second trimester fetal anatomy scan at 18-22 weeks' gestation. If a fetal anomaly is detected, the patient is referred to a specialist obstetrician or feto-maternal specialist, along with a genetic counsellor or clinical geneticist. They would then request genetic testing to be done, which includes GWMA (in current practice, most major Australian laboratories have already replaced karyotyping for GWMA for prenatal diagnosis.) *PASC noted that GWMA has replaced karyotyping in most large laboratories.* The fetal sample, obtained through CVS or amniocentesis, is sent to a National Association of Testing Authorities (NATA)-accredited testing facility for molecular chromosome analysis. The results are compiled into a report, which is then sent to the referring clinician. This clinician discusses the findings with the family, often in consultation with a clinical geneticist and genetic counsellor.

From July 2023 to June 2024, the MBS item 73388 for GWMA was requested 751 times (Table 5)[[9]](#footnote-10). With an estimated annual number of FAs on ultrasound of 5,740 – 14,350 (which equates to 2-5% of all pregnancies in Australia), the number of GWMAs requested was lower than expected. Clinical experts indicated that the primary reason for this discrepancy would be that many families currently go through State funded pathways. Other factors related to a low number of requests made could include (1) some families may not choose to have an invasive test; (2) those undergoing non-invasive prenatal screening (NIPS) may not choose to have a confirmatory test; (3) some families may have a miscarriage or choose TOP prior to invasive testing; or (4) there could be equity of access issues (families in remote/rural areas may have limited access to invasive testing). The intervention (WES/WGS) was proposed as an addition to the comparator (GWMA). However, as WGS becomes more commonly used, it is expected that WGS will eventually replace GWMA in a prenatal setting.

Table 5 Number of MBS requests made for GWMA

| **MBS item and use** | **Financial year** | | |
| --- | --- | --- | --- |
|  | **21/22** | **22/23** | **23/24** |
| MBS item [**73388**](https://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73388&qt=item&criteria=microarray): Analysis of chromosomes by genome‑wide microarray, of a sample from amniocentesis or chorionic villus sampling, including targeted assessment of specific regions for constitutional genetic abnormalities in diagnostic studies of a fetus, if (a) one or more major fetal structural abnormalities have been detected on ultrasound; or (b) nuchal translucency was greater than 3.5 mm  Applicable only once per fetus | 284 | 679 | 751 |

Source: http://medicarestatistics.humanservices.gov.au/statistics accessed on 27 February 2025

#### PICO set 2: Comparator to reanalysis of WES/WGS

The comparator of reanalysis of the WES/WGS data is “no reanalysis of the data”. In the absence of reanalysis of the WES/WGS data it would be an option to do diagnostic testing on a new DNA sample. This would be a secondary comparator for the purpose of the assessment.

*The HTA group had suggested that the secondary comparator to reanalysis was retesting on a new DNA sample. In their pre-PASC response, the applicant noted that testing a new sample (as opposed to data reanalysis) is extremely infrequent, and therefore would not be a feasible comparator. PASC confirmed that the comparator to reanalysis should be no reanalysis.*

#### PICO set 3: Comparator to cascade testing following identification of pathogenic/likely pathogenic variant through WES/WGS prenatally

The main comparator to cascade testing following identification of a heritable pathogenic/likely pathogenic variant from WES/WGS identified in the proband prenatally is suggested to be no cascade testing in family members. *PASC noted that there were two comparators to cascade testing after WES/WGS: either no cascade testing, or cascade testing of family members after a postnatal diagnosis of a monogenic condition.*

However, some cascade testing may occur in the absence of WES/WGS, due to a pathogenic/likely pathogenic copy number variant having been identified through GWMA in the proband. Alternatively, depending on the condition diagnosed in the proband, there may be (delayed) cascade testing after the birth and clinical diagnosis of the proband (clinical diagnosis may occur some time after birth, such as after detection of developmental delay). Currently there are MBS items allowing for cascade testing for biological family members of suspected monogenic conditions (MBS item 73363) and some other conditions (e.g. MBS item 73417, 73423, 73443, 73462). Cascade testing after postnatal diagnosis may therefore be considered a secondary comparator.

### Reference standard (for investigative technologies only)

The reference standard is a test that is used to determine the presence or absence of the target condition or clinical information of interest. Ideally, the reference standard is the best available, clinically accepted, error-free procedure to do so. In this case, WGS and interpretation using a large genomic database such as PanelApp is considered to be the reference standard. In the absence of this information, the accuracy of the proposed test itself would need to be demonstrated by direct from test to health outcomes evidence showing a health benefit from use of the test.

*PASC noted that the reference standard is WGS and interpretation using a large genomic database.*

*PASC noted that the applicant stated they had direct test to health outcomes that would be included in the Applicant Developed Assessment Report.*

### Outcomes

Although the most-common outcome reported on the benefit of WES/WGS testing after FAs are identified is the incremental diagnostic yield, in order to be supported by MSAC for MBS funding, the value of the service should be assessed in terms of health improvements, such as quality of life or quality-adjusted life years gained. The clinical value needs to reflect the entire tested population, and the consequences of receiving a negative or inconclusive result and prolonged waiting for a result should be considered (MSAC Stakeholder meeting – Genetic Testing in Childhood syndromes – 19 October 2018).

#### PICO set 1: Outcomes for WES/WGS for fetal anomalies

*PASC confirmed that the outcomes were appropriately defined for PICO set 1, 2 and 3.*

Test information related outcomes, according to each test methodology and time-point

* Incremental diagnostic yield of monogenic conditions
* Summary of additional diagnoses identified in the test population
* Proportion of diagnoses identified that are *de novo*
* Incremental proportion of fetuses where prognosis is informed
* Incremental proportion of fetuses where therapeutic intervention is informed
* Time to diagnosis
* Test turnaround time
* Rate of (i) fetal and (ii) parental incidental or secondary findings

Safety

* Physical harm from obtaining a sample for testing (from CVS or amniocentesis), e.g. miscarriage, infection, bleeding
* Impact of fetal or parental incidental or secondary findings

Impact on clinical management

* Change in pregnancy management
* Change in TOP rate
* Change in treatment of the fetus when an informative genomic test diagnosis is made (earlier treatment, access to more personalised treatment)
* Avoidance of unnecessary investigations and treatment after birth

Health/pregnancy outcomes

* Quality of life of the parents
* Rate of stillbirth / neonatal death
* Miscarriage rates
* Live births
* Psychological impact from receiving a genetic test result or not (e.g. impact of finding an informative genomic test result, or variant of uncertain significance (VUS), or no informative genomic test, or impact of making a pregnancy management decision in the absence of an informative result)

Family utility

* Change in reproductive decisions (e.g. preimplantation genetic testing or early diagnosis in future pregnancy)
* Value of knowing (e.g. possibility for increased social support)
* (Early) access to support programs/funding (e.g. National Disability Insurance Scheme, NDIS)

Cost effectiveness

* Cost per incremental monogenic diagnosis provided

Other relevant considerations

* Acceptability of testing
* Increased need for genetic counselling (e.g. after testing parents, after finding VUS)
* Ethics of expanding genetic testing to WGS/WES in a prenatal setting
* Avoidance of postnatal diagnostic odyssey due to earlier genetic diagnosis

#### PICO set 2: Outcomes for reanalysis

Test information

* Rate of repeat data analysis after WGS/WES
* Yield of new diagnoses
* Yield of new variant classification

Impact on clinical management

* Change in treatment
* Avoidance of unnecessary investigations and treatment after birth

Safety

* Impact of fetal or parental incidental or secondary findings

Health outcomes

* Quality of life of the parents
* Psychological impact from reanalysis or no reanalysis (e.g. impact of finding an informative genomic result, or VUS, or no informative genomic test result)

Family utility

* Change in future reproductive decisions (e.g. preimplantation genetic testing or early diagnosis in future pregnancy)
* Value of knowing (e.g. possibility for increased social support)
* (Early) access to support programs/funding due to a diagnosis (e.g. NDIS)

Cost-effectiveness

* Cost per incremental monogenic diagnosis provided
* Cost per reclassification of variant pathogenicity

Other relevant considerations

* Acceptability of retaining sample/ genetic results in database for retesting

#### PICO set 3: Outcomes for cascade testing

Test information

* Uptake of cascade testing
* Diagnostic yield

Impact on change in management

* Couples changing their reproductive decisions (e.g. in vitro fertilisation [IVF], pre-implantation genetic diagnosis [PGD], donated oocytes or sperm)
* Possible earlier detection and treatment of the condition (in cases where the prenatal test had an incidental finding for a (late-onset) condition)

Health outcomes

* Psychological impact of receiving a genetic test result or not (e.g. impact of finding a known germline pathogenic variant)

Safety

* Adverse events from obtaining a sample for testing
* Psychological effects of positive or negative test results, compared to no test information

Cost-effectiveness

* Cost per pathogenic variant detected

## Assessment framework (for investigative technologies)

The application made a clinical claim of superiority, with ‘a significantly increased diagnostic rate’ as the rationale. Clinical claims of superiority typically require evidence of improved health outcomes. However, this can be challenging with prenatal tests, as some pregnancies may be terminated, resulting in the ‘patient’ never being born. To prove superiority in this case, evidence should be provided that the information provided from the proposed test (WES/WGS) will alter decision-making and/or clinical management (e.g. termination of pregnancy, change in treatment, earlier access to treatment, avoidance of unnecessary investigations).

A graphical representation of each step in the linked evidence analysis is shown in the assessment framework below. Each step is an evidentiary requirement and corresponds to an assessment question.

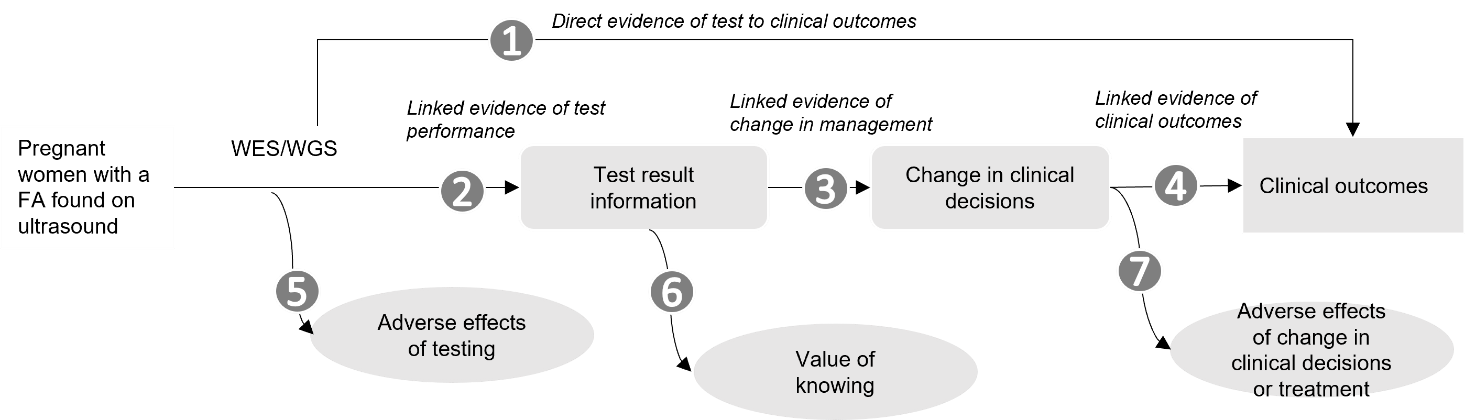


Figure 1 Assessment framework showing the links from the test population to clinical outcomes for WES/WGS of the fetus/trio testing

Figure notes: 1: direct from test to health outcomes evidence; 2: test performance; 3: change in management; 4: influence of the change in management on clinical outcomes; 5: adverse events due to testing; 6: No change in clinical management: value of knowing; 7: Potential harm due to change in management

1. What is the comparative safety, effectiveness and cost-effectiveness of WES or WGS (in addition or as a replacement to GWMA) versus GWMA alone in pregnancies where a structural FA likely to have a single gene germline aetiology has been found on ultrasound?
2. What is the incremental diagnostic yield of WES/WGS compared with GWMA in pregnancies where a FA has been found on ultrasound?
3. Do results of WES/WGS lead to a change in management compared with results from GWMA alone? (e.g. TOP rate, change and timing of treatment, avoidance of unnecessary investigations)
4. Does a change in management lead to a change in clinical outcomes (e.g. quality of life of the parents, pregnancy outcomes, neonatal outcomes)?
5. What is the comparative safety of WGS/WES + GWMA vs GWMA alone?
6. Will the information generated as a result of WGS/WES be of additional value even if there is no change in management (i.e. the value of knowing)? (e.g. psychological impact, impact on reproductive planning, access to support programs or funding)
7. Are there any harms from change in management? (e.g. psychological harms for the parent)

Assessment framework showing the links from the test population to clinical outcomes for reanalysis of WES/WGS results


Figure 2 Assessment framework showing the links from the test population to clinical outcomes for reanalysis of WES/WGS results

Figure notes: 1: direct from test to health outcomes evidence; 2: test performance; 3: change in management; 4: influence of the change in management on clinical outcomes; 5: adverse events due to testing; 6: No change in clinical management: value of knowing; 7: Potential harms due to change in management

1. What is the comparative safety, effectiveness and cost-effectiveness of reanalysis of the WES or WGS result versus no reanalysis, in a child (or fetus) who had a fetal anomaly detected on ultrasound and was tested with WES/WGS prenatally (either with or without a diagnostic result)?
2. What is the incremental diagnostic yield of reanalysis of WES/WGS results compared to not reanalysing results in children or fetuses who had a fetal anomaly detected on ultrasound and were tested prenatally?
3. What is the impact on clinical management when WES/WGS results are reanalysed (compared with no reanalysis) in children or fetuses who had fetal anomaly detected on ultrasound and were tested prenatally?
4. Does a change in management lead to a change in clinical outcomes (e.g. quality of life of the parents, pregnancy outcomes, neonatal outcomes)?
5. What is the comparative safety of reanalysis of WGS/WES data vs no reanalysis?
6. Will the information generated as a result of reanalysing WGS/WES data be of additional value even if there is no change in management (i.e. the value of knowing)? (e.g. psychological impact, impact on reproductive planning, access to support programs or funding)
7. Are there any harm from change in management? (e.g. psychological harm for the parent)

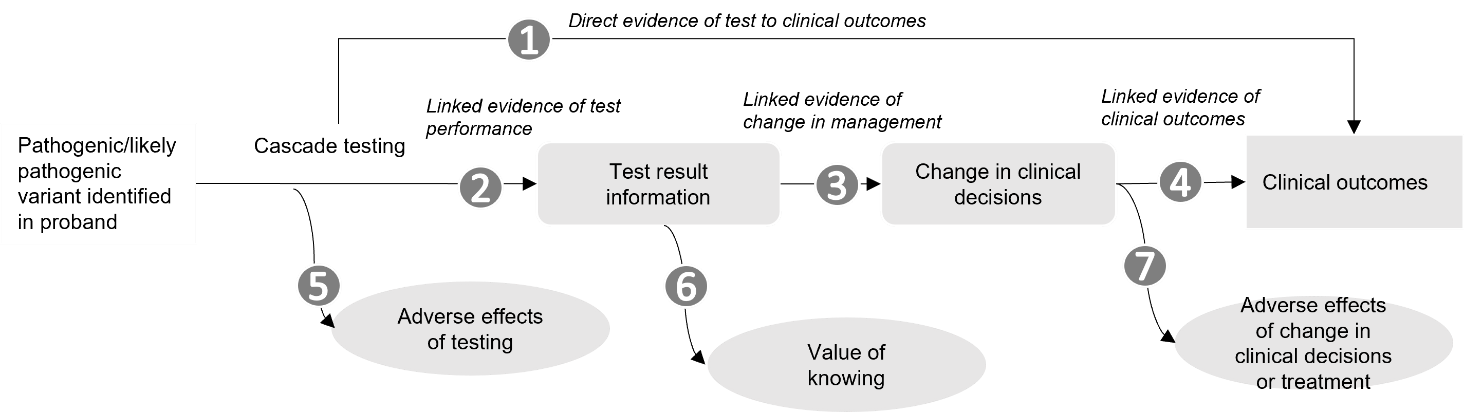


Figure 3 Assessment framework showing the links from the test population to clinical outcomes for cascade testing

Figure notes: 1: direct from test to health outcomes evidence; 2: test performance; 3: change in management; 4: influence of the change in management on clinical outcomes; 5: adverse events due to testing; 6: No change in clinical management: value of knowing; 7: Potential harm due to change in management

1. What is the comparative safety, effectiveness and cost-effectiveness of variant-specific testing versus no genetic testing or delayed cascade testing in biological relatives of an individual with a familial monogenic condition which was detected as a result of WES/WGS in a prenatal setting (through either trio testing or testing of fetal DNA)?
2. What is the diagnostic yield of variant-specific testing to determine the presence of a familial pathogenic/likely pathogenic variant in biological relatives of a patient with an identified pathogenic/likely pathogenic variant? *(this may be calculated based on mendelian inheritance patterns, rather than requiring evidence).*
3. Is there a change in management in individuals who undergo variant-specific testing?
4. Does change in management after cascade testing lead to a change in health outcomes? (e.g. psychological impact of genetic testing or no genetic testing)
5. What is the safety of variant-specific testing vs no testing?
6. Will the information generated as a result of variant-specific testing be of additional value in biological relatives of individuals with an identified pathogenic/likely pathogenic variant?
7. Are there any harm from change in management? (e.g. psychological harm for the parent)

*PASC noted the assessment questions for the three PICO sets.*

## Clinical management algorithms

### Current clinical practice

The current clinical management algorithm is shown in Figure 4. It shows the tests and investigations currently in use in the identified population, shown in the blue boxes. Outcomes are shown in the red boxes. Currently, pregnant women who are diagnosed with a FA on ultrasound can choose to forego invasive testing, followed by either a continuation or termination of pregnancy. The other option would be to undergo CVS or amniocentesis (based on the gestation of the pregnancy) to obtain a DNA sample from the fetus. This sample would then be used for GWMA, where a pathogenic variant may or may not be detected. If a pathogenic/likely pathogenic variant is detected, the parents could decide to either terminate the pregnancy or continue the pregnancy (with a diagnosis and a possible treatment/management plan). If the pathogenic/likely pathogenic variant found is germline and not *de novo*, biological relatives who are planning to have children could be eligible for cascade testing (variant-specific testing) to assist with reproductive decision making. In some cases (in cases where incidental findings show a significant risk of a serious condition which manifests later in life), biological relatives could be tested to see if they carry the same pathogenic variant, which could then lead to earlier detection and treatment of this condition.

When no pathogenic/likely pathogenic variant is found, or one or more VUSs are detected, women could decide to either terminate the pregnancy (e.g. if the fetal anomalies are considered to be too severe) or continue the pregnancy (without knowing whether the fetal anomaly is caused by the variant).

If GWMA identifies a monogenic condition that is likely hereditary, then the proband’s relatives may undergo cascade testing. It is also possible that if the pregnancy is continued, and clinical features prompt genetic testing after the child is born, and a pathogenic/likely pathogenic variant is identified, then cascade testing of family members may occur at this point.

*PASC noted that the applicant had provided edits to the current clinical management algorithm, clarifying that GWMA alone would most often diagnose a chromosomal disorder, and sometimes a monogenic disorder. Cascade testing would occur in cases where a germline pathogenic or likely pathogenic CNV is found. The applicant advised that GWMA has replaced karyotyping.*

### Proposed clinical practice

The proposed intervention (WES/WGS) would be done after a diagnosed fetal anomaly on (1) first trimester ultrasound at 11-14 weeks gestation, or (2) second trimester ultrasound at 18-22 weeks gestation. WES would likely be done in parallel to GWMA. The second option would be to do WGS only, and to forego GWMA, as it is claimed that WGS would be able to diagnose all variants which would be found GWMA (and therefore these tests would not need to be done). When WES/WGS shows a pathogenic/likely pathogenic variant and this variant is considered to be germline, biological relatives would be able undergo variant-specific testing for reproductive purposes. The options regarding continuation or termination of the pregnancy after finding no, one or multiple pathogenic variants remain the same. As reanalysis of the WES/WGS data may be done once during pregnancy and once after live birth if additional clinical factors/signs are found, which may suggest a[n additional] diagnosis, or if more information on in scope pathogenic/likely pathogenic variants becomes available, this is shown in the algorithm when VUS(s) is detected.

Cascade testing in biological relatives would then also be an option if the pathogenic/likely pathogenic variant is hereditary.

*The proposed algorithms in the pre-PASC PICO confirmation had shown that all patients with a FA on first trimester ultrasound would first receive a GWMA, and only those negative on the GWMA would receive WES or WGS. A separate algorithm had been provided where a FA was found on a second trimester ultrasound, to show either concurrent GWMA and WES, or WGS only. PASC noted that in their pre-PASC response the applicants provided a single updated proposed clinical management algorithm, that showed the approach used would not differ by gestational timing, and that all patients would receive either WGS only or WES plus GWMA (without using GWMA as a pre-requisite test).*

*PASC commented that the revised proposed algorithm showed that reanalysis after birth would only occur in cases where a prenatal reanalysis had occurred. PASC requested this be amended to also allow for a reanalysis of the WES/WGS data postnatally, in the absence of a prenatal reanalysis.*

The current clinical management algorithm on genetic testing and cascade testing (green box) after finding a fetal anomaly on ultrasound


Figure 4 The current clinical management algorithm on genetic testing and cascade testing (green box) after finding a fetal anomaly on ultrasound

aThis could be one or two variants of uncertain significance (VUSs). In some cases it could be one pathogenic variant and one VUS.

CNV = copy number variant; CVS = chorionic villous sampling; GWMA = genome-wide microarray; VUS = variant of uncertain significance

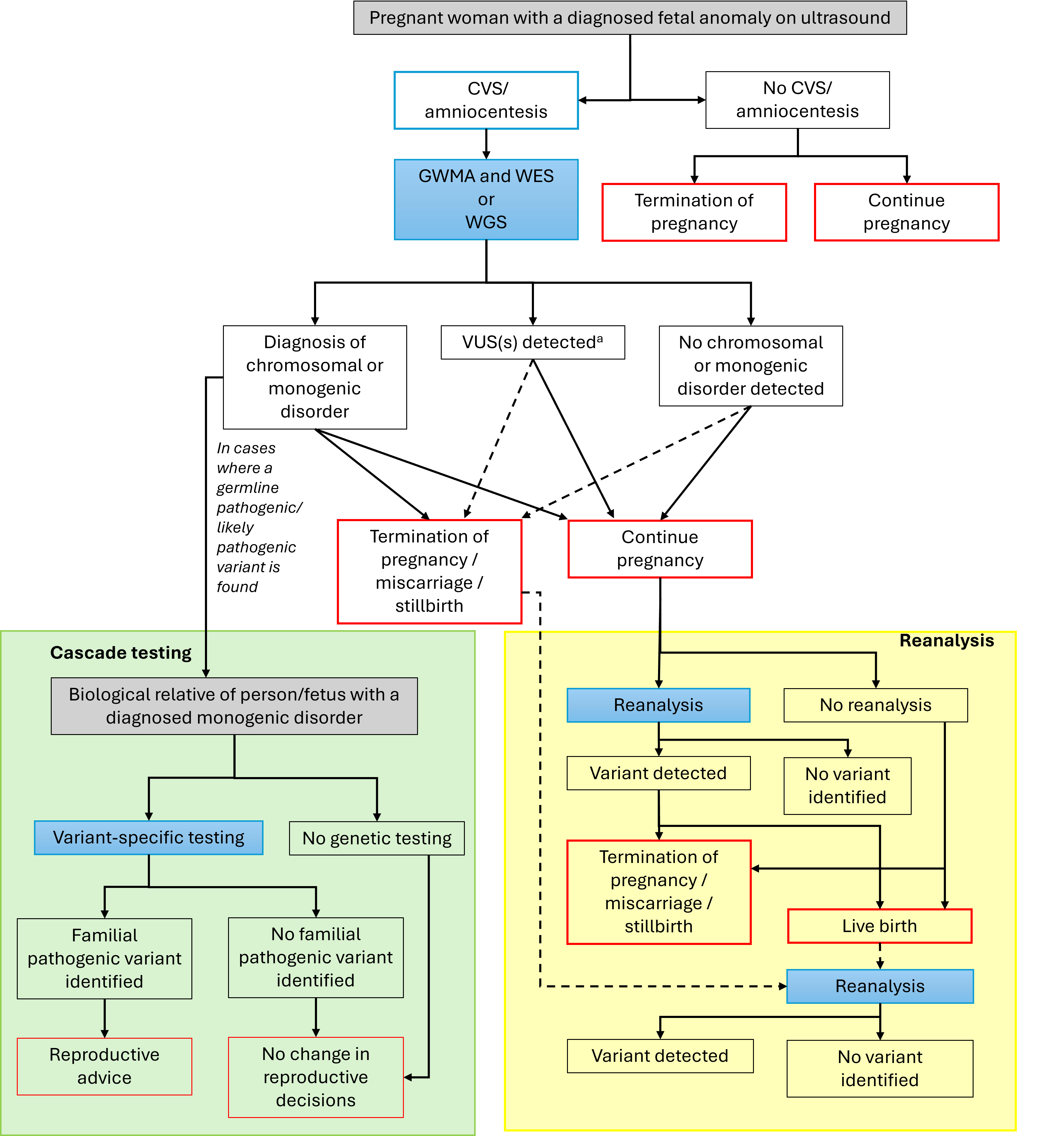


Figure 5 The proposed clinical management algorithm on genetic testing, reanalysis (yellow box) and cascade testing (green box) after finding a fetal anomaly on ultrasound

aThis could be one or two variants of uncertain significance (VUSs). In some cases it could be one pathogenic/likely pathogenic variant and one VUS.

CNV = copy number variant; CVS = chorionic villous sampling; GWMA = genome-wide microarray; VUS = variant of uncertain significance

## Other considerations

MSACs remit is to advise the federal health minister on whether a medical service, health technology or health program should be publicly funded, and what circumstances, if any, should apply to such funding based on an assessment of the comparative safety, clinical effectiveness, cost effectiveness and total cost using the best available evidence. However, they may also consider aspects such as ethical, patient and social considerations. The “Other relevant considerations” section of the assessment report could include consideration of issues such as:

* Informed consent
* Implications for life insurance
* Privacy and confidentiality issues
* Psychological stress
* Social stigmatisation
* Potential for discrimination
* Equity and access to testing and TOP if needed
* Availability of knowledge required for genetic counselling / access to genetic counsellors
* Other societal/ethical issues

*PASC noted that there were outcomes broader than the safety, effectiveness and cost-effectiveness of prenatal WES/WGS that were relevant for the assessment and should be included under “Other relevant considerations”.*

## Proposed economic evaluation

The application made a clinical claim of superior effectiveness. Considering the fact that WES/WGS uses the same DNA samples as GWMA, it is assumed that the comparative safety of WES/WGS and microarray is noninferior. Based on these assumptions, the appropriate economic evaluation would be a cost-effectiveness (or cost-utility) analysis.

The time horizon was proposed to be 3 months after birth. This is similar to the MSAC Assessment on Non-Invasive Prenatal Testing for trisomies (MSAC 1492 and 1574) that used the time horizon of the point of birth or termination of pregnancy or time of stillbirth. The time horizon of 3 months after birth allows for the costs associated with extended hospital stays.

Table 6 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

| Comparative safety- |  | Comparative effectiveness |  |  |
| --- | --- | --- | --- | --- |
| Inferior | Uncertaina | Noninferiorb | Superior |
| Inferior | Health forgone: need other supportive factors | Health forgone possible: need other supportive factors | Health forgone: need other supportive factors | ? Likely CUA |
| Uncertaina | Health forgone possible: need other supportive factors | ? | ? | ? Likely CEA/CUA |
| Noninferiorb | Health forgone: need other supportive factors | ? | CMA | CEA/CUA |
| Superior | ? Likely CUA | ? Likely CEA/CUA | CEA/CUA | CEA/CUA |

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

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

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

b An adequate assessment of ‘noninferiority’ is the preferred basis for demonstrating equivalence

It is assumed that reanalysis of WES/WGS data would also have a clinical claim of superior effectiveness and non-inferior safety. If sufficient data are available, a cost-effectiveness (or cost-utility) analysis would therefore be appropriate.

Likewise, it assumed that cascade testing following a WES/WGS identification of a germline pathogenic/likely pathogenic variant would be claimed to be superior to no cascade testing, and potentially superior to delayed cascade testing. If sufficient data are available, this use would likewise also benefit from a cost-effectiveness analysis (or cost-utility analysis).

*In the applicant comments on the pre-PASC PICO confirmation, it was suggested that the assessment would include the cost per case diagnosed (as the primary evaluation), and that utilities would also be provided. Given that utility data are available, PASC considered that a cost-utility analysis would be preferable over the cost per case diagnosed, as the former can capture a broader range of outcome measures, including the proportion of cases where the WES/WGS results altered management.*

*PASC noted from their pre-PASC response that the applicants considered a 3-month time horizon after birth appropriate.*

## Proposal for public funding

The application proposed 3 different items for funding through the MBS: (1) trio testing (either WES or WGS), (2) testing fetal DNA only (either WES or WGS), and (3) reanalysis of WES or WGS data obtained during (1) or (2). The assessment group presented the item descriptors as proposed by the applicants, with minor edits.

During the Pre-PASC meeting with the assessment group, the department suggested that there should be an additional MBS item for cascade testing of family members when a germline pathogenic/likely pathogenic variant is identified (Table 10). *PASC noted that 4 new MBS items were proposed (three proposed by the applicants, and one by the HTA group after input from the department). PASC suggested that the items proposed for singleton testing, trio testing and reanalysis should be amended to use the term “monogenic” rather than “Mendelian”, to be consistent with existing comparable items on the MBS.*

*PASC considered that WGS should not be used in conjunction with GWMA for the same indication, and that this should be specified in the item descriptors for singleton testing and trio testing. PASC queried whether separate items should be created for WES and WGS, so that co-claiming of WGS and GWMA could be restricted. The applicant’s clinical expert explained that there are rare cases where a GWMA may have been used after the first trimester ultrasound, and another abnormality on a second trimester ultrasound would trigger the use of WGS. PASC noted that this rare scenario would be for two different indications (i.e. one fetal anomaly detected at the 1st trimester ultrasound and another at the second trimester ultrasound) and agreed with the applicant that the item restrictions should not prevent clinically appropriate WGS testing.*

The application stated that currently, prenatal genomic testing is funded through a combination of research funding, State-based funding or it’s paid for by patients out-of-pocket.

The application proposed that a consultant obstetrician could request the test in consultation with a clinical geneticist OR a genetic counsellor practising in prenatal genetics and supervised by a clinical geneticist. Advice from the department was that genetic counsellors should be excluded from the MBS item descriptor (as genetic counsellors, as a profession, are not a recognised specialty under the National Registration and Accreditation Scheme).

*PASC suggested that for the proposed MBS items for singleton testing and trio testing (items AAAA and BBBB), any exclusion criteria which assist in determining patient eligibility should be added in an explanatory note.*

*PASC noted from the applicant that prenatal testing is typically processed urgently in laboratories, and that the TAT in the PreGen study was 2-3 weeks for WGS and 3-4 weeks for WES. PASC noted that in most clinical laboratories in Australia the TAT for WES is typically 6-12 weeks, and considered whether a maximum TAT should be specified in the descriptors of the proposed items. PASC considered that it would be difficult to incorporate a maximum TAT into the item descriptors, although noted that an appropriate recommendation relating to TAT could be included in quality assurance programs.*

The proposed fee for trio testing is $3,300.00 (Benefit: 75% = $2,475.00 85% = $3,197.60), which is consistent with trio testing under MBS 73457 (WGS/WES and mitochondrial DNA sequencing in those suspected of mitochondrial disease), but more expensive than trio testing under MBS 73359 (WES or WGS of germline variants known to cause monogenic disorders in children), which has a fee of $2,900 (Benefit: 75% = $2,175.00 85% = $2,797.60).

The proposed fee for singleton testing is $2,500 (Benefit: 75% = $1,875, 85% = $2,397.60), which is more expensive than both MBS items 73358 and 73456 (singleton testing for monogenic disorders, and singleton testing for mitochondrial disease), which both have a fee of $2,100.00 (Benefit: 75% = $1,575.00 85% = $1,997.60).

*PASC noted that the fees for singleton and trio testing were equivalent to the fees testing for monogenic conditions (MBS items 73358 and 73359, respectively) in conjunction with testing for maternal cell contamination.*

Victorian Clinical Genetic Services currently offers WGS and WES. They offer two options for WGS and WES (not specifically for fetal testing): a focused genome/exome test (1-400 genes) and a comprehensive genome/exome test (>400 genes +/- Mendeliome). The focused and comprehensive singleton WGS analyses currently cost $2,800 and $4,300, respectively; whereas the focused and comprehensive trio WGS analyses cost $5,900 and $7,400, respectively. WGS reanalysis is currently offered for $425. WES currently costs $1,800 and $3,100 for focused singleton and comprehensive singleton analyses, whereas focused trio and comprehensive trio testing costs $2,800 and $4,100, respectively.

Table 7 Proposed item descriptor for trio WGS/WES based on PASC advice

| Category 6 – Pathology services |
| --- |
| MBS item AAAA  Prenatal diagnostic testing by trio whole exome sequencing or trio whole genome sequencing on a DNA sample from an amniocentesis or chorionic villus sample and samples from the biological parents for fetal anomalies with a likely monogenic aetiology IF:  (a) both biological parents are available for testing; AND  (b) the characterisation is requested by:  (i) a consultant clinical geneticist, OR  (ii) a consultant obstetrician in consultation with a clinical geneticist; AND  (c) a single fetal anomaly has been identified by fetal imaging, may include (but not limited to):  (i) a significant brain anomaly  (ii) a significant cardiac, renal or gastrointestinal anomaly  (iii) evidence of skeletal dysplasia including unexplained short long bones under the 1st centile  (iv) an increased first trimester nuchal translucency 5mm or greater  (v) hydrops fetalis  (vi) ambiguous genitalia  (vii) fetal growth restriction: (1) unexplained small for gestational age, under the 1st centile, and (2) no other evidence of placental insufficiency  (viii) other significant single anomalies, OR  (d) multi-system fetal anomalies have been identified by fetal imaging; AND  (e) the characterisation is not performed in conjunction with item BBBB.  Applicable once per fetus. |
| Fee: $3,300 Benefit: 75% = $2,475, 85% = $3,197.60\* |

\* Reflects the 1 November 2024 Greatest Permissible Gap (GPG) of $102.40. All out-of-hospital Medicare services which have an MBS fee of $683.00 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

Table 8 Proposed item descriptor for singleton WGS/WES based on PASC advice

| Category 6 – Pathology services |
| --- |
| MBS item BBBB  Prenatal diagnostic testing by singleton whole exome sequencing or singleton whole genome sequencing on a DNA sample from an amniocentesis or chorionic villus sample, for fetal anomalies with a likely monogenic aetiology if:  (a) one or both biological parents are unavailable for testing; AND  (b) the characterisation is requested by:  (i) a consultant clinical geneticist, OR  (ii) a consultant obstetrician in consultation with a clinical geneticist; AND  (c) a single fetal anomaly has been identified by fetal imaging, may include (but not limited to):  (i) a significant brain anomaly  (ii) a significant cardiac, renal or gastrointestinal anomaly  (iii) evidence of skeletal dysplasia including unexplained short long bones under the 1st centile  (iv) an increased first trimester nuchal translucency 5mm or greater  (v) hydrops fetalis  (vi) ambiguous genitalia  (vii) fetal growth restriction: (1) unexplained small for gestational age, under the 1st centile, and (2) no other evidence of placental insufficiency  (viii) other significant single anomalies, OR  (d) multi-system fetal anomalies have been identified by fetal imaging; AND  (e) the characterisation is not performed in conjunction with item AAAA.  Applicable once per fetus. |
| Fee: $2,500 Benefit: 75% = $1,875, 85% = $2,397.60\* |

\* Reflects the 1 November 2024 Greatest Permissible Gap (GPG) of $102.40. All out-of-hospital Medicare services which have an MBS fee of $683.00 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter)

The fee of $500.00 for reanalysis is consistent with MBS 73458 (re-analysis of whole genome or whole exome or mitochondrial DNA obtained for testing for mitochondrial disorders) and MBS 73428 (re-analysis of whole genome or whole exome obtained for testing for neuromuscular disorders).

*PASC noted that the proposed fees for reanalysis and cascade testing items were consistent with other comparable reanalysis and cascade testing items on the MBS.*

Table 9 Proposed item descriptor for reanalysis of WGS/WES data based on PASC advice

| Category 6 – Pathology services |
| --- |
| MBS item CCCC  Re-analysis of whole genome or whole exome data obtained in performing a service to which item AAAA or BBBB applies, for characterisation of previously unreported germline variants related to the clinical phenotype, IF:  (a) the re-analysis is requested by:  (i) a consultant clinical geneticist, OR  (ii) a consultant obstetrician in consultation with a clinical geneticist; AND  (b) there is a strong clinical suspicion of a monogenic disorder affecting the fetus/newborn/infant; AND  (c) the re-analysis is requested in the event of new clinical information during the pregnancy or after the delivery  Applicable once in pregnancy and once postnatally |
| Fee: $500.00 Benefit: 75% = $375, 85% = $425 |

The MBS item descriptor DDDD was written by the assessment group. The proposed fee for the proposed MBS item DDDD was based on the fees for MBS items 73363, 73393, 73417, 73443 and 73462.

*PASC noted that as the ‘biological relative’ referred to was tested as a fetus, the wording of the proposed item descriptor will need to be examined further by the department to inform ESC/MSAC consideration.*

Table 10 Proposed item descriptor for cascade testing based on PASC advice

| Category 6 – Pathology services |
| --- |
| MBS item DDDD  Testing of a person (the person tested) for the detection of a single pathogenic/likely pathogenic gene variant for the purpose of reproductive decision making, if:  (a) The person tested has a biological relative with a known inheritable monogenic pathogenic/likely pathogenic variant; AND  (b) a service to which item numbers AAAA, BBBB, or CCCC applies has identified the pathogenic/likely pathogenic variant for the relative; AND  (c) a sample from a person tested has not previously been tested in relation to the biological relative for a service to which items AAAA or BBBB apply; AND  (d) the detection is requested by a consultant clinical geneticist  Applicable only once per variant per lifetime. |
| Fee: $400.00 Benefit: 75% = $300.00 85% = $340.00 |

*PASC advised out of session to include the term ‘likely pathogenic’ in the MBS item descriptor DDDD.*

## Summary of public consultation input

*PASC noted and welcomed consultation input from* *5 organisations and 28 individuals, 20 of whom were consumers and 8 were health professionals. The 5 organisations that submitted input were:*

* Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)
* Australasian Association of Clinical Geneticists
* Genetic Alliance Australia
* Through the Unexpected
* Australian Genomics

The consultation input received was all supportive of public funding for diagnostic genomic testing for fetal anomalies. The consultation input raised a number of concerns, predominately in relation to the need to increase support services including access to genetic counselling.

**Consumer Input**

Most of the consumers had accessed the genomic testing proposed in the application and those who had received results that included a genetic finding stated they would not have had answers or a diagnosis without access to the testing.

All of the consumers who had accessed the genomic testing were grateful for the additional information the testing provided, including when the results were negative i.e. did not provide a genetic finding or diagnosis. Having the additional information provided confidence to continue with the pregnancy for some families. Other families who had made the decision to terminate the pregnancy for medical reasons based on information from the fetal scans were grateful for the additional information from genomic testing, which in some cases influenced the decision to have additional children.

A consumer noted that many small or premature babies have an undiagnosed genetic condition, which parents end up finding out several years later after extensive testing during the baby’s lifetime. An early intervention and diagnosis can support parents and their children and prevent a diagnostic odyssey.

**Benefits and Disadvantages**

The main benefits of public funding received in the consultation input included that WES/WGS can identify genetic causes of fetal anomalies that would otherwise remain undiagnosed, providing additional information allowing families to make informed choices and access additional support. Consultation input stated that genomic testing is best practice, and that trio analysis could provide information on whether a genetic variant was inherited, allowing planning for future pregnancies. Consultation input also stated that early identification of genetic syndromes allows families and the medical team to prepare for lifelong care needs and early interventions. Through the Unexpected stated that the uncertainty of prenatal diagnosis can lead to poor psychosocial outcomes for parents that remain for many years, and that genomic testing can reduce the uncertainty and is valuable for coping and planning, including access to condition-specific support groups. Consultation input noted that knowledge of a genetic finding or a lack of such was considered meaningful and could provide mental closure for families.

The main disadvantages stated in the consultation input included concerns over delays to get test results, gaining timely access to genetic counsellors and limited access to testing and services in regional and remote areas. Organisational input highlighted the concerns over health inequities in prenatal diagnosis for people in rural and remote areas, from culturally and linguistically diverse (CALD) backgrounds and First Nations people in Australia. Genetic Alliance Australia and Australian Genomics stated that many families in these groups face systemic barriers to accessing genetic healthcare, including long wait times, financial constraints, communication and language barriers, poor continuity of care, and access to culturally safe care. Consumer input noted that a disadvantage of genomic testing was the limitation in knowledge linking conditions to genetic abnormalities and the potential to over medicalise the situation, with several consumers having had an unsatisfactory experience with genetic counselling.

**Population, Comparator (current management) and Delivery**

The consultation input agreed with the proposed populations, with support for singleton and trio analysis. Genomics Australia stated that where only one parent was able to be included in genomic analysis, duo analysis could provide benefits beyond singleton analysis.

The consultation input agreed with the proposed comparator of CMA, noting that CMA and genomic testing may be done concurrently or as a staged approach depending on the gestation and clinical information.

Other services identified in the consultation input as being needed to be delivered before or after the intervention included counselling from genetic counsellors and psychologists, and access to a multidisciplinary team to assist families plan the best care pathway for mother and baby. Australian Genomics stated culturally specific training would be required to support equity of access.

**MBS Item Descriptor and Fee**

The consultation input from health professionals and organisations largely agreed with the proposed service descriptor. The Australasian Association of Clinical Geneticists input stated that the term “significant” is not defined which may lead to overuse of the item, however the proposed limitation that testing must be requested by (or in consultation with) a consultant clinical geneticist would minimise the risk of overuse in cases where the structural anomaly is unlikely to have a genetic cause. Australian Genomics noted that genetic counsellors are not listed as an eligible requesting practitioner, and that the requirement for supervision by a clinical geneticist will need to be accounted for in terms of billing and enabling patients to access the proposed testing in a timely manner.

The consultation input from health professionals and organisations on the MBS item fee agreed with the proposed service fee, with one clinical geneticist stating the fee could be a bit higher. A consumer noted that public funding would remove the enormous financial burden of testing, as access to complete genetic testing costs approximately $7,000.

*PASC noted that there were 33 public consultation responses received, and that they were all supportive of public funding for diagnostic genomic testing for fetal anomalies. PASC noted that a lot of consultation responses mentioned the need for genetic counselling for families, and queried the availability of a funding mechanism to support genetic counselling which is not available under the MBS.*

*PASC discussed laboratory testing and genetic counselling capacity. The applicant stated that the three laboratories that conducted testing for the PreGen study have capacity to undertake the estimated number of tests each year, and that the creation of MBS items will encourage additional laboratories to gain the relevant accreditation, thus contributing to an increase in testing capacity. The applicant also stated that genetic counselling capacity is increasing in Australia, with large enrolments in genetic counselling training programs ensuring that more people will be qualified to provide genetic counselling in the future.*

*PASC noted the input from Australian Genomics that duo testing should also be offered. PASC noted from their pre-PASC response that the applicant does not recommend including duo testing as an option as it does not provide additional benefits over singleton analysis.*

*PASC also noted from the Australian Genomics input that the current application does not explicitly list exclusion criteria and that these can be informed by the PreGen study and similar prenatal testing services implemented internationally. PASC noted from their pre-PASC response that the applicant was supportive of including specific exclusion criteria from the PreGen study if required, however noted that the decision that prenatal genomic testing is indicated is within the scope of practice of clinicians working in prenatal genomics.*

## Next steps

*The applicant confirmed that they will be producing an Applicant Developed Assessment Report (ADAR).*

## Applicant Comments on Ratified PICO

As this is part of the MBS item number text, we comment that the word "germline" could be omitted in proposed MBS item CCCC as any variant/s that is/are relevant to the evolving fetal or neonatal diagnosis will be reported according to laboratory reporting protocols whether they inherited, *de novo* or somatic mosaic. As such, we recommend removing "germline" from the descriptor.

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1. Note: “proband” is used in this document to mean an affected individual (i.e. a person who has signs and/or symptoms consistent with the disease phenotype) who has received a confirmatory genetic (and/or other accepted diagnostic test) diagnosis [↑](#footnote-ref-2)
2. Note: “affected individuals/cases” is used in this document to mean a case/individual who has a presumptive phenotypic diagnosis who will be tested to receive a genetic diagnosis [↑](#footnote-ref-3)
3. <https://www.abs.gov.au/statistics/people/population/births-australia/latest-release> accessed on 11 March 2025 [↑](#footnote-ref-4)
4. <https://pregen.neura.edu.au/wp-content/uploads/2024/03/PreGen-Inclusion-Exclusion-Criteria-March-2024.pdf> accessed on 13 March 2025 [↑](#footnote-ref-5)
5. <https://pregen.neura.edu.au/wp-content/uploads/2025/04/PreGen-Updates-Mar-2025.pdf,a> <https://pregen.neura.edu.au/wp-content/uploads/2025/04/PreGen-Updates-Mar-2025.pdf>, accessed on 2 May 2025 [↑](#footnote-ref-6)
6. https://www.cdc.gov/advanced-molecular-detection/about/what-is-genomic-sequencing.html accessed 13 March 2025 [↑](#footnote-ref-7)
7. <https://www.rcpa.edu.au/Patients/Lab-Accreditation?form=MG0AV3> accessed 13 March 2025 [↑](#footnote-ref-8)
8. <https://pathology.health.nsw.gov.au/wp-content/uploads/2024/07/NSWHP_PD_029-Incidental-Findings-for-Genomics-V2.pdf> accessed 11 March 2025 [↑](#footnote-ref-9)
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