**MSAC Application 1793**

**Diagnostic genomic testing for fetal**

**anomalies**

**PICO Set**

# Population

**Describe the population in which the proposed health technology is intended to be used:** Approximately 3-5% of pregnancies will have a FA detected on ultrasound (Jelin and Vora 2018, Wou et al 2018), and more than 80% of these have a Mendelian genetic aetiology (Mone et al 2020).

Mendelian disorders result from genetic variants in disease associated genes.

FA may affect any organ system and severe FA may result in fetal or neonatal death or serious perinatal or lifelong conditions with increased morbidity or mortality. FA may be specific or may be markers of a more complex syndrome or condition affecting many organ systems. A fetus with FA significant enough to be detected by prenatal imaging is more likely to have a single gene germline aetiology. Some examples include (but are not limited to): significant/severe brain anomalies including neuronal migration disorders, enlarged ventricles, severe cardiac or renal anomalies, skeletal dysplasias, increased nuchal translucency and fetal hydrops. Other anomalies including orofacial clefting, talipes, and anomalies of the corpus callosum (particularly when accompanied by other anomalies) also have significant genomic diagnostic rates.

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

Major FA may be identified by the routine first trimester scan at 11-14 weeks (Medicare eligible) or the routine antenatal anatomy scan at 18-20 weeks (Medicare eligible). When FA is thought to have a genetic aetiology, families may be offered testing through chromosome microarray after chorionic villus sample (CVS) or amniocentesis. It is typical for feto-maternal specialists or obstetricians to perform the initial ultrasound assessment. These assessments may be in association with a clinical geneticist and/or a genetic counsellor who provide management expertise for genetic conditions in pregnancy. Standard of care testing includes qfPCR/FISH and chromosome microarray to detect chromosome aneuploidies or other chromosomal anomalies after an invasive procedure. This level of testing is not able to provide a diagnosis in the majority of situations where a Mendelian genetic condition is present. Genomic testing such as whole exome sequencing (WES) or whole genome sequencing (WGS) may be requested to increase the diagnostic rate. WES or WGS are not currently available to families uniformly across Australia.

## Provide a rationale for the specifics of the eligible population:

A pregnancy with an FA significant enough to be detected by prenatal imaging is more likely to have a single gene (Mendelian) aetiology detectable by WES/WGS. Single gene (Mendelian) conditions are not detectable by qfPCR/FISH (Fluorescence in situ hybridization) and/or chromosome microarray.

## Are there any prerequisite tests?

Yes

## Are the prerequisite tests MBS funded?

Yes

## Provide details to fund the prerequisite tests:

The prerequisite tests that may identify FA include one or more of the following ultrasounds, which are already funded (no additional funding needed):

Pre-requisite tests

* 55707 - Ultrasound OR
* 55708 - Ultrasound OR
* 55706 - Ultrasound OR
* 55709- Ultrasound OR/AND
* 55712- Ultrasound (re-scan)

In addition, DNA samples for prenatal genomic trio testing are required from the pregnancy through either a chorionic villus sample (CVS) or amniocentesis and also a DNA sample from both parents. The invasive tests that may obtain such samples from the pregnancy include the following:

* 16603 - Chorionic villus sampling, by any route
* 16600 - Amniocentesis, diagnostic

These invasive tests are already funded (no additional funding needed).

# Intervention

## Name of the proposed health technology:

Prenatal genomic sequencing for fetal anomalies

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

Typically, a referral would be made to a specialist obstetrician for a routine first trimester scan at 11-14 weeks or the 19-20 week anatomy scan, usually from a family physician. Should an anomaly be identified, the feto-maternal specialist in association with a genetic counsellor or clinical geneticist, would request a prenatal genomic test. The samples from the pregnancy (and parents if a trio is performed) are delivered to the NATA-accredited genomic testing facility for genomic sequencing, analysis and reporting. A genomic report is written and then sent to the referring clinician for discussion with the family. These discussions often occur in consultation with a clinical geneticist and genetic counsellor. The current request for item numbers is limited to genomic testing.

## Identify how the proposed technology achieves the intended patient outcomes:

* Early diagnosis of a Mendelian disorder in the pregnancy
* Provision of tailored perinatal plans to assist with pregnancy management and management of neonates
* Providing broader choices for reproductive management for families in the future

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

No

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

N/A

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

If a genetic diagnosis is made, one initial sequence and analysis per fetus and biological parents will be required. If no diagnosis is made or if new clinical information becomes available during the pregnancy or after the delivery, up to two re-analyses of existing genomic data may be required.

## Provide details and explain:

Re-analysis only occurs where there is no diagnosis, the patient is strongly suspected of having a Mendelian disorder, and new clinical information becomes available during the pregnancy or after the delivery that could increase the diagnostic potential through re-analysis.

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

* Obstetricians including feto-maternal specialists
* Clinical Geneticists and other physicians experienced in the provision of prenatal genomic testing

## If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

No, above list is inclusive

## If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

Health professional who can provide a referral for prenatal genomic testing are limited to:

* Obstetricians, including feto-maternal specialists
* Clinical Geneticists and other physicians experienced in the provision of prenatal genomic testing

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

Yes

## Provide details and explain:

Feto-maternal specialists with specific training in fetal anomaly scanning and interpretation, and clinical geneticists/genetic counsellors with specialist training in human clinical genetics. There is a requirement for specific NATA accreditation for genomic testing, scientists trained in the generation and analysis of genomic data and accredited pathologists to report findings and supervise genomic laboratories. Currently, the laboratory infrastructure and accredited staff are already in place in the PreGen associated laboratories to be able to provide clinically accredited prenatal genomic testing.

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

*(Select all relevant settings)*

* Consulting rooms
* Day surgery centre
* Emergency Department
* Inpatient private hospital
* Inpatient public hospital

X Laboratory

* Outpatient clinic
* Patient’s home
* Point of care testing
* Residential aged care facility
* Other (please specify)

## Specify further details here

The genomic sequencing technology in this application will be delivered in a genomic laboratory.

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

Yes.

## Provide additional details on the proposed health technology to be rendered outside of Australia:

N/A

# Comparator

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

Currently, funded genetic testing available for families in pregnancy includes a karyotype (chromosome analysis) and chromosome microarray (molecular chromosome analysis).

Traditionally, banded karyotyping was offered by some services but in most major laboratories, chromosome microarray has replaced karyotyping for prenatal diagnosis.. Therefore, this application uses only chromosome microarray as the comparator.

Typically, a family physician referral would be made to a specialist obstetrician or a specialist sonographer for a routine first trimester fetal anatomy scan at 11-14 weeks’ gestation followed by a routine 18-22 week second trimester fetal anatomy scan. Should an anomaly be identified, the patient would be referred to a specialist obstetrician or feto-maternal specialist in association with a genetic counsellor or clinical geneticist, who would request a diagnostic fetal chromosome microarray. The sample representing the fetus, taken by chorionic villus sample (CVS) or amniocentesis, is delivered to the NATA-accredited testing facility for molecular chromosome analysis and reporting. A report is written and then sent to the referring clinician for discussion with the family. These discussions often occur in consultation with a clinical geneticist and genetic counsellor.

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

Chromosome microarray - 73388

## Provide a rationale for why this is a comparator:

Chromosome microarray is the current Medicare funded standard of diagnostic care for diagnosis of fetal anomaly.

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

*(Please select your response)*

X None (used with the comparator)

* Displaced (comparator will likely be used following the proposed technology in some patients)
* Partial (in some cases, the proposed technology will replace the use of the comparator, but not all)
* Full (subjects who receive the proposed intervention will not receive the comparator)

**Outline and explain the extent to which the current comparator is expected to be substituted:** Whole genome sequencing (WES) would be performed after or concurrently with chromosome microarray (depending on gestation of pregnancy) and would increase the diagnostic rate by more than 30-40%.

If gestation permits, a chromosome microarray should be performed before WES in case there is a chromosome anomaly that would remove the need for additional genomic testing. Given the urgency of prenatal samples, at later gestations, chromosome microarray and WES may need to be run in parallel to avoid creating delays in providing results to families.

As whole genome sequencing (WGS) becomes the genomic test of choice, there will be reduced use of chromosome microarray as WGS has equivalent detection rates for aneuploidy and copy number changes.

# Outcomes

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

*(Please select your response)*

X Health benefits (major) X Health harms (major) X Resources (major)

X Value of knowing (major)

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

The federally funded Australian MRFF PreGen prenatal genomics implementation program has assessed all four elements listed in the health outcomes to provide national data from, and relevant to, the Australian population.

**Health benefits** - A molecular diagnosis provides a framework for management or therapy and supports parents to prepare for an affected child or choose to end an affected pregnancy. When no clinically significant variant is identified this may be reassuring for parents and facilitate their decision to continue a pregnancy. Medical plans can be put in place for the birth of an affected child. Early intervention can also be arranged leading to improved long term health outcomes for the child. As an example, a PreGen participant had biallelic *ADAMTS13* variants identified prenatally which led to life- saving proactive treatment at birth with recombinant ADAMTS13. This condition would not have been diagnosed without prenatal genomic testing and the baby would have died. The possibilities for gene specific treatments are increasing and require prenatal genomic diagnostic results to be implemented.

**Health harms** - The PreGen national implementation program has interviewed more than 100 families where the data have shown that families agreed that prenatal genomic testing was the right decision for them.

At 6 months after testing, 98.3% of PreGen participants (n=116) agreed or strongly agreed that undergoing prenatal genomic testing was the right decision, and the same number said that they would make the same choice if they were given the opportunity again. None of the parents interviewed for PreGen after receiving results thought they made the wrong decision, or that they would make a different decision given the chance again. No PreGen participant reported a level of decisional regret that would equate to health harm.

In addition, the increased yield of genomic testing compared to chromosome microarray may lessen harm by providing a diagnosis and reducing ambiguity.

**Resources -** Prenatal diagnosis promotes earlier appropriate management and the avoidance of unnecessary investigations or treatments after delivery. If a specific fetal syndrome or single gene

disorder is diagnosed, reproductive options for future pregnancies can be offered, including preimplantation genetic testing/IVF or early prenatal diagnosis. This reduces the need for more frequent targeted fetal ultrasound surveillance in future pregnancies. As whole genome sequencing becomes the genomic test of choice, there will be cost offsets from the reduced use of chromosome microarray as WGS has equivalent detection rates for aneuploidy and copy number changes. In depth health economic data analysis for prenatal genomic testing is currently being undertaken through the PreGen program.

**Value of knowing** - It is well accepted that prenatal genetic testing results are valued by families. Prenatal genomic testing has two different types of value. Firstly, a clear diagnosis provides certainty and can enable family specific management plans as outlined in the health benefits section. Even in the absence of specific management, the value of knowing cannot be underestimated in terms of ending the diagnostic odyssey and providing closure for families.

In addition, there is also great value when no clinically significant variants are identified as this may provide families with the confidence to continue a pregnancy. The experience of the Australian families taking part in PreGen has been that in many instances it can be reassuring where no clinically significant variant is identified. 72.2% of PreGen participants who received no diagnosis (n=97) continued with their pregnancy, compared with 48.6% of those who received a diagnosis (n=70). We believe these results show that there is a benefit to families undergoing prenatal genomic testing where no genomic diagnosis is identified.

To date, 57% of the PreGen results where a genetic diagnosis was identified were *de novo* and 43% were inherited (n=91). Both of these outcomes have significant implications for future pregnancies. For both autosomal recessive and X-linked recessive conditions, the chance of recurrence for a given couple is high and they could access and benefit from reproductive options for any future pregnancy. For those women who are identified to be carriers of an X-linked condition, they are likely to have female relatives who could also be unaffected carriers who have an increased chance of having an affected child. These relatives could also benefit from reproductive options. For those families who have consanguineous unions, other relatives could also benefit from variant segregation as they may also have an increased chance of having an affected child. Conversely, for those couples who have had a baby with FA due to a *de novo* mutation, their chance of having another child is very low. This information can also be enormously reassuring, restoring reproductive confidence and preventing unnecessary invasive testing in future pregnancies.

# Proposed MBS items

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

Currently prenatal genomic testing is funded through a combination of research funding, state-based funding or patient self-funding. At present access to testing is not equitable and is not uniformly funded across Australia leading to inconsistent availability of services in rural versus urban areas and between states.

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

|  |  |
| --- | --- |
| MBS item number (where used as a template for theproposed item) | AAAA |
| Category number | Pathology Services |
| Category description | Genetics |
| Proposed item descriptor | 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 Mendelian (single gene) aetiology IF:1. both biological parents are available for testing; AND
2. the characterisation is requested by:
	1. a consultant clinical geneticist, OR
	2. a consultant obstetrician in consultation with:
		1. a clinical geneticist OR
		2. a certified genetic counsellor practising in prenatal genetics and supervised by a clinical geneticist; AND
		3. a single fetal anomaly has been identified by fetal imaging, may include (but not limited to):
			1. a significant brain anomaly
			2. a significant cardiac, renal or gastrointestinal anomaly
			3. evidence of skeletal dysplasia including:
				1. unexplained short long bones under the 1st centile
			4. an increased first trimester nuchal translucency 5mm or greater
			5. hydrops fetalis
			6. ambiguous genitalia
			7. fetal growth restriction either:
				1. unexplained small for gestational age, under the 1st centile, and
				2. no other evidence of placental insufficiency
			8. other significant single anomalies, OR
		4. multi-system fetal anomalies have been identified by fetal imaging; AND
		5. the characterisation is not performed in conjunction item BBBB Applicable once per fetus.
 |
| Proposed MBS fee | Fee: $3,300 Benefit: 75% = $2,475, 85% = $2,805 |
| Indicate the overall cost perpatient of providing the | $3,300 |

|  |  |
| --- | --- |
| proposed healthtechnology |  |
| Please specify anyanticipated out of pocket expenses | Nil |
| Provide any further detailsand explain | N/A |

|  |  |
| --- | --- |
| MBS item number (where used as atemplate for the proposed item) | BBBB |
| Category number | Pathology Services |
| Categorydescription | Genetics |
| Proposed item descriptor | 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 Mendelian (single gene) aetiology if:1. one or both of the biological parents are unavailable for testing; AND
2. the characterisation is requested by:
	1. a consultant clinical geneticist, OR
	2. a consultant obstetrician in consultation with:
		1. a clinical geneticist OR
		2. a certified genetic counsellor practising in prenatal genetics and supervised by a clinical geneticist; AND
		3. a single fetal anomaly has been identified by fetal imaging, may include (but not limited to):
			1. a significant brain anomaly
			2. a significant cardiac, renal or gastrointestinal anomaly
			3. evidence of skeletal dysplasia including:
				1. unexplained short long bones under the 1st centile
			4. an increased first trimester nuchal translucency 5mm or greater
			5. hydrops fetalis
			6. ambiguous genitalia
			7. fetal growth restriction either:
				1. unexplained small for gestational age, under the 1st centile, and
				2. no other evidence of placental insufficiency
			8. other significant single anomalies, OR
		4. multi-system fetal anomalies have been identified by fetal imaging; AND
		5. the characterisation is not performed in conjunction item BBBB Applicable once per fetus.
 |
| Proposed MBS fee | Fee: $2,500 Benefit: 75% = $1,875, 85% = $2,125 |
| Indicate the overall cost per patient of providing theproposed health technology | $2,500 |

|  |  |
| --- | --- |
| Please specify anyanticipated out of pocket expenses | Nil |
| Provide any further details and explain | N/A |

|  |  |
| --- | --- |
| MBS item number (where used as atemplate for the proposed item) | CCCC |
| Category number | Pathology Services |
| Categorydescription | Genetics |
| Proposed itemdescriptor | Re-analysis of whole genome or whole exome data obtained in performing aservice to which item AAAA or BBBB applies, for characterisation of previously unreported germline variants related to the clinical phenotype, IF:1. the re-analysis is requested by:
	1. a consultant clinical geneticist, OR
	2. a consultant obstetrician in consultation with:
		1. a clinical geneticist OR
		2. a certified genetic counsellor practising in prenatal genetics and supervised by a clinical geneticist; AND
2. there is a strong clinical suspicion of a Mendelian disorder affecting the fetus/newborn/infant; AND
3. 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. |
| Proposed MBS fee | Fee: $500.00 Benefit: 75% = $375, 85% = $425 |
| Indicate the overall cost per patient of providing the proposed healthtechnology | $500 |
| Please specify any anticipated out ofpocket expenses | Nil |
| Provide any furtherdetails and explain | N/A |

# Algorithms

**PREPARATION FOR USING THE HEALTH TECHNOLOGY**

**Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:** 1a) First trimester scan usually arranged by a family physician at 11-14 weeks gestation

1. If no FA is detected - a routine 20 week anatomy scan is performed
2. If an FA is detected - the family is referred to a feto-maternal medicine team and/or clinical genetic specialist for assessment and discussion of further testing by CVS or amniocentesis

with qfPCR/FISH (for the rapid detection of chromosomal aneuploidy, non MBS items). qfPCR/FISH has a turnaround time of 1-2 days.

* 1. If qfPCR/FISH identifies a fetal chromosome abnormality that explains the baby’s anomalies, the laboratory will confirm this finding with an orthogonal chromosome test and genetic counselling will be provided by the referring clinician. Additional genomic testing will no longer be required if the FA is explained adequately.
	2. If qfPCR/FISH does not identify a cause for the fetal anomaly, chromosome microarray is undertaken routinely to detect aneuploidy and copy number variant as a cause for FA. Chromosome microarray has a turn around time of 5-10 days prenatally.
		1. If chromosome microarray identifies a fetal chromosome abnormality that explains the baby’s anomalies, no further testing is required and genetic counselling will be provided by the referring clinic.
		2. If chromosome microarray does not identify a cause for the FA, the family may be consented for prenatal genomic analysis with WES/WGS.

1b) If no anomaly is detected at 11-14 weeks, it is routine to proceed to a 20 week anatomy scan

1. If no anomaly is detected at the routine 20 week scan, standard care proceeds.
2. If an anomaly is detected the family is referred to a feto-maternal medicine team and/or clinical genetic specialist for assessment and discussion of further testing by amniocentesis with qfPCR/FISH.
	1. If qfPCR/FISH identifies a fetal chromosome abnormality that explains the baby’s anomalies, the laboratory will confirm this finding with an orthogonal chromosome test and genetic counselling will be provided by the referring clinician. Additional genomic testing will no longer be required if the FA is explained adequately.
	2. If qfPCR/FISH does not identify a cause for the FA, chromosome microarray is undertaken routinely to detect aneuploidy and copy number variant as a cause for FA. Chromosome microarray has a turn around time of 5-10 days prenatally.
		1. If chromosome microarray identifies a fetal chromosome abnormality that explains the baby’s anomalies, no further testing is required and genetic counselling will be provided by the referring clinic.
		2. If chromosome microarray does not identify a cause for the fetal anomaly, the family may be consented for prenatal genomic analysis with WES/WGS\*.

\*Chromosome microarray may need to be run concurrently with WES depending on the pregnancy gestation. As whole genome sequencing (WGS) becomes the genomic test of choice, there will be reduced use of chromosome microarray as WGS has equivalent detection rates for aneuploidy and copy number changes.

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

Yes.

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

*Please provide a response if you answered 'Yes' to the question above*

## Addition of genomic sequencing compared with current standard of care (chromosome microarray)

The addition of genomic testing, whether WES or WGS, would result in the need for test specific consent. Currently best practice is to obtain consent for chromosome microarray where the consenting

issues are similar to genomic testing, and so the additional time/resources required for genomic consent should not be substantial.

## Timing of the WES

If gestation permits, a chromosome microarray should be performed before WES in case there is a chromosome anomaly that would remove the need for additional genomic testing. At later gestations, chromosome microarray and WES may need to be run in parallel to reduce the time to a diagnostic report. Reducing turnaround times in prenatal testing is particularly important. It is therefore anticipated that as WGS is implemented that chromosome microarray will no longer be required which will further reduce the time to diagnosis.

**USE OF THE HEALTH TECHNOLOGY**

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

Antenatal imaging (including ultrasound or MRI) to identify FA is a prerequisite for prenatal genomic testing. It is routine for feto-maternal specialists, clinical geneticists and genetic counsellors to provide expert management during this process. There is a requirement for genomic consent.

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

Antenatal imaging (including ultrasound or MRI) to identify FA is a prerequisite for prenatal genomic testing. It is routine for feto-maternal specialists, clinical geneticists and genetic counsellors to provide expert management during this process. There is a requirement for chromosome microarray consent.

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

The differences in healthcare resources required relate to the laboratory testing infrastructure. There is a requirement for specific NATA accreditation for genomic testing (as opposed to NATA accreditation for microarray), scientists trained in the generation and analysis of genomic data and accredited pathologists to report findings and supervise genomic laboratories. Currently, the laboratory infrastructure and accredited staff are already in place in the PreGen associated laboratories to be able to provide clinically accredited prenatal genomic testing.

**CLINICAL MANAGEMENT AFTER THE USE OF HEALTH TECHNOLOGY**

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

For the families with FA who do not have an informative result with qfPCR/FISH and/or chromosome microarray, WES/WGS has a diagnostic rate of 30-40% and the turnaround time is 2-4 weeks. Once results are available an appointment with a feto-maternal medicine and genetics team is organised to discuss results:

1. If the family decides to continue the pregnancy, they may need ongoing care with genetics and feto-maternal medicine teams and other specialist involvement before birth, such as cardiologists, neurologists and/or paediatricians.
2. If a family decides to end the pregnancy, a referral may be made to pregnancy support services and counselling services.

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

Chromosome microarray turnaround time is 5-10 days. Once results are available an appointment with a feto-maternal medicine and genetics team is organised to discuss results.

1. If the family decides to continue the pregnancy, they may need ongoing care with genetics and feto-maternal medicine teams and other specialist involvement before birth, such as cardiologists, neurologists and/or paediatricians.
2. If a family decides to end the pregnancy, a referral may be made to pregnancy support services and counselling services.

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

Currently the addition of genomic testing in pregnancy adds between one and three weeks to obtain a diagnostic report, the timing of which depends on local laboratory processes to complete fetal genomic investigations and whether chromosome microarray is required.

The primary difference after the use of the proposed technology is the significantly improved diagnostic rate achieved through WES/WGS. Paradoxically families may need fewer medical appointments after a specific genomic diagnosis as the diagnostic odyssey has been curtailed.

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

*(Please ensure that the diagrams provided do not contain information under copyright)*

## Flow diagram A - Current clinical algorithm (chromosome microarray)



**Flow diagram B - clinical algorithm after proposed health technology introduced (WES/WGS)**



\*Chromosome microarray may need to be run concurrently with WES depending on the pregnancy gestation. As whole genome sequencing (WGS) becomes the genomic test of choice, there will be reduced use of chromosome microarray as WGS has equivalent detection rates for aneuploidy and copy number changes.

# Claims

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

X Superior

* Non-inferior
* Inferior

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

The proposed technology is superior because it provides a significantly increased diagnostic rate. Medicare currently funds diagnostic testing for FA by karyotype and chromosome microarray on amniocytes or CVS. The karyotypes and/or chromosome microarray are abnormal in 10-12% of pregnancies overall and in 25-45% of pregnancies with FA (Callaway et al 2013, Hillman et al 2013). Next generation sequencing with WES/WGS provides diagnoses in an additional 30-40% of people with Mendelian disorders (Chung et al 2023) with robust evidence of similar diagnostic rates in prenatal testing (Mellis et al 2022).

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

Prenatal genomic testing has a markedly increased diagnostic rate to identify the genetic cause and provide accurate prognosis of FA. The provision of a precise diagnosis allows for personalised perinatal management of high risk newborns. It can also enable informed reproductive decision making for families for current and future pregnancies. Requestors would seek to use the proposed investigative technology for all of these reasons.

## Identify how the proposed technology achieves the intended patient outcomes:

A molecular diagnosis provides a framework for management or therapy and supports parents to prepare for an affected child, or choose to end an affected pregnancy. When no clinically significant variant is identified this may be reassuring for parents and facilitate their decision to continue a pregnancy. Medical plans can be put in place for the birth of an affected child. Early intervention can also be arranged leading to improved long term health outcomes for the child.

In addition, there is also great value when no clinically significant variants are identified as this may provide families with the confidence to continue a pregnancy. The experience of the Australian families taking part in PreGen has been that in many instances it can be reassuring where no clinically significant variant is identified.

The proposed technology also has important reproductive implications for families. For both autosomal recessive and X-linked recessive conditions, the chance of recurrence for a given couple is high and they could access and benefit from reproductive options for any future pregnancy. Those couples who have had a baby with FA due to a *de novo* mutation, have a low chance of recurrence.

This information can also be enormously reassuring, restoring reproductive confidence and preventing unnecessary invasive testing in future pregnancies.

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

*(Please answer either Yes or No, deleting text as required)*

## A change in clinical management? Yes A change in health outcome? Yes Other benefits? Yes

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

It is well accepted that prenatal genetic testing results are valued by families. Prenatal genomic testing has two different types of value. Firstly, a clear diagnosis provides certainty and can enable family specific management plans as outlined in the health benefits section. Even in the absence of specific management, the value of knowing cannot be underestimated in terms of ending the diagnostic odyssey and providing closure for families.

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

*(Please select your response)*

X More costly

* Same cost
* Less costly

## Provide a brief rationale for the claim:

Generation of the sample is the same cost as chromosome microarray as the sample is collected by CVS or amniocentesis. Test counselling is broadly equivalent and so would be expected to take a similar amount of time for a similar cost. The differences in cost derive from the increased cost requirements for data generation, analysis and reporting for genomic testing.

It is more costly because it is an additional prenatal test that increases the diagnostic rate through the detection of a different class of mutations with a consequent increased clinical utility for fetal medicine units and for families.

# Summary of Evidence

## Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Type of study design\*** | **Title of journal article or research project** (including any trialidentifier or study lead if relevant) | **Short description of research** (max 50 words)\*\* | **Website link to journal article or research** (if available) | **Date of publication\*\*\*** |
| 1. | Prospective cohort study (Germany) | Trio exome sequencing is highly relevant in prenatal diagnostics | 500 pregnancies with fetal ultrasound anomalies analysed using WES trios. Average time from sample receipt to report- 12 days.Diagnostic rates:* All FSA - 38%
* Skeletal – 52%
* Complex (2+ FSAs) – 44%
* Urogenital – 44%
* Brain – 43%
* NT >3mm – 33%
* IUGR – 26%
* Cardiac – 24%
* Eye – 20%
* Arthrogryposis - 20%
* Internal organs – 19%
* Other – 29%
 | <https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/pd.6081>  | 27 December2021 |

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|  | **Type of study design\*** | **Title of journal article or research project** (including any trialidentifier or study lead if relevant) | **Short description of research** (max 50 words)\*\* | **Website link to journal article or research** (if available) | **Date of publication\*\*\*** |
| 2. | Systematic Review and Meta Analysis (UK) | Diagnostic yield of exome sequencing for prenatal diagnosis of fetal structural anomalies: a systematic review and meta‐analysis. | Reviewed 66 studies, representing 4350 fetuses. Diagnostic yield can be optimised by pre-selection of cases where a monogenic cause is likely.Diagnostic rates:* All FSA - 31%
* Skeletal - 53%
* Neuromuscular - 37%
* Multisystem - 29%
* Hydrops - 22%
* CNS - 17%
* Cardiac - 11%
* IUGR - 4%
* Isolated increased NT - 2%
* Craniofacial - 9%
* Kidney / urinary tract - 9%
 | [Diagnostic yield of exome sequencing for prenatal diagnosis of fetal structural anomalies: A systematic review and meta‐analysis - Mellis - 2022 - Prenatal Diagnosis - Wiley Online Library](https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/pd.6115) | 15 February2022 |

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| 3. | Prospective cohort study (USA) | Whole-exome sequencing in the evaluation of fetal structural anomalies: a prospective cohort study. | Analysis of 234 WES trio of fetuses with FSA. Findings suggest WES can add clinically relevant information that could assist current management of a pregnancy.Diagnostic rates:* All FSA - 10%
* Multiple FSA - 19%
* Cardiac - 5%
* Skeletal - 24%
* NT >4mm (not isolated) - 12%
* Lymphatic or effusion - 24%
* Renal - 16%
* CNS - 22%
 | [Whole-exome sequencing in the evaluation of fetal structural anomalies: a prospective cohort study - PubMed](https://pubmed.ncbi.nlm.nih.gov/30712878/) | 31 January2019 |
| 4. | Systematic Review and Meta Analysis (Spain) | Diagnostic yield of exome sequencing in fetuses with multisystem malformations: systematic review and meta‐analysis. | Analysis of 17 articles representing 694 fetuses with multisystem malformations. WES applied in fetuses with 2+ FSA was able to identify a potentially causative gene when CMA or karyotyping had failed to do so in an additional one-third of cases.Diagnostic rate:* Multiple FSA - 33%
 | <https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/uog.24862> | 18 January2022 |

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| 5. | Prospective cohort study (UK) | Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study. | Analysis of 596 WES trios with FSA. Found WES enables more accurate predictions of fetal prognosis and risk of recurrence in future pregnancies.Diagnostic rates:* All FSA - 8.5%
* Multiple FSA - 15.4%
* Cardiac - 11%
* Skeletal - 15%
* Isolated NT >4mm - 3%
 | [Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study - PubMed](https://pubmed.ncbi.nlm.nih.gov/30712880/) | 23 Feb 2019 |
| 6. | Prospective cohort study and systematic review (UK) | Fetal hydrops and the Incremental yield of Next generation sequencing over standard prenatal Diagnostic testing (FIND) study: prospective cohort study and meta-analysis. | 28 cases of prenatally diagnosed non immune hydrops fetalis (NIHF) undergoing WES were combined with data from a systematic review for analysis of a total of 306 cases.Diagnostic rates:* All NIHF - 29%
* Isolated NIHF - 24%
* NIHF associated with additional anomalies - 38%
 | [Fetal hydrops and the Incremental yield of Next‐generation sequencing over standard prenatal Diagnostic testing (FIND) study: prospective cohort study and meta‐analysis](https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/uog.23652) | 29 March 2021 |

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| 7. | Prospective cohort study (UK) | Fetal exome sequencing for isolated increased nuchal translucency: Should we be doing it? | 213 fetuses with increased NT ≥3.5 mm at 11–14 weeks of gestation were identified and WES trios analysed.Diagnostic rates:* Isolated NT in first trimester (no other anomalies) - 1.8%
* Non-isolated increased NT at presentation - 22%
* initially isolated increased NT with

additional anomalies detected later in pregnancy- 32% | [https://obgyn.onlineli](https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1111/1471-0528.16869) [brary.wiley.com/doi/e](https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1111/1471-0528.16869) [pdf/10.1111/1471-](https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1111/1471-0528.16869) [0528.16869](https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1111/1471-0528.16869)  | 17 June 2021 |
| 8. | Prospective cohort study and systematic review (UK) | Congenital heart disease and the Diagnostic yield with Exome sequencing (CODE) study: prospective cohort study and systematic review. | 197 trios undergoing WES following prenatally identified congenital heart disease (CHD) were combined with data from a systematic review for analysis of a total of 636 cases.Diagnostic rates:* All CHD - 21%
* Isolated CHD - 11%
* CHD associated with extracardiac anomaly - 37%
 | [https://obgyn.onlineli](https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/uog.22072) [brary.wiley.com/doi/e](https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/uog.22072) [pdf/10.1002/uog.2207](https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/uog.22072) [2](https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/uog.22072) | 29 April 2020 |

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| 9. | Systematic review (Italy) | Prenatal Exome Sequencing: Background, Current Practice and Future Perspectives-A Systematic Review | WES results analysed for 3261 cases of FSA within 75 studies.Diagnostic rates:* Any structural anomaly, either associated or isolated - weighted average 19%
* Specific single class anomalies - ranged from 6% to 92%, with an average of 32%.
	+ Skeletal dysplasias - 86%
	+ CNS anomalies - 44%
	+ CHD - 11%
	+ Increased NT - 8%
 | [https://www.ncbi.nlm.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7913004/) [nih.gov/pmc/articles/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7913004/) [PMC7913004/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7913004/) | 2 Feb 2021 |
| 10. | Systematic review (Spain) | Prenatal Exome Sequencing in Recurrent Fetal Structural Anomalies: Systematic Review and Meta-Analysis. | Analysed 9 studies on WES diagnostic yield that included 140 fetuses with recurrent structural anomalies.DIagnostic rate:* Similar anomalies in consecutive pregnancies - 40%
 | [https://pubmed.ncbi.n](https://pubmed.ncbi.nlm.nih.gov/34682862/) [lm.nih.gov/34682862/](https://pubmed.ncbi.nlm.nih.gov/34682862/) | 15 Oct 2021 |
| 11. | Scientific impact paper (UK) | Evidence to Support the Clinical Utility of Prenatal Exome Sequencing in Evaluation of the Fetus with Congenital Anomalies | In the presence of FSA, WES provides an additional diagnostic yield of 8.5–10.3% over and above standard prenatal genetic/ chromosomal testing in unselected fetuses. This increases to between 15.4 and 18.9% in fetuses with multisystem anomalies. WES is limited to assessing 85% of known disease- causing variants, which represent 1–2% of the genome. | [https://pubmed.ncbi.n](https://pubmed.ncbi.nlm.nih.gov/33590639/) [lm.nih.gov/33590639/](https://pubmed.ncbi.nlm.nih.gov/33590639/) | 15 Feb 2021 |

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| 12. | Prospective cohort study (UK, USA) | Fetal central nervous system anomalies: When should we offer exome sequencing? | WES was performed in 268 pregnancies with a CNS anomaly identified using ultrasound.Diagnostic rates:* Single isolated CNS anomaly - 7.2%
* isolated agenesis of Corpus Callosum - 30%
* Multiple CNS anomalies - 19%
* CNS anomalies plus other organ system anomaly - 16.7%
 | [https://obgyn.onlineli](https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/pd.6145) [brary.wiley.com/doi/f](https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/pd.6145) [ull/10.1002/pd.6145](https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/pd.6145) | 7 April 2022 |
| 13. | Prospective cohort study (China) | Prenatal exome sequencing in fetuses with callosal anomalies. | 50 trios with fetal callosum anomalies were analysed by WES. 17 likely pathogenic or pathogenic variants were found. 70% of fetuses with isolated callosum anomalies and negative results for genetic causes will have a favorable postnatal prognosis in early childhood.Diagnostic rates:* All callosum anomalies- 34%
 | [https://obgyn.onlineli](https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/pd.6107) [brary.wiley.com/doi/f](https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/pd.6107) [ull/10.1002/pd.6107](https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/pd.6107) | 22 January2022 |

*\* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

*\*\*Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

*\*\*\* If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).*

## Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

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| 1. | Retrospective review | Multidisciplinary Team Approach In Prenatal Exome Sequencing(Australian National PreGen Program) | WES results analysed for 260 cases of FSA with an overall diagnostic rate of 36.9%Diagnostic rates:* Multisystem - 40%
* Skeletal - 36%
* Fetal hydrops - 39%
* SGA/IUGR - 16%
* Renal anomalies - 50%
* Cardiac - 11%

Diagnostic yield of trio vs. singleton analysis was 44.2% vs. 7.7%. | Will be submitted to Prenatal Diagnosis in November 2024. | N/A |

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| 2. | Qualitative research paper | Australian patients’ experiences of undergoing whole exome sequencing for fetal structural anomalies prior to receiving results(Australian National PreGen Program) | 40 expectant parents undergoing WES were interviewed.Key findings:* Parents wanted as much information as possible about their unborn child
* Waiting for results made WES in pregnancy especially difficult emotionally
* Participants had mostly positive experiences with health professionals
* Nuanced understanding of participants' experiences can help guide clinical practice
 | Submitted to Prenatal Diagnosis in September 2024. Currently undergoing review. | N/A |
| 3. | Perspective paper | The PreGen Research Program: Implementing prenatal genomic testing in Australia - a commentary(Australian National PreGen Program) | Barriers to implementing prenatal genomic testing:* Access to funding,
* Availability of genomic testing
* Availability of specialist genomic centres.

A federal item number for prenatal genomic testing would increase equitable test availability and reduce delays to diagnoses by making them in pregnancy whilstremoving the need for low-yield diagnostic interventions. | Was submitted to the Australian and New Zealand Journal of Obstetrics and Gynaecology (ANZJOG) in October 2024 and is currently under review. | N/A |

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| 4. | Case Report | A life-saving diagnosis through prenatal genomic sequencing(Australian National PreGen Program) | Prenatal WES identified biallelic ADAMTS13 and monoallelic FLNC variants consistent with potentially lethal neonatal-onset cTTP and arrhythmogenic cardiomyopathy. This enabled immediate management from birth.Recombinant ADAMTS13 was initiated at 16 days and remains ongoing. This represents the first case of prenatal-onset cTTP whereprenatal genomic sequencing led to life-saving proactive treatment. | Will be submitted to New England Medical Journal in December 2024. | N/A |

*\* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

*\*\*Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

*\*\*\* If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).*