

MSAC application 1793

Diagnostic genomic testing for fetal anomalies

Application for MBS eligible service or health technology

HPP Application number:

HPP200231

Application title:

Diagnostic genomic testing for fetal anomalies

Submitting organisation:

NEUROSCIENCE RESEARCH AUSTRALIA

Submitting organisation ABN:

94050110346

Application description

Succinct description of the medical condition/s:

Fetal anomalies (FA) refer to structural abnormalities detected in a fetus during pregnancy. Severe FA may result in fetal or neonatal death, or neonatal or childhood disease with severe morbidity or increased mortality. Approximately one third of FA have been shown to be due to a complex genetic syndrome.

The identification of FA can be devastating for pregnant women and their partners. They often seek answers about the cause, prognosis and management options for their baby. A specific diagnosis is crucial in addressing these questions.

FA identified antenatally are more likely to have a single gene (Mendelian) aetiology. Some examples include severe brain, cardiac or renal anomalies, skeletal dysplasias and hydrops fetalis. Most fetal Mendelian disorders cannot be diagnosed by current testing (chromosome microarray or karyotype).

Whole exome sequencing or whole genome sequencing are technologies that give the highest change of diagnosis.

Succinct description of the service or health technology:

Fetal anomalies (FA) are present in 3-5% of pregnancies. Medicare already funds diagnostic testing for FA by karyotype and chromosome microarray which are abnormal in 25-45%. Approximately 60% of pregnancies with FA still remain without a diagnosis after this first tier of testing. It is already known that next generation

sequencing with whole exome or whole genome in the postnatal setting yields an additional diagnostic rate of 30-40%. There is compelling evidence for a similar diagnostic rate for prenatal testing (Mellis et al 2022; this application).

Diagnostic genomic laboratories with NATA accreditation for prenatal genomic testing are now operating in many Australian state capitals, linked to clinical genetic services providing patient care through both the public and private sectors. In this application we show that fetal genomic testing is required to provide additional diagnoses for conditions that cannot be diagnosed by karyotype or chromosome microarray.

Application contact details

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

Applicant

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

Organisation

Applicant organisation name:

PreGen National Implementation Consortium

Application details

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

No

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

New

Relevant MBS items

Please select any relevant MBS items.

MBS item number	Selected reason type
55707	Prerequisite item
55708	Prerequisite item
55706	Prerequisite item
55709	Prerequisite item
55712	Prerequisite item
16603	Prerequisite item
16600	Prerequisite item

What is the type of service or health technology?

Investigative

Please select the type of investigative health technology:

Molecular diagnostic tests

Please select the type of molecular diagnostics health technology:

Whole exome/genome sequencing

PICO sets

Application PICO sets:

PICO set name

Genomic testing in pregnancy

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

Purpose category:

Diagnosis / sub-classification

Purpose description:

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

Purpose category:

Predictive

Purpose description:

To provide predictive information to support selection of a specific therapy or intervention

Purpose category:

Value of knowing

Purpose description:

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

Population

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

Approximately 3-5% of pregnancies will have a fetal anomaly (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 occur in any population and is therefore relevant to the whole of the Australian community.

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.

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

Congenital anomaly

Intervention

Name of the proposed health technology:

Diagnostic genomic testing for fetal anomalies

Comparator

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

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.

Outcomes

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

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

Proposed item: AAAAA

Proposed category:

PATHOLOGY SERVICES

Proposed group:

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:

- (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) a clinical geneticist OR
 - (b) a certified genetic counsellor practising in prenatal genetics and supervised by 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:
 - (a) 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 either:
 - (a) unexplained small for gestational age, under the 1st centile, and
 - (b) 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 item BBBB

Applicable once per fetus.

Proposed MBS fee:

\$3,300.00

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

\$3,300.00

Please specify any anticipated out of pocket expenses:

\$0.00

Provide any further details and explain:

N/a

Proposed item: BBBBB

Proposed category:

PATHOLOGY SERVICES

Proposed group:

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:

- (a) one or both of the 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) a clinical geneticist OR
 - (b) a certified genetic counsellor practising in prenatal genetics and supervised by 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:
 - (a) 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 either:
 - (a) unexplained small for gestational age, under the 1st centile, and
 - (b) 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 item AAAA

Applicable once per fetus.

Proposed MBS fee:

\$2,500.00

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

\$2,500.00

Please specify any anticipated out of pocket expenses:

\$0.00

Provide any further details and explain:

N/a

Proposed item: CCCCC

Proposed category:

PATHOLOGY SERVICES

Proposed group:

GENETICS

Proposed item descriptor:

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) a clinical geneticist OR

(b) a certified genetic counsellor practising in prenatal genetics and supervised by a clinical geneticist; AND

(b) there is a strong clinical suspicion of a Mendelian 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.

Proposed MBS fee:

\$500.00

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

\$500.00

Please specify any anticipated out of pocket expenses:

\$0.00

Provide any further details and explain:

N/a

How is the technology / service funded at present? (For example: 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.

Claims

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

Superior

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

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. Karyotype and/or chromosome microarray are abnormal in 25-45% of pregnancies with FA (Callaway et al 2013, Hillman et al 2013). This leaves approximately 60% of pregnancies with FA without a genetic diagnosis. Next generation sequencing with WES/WGS provides diagnoses in 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).

Estimated utilisation

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

Approximately 3-5% of pregnancies will have a FA detected on ultrasound (Jelin and Vora 2018, Wou et al 2018).

In Australia in 2023 there were 286,998 births. Approximately, 8,600-14,400 would be FA affected pregnancies.

The predicted number of prenatal genomic tests is likely to be a proportion of the total number of FA affected pregnancies due to a number of factors as described below. When FA is identified on fetal imaging, families are offered a referral for a diagnostic test to take a sample via CVS or amniocentesis. Not all patients will choose to have a CVS or amniocentesis. For those that elect to undergo testing only a portion will have testing in a Medicare eligible service. Currently, a larger portion of patients will obtain testing through a state government funded service.

Medicare claim reports show that 888 CVS and 1,597 amniocenteses were claimed in the 2023/24 financial year. Therefore approximately 2,500 patients are having testing in a Medicare eligible service.

Currently, DNA extracted from the CVS/amniocentesis sample will then be used to perform a chromosome microarray analysis. Karyotype and/or chromosome microarray are abnormal in 25-45% of pregnancies with FA (Callaway et al 2013, Hillman et al 2013). This leaves approximately 60% of pregnancies with FA without a genetic diagnosis. Therefore, approximately 60% of the 2,500 patients claiming CVS/amniocentesis would be eligible for genomic testing. Based on the combined experience of NSW Health Pathology, Victorian Clinical Genetics Service (VCGS) and SA Pathology, two thirds of eligible patients would be expected to take up genomic testing, i.e. $2,500 \times 0.60 \times 0.66 = 990$ patients per annum on current numbers.

The Australian fertility rate is stable therefore the number of families eligible for prenatal genomic testing is not likely to increase, assuming stable migration rates.

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

Year 1 estimated uptake (%):

50

Year 2 estimated uptake (%):

60

Year 3 estimated uptake (%):

70

Year 4 estimated uptake (%):

80

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

495

Will the technology be needed more than once per patient?

Yes, multiple times

Over what duration will the health technology or service be provided for a patient? (preferably a number of years):

1x initial analysis, max 2x re-analysis

Optionally, provide details:

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.

What frequency will the health technology or service be required by the patient over the duration? (range, preferably on an annual basis):

1x initial analysis, max 2x re-analysis

Optionally, provide details:

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.

Consultation

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

Entity who provides the health technology/service

Royal College of Pathologists of Australasia (RCPA)

Entities who request the health technology/service

The Australasian Association of Clinical Geneticists (AACG)

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)

Entity who may be impacted by the health technology/service

The Australasian Society of Genetic Counsellors (ASGC)

The Royal Australasian College of Physicians (RACP)

The Royal College of Pathologists of Australasia (RCPA)

Human Genetics Society of Australasia (HGSA)

The Australasian Association of Clinical Geneticists (AACG)

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)

Australian Genomics

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

Rare Voices Australia (RVA)

Genetic Alliance Australia (GAA)

Entity who produces similar products

Illumina

Regulatory information

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

Yes

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

No

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

No

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

No

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

No