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Protocol to guide the  
assessment of  
Preimplantation  
Genetic Diagnosis

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June 2014

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FINAL

## MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

### Purpose of this document

This document is intended to provide a protocol that will be used to guide the assessment of Preimplantation Genetic Diagnosis for couples who carry a specific mutation(s) for a serious genetic disorder (and know the exact nature of that mutation) which is at high risk of being passed onto their offspring. The protocol has been finalised after inviting relevant stakeholders to provide input and will provide the basis for the assessment of the intervention.

This protocol has been developed using the widely accepted “PICO” approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

- Population** – specification of the characteristics of the people in whom the intervention is to be considered for use;
- Intervention** – specification of the proposed investigative service;
- Comparator** – specification of the investigative service most likely to be replaced, or supplemented by the proposed investigative service; and
- Outcomes** – specification of the health outcomes likely to be affected by the introduction of the proposed investigative service.

## Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of Preimplantation Genetic Diagnosis (PGD) for couples who carry a specific mutation(s) for a serious genetic disorder (and know the exact nature of that mutation) which is at high risk of being passed onto their offspring was received from Genea (formerly Sydney IVF) by the Department of Health and Ageing in July 2011. PGD is currently available in Australia, but is not reimbursed by the MBS. Costs are currently covered by the facility providing the test or the couple planning a pregnancy. The Department has informed PASC that without amendment, current legislation governing MBS funding would prevent subsidy under the Medicare scheme. It has been suggested that an alternate funding mechanism for PGD could be established, which could be considered following health technology assessment through the MSAC process.

The Applicant's proposal relates to a new diagnostic intervention for testing cells harvested from embryos created *in vitro*, for the purpose of detecting genetic and/or chromosomal disorders before embryo implantation. PGD is intended for couples who carry a specific mutation(s) for a serious genetic disorder (and know the exact nature of that mutation) which is at high risk of being passed onto their offspring. A serious genetic disorder conferring eligibility for PGD may result from a single gene mutation or chromosome rearrangement (translocation). It is expected that there would be no preventative therapy or treatment for the disorder apart from symptomatic care. Genetic disorders for which PGD is typically sought include cystic fibrosis, Duchenne muscular dystrophy and Fragile X syndrome. PGD involves the design of a genetic test specific to the couple at risk of having an affected child, harvesting cells from an embryo produced by *in vitro* fertilisation (IVF), followed by analysis of the cells' DNA to determine whether the embryo would develop that specific disorder. PGD is followed by transfer of an unaffected embryo to the female uterus and progression of the pregnancy.

The applicant is proposing three items for funding to cover the procedures encompassed by PGD:

- Item 1. PGD test design and validation for a known specific genetic mutation(s)
- Item 2. PGD embryo biopsy
- Item 3. PGD embryo analysis

Adelaide Health Technology Assessment (AHTA), in the School of Population Health, University of Adelaide, as part of its contract with the Department of Health, has drafted this protocol to guide the assessment of the safety, effectiveness and cost-effectiveness of the PGD in order to inform MSAC's decision-making regarding public funding of this proposed service.

## Background

### Current arrangements for public reimbursement

Preimplantation Genetic Diagnosis (PGD) is being proposed as a three stage diagnostic procedure, the stages being: (1) genetic test design and validation, (2) embryo biopsy, and (3) embryo analysis. Currently there is no reimbursement of the proposed service through Medicare or other Department funds. The applicant claims that PGD has been used in the determination of more than 150 single gene disorders and chromosome rearrangements in Australia for couples seeking a child free of a genetic disorder. Preimplantation genetic diagnosis and/or screening services are currently provided by private fertility and assisted conception clinics to couples who are concerned about carrying genetic conditions, and are prepared to undergo *in vitro* fertilisation (IVF). The costs are currently met through a range of pathways including funding assistance programs (for example funds created from donations), self-funding, by the facility conducting the PGD service, or through a combination of these mechanisms.

The population to which PGD is currently offered is broader than that for which Commonwealth funding is sought. Current reasons for seeking PGD include family history of a chromosomal or genetic disorder, repeated IVF failure, repeated miscarriage, advanced maternal age, previous chromosomal disorder in pregnancy, and sex selection for medical reasons<sup>1</sup>. The current application from Genea proposes that subsidy for PGD be offered to:

1. couples who carry a specific mutation(s) for a serious genetic disorder (and know the exact nature of that mutation) which is at high risk of being passed onto their offspring, or
2. couples in whom one or both partners know that they carry a specific rearrangement of chromosomes which is at high risk of causing unbalanced genetic content leading to miscarriage, stillbirth, serious congenital abnormality or a genetic disorder in their offspring.

In line with the proposed eligible population it is requested that PGD be reimbursed for the detection of:

1. Single gene disorders, and
2. Chromosomal rearrangements (e.g. translocations)

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<sup>1</sup> Genea offered sex selection for family balancing reasons until February 2005 when the service was suspended due to the publication of clinical practice guidelines by the Australian Health Ethics Committee which opposed the practice.

PGD occurs in conjunction with IVF, with the latter procedure supplying the embryos for genetic analysis. Medicare reimburses costs for IVF services under the Assisted Reproductive Technology (ART) services item numbers 13200 to 13221 (see Appendix A, Table 14). Associated Note T1.4 (see Appendix A, Box 1) provides further information regarding the application of these item numbers. The applicant is proposing a change in Associated Note T1.4 to enable IVF and proposed PGD item numbers to be used together.<sup>2</sup> While IVF is a procedure largely used by couples who have problems with fertility and conception, those couples who would be offered PGD would not necessarily have the same fertility issues.

MBS items associated with the comparator are given in Appendix A, Table 15 and Table 16. Data on the current and projected use (assuming an MBS listing) of PGD are given in Table 3.

### Regulatory status

PGD involves the design of unique genetic tests to identify the specific familial genetic pattern of the couple receiving the service. It uses molecular and genetic analysis techniques which are in-house in vitro diagnostic tests and as such are regulated by the National Pathology Accreditation Advisory Council (NPAAC). NPAAC have published the following guidelines which are relevant to the regulation of in-house molecular and genetic testing:

- Requirements for the Development and Use of In-house In Vitro Diagnostic Devices (IVDs) (2007)(National Pathology Accreditation Advisory Council 2007)
- Laboratory Accreditation Standards and Guidelines for Nucleic Acid Detection and Analysis (2012)(National Pathology Accreditation Advisory Council 2012)
- Classification of Human Genetic Testing (2012)(National Pathology Accreditation Advisory Council 2012)

#### *In-house In Vitro Diagnostic Devices*

PGD is a Class 3 IVD according to Rule 6 of the *Rules relating to IVDs used in patient management* (National Pathology Accreditation Advisory Council, 2007). As a result of IVD regulatory reforms PGD tests will be subject to listing with TGA from 1 July 2014 (Therapeutic Goods Administration 2010). Currently PGD is governed by the Fertility Society of Australia's *Code of Practice for Assisted Reproductive Technology Units*. The Code of Practice specifically includes IVF and embryo biopsy for PGD as ART procedures that fall under its governance. Compliance with the *Code* is mandatory for the practice of ART (Reproductive Technology Accreditation Committee 2010 (revised))

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<sup>2</sup> Depending on the funding arrangement for PGD, this amendment to associated note T1.4 may not be necessary.

PGD is a level 2 DNA test, according to the *Laboratory Accreditation Standards and Guidelines for Nucleic Acid Detection and Analysis (2012)* (National Pathology Accreditation Advisory Council 2012) (see Table 1). As such, genetic counselling should be provided for couples at appropriate stages throughout the process of PGD.

Table 1 Levels of DNA testing(National Pathology Accreditation Advisory Council 2012)

Type of DNA test for an inherited genetic disorder	Explanatory notes <sup>a</sup>
Level 1 DNA test (standard)	Included here would be: a) DNA testing for diagnostic purposes (eg the patient has clinical indicators or a family history of an established inherited disorder and DNA testing is being used to confirm the disorder) or any other DNA test that does not fall into level 2. b) Population-based screening programs.
Level 2 DNA test (ie the test has the potential to lead to complex clinical issues)	DNA testing for which specialised knowledge is needed for the DNA test to be requested, and for which professional genetic counselling should precede and accompany the test. Predictive or presymptomatic DNA testing, for conditions for which there are no simple treatment would usually be included in this grouping. Specific written consent and counselling issues are associated with this grouping.

<sup>a</sup>The distinction between Level 1 (standard DNA test) and Level 2 (DNA test with potential complex issues) would usually be made by the doctor ordering the test, since that individual will be best placed to appreciate the short-term and long-term implications of the test for the patient and other family members.

The Human Genetics Society of Australasia outlines practice requirements and standards for genetic services in their document Clinical Genetic Services Standards Framework (Human Genetics Society of Australasia 2013).

#### *State and Federal government legislation for ART practice*

The states of New South Wales, Western Australia, South Australia and Victoria currently have legislation in place to govern the practice of ART, with legislative acts varying between these states<sup>3</sup>. There is currently no Commonwealth legislation for ART practice, however The Reproductive Technology Accreditation Committee (RTAC, established by the Fertility Society of Australia) oversees the practice of ART in Australia, including compliance with the *Code*. The RTAC also require compliance with published NHMRC ethical guidelines and standards (National Health and Medical Research Council 2007).

The NHMRC recommendations for clinical practice in PGD are summarised in Appendix B, Table 17. The NHMRC guideline also describes the regulatory framework for ART clinical

<sup>3</sup> The state acts can be viewed by following the link: <http://www.nhmrc.gov.au/health-ethics/australian-health-ethics-committee-ahec/assisted-reproductive-technology-art/assisted->



practice and research in Australia, under which the guidelines are enforced. The regulatory framework is outlined in Appendix B, Box 4.

## Intervention

### Current use

Australia and New Zealand Assisted Reproduction Database (ANZARD) collect data on the number of PGD fresh cycles (including PGD testing) and the number of live deliveries resulting from PGD in Australia on an annual basis (Table 2). The total number of PGD cycles represents 1.8% (for 2007 and 2008), 1.7% (for 2009 and 2010) and 2.0% (for 2011) of all ART cycles for which embryos were created or thawed in that year (ANZARD).

Table 2 ANZARD data for the number of PGD cycles initiated outcomes for 2007 to 2011 (ANZARD)

ANZARD data (% of total PGD cycles)	2007	2008	2009	2010	2011
PGD fresh cycle (including PGD testing)	762 (82)	795 (82)	928 (89)	704 (77)	908 (77)
PGD cryofrozen cycle (transfer of frozen embryo from previous PGD cycle)	144 (16)	176 (18)	116 (11)	211 (23)	274 (23)
Total PGD cycles	906	971	1,044	915	1,182
Number of embryos transferred	656 (72.4)	699 (72)	NA	627 (68.5)	777 (65.7)
Number of clinical pregnancies	212 (23.4)	231 (23.8)	NA	177 (19.3)	262 (22.2)
Number of live deliveries	161 (17.8)	178 (18.3)	NA	139 (15.2)	210 (17.8)

NA = not available

The applicant Genea estimates - from internal data - that the number of PGD cycles that would be initiated for the population proposed in this document (i.e. single gene disorders and gene rearrangements associated with a serious medical condition) is 45% of the totals given in Table 2. PGD uptake has increased at a rate of approximately 5% per year according to ANZARD data. Although an increase in cycle numbers are expected as a result of MBS listing, it is suggested that this increase may be limited by the following factors:

- PGD technology is to be used for a defined population and not for general screening
- Some couples will not want to undergo the IVF process

Estimates of PGD uptake calculated from stakeholder guidance, ANZARD data and Genea internal data are shown in Table 3. Calculations allow for approximately 50% growth in 2013, 25% growth in 2014, and 15% growth in 2015. Following this initial period, the

applicant estimates that growth will to settle at around 10% allowing for population growth in Australia.

**Table 3 Potential utilisation of PGD in Australia (data supplied by applicant, sourced from ANZARD and Genea)**

	2011	2012	2013	2014	2015	2016
Estimated number of single gene and translocation fresh cycles	550	605	908	1,135	1,305	1,436
Estimated growth	10%	10%	50%	25%	15%	10%

## Description

### The population eligible for PGD

PGD can be defined as the testing of embryos for specific genetic abnormalities known to exist in one or both parents (Brezina, Brezina & Kearns 2012). In line with this, the applicant is proposing that PGD is subsidised for couples seeking their own biological children, who know that one or both of them carry a specific genetic mutation(s) for a serious genetic disorder that is at high risk of being passed on to their children. The purpose of PGD is to prevent pregnancy with an embryo carrying a serious genetic disorder and ultimately to assist prospective parents in having a child free of that disorder. The PGD eligible population can be described as:

- couples who have been diagnosed with or know that they carry a genetic condition, and who are therefore at risk (usually a 1 in 2 or 1 in 4 risk) of having a child with a serious genetic disorder, or
- couples where one or both partners carry a rearrangement of their chromosomes, who are therefore at risk of conceiving an embryo with an unbalanced genetic content leading to miscarriage, stillbirth or a serious congenital abnormality or genetic disorder at birth (for balanced translocations there is a 1 in 2 risk of transmission).

A prospective parent would know that they carry a specific genetic mutation for a serious genetic disorder through having consultation and assessment with a clinical geneticist, who would have conducted genetic and molecular analysis to determine the exact nature of the mutation/s. The parents may have sought this consultation in the event that they have a child with the disorder, there is a family history of the disorder for which the prospective parent has had prior genetic testing, or they themselves having been diagnosed with the disease. A serious genetic disorder conferring eligibility for PGD may result from a single gene mutation or chromosome rearrangement (translocation). A serious genetic disorder would be considered as being one which is untreatable, apart from symptomatic care, and unable to be prevented. Examples of the type of disorders that are eligible for PGD include cystic fibrosis (an autosomal recessive disorder), Duchenne muscular dystrophy (an x-linked

disorder), Huntington's disease (an autosomal dominant disorder) and Fragile X syndrome and other x-linked disorders).

Preimplantation genetic *diagnosis* is different to preimplantation genetic *screening* (PGS). PGS is conducted to screen for unspecified and multiple genetic anomalies including aneuploidy in embryos from parents who do not have any diagnosed genetic abnormality (Brezina, Brezina & Kearns 2012). It may be performed to improve embryo to uterine transfer and pregnancy success rates in couples undergoing IVF and has been used in cases of advanced maternal age and repeated implantation failure (Bodurtha & Strauss 2012). This application does not include the use of PGS, the use of which tends to be more controversial than PGD. PGD as described in the application does *not* include the following:

- Screening for aneuploidy (abnormal chromosome number)
- Sex selection for family balancing
- Embryos which may carry the genetic defect but may not be affected by the genetic disorder, i.e.
  - Embryos which carry a single copy of a recessive gene disorder
  - Embryos which require a combination of multiple factors in order that the disease manifests itself

According to the applicant, PGD has been used in Australia for the diagnosis of over 150 genetic disorders. While the disorders on this list may have been tested for with PGD in the private setting, they may or may not be classified as 'serious genetic disorders' or at 'high risk' of being passed on to offspring. Under the current proposal they would not all be eligible for PGD subsidy.

- To define the eligible population PASC has agreed that there should be a list of approved severe genetic disorders which would be supported by a review process. The review process would involve a committee who would decide whether an unlisted condition would warrant public funding. Review of unlisted disorders such as rare<sup>4</sup> genetic disorders would be guided by a criteria check list similar to the following (the list is not intended to be complete or definitive): Single gene mutation or a chromosomal rearrangement
- Severe to very severe symptoms
- Chronic (lifelong) complications
- Degenerative and life-threatening disease

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<sup>4</sup> The threshold for 'rarity' varies between states and should be clearly defined for the purpose of determining PGD eligibility. It was noted that 'Rare Voice Australia' have criteria to define rare disease, and this could be used to guide the checklist.

- Disabling disease i.e. the quality of life of patients is compromised by the lack or loss of autonomy
- There is a significant psychosocial burden for patients, carers and their families
- Incurable disease, without effective treatment, except for symptomatic treatment to improve quality of life or life expectancy
- Very difficult to manage with families encountering enormous emotional and financial difficulties in providing appropriate treatment and care

It is suggested that the list be further expanded through consideration of the ethical underpinnings of each criterion. Furthermore, consideration should be given regarding the implications of serious genetic diseases and the impact of their symptoms and limitations on families in addition to a list of clinical criteria. The Applicant has proposed a checklist for the purpose of identification of an eligible population, which can be seen in Appendix C.

A list of genetic disorders commonly tested for by the applicant (Genea) with PGD is shown in Table 4. Disorders are listed in order of the percentage of PGD cycles used.

Table 4 Sydney IVF 2007 - Data as a percentage of PGD cycles per gene disorder

Gene Disorder	No. of PGD cycles initiated	%
Various single gene disorders (1 cycle)	26	21.7%
Huntington's disease	21	17.5%
Cystic fibrosis	23	19.2%
Charcot-Marie-tooth 1A	9	7.5%
Myotonic dystrophy 1	8	6.7%
I Becker muscular dystrophy	4	3.3%
Fragile X	3	2.5%
Haemophilia A	3	2.5%
Tuberous sclerosis	3	2.5%
Proximal myotonic myopathy	3	2.5%
Spinal muscular atrophy 1	3	2.5%
Connexin 26	2	1.7%
Duchenne muscular dystrophy	2	1.7%
Familial adenomatous polyposis	2	1.7%
Metachromatic leucodystrophy	2	1.7%
Nephrogenic diabetes insipidus	2	1.7%
Saethre-chotzen syndrome	2	1.7%
Von Hippel-Lindau disease	2	1.7%

NB: The name Muscular Dystrophy applies to a large group of genetic and hereditary muscular and neuromuscular diseases.

## ***Description of the PGD process***

Before PGD could commence the couple would need confirmation from a clinical geneticist that they carry specific genetic mutations for a serious genetic disorder that are at high risk of being passed on to their children. The exact nature of the genetic mutation must be known as well as the disorder which it causes. The disorder must be known to be either a single gene disorder of simple inheritance pattern or a chromosome rearrangement. PGD is a three stage process involving: (1) test design and validation for a known specific genetic mutation(s) (2) embryo biopsy, and (3) embryonic DNA analysis. These three steps are reflected in the three proposed items for PGD. The PGD process begins with:

### *Stage 1. Test design and validation for known specific genetic mutations*

Through the determination of flanking molecular markers, linkage markers, and the exact base sequence in the gene of interest in both parents, linkage and/or sequencing primers (probe) can be designed that will enable detection of the parental mutation(s) in the embryos. Increasing the number of known markers can increase the accuracy of the test.

To validate the test, DNA from the family members or parents undergoes PCR using the designed primers and testing/sequencing to confirm that the tailored test is able to identify the mutation or chromosome translocation. The test regime should be optimised to ensure it is efficient when used on the minimal DNA quantities available from the embryo cells.

Stage 1 is expected to take a number of weeks and the couple should be informed of the test results.

### *Stage 2. Embryo biopsy*

For the next step in PGD the prospective mother undergoes IVF to provide fertilised embryos for biopsy and DNA analysis. Once the eggs are collected and fertilised they are matured to the stage at which biopsy of cells can be conducted. An IVF cycle involves the following steps:

- Stimulation of the ovaries with injections of follicle stimulating hormone
- Preventing premature ovulation so that the eggs are not ovulated before they can be collected
- 'Triggering' preparation for egg collection
- Collecting the eggs and sperm
- Inseminating the eggs
- Culturing in the laboratory to fertilisation
- Culturing fertilised embryos to biopsy stage\*
- Transferring the embryo/s
- Supporting the endometrium in the luteal phase

\*The biopsy part of the PGD process occurs once fertilisation has taken place and the embryos have been cultured for several days before being transferred.

Biopsy can occur at three developmental stages: (1) polar bodies can provide maternal DNA; (2) cleavage stage embryos can provide one or two cells; or (3) the blastocyst stage embryo can provide trophectoderm cells. Current opinion suggests that the third stage (blastocyst) is more robust. At 5 days old the blastocyst embryo is more developed (and contains both inner cell mass cells and trophectoderm cells) than the cleavage stage embryo (at 3 days old the cleavage stage embryo contains only 6 to 8 omnipotent cells). The blastocyst embryo is able to better withstand removal of cellular material (Brezina, Brezina & Kearns 2012) and may also have less chance of providing inaccurate DNA results from mosaicism (Hens et al. 2013; Martin et al. 2013).

### *Stage 3. Embryo DNA analysis*

For the final stage of PGD, DNA prepared from the embryo undergoes analysis using the primers (probe) prepared in the test design stage to identify the unique genetic mutation. Results can be compared to the genetic pattern of the parents or other family members to confirm the presence or absence of the genetic abnormality. Embryos identified with a normal DNA sequence can be transferred to the mother.

If no suitable embryos are found, the couple may choose to begin the process again, in the hope of achieving this goal in another attempt. Currently this procedure usually involves the implantation of a single embryo. Should more than one suitable embryo be found in the analysis stage, then remaining embryos will be cryopreserved, and accessed should the first pregnancy be unsuccessful, or should the couple want further children.

### **Delivery of the intervention**

Consultation with a clinical geneticist is required for a couple to be referred for PGD services that will be eligible for subsidy for PGD. The clinical geneticist can identify the exact mutation that the couple carry and the genetic disorder (including its inheritance mode) that that mutation confers. Consultation may take place in private practice (e.g. fertility clinic) or in the public domain (e.g. hospital outpatient department). Once an exact mutation is identified and genetic disorder confirmed, a couple would be referred to a fertility specialist and an IVF clinic where PGD services are provided. Mutation test design and validation would follow. Once test design and validation is complete, the couple would receive preparation prior to undergoing an IVF cycle. The IVF clinic takes overall responsibility for delivery of all three PGD stages.

Test design will vary in complexity between couples undergoing PGD. In many cases a common mutation may be present which has undergone analysis and validation in other couples, or a couple may carry a unique and previously undetected mutation which requires

complex and original molecular analysis. In all cases test design will require analysis of DNA from both parents to determine markers associated with the mutation and gene of interest in the embryo. It may therefore be appropriate to use a tiered approach for the costing of Stage 1 which would be stratified according to the level of time, expertise and technology required. If Stage 1 is only reimbursed once per couple, it would be expedient if information provided by testing in this stage was made accessible to those requiring it in the future and not be treated as intellectual property by the clinic that performed the test.<sup>5</sup>

As outlined above, PGD occurs in three stages, each of which can take considerable time and use numerous resources. If PGD is successful i.e. results in the birth of a healthy child, then only one claim for each PGD item may be required. Further successful births may result from additional embryos in cryostorage if available, requiring no further claim on PGD items. If the stages are listed separately for funding, and PGD fails at stage 2 or 3 (for example if no embryo is identified that is free of the specific genetic mutation) then a couple may want to undergo another IVF cycle and use additional PGD stage 2 and 3 items. Under the applicant's proposal, the stage one PGD item can be claimed only once, but there is no limit on the number of claims that can be made for items 2 and 3.

### Prerequisites

To access subsidised PGD services a couple needs to be referred to a fertility specialist and IVF clinic where the services would be performed. To gain this referral the couple would need to be assessed by a genetic clinical geneticist. Genetic counselling services provided by a clinical geneticist can be claimed under the Medicare item number 132 for the first session, and item 133 for subsequent sessions. Most couples will require one initial counselling session followed by a second session when testing is ordered.

Each step of the PGD service would be delivered by the following professionals:

1. Genetic test design and validation – performed by trained molecular geneticists
2. Biopsy of embryo – performed by trained embryologists or molecular geneticists
3. Analysis of genetic information from the embryo biopsy – performed by trained molecular geneticists

IVF and PGD are performed in specialist centres that provide access to trained medical professionals and counsellors. Specialised equipment for services such as blastocyst biopsy and cryostorage will normally be located at the centre or clinic. IVF clinics should have

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<sup>5</sup> MBS reimbursement for design and validation of a test is unprecedented, the cost is being normally recouped from performing the test. However, for rare disorders this may not be practical. Implementation issues surrounding fee structure and quality assurance will be under taken by the department.

specialists and staff who manage IVF and PGD cycles that include fertility specialists, geneticists, genetic counsellors, nurses, embryologists and molecular geneticists.

Fertility clinics that perform IVF are currently located in most cities and many regional areas of Australia, providing for the needs of most couples. However, PGD requires a higher level of expertise, technology and quality assurance than IVF and is likely to be available in only 2 or 3 major clinics in Australia. Biopsy material (DNA) will need to be transferred to one of these clinics for analysis (unless performed at the clinic itself). Transfer of biopsy material may incur additional costs which are not expected to be large (there is no cold chain required) and may be incorporated into the item fees.

PGD services are already being provided in one or two fertility clinics, and it is not expected that additional equipment or quality assurance for testing platforms would be required by these facilities. Increased demand may put pressure on output capabilities and so upgraded equipment with larger/faster output capacity may be required to meet this demand. Alternatively, more clinics may provide the service. Ethical guidance could be required if testing platforms such as whole genome testing and microarrays are used. These provide more information than is necessary for a PGD service and questions may arise as to how to manage the additional data.

### Co-administered and associated interventions

PGD would be co-administered with IVF services. IVF is a requirement for PGD as fertilised eggs produced through this method are then analysed for genetic content before being implanted. IVF services are MBS listed as part of the ART services and are not being assessed for this application. The current listing for IVF is an ART service under *MBS Category 3 Therapeutic Procedures* items 13200 to 13221. ART item descriptors can be seen in Appendix A, Table 14 (not all ART services are relevant to IVF).

### Listing proposed and options for MSAC consideration

#### Proposed items descriptors for funding

The proposal for PGD subsidy includes three new items. These are illustrated in Table 5 and relate to each of the three PGD stages as previously described. Amendments which have been suggested by HESP members are shown highlighted in blue.

Table 5 Proposed descriptors for PGD items 1, 2 and 3

Category 6– PATHOLOGY (Group P7 Genetics)	
Item [xxxxx]	
<u>PGD Stage 1 Genetic test design and validation</u> of a specific test that detects the individual mutation/chromosome location pattern causative of a severe disease: by examination of genetic material from person(s) and/or blood relatives to persons commencing Assisted Reproduction Technologies in	



conjunction with Preimplantation Genetic Diagnosis for genetic abnormality(s).

Explanatory Note:

Item number is relevant for couples undergoing PGD for the following reason:

- couples who carry a specific mutation(s) for a serious genetic disorder (and know the exact nature of that mutation) and are at high risk (usually 1 in 2 or 1 in 4) of having a child with a serious genetic disorder, or
- couples where one or both partners carry a specific rearrangement of their chromosomes, who are therefore at risk of conceiving a pregnancy which has an unbalanced genetic content which could cause miscarriage, stillbirth or have serious congenital abnormalities or a genetic disorder at birth.

The fee must only be applied once per couple (the PGD test is developed once and it does not need to be repeated on a per cycle basis; **information provided by the test must be made accessible**)

The ordering practitioner should ensure the patient(s) have given informed consent and appropriate genetic counselling is provided to the patient either by the treating practitioner, a genetic counselling service or by a clinical geneticist on referral. Further counselling **should be provided** subsequent to the development of the PGD test in order to explain the diagnostic risks and limitations for their particular test.

Fee structure

Level 1: \${fee} Design and validation of a probe for simple/common mutations

Level 2: \${fee} Design and validation of probe requiring complex analysis and/or high level of technical expertise,

[Relevant explanatory notes]

Category 3 – THERAPEUTIC PROCEDURE

Item [xxxxx]

**PGD Stage 2 Embryo biopsy:** Biopsy of one or more embryos per cycle, conducted in association with Assisted Reproductive Technologies (MBS subsidised) in conjunction with Preimplantation Genetic Diagnosis for genetic abnormality(s).

Explanatory Note:

This item number can only be used as part of persons commencing Assisted Reproduction Technologies in conjunction with Preimplantation Genetic Diagnosis for genetic abnormality(s).

Fee: \${fee}

[Relevant explanatory notes]

Category 6– PATHOLOGY (Group P7 Genetics)

Item [xxxxx]

**PGD Stage 3 Embryo genetic analysis:** The study of biopsied embryo tissue using molecular techniques for single gene disorders or the whole of every chromosome. (One or more embryos)

Explanatory Note:

This item number can only be used following item number 2 Embryo biopsy as part of persons commencing Assisted Reproduction Technologies in conjunction with Preimplantation Genetic Diagnosis for genetic abnormality(s).

Embryo(s) that are not affected by the genetic disorder can be transferred to the uterus of the female or vitrified.

**This item number must not be used for the purpose of positive selection for gender or a genetic disorder.**

Fee: \${fee}

[Relevant explanatory notes]

The applicant makes the following points regarding the proposed items.

- 3 item numbers have been proposed so that the payer only pays for the exact service provided to the patient.
- In some cases, couples may access Item 1 but they may not be able to produce a viable embryo for biopsy because the female does not produce any eggs or the embryos do not develop to the correct stage for biopsy.
- Item 1 will only need to be accessed once per couple. If they come back for a further PGD cycle they will not need to repeat this step.
- Item 2: The average number of biopsies taken per PGD cycle is 3.4 (Genea data). The embryo biopsy/biopsies may be undertaken at a different IVF clinic from the PGD testing IVF clinic.
- Item 3: This analysis is only done once per PGD cycle as biopsy material from many embryos of the same couple can be batched to run the genetic test at the same time.

The applicant requested a change to the Associated Note T1.4 is requested to enable IVF and PGD item numbers to be used together. The relevant section of current Note T1.4 is shown in Table 6 and proposed version is given in Table 7 with additions highlighted.

Table 6 Current MBS Associated Note T1.4

Note T1.4
Medicare benefits are not payable in respect of ANY other item in the Medicare Benefits Schedule (including Pathology and Diagnostic Imaging) in lieu of or in conjunction with items 13200 – 13221 but excluding item 13202. Specifically, Medicare benefits are not payable for these items in association with items 104, 105, 14203, 14206, 35637, pathology tests or diagnostic imaging

Table 7 Proposed MBS Associated Note T1.4

Note T1.4
Medicare benefits are not payable in respect of ANY other item in the Medicare Benefits Schedule (including Pathology and Diagnostic Imaging) in lieu of or in conjunction with items 13200 – 13221 but excluding items 13202, <i>Item 1 PGD test design and validation, Item 2 PGD embryo biopsy and Item 3 PGD embryo genetic testing</i> . Specifically, Medicare benefits are not payable for these items in association with items 104, 105, 14203, 14206, 35637, pathology tests or diagnostic imaging.

To support these additions, there may be other amendments or clarifications required, such as:

- Rules for the Interpretation of the Pathology Services Table; and

- Ensuring that Item 13251, intracytoplasmic sperm injection (ICSI), may be used with PGD. This is required because it is important that there is no extraneous sperm attached to the embryos because this could give false genetic testing results.

Genetic counselling is provided for in the descriptor for item 1.

As IVF is an integral part of the PGD process, couples undergoing PGD would need to meet eligibility criteria for that procedure (Appendix A, Box 1).

### **Clinical place for proposed intervention**

PGD services are already offered in the community, but to a broader population than proposed for the PGD items. It is suggested that PGD services would be offered to those couples who carry a specific mutation(s) for a serious genetic disorder (and know the exact nature of that mutation) which is at high risk of passing on to their children, and couples who know that they carry a specific rearrangement of chromosomes which is at high risk of leading to serious genetic disorder in their children. It is likely that not all eligible couples would choose to undergo PGD. They could choose to try for a natural pregnancy, followed by prenatal diagnosis and the possibility of termination of pregnancy, or will pursue another pathway to have a family such as pregnancy with donor egg or sperm, or adoption. Some couples may choose not to have children. PGD is therefore provided in addition to other services already being utilised. It would be expected that there would be a decrease in the use of natural pregnancy with prenatal diagnosis (or post-natal diagnosis) for the proposed population and an increased uptake of PGD should the service be funded by the Commonwealth.

The pathway of a couple undergoing PGD is demonstrated in the proposed pathway illustrated in the algorithm in Figure 1.

Mothers pregnant after IVF followed by PGD selection and fitting the criteria (i.e. over 35 years, other risk factors) would have the option to undergo routine genetic screening. Depending on the screening test results, parents would then need to decide on whether to undergo prenatal diagnosis and possible termination of pregnancy (TOP). Routine genetic screening would be an option available to both the intervention and the comparator pathways, and is therefore not represented in the clinical pathways illustrated in Figure 1.

It is likely that some parents who conceive following PGD embryo selection will choose to undergo prenatal genetic testing, either to confirm the genotype of the fetus determined by PGD, and/or to test for other genetic conditions. PGD is not 100% accurate and misdiagnosis can occur for a number of reasons:

- Biological factors such as mosaicism in the embryo

- Rearrangement of genetic material<sup>6</sup>
- Failure of the test, leading to diagnosis of no abnormality where the genetic mutation is there in reality<sup>5</sup>
- Apparent misdiagnosis can occur if the tested embryo fails to implant and the patient becomes pregnant naturally (patients are instructed not to have unprotected intercourse during a PGD cycle).
- The baby may be affected by an unrelated disorder
- There could be unrelated complication during development or birth

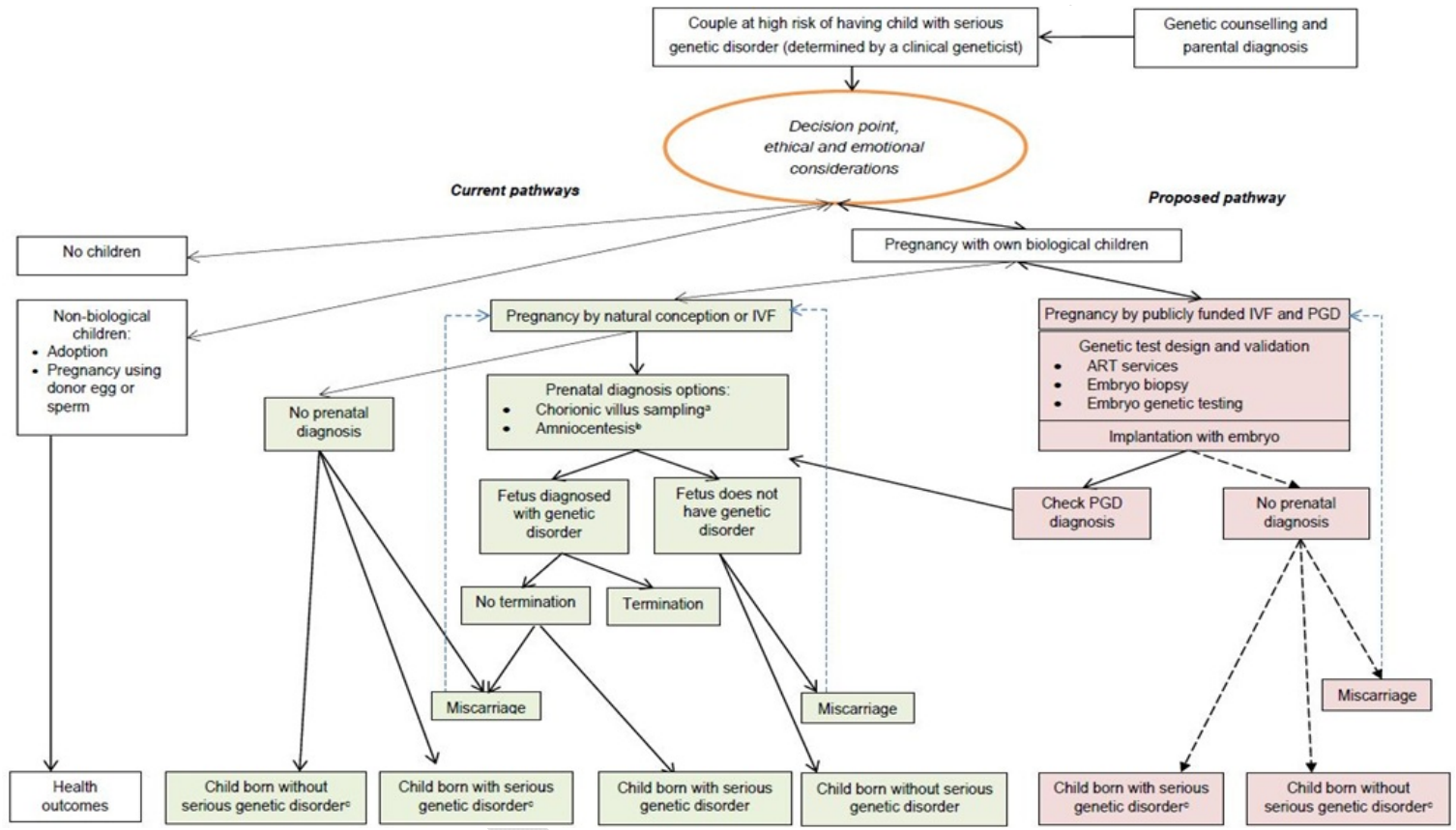
The current and proposed clinical pathways have been prepared by the assessment group and illustrated in Figure 1.

PRELIMINARY

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<sup>6</sup> this should be reduced by accurate test design and validation and linkage/genetic fingerprint data

**Figure 1 Algorithm comparing clinical treatment pathways for PGD versus pregnancy by natural conception or IVF followed by prenatal diagnosis and possible TOP**



<sup>a</sup> CVS is carried out at 10-12 weeks of pregnancy. Termination is performed by evacuation and curettage at this stage of pregnancy.

<sup>b</sup> Amniocentesis is carried out at 14-16 weeks of pregnancy. Termination is performed by induction of labour.

<sup>c</sup> Children born not having undergone prenatal testing, may undergo clinical or genetic/molecular post-natal testing

## Comparator

### Comparators for direct evidence in couples and children

As PGD is considered high risk, requiring a formal assessment of safety, effectiveness and cost-effectiveness, the proposed comparator for PGD in couples is pregnancy by natural conception or IVF followed by prenatal diagnosis and the option of termination of the pregnancy (TOP). Prenatal diagnosis may be performed using either chorionic villus sampling (CVS; suitable at 10 to 12 weeks pregnancy), amniocentesis (suitable at 14 to 16 weeks pregnancy), or fetal blood sampling (FBS; rarely used). The timing of the prenatal test will affect the risk of miscarriage which varies with weeks of pregnancy. Alternatively parents who undergo natural pregnancy or pregnancy by IVF may choose post-natal genetic diagnosis (without the option of TOP) rather than pre-natal diagnosis.

A secondary comparator that PASC recommended is the option of parents who decide *not* to have their own biological children due to the risks of having a child with a serious genetic disorder or choosing to have a termination. Parents in this category may choose PGD if it were subsidised over the current choices of adoption or conception with donor egg or sperm, or may choose not to have children by any means. This comparator should only be evaluated if it has been determined that a significant proportion of couples carrying a mutation choose this option.

To assess the safety and effectiveness in *children* born as a result of PGD, it has been proposed that only those children who have been born *without* the genetic disorder carried by the parents should be considered. The health outcomes for children born with the genetic disorder can be assumed to be similar in for those born either as a results of natural conception or PGD and therefore do not need to be assessed. To investigate the effects of the PGD process on children's health, the comparison should be between children without the disorder born by PGD and those born by IVF alone followed by prenatal diagnosis. As IVF is an accepted practice in Australia, this assessment will look for effects on health in children that are additional to those of IVF.

### Comparators for linked evidence

For assessment of diagnostic accuracy, diagnosis using PGD (test design and validation based on parental DNA) will be compared with prenatal diagnosis of the fetus (no test design and validation using parental DNA). In addition a comparison of accuracy of PGD testing methods should be undertaken. Methods currently used for PGD and which could be considered for assessment are SNP screening, whole genome sequencing and microarray complete genome hybridisation. To assess the rate of change in management should PGD prove to be more accurate than prenatal diagnosis, 'PGD stage 3 (embryo genetic analysis followed by selective implantation)' will be compared with 'prenatal diagnosis by genetic analysis followed by possible termination of pregnancy' in couples who know that they carry

a severe genetic disorder. The decision to terminate is considered likely to be the major change in management. The assessment of the impact of this change in management should compare the effects 'the decision to terminate a pregnancy' with 'not having to decide to terminate a pregnancy' in couples who are pregnant with a child at risk of having a serious genetic disorder, as well as comparing the effects of 'TOP' with 'no TOP' in the same population.

#### MBS subsidy associated with the comparators

The MBS provides subsidy for various pathology services which may be used for prenatal diagnosis in the comparator population. The prenatal embryonic sampling techniques of CVS, amniocentesis, and FBS (Category 3 Therapeutic Procedures item 16600, 16603 and 16606) are currently MBS subsidised (see Appendix A, Table 16). While these items are not suitable for PGD, they are related service items and are used to carry out current alternative forms of prenatal diagnosis. Prenatal diagnosis, when performed following CVS, amniocentesis or FBS can give the opportunity of offering a couple the termination of a pregnancy should test results show that a fetus carries a serious genetic disorder and depending on the timing of the test.

Genetic testing for Fragile X (A) (Category 6 Pathology Services items 73300 and 73305), and various chromosome analysis services (Category 6 Pathology Services items 73287, 73289, 73291, 73292, 73293) are listed on the MBS and are shown in Appendix A, Table 15.

Once a couple becomes pregnant by natural conception or IVF they may choose to undergo prenatal testing. If a couple choose not to undergo testing, they will bypass the option of TOP and will remain at high risk of having a child with the genetic disorder they carry. However for some couples, taking this risk is preferable to choosing between TOP or continuing a pregnancy if a prenatal test indicates that their child is going to have a genetic disorder.

If a couple choose to undergo prenatal testing there are several techniques for obtaining a DNA sample from the fetus. The earliest available fetal biopsy technique is CVS, which is carried out at 10 to 12 weeks. CVS takes a sample of cells from the placenta with the test giving a risk of procedure related miscarriage of around 1 - 2%. Once DNA is extracted from the cells it is screened for genetic abnormality. In the case of the population proposed for this assessment, the genetic condition for which testing is required is known by the couple, although in this case a specific validated test tailored to the couple has not been designed. Without the benefit of a specific and validated test, there is a greater likelihood of test inaccuracy. Once the result is known, the couple will have the option of TOP if their child is found to have a severe genetic disorder.

If prenatal testing is required at the 14 to 16 week mark, amniocentesis is the usual choice. The risk of procedure related miscarriage after amniocentesis is slightly less than for CVS (0.5 - 1%), however the option for TOP via curettage is reduced by the time taken for genetic testing to be completed. If curettage cannot be performed due to the stage of pregnancy then TOP is performed by induction of labour.

FBS is an option later in pregnancy but carries a procedure related miscarriage risk of up to 3%. Blood can be extracted from the fetus itself or from the umbilical cord. This type of sample provides a reliable DNA source without contamination by mosaicism.

### Termination of pregnancy

As with the PGD pathway, testing accuracy and pregnancy outcomes are affected by a number of factors. A couple is not restricted in the number of pregnancies for which they may access prenatal testing support and some will choose prenatal testing even after undergoing PGD. Performing and/or choosing to undergo TOP can underline ethical issues associated with the procedure. The applicant highlights the following issues that couples can face, and which can impact on the length of time taken for a woman to access termination:

- Limited access to termination can result in women having a termination after 20 weeks. Abortion falls under the Criminal Statutes in all states except ACT, and fetal abnormality is not legal grounds for TOP.
- Conflicting guidance from medical and ancillary health practitioners due to personal, ethical or religious perspectives.
- Medical practitioners may be unsure of the legality of supporting a termination for their patient.
- Some Catholic hospitals do not perform terminations and therefore women may need to change hospital, and in some cases their doctor, in order to obtain a termination.
- Some hospitals have Ethics Committees to determine whether an abortion is acceptable in each case.
- The emotional and psychological impact of TOP and the process of termination (de Crespigny LJ 2008; Korenromp et al. 2009).
- Women may not be given adequate counselling regarding the accuracy of prenatal testing, miscarriage risk and risks associated with TOP prior to making the decision to undergo prenatal testing (Hodgson et al. 2010).

MBS descriptors for techniques for fetal sampling that form part of the comparator for this assessment are shown in Appendix A, Table 16. MBS descriptors for genetic tests that may be used as part of the comparator for this assessment are shown in Appendix A, Table 15.



## Outcomes for safety and effectiveness evaluation

The health outcomes upon which the comparative clinical performance of PGD can be measured, are considered under the headings of effectiveness, safety and diagnostic accuracy. It should be noted that if there is a paucity of direct evidence available, then the linked evidence approach should be used and outcomes specified for each step of linkage.

### Effectiveness (couples)

Primary outcomes:

- Rate of live births without severe genetic disorder
- Rate of cycles required to achieve a healthy live birth
- Implantation rate
- Parental psychological health benefits
- Parental quality of life

Secondary outcomes

- Termination rate due to presence of specific mutation
- Implantation rate for other reasons
- Pregnancy rate
- Time to live birth

### Effectiveness (offspring)

- Quality of life
- Functional status

### Safety (couples)

- Physical harms to woman from DNA sampling procedures
- Physical harms to woman from TOP
- Miscarriage rate
- Psychological harms from miscarriage, termination, decision making or other aspects of the procedures
  - Depression
  - Post-traumatic stress symptoms
  - Harms resulting from misdiagnosis
  - Physical and psychological effects of genetic disease on a child
  - Physical and psychological effects of genetic disease on parent
  - Physical and psychological harms from not achieving a pregnancy
  - Physical and psychological impact of time delay to diagnosis
  - Physical and psychological impact of time delay to live birth

## **Safety (offspring)**

Physical disability  
Intellectual disability  
Developmental delay  
Peri-natal mortality (eg still-birth)

## **Technical efficacy**

Successful biopsy  
Rebiopsy  
Resampling  
Implantation rate

## ***Linked evidence outcomes***

### **Diagnostic accuracy**

Analytic validity:

Sensitivity – how often is the test positive when the mutation is present?

Specificity – how often is the test negative when a mutation is not present?

Rate of repeat testing required

Time taken to achieve confirmed result (and to resolve false positive results)

### **Change in management**

% change in pregnancy planning

% change in termination rate

% change in pregnancy rate

% increase in IVF usage

% increase in healthy babies compared with those who have other medical conditions not identified through prenatal testing

## Summary of PICO to be used for assessment of evidence (systematic review)

Table 8 and Table 9 provide a summary of the PICO for assessment of direct evidence. The PICO summaries for direct evidence will be used to select the evidence to assess the safety and effectiveness of PGD for *couples* (Table 8) who know that they carry a specific mutation(s) for a serious genetic disorder (and know the exact nature of that mutation) which is at high risk of being passing on to their *offspring* (PICO shown in Table 9). The PICO summaries would be used to:

- (1) define the question for public funding,
- (2) select the evidence to assess the safety and effectiveness of PGD for *couples* with a serious genetic disorder at high risk of passing it on to their offspring, the safety and effectiveness of PGD for *offspring* of couples with a serious genetic disorder at high risk of being passed on, and
- (3) provide the evidence-based inputs for any decision-analytical modelling to determine the cost-effectiveness of the PGD service.

**Table 8 Summary of PICO to assess direct evidence for the safety, effectiveness and technical efficacy of PGD in couples (probands) undergoing PGD**

Population	Intervention	Comparator	Outcomes to be assessed
Couples who know that they carry a severe genetic disorder and are at high risk of passing it onto offspring	PGD (stages 1-3) in conjunction with IVF with/without subsequent prenatal genetic diagnosis	<p>1. Natural pregnancy (or pregnancy by IVF) in conjunction with prenatal genetic diagnosis and the possibility of TOP</p> <p>2.*Natural pregnancy (or pregnancy by IVF) followed by post-natal diagnosis</p> <p>3. *No children, or non-biological children through adoption or donor egg/sperm</p> <p>*The second and third comparator are only required if a significant proportion of couples carrying a mutation choose this option, who would possibly consider PGD if funded.</p>	<p><b>Safety</b></p> <p>Physical harms to woman from DNA sampling procedures</p> <p>Physical harms to woman from TOP</p> <p>Miscarriage rate</p> <p>Psychological harms from miscarriage, termination, decision making or other aspects of the procedures</p> <p>Depression</p> <p>Post-traumatic stress symptoms</p> <p>Harms resulting from misdiagnosis</p> <p>Physical and psychological effects of genetic disease on parent</p> <p>Physical and psychological harms from not achieving a pregnancy</p> <p>Physical and psychological impact of time delay to diagnosis</p> <p>Physical and psychological impact of time delay to live birth</p> <p><b>Effectiveness</b></p> <p>Primary</p> <p>Rate of live births without severe genetic disorder</p> <p>Rate of cycles required to achieve a healthy live birth</p> <p>Implantation rate</p> <p>Parental psychological health benefits</p> <p>Parental quality of life</p> <p>Secondary</p> <p>Termination rate due to presence of specific mutation</p> <p>Termination rate for other reasons</p> <p>Pregnancy rate</p> <p>Time to live birth</p> <p><b>Technical efficacy</b></p> <p>Successful biopsy</p> <p>Rebiopsy</p> <p>Resampling</p> <p>Implantation rate</p>

**Question 1. Is PGD as safe and effective as natural pregnancy (or pregnancy by IVF) followed by prenatal testing and the possibility of TOP for couples who carry a serious genetic disorder and are at high risk of passing it on to their offspring?**

**Question 2. Is PGD as safe and effective as natural pregnancy (or pregnancy by IVF) followed by post-natal testing for couples who carry a serious genetic disorder and are at high risk of passing it on to their offspring? (note: this question only required if a significant proportion of couples would choose between these options)**

**Question 3. Is PGD as safe and effective as choosing to have no children, or choosing to have non-biological children through adoption or donor egg/sperm? (note: this question only required if a significant proportion of couples would choose between these options)**

Abbreviations: DNA deoxyribonucleic acid; PGD preimplantation genetic diagnosis; IVF in vitro fertilisation; TOP termination of pregnancy

Table 9 Summary of PICO to assess direct evidence for the safety and effectiveness of PGD in *offspring* born to couples who have undergone PGD

Population	Intervention	Comparator	Outcomes to be assessed
Neonates /children without genetic disorder, born to couples who know that they carry a severe genetic disorder and are at high risk of passing it onto offspring	Conceived via IVF and undergone PGD (stages 2-3) with/without subsequent prenatal genetic diagnosis	Conceived via IVF, and followed by prenatal diagnosis	<p><u>Safety (where possible distinguish from disease related issues)</u></p> <p>Physical disability Intellectual disability Developmental delay Peri-natal mortality (eg still-birth)</p> <p><u>Effectiveness</u></p> <p>Quality of life Functional status</p>

Question 1. Is having been conceived through IVF and PGD as safe, and effective as conception by IVF followed by prenatal testing in *offspring* who were at risk, but are free from having a serious genetic disorder?

Abbreviations: PGD preimplantation genetic diagnosis; IVF in vitro fertilisation

Table 10, Table 11 and Table 12 provide PICO summaries for assessment of linked evidence should insufficient direct evidence be identified. The PICO summaries would be used to select evidence to:

- (1) Assess the accuracy of PGD compared to prenatal diagnosis,
- (2) Determine the change in management of couples who know that they carry a serious genetic disorder that is at high risk of being passed on to their offspring, and
- (3) Assess the impact of change in management, in particular the impact of termination of a pregnancy on couples and mothers.

Table 10 Summary of PICO to assess the accuracy of PGD (linked evidence)

Population	Intervention	Comparator	Reference standard/ evidentiary standard	Outcomes to be assessed
Couples who know that they carry a severe genetic disorder and are at high risk of passing it onto offspring	PGD stage 3: Genetic testing of embryonic DNA using designed and validated test -SNP screening -whole genome sequencing -microarray complete genome hybridisation -other relevant test methods	Genetic testing of fetal DNA (without test design using DNA from parents or affected relatives)	Mutation analysis in gene/ rearrangement in question	<b><u>Analytic validity</u></b> Sensitivity Specificity Rate of repeat testing required Time taken to achieve confirmed result (and to resolve false positive results)  <b><u>Comparison of accuracy of PGD stage 3 testing methods</u></b>

Question 1. Is PGD as accurate as natural pregnancy (or pregnancy by IVF) followed by prenatal testing and the possibility of TOP for couples who carry a serious genetic disorder and are at high risk of passing it on to their offspring?

Question 2. Is a method for determination of the presence of the mutation in question more accurate than any other method for couples who carry a serious genetic disorder and are at high risk of passing it on to their offspring?

Abbreviations: DNA deoxyribonucleic acid; PGD preimplantation genetic diagnosis

Table 11 Summary of PICO for evidence of change in management (linked evidence)

Population	Intervention	Comparator	Outcomes to be assessed
Couples who know that they carry a severe genetic disorder and are at high risk of passing it onto offspring	PGD stage 3: Embryo genetic analysis followed by selective implantation	Prenatal diagnosis by genetic analysis followed by possible termination of pregnancy	<b><u>Change in management</u></b> % change in pregnancy planning % change in termination rate % change in pregnancy rate % increase in IVF usage % increase in healthy babies compared with those who have other medical conditions not identified through prenatal testing

Question 1. Is there a change in management of couples wanting their own biological children through the use of PGD compared to natural pregnancy (or pregnancy by IVF) followed by prenatal diagnosis and the possibility of TOP in couples who are at high risk of passing on a serious genetic disorder to their offspring?

Abbreviations: PGD preimplantation genetic diagnosis

Table 12 outlines the proposed PICO criteria, which may be used to assess the impact of being faced with the decision regarding whether to terminate a pregnancy, and the impact of that termination, or the impact of having a child with a serious genetic disorder, if direct evidence comparing the PGD and prenatal diagnosis is not available.

Table 12 Summary of PICO for impact of change in management (linked evidence)

Population	Intervention	Comparator	Outcomes to be assessed
Couples who are pregnant and whose offspring is at risk of a serious genetic disorder, who undergo prenatal testing.	A negative result from prenatal testing, resulting in couples not needing to consider termination of pregnancy, as their child is free of a serious disorder.*	A positive result from prenatal testing, resulting in couples being faced with the decision regarding whether to terminate the pregnancy, or have a child with a serious disorder, and the consequences of these.	<u>Psychological impact</u> <u>Physical harms</u>

Question 1. What is the psychological impact of the decision regarding whether to terminate a pregnancy, and termination of pregnancy to a couple whose offspring is affected by a serious genetic disorder?

Question 2. What are the physical safety concerns to the mother regarding termination of pregnancy?

\*The outcomes of couples following a negative pre-natal test result are assumed to be similar to those who use PGD and avoid having an embryo with the serious genetic disorder implanted.

### Clinical claim

The applicant has submitted the clinical claim that PGD is *as effective* in identifying genetic disorders as prenatal diagnosis. In addition because PGD is completed prior to transfer of the embryo the parents have immediate confirmation that the embryo is free of the genetic condition whereas those who have prenatal diagnosis will wait 11-24 weeks to know whether their fetus is healthy or whether they will need to consider termination. The applicant claims that the time delay associated with prenatal diagnosis and 1 in 2 or 1 in 4 risk with natural conception (or IVF), make PGD a *superior* option for couples at high risk of having a child with a genetic disorder.

### Safety

Potential gains for couples are dependent on the particular disorder that has been prevented in their offspring. For the parents, superior safety may be found with PGD due to (1) the absence of the requirement of TOP and its associated psychological trauma, or (2) possible reduction in negative outcomes due to not having a child with a severe genetic disorder.

### Effectiveness

The comparative effectiveness of PGD would relate to the claimed accuracy of the genetic diagnosis at preimplantation when compared to prenatal diagnostic testing methods.

## Outcomes and health care resources affected by introduction of proposed intervention

### Outcomes for economic evaluation

Should any differences in the safety or effectiveness of the two procedures be identified, then a cost-effectiveness analysis or a cost-utility analysis would be required. It is not expected that a formal literature review of cost-effectiveness outcomes will be conducted but rather costs will be modelled.

Cost outcomes to be considered for couples undergoing PGD

Cost; cost per relevant health outcome (eg QALYs, LYG)

Cost outcomes to be considered for neonates/children without genetic disorder born to couples as a result of PGD undergoing PGD:

Cost of relevant health outcome (eg QALYs) per eligible disease

Table 13 Classification of economic evaluation to be presented for PGD versus natural pregnancy followed by possible termination

		Comparative effectiveness versus comparator					
		Superior		Non-inferior		Inferior	
Comparative safety versus comparator	Superior	CEA/CUA		CEA/CUA		Net clinical benefit	CEA/CUA
						Neutral benefit	CEA/CUA*
						Net harms	None <sup>^</sup>
	Non-inferior	CEA/CUA		CEA/CUA*		None <sup>^</sup>	
	Inferior	Net clinical benefit	CEA/CUA	None <sup>^</sup>		None <sup>^</sup>	
Neutral benefit		CEA/CUA*					
Net harms		None <sup>^</sup>					

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

\* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

<sup>^</sup> No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

### Proposed structure of economic evaluation (decision-analytic)

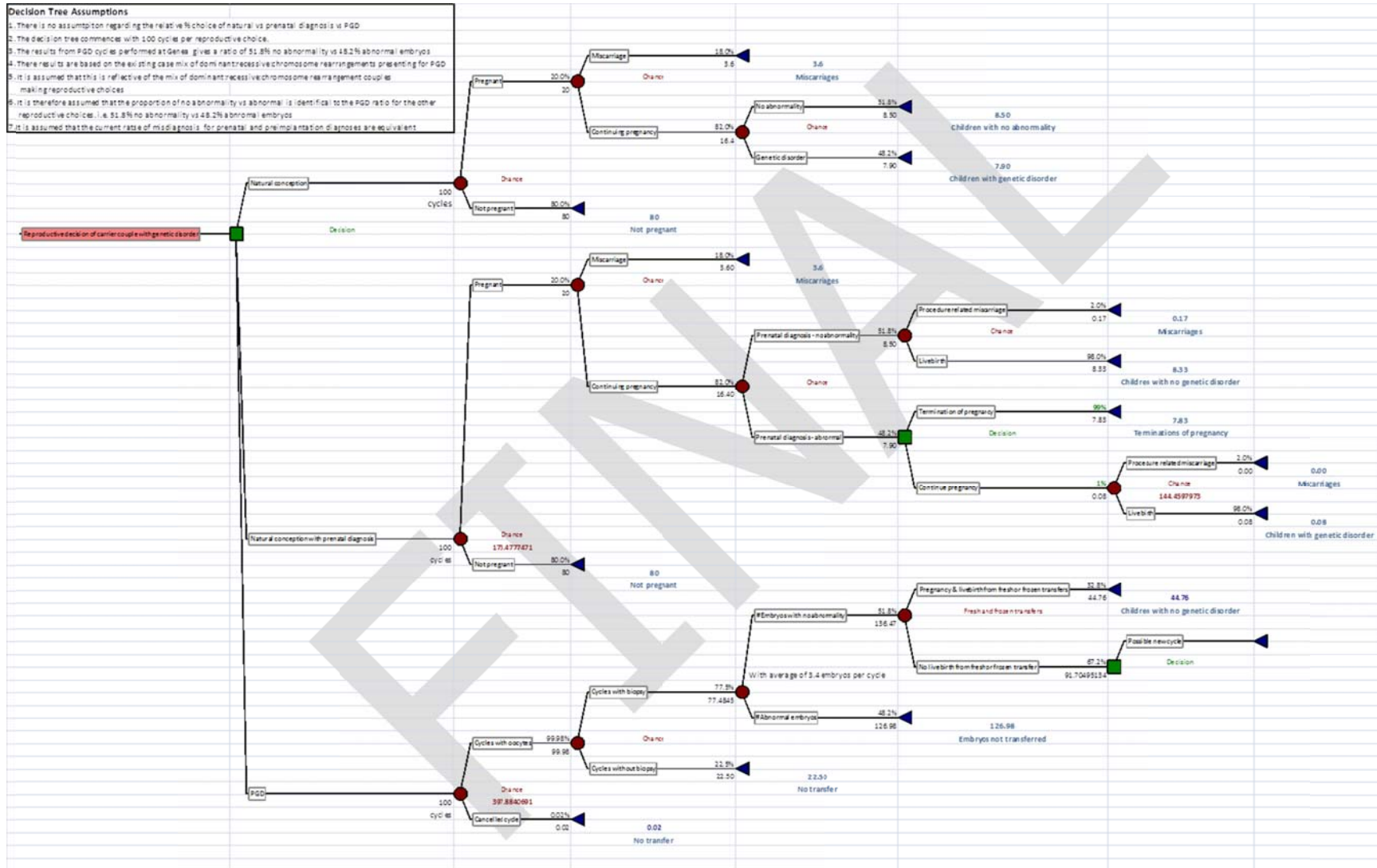
A draft decision analytic was developed by the applicant and is shown in Figure 2, which illustrates the treatment choices and possible outcomes for the proposed population. The starting population is couples who have been assessed by a geneticist as being carriers of a



serious genetic disease and at high risk of passing it on to their children. Once assessed, a couple faces the decision of natural pregnancy with or without prenatal diagnosis, or PGD.

FETAL

Figure 1 Decision analytic for PGD versus natural pregnancy followed by prenatal diagnosis and possible TOP



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- Therapeutic Goods Administration 2010, *Medical Devices and IVDs*, Australian Government.

## Appendix A: Currently listed MBS items relevant to PGD

Table 14 Current MBS items for IVF services relevant to PGD

Category 3 – THERAPEUTIC PROCEDURES	
MBS 13200	<p>ASSISTED REPRODUCTIVE TECHNOLOGIES SUPEROVULATED TREATMENT CYCLE PROCEEDING TO OOCYTE RETRIEVAL, involving the use of drugs to induce superovulation, and including quantitative estimation of hormones, semen preparation, ultrasound examinations, all treatment counselling and embryology laboratory services but excluding artificial insemination or transfer of frozen embryos or donated embryos or ova or a service to which item 13201, 13202, 13203, 13206, 13218 applies - being services rendered during 1 treatment cycle - INITIAL cycle in a single calendar year</p> <p>Fee: \$3,110.75 Benefit: 75% = \$2,333.10 85% = \$3,036.25</p> <p>(See para T.1.4 of explanatory notes to this Category)</p> <p>Extended Medicare Safety Net Cap: \$1,675.50</p>
MBS 13201	<p>ASSISTED REPRODUCTIVE TECHNOLOGIES SUPEROVULATED TREATMENT CYCLE PROCEEDING TO OOCYTE RETRIEVAL, involving the use of drugs to induce superovulation, and including quantitative estimation of hormones, semen preparation, ultrasound examinations, all treatment counselling and embryology laboratory services but excluding artificial insemination or transfer of frozen embryos or donated embryos or ova or a service to which item 13200, 13202, 13203, 13206, 13218 applies - being services rendered during 1 treatment cycle - each cycle SUBSEQUENT to the first in a single calendar year</p> <p>Fee: \$2,909.75 Benefit: 75% = \$2,182.35 85% = \$2,835.25</p> <p>(See para T1.4 of explanatory notes to this Category)</p> <p>Extended Medicare Safety Net Cap: \$2,432.15</p>
MBS 13202	<p>ASSISTED REPRODUCTIVE TECHNOLOGIES SUPEROVULATED TREATMENT CYCLE THAT IS CANCELLED BEFORE OOCYTE RETRIEVAL, involving the use of drugs to induce superovulation and including quantitative estimation of hormones, semen preparation, ultrasound examinations, but excluding artificial insemination or transfer of frozen embryos or donated embryos or ova or a service to which Item 13200, 13201, 13203, 13206, 13218, applies being services rendered during 1 treatment cycle</p> <p>Fee: \$465.55 Benefit: 75% = \$349.20 85% = \$395.75</p> <p>(See para T1.4 of explanatory notes to this Category)</p> <p>Extended Medicare Safety Net Cap: \$64.95</p>
MBS 13206	<p>ASSISTED REPRODUCTIVE TECHNOLOGIES TREATMENT CYCLE using either the natural cycle or oral medication only to induce oocyte growth and development, and including quantitative estimation of hormones, semen preparation, ultrasound examinations, all treatment counselling and embryology laboratory services but excluding artificial insemination, frozen embryo transfer or donated embryos or ova or treatment involving the use of injectable drugs to induce superovulation being services rendered during 1 treatment cycle but only if rendered in conjunction with a service to which item 13212 applies</p> <p>Fee: \$465.55 Benefit: 75% = \$349.20 85% = \$395.75</p> <p>(See para T1.4 of explanatory notes to this Category)</p> <p>Extended Medicare Safety Net Cap: \$64.95</p>
MBS 13209	

PLANNING and MANAGEMENT of a referred patient by a specialist for the purpose of treatment by assisted reproductive technologies or for artificial insemination payable once only during 1 treatment cycle

Fee: \$84.70 Benefit: 75% = \$63.55 85% = \$72.00

(See para T1.4 of explanatory notes to this Category)

Extended Medicare Safety Net Cap: \$10.90

MBS 13212

OOCYTE RETRIEVAL for the purposes of assisted reproductive technologies - only if rendered in conjunction with a service to which Item 13200, 13201 or 13206 applies (Anaes.)

Fee: \$354.45 Benefit: 75% = \$265.85 85% = \$301.30

(See para T1.4 of explanatory notes to this Category)

Extended Medicare Safety Net Cap: \$70.35

MBS 13215

TRANSFER OF EMBRYOS or both ova and sperm to the female reproductive system, excluding artificial insemination - only if rendered in conjunction with a service to which item 13200, 13201, 13206 or 13218 applies, being services rendered in 1 treatment cycle (Anaes.)

Fee: \$111.10 Benefit: 75% = \$83.35 85% = \$94.45

(See para T1.4 of explanatory notes to this Category)

Extended Medicare Safety Net Cap: \$48.70

MBS 13218

PREPARATION of frozen or donated embryos or donated oocytes for transfer to the female reproductive system, by any means and including quantitative estimation of hormones and all treatment counselling but excluding artificial insemination services rendered in 1 treatment cycle and excluding a service to which item 13200, 13201, 13202, 13203, 13206, 13212 applies (Anaes.)

Fee: \$793.55 Benefit: 75% = \$595.20 85% = \$719.05

(See para T1.4 of explanatory notes to this Category)

Extended Medicare Safety Net Cap: \$702.65

MBS 13251

INTRACYTOPLASMIC SPERM INJECTION for the purposes of assisted reproductive technologies, for male factor infertility, excluding a service to which Item 13203 or 13218 applies

Fee: \$417.95 Benefit: 75% = \$313.50 85% = \$355.30

(See para T1.5 of explanatory notes to this Category)

Extended Medicare Safety Net Cap: \$108.15

Table 15 Current MBS item descriptors for genetic testing services relevant to the comparator

Category 6 – PATHOLOGY SERVICES
<p>MBS 73300</p> <p>Detection of mutation of the FMR1 gene where:</p> <p>(a) the patient exhibits intellectual disability, ataxia, neurodegeneration, or premature ovarian failure consistent with an FMRI mutation; or</p> <p>(b) the patient has a relative with a FMR1 mutation</p> <p>1 or more tests</p> <p>Fee: \$101.30 Benefit: 75% = \$76.00 85% = \$86.15</p>
<p>MBS 73305</p> <p>Detection of mutation of the FMR1 gene by Southern Blot analysis where the results in item 73300 are inconclusive</p> <p>Fee: \$202.65 Benefit: 75% = \$152.00 85% = \$172.30</p> <p>(See Para p16.12 of explanatory notes to this Category)</p>
<p>MBS 73287</p> <p>The study of the whole of every chromosome by cytogenetic or other techniques, performed on 1 or more of any tissue or fluid except blood (including a service mentioned in item 73293, if performed) - 1 or more tests</p> <p>Fee: \$394.55 Benefit: 75% = \$295.95 85% = \$335.40</p>
<p>MBS 73289</p> <p>The study of the whole of every chromosome by cytogenetic or other techniques, performed on blood (including a service mentioned in item 73293, if performed) - 1 or more tests</p> <p>Fee: \$358.95 Benefit: 75% = \$269.25 85% = \$305.15</p>
<p>MBS 73291</p> <p>Analysis of one or more chromosome regions for specific constitutional genetic abnormalities of blood or fresh tissue in</p> <p>a) diagnostic studies of a person with developmental delay, intellectual disability, autism, or at least two congenital abnormalities, in whom cytogenetic studies (item 73287 or 73289) are either normal or have not been performed; or</p> <p>b) studies of a relative for an abnormality previously identified in such an affected person.</p> <p>- 1 or more tests.</p> <p>Fee: \$230.95 Benefit: 75% = \$173.25 85% = \$196.35</p>
<p>MBS 73292</p> <p>Analysis of chromosomes by genome-wide micro-array including targeted assessment of specific regions for constitutional genetic abnormalities in diagnostic studies of a person with developmental delay, intellectual disability, autism, or at least two congenital abnormalities (including a service in items 73287, 73289 or 73291, if performed)</p> <p>- 1 or more tests.</p> <p>Fee: \$589.90 Benefit: 75% = \$442.45 85% = \$515.40</p>
<p>MBS 73293</p> <p>Analysis of one or more regions on all chromosomes for specific constitutional genetic abnormalities of fresh tissue in diagnostic studies of the products of conception, including exclusion of maternal cell contamination.</p>

- 1 or more tests.

Fee: \$230.95 Benefit: 75% = \$173.25 85% = \$196.35

Table 16 Current MBS item descriptors for fetal sampling methods relevant to the comparator

Category 3 – THERAPEUTIC PROCEUDRES
<p>MBS 16603 CHORIONIC VILLUS SAMPLING, by any route Fee: \$121.85 Benefit: 75% = \$91.40 85% = \$103.60 (See para T4.11 of explanatory notes to this Category) Extended Medicare Safety Net Cap: \$65.90</p>
<p>MBS 16600 INTERVENTIONAL TECHNIQUES AMNIOCENTESIS, diagnostic Fee: \$63.50 Benefit: 75% = \$47.65 85% = \$54.00 (See para T4.11 of explanatory notes to this Category) Extended Medicare Safety Net Cap: \$32.95</p>
<p>MBS 16606 FETAL BLOOD SAMPLING, using interventional techniques from umbilical cord or fetus, including fetal neuromuscular blockade and amniocentesis (Anaes.) Fee: \$243.25 Benefit: 75% = \$182.45 85% = \$206.80 (See para T4.11 of explanatory notes to this Category) Extended Medicare Safety Net Cap: \$131.75</p>

#### Box 1 MBS Note T1.4

##### T.1.4 Assisted Reproductive Technology ART Services - (Items 13200 to 13221)

From 1 January 2010, the Medicare items for ART services, including In-Vitro Fertilisation (IVF), have been restructured in consultation with the ART profession and the patient group ACCESS. The new structure better reflects current clinical practice and will help to spread the cost of EMSN caps across the treatment cycle. For further information on the changes to the EMSN see the fact sheet under Latest News on MBS Online.

There are no restrictions on the number of cycles that patients can have nor are there any age restrictions for these items.

The new structure includes two new items (13201 and 13202) and a number of amended items. Item 13200 has been amended and will provide for an initial treatment cycle in a single calendar year. New item 13201 has been introduced for a subsequent treatment cycle in association with items 13200 and 13202. New item 13202 covers an incomplete stimulated cycle, and can be billed as an initial treatment cycle in a single calendar year.

Embryology laboratory services covered by Items 13200, 13201 and 13206 have been amended to include the preparation of sperm together with egg recovery from aspirated follicular fluid, insemination, monitoring of fertilisation and embryo development, and preparation of gametes or embryos for transfer and freezing.

Items 13200, 13201, 13202, 13206, 13215 and 13218, do not include services provided in relation to artificial insemination.

Item 13221 has been amended to exclude sperm preparation for assisted reproductive technology using IVF. This item now provides for the preparation of sperm for the purpose of artificial insemination and can only be rendered in conjunction with item 13203.

Medicare benefits are not payable in respect of ANY other item in the Medicare Benefits Schedule (including Pathology and Diagnostic Imaging) in lieu of or in conjunction with items 13200 - 13221 but excluding item 13202. Specifically, Medicare benefits are not payable for these items in association with items 104, 105, 14203, 14206, 35637, pathology tests or diagnostic imaging.

A treatment cycle that is a series of treatments for the purposes of ART services is defined as beginning either on the day on which treatment by superovulatory drugs is commenced or on the first day of the patient's menstrual cycle, and ending not more than 30 days later.

The date of service in respect of treatment covered by Items 13200, 13201, 13203, 13206, 13209 and 13218 is DEEMED to be the FIRST DAY of the treatment cycle.

Items 13200, 13201, 13202 and 13203 are linked to the supply of hormones under the Section 100 (National Health Act) arrangements. Providers must notify Medicare Australia of Medicare card numbers of patients using hormones under this program, and hormones are only supplied for patients claiming one of these four items.

Medicare benefits are not payable for assisted reproductive services rendered in conjunction with surrogacy arrangements where surrogacy is defined as 'an arrangement whereby a woman agrees to become pregnant and to bear a child for another person or persons to whom she will transfer guardianship and custodial rights at or shortly after birth'.

NOTE: Items 14203 and 14206 are not payable for artificial insemination.

Related Items: 13200, 13201, 13202, 13203, 13206, 13209, 13212, 13215, 13218, 13221



## Appendix B: Regulatory statements

### Box 2 NPAAC statement on use of in vitro Devices (National Pathology Accreditation Advisory Council 2007)

*An In vitro diagnostic device is: Any medical device that is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, whether used alone or in combination (with other diagnostic goods for in vitro use), intended by the manufacturer to be used in vitro for the examination of specimens derived from the human body, solely or principally for the purpose of giving information about a physiological or pathological state or a congenital abnormality, or to determine safety and compatibility with a potential recipient or to monitor therapeutic measures.*

*An IVD that is developed de novo, or developed or modified from a published source, or developed or modified from any other source, or its intended purpose, within the confines or scope of a laboratory or laboratory network (as defined). All in-house assays for Class 4 IVDs, or assays that fall outside of the definition of in-house IVD, are subject to the full TGA regulatory requirements for commercial IVDs. Commercial IVDs being used clinically for a purpose other than that originally intended by the manufacturer are also classed as in-house IVDs and are subject to the requirements of this standard.*

*Where it can be demonstrated that the IVD falls into one or more of the following categories:*

- (a) a diagnostic IVD that is for an uncommon condition where its rarity precludes the laboratory from fulfilling the validation requirements entirely*
- (b) the diagnostic IVD is used for an uncommon application where it is not possible to fulfill the validation requirements entirely*
- (c) a diagnostic IVD that is provided as a matter of urgency for a disease that poses a serious risk to public health then where the IVD is used in these circumstances,*

*the report issued with the test result must contain the following statement:*

*'The test used has not yet been validated to the current NPAAC standards and results should be interpreted accordingly'.*

### Box 3 Rule 6 from Rules relating to IVDs used in patient management (National Pathology Accreditation Advisory Council 2007)

#### Rule 6

(1) Subject to subrule (2), an IVD intended for use in genetic diagnosis, screening or in the management of genetic conditions, is classified as Class 2.

(2) An IVD intended for use in predictive, prenatal, pre-implantation or neonatal genetic screening, when the outcome of the test would ordinarily result in a substantial impact on the life of the individual, is classified as Class 3.

#### Explanatory note

- An IVD that is intended to screen for the presence of a genetic condition where the diagnosis is made after additional testing would be classified as Class 2 (e.g. maternal serum screening for Down syndrome risk, Immune Reactive Trypsinogen testing for Cystic Fibrosis and genetic thrombophilia mutation screening), whereas IVDs intended to diagnose Huntington's Disease in a pre-symptomatic person, or to be used in the prenatal diagnosis for Cystic Fibrosis would be classified as Class 3.

Table 17 NHMRC Ethical guidelines for practice of PGD (National Health and Medical Research Council 2007)

Guideline for practice of PGD	Associated ethical considerations
<p>Carefully evaluate any use of PGD</p> <p>PGD is currently used to detect serious genetic conditions, to improve ART outcomes and, in rare circumstances, to select an embryo with compatible tissue for a sibling.</p>	<ul style="list-style-type: none"> <li>• what counts as a serious genetic condition is controversial;</li> <li>• there are different perceptions of disability;</li> <li>• the practice of selecting against some forms of abnormality may threaten the status and equality of opportunity of people who have that form of abnormality;</li> <li>• the procedures involve the disposal of some healthy embryos; and the procedures have technical limitations (such as the failure to identify the genetic abnormality of interest)</li> </ul>
<p>Restrict the use of PGD</p>	<ul style="list-style-type: none"> <li>• Pending further community discussion PGD must not be used for: <ul style="list-style-type: none"> <li>prevention of conditions that do not seriously harm the person to be born;</li> <li>selection of the sex of an embryo except to reduce the risk of transmission of a serious genetic condition; or</li> <li>selection in favour of a genetic defect or disability in the person to be born.</li> </ul> </li> </ul>
<p>Seek advice before using PGD to select an embryo with compatible tissue for a sibling</p>	<ul style="list-style-type: none"> <li>• Except in the case of siblings, PGD must not be used to select a child to be born with compatible tissue for use by another person.</li> <li>• When requested to select an embryo with tissues compatible with a sibling of a child to be born, clinics must seek advice from a clinical ethics committee (or relevant state or territory regulatory agency). The ethics committee or relevant agency should ascertain that: <ul style="list-style-type: none"> <li>the use of PGD will not adversely affect the welfare and interests of the child who may be born;</li> <li>the medical condition of the sibling to be treated is life-threatening;</li> <li>other means to manage the medical condition are not available;</li> <li>and the wish of the parents to have another child as an addition to their family and not merely as a source of tissue.</li> </ul> </li> </ul>
<p>Provide access to a geneticist and genetic counsellor</p>	<ul style="list-style-type: none"> <li>• It is essential that participants in ART seeking PGD testing of embryos understand the technology and how it applies to their embryos.</li> <li>• Clinics must ensure that people seeking PGD testing have access both to clinical geneticists and to genetic counsellors.</li> </ul>
<p>Provide relevant information and counselling</p> <p>To make informed decisions about their treatment, participants in ART seeking PGD need to understand all the procedures involved. Clinics must give up-to-date, objective, accurate information in line with the guidelines provided in paragraphs 9.1 and 9.2.</p>	<ul style="list-style-type: none"> <li>• In dealing with a specific situation, the people seeking testing should be encouraged to consider the following factors when deciding the appropriateness of PGD: <ul style="list-style-type: none"> <li>information about the likelihood of false positive and false negative results;</li> <li>genetic and clinical information about the specific condition;</li> <li>their previous reproductive experience;</li> <li>the distinction between the genotypic and phenotypic expression of the condition, disease or abnormality;</li> <li>the variable range of effects of the condition, disease or abnormality, including the likely rate of degeneration in the case of progressive disorders;</li> <li>the experiences of families living with the condition;</li> <li>the likely availability of effective therapy or management now and in the future; and</li> <li>the extent of social support available.</li> </ul> </li> </ul>

**Box 4 NHMRC regulatory framework for ART clinical practice and research in Australia (National Health and Medical Research Council 2007)**

- Legislation: Clinical practice and research must comply with
  - Relevant national legislation, including the PHCR Act, the RIHE Act and the Privacy Act 1988; and
  - Relevant state and territory legislation, including privacy legislation
- NHMRC licensing arrangements
  - Activities that require a licence are specified under the RIHE Act
- Professional and accreditation standards
- NHMRC Guidelines
  - Clinical practice, research and all other related activities using ART are to adhere to these ethical guidelines as follows:
    - they must comply with all relevant legislation relating to the activities described in these guidelines;
    - they must conform with ethical principles outlined in Parts B and C of the guidelines; and
    - they should follow the practical guidelines provided in Parts B and C to ensure conformity with ethical principles (see paragraph 2.13).
- Human research ethics committees
- Monitoring



**Body Structure qualifiers**

- s1. STRUCTURE OF THE NERVOUS SYSTEM
  - s110 Brain
  - s120 Spinal cord and peripheral nerves
- s2. THE EYE, EAR AND RELATED STRUCTURES
- s3. STRUCTURES INVOLVED IN VOICE AND SPEECH
- s4. STRUCTURE OF THE CARDIOVASCULAR, IMMUNOLOGICAL, ANY OTHER BODY FUNCTIONS AND RESPIRATORY SYSTEMS
  - s410 Cardiovascular system
  - s430 Respiratory system
- s5. STRUCTURES RELATED TO THE DIGESTIVE, METABOLISM AND ENDOCRINE SYSTEMS
- s6. STRUCTURE RELATED TO GENITOURINARY AND REPRODUCTIVE SYSTEM
  - s610 Urinary system
  - s630 Reproductive system
- s7. STRUCTURE RELATED TO MOVEMENT
  - s710 Head and neck region
  - s720 Shoulder region
  - s730 Upper extremity (arm, hand)
  - s740 Pelvis
  - s750 Lower extremity (leg, foot)
  - s760 Trunk
- s8. SKIN AND RELATED STRUCTURES
- ANY OTHER BODY STRUCTURES


The genetic disorder is considered **SERIOUS** if any qualifier is rated severe or a complete problem **AND** is an degenerative, chronic, lifelong or life threatening qualifier.

If the above criteria were not met then the couple is not eligible for PGD.

Based on the above review, the genetic disorder is considered:

Serious	Not Serious

**ETHICAL CONSIDERATIONS (NHMRC)**

If the genetic disorder is deemed **SERIOUS** then complete the Ethical Consideration section by circling the appropriate answer,

- PGD is being used to
- a. prevent a genetic condition that seriously harms the person to be born
  - b. Select of the sex of an embryo to reduce the risk of transmission of a serious genetic condition
  - c. Select to prevent a genetic defect or disability in the person i.e. not selecting for the genetic defect or disability
  - d. select a child to be born with compatible tissue for use by a sibling
- If PGD is being used for tissue comparability, confirm that:
- 1. The use of PGD to select an embryo with compatible tissue for a sibling will not adversely affect the welfare and interests of the child who may be born;
  - 2. The medical condition of the sibling to be treated is life-threatening ( see above qualifiers).
  - 3. Other means to manage the medical condition are not available;
  - 4. The wish of the parents to have another child as an addition to their family and not merely as a source of tissue.
- If PGD is being used for compatible tissues for a sibling, then only proceed if all relevant questions have been answered yes.

NO	YES
NO	YES
NO	YES
NO	YES
NO	YES
NO	YES
NO	YES
NO	YES
NO	YES

If PGD is being used for at least one of the above ethical considerations and the condition for compatible tissue use has been met, if relevant, then the couple may proceed with PGD.

If the above criteria were not met then the couple is not eligible for PGD.

Based on the above review, if the genetic disorder **HIGH RISK, SERIOUS** and has met **ETHICAL CONSIDERATIONS**, the couple is eligible for PGD.

**Severity Qualifier Codes**

- 0 No problem (none, absent, negligible, ...) 0-4%
- 1 MILD problem (slight, low, ...) 5-24%
- 2 MODERATE problem (medium, fair, ...) 25-49%
- 3 SEVERE problem (high, extreme, ...) 50-95%
- 4 COMPLETE problem (total, ...) 96-100%
- 8 not specified
- 9 not applicable

**Occurrence Qualifiers**

- LT - Life threatening
- L - Lifelong
- D - Degenerative
- C - Chronic
- I - Intermittent
- N - Never

**Definitions**

- Progressing to death
- Evident through out life
- Deterioration of a tissue or an organ in which its vitality is diminished or its structure impaired
- Chronic disease has been defined as illness that is prolonged in duration, does not often resolve spontaneously, and is rarely cured completely
- Coming and going at intervals : not continuous
- Never occurs