Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1165 – Pre-implantation genetic diagnosis (PGD) assessment

Applicant: **Genea - formerly Sydney IVF**

Date of MSAC consideration: **MSAC 64th Meeting, 30-31 July 2015**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

An application requesting Medicare Benefits Schedule (MBS) listing of Preimplantation Genetic Diagnosis (PGD) was received from Genea (formerly Sydney IVF). The evidence for assessment of this application was submitted on April 2015.
The applicant proposed that public funding be made available for couples:

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

2. MSAC's advice to the Minister

After considering the available evidence presented in relation to safety, clinical effectiveness and cost-effectiveness of pre-implantation genetic diagnosis (PGD) assessment, MSAC deferred the application to obtain further information to address the following issues:

- the best estimate of how many healthy babies would be delivered/pregnancy using PGD compared with current practice without PGD (acknowledging that significant variables may not be incorporated into the analysis);
- the best estimate of the associated costs across this comparison, and thus an estimate of the incremental cost per extra live healthy birth (acknowledging that significant variables may not be incorporated into the analysis);
- a re-calculation of the annual financial implications to the MBS;
- examples of the costs and health consequences associated with babies with significant disability and/or ill-health; and

- comments from the applicant on the revised MBS item descriptors and on implementation strategies to minimise using PGD in less severe medical conditions.

MSAC suggested that the updated information should be provided via ESC, prior to re-consideration by MSAC.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that the birth of a child who has, or will develop, a severe avoidable disease represents a significant financial cost to the community with additional tangible and intangible costs for the parents. MSAC noted that support via the National Disability Insurance Scheme is approximately $12 - 16,000 per year for some circumstances – individualised transdisciplinary services for children with disability Level 3 – high needs[1]. This application requested public funding for the process of genetic diagnosis, laboratory procedures and testing, to enable delivery of an unaffected child without relying on termination of pregnancy. The three steps involved in the process of PGD are:

1. develop a family-specific assay for detection of mutations from a single cell;
2. remove a cell from early-stage embryo; and
3. test the cell for the family-specific mutation.

MSAC noted that separate funding is being proposed for each step.

MSAC proposed modifications to the proposed item descriptor to include appropriate genetic counselling by the treating practitioner and omission of Level 1 and Level 2 fee structures. MSAC noted that the definition in the item descriptor of 'serious' or 'severe' in the context of genetic testing would likely be subject to wide interpretation, and may contribute to scope creep.

MSAC noted that the main comparator, prenatal testing in pregnancy via natural conception (or pregnancy via in vitro fertilisation (IVF)), is currently funded on the MBS. MSAC considered that pregnancy via natural conception or IVF with pre-natal testing alone is an appropriate technical comparator. However, it is not an appropriate overall comparator due to non-medical considerations, such as psychological, ethical and social issues, regarding management of genetic risk. MSAC advised that a mixed comparator including not having biological children, natural pregnancy or IVF conception with post-natal testing or pre-natal testing may be more appropriate to account for the risks and consequences.

MSAC agreed with the proposed clinical management algorithm, but noted that the clinical need was difficult to determine. There is uncertainty regarding the number of couples who would choose not to have biological children, have IVF with donor gametes, or patients who would consider PGD if informed, or who found it affordable.

MSAC noted that safety data was presented for the test procedure for the mother regarding risk of miscarriage which demonstrated that PGD is no riskier for the mother than any other available option. However, MSAC considered that it would have been informative if safety data was also provided on risks of:

- procedural harm from chorionic villus sampling (CVS) or amniocentesis;

[1] National Disability Insurance Scheme - Individualised transdisciplinary services for children with disability Fact sheet for NDIA staff, service providers and participant families – 6 May 2014

- psychological distress from prenatal testing;
- preference for prenatal testing *vs* PGD;
- termination of pregnancy; and
- fear as a factor limiting family size.

Safety data were also presented on perinatal mortality and major malformations which showed no difference versus IVF in separate cohorts and data presented for developmental delay after PGD also showed no difference versus IVF or natural pregnancy in independent cohorts.

MSAC noted that data on the analytical validity of the assay showed greater than 97% sensitivity and approximately 90% specificity (including flanking markers) with a small but significant false negative rate of 1:75 at 12 weeks and 1:250 at term. MSAC considered that it would also be helpful to see further information including:

- accuracy data on prenatal testing to compare analytical validity of assay;
- estimates of uptake or changes in family size with PGD or prenatal test to assess the reduction in frequency of affected babies;
- efficiency data on IVF; and
- parental satisfaction.

MSAC concluded from the evidence provided that PGD is, at least, no worse in terms of safety or effectiveness than other options to reduce the risk of a liveborn affected child.

MSAC noted that the economic analysis excluded downstream costs and termination of pregnancy, leading to overestimated incremental costs. The analysis also assumed that the benefit of avoiding termination was captured by reversing the disutility of a termination, which MSAC considered to be biased against PGD because it underestimated the full psychological consequence of CVS and termination of pregnancy. MSAC also expressed reservations about the plausibility of other derived utility differences, which did not appear to be adequately assessed in the sensitivity analyses. MSAC further noted that the analysis was insensitive to rates of natural conception and miscarriage.

In terms of financial and budgetary impacts, MSAC noted the lack of data presented on the current gap paid by PGD patients, and also by how much gap payments are likely to be reduced for patients if funded. MSAC further noted that implications for the Medicare Safety Net were not included in the application. MSAC considered that the financial costs could potentially be offset by reduced costs of care to parents for affected children, as well as broader, less tangible savings.

MSAC advised that the following information should be included in any future application:

- For a cohort of 1000 women in the intended population, estimated number of healthy babies delivered/pregnancy using PGD compared with number of healthy babies which would be delivered/conception using the mixed comparator of:
    - not having biological children (MSAC noted the difficulty of defining this figure and suggested an approximate figure of 5% of women may be reasonable to include for exploratory and sensitivity analyses, subject to any real data that may be able to be obtained)
    - having a child by natural or IVF conception (with increased risk of miscarriage) and post-natal diagnosis

- having a child by natural or IVF conception, with pre-natal diagnosis and the option of termination of the pregnancy (the comparator presented to MSAC).

This information could be presented as a flowchart quantifying the proportions of women who would proceed to important consequential outcomes:

- using the above mixed comparator of current arrangements without PGD;
- using PGD as proposed; and
- generating the difference between the current and proposed scenarios.

Other possible outcomes to be considered in the flowchart to help explain any estimated difference in the number of healthy babies delivered across the comparison might include:

- successful biopsies (both arms);
- successful testing (both arms);
- test (TP, FP, TN, FN) results (both arms);
- clinical pregnancies (both arms);
- number of cycles per successful clinical pregnancy (PGD arm);
- terminations (non-PGD arm);
- other miscarriages and unsuccessful deliveries (both arms); or
- live affected births (both arms).

- Estimated associated costs for each of these compared scenarios, thus estimating the incremental cost per extra live healthy birth, noting the relevant cost offsets most likely to be quantified if PGD can also be shown to reduce the estimated number of affected babies delivered/pregnancy and/or the estimated numbers of terminations/pregnancy.

- Recalculated annual financial implications to the MBS, noting that the $9 million presented was considered to be an underestimate, taking into consideration the following:
  - re-define the population for testing;
  - avoid double counting when calculating net costs from total costs; and
  - consider this question in the light of alternative funding for PGD, and the future possibility that many people may have had genomic testing as an adult, and may want PGD to avoid prenatal testing and termination.

- Examples of the costs and health consequences of babies born with significant disability or illness, noting the National Disability Insurance Scheme (NDIS) estimate of $12 - 16,000 per year, perhaps selecting a minimum of two medical conditions across the severity spectrum (very severe, eg. Duchenne muscular dystrophy or severe cystic fibrosis; and less severe, eg. BRCA mutation) and both paediatric and adult-onset conditions.

- Comments from the applicant on:
  - the MSAC-revised MBS item descriptors
  - any modification to its request for public funding given concerns that PGD might “leak” into less severe medical conditions, but without becoming unnecessarily cumbersome in defining severity.

4. Background

PGD is currently available in Australia, but is not reimbursed by the MBS or any other means.

5. Prerequisites to implementation of any funding advice

PGD tests are a Class 3 *in-vitro* diagnostic device (IVD). As of June 2015, all commercial Class 3 IVDs are required to the listed on the Australian Register of Therapeutic Goods (ARTG). Manufacturers of in-house Class 3 IVDs are required to submit a notification to the TGA by June 2017.

The assessment report noted that IVF and PGD services 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 specialists and staff who manage IVF and PGD cycles that include fertility specialists, geneticists, genetic counsellors, nurses, embryologists and molecular geneticists.

To access subsidised PGD services, a couple would need to be referred to a fertility specialist and IVF clinic where the services would be performed. Each step of the PGD service would be delivered by the following professionals:

- genetic test design and validation are performed by trained molecular geneticists;
- embryo biopsy is performed by trained embryologists or molecular geneticists;
- analysis of genetic information from the embryo biopsy is performed by trained 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 currently available in only three major clinics in Australia. Biopsy material (DNA) obtained at other clinics would need to be transferred to one of these specialist clinics for analysis. Transfer of biopsy material may incur additional costs which are not expected to be large (there is no cold chain required). In this circumstance the Approved Pathology Practitioner who receives the biopsy material can raise a “specimen referred fee” covered under the MBS.

With PGD services provided privately in a small number of fertility clinics, 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. However, these provide more information than is necessary for a PGD service, and additional data and findings may give rise to complications regarding management.

6. Proposal for public funding

The application proposed to list 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 a technique which is applied within the IVF process to detect whether an embryo created in vitro has a specific genetic defect. It should be noted that where IVF is undertaken for the purpose of PGD, intra-cytoplasmic sperm injection (ICSI) must also be included in the

IVF procedures. PGD is defined as the testing of cells from pre-implantation embryos for the detection of genetic and/or chromosomal disorders before embryo transfer.

A PGD cycle is composed of three stages: (1) test design and validation for known specific genetic mutations, (2) embryo biopsy, and (3) embryo DNA analysis.

Stage 1: test design and validation for known specific genetic mutations
The first stage of PGD requires the design of the probes that will enable detection of the parental mutation(s) in the embryos. To validate the test, DNA from the couples or family members undergoes polymerase chain reaction (PCR) using the designed primers and testing/sequencing to confirm that the tailored test is able to identify the mutation or chromosome translocation of interest. The test regime is optimised to ensure it is efficient when used on the minimal DNA quantities available from the biopsied embryo cells.

Stage 2: embryo biopsy
The second stage of PGD requires 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. The applicant has noted that blastocyst stage (day 5) biopsy is the method used in its PGD practice.

Stage 3: embryo DNA analysis
For the final stage of PGD, DNA prepared from the embryo undergoes analysis using the primers (probe) prepared and optimised in the test design stage (Stage 1) to identify the unique genetic mutation. Embryos identified with a normal DNA sequence can be transferred to the mother's uterus. Currently in Australia this procedure usually involves the implantation of a single embryo. Should more than one suitable embryo be found in the analysis stage, the remaining embryos may be cryopreserved and accessed should the first pregnancy be unsuccessful, or should the couple want more children. If no suitable embryos are found, the couple may choose to start a new IVF cycle; they are not required to undergo Stage 1 (work-up) of the PGD cycle again.

Given these three PGD stages, a three-item structure was proposed so that the payer would only pay for the exact service provided to the patient.

The application claimed that PGD is effective in identifying genetic disorders and would be specifically offered to:

- couples in whom one or both partners have been diagnosed with, or know that they carry, a serious genetic disorder, 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 in whom 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 in their offspring (for balanced translocations there is a 1 in 2 risk of transmission).

The box below presents the proposed PGD item descriptors as shown in the Protocol.

Proposed descriptors for PGD items 1, 2, and 3

Category 6– PATHOLOGY (Group P7 Genetics)
Item [xxxxx] **PGD Stage 1 Genetic test design and validation** 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 xxxxx PGD Stage 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 proposed the following fees for each stage of the PGD cycle:

- Stage 1: $1,736;
- Stage 2: $115 per embryo; and
- Stage 3: $635 per embryo,

The assessment report noted that clinics offering PGD should have specialists and staff who manage IVF and PGD cycles that include fertility specialists, geneticists, genetic counsellors, nurses, embryologists and molecular geneticists. In order to access subsidised PGD services, a couple needs to be referred to a fertility specialist and IVF clinic where the services would be performed. Each step of the PGD service would be delivered by the following professionals:

- genetic test design and validation are performed by trained molecular geneticists;
- biopsy of embryo is performed by trained embryologists or molecular geneticists; and
- analysis of genetic information from the embryo biopsy is performed by trained molecular geneticists.

7. Summary of Public Consultation Feedback/Consumer Issues

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 two or three major clinics in Australia.

Consumers supported the intervention and noted that approval of the intervention will allow access to everyone in the community.

8. Proposed intervention's place in clinical management

PGD occurs in conjunction with IVF, with the latter procedure supplying the embryos for analysis of genetic content before implantation.

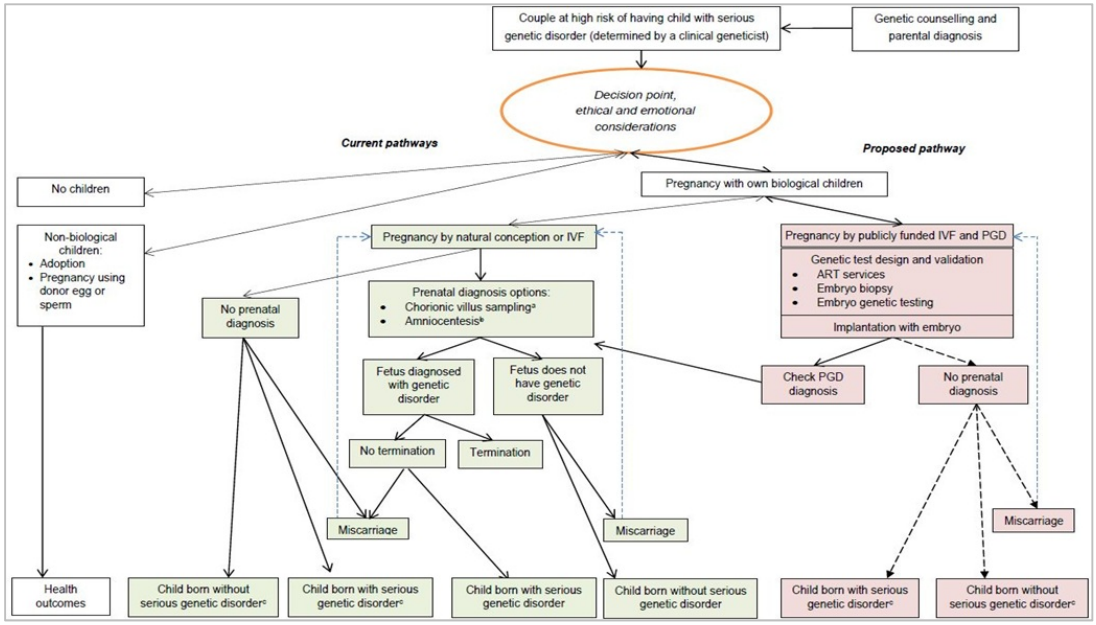
The assessment report noted that preimplantation genetic screening (PGS) services are already offered in the community, but to a broader population than proposed for the funding of PGD. The main purpose of PGD is to improve the chance of conception for patients with a genetic condition or mutation, and to make it likely that their offspring will not suffer from the genetic defect carried by the family. As PGS is strictly used to screen for embryos with a complete set of chromosomes, PGD is the only method that tests for specific genetic conditions at the embryonic stage.

Alternatively, couples may choose to try for a natural pregnancy, followed by prenatal diagnosis and the possibility of termination of pregnancy or 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 postnatal diagnosis) for the proposed population, and an increased uptake of PGD should the service be publically funded.

The below diagram illustrates the current and proposed clinical management algorithm for patients undergoing PGD services.

Figure 1 Current and proposed clinical management algorithm



Source: Figure 1, p22 of the Final Protocol

[a] CVS is carried out at 10-12 weeks of pregnancy. Termination is performed by evacuation and curettage at this stage of pregnancy.

[b] Amniocentesis is carried out at 14-16 weeks of pregnancy. Termination is performed by induction of labour.

[c] Children born not having undergone prenatal testing, may undergo clinical or genetic/molecular post-natal testing

9. Comparator

The comparator for PGD in couples is pregnancy by natural conception or IVF followed by prenatal diagnosis and the option of termination of the pregnancy.

The MBS provides subsidy for various pathology services which may be used for prenatal diagnosis in the comparator. Category 3 - Therapeutic Procedures items 16600, 16603 and 16606, are currently MBS subsidised. However, 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.

10. Comparative safety

The assessment report advised that, for couples undergoing PGD, no comparative data was identified that compared PGD with prenatal testing, so outcomes could only be assessed for PGD alone.

A summary of the overall results for miscarriage from the European Society of Human Reproduction and Embryology (ESHRE) PGD Consortium dataset for chromosomal abnormalities and single gene disorders (SGD) is presented in Table 1.

Results were similar for the two indications. In addition to the ESHRE dataset, data were also available from an additional 20 studies that had > 200 cycles of PGD. In the studies that reported on clinical outcome after PGD for single gene disorders, the miscarriage rate ranged from 6% to 15%. In the studies that reported on clinical outcome after PGD for chromosomal rearrangements, the miscarriage rate ranged from 0% to 52%.

Table 1 Summary of ESHRE PGD Consortium safety data on PGD, data collection I – XII

Indication	Miscarriage rate (% per CP)
CAs	76/686 (11.1)
SGDs	143/1274 (11.2)

Abbreviations: CA, chromosomal abnormality; CP, clinical pregnancy; ESHRE, European Society of Human Reproduction and Embryology; PGD, preimplantation genetic diagnosis; SGD, single gene disorder

Note: PGD for chromosomal abnormalities includes Robertsonian translocation (male and female carrier), reciprocal translocation (male and female carrier), sex chromosome aneuploidy, deletion, and inversion. PGD for single gene disorders includes X-linked, autosomal recessive and autosomal dominant conditions, as well as human leukocyte antigen compatability. Miscarriage rate is defined as the number of miscarriages per number of clinical pregnancy minus the number of pregnancies that were lost to follow-up.

The assessment report noted that a large number of outcomes defined for this safety question could not be assessed based on the available evidence. These included: physical harms to women from DNA sampling procedures; physical harms to women from termination of pregnancy; 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 parents; physical and psychological harms from not achieving a pregnancy; physical and psychological impact of time delay to diagnosis; and physical and psychological impact of time delay to live birth.

MSAC considered that evidence on the medical and psychological consequences of terminating a pregnancy would be informative to assess the comparative safety of PGD and prenatal testing more completely.

Due to the lack of studies comparing PGD with prenatal testing, the acquisition of data for effectiveness outcomes for prenatal testing to be included in the economic model was addressed in the assessment report.

The assessment report indicated that, for offspring born to couples who have gone PGD, two observational studies provided data on perinatal mortality and major malformations following PGD alone, and PGD/PGS compared with intra-cytoplasmic sperm injection (ICSI) alone. However, only one of these studies performed a multivariate analysis which attempted to adjust for potential confounders; the results of this study are shown below. In a univariate analysis comparing total perinatal deaths in a cohort of Belgian PGD/PGS children compared with ICSI alone children, Desmyttere et al (2012), showed no statistically significant difference (Table 2).

Multivariate analyses also showed no increased risk of perinatal death associated with PGD/PGS compared with ICSI alone; however, a numerically higher risk was seen for PGD/PGS versus ICSI alone in multiple births compared with singleton births. It should be noted that multiple births are more likely to be premature and this is a known risk factor for increased perinatal mortality. Multivariate analysis of major malformation risk also suggests no difference between PGD/PGS and ICSI.

Table 2 Perinatal mortality following PGD/PGS – Level III evidence

- -	Perinatal mortality - -			Major malformations - -		
	PGD/PGS n/N (%)	ICSI n/N (%)	Risk estimate (95% CI) [P value]	PGD/PGS n/N (%)	ICSI n/N (%)	Risk estimate (95% CI) [P value]
Desmyttere 2012	36/1022 (3.5)	45/1542 (2.9)	[0.42][b] S: OR 0.60 (0.23, 1.42) M: OR 1.63 (0.89, 2.99)[c]	23/995 (2.3)	40/1507 (2.7)	OR 0.87 (0.49, 1.50)[b]

Abbreviations: CI, confidence interval; ICSI, intracytoplasmic sperm injection; M, multiple births; OR, odds ratio; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening; S, singleton birth

a Univariate analysis

b Multivariate analyses adjusted for maternal age, pre-pregnancy BMI, parity, nicotine abuse, intake of alcohol and complications during pregnancy

The corresponding results for PGD/PGS from the ESHRE PGD Consortium dataset are presented in the table below. The rate of perinatal mortality is slightly lower than that seen in the PGD group Level III study, while the occurrence of malformations is similar.

Table 3 Summary of ESHRE PGD Consortium data on PGD/PGS, data collection IV – XII

Study	Stillbirths n/N (%)[a]	Neonatal deaths n/N (%)[a]	Perinatal deaths n/N (%)	Major malformations n/N [mal/birth][b]
Pooled	59/5455 (1.1)	36/5414 (0.7)	95/5455 (1.7)	102/5474 [0.019]

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; mal, malformations; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening

a Denominator for stillbirths is all births with neonatal complication data available; denominator for neonatal births is all births with neonatal complication data available minus the number of still births. Perinatal deaths calculated from stillbirths + neonatal deaths.

b Numerator is number of malformations, denominator is number of babies (live births and stillbirths); may be more than one malformation per baby.

The assessment report noted that three Level III observational studies provided comparative analyses, adjusted for possible confounders, on development delay in two cohorts of children born following PGD (± PGS) and natural conception. On the basis of this evidence, conception after embryo biopsy for PGD/PGS appears to have no adverse impact on the mental and psychomotor development of two-year old children when compared with conception via IVF/ICSI and natural conception. Furthermore, PGD/PGS conception did not appear to adversely affect children's socio-emotional and language development at age two. In children aged 5 to 6 years, a study using multivariate analysis found no significant difference in motor development and intelligence between children conceived via PGD compared with IVF/ICSI or natural conception.

While not from high level evidence, the results suggested that PGD, and in particular the biopsy technique used in PGD, may not cause harm to the developing fetus and child.

MSAC considered that evidence on the risks to the fetus from CVS for prenatal testing would be informative to assess the comparative safety of PGD and prenatal testing more completely.

11. Comparative effectiveness

According to the assessment report, no comparative data was identified for couples undergoing PGD that compared PGD with prenatal testing, so outcomes could only be assessed for PGD alone. A summary of the overall results from the ESHRE PGD Consortium dataset for chromosomal abnormalities and SGDs are presented in Table 4. Results were similar for the two indications.

Table 4 Summary of ESHRE PGD Consortium data on effectiveness of PGD, data collection I – XII

Indication	Successfully biopsied embryos	CP rate (% per ET cycle)	Implantation rate (% per ET)	Delivery rate (% per ET cycle)	Live birth rate (% per ET cycle)	No. of PGD cycles to achieve ChP
CAs	36317/36807 (98.7%)	1062/3809 (27.9)	1144/5364 (21.3)	610/2331 (26.2)	NR	5169/1253 (4.1)
SGDs	46551/47124 (98.8%)	1779/6061 (29.4)	1955/9414 (20.8)	1133/6061 (26.0)	NR	6826/2094 (3.3)

Abbreviations: CA, chromosomal abnormality; CP, clinical pregnancy; ChP, chemical pregnancy; ESHRE, European Society of Human Reproduction and Embryology; ET, embryo transfer; PGD, preimplantation genetic diagnosis; SGD, single gene disorder

Note: PGD for chromosomal abnormalities includes Robertsonian translocation (male and female carrier), reciprocal translocation (male and female carrier), sex chromosome aneuploidy, deletion, and inversion. PGD for single gene disorders includes X-linked, autosomal recessive and autosomal dominant conditions, as well as human leukocyte antigen compatability. Clinical pregnancies are defined as the presence of one or more fetal hearts at six weeks of gestation. Clinical pregnancy rate is defined as the number of clinical pregnancies expressed per ET cycles. Implantation rate is defined as the number of fetal hearts per embryos transferred. Delivery rate is defined as the number of pregnancies with delivery per ET procedure. Number of PGD cycles to pregnancy is defined as the number of PGD cycles to achieve a chemical pregnancy (hCG positive).

In addition to the ESHRE PGD Consortium dataset, the assessment report noted that data was also available from an additional 20 studies that each included > 200 cycles of PGD. In the studies that reported on clinical outcome after PGD for single gene disorders, the clinical pregnancy rate ranged from 24% to 51%; implantation rate ranged from 13% to 49%; and delivery rate ranged from 24% to 29%. The live birth rate per embryo transfer ranged from 17% to 43% for single gene disorders. In the studies that reported on clinical outcome after PGD for chromosomal rearrangements, the clinical pregnancy rate ranged from 27% to 72%; implantation rate ranged from 21% to 56%; and delivery rate ranged from 27% to 75%. The live birth rate per embryo transfer ranged from 23% to 75% for chromosomal rearrangements. In studies that included any PGD, clinical pregnancy rate ranged from 27% to 51%; implantation rate ranged from 7% to 45%; and delivery rate ranged from 24% to 28%. In addition, the miscarriage rate ranged from 6% to 25% and live birth rate ranged from 28% to 39%.

A number of studies (including one RCT) also assessed the effect of biopsy method on pregnancy outcomes. The studies found higher rates of pregnancy, implantation, delivery and live birth following blastocyst biopsy (day 5) compared with blastomere biopsy (day 3).

A number of the primary outcomes defined for this effectiveness question could not be assessed based on the available evidence. These included: parental psychological health benefits and parental quality of life.

Due to the lack of studies comparing PGD with prenatal testing, the acquisition of data for effectiveness outcomes for prenatal testing to be included in the economic model was addressed in Section C of the assessment report. MSAC noted that studies investigating the parental perception and preference for prenatal diagnosis over postnatal diagnosis exist and may assist in assessing this comparison.

The assessment report stated that no studies were identified that provided data for the effectiveness outcomes for offspring born to couples who have gone PGD in terms of quality of life and functional status.

The assessment report noted that there was no comparative evidence available to determine whether PGD is as accurate as prenatal diagnosis. The absolute accuracy of PGD was difficult to estimate since it is impossible to confirm the diagnosis in every embryo. Access for reanalysis was available either during pregnancy (prenatal diagnosis) or after birth (postnatal diagnosis); however, a substantial number of embryo transfers did not result in

pregnancy and confirmatory testing was done on only a proportion of non-transferred embryos.

Misdiagnosis rates have been estimated based on reporting of the ESHRE PGD Consortium membership centres. Confirmation of diagnosis was performed prenatally in approximately 34% (3380/9813) of fetal sacs, and/or postnatally in approximately 28% (2742/9813) of births. The rate of misdiagnosis for single gene disorders diagnosed via PCR was estimated at approximately 1.3% prenatally (per fetal sac) and 0.4% postnatally (per birth). The rate of misdiagnosis for chromosomal abnormalities diagnosed via fluorescence in situ hybridisation (FISH) was estimated at approximately 0.2% prenatally and 0.1% postnatally.

For the purpose of applying a false negative rate of PGD in the economic model and financial analysis, misdiagnosis was recalculated per embryo transferred and resulted in an average misdiagnosis rate of 0.079%.

The validity of PCR- and FISH-based PGD methods was tested in a number of studies by reanalysing embryos that were not transferred. PCR-based methods resulted in sensitivities of between 96.9% and 100%, across both one- and two-cell blastomere biopsies. Specificities varied depending on the number of cells biopsied, ranging from 87.4% to 93.8% for two-cell biopsies and from 78.3% to 100% for one-cell biopsies. Analyses of singleplex versus multiplex and one-cell versus two-cell PCR analysis showed a similar result; there was little difference between the methods in sensitivity (ranging from 95.7% to 100% across the different analyses), while specificity ranged from 72.4% to 89.7% (with the highest specificities seen for multiplex methods and two-cell biopsies). In the single study that assessed FISH-based analysis, sensitivity was 100% and specificity was 74.9%.

MSAC noted that publications exploring the false -negative rate of prenatal diagnosis by CVS or amniocentesis exist and may be useful in assessing this comparison with PGD.

12. Economic evaluation

The assessment report noted that, given the limited body of evidence presented, it cannot be confirmed that the diagnostic accuracy of PGD was as effective, or any better than, prenatal testing in couples known to be carrying genetic mutations or rearrangements. Nonetheless, a cost-utility analysis (CUA) was undertaken, as suggested by PASC, assuming decreased miscarriage and termination of pregnancy for couples undergoing PGD compared with prenatal testing, as well as a shorter timeframe to an unaffected live birth.

The assessment report has indicated that a literature search was conducted which identified six published economic evaluations of PGD/PGS. In all, the published models did not correspond well with the research questions at hand. Two studies were conducted in a population of women who were already pregnant, two were analyses of PGS, and two were cost-benefit studies. Nonetheless, examination of the way in which the studies were conducted did provide insights that were informative to the current economic evaluation. Together, these studies informed the structure of the economic model, which had three arms: (1) IVF/PGD; (2) natural conception with prenatal testing; and (3) natural conception with no diagnostic testing. The cost-effectiveness of PGD is assessed against both other arms of the model.

According to the assessment report, while the published studies ranged from simple decision analytic models through to more advanced Markov models, it was clear that a Markov structure would be required to allow scope for consideration of multiple attempts at

conception. Thus, the model takes the form of a state-transition Markov model with non-constant transition probabilities applied where appropriate (eg. the probability of re-attempting conception after failure to do so was reduced over time, to ensure the model appropriately represents reality).

Half-cycle correction was appropriately applied to the utility weights used in the model. It was not, however, applied to costs. In the case of costs, the nature of the costs means this was not appropriate. For example, the cost of IVF is an upfront cost applied to all women in that arm of the model; it is unaffected by women's transition to other health states over the course of the model cycle.

The assessment report noted that the model was run for 10 cycles of 20 weeks each in the base case. This represented a highly conservative approach, since it accounted for all costs associated with conception, pregnancy and birth, but limits the accrual of utility to a short-term period, even though utility weights were likely to accrue over a much longer time horizon. The approach taken in the base case was invoked to minimise the uncertainty inherent in estimates of HRQoL. The impact of this was tested in sensitivity analyses, as was the impact of including long-term costs associated with the ongoing medical treatment required by children born with genetic abnormalities.

To reflect the preferences of the parents to have a child who is free of chromosomal abnormalities, it is the utility of the parents that is considered, rather than that of the child, which is similar to the approach taken by other published cost-utility studies in PGD. While the birth of an unaffected child or otherwise would impact on the utility of both parents, only the utility of the mother is considered in this analysis. This is a simplifying step which has no impact on the incremental cost-utility estimated.

On the basis of the total costs and quality-adjusted life years (QALYs) included in the model, Table 5 presents the base case incremental cost-effectiveness ratio (ICER) in terms of the QALY gain offered by PGD relative to natural conception with prenatal testing, while Table 6 presents the base case ICER in terms of the QALY gain offered by PGD relative to natural conception alone. While it is acknowledged that some PGD-eligible couples may not be able to conceive naturally and would need to undergo IVF even if PGD is not available, this small, specific patient group has not been included in the economic analysis for simplicity.

Table 5 Incremental cost per QALY ratio of PGD versus natural conception with PNT

Parameter	PGD arm	Natural conception with PNT arm	Incremental
Cost	$22,647	$5561	$17,087
QALY	3.36	3.01	0.35
Incremental cost per QALY	-	-	$48,875

Abbreviations: PGD, preimplantation genetic diagnosis; PNT, prenatal testing; QALY, quality-adjusted life year
Note: Rounding may impact on some figures

Table 6 Incremental cost per QALY ratio of PGD versus natural conception only

Parameter	PGD arm	Natural conception only arm	Incremental
Cost	$22,647	$6106	$16,541
QALY	3.36	2.84	0.52
Incremental cost per QALY	-	-	$31,620

Abbreviations: PGD, preimplantation genetic diagnosis; QALY, quality-adjusted life year
Note: Rounding may impact on some figures

The table below presents the results of an analysis of the incremental cost per unaffected live birth for PGD relative to natural conception with prenatal testing. The results of a similar analysis, but for PGD versus natural conception only, are presented in Table 8.

Table 7 Incremental cost per unaffected live birth ratio of PGD versus natural conception with PNT

Parameter	PGD arm	Natural conception with PNT arm	Incremental
Cost	$22,647	$5561	$17,087
Unaffected live births	0.965	0.512	0.453
Incremental cost per unaffected live birth	-	-	$37,719

Abbreviations: PGD, preimplantation genetic diagnosis; PNT, prenatal testing
Note: Rounding may impact on some figures

Table 8 Incremental cost per unaffected live birth ratio of PGD versus natural conception only

Parameter	PGD arm	Natural conception only arm	Incremental
Cost	$22,647	$6106	$16,541
Unaffected live births	0.965	0.425	0.250
Incremental cost per unaffected live birth	-	-	$30,632

Abbreviations: PGD, preimplantation genetic diagnosis
Note: Rounding may impact on some figures

The assessment report noted that increasing the duration of the model improved the cost-effectiveness of PGD relative to natural conception with prenatal testing. This result is expected, as it extrapolates the benefits of PGD's impact on unaffected live births while keeping costs stable (downstream healthcare costs were not applied in the base case).

Reducing the rate of pregnancy from IVF from 100% over 20 weeks to 80% over 20 weeks increases the ICER from $48,875 to $63,184. The assessment report noted that this result is unsurprising given the cost of IVF relative to other costs in the model. It can be seen, therefore, that any downside risk on the likelihood of pregnancy will have a negative impact on the value offered by PGD.

The cost of IVF has a marked impact on the results of the model (increasing the cost of IVF by 25% increases the ICER to $59,790). IVF is the most expensive resource in the model and increases in this cost (which could also be thought of as a proxy for the resource use required for successful IVF, which is inherently uncertain) expectedly increases the ICER. The uncertainty of these costs and the resource use required for successful use of IVF should, therefore, be carefully considered in light of the impact they have on the results of the model.

Likewise, it was observed that an increase in the likelihood of couples re-attempting pregnancy following miscarriage or termination will worsen the ICER. An increase in this probability gives couples using natural conception with prenatal testing further chances to better their chance of an unaffected birth, moving their prospects closer to that which they would have if using PGD and IVF.

The results of the base case analysis were observed to be somewhat stable with regard to the rate of success with natural conception, the rate of miscarriage and the utility weights applied to the model (including analysis examining the utility of affected live births, which was uncertain due to the use of a utility weight representative of Down syndrome specifically). Changing the utility of an affected live birth from 0.55 to 0.45 and 0.65 had little effect on the ICER, changing it to $48,997 and $48,754, respectively. Additionally, an analysis exploring the average cost of embryo biopsy was included, given that the item description proposed by PASC stated that the cost applied to the biopsy of multiple embryos, while the cost proposed by the applicant is applied per embryo biopsied. This analysis has a limited impact on the ICER.

In addition to the sensitivity analyses on the comparison between PGD and natural conception with prenatal testing, secondary sensitivity analyses were conducted on the PGD arm versus the natural conception only arm to explore the sensitivity of this comparison's

results to the miscarriage rate in the natural conception arm. Adjusting for the rate of miscarriages in the natural conception arm of the model had very little impact on the conclusions to be drawn when comparing PGD against natural conception only.

13. Financial/budgetary impacts

The assessment report provided the below estimates for the number of PGD services and the cost of these services, over the first five years of proposed public funding.

Table 9 Estimated number of PGD services and cost of PGD services with public funding

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Number of services for PGD Stage 1: genetic test design and validation	2033	2541	2923	3215	3536
Number of services for PGD Stage 2: embryo biopsy	2206	2757	3171	3488	3836
Number of services for PGD Stage 3: embryo analysis	2206	2757	3171	3488	3836
Cost of services for PGD Stage 1: genetic test design and validation	$3,529,629	$4,412,036	$5,073,842	$5,581,226	$6,139,348
Cost of services for PGD Stage 2: embryo biopsy	$253,641	$317,052	$364,609	$401,070	$441,177
Cost of services for PGD Stage 3: embryo analysis	$1,400,541	$1,750,677	$2,013,278	$2,214,606	$2,436,067
Total cost of services for PGD Stage 1, Stage 2 and Stage 3	**$5,183,812**	**$6,479,765**	**$7,451,729**	**$8,196,902**	**$9,016,592**

Source: Excel Section E workbook, <PGD assumptions - Proposed>
Abbreviations: PGD, preimplantation genetic diagnosis

The assessment report noted that the availability of public funding for PGD would lead to an increase in costs to government. This is attributed to the expected increase in uptake of PGD (and therefore IVF) services by couples who would otherwise choose natural conception with prenatal diagnosis (as well as couples who would otherwise choose natural conception without prenatal diagnosis, or choose to have children by other means, or have no children).

Table 10 shows the total incremental cost to the MBS of public funding for PGD, assuming that the proposed PGD service items are listed on the MBS.

Table 10 Estimated total net financial impact of a successful listing for PGD on the MBS

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Total incremental cost to the MBS of public funding for PGD	$7,849,380	$10,867,637	$12,793,777	$13,967,452	$15,391,117

Source: Excel Section E workbook <Total incremental cost>
Abbreviations: MBS, Medicare Benefits Schedule; PGD, preimplantation genetic diagnosis

14. Key issues from ESC for MSAC

ESC advised that this application should be considered in the context of work currently underway to develop a clinical utility card to inform consideration of genetic testing, and the concurrent consideration of the separate application 1216 for cystic fibrosis transmembrane regulator testing.

ESC considered that the ICERs derived in the economic analysis were borderline, and that there were a range of uncertainties in the analysis, due to assumptions of unknown validity, exclusion of downstream costs of care and termination of pregnancy, and the time horizon analysed. ESC noted, however, that the analysis was conservative, with the direction of bias against PGD. ESC advised that, if MSAC considered the ICER in the current analysis cost effective, resolution of the uncertainty would be unlikely to impact decision making.

ESC considered that the item descriptor could be improved by clarifying the definition of 'rare' so that it aligned with other Government guidance, and that the definition of serious or severe also required clarification.

ESC noted that there is a current disparity in equity of access, as the procedure is currently only available to those who can afford it.

15. Other significant factors

Current legislation governing MBS would need to be amended to allow subsidy of PGD under the Medicare Benefits Scheme. It has been suggested that an alternate funding mechanism for PGD could be considered following assessment through the MSAC process

16. Applicant's comments on MSAC's Public Summary Document

For clarification, the Assessment Report prepared for the ESC was a contracted technical report for use by the Medical Services Advisory Committee (MSAC) to inform its deliberations.

REFERENCE
Elhassen D, Coleman K, Mernagh P, Campbell S, Fodero L, Scuteri J. (2015). *Preimplantation genetic diagnosis*. MSAC Application 1165, Assessment Report. Commonwealth of Australia, Canberra, ACT

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: www.msac.gov.au.