

***Assessment of preimplantation  
genetic diagnosis***

April 2015

MSAC application 1165

Assessment Report

## Assessment 1165 – Preimplantation Genetic Diagnosis – April 2015

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**MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.**

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# Abbreviations

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AC	Amniocentesis
aCGH	Array comparative genomic hybridisation
ADO	Allele drop-out
ANCOVA	Analysis of covariance
ANZARD	Australia and New Zealand Assisted Reproduction Database
ARPKD	Autosomal recessive polycystic kidney disease
ART	Assisted reproductive technology
ASRM	American Society for Reproductive Medicine
BMI	Body mass index
BSID	Bayley Scales of Infant Development
CA	Chromosomal abnormality
CBCL	Child Behavioural Checklist
CF	Cystic fibrosis
CGH	Comparative genomic hybridisation
CHERE	Centre for Health Economics Research and Evaluation
ChP	Chemical pregnancy
CI	Confidence interval
CMT	Charcot-Marie-Tooth
CP	Clinical pregnancy
CUA	Cost-utility analysis
CVS	Chorionic villus sampling
DMD	Duchenne muscular dystrophy
DNA	Deoxyribonucleic acid
DQ	Development quotient
EMSN	Extended Medicare Safety Net

ESHRE	European Society of Human Reproduction and Embryology
ET	Embryo transfer
FBS	Fetal blood sampling
FISH	Fluorescence in situ hybridisation
FSIQ	Full-scale intelligence score
HCG	Human chorionic gonadotropin
HD	Huntington's disease
HESP	Health Expert Standing Panel
HFEA	Human Fertilisation and Embryology Authority
HGSA	Human Genetics Society of Australia
HLA	Human leukocyte antigen
HREC	Human research ethics committee
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICMART	International Committee for Monitoring Assisted Reproductive Technolog
ICSI	Intracytoplasmic sperm injection
IVD	In vitro Diagnostic Devices
IVF	In vitro fertilisation
LFU	Lost to follow-up
LR	Likelihood ratio
M ABC	Movement ABC
MBS	Medicare Benefits Schedule
MDA	Multiple displacement amplification
MDI	Mental Developmental Index
MDS	Mental Development Scales
MSAC	Medical Services Advisory Committee

NA	Not applicable
NC	Natural conception
NGS	Next-generation sequencing
NHMRC	National Health and Medical Research Council
NPAAC	National Pathology Accreditation Advisory Council
NS	Not statistically significant
OCC	Oocyte collection cycle
OR	Odds ratio
ORt	Oocyte retrieval
PASC	Protocol Advisory Sub-Committee
PBS	Pharmaceutical Benefits Schedule
PCR	Polymerase chain reaction
PDI	Psychomotor Developmental Index
PGD	Preimplantation genetic diagnosis
PGDIS	PGD International Society
PGS	Preimplantation genetic screening
PICO	Population, intervention, comparator, outcomes
PND	Prenatal diagnosis
PNT	Prenatal testing
QALY	Quality-adjusted life year
QoL	Quality of life
RCPA	Royal College of Pathologists of Australasia
RCT	Randomised controlled trial
RTAC	Reproductive Technology Accreditation Committee
S	Singleton birth
SA	South Australia
SGD	Single gene disorder

SNP	Single nucleotide polymorphism
STST	Short Temperament Scale for Toddlers
TGA	Therapeutic Goods Administration
TOP	Termination of pregnancy
TTO	Time trade off
UK	United Kingdom
US	United States
VARTA	Victorian Assisted Reproductive Treatment Authority
WGA	Whole genome amplification
WHO	World Health Organization

# Executive summary

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## Assessment of preimplantation genetic diagnosis

### A.1.1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of preimplantation genetic diagnosis (PGD) was received from Genea (formerly Sydney IVF) by the Department of Health and Ageing in July 2011. Genea proposed that public funding be available 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 Final Protocol was published in June 2014 after consideration by the Protocol Advisory Sub-Committee (PASC) at their December 2013 and April 2014 meetings.

It should be noted that current legislation governing MBS funding prevents subsidy of PGD under the Medicare Benefits 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. Thus, the aim of this assessment is to inform a decision as to whether the proposed service should be funded via an alternate mechanism. This report, guided by the framework specified in the Final Protocol, considers the impact on the Commonwealth budget of introducing three specific items to cover the procedures encompassed by PGD.

### A.1.2. Current arrangement for public reimbursement

In Australia, PGD is provided by private fertility and assisted conception clinics to couples who are concerned about carrying genetic conditions, and are prepared to undergo IVF. PGD is not currently publicly funded and costs are met through a range of pathways including funding assistance programs (for example funds created from donations), self-funding, funding by the facility conducting the PGD service, or through a combination of these mechanisms.

### A.1.3. Background

PGD is a form of prenatal diagnosis performed on early embryos – prior to implantation – to identify genetic defects that are known to exist in one or both parents. The embryos are created through assisted reproductive technology (ART), whereby oocytes aspirated following ovarian stimulation are fertilised by intracytoplasmic injection of individual spermatozoa (ICSI); these techniques are collectively known as in vitro fertilisation (IVF). Therefore, unlike conventional prenatal diagnosis, PGD is not performed on an ongoing intrauterine pregnancy but on embryos developed in the IVF laboratory prior to transfer to the uterus.

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.

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 biopsy is the method used in their 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.

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: Stage 1 – molecular geneticists; Stage 2 – embryologists or molecular geneticists; and Stage 3 –molecular geneticists.

#### **A.1.4. Clinical need**

PGD 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 genetic abnormalities, and to make it likely that their offspring will not suffer from the genetic defect carried by the family. As preimplantation genetic screening (PGS) is strictly used to screen embryos for normal chromosome numbers, 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 (TOP), 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 Final Protocol (p6) proposes that funding for PGD be restricted to:

- Couples who 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 know that they 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 Protocol defines a serious genetic disorder as being one which is untreatable, apart from symptomatic care, and is unable to be prevented. 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. For conditions that fall outside the list, the review process would involve a committee who would decide whether an unlisted condition would warrant public funding.

Examples of serious single gene disorders (SGDs) include autosomal recessive disorders such as cystic fibrosis, autosomal dominant disorders such as Huntington's disease and Marfan syndrome, and X-linked disorders such as Duchenne muscular dystrophy, Haemophilia A and Fragile X syndrome. Structural chromosome rearrangements include reciprocal and Robertsonian translocations and inversions.

A prospective parent would know that they carry a specific genetic mutation for a serious genetic disorder, or a chromosomal rearrangement, 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/rearrangement. The parents may have sought this consultation in the event that they have had a child with the disorder, there is a family history of the disorder, they have been diagnosed with the disease, or they have suffered recurrent miscarriage.

#### **A.1.5. Proposed funding item**

Table ES.0.1 presents the proposed PGD item descriptors as shown in the Final Protocol. The proposal for PGD subsidy includes three separate service items relating to each of the three PGD stages: (1) Genetic test design and validation; (2) Embryo biopsy; and (3) Embryo genetic analysis. The three items have been proposed so that the payer only pays for the exact service provided to the patient. Due to the nature of some serious genetic disease mutations warranting a more complex and/or more analysis than others, PASC approved a tiered approach to the fees for PGD Stage 1, where one is for rare (or complex) mutation test design and validation, and one for more common or known mutations (for which a test is likely to have been designed before).

Table ES.0.1 Proposed descriptors for PGD items 1, 2, and 3

<p>Category 6– PATHOLOGY (Group P7 Genetics)</p> <p>Item [xxxxx]</p> <p><b>PGD Stage 1 Genetic test design and validation</b> 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).</p> <p>Explanatory Note:</p> <p>Item number is relevant for couples undergoing PGD for the following reason:</p> <ul style="list-style-type: none"> <li>• 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</li> <li>• 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.</li> </ul> <p><u>The fee must only be applied once per couple</u> (the PGD test is developed once and it does not need to be repeated on a per cycle basis; <i>information provided by the test must be made accessible</i>)</p> <p>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 <i>should be provided</i> subsequent to the development of the PGD test in order to explain the diagnostic risks and limitations for their particular test.</p> <p><u>Fee structure</u></p> <p>Level 1: \$[fee] Design and validation of a probe for simple/common mutations</p> <p>Level 2: \$[fee] Design and validation of probe requiring complex analysis and/or high level of technical expertise,</p> <p>[Relevant explanatory notes]</p>
<p>Category 3 – THERAPEUTIC PROCEDURE</p> <p>Item [xxxxx]</p> <p><b>PGD Stage 2 Embryo biopsy:</b> 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).</p> <p>Explanatory Note:</p> <p>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).</p> <p>Fee: \$[fee]</p> <p>[Relevant explanatory notes]</p>
<p>Category 6– PATHOLOGY (Group P7 Genetics)</p> <p>Item [xxxxx]</p> <p><b>PGD Stage 3 Embryo genetic analysis:</b> The study of biopsied embryo tissue using molecular techniques for single gene disorders or the whole of every chromosome. (One or more embryos)</p> <p>Explanatory Note:</p> <p>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).</p> <p>Embryo(s) that are not affected by the genetic disorder can be transferred to the uterus of the female or vitrified.</p> <p>This item number must not be used for the purpose of positive selection for gender or a genetic disorder.</p> <p>Fee: \$[fee]</p> <p>[Relevant explanatory notes]</p>

Source: Final Protocol, Table 5, p17

The Applicant has proposed the following fees for each stage:

- Stage 1: \$1,736
- Stage 2: \$115 per embryo
- Stage 3: \$635 per embryo.

The fees proposed by the Applicant do not exactly match the descriptors for Stages 1-3 above as follows:

- For Stage 1, the Applicant has proposed a single fee, whereas PASC have proposed a two-tier fee structure based on complexity of the test design. In their feedback on the

Consultation Protocol, the Applicant notes the simple test design for common mutations proposed by PASC does not take into account the use of flanking markers, which is standard practice for PGD and critical for test accuracy.

- For Stage 2, the Applicant has proposed a ‘per embryo’ fee, while the proposed item descriptor is for ‘one or more embryos’. The Applicant has advised that an average of four embryos are biopsied per PGD cycle.
- For Stage 3, the Applicant has proposed a ‘per embryo’ fee, while the proposed item descriptor is for ‘one or more embryos’.

The fee for Stage 1 provides for genetic counselling to explain the diagnostic risks and limitations of the particular test that will be undertaken.

Consistent with the Final Protocol, the economic evaluation (Section D) and financial estimates (Section E) assume that the Stage 2 and Stage 3 fees are applied only once to embryos harvested from a single cycle, in acknowledgment that there may be efficiencies when multiple embryos from a single cycle are biopsied and tested together.

As IVF is an integral part of the PGD process, couples undergoing PGD would need to meet eligibility criteria for that procedure. The Applicant has proposed a change in Associated Note T1.4 to enable IVF and the proposed PGD items numbers to be used together. Additionally, amendments are required to ensure that MBS item 13251 (for 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.

#### **A.1.6. Comparator**

The MBS provides subsidy for various pathology services which may be used for prenatal diagnosis (after conception via natural conception (or IVF)), which is the comparator for PICO 1, 3 and 4 in the Final Protocol. The prenatal sampling techniques of amniocentesis, chorionic villus sampling (CVS), and fetal blood sampling (FBS) are currently MBS subsidised (Category 3 Therapeutic Procedures item 16600, 16603 and 16606), although there is very limited use of FBS. According to the Final Protocol, genetic tests on samples retrieved via amniocentesis, CVS or FBS are also listed on the MBS (Category 6 – Pathology Services – items 73300, 73305, 73287, 73289, 73291, 73292, and 73293).

As mentioned above, IVF (which is the comparator for PICO 2), is subsidised on the MBS (items 13200 through 13221, and item 13251 for ICSI). There are no restrictions on the number of cycles that patients can have nor are there any age restrictions for these items.

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 has not been included in the assessment of PGD as there is insufficient evidence to support the assumption that a significant proportion of couples carrying a mutation would choose this option.

### A.1.7. Clinical claim

The clinical claim in the Final Protocol is that PGD is as effective in identifying genetic disorders as prenatal diagnosis. In addition, the Applicant also states that 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 TOP. The Applicant claims that the time delay associated with prenatal diagnosis and the 1 in 2 or 1 in 4 risk of passing on a serious genetic disorder with natural conception (or IVF), makes PGD a superior option for couples at high risk of having a child with a genetic disorder. Further, PGD offers superior safety for couples 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 serious genetic disorder.

### A.1.8. Scientific basis of comparison

The Final Protocol outlined a list of the clinical questions to be answered by this clinical assessment. A list of these questions is presented in Table ES.0.2. The details of the PICO criteria they refer to can be found in Section B.4.8.

Table ES.0.2 Clinical questions to be answered by this assessment

PICO/Q #	Question
PICO 1/Q1:	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?
PICO 1/Q2:	Is PGD as safe and effective as natural pregnancy (or pregnancy by IVF) followed by postnatal 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)
PICO 1/Q3:	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)
PICO 2/Q1:	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?
PICO 3/Q1:	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?
PICO 3/Q2:	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?
PICO 4/Q1:	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 termination of pregnancy in couples who are at high risk of passing on a serious genetic disorder to their offspring?
PICO 5/Q1:	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?
PICO 5/Q2:	What are the physical safety concerns to the mother regarding termination of pregnancy?

Following the literature search conducted to identify studies relating to PICO 1 to PICO 4, little comparative evidence was found to allow a comparison between PGD and the main comparators of interest: prenatal testing for PICO 1 and PICO 3, and IVF+ICSI alone (without embryo biopsy) for PICO 2. The majority of evidence available for PGD comes from single arm studies and case series. For PICO 2 (safety and effectiveness of

PGD in offspring), a small number of observational studies were available which compared children’s outcomes following PGD and IVF, natural conception, or both.

There were a number of randomised controlled trials (RCTs) identified and included in this assessment. However these compared different PGD methodologies, not PGD with the comparators.

The majority of the clinical evidence for PGD comes from the European Society of Human Reproduction and Embryology (ESHRE) PGD Consortium. It should be noted that despite providing a low level of evidence, the 12 published annual reports from the Consortium (including data from 1997 to 2009) cover all applications of PGD (including autosomal and sex-linked single gene disorders (SGDs) and chromosomal rearrangements, PGS and social sex selection) from various fertility centres worldwide, and thus, provide a substantial body of evidence.

Comparative data in the target population were not available for a large number of the outcomes defined in the clinical questions relating to PICO 1, 2 and 3, and no studies were identified that satisfied the criteria in PICO 4. In addition, no relevant comparative studies were identified for PICO 5; this question has been addressed within Section C in terms of health-related quality of life (HRQoL) related to the decision to terminate a viable pregnancy and its consequences.

### A.1.9. Effectiveness

#### PICO 1

No comparative data were identified 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 single gene disorders (SGD) is presented in Table ES.0.3. Results were similar for the two indications.

Table ES.0.3 PICO 1: 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 compatibility. 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, data were 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 D.

#### **PICO 2**

No studies were identified that provided data for the effectiveness outcomes for this question: quality of life and functional status.

#### **PICO 3**

There was no comparative evidence available to determine whether PGD is as accurate as prenatal diagnosis. The absolute accuracy of PGD is difficult to estimate since it is impossible to confirm the diagnosis in every embryo. Access for reanalysis is available either during pregnancy (prenatal diagnosis) or after birth (postnatal diagnosis); however, a substantial number of embryo transfers do not result in pregnancy and confirmatory testing is 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 were 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%.

### A.1.10. Safety

#### PICO 1

No comparative data were 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 ESHRE PGD Consortium dataset for chromosomal abnormalities and SGDs is presented in Table ES.0.4. 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 ES.0.4 PICO 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 compatibility. 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.

A large number of outcomes defined for this safety question could not be assessed based on the available evidence. These included: 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 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.

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 D.

#### PICO 2

Two observational studies provided data on perinatal mortality and major malformations following PGD alone, PGD/PGS compared with ICSI alone. However, it should be noted that 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 ES.0.5). 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 ES.0.5 PICO 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] <sup>b</sup> S: OR 0.60 (0.23, 1.42) <sup>c</sup> M: OR 1.63 (0.89, 2.99) <sup>c</sup>	23/995 (2.3)	40/1507 (2.7)	OR 0.87 (0.49, 1.50) <sup>b</sup>

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 Table ES.0.6. 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 ES.0.6 PICO 2: Summary of ESHRE PGD Consortium data on PGD/PGS, data collection IV – XII**

Study	Stillbirths n/N (%) <sup>a</sup>	Neonatal deaths n/N (%) <sup>a</sup>	Perinatal deaths n/N (%)	Major malformations n/N [mal/birth] <sup>b</sup>
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 deaths is all births with neonatal complication data available minus the number of stillbirths. 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

Three Level III observational studies provided comparative analyses, adjusted for possible confounders, on development delay in two cohorts of children born following PGD ( $\pm$  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 does 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, these results suggest that PGD, and in particular the biopsy technique used in PGD, may not cause harm to the developing fetus and child.

### A.1.11. Pre-modelling studies

Section D presents each of the translation issues identified to move from the clinical evidence discussed in Section C to the economic evaluation presented in Section E. Applicability, extrapolation and transformation issues were considered to identify each of the issues presented in Table ES.0.7. In each instance, a focused analytical plan is presented prior to presenting the results of the pre-modelling study and the relationship between these and the economic evaluation presented in Section E.

Table ES.0.7 Translation issues identified in preparing the economic evaluation

Translation issue	Comments	Section C subsection
<i>Applicability issues</i>		
Population and circumstances of use	There is a scarcity of publications that directly compare PGD with the comparators defined in the Protocol, in the population that would be eligible for public funding under the proposed listing. Nonetheless, the link between the population of the requested listing and the economic model presented in Section D is discussed.	Section D.1 Appendix 4
<i>Extrapolation issues</i>		
Downstream impacts related to affected live births	The ultimate aim of both PGD and prenatal testing is to avoid the potential consequence of conception between parents carrying single gene disorders or translocations; that is, birth of an affected child. This impacts on both quality of life and healthcare costs. Estimates of the downstream costs are sourced and discussed in this pre-modelling study to ensure they are adequately applied to the model presented in Section E.	Section D.2 Appendix 4
<i>Transformation issues</i>		
Modelling the natural history of pregnancy and the IVF cycle	Although the focus of the analysis is on the birth of a child, an understanding of conception rates, miscarriage rates and the rate at which terminations occur in fetuses with abnormalities was a crucial step in the development of a cost-utility model.	Section D.4 Appendix 4
Utility weights applied to the economic model	To undertake the cost-utility modelling presented in Section E, it was necessary to source utility weights to be applied to the health states included in the economic model. As discussed, these needed to account for live births affected by abnormalities and those unaffected, as well as miscarriages, terminations and failure to conceive.	Section D.5 Appendix 4
Healthcare resource use and associated costs	The economic model required costs to be calculated for a variety of health states and events related to the use of IVF and ongoing pregnancy. In doing so, the incremental differences between the model arms could be better estimated.	Section D.6 Appendix 4

Abbreviations: IVF, in vitro fertilisation; PGD, preimplantation genetic diagnosis

### A.1.12. Economic evaluation

Based on the limited body of evidence presented in Section B, it cannot be confirmed that the diagnostic accuracy of PGD is as effective, or any better than, prenatal testing in couples known to be carrying genetic mutations or rearrangements. Also, based on the evidence available in Section B, it is not possible to confirm a decreased time to unaffected live birth or a reduction in psychological trauma in the intended population due to a decreased need for TOP. Nonetheless, a cost-utility analysis (CUA) has been undertaken, as suggested by PASC, assuming decreased miscarriage and TOP for couples undergoing PGD compared with prenatal testing, as well as a shorter timeframe to an unaffected live birth.

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.

Although 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 (e.g. 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 model was run for 10 cycles of 20 weeks each in the base case. This represents a highly conservative approach, since it accounts for all costs associated with conception, pregnancy and birth but limits the accrual of utility to a short-term period even though utility weights are 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 is tested in sensitivity analyses, as is the impact of including long-term costs associated with the ongoing medical treatment required in 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 will 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 ES.0.8 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 ES.0.9 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, for simplicity, this small, specific patient group has not been included in the economic analysis.

**Table ES.0.8 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
<i>Incremental cost per QALY</i>	-	-	<i>\$48,875</i>

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

**Table ES.0.9 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
<i>Incremental cost per QALY</i>	-	-	<i>\$31,620</i>

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

Table ES.0.10 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 ES.0.11.

**Table ES.0.10 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
<i>Incremental cost per unaffected live birth</i>	-	-	<i>\$37,719</i>

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

**Table ES.0.11 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
<i>Incremental cost per unaffected live birth</i>	-	-	<i>\$30,632</i>

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

Sensitivity analyses are presented in Section E.6. Increasing the duration of the model improves 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). While an interesting result, it is anticipated the base case analysis would be most helpful for decision-making purposes, as it avoids the risk of making decisions based on a magnification of the inherent uncertainty of the utility weight estimates and avoids any potential bias in favour of PGD.

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. 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 couples re-attempt 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 in to the model (including analysis examining the utility of affected live births, which is 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 has 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 states that the cost applies to the biopsy of multiple embryos, while the cost proposed by the Applicant is applied per embryo biopsied (see Section A.3.1 for further details). 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.

#### **A.1.13. Estimated utilisation and financial implications**

The estimated number of PGD services and the estimated cost of these services over the first five years of proposed public funding is shown in Table ES.0.12.

**Table ES.0.12 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
<b>Total cost of services for PGD Stage 1, Stage 2 and Stage 3</b>	<b>\$5,183,812</b>	<b>\$6,479,765</b>	<b>\$7,451,729</b>	<b>\$8,196,902</b>	<b>\$9,016,592</b>

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

The availability of public funding for PGD will lead to an increase in costs to the MBS. This is attributed to the expected increase in uptake of PGD and 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). The total cost of other MBS services associated with PGD and the total cost of MBS services associated with natural conception with prenatal testing are presented in Section E.3.

For illustrative purposes, Table ES.0.13 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. In order for PGD to be listed on the MBS, a change to the legislation would be required.

**Table ES.0.13 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	\$7,852,163	\$10,874,044	\$12,807,527	\$13,980,249	\$15,402,935

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

# Background

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Preimplantation Genetic Diagnosis (PGD) is a technique used to identify certain genetic defects in embryos created through assisted reproductive technologies (such as in vitro fertilisation) prior to implantation. Although not exclusively used for this purpose, PGD is currently available in Australia for couples who carry a specific mutation for a serious genetic disorder which is at high risk of being passed onto their offspring. The serious genetic disorder may result from a single gene mutation or chromosome rearrangement (e.g. translocation). Serious genetic disorders for which PGD is typically sought include, but are not limited to, cystic fibrosis, Duchenne muscular dystrophy and Fragile X syndrome. There is no preventative therapy for such disorders and treatment is limited to symptomatic care.

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 the transfer of an unaffected embryo to the female uterus and progression of the pregnancy.

In Australia, PGD is provided by private fertility and assisted conception clinics to couples who are concerned about carrying genetic conditions, and are prepared to undergo IVF. PGD is not currently publicly funded and costs are met through a range of pathways including funding assistance programs (for example funds created from donations), self-funding, funding by the facility conducting the PGD service, or through a combination of these mechanisms.

An application requesting Medicare Benefits Schedule (MBS) listing of PGD was received from Genea (formerly Sydney IVF) by the Department of Health and Ageing in July 2011. Genea proposed that public funding be available 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 Final Protocol for the assessment of PGD was published in June 2014.

It should be noted that, without amendment, current legislation governing MBS funding would prevent subsidy of PGD under the Medicare Benefits Scheme. It has been suggested that an alternate funding mechanism for PGD could be established following health technology assessment through the MSAC process.

HealthConsult Pty Ltd was engaged in October 2014 to conduct an assessment in order to inform a decision as to whether the proposed service should be publicly funded. This report, guided by the framework specified in the Final Protocol, considers the safety, effectiveness, cost-effectiveness and financial implications of introducing three specific items to cover the procedures encompassed by PGD.

# Section B. Details of the proposed medical service and its intended use

## B.1. Address all items in the Protocol

The Final Protocol for the current assessment outlines the questions that need to be answered in this Assessment Report. The Final Protocol was developed through considerations by the Protocol Advisory Sub-Committee (PASC) at meetings held on 12-13 December 2013 and 16-17 April 2014, including public consultation from 7 February to 21 March 2014.

Table B.1.1 provides a summary of how the current assessment conforms to the Final Protocol, with any differences or changes justified.

Table B.1.1 Items addressed in the Protocol and Assessment Report

Items in the Final Protocol	Location in Assessment Report	Concurs with Protocol	Change and justification
Proposed descriptors and fees for public funding	Section A.3.1	Partly	The Final Protocol proposes a two-tiered fee structure for PGD Stage 1 (test design and validation); however the Applicant has proposed a single fee (justification provided in Section A.3.1).  For PGD Stage 2 (embryo biopsy) and Stage 3 (embryo DNA analysis), the Applicant proposed a "per embryo" fee rather than a single fee for "one or more embryos", as per the Final Protocol. The Assessment Report is consistent with the Protocol, assuming that there are efficiencies when handling multiple embryos from the same cycle. As such, the fees proposed by the Applicant are only applied once per cycle (rather than per embryo).
Comparator	Section A.4	Yes	However, PASC proposed that a secondary comparator may be the option of parents who decide not to have their own biological children but may choose PGD if it were subsidised over the current choices of adoption or conception with donor egg or sperm, or no children by any means. This comparator has not been incorporated in the assessment of PGD as there is insufficient evidence to support the assumption that a significant proportion of couples carrying a mutation would choose this option.
Clinical management algorithm	Section A.5, Figure B.1	Yes	N/A
Clinical outcomes assessed	Section A.8, Table B.4.4 to Table B.4.8	Yes	
Healthcare resources	Section C.6, Section D.4.1, Section E.2, Section E.3	Yes	The Final Protocol did not provide a full list of healthcare resources but did provide a list of MBS items relevant to PGD.



Items in the Final Protocol	Location in Assessment Report	Concurs with Protocol	Change and justification
Economic evaluation structure	Section D.3	Partly	The structure of the economic model was informed by the health economics literature and the decision analytic proposed by the Applicant. The modelled economic evaluation incorporates misdiagnosis, which was not explicitly considered in the Applicant's decision analytic but is associated with some uncertainty (although rates of misdiagnosis are very low overall). The results of the modelled economic evaluation are presented as cost per QALY for couples (the mother in particular) undergoing PGD. The HRQoL of the neonate/child is not considered in the economic evaluation due to the large range of genetic conditions, with variable life expectancy and associated costs, and issues with the reliability of utility weights for children.

Abbreviations: HRQoL, health-related quality of life; MBS, Medicare Benefits Schedule; N/A, not applicable; PGD, preimplantation genetic diagnosis; QALY, quality-adjusted life year

The Assessment Report has addressed all the questions outlined in the Final Protocol.

## B.2. Proposed medical service

### B.2.1. Description of PGD

PGD is a form of prenatal diagnosis performed on early embryos prior to implantation to identify genetic defects that are known to exist in one or both parents. The embryos are created through assisted reproductive technology (ART), whereby oocytes aspirated following ovarian stimulation are fertilised by either in vitro immersion in semen or by intracytoplasmic injection of individual spermatozoa (ICSI); these techniques are collectively known as in vitro fertilisation (IVF). Therefore, unlike conventional prenatal diagnosis, PGD is not performed on an ongoing intrauterine pregnancy but on embryos developed in the IVF laboratory prior to transfer to the uterus. It should be noted that for the purposes of PGD, the preferred method of fertilisation is via ICSI, as this ensures no contamination of the embryo sample to be tested with the father's genetic material.

Before PGD can commence, couples need confirmation from a clinical geneticist that one or both parents carry specific genetic mutations for a serious genetic disorder (a single gene disorder of simple inheritance pattern: autosomal dominant or autosomal recessive), or at least one partner carries a chromosome rearrangement, that is at high risk of being passed on to their offspring.

A PGD cycle is composed of three stages: (i) test design and validation, (ii) embryo biopsy and (iii) 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. These include: (a) primers for the mutation(s) (also known as the sequencing primers), and (b) primers for at least two short tandem repeats linked to the relevant gene (linkage primers). Probes used in PGD are single stranded

DNA molecules that are complementary to the target DNA (in this case the mutation responsible for the genetic disorder and the short tandem repeats (linkage markers)).

To validate the test, DNA from the couples or family members undergoes 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 should be optimised to ensure it is efficient when used on the minimal DNA quantities available from the biopsied embryo cells.

Stage 1 is expected to take a number of weeks and the couple should be informed of the test results. However, there may be situations where individuals or couples do not want their genetic status disclosed (for example, those with Huntington's disease or other late onset diseases). Stage 1 is completed before the IVF cycle begins.

## **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. An IVF cycle involves the following steps:

- stimulating 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 the inseminated eggs in the laboratory to fertilisation;
- culturing the fertilised embryos to biopsy stage;
- transferring the abnormality-free embryo/s into the uterus; and
- supporting the endometrium in the luteal phase.

The biopsy stage of the PGD process may be performed at three different embryonic developmental stages: (1) just prior to and following fertilisation on polar bodies; (2) at Day 3 cleavage-stage which involves blastomere removal at the 5-8 cell embryonic stage; or (3) at Day 5-6 on blastocyst stage embryos that consist of approximately 120 cells (five to eight cells are removed from the trophectoderm of the blastocyst). The stage at which a biopsy is performed is usually dependent on the specific legal regulations and technical preferences at individual reproductive and genetic centres. A five-day-old blastocyst is more developed, and contains both inner cell mass cells and trophectoderm cells, compared with a cleavage-stage embryo, which contains only six to eight omnipotent cells.

Best practice guidelines from the European Society for Human Reproduction and Embryology (ESHRE) PGD Consortium describe blastomere stage biopsy on Day 3 as being associated with a higher risk of damaging the embryo and misdiagnosis secondary to possible mosaicism, whereas trophectoderm biopsy performed at the blastocyst stage on Day 5 is associated with better results and a more accurate diagnosis (Harton et al, 2011d). A recent randomised clinical trial provides further support that blastomere biopsy is more detrimental to the embryo than biopsy at the blastocyst stage (Scott et al, 2013). Although the most recent ESHRE dataset collected from 60 centres internationally (Moutou et al, 2014) indicated that 79.8% of biopsies were performed at

the Day 3 blastomere stage compared with only 2.3% at the Day 5 blastocyst stage, the Applicant has advised that Genea only perform biopsy at the blastocyst stage.

### **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. 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's uterus. In their response to the Consultation Draft Protocol, the Applicant noted that they only perform single embryo transfer. 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.

It should be noted that PGD is not 100% accurate and misdiagnosis can occur for a number of reasons including:

- biological factors such as mosaicism in the embryo;
- rearrangement of genetic material<sup>1</sup>; and
- failure of the test, leading to diagnosis of no abnormality where the genetic mutation is present.

Apparent misdiagnosis can occur if the tested embryo fails to implant and the patient becomes pregnant naturally; for this reason, patients are instructed not to have unprotected intercourse during a PGD cycle. Other negative birth outcomes may also occur after PGD if the embryo is damaged during the biopsy stage, the baby is affected by an unrelated disorder, or there is an unrelated complication during development or birth.

#### **B.2.2. Current technologies for PGD**

There are a number of laboratory techniques that allow the identification of genetic defects in embryos, including polymerase chain reaction (PCR)-based techniques, fluorescence in situ hybridisation (FISH), array comparative genomic hybridisation (aCGH), single nucleotide polymorphism (SNP) array, next-generation sequencing (NGS), as well as advanced methods for the detection of chromosomal rearrangements using whole genome amplification (WGA). The genetic abnormalities that can be diagnosed by each methodology are shown in Table B.2.1.

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<sup>1</sup> this should be reduced by accurate test design and validation and linkage/genetic fingerprint data

Table B.2.1 Current technologies for PGD

Indications	PCR	FISH	aCGH	SNP array	NGS
Sex selection (social or X-linked disease)	Yes	Yes*	Yes	Yes	Yes
Aneuploidy screening	Yes	Yes*; locus specific	Yes*; generic	Yes; generic	Yes; generic
DNA copy-number aberrations	Yes	Yes*; locus specific	Yes; generic	Yes; generic	Yes; generic
Carriership of balanced chromosome rearrangements	No	No	No	Yes	Yes
Single gene disorder	Yes*, family specific	No	No	Yes; generic	Yes; generic
De novo segmental copy-number aberrations	No	No	Yes; generic	Yes; generic	Yes; generic
De novo base mutations	No	No	No	No	Yes; generic
Mitochondrial mutations	Yes*; family specific	No	No	No	Yes; generic

Source: PGD guided by single cell genomics (Van der Aa et al, 2013)

Note: The genetic conditions that can be diagnosed by each methodology are indicated, with the current methodology in common practice marked with an asterisk.

Abbreviations: aCGH, array comparative genomic hybridisation; FISH, fluorescence in situ hybridisation; NGS, next-generation sequencing; SNP, single nucleotide polymorphism.

The two methods currently in use for genetic testing of embryo tissue during PGD at Geneva are: (i) PCR-based techniques for the molecular examination for a particular gene or mutation, and (ii) CGH for the detection of chromosomal abnormalities (including chromosomal rearrangement and aneuploidy). According to the Pre-assessment documentation provided by the Applicant, CGH has many advantages over the commonly used method of FISH, the main one being that it can accurately analyse the integrity of all of an embryo's chromosomes (whereas FISH can analyse up to 12 chromosomes). All embryos undergoing CGH analysis are vitrified (quick frozen and stored in liquid nitrogen) while the analysis is conducted. Embryos found to have a normal chromosome complement can then be transferred in subsequent frozen embryo cycles.

In 2005, the ESHRE PGD Consortium published a set of *Guidelines for Best Practice PGD* to give information, support and guidance to potential, existing and fledgling PGD programmes (Thornhill et al, 2005). However, the rapidly changing nature of PGD (and preimplantation genetic screening [PGS]) – specifically the introduction of new technologies associated with its use and increasing patient access – has necessitated revision and update of the original ESHRE PGD Consortium guidelines. As a result, the Consortium has prepared four sets of guidelines; one relating to the organisation of the PGD centre and three relating to the methods used (amplification-based-PGD, FISH-based PGD and PGS, and embryology) (Harton et al, 2011a; Harton et al, 2011b; Harton et al, 2011c; Harton et al, 2011d). There are currently no available guidelines on the use of array CGH (a more specific form of CGH) in PGD. Attachment A contains a summary of the recommendations from the ESHRE PGD Consortium *Best Practice Guidelines for Amplification-based PGD*.

### B.2.3. Proposed indications

The Final Protocol (p6) proposes that funding for PGD be offered specifically to:

- Couples who 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 know that they 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).

A prospective parent would know that they carry a specific genetic mutation for a serious genetic disorder, or a chromosomal rearrangement, 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/rearrangement. The parents may have sought this consultation in the event that they have had a child with the disorder, there is a family history of the disorder, they have been diagnosed with the disease, or they have suffered recurrent miscarriage.

Single gene disorders are inherited in either an autosomal dominant, autosomal recessive, or an X-linked pattern. In carriers of autosomal dominant disorders, the risk that any given embryo may be affected is 50%. For carriers of autosomal recessive disorders, the risk is 25%. For female carriers of X-linked disorders, the risk of having an affected embryo is 25% (half of male embryos) (see Table B.2.2) (American Society for Reproductive Medicine (ASRM) 2008).

Table B.2.2 Percentage of embryos that will be affected, normal, and carriers of single gene mutations having different patterns of inheritance<sup>a</sup>

Mutation	Affected	Normal	Carrier	Example
Autosomal dominant	50%	50%	-	Marfan syndrome
Autosomal recessive	25%	25%	50%	Cystic fibrosis
X-linked (female carrier)	25% (male)	50%	25% (female)	Haemophilia A

Source: ASRM Practice Committee, 2008

<sup>a</sup> For each type of mutation, the sum of normal and carrier embryos equals the total percentage of all embryos potentially available for transfer.

Some examples of single gene disorders where PGD has been used include autosomal recessive disorders such as cystic fibrosis, autosomal dominant disorders such as Huntington's disease and Marfan syndrome, and X-linked disorders such as Duchenne muscular dystrophy, Haemophilia A and Fragile X syndrome.

Structural chromosome rearrangements include reciprocal and Robertsonian translocations and inversions. These can be seen in approximately 1/500 live born infants and 1/250 prenatal samples (Van Dyke et al, 1983). Individuals who carry balanced chromosome translocations (or inversions) generally have no clinical findings related to the translocation, but will produce high rates of abnormal gametes after meiotic segregation, which can lead to pregnancy loss, failed implantation, apparent infertility or the birth of a child with physical and/or developmental disability (Luthardt and Keitges, 2001).

Based on the wording of the indication presented in the Final Protocol, the use of PGD is not intended for genetic disorders that are classified to be ‘non-serious’ or are not at ‘high risk’ of being passed on to offspring. The Applicant defines a serious genetic disorder as “being one which is untreatable, apart from symptomatic care, and unable to be prevented” (Final Protocol, p10). However, it remains unclear as to what specifically defines a ‘serious’ genetic disorder.

As noted in the Final Protocol (p11), 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. For conditions that fall outside the list, 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>2</sup> genetic disorders would be guided by a criteria check list similar to the following (this 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;
- Disabling disease i.e. the quality of life of patients is compromised by the lack or loss of autonomy;
- 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 in the Final Protocol (p12) 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 (Final Protocol, Appendix C) for the purpose of identification of an eligible population.

Internationally, regulatory and clinical specialty groups have published recommendations on the intended use of PGD (see Attachment A).

The Applicant has provided a list of genetic disorders that are commonly tested using PGD (see Table B.2.3, which lists disorders in order of the percentage of PGD cycles initiated). According to the Applicant, PGD has been used in Australia for the diagnosis of over 150 genetic disorders; the Applicant notes that more than 2000 gene disorders have been identified. The most common single gene disorders tested for are cystic fibrosis (14.1%) and Huntington’s disease (6.7%). While the disorders listed in Table B.2.3 may have been tested using 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. The

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<sup>2</sup> The threshold for ‘rarity’ varies between states and should be clearly defined for the purpose of determining PGD eligibility. The Final Protocol (p11) notes that ‘Rare Voice Australia’ have criteria to define rare disease, and this could be used to guide the checklist.

Applicant did not provide the total number of PGD cycles performed for chromosomal rearrangements.

Table B.2.3 Genea 2014 – Data as a percentage of PGD cycles per gene disorder

Genetic disorder	Number of PGD cycles initiated	Percentage
Cystic fibrosis	21	14.1%
Huntington's disease	10	6.7%
Facioscapulohumeral muscular dystrophy	7	4.7%
Marfans syndrome	7	4.7%
Beta thalassemia	5	3.4%
Haemophilia A	5	3.4%
Cardiomyopathy	4	2.7%
Central core disease	4	2.7%
Fragile X syndrome	4	2.7%
Microcephaly	4	2.7%
Neurofibromatosis type 1	4	2.7%
Tuberous sclerosis	4	2.7%
Choroideremia	3	2.0%
Connexin 26	3	2.0%
Myotonic dystrophy 1	3	2.0%
Neurofibromatosis type 2	3	2.0%
Simpson-Golabi-Behmel	3	2.0%
Ataxia te langiectasia	2	1.3%
Charcot-Marie-tooth 1A	2	1.3%
Charcot-Marie-tooth X-linked	2	1.3%
Congenital stationary night blindness	2	1.3%
Epidermolysis simplex	2	1.3%
Familial adenomatous polyposis	2	1.3%
Hereditary multiple exostoses	2	1.3%
Impaired mtrna import	2	1.3%
Osteogenesis imperfecta type 1	2	1.3%
Wiskott Aldrich	2	1.3%
Various other single gene disorders (1 cycle)	35	23.5%
TOTAL	149	100%

Source: Provided by the Applicant, January 2015  
Abbreviations: PGD, preimplantation genetic diagnosis.

Table B.2.4 shows the different single gene disorders for which PGD was carried out between 1997 and 2007 according to the ESHRE<sup>3</sup> data (Harper et al, 2012). Beta-thalassaemia and sickle cell anaemia (combining the number of PGD cycles for both disorders) were reported by ESHRE to be the most common indications (shown in

<sup>3</sup> The European Society of Human Reproduction and Embryology (ESHRE) PGD Consortium monitors the accuracy, reliability, effectiveness and safety of PGD/PGS (internationally).

Table B.2.4); however, these disorders are more common in Mediterranean countries than they are in Australia.

Table B.2.4 Most common clinical applications of PGD for single gene disorders in the ESHRE Consortium 1997-2007 (data collection I-X)

Genetic disorder	Number of PGD cycles <sup>a</sup>	Percentage
B-thalassaemia and sickle cell anaemia	700	14.8%
Cystic fibrosis	643	13.6%
Myotonic dystrophy type 1	586	12.4%
Huntington disease	530	11.2%
Fragile X syndrome	311	6.6%
Spinal muscular atrophy	280	5.9%
Duchenne muscular dystrophy	148	3.1%
Haemophilia	75	1.6%
Various other single gene disorders	1460	30.8%
TOTAL	4,733	100%

Source: The ESHRE PGD Consortium: 10 years of data collection (Harper et al, 2012)

Abbreviations: ESHRE, European Society for Human Reproduction and Embryology; PGD, preimplantation genetic diagnosis. a Cycles performed for calendar years 1997 to 2007, adapted from Harper et al, 2012 (current data reported by ESHRE).

#### B.2.4. Restrictions to the provision of PGD

PGD is currently offered to a broader population than that for which Commonwealth funding is sought. In addition to being performed for couples with known autosomal single gene disorders and chromosome rearrangements, PGD is currently being used for IVF failure, repeated miscarriage, advanced maternal age, screening for aneuploidy, previous chromosomal disorder in pregnancy, and sex selection for medical reasons (ANZARD). Thus, there are a number of indications where the use of PGD will not be funded, as they do not meet the criteria defined by PASC. As described in the Final Protocol (p11), listing of PGD will not include the following indications:

- screening for aneuploidy;
- sex selection for family balancing (known as social sexing); and
- 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 and/or embryos which require a combination of multiple factors in order that the disease manifests itself.

The ESHRE PGD Consortium has collected data on the number of PGD cycles reported by 115 registered centres worldwide (including Australia) (Moutou et al, 2014). The dataset contains information on 51,589 PGD cycles with the breakdown of indications shown in Table B.2.5. As can be seen, the most common reason for undergoing PGD is for aneuploidy screening (58%). Single gene disorders and inherited chromosome abnormalities account for 37% of PGD cycles.



Table B.2.5 Data from the ESHRE PGD Consortium and the recorded indications for PGD (in 51,589 cycles)

Indication	Number of PGD cycles	Percentage
Aneuploidy screening	30,033	58%
Various single gene disorders (monogenic disorders)	11,084	21%
Inherited chromosome abnormalities	8,104	16%
Sexing for X-linked disease	1,603	3%
Nonmedical (social) sexing	765	2%

Source: Moutou et al (2014)

Abbreviations: ESHRE, European Society for Human Reproduction and Embryology; PGD, preimplantation genetic diagnosis

The PGD International Society (PGDIS)<sup>4</sup> currently estimates that approximately 100,000 PGD cycles have been performed worldwide over the past 23 years, and that nearly 80% of these cycles have been performed for aneuploidy screening, 12% for single gene disorders, 6% for chromosome rearrangements and 2% for sibling human leukocyte antigen (HLA) matching.

According to the Final Protocol (p9), the Applicant estimates – from internal data – that 45% of all PGD cycles are initiated for the population proposed for public funding (i.e. single gene disorders and gene rearrangements associated with a serious medical condition).

### B.2.5. Regulatory status

Utilisation of PGD services is regulated or prohibited in many countries based on national and/or local laws (Knoppers and Isasi, 2004). The majority of countries require that PGD be limited to conditions that produce significant, incurable medical illness and in which there is a significant risk that the fetus will be affected with the condition through typical Mendelian inheritance. In Australia, the National Pathology Accreditation Advisory Council (NPAAC) regulates the use of molecular and genetic analysis techniques, including the in-house in vitro diagnostic tests used in PGD to identify the specific familial genetic pattern of the couple receiving the service. NPAAC has 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)
- Laboratory Accreditation Standards and Guidelines for Nucleic Acid Detection and Analysis (2012)
- Classification of Human Genetic Testing (2013)<sup>5</sup>

#### In-house in vitro diagnostic devices

PGD is a Class 3 IVD according to the Therapeutic Goods Administration (TGA). As a result of IVD regulatory reforms, IVDs will be subject to listing with the TGA by 1<sup>st</sup> July 2017. Laboratories are required to submit a 'notification' to TGA for in-house Class 3 IVD's by June 2017; commercial Class 3 IVDs must be listed on the ARTG.

<sup>4</sup> Retrieved from [www.pgdis.org](http://www.pgdis.org)

<sup>5</sup> DoH. NPAAC 2013. Requirements for medical testing of human nucleic acids (Appendix A). Retrieved from <http://www.health.gov.au/internet/publications/publishing.nsf/Content/npaac-pub-nucleic-acids-drft~npaac-pub-nucleic-acids-drft-appa>

PGD is a Level 2 DNA test, according to the Laboratory Accreditation Standards and Guidelines for Nucleic Acid Detection and Analysis (2013) (NPAAC, 2013) (see Attachment C). As such, genetic counselling should be provided for couples at appropriate stages throughout the process of PGD.

The Human Genetics Society of Australasia (HGSA) outlines practice requirements and standards for genetic services in their *Clinical Genetic Services Standards Framework* (HGSA, 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>6</sup>. There is currently no Commonwealth legislation for ART practice; however, the Reproductive Technology Accreditation Committee (RTAC), which was established by the Fertility Society of Australia, oversees the practice of ART in Australia, including compliance with the Code of Practice (Reproductive Technology Accreditation Committee 2010). The RTAC also requires compliance with published NHMRC ethical guidelines on the use of ART (NHMRC, 2007).

The NHMRC (2007) recommendations for clinical practice in PGD are summarised in Table B.2.6. The NHMRC guideline also describes the regulatory framework for ART clinical practice and research in Australia, under which the guidelines are enforced (see Attachment D).

Table B.2.6 NHMRC ethical guidelines for practice of PGD

Guideline for practice of PGD	Associated ethical considerations
Carefully evaluate any use of PGD. 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.	<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.</li> <li>• The procedures have technical limitations (such as the failure to identify the genetic abnormality of interest).</li> </ul>
Restrict the use of PGD.	<p>Pending further community discussion, PGD must not be used for:</p> <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>
Seek advice before using PGD to select an embryo with compatible tissue for a sibling.	<p>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.</p> <p>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).</p> <p>The ethics committee or relevant agency should ascertain that:</p>

<sup>6</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->

Guideline for practice of PGD	Associated ethical considerations
	<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; and</li> <li>• 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>
Provide access to a geneticist and genetic counsellor.	<p>It is essential that participants in ART seeking PGD testing of embryos understand the technology and how it applies to their embryos.</p> <p>Clinics must ensure that people seeking PGD testing have access both to clinical geneticists and to genetic counsellors.</p>
<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>	<p>In dealing with a specific situation, the people seeking testing should be encouraged to consider the following factors when deciding the appropriateness of PGD:</p> <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>

Source: National Health and Medical Research Council, 2007  
Abbreviations: ART, Assisted reproductive technology; PGD, preimplantation genetic diagnosis

### B.3. Proposed listing sought for funding

#### B.3.1. Item descriptor

Table B.3.1 presents the proposed PGD item descriptors as shown in the Final Protocol (Table 5, pp 16-17). The proposal for PGD subsidy includes three new items relating to each of the three PGD stages. The three 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 the PGD Stage 1 item 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 (PGD Stage 2). Those couples can return to undertake a new PGD cycle, but they do not need to repeat Stage 1.

The Stage 1 descriptor specifies that counselling should be provided on referral for PGD and that 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. It is assumed that the Stage 1 fee is intended to incorporate any genetic counselling that specifically relates to the test. As such, the economic evaluation (Section D) and financial estimates (Section E) do not incorporate any test-related fees for genetic counselling (other than at the time of referral).

Due to the nature of some serious genetic disease mutations warranting a more complex and/or more analysis than others, PASC suggested a tiered approach to the fees for PGD Stage 1, where one is for rare (or complex) mutation test design and validation, and one is for more common or known mutations (for which a test is likely to have been designed before)<sup>7</sup>. The Final Protocol did not present fees for any of the proposed items; however, the Applicant provided fees during the preparation of the Assessment Report (see below for further details).

Although the Applicant originally proposed that the descriptor for Stage 2 specify 'blastocyst' embryo biopsy, the descriptor in the Final Protocol does not restrict embryo transfer to blastocyst stage biopsy only. Likewise, the descriptor does not dictate the type of genetic analysis that may be undertaken during Stage 3.

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<sup>7</sup> PASC meeting minutes, 16-17 April 2014

Table B.3.1 Proposed descriptors for PGD items 1, 2, and 3

<p>Category 6– PATHOLOGY (Group P7 Genetics)</p> <p>Item [xxxxx]</p> <p><b>PGD Stage 1 Genetic test design and validation</b> 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).</p> <p>Explanatory Note:</p> <p>Item number is relevant for couples undergoing PGD for the following reason:</p> <ul style="list-style-type: none"> <li>• 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</li> <li>• 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.</li> </ul> <p><b>The fee must only be applied once per couple</b> (the PGD test is developed once and it does not need to be repeated on a per cycle basis; <i>information provided by the test must be made accessible</i>)</p> <p>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 <i>should be provided</i> subsequent to the development of the PGD test in order to explain the diagnostic risks and limitations for their particular test.</p> <p><b>Fee structure</b></p> <p>Level 1: \$[fee] Design and validation of a probe for simple/common mutations</p> <p>Level 2: \$[fee] Design and validation of probe requiring complex analysis and/or high level of technical expertise,</p> <p>[Relevant explanatory notes]</p>
<p>Category 3 – THERAPEUTIC PROCEDURE</p> <p>Item [xxxxx]</p> <p><b>PGD Stage 2 Embryo biopsy:</b> 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).</p> <p>Explanatory Note:</p> <p>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).</p> <p>Fee: \$[fee]</p> <p>[Relevant explanatory notes]</p>
<p>Category 6– PATHOLOGY (Group P7 Genetics)</p> <p>Item [xxxxx]</p> <p><b>PGD Stage 3 Embryo genetic analysis:</b> The study of biopsied embryo tissue using molecular techniques for single gene disorders or the whole of every chromosome. (One or more embryos)</p> <p>Explanatory Note:</p> <p>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).</p> <p>Embryo(s) that are not affected by the genetic disorder can be transferred to the uterus of the female or vitrified.</p> <p>This item number must not be used for the purpose of positive selection for gender or a genetic disorder.</p> <p>Fee: \$[fee]</p> <p>[Relevant explanatory notes]</p>

Source: Final Protocol, Table 5, p17

### B.3.2. Proposed fees

*For Stage 1, the Applicant has proposed a single fee of \$1736, which does not take into account the complexity of the test design, as per the tiered fee structure proposed by PASC. In their feedback on the Consultation Protocol, the Applicant argues that the simple test design for common mutations proposed by PASC does not take into account flanking markers, which is standard practice for PGD and critical for test accuracy. They thus note that “there is no difference in the process or cost of test development for either a rare or common disease mutation” and that “each PGD test is unique to a couple and cannot be reliably used on another couple.”*

*The Applicant has proposed a fee for Stage 2 of \$115 “per embryo biopsied”, which is not consistent with the descriptor in the Final Protocol for biopsy of “one or more embryos”. Numerous embryos may be produced in a PGD cycle and a biopsy is needed from each individual embryo. However, there may be some efficiencies when multiple embryos are biopsied from a single cycle. According to the Applicant, the average number of embryos biopsied and tested per PGD cycle is 3.4 (according to the Final Protocol, p18) or four (according to the Applicant when fees were proposed). The economic evaluation (Section D) and financial estimates (Section E) assume that the Stage 2 fees are applied only once to genetic analysis of embryos harvested from a single cycle.*

*The Applicant has proposed a fee of \$635 “per embryo tested” for the Stage 3 item, while PASC has proposed a single fee for testing of “one or more embryos”. The rationale for a single fee is that biopsy material from many embryos from the same cycle could be batched to run the genetic test at the same time. Consistent with this rationale, the economic evaluation (Section D) and financial estimates (Section E) assume that the Stage 3 fees are applied only once to embryos harvested from a single cycle.*

PASC noted that there should be no limitation on the number of claims for Stages 2 and 3 of the PGD process, as it may restrict access to couples that have failed to obtain disease free embryos from initial cycles.<sup>8</sup>

The Final Protocol included current MBS item descriptors for genetic testing services relevant to the comparator (equivalent to the proposed Stage 3 item), that are performed postnatally or prenatally. According to a response to the PGD Consultation Protocol from the Royal College of Pathologists of Australasia (RCPA), the genetic testing costs for PGD may not be comparable to costs in the prenatal setting. It is the view of the RCPA that testing in the prenatal setting is always more urgent, with shorter turnaround times required, and much greater need for defined accuracy and precision. The College advised that in most genetic laboratories, prenatal testing is charged at a flat fee (non-MBS) of \$600-\$1200, depending on the cost and complexity, and which does not include test design and validation (as worded in the proposed Stage 1 item).

### **B.3.3. Co-administered and associated interventions**

PGD occurs in conjunction with IVF, with the latter procedure supplying the embryos for analysis of genetic content before implantation. Medicare reimburses costs for IVF services under the ART services item numbers 13200 to 13221, and for ICSI under MBS item number 13251. The MBS items for IVF and ICSI relevant to PGD are shown in

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<sup>8</sup> Ibid

Table B.3.2.

**Table B.3.2 Current MBS items for IVF and ICSI 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% = \$3,032.35 (See para T.1.4 of explanatory notes to this Category) 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% = \$2,831.35 (See para T.1.4 of explanatory notes to this Category) 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 (See para T.1.4 of explanatory notes to this Category) 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 (See para T.1.4 of explanatory notes to this Category) Extended Medicare Safety Net Cap: \$64.95</p>
MBS 13209	<p>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</p> <p>Fee: \$84.70 Benefit: 75% = \$63.55 85% = \$72.00 (See para T.1.4 of explanatory notes to this Category) Extended Medicare Safety Net Cap: \$10.90</p>
MBS 13212	<p>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.)</p> <p>Fee: \$354.45 Benefit: 75% = \$265.85 85% = \$301.30 (See para T.1.4 of explanatory notes to this Category) Extended Medicare Safety Net Cap: \$70.35</p>



<p><b>MBS 13215</b>  <b>TRANSFER OF EMBRYOS</b> 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</p>
<p><b>MBS 13218</b>  <b>PREPARATION</b> 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% = \$715.15  (See para T1.4 of explanatory notes to this Category)  Extended Medicare Safety Net Cap: \$702.65</p>
<p><b>MBS 13251</b>  <b>INTRACYTOPLASMIC SPERM INJECTION</b> 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</p>

March 26, 2015

Associated Note T1.4 (Final Protocol, Appendix A, Box 1) provides further information regarding the application of these item numbers. As IVF is an integral part of the PGD process, couples undergoing PGD would need to meet eligibility criteria for that procedure. The Applicant is proposing a change in Associated Note T1.4 to enable IVF and the proposed PGD items to be used together. However, the Final Protocol noted that whilst 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.

The relevant section of current Note T1.4 is shown in Table B.3.3. The Applicant has provided a modified version, shown in Table B.3.4, with additions italicised. However, if PGD is funded via an alternative mechanism (not the MBS), this may need to be expressed in a different way.

**Table B.3.3 Current MBS Associated Note T1.4**

<p>Note T1.4</p> <p>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</p>
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Source: Final Protocol, Table 6, p18

**Table B.3.4 Proposed MBS Associated Note T1.4**

<p>Note T1.4</p> <p>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.</p>
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Source: Final Protocol, Table 7, p18

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 MBS Item 13251 for ICSI may be used with PGD. ICSI is required during PGD because it ensures there are no extraneous sperm attached to the embryos, which might lead to false genetic testing results.

Prior to being referred to a fertility specialist and IVF clinic where PGD services are performed, the couple would need to be assessed by a clinical geneticist. Genetic counselling services provided by a clinical geneticist can be claimed under MBS item 132 for the first session, and MBS item 133 for subsequent sessions, as shown in Table B.3.5. Most couples will require one initial counselling session followed by a second session when testing is ordered. As mentioned above, the proposed descriptor for PGD Stage 1 provides for genetic counselling to explain the diagnostic risks and limitations of the particular test that will be undertaken.

**Table B.3.5 Current MBS items associated with genetic counselling for PGD**

Category 1 – PROFESSIONAL ATTENDANCES
<p><b>MBS 132</b>  <b>CONSULTANT PHYSICIAN (OTHER THAN IN PSYCHIATRY) REFERRED PATIENT TREATMENT AND MANAGEMENT PLAN - SURGERY OR HOSPITAL</b>  Professional attendance of at least 45 minutes duration for an initial assessment of a patient with at least two morbidities (this can include complex congenital, developmental and behavioural disorders), where the patient is referred by a referring practitioner, and where</p> <p>a) assessment is undertaken that covers:</p> <ul style="list-style-type: none"> <li>- a comprehensive history, including psychosocial history and medication review;</li> <li>- comprehensive multi or detailed single organ system assessment;</li> <li>- the formulation of differential diagnoses; and</li> </ul> <p>b) a consultant physician treatment and management plan of significant complexity is developed and provided to the referring practitioner that involves:</p> <ul style="list-style-type: none"> <li>- an opinion on diagnosis and risk assessment</li> <li>- treatment options and decisions</li> <li>- medication recommendations</li> </ul> <p>Not being an attendance on a patient in respect of whom, an attendance under items 110, 116 and 119 has been received on the same day by the same consultant physician.</p> <p>Not being an attendance on the patient in respect of whom, in the preceding 12 months, payment has been made under this item for attendance by the same consultant physician.</p> <p>Fee: \$263.90 Benefit: 75% = \$197.95 85% = \$224.35  (See para A12 of explanatory notes to this Category)  Extended Medicare Safety Net Cap: \$500.00</p>
<p><b>MBS 133</b>  <b>CONSULTANT PHYSICIAN (OTHER THAN IN PSYCHIATRY) REVIEW OF REFERRED PATIENT TREATMENT AND MANAGEMENT PLAN - SURGERY OR HOSPITAL</b>  Professional attendance of at least 20 minutes duration subsequent to the first attendance in a single course of treatment for a review of a patient with at least two morbidities (this can include complex congenital, developmental and behavioural disorders), where</p> <p>a) a review is undertaken that covers:</p> <ul style="list-style-type: none"> <li>- review of initial presenting problem/s and results of diagnostic investigations</li> <li>- review of responses to treatment and medication plans initiated at time of initial consultation comprehensive multi or detailed single organ system assessment,</li> <li>- review of original and differential diagnoses; and</li> </ul> <p>b) a modified consultant physician treatment and management plan is provided to the referring practitioner that involves, where appropriate:</p> <ul style="list-style-type: none"> <li>- a revised opinion on the diagnosis and risk assessment</li> <li>- treatment options and decisions</li> </ul>

<b>Category 1 – PROFESSIONAL ATTENDANCES</b>
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- revised medication recommendations
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Not being an attendance on a patient in respect of whom, an attendance under item 110, 116 and 119 has been received on the same day by the same consultant physician or locum tenens.
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Being an attendance on a patient in respect of whom, in the preceding 12 months, payment has been made under item 132. Item 133 can be provided by either the same consultant physician or a locum tenens.
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Payable no more than twice in any 12 month period.
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Fee: \$132.10 Benefit: 75% = \$99.10 85% = \$112.30
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(See para A12 of explanatory notes to this Category)
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Extended Medicare Safety Net Cap: \$396.30
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Source: MBS online, accessed March 26, 2015

### **B.3.4. Prerequisites**

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 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 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;
- 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 likely to be available in only two or three major clinics in Australia. Biopsy material (DNA) obtained at other clinics will 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) *and may be incorporated into the item fees.*

PGD services are already being provided in the private setting in a couple of 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 any additional data.

### **B.3.5. Clinical need**

PGD services are already offered in the community, but to a broader population than proposed for public funding of PGD. The main purpose of PGD is to improve the chance of conception for patients with genetic abnormalities, 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 embryos for normal chromosome numbers, 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 (TOP), 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. Other issues related to equity of access are discussed in Section F.

## **B.4. Comparator details**

### **B.4.1. 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 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 in Australia). The timing of the prenatal test will affect the risk of miscarriage, which varies with weeks of pregnancy. For example, if a couple who becomes pregnant by natural conception or IVF choose to undergo prenatal testing, the earliest available fetal biopsy technique is CVS. CVS requires a sample of cells from the placenta; the test is thought to result in a risk of procedure-related miscarriage of around 1 – 2%. Once DNA is extracted from the cells obtained via CVS, it is screened for genetic abnormality.

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 thought to be 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. However, FBS is uncommon in Australia and will not be discussed further.

Alternatively, parents who undergo natural pregnancy or pregnancy by IVF may choose postnatal genetic diagnosis rather than prenatal diagnosis, thus bypassing the option of TOP. 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.

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 has not been included in the assessment of PGD as there is insufficient evidence to support the assumption that a significant proportion of couples carrying a mutation would choose this option.

To assess the safety and effectiveness of PGD 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.

#### **B.4.2. 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, the assessment will consider a comparison of accuracy of different PGD testing methods (e.g. SNP screening, whole genome sequencing and microarray CGH).

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 TOP 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 will consider the effects of '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.

#### **B.4.3. 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 sampling techniques of CVS and amniocentesis are currently subsidised on the MBS (Category 3 Therapeutic Procedures items 16600 and 16603; see Table B.4.1). Prenatal diagnosis, when performed following CVS and amniocentesis, can provide couples with the opportunity for TOP if test results show that a fetus carries a serious genetic disorder (and depending on the timing of the test).

**Table B.4.1 Current MBS item descriptors for prenatal sampling techniques relevant to the comparator**

Category 3 – THERAPEUTIC PROCEEDURES
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
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

Source: MBS Online, accessed March 26, 2015

As noted in the Final Protocol, 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 Table B.4.2. With the exception of MBS item 73305, all of the item descriptors for the genetic tests specify that the fee applies to “one or more tests”.

**Table B.4.2 Current MBS item descriptors for genetic testing services relevant to the comparator**

Category 6 – PATHOLOGY SERVICES
MBS 73300 Detection of mutation of the FMR1 gene where: (a) the patient exhibits intellectual disability, ataxia, neurodegeneration, or premature ovarian failure consistent with an FMR1 mutation; or (b) the patient has a relative with a FMR1 mutation 1 or more tests Fee: \$101.30 Benefit: 75% = \$76.00 85% = \$86.15
MBS 73305 Detection of mutation of the FMR1 gene by Southern Blot analysis where the results in item 73300 are inconclusive Fee: \$202.65 Benefit: 75% = \$152.00 85% = \$172.30 (See Para p16.12 of explanatory notes to this Category)
MBS 73287 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 Fee: \$394.55 Benefit: 75% = \$295.95 85% = \$335.40
MBS 73289 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 Fee: \$358.95 Benefit: 75% = \$269.25 85% = \$305.15
MBS 73291 Analysis of one or more chromosome regions for specific constitutional genetic abnormalities of blood or fresh tissue in 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 b) studies of a relative for an abnormality previously identified in such an affected person. - 1 or more tests. Fee: \$230.95 Benefit: 75% = \$173.25 85% = \$196.35

Category 6 – PATHOLOGY SERVICES
<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% = \$511.50</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> <p>- 1 or more tests.</p> <p>Fee: \$230.95 Benefit: 75% = \$173.25 85% = \$196.35</p>

Source: MBS Online, accessed March 26, 2015

#### B.4.4. 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 Final Protocol (p24) 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 each State and Territory has legislation prohibiting unlawful abortion. South Australia and the Northern Territory both include serious fetal abnormality as a legal reason for abortion; however, in the Northern Territory, this is only until 14 weeks. A summary of the indications for abortion in each State and Territory is presented in Table B.4.3.

Table B.4.3 Legality of abortion in Australian States and Territories<sup>9</sup>

State/Territory	Restrictions
NSW	Legal when a doctor believes a woman's physical and/or mental health is in serious danger. Social and economic factors may be taken into account too.
ACT	Legal; must be provided by medical doctor.
Victoria	Legal to 24 weeks; legal post 24-weeks with two doctors' approval.
South Australia	Legal if two doctors agree that a woman's physical and/or mental health is endangered by the pregnancy, or for serious fetal abnormality. Unlawful abortion is a crime.
Tasmania	Legal to 16 weeks on request; post 16 weeks legal with approval of two doctors.
Western Australia	Legal up to 20 weeks; some restrictions apply for under 16s. Very restricted after 20 weeks.
Northern Territory	Legal to 14 weeks if two doctors agree that a woman's physical and/or mental health is endangered by pregnancy, or for serious fetal abnormality. Up to 23 weeks in an emergency.
Queensland	Legal when a doctor believes a woman's physical and/or mental health is in serious danger.

- Medical practitioners may be unsure of the legality of supporting a termination for their patient.

<sup>9</sup> <http://www.childrenbychoice.org.au/info-a-resources/facts-and-figures/australian-abortion-law-and-practice>; accessed

- Conflicting guidance from medical and ancillary health practitioners due to personal, ethical or religious perspectives.
- 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 et al, 2008; Korenrump 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).

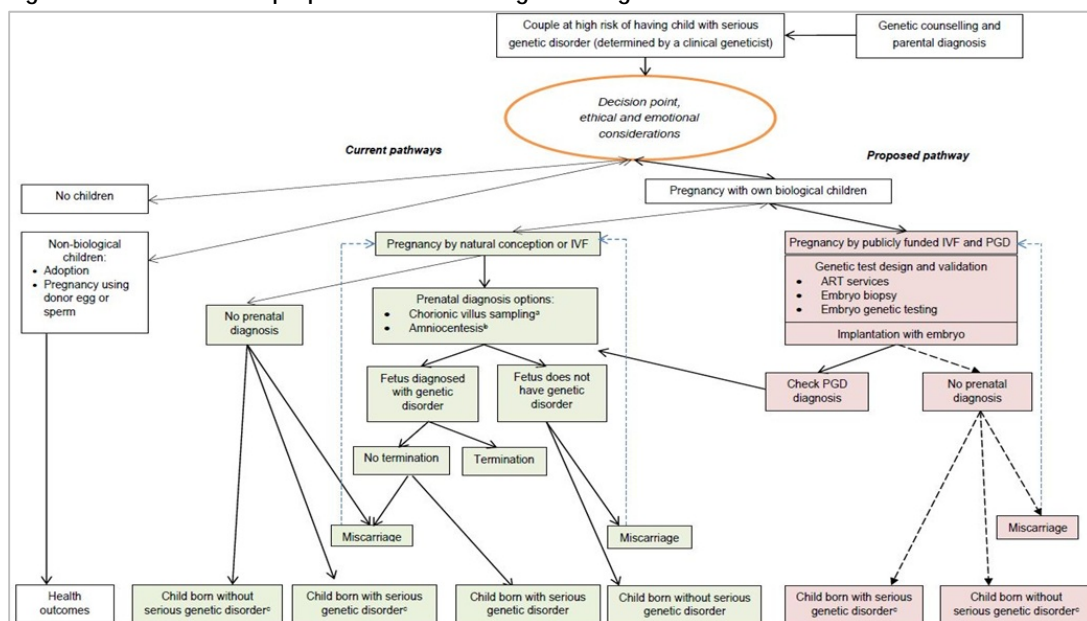
#### B.4.5. Clinical management algorithms

Figure B.1 presents the current (and proposed) clinical management algorithm for patients undergoing PGD services.

Mothers pregnant after PGD and fulfilling specific 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 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 B.1.

It is likely that not all eligible couples would choose to undergo PGD. Some couples may choose to try for a natural pregnancy, followed by prenatal diagnosis and the possibility of TOP, 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.

Figure B.1 Current and proposed clinical management algorithm



Source: Figure 1, p22 of the Final Protocol

<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 postnatal testing



#### **B.4.6. Differences between the proposed medical service and the main comparator**

The main difference between the proposed medical service and the comparator is that PGD services that are already being offered in the private setting will be publically funded. The main comparator, pregnancy via natural conception (or pregnancy via IVF) with prenatal genetic testing, is currently funded on the MBS.

#### **B.4.7. Clinical claim**

The Applicant claims that PGD is as effective in identifying genetic disorders as prenatal diagnosis. In addition, the Applicant also states that 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 TOP. The Applicant claims that the time delay associated with prenatal diagnosis and the 1 in 2 or 1 in 4 risk of passing on a serious genetic disorder with natural conception (or IVF), makes PGD a superior option for couples at high risk of having a child with a genetic disorder.

Further, the Applicant claims that PGD offers superior safety for couples 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.

#### **B.4.8. Primary elements of the decision analysis**

##### **PICO 1 – safety, effectiveness and technical efficacy in parents**

Table B.4.4 presents a summary of the Patient/Intervention/Comparator/Outcome (PICO) criteria used to select the evidence to assess the safety and effectiveness of PGD for *couples* 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*.

The questions for public funding addressed in this Assessment Report are:

*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 postnatal 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)*

Table B.4.4 Summary of PICO 1 to assess direct evidence for the safety, effectiveness and technical efficacy of PGD in couples (proband) 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 postnatal diagnosis</p> <p>3. No children, or non-biological children through adoption or donor egg/sperm<sup>a</sup></p>	<p><u>Safety</u></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><u>Effectiveness</u></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><u>Technical efficacy</u></p> <p>Successful biopsy</p> <p>Rebiopsy</p> <p>Resampling</p> <p>Implantation rate</p>

Source: Final Protocol, Table 6, p28

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

<sup>a</sup> The second and third comparators are only required if a significant proportion of couples carrying a mutation choose this option, who would possibly consider PGD if funded.

## PICO 2 – Safety and effectiveness in offspring

Table B.4.5 presents a summary of the PICO criteria used to select the evidence to assess the safety and effectiveness of PGD in *offspring* born to couples who have undergone PGD.

*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?*

Table B.4.5 Summary of PICO 2 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	<u>Safety (where possible distinguish from disease related issues)</u> Physical disability Intellectual disability Developmental delay Perinatal mortality (e.g. stillbirth) <u>Effectiveness</u> Quality of life Functional status

Source: Final Protocol, Table 9, p29  
 Abbreviations: PGD, preimplantation genetic diagnosis; IVF, in vitro fertilisation.

### PICOs for the assessment of linked evidence

In the case where direct evidence is insufficient, the Final Protocol provided PICO summaries for the assessment of linked evidence as shown in Table B.4.6, Table B.4.7, and Table B.4.8. The PICO summaries would be used to select evidence to assess the diagnostic accuracy of PGD compared to prenatal diagnosis, 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 assess the impact of change in management, in particular the impact of TOP on couples and mothers.

### PICO 3 – Analytical validity

*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?*

Table B.4.6 Summary of PICO 3 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	<u>Analytic validity</u> Sensitivity Specificity Rate of repeat testing required Time taken to achieve confirmed result (and to resolve false positive results) <u>Comparison of accuracy of PGD Stage 3 testing methods</u>

Source: Final Protocol, Table 10, p30  
 Abbreviations: DNA, deoxyribonucleic acid; PGD, preimplantation genetic diagnosis; SNP, single nucleotide polymorphism.

## PICO 4 – Change in management

*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 termination of pregnancy in couples who are at high risk of passing on a serious genetic disorder to their offspring?*

Table B.4.7 Summary of PICO 4 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	<u>Change in management</u> % 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

Source: Final Protocol, Table 11, p30

Abbreviations: IVF, in vitro fertilisation; PGD, preimplantation genetic diagnosis.

## PICO 5 – Psychological and physical harms of pregnancy termination

*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?*

Table B.4.8 Summary of PICO 5 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>

Source: Final Protocol, Table 12, p31

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

# Section C. Clinical evaluation for the main indication

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## C.1. Description of search strategies

### C.1.1. Literature sources and search strategies

A systematic literature search was conducted to identify studies that report on the following: (i) the safety, effectiveness, and technical efficacy of PGD in couples undergoing PGD compared to prenatal diagnosis in couples who conceive naturally or by IVF (PICO 1); (ii) the safety and effectiveness of PGD in children born to couples who have undergone PGD compared to children born to parents who have undergone IVF followed by prenatal diagnosis (PICO 2); (iii) the accuracy of PGD compared with prenatal testing (PICO 3); and (iv) the change in management of couples undergoing PGD compared to couples who conceive naturally or by IVF followed by prenatal diagnosis (PICO 4).

Electronic searches of EMBASE.com and the Cochrane Library were conducted using the search terms outlined in Appendix 2. The search of EMBASE.com (which concurrently searches Medline and Embase) was conducted on 25 September, 2014 and the Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect, Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, Economic Evaluation Database) was searched on 16 January, 2015.

In addition, reference lists of relevant reviews and primary studies were hand-searched to identify additional studies. Databases maintained by health technology assessment (HTA) agencies were also reviewed for relevant reports.

A separate literature search was conducted to identify studies relating to physical harms (safety) and psychological impact of prenatal diagnosis and the decision regarding whether to terminate a pregnancy (PICO 5) in couples. The search terms are outlined in Appendix 2.

### C.1.2. Selection criteria

The eligibility criteria for inclusion in this Assessment Report were underpinned by the main components of the research questions – population, intervention, comparator, (reference standard for the diagnostic accuracy) and outcomes – as outlined in Table B.4.4, Table B.4.5, Table B.4.6, Table B.4.7 and Table B.4.8. In summary, studies were excluded for the following reasons:

- Wrong publication type – literature reviews, case reports, non-human and in vitro studies, studies not fully published or peer-reviewed (editorials, letters, conference proceedings, abstracts).
- Wrong intervention – studies using PGD techniques for purposes other than monogenic disease or chromosomal abnormalities (for example aneuploidy by PGS, social sexing, cancer, and HLA matching).
- Wrong population – not in the following populations:

- Couples who 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).
- Technical description of test only – provides only a detailed description of technical aspects of different genetic tests; not diagnostic accuracy or comparative technical efficacy.
- Wrong outcomes (full text review only) – did not include at least one of the outcomes defined.
- Small sample size (for full test review only) – less than 200 PGD cycles (for studies meeting only PICO 1 criteria).

### **C.1.3. Search results**

A summary of the literature review process is presented in Table C.1.1. Following application of the exclusion criteria, a total of 47 studies were included in the assessment.

Table C.1.1 Summary of the process used to identify relevant studies

	EMBASE.com	Cochrane Library
<i>Number of citations retrieved by search</i>	1343	85
Number of duplicate citations removed	64	5
<i>Number of citations screened by title and abstract review</i>	1279	80
Number of citations excluded after title/abstract review:	-	-
Wrong publication type	325	7
Wrong intervention	604	38
Wrong population	172	20
Test technical description only	41	0
Other <sup>a</sup>	0	7
Total excluded	1142	72
<i>Number of citations screened by full text review</i>	137	8
Number of citations excluded after full text review:	-	-
Wrong publication type	13	0
Wrong intervention	7	3
Wrong population	10	1
Wrong outcomes	4	0
Small sample size	62	1
No usable data	4	0
Duplicate data	0	0
Total excluded	100	5
Total number of citations included from each database	37	3
Total number of citations (excluding duplicates)	40	-
Number of citations identified manually	11	-
Manual citations excluded <sup>b</sup>	4	-
Manual citations included	7	-
Total number of included studies	47	-

a Includes Not in English and Unable to be retrieved

b Reasons for exclusion were wrong intervention (1), wrong outcomes (1) and < 200 cycles (2)

## C.2. Listing of all included studies

### C.2.1. PICO 1

No studies were identified that specifically assessed the safety, clinical effectiveness, and technical efficacy of PGD in couples undergoing PGD versus couples who conceive naturally (or by IVF) followed with prenatal diagnosis. However, 33 non-comparative studies were identified that provided data on the safety, effectiveness, and technical efficacy of PGD (listed in Table C.2.1).

There was one systematic review (Franssen et al, 2011) that investigated the clinical outcome after natural conception and after PGD in couples with recurrent miscarriage and carrying a structural chromosome abnormality. However, no comparison with prenatal diagnosis was made.

Twelve studies were annual reports from the ESHRE PGD Consortium which collects data from a number of centres internationally, including Australia. Data collection from this series ranges from January 1997 to December 2009. The remaining 20 studies were large ( $\geq 200$  PGD cycles) single- or multi-centre studies that examined clinical outcomes after PGD.

Further, there were 67 additional studies that provided clinical outcome data after PGD for single gene disorders and/or chromosomal rearrangements. However, the number of PGD cycles in each of these studies was less than 200 cycles. These studies were excluded from further analysis and data were extracted from larger multi-centre or single centre studies. There were two exceptions to this restriction of sample size: (i) studies that assessed blastocyst biopsy (the technique used in Australia) were included regardless of size; and (ii) small studies that assessed specific outcomes that were not already covered by the larger studies were also included.

It should be noted that the majority of included studies performed biopsies at Day 3 (blastomere stage). Only four studies (McArthur et al, 2005; Kokkali et al, 2007; McArthur et al. 2008; Chang et al, 2013) performed PGD utilising blastocysts biopsied at Day 5-6.



Table C.2.1 List of included studies – PICO 1

Study ID	Citation
<i>ESHRE</i>	
Moutou 2014	Moutou C, Goossens V, Coonen E, De Rycke M, Kokkali G, Renwick P, SenGupta SB, Vesela K, Traeger-Synodinos J. ESHRE PGD Consortium data collection XII: cycles from January to December 2009 with pregnancy follow-up to October 2010. Hum Reprod. 2014 May;29(5):880-903.
Goossens 2012	Goossens V, Traeger-Synodinos J, Coonen E, De Rycke M, Moutou C, Pehlivan T, Derks-Smeets IA, Harton G. ESHRE PGD Consortium data collection XI: cycles from January to December 2008 with pregnancy follow-up to October 2009. Hum Reprod. 2012 Jul;27(7):1887-911.
Harper 2010	Harper JC, Coonen E, De Rycke M, Harton G, Moutou C, Pehlivan T, Traeger-Synodinos J, Van Rij MC, Goossens V. ESHRE PGD Consortium data collection X: cycles from January to December 2007 with pregnancy follow-up to October 2008. Hum Reprod. 2010 Nov;25(11):2685-707.
Goossens 2009	Goossens V, Harton G, Moutou C, Traeger-Synodinos J, Van Rij M, Harper JC. ESHRE PGD Consortium data collection IX: cycles from January to December 2006 with pregnancy follow-up to October 2007. Hum Reprod. 2009 Aug;24(8):1786-810.
Goossens 2008	Goossens V, Harton G, Moutou C, Scriven PN, Traeger-Synodinos J, Sermon K, Harper JC. ESHRE PGD Consortium data collection VIII: cycles from January to December 2005 with pregnancy follow-up to October 2006. Hum Reprod. 2008 Dec;23(12):2629-45.
Harper 2008	Harper JC, de Die-Smulders C, Goossens V, Harton G, Moutou C, Repping S, Scriven PN, SenGupta S, Traeger-Synodinos J, Van Rij MC, Viville S, Wilton L, Sermon K. ESHRE PGD Consortium data collection VII: cycles from January to December 2004 with pregnancy follow-up to October 2005. Hum Reprod. 2008 Apr;23(4):741-55.
Sermon 2007	Sermon KD, Michiels A, Harton G, Moutou C, Repping S, Scriven PN, SenGupta S, Traeger-Synodinos J, Vesela K, Viville S, Wilton L, Harper JC. ESHRE PGD Consortium data collection VI: cycles from January to December 2003 with pregnancy follow-up to October 2004. Hum Reprod. 2007 Feb;22(2):323-36.
Harper 2006	Harper JC, Boelaert K, Geraedts J, Harton G, Kearns WG, Moutou C, Muntjewerff N, Repping S, SenGupta S, Scriven PN, Traeger-Synodinos J, Vesela K, Wilton L, Sermon K. ESHRE PGD Consortium data collection V: cycles from January to December 2002 with pregnancy follow-up to October 2003. Hum Reprod. 2006 Jan;21(1):3-21.
Sermon 2005	Sermon K, Moutou C, Harper J, Geraedts J, Scriven P, Wilton L, Magli MC, Michiels A, Viville S, De Die C. ESHRE preimplantation genetic diagnosis (PGD) Consortium: data collection IV (May - December 2001). Hum Reprod. 2005 Jan;20(1):19-34.
Sermon 2002	Sermon K, Harper J, Geraedts J, Die-Smulders C, Handyside A, Hussey N, Magli M, Munne S, Ray P, Santalo J, Staessen C, Thornhill A, Viville S, Wilton L. ESHRE preimplantation genetic diagnosis (PGD) Consortium: data collection III (May 2001). Hum Reprod. 2002 Jan;17(1):233-46.
Geraedts 2000	Geraedts J, Handyside A, Harper J, Liebaers I, Sermon K, Staessen C, Thornhill A, Viville S, Wilton L. ESHRE preimplantation genetic diagnosis (PGD) Consortium: data collection II (May 2000). Hum Reprod. 2000 Dec;15(12):2673-83.
Geraedts 1999	Geraedts J, Handyside A, Harper J, Liebaers I, Sermon K, Staessen C, Thornhill A, Vanderfaeillie A, Viville S. ESHRE Preimplantation Genetic Diagnosis (PGD) Consortium: preliminary assessment of data from January 1997 to September 1998. ESHRE PGD Consortium Steering Committee. Hum Reprod. 1999 Dec;14(12):3138-48.
<i>PGD overall</i>	
Chang 2013	Chang LJ, Huang CC, Tsai YY, Hung CC, Fang MY, Lin YC, Su YN, Chen SU, Yang YS. Blastocyst biopsy and vitrification are effective for preimplantation genetic diagnosis of monogenic diseases. Hum Reprod. 2013 May;28(5):1435-44.
Tan 2013	Tan YQ, Tan K, Zhang SP, Gong F, Cheng DH, Xiong B, Lu CF, Tang XC, Luo KL, Lin G, Lu GX. Single-nucleotide polymorphism microarray-based preimplantation genetic diagnosis is likely to improve the clinical outcome for translocation carriers. Hum Reprod. 2013 Sep;28(9):2581-92.
Ginsburg 2011	Ginsburg ES, Baker VL, Racowsky C, Wantman E, Goldfarb J, Stern JE. Use of preimplantation genetic diagnosis and preimplantation genetic screening in the United States: a Society for Assisted Reproductive Technology Writing Group paper. Fertil Steril. 2011 Oct;96(4):865-8.

Study ID	Citation
Hamoda 2011	Hamoda H, Pepas L, Freed C, Grace J, Khalaf Y, Braude P, El-Toukhy T. Outcomes of ovarian stimulation in a two-day oocyte collection week with PGD cycles compared to a five-day oocyte collection week with conventional IVF/ICSI cycles. <i>Hum Fertil (Camb)</i> . 2011 Dec;14(4):254-60.
Verpoest 2009	Verpoest W, Haentjens P, De Rycke M, Staessen C, Sermon K, Bonduelle M, Devroey P, Liebaers I. Cumulative reproductive outcome after preimplantation genetic diagnosis: a report on 1498 couples. <i>Hum Reprod</i> . 2009 Nov;24(11):2951-9.
Goossens 2008	Goossens V, De Rycke M, De Vos A, Staessen C, Michiels A, Verpoest W, Van Steirteghem A, Bertrand C, Liebaers I, Devroey P, Sermon K. Diagnostic efficiency, embryonic development and clinical outcome after the biopsy of one or two blastomeres for preimplantation genetic diagnosis. <i>Hum Reprod</i> . 2008 Mar;23(3):481-92.
McArthur 2008	McArthur SJ, Leigh D, Marshall JT, Gee AJ, De Boer KA, Jansen RP. Blastocyst trophectoderm biopsy and preimplantation genetic diagnosis for familial monogenic disorders and chromosomal translocations. <i>Prenat Diagn</i> . 2008 May;28(5):434-42.
Feyereisen 2007	Feyereisen E, Steffann J, Romana S, Lelorc'h M, Ray P, Kerbrat V, Tachdjian G, Frydman R, Frydman N. Five years' experience of preimplantation genetic diagnosis in the Parisian Center: outcome of the first 441 started cycles. <i>Fertil Steril</i> . 2007 Jan;87(1):60-73.
Grifo 2007	Grifo J, Talebian S, Keegan D, Krey L, Adler A, Berkeley A. Ten-year experience with preimplantation genetic diagnosis (PGD) at the New York University School of Medicine Fertility Center. <i>Fertil Steril</i> . 2007 Oct;88(4):978-81. Epub 2007 Apr 18.
Kokkali 2007	Kokkali G1, Traeger-Synodinos J, Vrettou C, Stavrou D, Jones GM, Cram DS, Makrakis E, Trounson AO, Kanavakis E, Pantos K. Blastocyst biopsy versus cleavage stage biopsy and blastocyst transfer for preimplantation genetic diagnosis of beta-thalassaemia: a pilot study. <i>Hum Reprod</i> . 2007 May;22(5):1443-9.
Fiorentino 2006	Fiorentino F, Biricik A, Nuccitelli A, De Palma R, Kahraman S, Iacobelli M, Trengia V, Caserta D, Bonu MA, Borini A, Baldi M. Strategies and clinical outcome of 250 cycles of Preimplantation Genetic Diagnosis for single gene disorders. <i>Hum Reprod</i> . 2006 Mar;21(3):670-84.
Grace 2006	Grace J, El-Toukhy T, Scriven P, Ogilvie C, Pickering S, Lashwood A, Flinter F, Khalaf Y, Braude P. Three hundred and thirty cycles of preimplantation genetic diagnosis for serious genetic disease: clinical considerations affecting outcome. <i>BJOG</i> . 2006 Dec;113(12):1393-401.
McArthur 2005	McArthur SJ, Leigh D, Marshall JT, de Boer KA, Jansen RP. Pregnancies and live births after trophectoderm biopsy and preimplantation genetic testing of human blastocysts. <i>Fertil Steril</i> . 2005 Dec;84(6):1628-36.
Verlinsky 2004	Verlinsky Y, Cohen J, Munne S, Gianaroli L, Simpson JL, Ferraretti AP, Kuliev A. Over a decade of experience with preimplantation genetic diagnosis: a multicenter report. <i>Fertil Steril</i> . 2004 Aug;82(2):292-4.
Cieslak 1999	Cieslak J, Ivakhnenko V, Wolf G, Sheleg S, Verlinsky Y. Three-dimensional partial zona dissection for preimplantation genetic diagnosis and assisted hatching. <i>Fertil Steril</i> . 1999 Feb;71(2):308-13.
<i>Single gene disorders</i>	
Van Rij 2012	Van Rij MC, De Rademaeker M, Moutou C, Dreesen JC, De Rycke M, Liebaers I, Geraedts JP, De Die-Smulders CE, Viville S. Preimplantation genetic diagnosis (PGD) for Huntington's disease: the experience of three European centres. <i>Eur J Hum Genet</i> . 2012 Apr;20(4):368-75.
Kuliev 2011	Kuliev A, Rechitsky S, Verlinsky O, Tur-Kaspa I, Kalakoutis G, Angastiniotis M, Verlinsky Y. Preimplantation genetic diagnosis for hemoglobinopathies. <i>Hemoglobin</i> . 2011;35(5-6):547-55.
Gutiérrez-Mateo 2009	Gutiérrez-Mateo C, Sánchez-García JF, Fischer J, Tormasi S, Cohen J, Munné S, Wells D. Preimplantation genetic diagnosis of single-gene disorders: experience with more than 200 cycles conducted by a reference laboratory in the United States. <i>Fertil Steril</i> . 2009 Nov;92(5):1544-56.
<i>Chromosomal rearrangements</i>	
Keymolen 2012	Keymolen K, Staessen C, Verpoest W, Liebaers I, Bonduelle M. Preimplantation genetic diagnosis in female and male carriers of reciprocal translocations: clinical outcome until delivery of 312 cycles. <i>Eur J Hum Genet</i> . 2012 Apr;20(4):376-80.
Franssen 2011	Franssen MT, Musters AM, van der Veen F, Repping S, Leschot NJ, Bossuyt PM, Goddijn M, Korevaar JC. Reproductive outcome after PGD in couples with recurrent miscarriage carrying a structural chromosome abnormality: a systematic review. <i>Hum Reprod Update</i> . 2011 Jul-Aug;17(4):467-75.
Fischer 2010	Fischer J, Colls P, Escudero T, Munné S. Preimplantation genetic diagnosis (PGD) improves pregnancy outcome for translocation carriers with a history of recurrent losses. <i>Fertil Steril</i> . 2010 Jun;94(1):283-9.

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; PGD, preimplantation genetic diagnosis; PICO, population/ intervention/ comparator/ outcome

### C.2.2. PICO 2

Twenty six studies were identified that provide data for this question (Table C.2.2). Six of these studies were specifically conducted in children born to couples undergoing PGD for known severe genetic disorders; the remaining studies include children born to couples who have undergone a mix of PGD and PGS. Two of the studies provide level II (randomised controlled trial (RCT)) evidence in which different biopsy techniques are compared.

Seven of the studies provide comparative observational data (Level III evidence) although it should be noted that the comparators included in these studies were not specified in the Protocol for this assessment. The comparators in these studies are either any ICSI or any natural conception; i.e. the population for the comparator is not limited to couples undergoing prenatal testing for a known severe genetic disorder. While these are not the requested comparator, they been included for the following reasons: (i) they do allow for some comparison with PGD, and (ii) it is likely that the effectiveness and harms associated with prenatal testing following ICSI and natural conception are similar in the general population compared with a specific subgroup with known genetic disorders.

Of the studies providing comparative observational data, six are from the same centre in Belgium and include similar cohorts of children who have been assessed at different time points for different outcomes (Nekkebroeck et al, 2008a; 2008b; Desmyttere et al, 2009; 2012; Liebaers et al, 2010; Winter et al, 2014). The remaining comparative observational study includes children conceived at three IVF centres in the UK (Banerjee et al, 2008).

Of the 17 case series providing non-comparative data for PGD (level IV evidence), 12 are yearly reports from the ESHRE PGD Consortium which collects data from multiple centres internationally, including Australia. Data collection from this series ranges from January 1997 to October 2010. The remaining case series are from: Belgium (likely includes some of the children from the Level III Belgian studies; Keymolen et al (2012) and De Rademaeker et al (2009)); a single centre in Greece (Thomaidis et al, 2012); the UK (Grace et al, 2006); and the US (Strom et al, 2000).

Table C.2.2 List of included studies – PICO 2

Study ID	Citation
<i>Level II</i>	
Goossens 2008b	Goossens, V., M. De Rycke, et al. (2008). "Diagnostic efficiency, embryonic development and clinical outcome after the biopsy of one or two blastomeres for preimplantation genetic diagnosis." <i>Human Reproduction</i> 23(3): 481-492.
Kokkali 2007	Kokkali, G., J. Traeger-Synodinos, et al. (2007) Blastocyst biopsy versus cleavage stage biopsy and blastocyst transfer for preimplantation genetic diagnosis of beta-thalassaemia: a pilot study. <i>Human reproduction (Oxford, England)</i> 1443-1449.
<i>Level III</i>	
<i>Belgian cohort</i>	
Winter 2014	Winter, C., F. Van Acker, et al. (2014). "Cognitive and psychomotor development of 5- to 6-year-old singletons born after PGD: A prospective case-controlled matched study." <i>Human Reproduction</i> 29(9): 1968-1977.
Desmyttere 2012	Desmyttere, S., C. De Rycke M Fau - Staessen, et al. (2012). "Neonatal follow-up of 995 consecutively born children after embryo biopsy for PGD." <i>Human Reproduction</i> 27(1): 288-293.
Liebaers 2010	Liebaers, I., S. Desmyttere, et al. (2010). "Report on a consecutive series of 581 children born after blastomere biopsy for preimplantation genetic diagnosis." <i>Human Reproduction</i> 25(1): 275-282.
Desmyttere	Desmyttere, S., J. De Schepper, et al. (2009). "Two-year auxological and medical outcome of singletons

Study ID	Citation
2009	born after embryo biopsy applied in preimplantation genetic diagnosis or preimplantation genetic screening." Human Reproduction 24(2): 470-476.
Nekkebroeck 2008a	Nekkebroeck, J., M. Bonduelle, et al. (2008). "Mental and psychomotor development of 2-year-old children born after preimplantation genetic diagnosis/screening." Human Reproduction 23(7): 1560-1566.
Nekkebroeck 2008b	Nekkebroeck, J., M. Bonduelle, et al. (2008). "Socio-emotional and language development of 2-year-old children born after PGD/PGS, and parental well-being." Human Reproduction 23(8): 1849-1857.
<i>Other</i>	
Banerjee 2008	Banerjee, I., M. Shevlin, et al. (2008). "Health of children conceived after preimplantation genetic diagnosis: A preliminary outcome study." Reproductive BioMedicine Online 16(3): 376-381.
<i>Level IV</i>	
<i>ESHRE</i>	
Moutou 2014	Moutou, C., V. Goossens, et al. (2014). "ESHRE PGD Consortium data collection XII: Cycles from January to December 2009 with pregnancy follow-up to October 2010." Human Reproduction 29(5): 880-903.
Goossens 2012	Goossens, V., J. Traeger-Synodinos, et al. (2012). "ESHRE PGD Consortium data collection XI: Cycles from January to December 2008 with pregnancy follow-up to October 2009." Human Reproduction 27(7): 1887-1911.
Harper 2010	Harper, J. C., E. Coonen, et al. (2010). "ESHRE PGD Consortium data collection X: Cycles from January to December 2007 with pregnancy follow-up to October 2008." Human Reproduction 25(11): 2685-2707.
Goosens 2009	Goossens, V., G. Harton, et al. (2009). "ESHRE PGD Consortium data collection IX: Cycles from January to December 2006 with pregnancy follow-up to October 2007." Human Reproduction 24(8): 1786-1810.
Goosens 2008	Goossens, V., G. Harton, et al. (2008). "ESHRE PGD Consortium data collection VIII: cycles from January to December 2005 with pregnancy follow-up to October 2006." Hum Reprod 23(12): 2629-2645.
Harper 2008	Harper, J. C., C. de Die-Smulders, et al. (2008). "ESHRE PGD Consortium data collection VII: cycles from January to December 2004 with pregnancy follow-up to October 2005." Hum Reprod 23(4): 741-755.
Sermon 2007	Sermon, K. D., A. Michiels, et al. (2007). "ESHRE PGD Consortium data collection VI: Cycles from January to December 2003 with pregnancy follow-up to October 2004." Human Reproduction 22(2): 323-336.
Harper 2006	Harper, J. C., K. Boelaert, et al. (2006). "ESHRE PGD Consortium data collection V: Cycles from January to December 2002 with pregnancy follow-up to October 2003." Human Reproduction 21(1): 3-21.
Sermon 2004	Sermon, K., C. Moutou, et al. (2005). "ESHRE PGD Consortium data collection IV: May-December 2001." Hum Reprod 20(1): 19-34.
Sermon 2002	Sermon, K., J. Harper, et al. (2002). "ESHRE Preimplantation Genetic Diagnosis Consortium: Data collection III (May 2001)." Human Reproduction 17(1): 233-246.
Geraedts 2000	Geraedts, J., A. Handyside, et al. (2000). "ESHRE Preimplantation Genetic Diagnosis (PGD) Consortium: Data collection II (May 2000)." Human Reproduction 15(12): 2673-2683.
Geraedts 1999	Geraedts, J., A. Handyside, et al. (1999). "ESHRE Preimplantation Genetic Diagnosis (PGD) Consortium: Preliminary assessment of data from January 1997 to September 1998." Human Reproduction 14(12): 3138-3148.
<i>Other</i>	
Keymolen 2012	Keymolen, K., C. Staessen, et al. (2012). "Preimplantation genetic diagnosis in female and male carriers of reciprocal translocations: Clinical outcome until delivery of 312 cycles." European Journal of Human Genetics 20(4): 376-380.
De Rademaeker 2009	De Rademaeker, M., W. Verpoest, et al. (2009). "Preimplantation genetic diagnosis for myotonic dystrophy type 1: Upon request to child." European Journal of Human Genetics 17(11): 1403-1410.
Thomaidis 2012	Thomaidis, L., S. Kitsiou-Tzeli, et al. (2012). "Psychomotor development of children born after preimplantation genetic diagnosis and parental stress evaluation." World Journal of Pediatrics 8(4): 309-316.
Grace 2006	Grace, J., T. El-Toukhy, et al. (2006). "Three hundred and thirty cycles of preimplantation genetic

Study ID	Citation
	diagnosis for serious genetic disease: Clinical considerations affecting outcome." BJOG: An International Journal of Obstetrics and Gynaecology 113(12): 1393-1401.
Strom 2000	Strom, C. M., R. Levin, et al. (2000). "Neonatal outcome of preimplantation genetic diagnosis by polar body removal: The first 109 infants." Pediatrics 106(4 I): 650-653.

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; PICO, population/ intervention/ comparator/ outcome

### C.2.3. PICO 3

No studies were identified that specifically assessed the diagnostic accuracy of PGD compared to prenatal diagnosis. However, 17 studies were identified that provided useful data for Question 3 (listed in Table C.2.3).

The 12 individual data reports from the ESHRE PGD Consortium, in addition to the summary report on misdiagnosis by Wilton et al (2009), provided data on the rate of misdiagnosis after PGD using FISH and PCR, based on prenatal and postnatal testing. In addition, three studies assessed the validity of PCR-based PGD protocols (Dreesen et al, 2008; Goossens et al, 2008b; Dreesen et al, 2014); one study assessed the validity of a FISH-based PGD method (Scriven et al, 2013) and one study assessed the diagnostic efficiency of PCR and FISH techniques for PGD (Goossens et al, 2008b).

Table C.2.3 List of included studies – PICO 3

Study ID	Citation
Dreesen 2014	Dreesen J, Destouni A, Kourlaba G, Degn B4, Mette WC, Carvalho F, Moutou C, Sengupta S, Dhanjal S, Renwick P, Davies S, Kanavakis E, Harton G, Traeger-Synodinos J. Evaluation of PCR-based preimplantation genetic diagnosis applied to monogenic diseases: a collaborative ESHRE PGD Consortium study. Eur J Hum Genet. 2014 Aug;22(8):1012-8.
Scriven 2013	Scriven PN, Flinter FA, Khalaf Y, Lashwood A, Mackie Ogilvie C. Benefits and drawbacks of preimplantation genetic diagnosis (PGD) for reciprocal translocations: lessons from a prospective cohort study. Eur J Hum Genet. 2013 Oct;21(10):1035-41.
Dreesen 2008	Dreesen J, Drüsedau M, Smeets H, de Die-Smulders C, Coonen E, Dumoulin J, Gielen M, Evers J, Herbergs J, Geraedts J. Validation of preimplantation genetic diagnosis by PCR analysis: genotype comparison of the blastomere and corresponding embryo, implications for clinical practice. Mol Hum Reprod. 2008 Oct;14(10):573-9.
Goossens 2008	Goossens V, De Rycke M, De Vos A, Staessen C, Michiels A, Verpoest W, Van Steirteghem A, Bertrand C, Liebaers I, Devroey P, Sermon K. Diagnostic efficiency, embryonic development and clinical outcome after the biopsy of one or two blastomeres for preimplantation genetic diagnosis. Hum Reprod. 2008 Mar;23(3):481-92.
<i>ESHRE</i>	
Moutou 2014	Moutou C, Goossens V, Coonen E, De Rycke M, Kokkali G, Renwick P, SenGupta SB, Vesela K, Traeger-Synodinos J. ESHRE PGD Consortium data collection XII: cycles from January to December 2009 with pregnancy follow-up to October 2010. Hum Reprod. 2014 May;29(5):880-903.
Goossens 2012	Goossens V, Traeger-Synodinos J, Coonen E, De Rycke M, Moutou C, Pehlivan T, Derks-Smeets IA, Harton G. ESHRE PGD Consortium data collection XI: cycles from January to December 2008 with pregnancy follow-up to October 2009. Hum Reprod. 2012 Jul;27(7):1887-911.
Harper 2010	Harper JC, Coonen E, De Rycke M, Harton G, Moutou C, Pehlivan T, Traeger-Synodinos J, Van Rij MC, Goossens V. ESHRE PGD Consortium data collection X: cycles from January to December 2007 with pregnancy follow-up to October 2008. Hum Reprod. 2010 Nov;25(11):2685-707.
Goossens 2009	Goossens V, Harton G, Moutou C, Traeger-Synodinos J, Van Rij M, Harper JC. ESHRE PGD Consortium data collection IX: cycles from January to December 2006 with pregnancy follow-up to October 2007. Hum Reprod. 2009 Aug;24(8):1786-810.
Wilton 2009	Wilton L, Thornhill A, Traeger-Synodinos J, Sermon KD, Harper JC. The causes of misdiagnosis and adverse outcomes in PGD. Hum Reprod. 2009 May;24(5):1221-8.
Goossens 2008	Goossens V, Harton G, Moutou C, Scriven PN, Traeger-Synodinos J, Sermon K, Harper JC. ESHRE PGD Consortium data collection VIII: cycles from January to December 2005 with pregnancy follow-up to October 2006. Hum Reprod. 2008 Dec;23(12):2629-45.
Harper 2008	Harper JC, de Die-Smulders C, Goossens V, Harton G, Moutou C, Repping S, Scriven PN, SenGupta S,

Study ID	Citation
	Traeger-Synodinos J, Van Rij MC, Viville S, Wilton L, Sermon K. ESHRE PGD Consortium data collection VII: cycles from January to December 2004 with pregnancy follow-up to October 2005. <i>Hum Reprod.</i> 2008 Apr;23(4):741-55.
Sermon 2007	Sermon KD, Michiels A, Harton G, Moutou C, Repping S, Scriven PN, SenGupta S, Traeger-Synodinos J, Vesela K, Viville S, Wilton L, Harper JC. ESHRE PGD Consortium data collection VI: cycles from January to December 2003 with pregnancy follow-up to October 2004. <i>Hum Reprod.</i> 2007 Feb;22(2):323-36.
Harper 2006	Harper JC, Boelaert K, Geraedts J, Harton G, Kearns WG, Moutou C, Muntjewerff N, Repping S, SenGupta S, Scriven PN, Traeger-Synodinos J, Vesela K, Wilton L, Sermon K. ESHRE PGD Consortium data collection V: cycles from January to December 2002 with pregnancy follow-up to October 2003. <i>Hum Reprod.</i> 2006 Jan; 21(1):3-21.
Sermon 2005	Sermon K, Moutou C, Harper J, Geraedts J, Scriven P, Wilton L, Magli MC, Michiels A, Viville S, De Die C. ESHRE preimplantation genetic diagnosis (PGD) Consortium: data collection IV (May - December 2001). <i>Hum Reprod.</i> 2005 Jan;20(1):19-34.
Sermon 2002	Sermon K, Harper J, Geraedts J, Die-Smulders C, Handyside A, Hussey N, Magli M, Munne S, Ray P, Santalo J, Staessen C, Thornhill A, Viville S, Wilton L. ESHRE preimplantation genetic diagnosis (PGD) Consortium: data collection III (May 2001). <i>Hum Reprod.</i> 2002 Jan;17(1):233-46.
Geraedts 2000	Geraedts J, Handyside A, Harper J, Liebaers I, Sermon K, Staessen C, Thornhill A, Viville S, Wilton L. ESHRE preimplantation genetic diagnosis (PGD) Consortium: data collection II (May 2000). <i>Hum Reprod.</i> 2000 Dec;15(12):2673-83.
Geraedts 1999	Geraedts J, Handyside A, Harper J, Liebaers I, Sermon K, Staessen C, Thornhill A, Vanderfaeillie A, Viville S. ESHRE Preimplantation Genetic Diagnosis (PGD) Consortium: preliminary assessment of data from January 1997 to September 1998. ESHRE PGD Consortium Steering Committee. <i>Hum Reprod.</i> 1999 Dec;14(12):3138-48.

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; PGD, preimplantation genetic diagnosis; PICO, population/ intervention/ comparator/ outcome

#### C.2.4. PICO 4

No studies were identified that assessed the change in management of couples undertaking PGD compared to couples who conceive naturally (or by IVF) and the possibility of TOP.

#### C.2.5. PICO 5

No studies were identified that specifically compared the psychological impact in couples whose offspring is at risk of a serious genetic disorder, of being faced with a decision to terminate a 'planned' pregnancy or not having to make that decision, after prenatal diagnosis. There are several primary studies and systematic reviews that address psychological outcomes after diagnosis of fetal anomaly and after termination of pregnancy for fetal anomaly (Zeanah et al, 1993; Hunfeld et al, 1994; Kersting et al, 2005; Korenkamp et al, 2005; Kersting et al, 2009; Korenkamp et al, 2009; Wool et al, 2011). Although these studies report on the psychological consequences (such as post-traumatic stress, anxiety, depression) of termination for fetal malformation, Down syndrome, etc., the studies lack appropriate controls and the findings are not directly applicable to couples who know that they carry a serious genetic disorder or rearrangement of their chromosomes. These studies are therefore not discussed further in this report. However, Section C.5 of this report describes a pre-modelling study that includes the identification of utility weights that appropriately represent the termination of pregnancy health state in the economic model.

No studies were identified that specifically assessed the physical safety concerns of TOP in the population defined in Table A.8.5. However, there are a number of systematic reviews (including Cochrane Reviews) relating to different methods of surgical and medical TOP that would be sufficiently generalisable to the population of interest (for example, Lohr et al, 2008; Kulier et al, 2011; Wildschut et al, 2011). The economic model

described in Section D does not capture harms associated with termination of pregnancy, the omission of which is conservative as it biases against PGD. Thus a full review of the harms of termination of pregnancy has not been undertaken in Section B.

### **C.3. Assessment of the measures taken by investigators to minimise bias**

The following section includes a description of the methodological quality of the studies included in this assessment. The included studies are made up of primarily observational comparative studies (Level III) and non-comparative case series (level IV).

Observational studies are particularly susceptible to selection bias due to the lack of randomisation to the experimental and control groups. The effect of selection bias can be minimised in three ways: (i) drawing the groups to be compared from same overall cohort (based on location and time); (ii) matching the control group to the experimental group based on demographic and other characteristics considered to be potential confounders; and (iii) adjusting the analyses for potential confounders. Thus, assessment of the quality of the observational studies included in this assessment will focus on the way in which subjects were selected for the study, and the analysis methods that were used to minimise the impact of potential confounders on the results.

While case series provide non-comparative evidence, due to the small amount of comparative evidence available for this assessment they have been included here. The methodological quality of included case series will not be examined in detail.

A number of RCTs are included in this assessment; however, they provide comparison between PGD techniques only, not comparison between PGD and the main comparator, prenatal testing. As such, their methodological quality will not be discussed in detail.

#### **C.3.1. PICO 1**

There were no RCTs or non-randomised studies that specifically compared the safety, clinical effectiveness, and technical efficacy of PGD in couples undergoing PGD to couples who achieve natural conception (or conception through IVF) followed by prenatal diagnosis.

One systematic review (Franssen et al, 2011) compared PGD with natural conception in couples who were carriers of chromosomal translocations with recurrent miscarriage. The data in this review were derived from four observational studies and 21 case studies; there were no RCTs or non-randomised comparative studies identified. Taken as a whole, the quality of the included studies was considered by the authors to be of “poor quality”.

The evidence for PICO 1 is mainly derived from 17 observational studies (12 case series and five cohort studies) and 12 data reports published by the ESHRE PGD Consortium that provided data on the safety, effectiveness, and technical efficacy of PGD in the absence of a control or comparison group. Study designs in observational studies are limited by issues such as uncontrolled confounding factors and bias. These sources of bias mean that the findings reported by the included studies may not be generalisable to a larger population of patients, and therefore conclusions from these studies must be viewed with extreme caution.

The included case series are subject to selection bias as no criteria for patient selection was described (for example it was not stated whether patients were or were not consecutively selected). Thus, there is a possibility that reporting in this series is biased towards those patients with better reproductive outcomes, or excludes reporting of negative results (for example misdiagnosis), thus introducing observational and/or reporting bias. The included case series lack blinding which results in performance bias. The included cohort studies are also subject to selection bias and possible confounding by factors such as age of women, infertility (endometriosis) and quality/morphology of transferred embryos.

It should be noted that despite providing a low level of evidence, the 12 data reports published by the ESHRE PGD Consortium (from 1997 to 2009) covering all applications of PGD (including autosomal and sex-linked single gene disorders and chromosomal rearrangements, PGS and social sex selection) from various fertility centres worldwide do provide a substantial body of evidence. However, the validity of the reproductive outcomes reported from this data collection are dependent on the availability and accuracy of the data records from the participating centres, as well as the quality of reporting by the Consortium.

In addition to the studies above, there were a number of comparative studies that compared different PGD biopsy techniques.

One prospective RCT (Goossens et al, 2008) compared clinical outcomes using different PGD biopsy techniques (one blastomere versus two blastomeres), and does not compare PGD with prenatal diagnosis. Similarly, the RCT by Kokkali et al (2007) compared clinical outcome after the biopsy of either blastomere (Day 3) or blastocysts (Day 5) for PGD. An additional RCT compared clinical outcomes following two methods used to assist biopsy: three-dimensional partial and conventional partial zona dissection (Cieslak et al, 1999). A summary of the measures to minimise bias in the RCTs is shown in Table C.3.1. While the RCTs appear to be of reasonable methodological quality, it should be noted that the comparisons made in them are not relevant to the primary questions being asked in this assessment.

Table C.3.1 Measures to minimise bias in the included level II comparative studies – PICO 2

Trial ID	Concealment of randomisation	Blinding – participants	Blinding – investigators	Blinding – outcomes assessors	Basis of analysis
Goossens 2008b	A <sup>a</sup>	NR <sup>b</sup>	NR <sup>b</sup>	NR <sup>b</sup>	D <sup>c</sup>
Kokkali 2007	Unclear <sup>d</sup>	NR <sup>b</sup>	NR <sup>b</sup>	NR <sup>b</sup>	D <sup>c</sup>
Cieslak 1999	A <sup>e</sup>	Y	Y	Y	D

Abbreviations: A, central telephone randomisation service; D, intention to treat (all randomised patients/cycles); NR, not reported; PICO, population/ intervention/ comparator/ outcomes

a Described as a computer-generated randomisation list, concealed for allocation.

b Blinding not reported but outcomes were objective not subjective.

c All randomised cycles included.

d Described as randomisation in blocks with the use of random number tables.

e Described as randomised blindly.

Three retrospective observational studies compared reproductive outcomes after PGD using blastomere (Day 3) to blastocyst (Day 5) biopsy (McArthur et al, 2005; McArthur



et al, 2008; Chang et al, 2013). However, these studies included only small sample sizes (in terms of number of cycles and/or number of couples).

### **C.3.2. PICO 2**

Seven observational studies representing cohorts of children from two countries (Belgium and the UK) provide comparative evidence to assess the harms to children associated with PGD/PGS.

A summary of the methodological features of the included studies which are known to play a role in minimising bias in observational studies (i.e. recruitment of the cohort and methods for reducing variation between groups) is presented in Table C.3.2.

A number of the studies included control groups drawn from cohorts from different locations or time points. In all studies that included natural conception as a control, the natural conception cohort was recruited from different centres to the PGD/PGS and ICSI cohorts (e.g. childcare centres and paediatrician offices compared with the IVF clinic). In addition, one study used controls from the same centre conceived during a partially overlapping timeframe and published in a previous series.

In most studies arising from the Belgian cohort, control children were matched to the PGD children on a number of variables, analyses were adjusted for potential confounders, or both. In addition, a number of the Belgian cohort studies limited inclusion to singleton children. Prematurity and low birth weight are known to be associated with poorer outcomes in children and as they occur more frequently in multiple births, exclusion of twin and triplet children is another way to control for these potential confounders. For a number of outcomes, analysis was based on non-adjusted and/or non-matched comparisons. When this has occurred it will be noted with the results in Section B.6. The remaining study (Banerjee et al, 2008), which was conducted in the UK, included matched groups and all analyses were adjusted for confounders.

Overall, the quality of these studies would be considered poor to fair. The potential impact of bias on the results of these studies will be addressed in Section C.6.2.

In addition, 17 studies provide non-comparative level IV evidence of the potential harms to children of PGD ± PGS. Twelve of these studies are part of the ESHRE PGD Consortium data collection. While level IV studies are considered to provide poor quality evidence, it should be noted that the size and scope of the ESHRE data collection (nearly 40,000 cycles of PGD/PGS collected internationally over 12 years) offers a substantial body of evidence to support the small number of comparative studies identified. The remaining studies are case series Belgium, Greece and the UK. Given they provide level IV evidence, they are not discussed further here.

Two RCTs provide data on children's outcomes following PGD (Goossens et al, 2008b; Kokkali et al, 2007). However, it should be noted that both of these RCTs compare different PGD biopsy techniques, not PGD with prenatal testing, making the assessment of bias less important for this assessment. A summary of the measures to minimise bias in these studies was shown in Table C.3.1 in Section C.3.1.

Table C.3.2 Measures to minimise bias in the included Level III comparative studies – PICO 2

Study ID	Level of Evidence	Study type	Minimisation of bias
<i>Belgian cohort</i>			
Winter 2014	III-2	Prospective cohort – concurrent control (ICSI), different cohort (NC)	<b>Population:</b> PGD/ICSI and ICSI children from an established cohort at the same centre (Belgium). NC children recruited from a different cohort. <b>Analysis:</b> Singleton children included only. ICSI and NC children matched to PGD/ICSI children based on gender, age, birth order and maternal education level. Analyses adjusted for age, mother’s age at birth, educational level of mother and father and gender.
Desmyttere 2012	III-2	Prospective cohort – concurrent control	<b>Population:</b> PGD/ICSI and ICSI children conceived during the same period at the same centre (Belgium) <b>Analysis:</b> Univariate and multivariate analyses. Multivariate analyses adjusted for maternal age, pre-pregnancy BMI, parity, nicotine abuse, alcohol intake and pregnancy complications. No multivariate analysis performed for malformations outcome.
Liebaers 2010	III-3	Prospective cohort – historical control	<b>Population:</b> PGD/ICSI and ICSI children conceived during different (overlapping) timeframes at the same centre (Belgium). Control data from a cohort published separately (Bonduelle et al., 2002) <b>Analysis:</b> Univariate analyses only. No adjustment for potential confounders on included outcomes.
Desmyttere 2009	III-2	Prospective cohort – concurrent control (ICSI), different cohort (NC)	<b>Population:</b> PGD/ICSI and ICSI children conceived during the same timeframe at the same centre (Belgium). NC children recruited from a different cohort. <b>Analysis:</b> Singletons only included to reduce confounding (e.g. prematurity, low birth weight). Controls matched to PGD/ICSI children based on gender, maternal educational level, mother’s language and birth order. No analysis performed on included outcome (malformations).
Nekkebroeck 2008a	III-2	Prospective cohort – concurrent control (ICSI), different cohort (NC)	<b>Population:</b> PGD/ICSI and ICSI children conceived during the same timeframe at the same centre (Belgium). NC children recruited from a different cohort. <b>Analysis:</b> Singletons only included to reduce confounding (e.g. prematurity, low birth weight). Controls matched to PGD/ICSI children based on gender, maternal educational level, mother’s language and birth order. Univariate and multivariate analyses conducted. Multivariate analyses adjusted for socio-demographic variables including age at assessment, educational level of fathers, mother’s age at the birth of their child, father’s age at child assessment, employment, gestational age, marital status, attendance at a day-care centre.
Nekkebroeck 2008b	III-2	Prospective cohort – concurrent control (ICSI), different cohort control (NC)	<b>Population:</b> PGD/ICSI and ICSI children conceived during the same timeframe at the same centre (Belgium). NC children recruited from a different cohort. <b>Analysis:</b> Singletons only included to reduce confounding (eg. prematurity, low birth weight). Controls matched to PGD/ICSI children based on gender, maternal educational level, mother’s language and birth order, as per studies above, but only parents who could understand Dutch were included, thereby reducing benefit of matching. Univariate and multivariate analyses conducted. Multivariate analyses adjusted for socio-demographic variables including gender, birth order, mother’s language, age at assessment, educational level of mothers and fathers, mother’s age at the birth of their child, father’s age at child assessment, employment, gestational age, birth weight, Apgar score, marital status, attendance at a day-care centre.
<i>Other</i>			
Banerjee 2008	III-3	Cross-sectional – different cohort control (NC)	<b>Population:</b> PGD/ICSI children conceived from four centres in London (UK). NC children recruited from local nurseries and twins recruited via the London-based Multiple Birth Foundation. <b>Analysis:</b> Controls matched for age, gender, multiplicity, ethnicity, maternal educational level and socioeconomic status. Multivariate analysis used (MANOVA); no mention of adjusting for potential confounders.

Abbreviations: ICSI, intracytoplasmic sperm injection; MANOVA, Multivariate Analysis of Variance; NC, natural conception; PGD, preimplantation genetic diagnosis; PICO, population/ intervention/ comparator/ outcomes

### **C.3.3. PICO 3**

The 12 publications reporting data from the ESHRE PDG Consortium have been described previously. In these studies, conformation of PGD diagnosis was performed using prenatal testing on approximately 34% of fetal sacs. These studies are considered to provide Level III-1 data on diagnostic accuracy. As only a small proportion of all fetal sacs were tested, there is a substantial risk of selection bias associated with these results.

There were three studies that assessed the validity of PCR-based PGD protocols and one study that assessed the validity of FISH-based PGD testing methods. One study was an RCT (Goossens et al, 2008a), two studies were retrospective cohorts (Dreesen et al, 2008; Dreesen et al, 2014) and one was a prospective cohort (Scriven et al, 2013). None of the included studies compared the accuracy of PGD to that of prenatal diagnosis and none of the included studies fulfilled the reference standard criteria as defined by the Final Protocol; embryos that had not been transferred were retested with the same testing method to assess the effect testing one or two cells had on accuracy. Thus, none of these studies meet the levels of evidence for diagnostic studies defined by the NHMRC because they do not include a valid reference standard. They have been included only because they provide additional information that may be of interest to this assessment; as such, an assessment of the measures to reduce bias in these studies has not been conducted.

## **C.4. Characteristics of the studies**

### **C.4.1. PICO 1**

The characteristics of the 12 annual data reports published by the ESHRE PGD Consortium are presented in Table C.4.1. They encompass data published in each of the last 12 years (PGD cycles performed from 1997 to 2009), and highlight how the practice of PGD has evolved over the years. The fields collected include information relating to PGD cycles (for SGD and chromosomal abnormalities) as well as PGS and social sexing. Information related to cycles other than PGD were excluded from this assessment. ESHRE data has been submitted by membership centres worldwide, including Australia. The ESHRE data reports represent a large and important resource for information about the practice of PGD.

Table C.4.1 Characteristics of all included ESHRE PGD Consortium reports (Data I-XII) – PICO 1

Study	Location	Study design	PGD cycles <sup>a</sup>	Intervention	Outcomes assessed
Geraedts 1999	Multi-centre (Europe, North and South America, Asia, Africa, Australia and Russia)	Retrospective review of data, multi-centre (ESHRE PGD Consortium data collection)	NR	PGD for single gene disorders, PGD for chromosomal abnormalities, sexing for X-linked disease, PGS for aneuploidy screening, PGD for social sexing.	Clinical pregnancy rate (% per ORt, % per ET), delivery rate (% per ORt, % per ET), successful biopsy, miscarriages, misdiagnoses, live births without severe genetic disorder.
Geraedts 2000	As above	As above	NR	As above	As above
Sermon 2002	As above	As above	413	As above	As above
Sermon 2005	As above	As above	610	As above	As above
Harper 2006	As above	As above	793	As above	Clinical pregnancy rate (% per ORt, % per ET), delivery rate (% per ORt, % per ET), implantation rate, successful biopsy, miscarriages, misdiagnoses, live births without severe genetic disorder.
Sermon 2007	As above	As above	958	As above	As above.
Harper 2008	As above	As above	1107	As above	As above
Goossens 2008	As above	As above	1089	As above	As above
Goossens 2009	As above	As above	1768	As above	As above
Harper 2010	As above	As above	1989	As above	As above
Goossens 2012	As above	As above	2136	As above	As above
Moutou 2014	As above	As above	2524	As above	As above

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; ET, embryo transfer; NR, not reported; ORt, oocyte retrieval; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening; PICO, population/ intervention/ comparator/ outcomes  
<sup>a</sup> PGD cycles include single gene disorders and chromosomal abnormalities, excluding PGS and social sexing

Other than the ESHRE PGD Consortium data reports, there were 21 studies that have reported on the safety, effectiveness, and technical efficacy of PGD. However, 15 of these studies were generated by centres that provide data to the ESRHE PGD Consortium, and thus there is the likelihood that the results from these studies have already been accounted for within the ESHRE PGD data. The characteristics of these studies are presented in Table C.4.2. Overall, there was one systematic review, two RCTs, one case-control study, five cohort studies, and 12 case series.

The systematic review by Franssen et al (2011) compared live birth rates and miscarriage rates after natural conception and after PGD, in couples with a history of two or more miscarriages and carrying a structural chromosome abnormality. There were no RCTs or non-randomised comparative studies that compared the effects of PGD with natural conception. Data were derived from four observational studies and 21 case reports.

The study by Goossens et al (2008) was a prospective RCT at a single centre aimed to test the potential influences of analysing one or two blastomeres by either PCR or FISH on a clinically relevant set of primary outcomes (pregnancy outcomes and diagnostic efficiencies). In addition, the investigators assessed diagnostic accuracy by PCR. The study included both PGD and PGS patients with inclusion criteria not limited for age nor history of recurrent miscarriage.

It should be noted that the majority of these studies have utilised blastomeres biopsied at Day 3 to collect cells for PGD. There were four small studies that utilised blastocysts biopsied at Day 5 (trophectoderm), and these are presented separately in Table C.4.2. The reproductive outcomes from these studies have been analysed separately in Section B.6 as they are considered to be most relevant to the Australian setting. Two of these publications were from Geneva (previously Sydney IVF).

Table C.4.2 Characteristics of all included studies – PICO 1

Study ID	Country Period	Study design Level of evidence	Size	Intervention	Biopsy	Method of analysis	Outcome measure	Reporting to ESHRE
Tan 2013	China 2011-2012 SNP; 2005-2011 FISH	Retrospective case series (Level IV)	575 couples (169 SNP; 406 FISH)	PGD for translocations	Blastomere or blastocyst	FISH SNP	Clinical pregnancy rate Implantation rate Delivery rate Miscarriage rate Live birth rate	No
Keymolen 2012	Belgium 1997-2007	Retrospective case series (Level IV)	312 cycles 142 couples	PGD for translocations	Blastomere	FISH	Clinical pregnancy rate Delivery rate Live birth rate Miscarriage rate	Yes
Van Rij 2012	Europe (Netherlands, Belgium, France) 1995-2008	Prospective cohort (Level III- 2)	434 cycles 174/331 couples	PGD for SGD (HD)	Blastomere	Multiplex PCR	Clinical pregnancy rate Implantation rate Delivery rate Live birth rate	Yes
Ginsburg 2011	US 2007-2008	Retrospective case series (Level IV)	8,377 cycles	PGD (genetic and translocation) and PGS	NR	NR	Delivery rate	No
Hamoda 2011	UK 2006-2009	Retrospective case series (Level IV)	307 cycles	PGD (genetic, translocation, excluded aneuploidy)	Blastomere	NR	Clinical pregnancy rate Implantation rate	Yes
Kuliev 2011	US NR	Retrospective case series (Level IV)	395 cycles 226 couples	PGD for haemoglobinopathies	Polar body blastomere	Multiplex nested PCR	Pregnancy rate Live birth rate	No
Fischer 2010	US NR (through March 2008)	Retrospective case series (Level IV)	272 cycles 192 couples	PGD for translocations	Polar body blastomere	FISH	Miscarriage rate Delivery rate Timeframe to success (or length of time to success)	Yes

Study ID	Country Period	Study design Level of evidence	Size	Intervention	Biopsy	Method of analysis	Outcome measure	Reporting to ESHRE
Gutierrez-Mateo 2009	US, UK 2007-2008	Retrospective case series (Level IV)	224 cycles 162 couples	PGD for SGD	Blastomere	Multiplex PCR	Clinical pregnancy rate Implantation rate Delivery rate Live birth rate Miscarriage rate	Yes
Verpoest 2009	Belgium 1993-2005	Prospective cohort study (Level III)	1498 couples 2753 cycles	PGD/PGS (overall and per genetic category)	Blastomere	Multiplex PCR FISH	Clinical pregnancy rate Delivery rate	Yes
Goossens 2008b	Belgium 2001-2005	RCT (Level II)	592 cycles (overall): 288 (1 cell biopsy) 204 (2 cell biopsy)	PGD	Blastomere (one-cell vs two-cell biopsy)	Duplex or multiplex PCR FISH	Implantation rate Delivery rate Live birth rate	Yes
Feyereisen 2007	France 2000-2004	Retrospective case series (Level IV)	441 cycles 171 couples	PGD (overall and per genetic category)	Blastomere	Nested PCR FISH	Clinical pregnancy rate Implantation rate Live birth rate Miscarriage rate	Yes
Grifo 2007	US 1995-2005	Retrospective case series (Level IV)	304 cycles 190 couples	PGD (genetic and translocation) and PGS	Blastomere	PCR FISH	Clinical pregnancy rate Implantation rate Delivery rate Live birth rate Miscarriage rate	Yes
Fiorentino 2006	Italy 1999-2004	Retrospective case series (Level IV)	250 cycles 174 couples	PGD for SGD	Blastomere	Multiplex PCR	Clinical pregnancy rate Implantation rate Live birth rate	Yes
Grace 2006	UK 1997-2005	Retrospective case series (Level IV)	330 cycles (158 genetic; 172 translocations) 190 couples	PGD (overall and per genetic category)	Blastomere	PCR FISH	Clinical pregnancy rate Implantation rate Delivery rate Live birth rate	Yes
Verlinsky 2004	US Italy NR (12-year experience)	Retrospective case series (Level IV)	4,748 cycles (532 genetic; 469 translocations)	PGD	Polar body Blastomere	PCR FISH	Clinical pregnancy rate Implantation rate Live birth rate	Yes

Study ID	Country Period	Study design Level of evidence	Size	Intervention	Biopsy	Method of analysis	Outcome measure	Reporting to ESHRE
Cieslak 1999	US 1997 (January-September)	RCT (Level II)	371 cycles 340 couples	PGD (3D partial zona dissection compared to conventional partial zona dissection)	Blastomere	NR	Chemical pregnancy rate Implantation rate Delivery rate Miscarriage rate	No
<i>Blastocyst studies</i>								
Chang 2013	Taiwan 2008-2012	Prospective cohort study (Level III-2)	40 cycles 33 couples	PGD for SGD	Blastocyst Blastomere	WGA and STR analysis	Clinical pregnancy rate Implantation rate Delivery rate Live birth rate	No
McArthur 2008	Australia (Sydney IVF) 1999-2003 for blastomeres, 2003-2006 for blastocysts	Retrospective case series (Level IV)	Genetic: 177 OR (day 5 biopsy) Translocation: 73 OR (day 5 biopsy)	PGD (overall and per genetic category)	Blastocyst Blastomere	PCR FISH	Clinical pregnancy rate Implantation rate Live birth rate Miscarriage rate	Yes
Kokkali 2007	Greece Australia 2004-2005	RCT (Level II)	20 cycles 20 couples	PGD for SGD ( $\beta$ -thalassaemia)	Blastocyst Blastomere	Multiplex PCR	Clinical pregnancy rate Implantation rate Delivery rate Live birth rate Miscarriage rate	Yes
McArthur 2005	Australia 2002-2004	Retrospective case series (Level IV)	231 cycles (55 cycles for SGD and translocations) 119 couples	PGD (overall) and PGS	Blastocyst	PCR FISH	Clinical pregnancy rate Implantation rate Live birth rate Miscarriage rate	Yes

Abbreviations: ARPKD, autosomal recessive polycystic kidney disease; ET, embryo transfer; ESHRE, European Society of Human Reproduction and Embryology; FISH, fluorescence in situ hybridisation; HD, Huntington's disease; OCC, oocyte collection cycle; PCR, polymerase chain reaction; PGD, preimplantation genetic diagnosis; PICO, population/ intervention/ comparator/ outcomes; SGD, single gene disorders; UK, United Kingdom; US, United States; WGA, whole genome amplification



#### **C.4.2. PICO 2**

The characteristics of the included comparative Level III studies are summarised in Table C.4.3. Six of the seven included studies are from the same centre in Belgium and assess cohorts of children at a variety of ages from 2 months up to 5–6 years. At the earlier ages (< 2 years), children were assessed for perinatal mortality and malformations, while at the older ages ( $\geq$  2 years) developmental delay was assessed.

Five of the six studies assess PGD/PGS (Desmyttere et al, 2012; Desmyttere et al, 2009; Liebaers et al, 2010; Nekkebroeck et al, 2008a; 2008b), while one study assesses PGD only (Winter et al, 2014). Desmyttere et al (2012) and Liebaers et al (2010) compared PGD/PGS with ICSI only, while the remaining studies compared PGD (and PGS) with ICSI and natural conception.

The comparators included in the studies providing Level III evidence do not exactly match the comparator defined in the Final Protocol (i.e. children conceived via IVF followed by prenatal diagnosis, and born to parents who know they carry a genetic disorder and are at risk of passing it on). No identified studies included this specific group as a comparator. The comparator that most closely resembles the PICO is IVF/ICSI, with or without prenatal testing, not limited to children born to parents who know they carry a genetic disorder and are at risk of passing it on. An alternative comparator available in a number of studies is natural conception, with or without prenatal testing; once again, this is not limited to children born to parents who know they carry a genetic disorder and are at risk of passing it on.

The characteristics of the 16 included level IV studies are summarised in Table C.4.4. Twelve of these studies are from the ESHRE PGD Consortium and provide information on perinatal outcomes in approximately 7,000 children following PGD/PGS.

The majority of the included Level III and IV studies assess both PGD and PGS. While PGS is not under consideration in this review, both PGD and PGS involve biopsy of the developing embryo and are therefore likely to have similar impacts on outcomes in children.

Table C.4.3 Characteristics of the included Level III studies – PICO 2

Study ID	Study type	Population	Intervention	Comparator	Outcomes
<i>Belgian cohort</i>					
Desmyttere 2012	Prospective cohort – concurrent control	Children aged up to 2 months Singleton or multiple Conceived between Jan 94 and Dec 08	PGD/PGS (N=1022)	ICSI (N=1542)	Perinatal mortality Major malformations
Liebaers 2010	Prospective cohort – historical control	Children aged up to 2 months Singleton or multiple	PGD/PGS (N=581)	ICSI (N=2889)	Perinatal mortality Major malformations
Desmyttere 2009	Prospective cohort – concurrent control (ICSI), different cohort (NC)	Children aged up to 2 years Singletons only	PGD/PGS (N=70)	ICSI (N=70) NC (N=70)	Major malformations
Nekkebroeck 2008a	Prospective cohort – concurrent control (ICSI), different cohort (NC)	Children aged 2 years Singletons only	PGD/PGS (N=70)	ICSI (N=70) NC (N=70)	Developmental delay (mental and psychomotor)
Nekkebroeck 2008b	Prospective cohort – concurrent control (ICSI), different cohort control (NC)	Children aged 2 years Singletons only Only Dutch-speaking parents included	PGD/PGS (N=52)	ICSI (N=54) NC (N=69)	Developmental delay (socio-emotional and language)
Winter 2014	Prospective cohort – concurrent control (ICSI), different cohort (NC)	Children aged 5 to 6 years Singletons only Only Dutch-speaking, Caucasian parents included	PGD only (N=47)	ICSI (N=49) NC (N=48)	Developmental delay (psychomotor and cognitive)
<i>Other</i>					
Banerjee 2008	Cross-sectional – different cohort control (NC)	Mean age 18 months Singleton or twin	PGD/PGS (N=49)	NC (N=66)	Developmental delay (mental)

Abbreviations: ICSI, intracytoplasmic sperm injection; NC, natural conception; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening; PICO, population/ intervention/ comparator/ outcomes

Table C.4.4 Characteristics of the included level IV studies – PICO 2

Study ID	Country	Population	Intervention	Outcomes
<i>ESHRE</i>				
Moutou 2014	International	Children born following PGD/PGS who have birth data available (N=863/1022 births) Jan 09 to Dec 09 from 60 centres	PGD/PGS	Perinatal mortality Malformations
Goossens 2012	International	Children born following PGD/PGS who have birth data available (N=811/1016 births) Jan 08 to Dec 08 from 53 centres	PGD/PGS	Perinatal mortality Malformations
Harper 2010	International	Children born following PGD/PGS who have birth data available (N=718/1206 births) Jan 07 to Dec 07 from 57 centres	PGD/PGS	Perinatal mortality Malformations
Goossens 2009	International	Children born following PGD/PGS who have birth data available (N=1016/1183 births) Jan 06 to Dec 06 from 57 centres	PGD/PGS	Perinatal mortality Malformations
Goossens 2008	International	Children born following PGD/PGS who have birth data available (N=588/670 births) Jan 05 to Dec 05 from 39 centres	PGD/PGS	Perinatal mortality Malformations
Harper 2008	International	Children born following PGD/PGS who have birth data available (N=484/557 births) Jan 04 to Dec 04 from 45 centres	PGD/PGS	Perinatal mortality Malformations
Sermon 2007	International	Children born following PGD/PGS who have birth data available (N=426/441 births) Jan 03 to Dec 03 from 50 centres	PGD/PGS	Perinatal mortality Malformations
Harper 2006	International	Children born following PGD/PGS who have birth data available (N=357/382 births) Jan 02 to Dec 02 from 43 centres	PGD/PGS	Perinatal mortality Malformations
Sermon 2005	International	Children born following PGD/PGS who have birth data available (N=197/217 births) May 01 to Dec 01 from 43 centres	PGD/PGS	Perinatal mortality Malformations
Sermon 2002	International	Children born following PGD/PGS who have birth data available (N=180/279 births) May 2001 from 25 centres	PGD/PGS	Perinatal mortality Malformations
Geraedts 2000	International	Children born following PGD/PGS who have birth data available (N=150/162 births) May 2000 (# centres not reported)	PGD/PGS	Perinatal mortality Malformations
Geraedts 1999	International	Children born following PGD/PGS who have birth data available (N=70/79 births) Jan 97 to Sep 98 (# centres not reported)	PGD/PGS	Perinatal mortality Malformations
<i>Other</i>				
Keymolen 2012	Belgium	Children born following PGD to parents with reciprocal translocations Singleton or multiple	PGD only	Developmental delay
Thomaidis 2012	Greece	Children aged 2 months to 7.5 years Singleton or multiple	PDG only	Developmental delay (psychomotor)
De Rademaeker 2009	Belgium	Children born to parents at risk of passing on myotonic dystrophy 1 Singleton or multiple	PGD only	Perinatal mortality Developmental delay
Grace 2006	UK	Children born following PGD Singleton or multiple	PGD only	Perinatal mortality
Strom 2000	US	Children born following PGD/PGS using polar body biopsy Singleton or multiple	PGD/PGS	Perinatal mortality Malformations Developmental delay

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening; PICO, population/ intervention/ comparator/ outcomes; US, United States

The characteristics of the included level II studies are summarised in Table C.4.5. Both studies compared perinatal mortality in cycles randomised to different biopsy techniques.

**Table C.4.5 Characteristics of the included level II studies – PICO 2**

Study ID	Study type	Population	Intervention	Comparator	Outcomes
Goossens 2008b	RCT	IVF-PGD/PGS cycles in which PCR was available for monogenic diseases or FISH was performed for sexing, chromosomal abnormalities or aneuploidy screening	Blastomere biopsy (1 cell) (N=1022)	Blastomere biopsy (2 cells) (N=1542)	Perinatal mortality
Kokkali 2006	RCT	First PGD cycles in couples in whom both parents were $\beta$ -thalassemia carriers	Blastocyst biopsy + transfer (N=10)	Blastomere biopsy + blastocyst transfer N=10	Perinatal mortality

Abbreviations: FISH, fluorescence in situ hybridisation; IVF, in vitro fertilisation; PCR, polymerase chain reaction; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening; PICO, population/ intervention/ comparator/ outcomes; RCT, randomised controlled trial

### C.4.3. PICO 3

The characteristics of the four included studies are summarised in Table C.4.6. None of the included studies compared the diagnostic accuracy of PGD to that of prenatal diagnosis. None of the studies fulfilled the reference standard as specified in the Final Protocol.

Three studies assessed the overall PGD-PCR procedure based on reanalysing genotyped embryos that were not suitable for transfer or cryopreservation (Dreesen et al, 2008; Goossens et al, 2008b; Dreesen et al, 2014). These three studies also evaluated the number of cells biopsied (one-cell versus two-cell biopsy) on diagnostic accuracy. One of these studies also evaluated two different PCR-PGD protocol strategies (singleplex versus multiplex PCR method) (Dreesen et al, 2014). One study also evaluated the diagnostic efficiency of PCR and FISH techniques after the removal of one or two blastomeres (Goossens et al, 2008b). The final study assessed the validity of the PGD-FISH procedure (Scriven et al, 2013).

The diagnostic accuracy measures calculated in four of the included studies were false positive and false negative rates (incorrect abnormal and normal biopsy results calculated as the proportion of the total outcomes), overall accuracy (the proportion of all biopsy results that were correct), sensitivity (true positive or the proportion of abnormal embryos that had an abnormal biopsy result) and specificity (true negative or the proportion of normal embryos that had a normal biopsy result) (Dreesen et al, 2008; Goossens et al, 2008b; Scriven et al, 2013; Dreesen et al, 2014).

Most importantly, these four studies reanalysed embryos that had been genotyped for PGD using a blastomere biopsy. None of the studies assessed diagnostic accuracy by reanalysing embryos that were genotyped using a blastocyst biopsy.

Table C.4.6 Characteristics of the included studies – PICO 3

Study ID	Country Period	Study design Level of evidence	Size	Biopsy	Method of analysis	Outcome measure
Dreesen 2014	ESHRE-multi-centre 2009-2010	Retrospective case series NA <sup>a</sup>	940 embryos	Blastomere (one-cell vs two-cell biopsy)	Multiplex PCR Singleplex PCR	Sensitivity Specificity Diagnostic accuracy
Scriven 2013	UK	Prospective cohort NA <sup>a</sup>	558 embryos	Blastomere	FISH	Sensitivity Specificity Diagnostic accuracy
Dreesen 2008	Netherlands UK 1995-2005	Retrospective case series NA <sup>a</sup>	422 embryos	Blastomere (one-cell vs two-cell biopsy)	PCR	Sensitivity Specificity False positive False negative Diagnostic accuracy Misdiagnosis Likelihood ratio Predictive value
Goossens 2008b	Belgium 2001-2005	RCT NA <sup>a</sup>	322 embryos: 154 (1 cell biopsy) 168 (2 cell biopsy)	Blastomere (one-cell vs two-cell biopsy)	Duplex or multiplex PCR FISH	Diagnostic accuracy (false positive rate) Diagnostic efficiency

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; FISH, fluorescence in situ hybridisation; NA, not applicable; PCR, polymerase chain reaction; PGD, preimplantation genetic diagnosis; PICO, population/ intervention/ comparator/ outcomes; RCT, randomised controlled trial; SGD, single gene disorder

<sup>a</sup> As none of these studies used a reference standard (additional embryos were just retested using the same methods), this study does not meet any of the levels of evidence for diagnostic studies as defined by the NHMRC.

## C.5. Outcome measures and analysis

### C.5.1. PICO 1

Table C.5.1 presents the relevant clinical outcomes as reported in the included studies. There were no identified studies that reported outcomes related to psychological harms from miscarriage or the decision to terminate due to misdiagnosis, and the physical and psychological effects of genetic disease on parent, inability to achieve a pregnancy, time delay to diagnosis, and time delay to live birth. Similarly, there was no evidence available that assessed parental psychological health benefits, quality of life, time to live birth, as well as the technical efficacy outcomes related to rebiopsy and resampling.

Table C.5.1 Clinical outcomes as per the included studies – PICO 1

Outcome measure	Definition
Successful biopsy	The removal of a cell without lysis such that the cell could be used for analysis. Another definition is the ratio of intact blastomeres to the total number of aspirated blastomeres.
Clinical pregnancy	Defined by the visualisation of a gestational sac with a fetal heartbeat seen on ultrasound scanning at six weeks gestation.
Clinical pregnancy rate per ET	The number of clinical pregnancies expressed per embryo transfer cycles.
Implantation rate	The number of gestational sacs observed divided by the number of embryos transferred.
Delivery rate per ET	The percentage of pregnancies with delivery per ET procedure.
Miscarriage	Clinical pregnancy that ended in pregnancy loss prior to 20 weeks gestation.
Miscarriage rate	The percentage of miscarriages per number of clinical pregnancies minus the number of pregnancies that were lost to follow-up.
Live birth rate (or live born rate) per ET	The number of deliveries that resulted in at least one live born baby, expressed per embryo transfer cycles.
Success rate (rate of PGD cycles to pregnancy)	The number of PGD cycles to achieve a pregnancy (confirmed by measurement of $\beta$ HCG 12 days after blastocyst transfer, or 14 days if ET was done on day 3).

Source: As defined by the ESHRE PGD Consortium publications (Data I – XII)

Abbreviations: ET, embryo transfer; HCG; human chorionic gonadotropin; PGD, preimplantation genetic diagnosis; PICO, population/intervention/ comparator/ outcomes

### C.5.2. PICO 2

A summary of the relevant outcomes in the included Level III comparative studies, and the methods of analysis used, are summarised in Table C.5.2.

With regards to the PICO-defined of *perinatal mortality* outcome (which includes stillbirths, neonatal deaths and total perinatal deaths), different denominators were used for the analysis of each: stillbirths and total perinatal deaths (stillbirths plus neonatal deaths) were calculated as a proportion of the total number of births (stillbirths plus live births), while neonatal deaths were calculated as a proportion of the number of live births only.

While there were no data available for the PICO-defined outcome of *physical disability*, there was data available regarding malformations and this has been included under the physical disability heading. Malformations were analysed as a proportion of all births.

There was no data available for the PICO-defined outcomes of *intellectual disability*, *quality of life* or *functional status*.

A number of studies provided data for the PICO-defined outcome of *developmental delay*. Continuous scales were used in the included studies which measured different aspects of development including cognitive development, motor development, mental and psychomotor development, socio-emotional development and language development. For a number of these scales, results were classified via cut-offs to determine the level of development in the child.

As noted in Section C.3.2, one method to minimise the impact of selection bias in observational studies is to adjust the analyses for potential confounders. A number of studies did adjust analyses for various socio-demographic variables. The impact on the results of these adjustments, and other methods of minimising selection bias, are discussed in Section C.6.2.

Table C.5.3 summarises the outcomes assessed in the included Level IV studies. The ESHRE studies provided data on *perinatal mortality* and *physical disability* (via malformations). Additional level IV studies also provided data on *perinatal mortality* as well as *physical disability* (via malformations) and *developmental delay*.

Table C.5.2 Outcomes included in the Level III studies– PICO 2

Study ID	Outcome description	Statistical analysis
<i>Perinatal mortality</i>		
Desmyttere 2012	Stillbirth defined as intrauterine or intra-partum death of a child born at a gestation of $\geq 20$ weeks or with a birth weight of $\geq 500$ g. Neonatal death defined as the demise of a live born infant within 7 days after birth. Perinatal death defined as a stillbirth or neonatal death.	Denominator for stillbirth analysis is total number of births (stillbirths + live births). Denominator for neonatal death analysis is the number of live births. Denominator for perinatal death analysis is the total number of births (stillbirths + live births). Multivariate analysis conducted for perinatal deaths only, adjusting for maternal age, pre-pregnancy BMI, parity, nicotine abuse, alcohol intake and pregnancy complications.
Liebaers 2010	Stillbirth: defined as above. Neonatal death: defined as above. Perinatal death: defined as above.	As above. Univariate analysis only.
<i>Physical disability</i>		
Desmyttere 2012	Major malformations defined as malformations that cause functional impairment and/or require surgical correction.	Denominator for major malformation analysis is total number of births (stillbirths + live births). Univariate analysis only.
Liebaers 2010	Major malformations: defined as above	As above
Desmyttere 2009	Major malformations: defined as above	As above
Banerjee 2008	Major malformations: defined as above (different to study definition)	As above
<i>Developmental delay</i>		
Winter 2014	Cognitive development was measured using the WPPSI. Subscales VIQ and PIQ are combined to produce the FSIQ. Considered to have good criterion and construct validity and acceptable degree of reliability. Motor development was measured using the M ABC. Tests motor development of children aged 5–12 years via three subscales: manual dexterity, ball skills and static and dynamic balance.	ANCOVA including socio-demographic variables such as age, mother's age at birth and educational level of the mother and father, as well as gender.
Nekkebroeck 2008a	Mental and psychomotor development were measured using the BSID. Two subscales are included which result in the calculation of two scores: the MDI and the PDI. Scores $\geq 115$ = accelerated performance; 85-114 = normal performance; 70-84 = mildly delayed performance; $< 70$ = significantly delayed performance.	Multivariate analysis including age at assessment, educational level of father, age of the mother at the birth of their child, age of the father at child assessment, employment percentage of mother and father, gestational age, marital status, attendance at a day-care centre.



Study ID	Outcome description	Statistical analysis
Nekkebroeck 2008b	Socio-emotional development using the STST and CBCL. STST includes six dimensions (approach, cooperation/manageability, reactivity persistence, rhythmicity and distractibility). Average of first three used to classify children into easy, difficult or average categories. CBCL measures 113 problems on a 'not true' to 'very true' scale. Results normalised to T-scores and T-score $\geq 64$ representing marked problems. Language development measured using N-CDI. Parents are presented with a list of words and check whether the child understands or produces the word. Number of words understood and produced is summated and translated into a percentile score and corresponding 'language age'.	Multivariate analyses adjusted for socio-demographic variables including gender, birth order, mother tongue, age at assessment, educational level of mother and father, age of the mother at the birth of their child, age of the father at child assessment, employment percentage of mother and father, gestational age, birth weight, Apgar score, marital status, attendance at a day-care centre.
Banerjee 2008	Mental development measured using the Griffiths MDS. Includes five subscales (locomotor, personal social, hearing language, eye-hand and performance) and a Griffiths General Quotient. Behavioural development measured using the TTQ which includes nine subscales (activity, rhythmicity, approach, adaptability, intensity, mood, persistence, distractibility and threshold).	No adjustment for potential confounders.

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index; BSID, Bayley Scales of Infant Development; CBCL, Child Behavioural Checklist; FSIQ, full-scale intelligence score; Griffiths MDS, Griffiths Mental Development Scales; M ABC, Movement ABC; MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index; PICO, population/ intervention/ comparator/ outcomes; PIQ, performance intelligence score; STST, Short Temperament Scale for Toddlers; TTQ, Toddler Temperament Questionnaire; VIQ, verbal intelligence score; WPPSI, Wechsler Preschool and Primary Scale of Intelligence III

Table C.5.3 Outcomes included in the Level IV studies– PICO 2

Study ID	Outcome description	Statistical analysis
<i>Perinatal mortality</i> - -		
<i>ESHRE</i> - -		
Moutou 2014	Still born not defined. Neonatal death not defined (includes still born so included as perinatal death).	Denominator for stillbirths is births. Denominator for perinatal death is births.
Goossens 2012	As above	As above
Harper 2010	As above	As above
Goossens 2009	As above	As above
Goossens 2008	As above	As above
Harper 2008	As above	As above
Sermon 2007	As above	As above
Harper 2006	As above	As above
Sermon 2005	As above	As above
Sermon 2002	As above	As above
Geraedts 2000	As above	As above
Geraedts 1999	As above	As above
<i>Other</i> - -		
Thomaidis 2012	Perinatal death not defined.	Denominator for perinatal death is all births.
De Rademaeker 2009	Perinatal death defined as intrauterine or intrapartum deaths $\leq 7$ days after birth at a gestational age of $\geq 20$ weeks.	Denominator for perinatal death is all births.
Grace 2006	Perinatal death not defined.	Denominator for perinatal death is all births.
Strom 2000	Neonatal death not defined.	Denominator for neonatal deaths is singleton births.
<i>Physical disability</i> - -		
<i>ESHRE</i> - -		
Moutou 2014	Major malformations not defined.	Denominator for major malformations is births.
Goossens 2012	As above	As above
Harper 2010	As above	As above
Goossens 2009	As above	As above
Goossens 2008	As above	As above
Harper 2008	As above	As above
Sermon 2007	As above	As above
Harper 2006	As above	As above
Sermon 2005	As above	As above
Sermon 2002	As above	As above
Geraedts 2000	As above	As above
Geraedts 1999	As above	As above
<i>Other</i> - -		
Strom 2000	Major malformations not defined.	Denominator for major malformations is births.
<i>Developmental delay</i> - -		
<i>Other</i> - -		
Keymolen 2012	Neurodevelopmental delay.	Descriptive only.
Thomaidis 2012	Cognitive development measured using the DQ which incorporates data from the BSID, and	Descriptive only, no comparison.

Study ID	Outcome description	Statistical analysis
	Griffths MDS or Athina Test.	
De Rademaeker 2009	Developmental delay not defined.	Descriptive only.
Strom 2000	Developmental delay via parent report.	Descriptive only.

Abbreviations: BSID, Bayley Scales of Infant Development; DQ, development quotient; ESHRE, European Society of Human Reproduction and Embryology; Griffiths MDS, Griffiths Mental Development Scales; PICO, population/ intervention/ comparator/ outcomes

The two included RCTs (Goossens et al (2008b) and Kokkali et al (2006)) included only perinatal mortality data for this research question. It should be noted that Goossens et al (2008b) states that data on children born including malformations and neonatal complications are available in the Supplementary data; however this data was unable to be located. No definition of perinatal mortality is included in either study.

### C.5.3. PICO 3

In the absence of comparative evidence that assessed the diagnostic accuracy of PGD versus prenatal diagnosis, the most relevant outcome to this assessment is the false negative rate associated with the diagnostic test.

*False negative rate = proportion of false negatives divided by the total number of affected embryos*

The false negative rate is considered to be the most important outcome for clinical PGD application, as it results in the birth of an affected child. Although the impact of a false positive result is not as serious, false positive test results decrease the total number of embryos that are deemed suitable for transfer.

In addition to false negative and false positive rates, the included studies determined the validity specifically of a PCR-based PGD method, by calculating the sensitivity, specificity, and overall diagnostic accuracy following the categories presented in Table C.5.4 (Dreesen et al, 2008; Dreesen et al, 2014).

Table C.5.4 Embryo status PGD versus embryo status reanalysis

	Affected/aberrant embryos at reanalysis	Unaffected embryos at reanalysis	Total
Affected/aberrant embryos at PGD	a (TP)	b (FP)	a+b
Unaffected embryos at PGD	c (FN)	d (TN)	c+d
Total	a+c	b+d	

Source: Dreesen et al (2008, 2014)

Abbreviations: TP, true positive; FN, false negative; TN, true negative; FP, false positive; PGD, preimplantation genetic diagnosis

Sensitivity: TP/(TP+FN).

Specificity: TN/(TN+FP).

Diagnostic accuracy: TP+TN/(TP+FN+TN+FP).

False negative rate: FN/(FN+TP).

False positive rate: FP/(FP+TN).

Sensitivity was defined as the proportion of affected/aberrant embryos diagnosed correctly by PGD (true positive), whereas specificity was defined as the proportion of unaffected embryos diagnosed correctly by PGD (true negative). The diagnostic accuracy of PCR-based PGD was defined as the proportion of embryos whose genotype results at reanalysis were in agreement with the results at PGD (i.e. true positive and true negative results) (Dreesen et al, 2008; Goossens et al, 2008b; Dreesen et al, 2014). Dreesen et al (2008) expressed the diagnostic value by positive and negative predictive values. The

positive predictive value was defined as the proportion of PGD analysis that predicted embryos correctly as affected/aberrant, and the negative predictive value was defined as the proportion of PGD analysis that predicted embryos correctly as unaffected. Goossens et al (2008b) defined the success of diagnosis (termed diagnostic efficiency in their publication) using PCR and PGD-FISH methods as the number of embryos with a (diagnostic) result per number of embryos biopsied.

## C.6. Systematic overview of the results

### C.6.1. PICO 1

There were no studies that compared the safety and clinical effectiveness of PGD to prenatal diagnosis in couples who achieved conception naturally or by IVF.

To determine the success rate of PGD, reproductive outcomes after PGD cycles specifically for single gene disorders and chromosomal abnormalities were collated from the ESHRE PGD Consortium (data from 1997 to December 2009). The biopsy methods used in the ESHRE data collections are shown in Table C.6.1. This shows that blastomere biopsy is the most utilised biopsy method internationally (83.3% in 2009), followed by polar body biopsy (16.3% in 2009). Therefore, the clinical outcomes derived from the ESHRE PGD Consortium may not be reflective of current Australian clinical practice. PGD studies that evaluated the success rate of PGD utilising blastocysts biopsied at Day 5-6 are discussed separately.

Table C.6.1 Biopsy methods used in the ESHRE PGD Consortium series

Study	Cycles	Polar body %	Blastomere <sup>a</sup> %	Blastocyst %	Polar body and cleavage %	Unknown %
Geraedts 1999	Jan 97 to Sep 98	0.0	100.0	0.0	0.0	0.0
Geraedts 2000	Up to May 00	2.4	97.6	0.0	0.0	0.0
Sermon 2002	Up to May 001	0.5	99.5	0.0	0.0	0.0
Sermon 2005	May 01 to Dec 01	3.0	93.0	0.0	0.0	4.0
Harper 2006	Jan 02 to Dec 02	6.1	93.0	0.0	0.0	0.0
Sermon 2007	Jan 03 to Dec 03	7.2	91.8	0.9	0.0	0.0
Harper 2008	Jan 04 to Dec 04	10.9	88.7	0.1	0.3	0.0
Goossens 2008	Jan 05 to Dec 05	9.9	89.1	0.8	0.1	0.0
Goossens 2009	Jan 06 to Dec 06	15.0	84.4	0.3	0.3	0.0
Harper 2010	Jan 07 to Dec 07	16.0	83.1	0.3	0.5	0.0
Goossens 2012	Jan 08 to Dec 08	15.9	83.5	0.2	0.3	0.0
Moutou 2014	Jan 09 to Dec 09	16.3	83.3	0.1	0.2	0.0

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening  
<sup>a</sup> Includes cleavage aspiration, cleavage extrusion and cleavage flow displacement

### PGD for structural chromosomal abnormalities

Table C.6.2 summarises the PGD cycles with oocyte retrieval (ORt) collected by the ESHRE PGD Consortium between 1997 and 2009 for chromosomal abnormalities. During the 12 years of data collection, there have been 5,910 cycles of PGD for inherited chromosomal abnormalities (including male and female Robertsonian carriers and male and female reciprocal carriers) that have reached the stage of oocyte collection.

Overall, 98.7% of available embryos were successfully biopsied. The clinical pregnancy rate (the presence of one or more fetal hearts at six weeks of gestation over the number of embryo transfer [ET] cycles) was 28%. The implantation rate (the number of fetal hearts per embryo transferred; reported for data collection V to XII only) was 21%. The delivery rate (number of pregnancies with delivery per ET cycle; reported for data collection VIII to XII only) was 26%. The miscarriage rate (the number of miscarriages per number of clinical pregnancies, minus the number of pregnancies that were lost to follow-up; for data collection VIII to XII only) was 11%. Overall, the number of PGD cycles performed for structural chromosomal abnormalities increased annually, but there were no marked changes in rates of diagnosis and clinical outcomes, such as clinical pregnancy and embryo implantation rates (Moutou et al. 2014). However, there were marginal improvements in the clinical outcomes reported in the three most recent reports (data collections X to XII).

Overall, there were 1,253 pregnancies conceived from 5,169 PGD cycles. Using this data, the average number of PGD cycles to achieve pregnancy is 4.1.

Table C.6.2 Summary of ESHRE Consortium data on PGD for chromosomal abnormalities, data collection I - XII

Study ID	PGD Consortium report number and period	Successfully biopsied embryos (% per biopsied)	Clinical pregnancy rate (% per ET cycle)	Implantation rate (% per ET)	Delivery rate (% per ET cycle)	Miscarriage rate (% per CP)	No. of PGD cycles to achieve chemical pregnancy
Geraedts 1999	I (January 1997-September 1998)	259/272 (95.2)	7/27 (25.9)	NR	NR	NR	NR
Geraedts 2000	II (May 2000 (1999+2000))	1393/1471 (94.7)	30/159 (18.9)	NR	NR	NR	NR
Sermon 2002	III (May 2001)	1308/1323 (98.9)	32/131 (24.4)	NR	NR	NR	NR
Sermon 2005	IV (May to December 2001)	2086/2122 (98.3)	45/237 (19.0)	NR	NR	NR	299/60 (5.0)
Harper 2006	V (January to December 2002)	2935/2977 (98.6)	66/283 (23.3)	79/556 (14.2)	NR	NR	400/87 (4.6)
Sermon 2007	VI (January to December 2003)	2801/2833 (98.9)	67/282 (23.8)	76/499 (15.2)	NR	NR	419/85 (4.9)
Harper 2008	VII (January to December 2004)	3745/3769 (99.4)	90/359 (25.1)	115/614 (18.7)	NR	NR	512/109 (4.7)
Goossens 2008	VIII (January to December 2005)	3299/3342 (98.7)	94/328 (28.7)	122/540 (22.6)	81/328 (24.7)	12/93 (12.9)	492/121 (4.1)
Goossens 2009	IX (January to December 2006)	5015/5062 (99.1)	141/493 (28.6)	178/821 (21.7)	126/493 (25.6)	14/140 (10.0)	760/174 (4.4)
Harper 2010	X (January to December 2007)	3902/3947 (98.9)	152/450 (33.8)	176/681 (25.8)	120/450 (26.7)	18/138 (13.0)	698/184 (3.8)
Goossens 2012	XI (January to December 2008)	4452/4513 (98.6)	151/488 (30.9)	180/762 (23.6)	133/488 (27.3)	13/146 (8.9)	738/194 (3.8)
Moutou 2014	XII (January to December 2009)	5122/5176 (99.0)	187/572 (32.7)	218/891 (24.5)	150/572 (26.2)	19/169 (11.2)	851/239 (3.6)
<b>Cumulative data</b>	<b>I-XII</b>	<b>36317/36807 (98.7)</b>	<b>1062/3809 (27.9)</b>	<b>1144/5364 (21.3)</b>	<b>610/2331 (26.2)</b>	<b>76/686 (11.1)</b>	<b>5169/1253 (4.1)</b>

Abbreviations: CP, clinical pregnancy; ESHRE, European Society of Human Reproduction and Embryology; ET, embryo transfer; PGD, preimplantation genetic diagnosis.

Note: PGD for chromosomal abnormalities includes Robertsonian translocation (male and female carrier), reciprocal translocation (male and female carrier), sex chromosome aneuploidy, deletion, and inversion

Clinical pregnancy is 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 embryo transferred. Delivery rate is defined as the number of pregnancies with delivery per ET procedure. Miscarriage rate is defined as the number of miscarriages per number of clinical pregnancies minus the number of pregnancies that were lost to follow-up. Number of PGD cycles to pregnancy is defined as the number of PGD cycles to achieve a chemical pregnancy (hCG positive)

## **PGD for single gene disorders**

Table C.6.3 summarises the PGD cycles with OR collected by the ESHRE PGD Consortium between 1997 and 2009 for single gene disorders.

Overall, 98.8% of available embryos were successfully biopsied. The clinical pregnancy rate was 29% per ET, while the implantation rate was 21%. The delivery rate was 26%. Similar to chromosomal abnormalities, the miscarriage rate was 11%. Overall, the number of PGD cycles performed for single gene disorders increased annually; however, there were no marked changes with respect to the progress in the clinical outcomes, such as clinical pregnancy and embryo implantation rates (Moutou et al, 2014). However, there were marginal improvements in the clinical outcomes reported in the three most recent reports (data collections X to XII). Further, PGD for single gene disorders shows similar clinical outcomes compared with testing for chromosomal abnormalities.

Overall, there were 2,094 pregnancies conceived from 6,826 PGD cycles. Using this data, the average number of PGD cycles to achieve pregnancy is 3.3.

Table C.6.3 Summary of ESHRE Consortium data on PGD for single gene disorders, data collection I - XII

Study ID	PGD Consortium report number and period	Successfully biopsied embryos (% per biopsied)	Clinical pregnancy rate (% per ET cycle)	Implantation rate (% per ET)	Delivery rate (% per ET cycle)	Miscarriage rate (% per CP)	No. of PGD cycles to achieve chemical pregnancy
Geraedts 1999	I (January 1997-September 1998)	717/731 (98.1)	24/103 (23.3)	NR	NR	NR	NR
Geraedts 2000	II (May 2000 (1999+2000))	2331/2389 (97.6)	83/318 (26.1)	NR	NR	NR	NR
Sermon 2002	III (May 2001)	1123/1131 (99.3)	36/161 (22.4)	NR	NR	NR	NR
Sermon 2005	IV (May to December 2001)	1271/1286 (98.8)	47/181 (26.0)	NR	NR	NR	206/59 (3.5)
Harper 2006	V (January to December 2002)	1631/1654 (98.6)	63/228 (27.6)	73/436 (16.7)	NR	NR	283/82 (3.5)
Sermon 2007	VI (January to December 2003)	2595/2648 (98.0)	90/335 (26.9)	114/667 (17.1)	NR	NR	418/121 (3.5)
Harper et al 2008	VII (January to December 2004)	3011/3021 (99.7)	103/402 (25.6)	128/781 (16.4)	NR	NR	498/134 (3.7)
Goossens 2008	VIII (January to December 2005)	2808/2871 (97.8)	109/405 (26.9)	145/715 (20.3)	95/405 (23)	9/104 (8.7)	494/156 (3.2)
Goossens 2009	IX (January to December 2006)	5306/5342 (99.3)	237/724 (32.7)	300/1336 (22.5)	212/724 (29)	23/235 (9.8)	879/291 (3.0)
Harper 2010	X (January to December 2007)	7495/7568 (99.0)	298/952 (31.3)	366/1660 (22.0)	253/952 (27)	37/290 (12.8)	1182/374 (3.2)
Goossens 2012	XI (January to December 2008)	8070/8163 (98.9%)	321/1031 (31.1)	390/1758 (22.2)	269/1031 (26)	26/293 (8.9)	1301/414 (3.1)
Moutou 2014	XII (January to December 2009)	10193/10317 (98.8)	368/1221 (30.1)	439/2061 (21.3)	304/1221 (25)	48/352 (13.6)	1565/463 (3.4)
Cumulative data	I-XII	46551/47124 (98.8)	1779/6061 (29.4)	1955/9414 (20.8)	1133/6061 (26)	143/1274 (11.2)	6826/2094 (3.3)

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; ET, embryo transfer; PGD, preimplantation genetic diagnosis.

Note: PGD cycles performed for single gene disorders using PCR include autosomal recessive, autosomal dominant, and specific sex-linked disorders.

Clinical pregnancy is 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. Miscarriage rate is defined as the number of miscarriages per number of clinical pregnancies minus the number of pregnancies that were lost to follow-up. Number of PGD cycles to pregnancy is defined as the number of PGD cycles to achieve a chemical pregnancy (hCG positive).



Table C.6.4 summarises the PGD cycles with OR collected for data collection I to XII for all PGD and PGS cycles.

Overall, 98.9% of available embryos were successfully biopsied. The clinical pregnancy rate was 28%, the implantation rate was 20%, the delivery rate was 22% per ET, and the miscarriage rate was 13%.

There were approximately 7,506 PGD live births, with a live birth rate of 26% per ET. The ESHRE data does not provide separate data on the number of live births that were from single gene PGD and from PGD for aneuploidy testing (PGS).

Overall, there were 3,701 pregnancies conceived from 13,387 PGD cycles (excluding PGS and social sexing). Using this data, the average number of PGD cycles to achieve pregnancy is 3.6.

Compared with earlier years, data collection XII indicates that there was a marginal increase in clinical pregnancy rates, implantation rates and delivery rates over time, particularly in the most recent four years of data collection (data collections IX to XII).

Table C.6.4 Summary of ESHRE Consortium data on overall PGD and PGS cycles, data collection I-XII

Study ID	ESHRE report number and period	Successfully biopsied embryos (% per biopsied)	Clinical pregnancy rate (% per ET cycle)	Implantation rate (% per ET)	Delivery rate (% per ET cycle)	Miscarriage rate (% per CP)	Live birth rate (% per ET cycle)	No. of PGD cycles to chemical pregnancy (no PGS)
Geraedts 1999	I (January 1997-September 1998)	2330/2395 (97.3)	67/306 (21.9)	NR	63/306 (20.6)	NR	79/306 (25.8)	NR
Geraedts 2000	II (May 2000 (1999+2000))	7991/8218 (97.2)	284/1007 (28.2)	NR	123/1007 (12.2)	NR	162/1007 (16.1)	NR
Sermon 2002	III (May 2001)	5688/5748 (99.0)	175/663 (26.4)	NR	215/663 (32.4)	NR	279/663 (42.1)	413/107 (3.9)
Sermon 2005	IV (May to December 2001)	9918/10167 (97.6)	298/1266 (23.5)	NR	236/1266 (18.6)	38/285 (13.3)	293/1266 (23.1)	610/141 (4.3)
Harper 2006	V (January to December 2002)	12158/12300 (98.8)	365/1510 (24.2)	455/2842 (16.0)	325/1510 (21.5)	36/358 (10.1)	382/1510 (25.3)	793/198 (4.0)
Sermon 2007	VI (January to December 2003)	16030/16228 (98.8)	511/2039 (25.1)	628/3695 (17.0)	373/2039 (18.3)	49/485 (10.1)	441/2039 (21.6)	958/237 (4.0)
Harper 2008	VII (January to December 2004)	19430/19636 (99.0)	604/2386 (25.3)	749/4248 (17.6)	456/2386 (19.1)	50/586 (8.5)	557/2386 (23.3)	1107/269 (4.1)
Goossens 2008	VIII (January to December 2005)	19600/19813 (98.9)	663/2508 (26.4)	857/4246 (20.2)	558/2508 (22.2)	68/626 (10.9)	670/2508 (26.7)	1089/311 (3.5)
Goossens 2009	IX (January to December 2006)	31731/32004 (99.1)	1210/4216 (28.7)	1522/7283 (20.9)	993/4216 (23.6)	162/1177 (13.8)	1183/4216 (28.1)	1768/497 (3.6)
Harper 2010	X (January to December 2007)	31520/31867 (98.9)	1276/4199 (30.4)	1571/7183 (21.9)	995/4199 (23.7)	153/1148 (13.3)	1206/4199 (28.7)	1989/583 (3.4)
Goossens 2012	XI (January to December 2008)	30264/30541 (99.1)	1200/4006 (30.0)	1480/6665 (22.2)	969/4006 (24.2)	167/1119 (14.9)	1016/4006 (25.4)	2136/627 (3.4)
Moutou 2014	XII (January to December 2009)	35049/35294 (99.3)	1417/4519 (31.4)	1718/7618 (22.6)	1080/4519 (23.9)	193/1273 (15.2)	1238/4519 (27.4)	2524/731 (3.5)
Cumulative data	I-XII	221709/224211 (98.9)	8070/28625 (28.2)	8980/43780 (20.5)	6386/28625 (22.3)	916/7057 (13.0)	7506/28625 (26.2)	13387/3701 (3.6)

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; ET, embryo transfer; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening

Note: 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. 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. 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 data, further data on clinical outcomes after PGD were extracted from the included systematic review and additional 20 identified studies including > 200 cycles.

Franssen et al (2011) conducted a systematic review comparing the live birth rates and miscarriage rates after natural conception and after PGD, in couples with a history of two or more miscarriages and carrying a structural chromosome abnormality. Overall, four observational studies reporting on the reproductive outcome of 469 couples after natural conception and 21 case series reporting on the reproductive outcome of 126 couples after PGD were identified. Considering the poor quality and the heterogeneity of these studies, performing a meta-analysis was considered inappropriate. A summary of the results reported in the review is presented in Table C.6.5. After natural conception, live birth rate per couple varied between 33% and 60% (median 55%). After PGD, live birth rate per couple varied between 0% and 100% (median 31%). It was concluded that there is insufficient data to support the assumption that PGD improves the live birth rate in carrier couples with recurrent miscarriage (or recurrent pregnancy loss) compared with natural conception. The miscarriage rate ranged from 21% to 40% (median 34%) after natural conception and from 0% to 50% (median 0%) after PGD.

**Table C.6.5 Summary of results from the systematic review by Franssen et al (2011)**

	Median live birth rate % (range)	Median miscarriage rate % (range)
Natural conception	55.5 (33-60)	34 (21-40)
PGD	31 (0-100)	0 (0-50)

Source: Franssen et al (2011)

Abbreviation: PGD, preimplantation genetic diagnosis

Data on clinical outcome were extracted from the 20 additional included studies and summarised in Table C.6.6, Table C.6.7, and Table C.6.8. There was wide variability in the reporting of clinical outcomes and the number of PGD cycles and/or number of couples included. Studies were categorised into those reporting on clinical outcomes after overall PGD cycles (overall was described as per study, see Table C.6.6), single genetic disorders (cumulative or individual; see Table C.6.7), and chromosomal rearrangements (including translocations; see Table C.6.8).

As shown in Table C.6.6, clinical pregnancy rate per ET in the overall PGD studies varied between 27% and 51%; implantation rate ranged from 7% to 45%; delivery rate per ET ranged from 24% to 28% (excluding the study by Cieslak et al (1999) as 77% of pregnancies were ongoing). In addition, the miscarriage rate ranged from 6% to 25% and live birth rate per ET ranged from 28% to 39%.

Table C.6.6 Clinical outcome after PGD (overall) in the included studies

Study ID	Clinical pregnancy rate (% per ET cycle)	Implantation rate (% per ET)	Delivery rate (% per ET cycle)	Live birth rate (% per ET cycle)	Ongoing pregnancies (% per CP)	Miscarriage rate (% per CP)
Hamoda 2011 <sup>a</sup>	79/212 (37.3)	NR (35)	NR	NR	NR	NR
Verpoest 2009 <sup>b</sup>	611/1987 (30.7)	NR	481/1987 (24.2)	554/1987 (27.9%)	0 (0.0)	NR
Goossens 2008 <sup>c</sup>	ChP: 179/451 (39.7)	148/740 (20.0)	113/451 (25.1)	126/451 (27.9)	0 (0.0)	10/NR
McArthur 2008 <sup>d</sup>	79/155 (51.0)	80/177 (45.2)	NR	59/155 (38.1) <sup>i</sup>	NR	20/79 (25.3)
Feyereisen 2007 <sup>e</sup>	51/189 (27.0)	61/381 (16.0)	46/189 (24.3)	57/189 (30.2)	0 (0.0)	5/51 (9.8)
McArthur 2005 <sup>f</sup>	16/34 (47.1)	16/36 (44.4)	7/34 (20.6) <sup>e</sup>	7/34 (20.6)	8/16 (50.0)	1/16 (6.2)
Grace 2006 <sup>g</sup>	68/205 (33.2)	NR (7)	58/205 (28.3)	81 /205 (39.5)	0 (0.0)	12/68 (17.6)
Cieslak 1999 <sup>h</sup>	ChP: 62/186 (33.3)	88/600 (14.7)	13/186 (7.0)	NR	48/62 (77.4)	4/62 (6.5)

Abbreviations: CP, clinical pregnancy; ChP, Chemical pregnancy; ET, embryo transfer; NR, not reported; PGD, preimplantation genetic diagnosis

Clinical pregnancy rate is defined as the number of clinical pregnancies expressed per ET cycles. Chemical pregnancy is defined as a pregnancy where  $\beta$ hcg test is positive. Implantation rate is defined by the ratio between the number of gestational sacs with a fetal heartbeat and the total number of embryos transferred. Ongoing pregnancy is defined as a clinical pregnancy with a fetal heartbeat at >12 weeks of gestational age. Delivery rate is defined as the number of pregnancies with delivery per ET procedure. Miscarriage rate is defined as the number of miscarriages per number of clinical pregnancies.

a Overall included single gene disorders and chromosomal translocations

b Overall included genetic (50% and 25% inheritance), chromosomal translocations (Robertsonian and reciprocal), HLA typing, other chromosomal abnormalities, and PGS

c Overall included single gene disorders, chromosomal abnormalities, sexing, and aneuploidy

d Overall included single gene disorders, translocations (Robertsonian balanced reciprocal) and chromosomal inversions

e Overall included single gene disorders and translocation carriers (Robertsonian and reciprocal), X-linked disorders, and one case for a mitochondrial DNA disorder

f Overall included single gene disorder, unbalanced chromosome translocations, and aneuploidy

g Overall included single gene disorders (autosomal dominant, autosomal recessive), chromosomal rearrangements (Robertsonian, reciprocal, inversion, deletion, recurrent trisomy), and X-linked

h PGD overall, without specification of genetic category

i McArthur et al (2008), live birth also accounted for ongoing pregnancies

Goossens et al (2008) evaluated the embryonic outcomes after the biopsy of one or two cells in embryos of comparable quality initially, and demonstrated that embryo quality, as based on morphology, declined in vitro after the removal of two cells when compared with one. This finding could indicate that embryos become more stressed when two cells are removed, although additional detriment may also stem from culture conditions that are not yet up to par with those prevailing in the in vivo environment. The authors demonstrate that it is the quality of the embryos on Day 3 that predicts later (to Day 5 at least) developmental competence, rather than whether one or two cells were removed. The RCT further demonstrated that two-cell removal did not influence the implantation rate of transferred embryos, and the number of cells biopsied did not affect the availability or the transfer rates of blastocysts. Live birth rates also did not differ depending on the number of cells biopsied. In clinical terms, the trial showed that for every 33 cycles, one live birth is accrued with one- over two-cell biopsy (Goossens et al, 2008).

In the studies that reported on clinical outcome after PGD for single gene disorders (Table C.6.7), the clinical pregnancy rate varied between 24% and 51%; implantation rate ranged from 13% to 49%; and delivery rate ranged from 24% to 29%. In addition, the miscarriage rate ranged from 6% to 15% while the live birth rate ranged from 17% to 43%.

Table C.6.7 Clinical outcome after PGD for single gene disorders in the included studies

Study ID	Clinical pregnancy rate (% per ET cycle)	Implantation rate (% per ET)	Delivery rate (% per ET cycle)	Live birth rate (% per ET cycle)	Ongoing pregnancies (% per CP)	Miscarriage rate (% per CP)
Van Rij 2012a	84/310 (27.1)	94/511 (18.4)	77/310 (24.8)	90/310 (29)	NR	5/84 (5.9)
Ginsburg 2011b	NR	NR	NR	NR	NR	NR
Kuliev 2011c	ChP: 102/331 (30.8)	NR	NR	98/331 (29.6)	7/102 (6.9)	NR
Gutierrez-Mateo 2009	86/198 (43.4)	112/414 (27.1) <sup>d</sup>	56/198 (28.3)	73/198 (36.9%)	20/86 (23.3%)	8/86 (9.3%)
Verpoest 2009	235/765 (30.7)	NR	182/765 (23.8)	NR	NR	NR
McArthur 2008	58/113 (51.3)	59/121 (48.8)	NR	49/113 (43.4) <sup>e</sup>	NR <sup>e</sup>	9/58 (15.5)
Feyereisen 2007	15/62 (24.2)	19/129 (14.7)	NR	NR	0 (0.0%)	NR
Grifo 2007	NR (35.0)	NR (23.8)	38/158 (24.0)	48/158 (30.4)	2/NR	NR (12.0)
Fiorentino 2006	56/211 (26.5)	56/427 (13.1)	NR	35/211 (16.6)	9/56 (16.1)	6/56 (10.7)
Grace 2006	23/73 (31.5)	NR (28)	21/73 (28.8)	NR	0 (0.0)	NR
McArthur 2005	10/23 (43.5)	10/24 (41.7)	4/23 (17.4%)	4/23 (17.4)	5/10 (50.0)	1/10 (10.0)
Verlinsky 2004	142/466 (30.5)	NR	NR	108/466 (23.2)	NR	NR

Abbreviations: CP, clinical pregnancy; ET, embryo transfer; NR, not reported; PGD, preimplantation genetic diagnosis

Clinical pregnancy rate is defined as the number of clinical pregnancies expressed per ET cycles. Chemical pregnancy is defined as a pregnancy where  $\beta$ hcg test is positive. Implantation rate is defined by the ratio between the number of gestational sacs with a fetal heartbeat and the total number of embryos transferred. Ongoing pregnancy is defined as a clinical pregnancy with a fetal heartbeat at >12 weeks of gestational age. Delivery rate is defined as the number of pregnancies with delivery per ET procedure. Miscarriage rate is defined as the number of miscarriages per number of clinical pregnancies.

a Single gene disorder specifically for Huntington's disease

b The only relevant pregnancy outcome reported in this study was delivery rate per oocyte retrieval cycle

c Single gene disorder specifically for haemoglobinopathies

d Gutierrez-Mateo et al (2009), excluding 10 cycles with transfer without testing

e McArthur et al (2008), live birth also accounted for ongoing pregnancies

In the studies that reported on clinical outcome after PGD for chromosomal rearrangements (Table C.6.8), the clinical pregnancy rate varied between 27% and 72%; implantation rate ranged from 21% to 56%; and delivery rate ranged from 27% to 75%; In addition, the miscarriage rate ranged from 0 to 52% and the live birth rate per ET ranged from 23% to 75%. These results are largely consistent with the results shown in the systematic review by Franssen et al (2011).

Table C.6.8 Clinical outcome after PGD for chromosomal rearrangement in the included studies

Study ID	PGD	Clinical pregnancy rate (% per ET cycle)	Implantation rate (% per ET)	Delivery rate (% per ET cycle)	Live birth rate (% per ET cycle)	Ongoing pregnancies (% per CP)	Miscarriage rate (% per CP)
Tan 2013	SNP-PGD	70/97 (72.2)	79/140 (56.4)	14/70 (20.0)	14/70 (20.0)	48/70 (68.6)	8/70 (11.4)
	FISH-PGD	116/300 (38.7)	148/488 (30.3)	87/116 (75.0)	87/116 (75.0)	10/116 (8.6)	19/116 (16.4)
Keymolen 2012 <sup>a</sup>	FISH-PGD	40/150 (26.7)	NR	40/150 (26.7)	47/150 (31.3)	0 (0.0)	0/40 (0.0)
Ginsburg 2011 <sup>b</sup>	FISH-PGD	NR	NR	NR	NR	NR	NR
Fischer 2010	FISH-PGD	ChP: 69/176 (39.2)	NR	NR	NR	NR	9/69 (13.0)
Verpoest 2009	FISH-PGD	82/254 (32.3)	NR	72/254 (28.3)	NR	NR	NR
McArthur 2008	FISH-PGD	21/42 (50.0)	21/56 (37.5)	NR	10/42 (23.8) <sup>c</sup>	NR	11/21 (52.4)
Feyereisen 2007	FISH-PGD	25/80 (31.2)	31/148 (20.9)	NR	NR	0 (0.0)	NR
Grifo 2007	FISH-PGD	NR (66.7)	NR (46.7)	4/9 (44.4)	5/9 (55.6)	1/NR	NR (14.0)
Grace 2006	FISH-PGD	30/92 (32.6)	NR (25)	25/92 (27.2)	NR	0 (0.0)	NR
McArthur 2005	FISH-PGD	6/11 (54.5)	6/12 (50.0)	3/11 (27.3)	3/11 (27.3)	3/6 (50.0)	0 (0.0)
Verlinsky 2004	FISH-PGD	123/356 (34.6)	NR	NR	82/356 (23.0)	NR	NR

Abbreviations: CP, clinical pregnancy; ET, embryo transfer; FISH, fluorescence in situ hybridisation; NR, not reported; PGD, preimplantation genetic diagnosis; SNP, single nucleotide polymorphism

Clinical pregnancy rate is defined as the number of clinical pregnancies expressed per ET cycles. Chemical pregnancy is defined as a pregnancy where  $\beta$ hcg test is positive. Implantation rate is defined by the ratio between the number of gestational sacs with a fetal heartbeat and the total number of embryos transferred. Ongoing pregnancy is defined as a clinical pregnancy with a fetal heartbeat at >12 weeks of gestational age. Delivery rate is defined as the number of pregnancies with delivery per ET procedure. Miscarriage rate is defined as the number of miscarriages per number of clinical pregnancies.

<sup>a</sup> Reciprocal translocation cases only

<sup>b</sup> The only relevant pregnancy outcome reported in this study was delivery rate per oocyte retrieval cycle

<sup>c</sup> McArthur et al (2008), live birth also accounted for ongoing pregnancies

### Timeframe to success

Fischer et al (2010) reported that 69 pregnancies were conceived from 99 cycles in couples with reciprocal or Robertsonian translocations and three or more previous miscarriages. This results in an average of 1.4 cycles to achieve pregnancy (a timeframe of <3 months), compared to successful pregnancies that were achieved after 4-6 years in non-PGD cycles, as reported in the literature.

The study by Keymolen et al (2012) reported that, in couples who were carriers of reciprocal translocations, the median time between finishing the PGD work-up and the delivery of the couples' first PGD child was 15.0 months (range 11-76 months) for male carriers and 15.5 months (range 9-36 months) for female carriers.

According to the most recent data from the ESHRE reports, 239 pregnancies were conceived from 851 cycles in the chromosomal abnormalities cohort, and 463

pregnancies were conceived from 1,565 cycles in the single gene disorders cohort. Using this data, the average number of cycles to achieve pregnancy (defined as a positive  $\beta$ HCG) is 3.6 in the chromosomal abnormalities group and 3.4 in the single gene disorders groups (Moutou et al, 2014).

### **Blastocyst biopsy**

Studies reporting data on blastocyst biopsy were included in this assessment regardless of study size, because blastocyst biopsy is used exclusively by the Applicant. There were three studies that compared the clinical outcome after multiple-cell trophoctoderm biopsy for PGD from Day 5-6 blastocysts, with that of Day 3 cleavage-stage embryos (blastomere) (Kokkali et al, 2007; McArthur et al, 2008; Chang et al, 2013), and one small study that performed a blastocyst biopsy only (McArthur et al, 2005). It should be noted that these are all small studies; as such, the results should be interpreted keeping this in mind.

The clinical outcomes are presented in Table C.6.9. For single gene disorders, the clinical pregnancy rate per ET ranged from 51% to 66% utilising blastocysts biopsied on Day 5-6, which was higher than the rate when utilising blastomeres biopsied on Day 3 (range from 33% to 60%). Similarly, implantation rate ranged from 42% to 50% utilising blastocysts biopsied on Day 5-6, which was higher than the rate when utilising blastomeres biopsied on Day 3 (range from 16% to 27%). The effect of cleavage-stage biopsy versus a multiple-cell trophoctoderm biopsy on miscarriage rate remains inconclusive. Comparison of data presented in Table C.6.9 to ESHRE's most recent publication for single gene disorders (Moutou et al, 2014)(see Table C.6.3) suggests that clinical outcome results after a blastocyst biopsy may be better than the clinical outcome where a blastomere biopsy is performed, as was the case for the majority of ESHRE PGD cycles (refer to Table C.6.3, clinical pregnancy rate of 30% and implantation rate of 21% (Moutou et al, 2014)).

For translocations, the clinical pregnancy rate ranged from 50% to 54% using blastocysts biopsied on Day 5-6, which is higher than the rate achieved using blastomeres biopsied on Day 3 (36% reported in a single study). Similarly, implantation rate ranged from 37% to 42% using blastocysts biopsied on Day 5-6, which is higher than the rate achieved using blastocysts biopsied on Day 3 (25% from a single study).

A relatively high miscarriage rate (52%) in the translocation group was reported in the study by McArthur et al (2008). This may be attributed to the inclusion of couples who have experienced recurrent pregnancy loss; however, patient characteristics were not described by the authors. The systematic review by Franssen et al (2011) reported that the miscarriage rate ranged from 0% to 50% after PGD in couples with recurrent miscarriage carrying a structural chromosome abnormality.

Overall, the trophoctoderm biopsy (blastocyst) transfers resulted in a higher clinical pregnancy rate and implantation rate than the cleavage-stage biopsy (blastomere) transfers for single gene disorders and chromosomal translocations. However, these findings are based on low level evidence of small study size and thus should be interpreted with caution.

Table C.6.9 Summary of results of PGD in studies that performed a blastocyst biopsy

Study	PGD	Clinical pregnancy rate (% per ET cycle)	Implantation rate (% per ET)	Delivery rate (% per ET cycle)	Live birth rate (% per ET cycle)	Ongoing pregnancies (% per CP)
Chang 2013 <sup>a</sup>	Genetic (Day 5 biopsy)	25/38 (65.8)	32/64 (50.0)	24/38 (63.2)	29/38 (76.3)	NR
	Genetic (Day 3 biopsy)	5/15 (33.3)	5/31 (16.1)	NR	NR	NR
McArthur 2008 <sup>b</sup> ( <i>Sydney IVF</i> )	Genetic (Day 5 biopsy)	58/113 (51.3)	59/121 (48.8)	49/113 (43.4)	50/113 (44.2) <sup>d</sup>	9/58 (15.5)
	Genetic (Day 3 biopsy)	24/69 (34.8)	27/103 (26.2)	18/69 (26.1)	22/69 (31.9) <sup>d</sup>	5/24 (20.8)
	Translocation (Day 5 biopsy)	21/42 (50.0)	21/56 (37.5)	10/42(23.8)	11/42 (26.2) <sup>d</sup>	11/21 (52.4)
	Translocation (Day 3 biopsy)	14/39 (35.9)	14/55 (25.5)	10/39 (25.6)	10/39 (25.6) <sup>d</sup>	4/14 (28.6)
Kokkali 2007 <sup>c</sup>	B-thalassaemia (Day 5 biopsy)	NR (ChP: 6/10 (60.0))	10/21 (47.6)	5/10 (50.0)	7/10 (70.0)	1/6 (16.7)
	B-thalassaemia (Day 3 biopsy)	NR (ChP: 6/10 (60.0))	8/30 (26.7)	4/10 (40.0)	5/10 (50.0)	0/6 (0.0)
McArthur 2005 <sup>b</sup> ( <i>Sydney IVF</i> )	Genetic (Day 5 biopsy)	10/23 (43.5)	10/24 (41.7)	4/23 (17.4)	4/23 (17.4)	1/10 (10)
	Translocation (Day 5 biopsy)	6/11 (54.5)	6/12 (50.0)	3/11 (27.3)	3/11 (27.3)	0 (0.0)

Abbreviations: CP, clinical pregnancy; ChP, chemical pregnancy; ET, embryo transfer; NR, not reported; PGD, preimplantation genetic diagnosis

Clinical pregnancy rate is defined as the number of clinical pregnancies expressed per ET cycles. Chemical pregnancy is defined as a pregnancy where  $\beta$ hcg test is positive. Implantation rate is defined by the ratio between the number of gestational sacs with a fetal heartbeat and the total number of embryos transferred. Ongoing pregnancy is defined as a clinical pregnancy with a fetal heartbeat at >12 weeks of gestational age. Delivery rate is defined as the number of pregnancies with delivery per ET procedure. Miscarriage rate is defined as the number of miscarriages per number of clinical pregnancies.

a Frozen embryos were used for transfer with Day 5 biopsy, fresh embryos were used for transfer with Day 3 biopsy

b The analysis was restricted to embryos that were transferred fresh during the egg retrieval cycle and excluded subsequent pregnancies from additional diagnosed blastocysts that had been cryostored.

c Only the first cycle for each couple was included in the study

d McArthur et al (2008), live birth also accounted for ongoing pregnancies

### C.6.2. PICO 2

Twenty six studies provide data to assess the impact of PGD on neonates and children: two studies provide level II evidence in which different biopsy techniques are compared, seven studies provide Level III evidence in which PGD  $\pm$  PGS is compared with ICSI or natural conception, and 17 studies provide level IV non-comparative evidence for PGD  $\pm$  PGS. It should be noted that the level IV evidence has been included because it largely comes from the ESHRE PGD Consortium data collection which is provided by PGD centres all over the world, including centres in Australia.

Due to the non-randomised nature of Level III comparative evidence, it is important to interpret the results of these studies with caution. As there are likely to be non-random differences between conception groups, data that has a matched control group or has been adjusted for potential confounders are more likely to be reasonably robust. One particular confounder for the data on developmental delay is the presence of twins and triplets in the cohorts. Twins and triplets are more likely to be premature and have a low birth weight; both of which have been linked with developmental delay.



## Perinatal mortality

Two RCTs were identified that assessed the effect of different biopsy techniques on perinatal mortality, as shown in Table C.6.10.

Goossens et al (2008b) randomised 592 ICSI cycles to blastomere biopsy with either one or two cells; there was no difference in rates of perinatal mortality between biopsy arms. Kokkali et al (2007) randomised 20 cycles to either blastocyst biopsy (Day 5) or blastomere biopsy (Day 3) followed by blastocyst transfer. There was no perinatal mortality in either arm in this small study.

Table C.6.10 Perinatal mortality following PGD – Level II evidence

Goossens 2008	PGD – 1 cell blastomere biopsy n/N (%)	PGD – 2 cell blastomere biopsy n/N (%)
Stillborn	2/68 (2.9)	2/61 (3.3)
Neonatal death	1/66 (1.5)	0/59 (0)
Perinatal death	3/68 (4.4)	2/61 (3.3)
Kokkali 2007	PGD – blastocyst biopsy n/N (%)	PGD – blastomere biopsy n/N (%)
Stillborn	0/5 (0)	0/7 (0)
Neonatal death	0/5 (0)	0/7 (0)
Perinatal death	0/5 (0)	0/7 (0)

Abbreviations: PGD, preimplantation genetic diagnosis

The assessment of perinatal mortality following PGD in the comparative Level III studies is presented in Table C.6.11. Two studies provided comparative evidence against ICSI alone (not limited to ICSI in patients carrying a severe genetic disorder at risk of passing it on to their offspring). The PGD groups from both studies are from the same Belgian cohort (Liebaers et al (2010) collected data from 1992 to 2005, while Desmyttere et al (2012) collected data from 1994 to 2005). However, the control groups used in these two studies differ: Liebaers et al (2010) used a historical control group while Desmyttere et al (2012) uses a concurrent control group. Due to the overlap in the population included in these two studies, the results have not been pooled.

In a univariate analysis comparing total perinatal deaths in PGD/PGS children compared with ICSI alone children, Desmyttere et al (2012) showed no statistically significant difference ( $P=0.42$ ). 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 (OR 1.63; 95% CI 0.89, 2.99) compared with singleton births (OR 0.60; 95% CI 0.23, 1.42).

In Liebaers et al (2010), perinatal mortality was significantly greater for PGD/PGS children compared with ICSI alone children (OR 2.56; 95% CI 1.54, 4.18). However, after stratifying by number per birth, no increased risk was seen in singleton births (OR 0.83; 95% CI 0.28, 2.44) and a very high risk was seen for multiple births (OR 5.09; 95% CI 2.80, 9.90). The results of this analysis should be interpreted with caution given the analyses were not adjusted for other potential confounders.

Table C.6.11 Perinatal mortality following PGD – Level III evidence

	PGD n/N (%)	PGD/PGS n/N (%)	ICSI n/N (%)	Risk Estimate (95% CI) [P value]
<i>Stillbirth</i>				
Desmyttere 2012	NR <sup>a</sup>	27/1022 (2.6)	35/1542 (2.3)	NR
Liebaers 2010	11/311 (3.5)	18/581 (3.1)	49/2889 (1.7)	NR
<i>Neonatal death</i>				
Desmyttere 2012	NR <sup>a</sup>	9/995 (0.9)	10/1507 (0.7)	NR
Liebaers 2010	5/300 (1.7)	9/563 (1.6)	5/2840 (0.2)	NR
<i>Perinatal death</i>				
Desmyttere 2012	NR <sup>a</sup>	36/1022 (3.5)	45/1542 (2.9)	[0.42] <sup>b</sup> S: OR 0.60 (0.23, 1.42) <sup>c</sup> M: OR 1.63 (0.89, 2.99) <sup>c</sup>
Liebaers 2010	16/311 (5.1)	27/581 (4.6)	54/2889 (1.9)	OR 2.56 (1.54, 4.18) <sup>d</sup> S: OR 0.83 (0.28, 2.44) <sup>d</sup> M: OR 5.09 (2.80, 9.90) <sup>d</sup>

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

<sup>a</sup> Publication states no difference seen between PGD and PGS so results combined

<sup>b</sup> Univariate analysis

<sup>c</sup> Multivariate analyses adjusted for maternal age, pre-pregnancy BMI, parity, nicotine abuse, intake of alcohol and complications during pregnancy

<sup>d</sup> No details on whether these analyses are univariate or multivariate have been provided in the publication

The assessment of perinatal mortality following PGD in the level IV studies is presented in Table C.6.12. The majority of included studies were part of the ESHRE PGD Consortium series and provided data on stillbirths and neonatal deaths for PDG and PGS combined. Data has been pooled for the period May 2001 to December 2009 only because it is unclear if data from January 1997 to April 2001 is mutually exclusive.

Over the last nine years of data collection, the stillbirth rate (based on available data) averages 1.1% per year and ranges from 0% to 3.5%. The highest rate was seen in the second-last year of data collection; there is no discussion in the publication regarding why so many stillbirths were seen that year. The rate of neonatal death ranges from 0.2% to 1.1% from 2001 to 2009, with an average of 0.7% per year. The stillbirth rate in these studies is lower than that seen for PGD/PGS in the Belgian cohort and the perinatal death rate is similar to that seen in the Belgian cohort.

Three additional studies provided level IV data on perinatal mortality. De Rademaeker et al (2009) showed no perinatal mortality in 49 children born to parents at risk of passing on myotonic dystrophy type 1. Grace et al (2006) assessed perinatal mortality following PGD cycles for chromosome rearrangements (N=172), single gene disorders (N=96) and X-linked disorders (N=62). Two of the 83 babies that were born did not survive, although the timing of their deaths is not reported and so they may not be considered neonatal deaths. An additional study provided data on neonatal deaths following PGD/PGS using polar body biopsy (Strom et al, 2000). Of 80 singleton-only pregnancies, one resulted in a neonatal death.

Table C.6.12 Perinatal mortality following PGD – Level IV evidence

Study	Cycles	Follow-up	Stillbirths PGD/PGS n/N (%) <sup>a</sup>	Neonatal deaths PGD/PGS n/N (%) <sup>a</sup>
<i>ESHRE</i>				
	-	-	-	-
Geraedts 1999	Jan 1997 to Sep 1998	NR	0/73 (0)	2/73 (2.7)
Geraedts 2000	Up to May 2000	NR	0/130 (0)	3/130 (2.3)
Sermon 2002	Up to May 2001	NR	0/180 (0)	3/180 (1.7)
Sermon 2005	May 2001 to Dec 2001	NR	3/217 (1.4)	1/214 (0.5)
Harper 2006	Jan 2002 to Dec 2002	Oct 2003	4/382 (1.0)	2/378 (0.5)
Sermon 2007	Jan 2003 to Dec 2003	Oct 2004	1/441 (0.2)	1/440 (0.2)
Harper 2008	Jan 2004 to Dec 2004	Oct 2005	0/444 (0)	3/444 (0.7)
Goossens 2008	Jan 2005 to Dec 2005	Oct 2006	1/574 (0.2) <sup>c</sup>	5/573 (0.9)
Goossens 2009	Jan 2006 to Dec 2006	Oct 2007	4/988 (0.4)	5/984 (0.5)
Harper 2010	Jan 2007 to Dec 2007	Oct 2008	5/735 (0.7) <sup>b</sup>	8/730 (1.1)
Goossens 2012	Jan 2008 to Dec 2008	Oct 2009	28/811 (3.5)	3/783 (0.4)
Moutou 2014	Jan 2009 to Dec 2009	Oct 2010	13/863 (1.5)	8/850 (0.9)
Pooled	May 2001 to Dec 2008	-	59/5455 (1.1)	36/5414 (0.7)
<i>Other</i>				
	-	-	-	-
De Rademaeker 2009	1992 to 2005	NA	0/49 (0)	0/49 (0)
Grace 2006	1997 to 2005	NA	0/83 (0)	2/83 (2.4) <sup>d</sup>
Strom 2000	NR	NA	-	1/80 (1.3)

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; NA, not applicable; NR, not reported; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening

<sup>a</sup> Denominator for stillbirths is all births with neonatal complication data available; denominator for neonatal deaths is all births with neonatal complication data available minus the number of still births

<sup>b</sup> 'Intrauterine death cause unknown' classified as stillbirth

<sup>c</sup> 'mors in utero' classified as stillbirth

<sup>d</sup> Two of the 83 babies born did not survive: one was lost due to prematurity and one died due to misdiagnosis in a case of spinal muscular atrophy. These have both been included as neonatal deaths above but may not have been depending on timing.

## Physical disability

No included studies specifically assessed physical disability in terms of its presence or absence. However, data were available regarding major malformations present at birth.

The assessment of major malformations following PGD in the comparative Level III studies is presented in Table C.6.13. Three studies provided comparative evidence against ICSI (Desmyttere et al, 2009; Liebaers et al, 2010; Desmyttere et al, 2012); one of these studies also included natural conception as a comparator (Desmyttere et al, 2009). An additional study compared malformations in children conceived through PGD/PGS versus natural conception (Banerjee et al, 2008).

The PGD groups from the initial three studies are from the same Belgian cohort: Desmyttere et al (2009) collected data from 2005 to 2007; Liebaers et al (2010) collected data from 1992 to 2005; Desmyttere et al (2012) collected data from 1994 to 2005. As previously mentioned, the control groups used in these studies differ: Liebaers et al (2010) used a historical control group while Desmyttere et al (2009 and 2012) used a concurrent control group. Due to the overlap in the population included in these studies, the results have not been pooled. Major malformations were defined as malformations that cause functional impairment and/or require surgical correction.

Similar rates of major malformations were seen in the PGD/PGS group across the three studies. The multivariate adjusted analyses conducted by Liebaers et al (2010) showed no significant increase in risk of major malformations associated with PGD/PGS compared with ICSI. A similar result was seen for the study by Desmyttere et al (2012), although the method of analysis is unknown. No analysis was conducted for the Desmyttere et al (2009) study but there were very few major malformations and no apparent differences between groups.

In the study by Banerjee et al (2008), a greater proportion of children conceived via PGD had major malformations compared with children conceived via natural conception. However, this result is based on a very small number of children and should be interpreted with caution.

Table C.6.13 Major malformations in live born children following PGD – Level III evidence

Study	PGD n/N (%)	PGD/PGS n/N (%)	ICSI n/N (%)	NC n/N (%)	Risk Estimate (95% CI) [P value]
<i>Belgian cohort</i>					
Desmyttere 2012	NR <sup>a</sup>	23/995 (2.3)	40/1507 (2.7)	-	OR 0.87 (0.49, 1.50) <sup>b</sup>
Liebaers 2010	NR <sup>a</sup>	12/563 (2.1)	96/2840 (3.4)	-	OR 0.62 (0.31, 1.15) <sup>c</sup>
Desmyttere 2009	-	2/70 (2.9)	1/70 (1.4)	2/70 (2.9)	NR
<i>Other</i>					
Banerjee 2008	-	2/49 (4.1)	-	0/66 (0)	NR

Abbreviations: ICSI, intracytoplasmic sperm injection; M, multiple births; NC, natural conception; OR, odds ratio; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening; S, singleton birth

<sup>a</sup> Publication states no difference seen between PGD and PGS so results combined

<sup>b</sup> Multivariable analyses adjusted for maternal age, pre-pregnancy BMI, parity, nicotine abuse, intake of alcohol and complications during pregnancy

<sup>c</sup> No details on whether these analyses are univariate or multivariate have been provided in the publication

The assessment of major malformations following PGD in the level IV studies is presented in Table C.6.14. The majority of included studies were part of the ESHRE PGD Consortium series and provided data on malformations for PDG and PGS combined. Data has been pooled for the period from May 2001 to December 2009 only, because it is unclear if data from January 1997 to April 2001 is mutually exclusive.

Over the last nine years of data collection, the average rate of malformations per child (based on available data) is 0.019 and ranges from 0.012 to 0.033. The highest rates were seen in the earlier years of data collection. It is possible that improved PGD/PGS technique may have resulted in a reduction in the number of major malformations over time. Analysis of the biopsy methods used in each of the series shows a reduction in blastomere biopsy from 1997/1998 to 2009, and an increase in polar body biopsy from 1997/1998 to 2009 (Table C.6.1).

Two additional studies provided level IV evidence of malformations: De Rademaker et al (2009) reported no major malformations out of 49 children born, while Strom et al (2000) reported two major malformations out of 109 births using polar body biopsy for PGD/PGS.

The proportion of children with major malformations following PGD/PGS is similar between the Level III comparative studies and the level IV studies.

Table C.6.14 Major malformations in live and stillborn children following PGD – Level IV evidence

Study	Cycles	Follow-up	PGD/PGS n/N (%) [malformations/birth]
<i>ESHRE</i>			
	-	-	
Geraedts 1999	Jan 1997 to Sep 1998	NR	NR <sup>d</sup>
Geraedts 2000	Up to May 2000	NR	NR <sup>c</sup>
Sermon 2002	Up to May 2001	NR	7/180 (3.9) [0.039]
Sermon 2005	May 2001 to Dec 2001	NR	7/211 <sup>b</sup> (3.3) [0.033]
Harper 2006	Jan 2002 to Dec 2002	Oct 2003	10/357 <sup>b</sup> (2.8) [0.028]
Sermon 2007	Jan 2003 to Dec 2003	Oct 2004	11/426 <sup>b</sup> (2.6) [0.026]
Harper 2008	Jan 2004 to Dec 2004	Oct 2005	6/484 <sup>b</sup> (1.2) [0.012]
Goossens 2008	Jan 2005 to Dec 2005	Oct 2006	10/588 <sup>b</sup> (1.7) [0.017]
Goossens 2009	Jan 2006 to Dec 2006	Oct 2007	17/1016 <sup>a</sup> [0.017]
Harper 2010	Jan 2007 to Dec 2007	Oct 2008	16/718 <sup>a</sup> [0.022]
Goossens 2012	Jan 2008 to Dec 2008	Oct 2009	14/811 <sup>a</sup> [0.017]
Moutou 2014	Jan 2009 to Dec 2009	Oct 2010	11/863 [0.013]
Pooled	May 2001 to Dec 2009	-	102/5474 [0.019]
<i>Other</i>			
	-	-	-
De Rademaeker 2009	1992 to 2005	NA	0/49 (0)
Strom 2000	NR	NA	2/109 (1.8)

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

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

b One malformation per baby

c Data not formally separated into major and minor malformations. Nine malformations in total – two babies died due to severe malformations.

d Data not formally separated into major and minor malformations. Two malformations in total – one baby died due to exencephaly.

### Intellectual disability

No included studies specifically assessed intellectual disability.

### Developmental delay

Four comparative studies provided Level III evidence on developmental delay in children born following PGD/PGS (Banerjee et al, 2008; Nekkebroeck et al. 2008a; 2006b; Winter et al, 2014). Three of the studies were conducted on children born in the Belgian cohort described previously. In Nekkebroeck et al (2008a and 2008b), data were collected between 2005 and 2007; in Winter et al (2014), data were collected between 2011 and 2013. Although not stated in the publication, it is possible that the Winter et al (2014) cohort includes some of the same children included in the Nekkebroeck et al (2008) cohort.

Banerjee et al (2008) used the Griffiths Scales of Mental Development to perform psychometric scoring on PGD/PGS children and a matched cohort of natural conception children with a mean age of 18 months. As shown in Table C.6.15, the locomotor subscale score was significantly lower in the PGD/PGS group compared with the natural conception group, while the hearing language subscale was significantly higher for the PGD/PGS group compared with the natural conception group. The authors made no comment on these specific findings, but noted overall that “the study

showed no major ill effects from PGD on the child health.” Other child-related outcomes from the Banerjee et al (2008) study included various subscales of the Toddler Temperament Questionnaire; there were no statistically significant differences between children conceived via PGD/PGS or natural conception for any of these subscales.

**Table C.6.15 Neurodevelopmental status following PGD – Level III evidence (Banerjee et al, 2008)**

Outcome	Age	PGD/PGS Mean ± SD [N] (%)	NC Mean ± SD [N] (%)	P value Univariate analysis
<i>Banerjee 2008</i>				
Griffiths MDS	Mean 18 mo			
Locomotor		101.0 ± 14.2 [49]	111.4 ± 14.4 [66]	0.0001
Personal social		100.3 ± 18.9 [49]	103.7 ± 16.6 [66]	NS
Hearing language		106.4 ± 15.1 [49]	99.9 ± 6.5 [66]	0.03
Eye-hand		100.7 ± 15.5 [49]	102.6 ± 16.3 [66]	NS
Performance		104.0 ± 16.5 [49]	100.8 ± 19.7 [66]	NS
Griffiths GQ		102.7 ± 13.1 [49]	103.3 ± 12.8 [66]	NS
TTQ	Mean 18 mo			
Activity		4.0 ± 0.7	4.0 ± 0.6	NS
Rhythmicity		2.7 ± 0.8	2.6 ± 0.7	NS
Approach		2.5 ± 0.9	2.8 ± 1.0	NS
Adaptability		2.9 ± 0.8	3.0 ± 0.8	NS
Intensity		3.7 ± 0.8	4.0 ± 0.7	NS
Mood		2.7 ± 0.6	2.9 ± 0.7	NS
Persistence		3.3 ± 1.0	3.4 ± 0.7	NS
Distractibility		3.6 ± 1.2	3.8 ± 0.9	NS
Threshold		3.7 ± 0.8	3.6 ± 0.8	NS

Abbreviations: MDS, Mental Development Scale; mo, months; NC, natural conception; NS, not statistically significant; PDI, Psychomotor Development Index; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening; SD, standard deviation; TTQ, Toddler Temperament Questionnaire; y, years

Nekkebroeck et al (2008a) used the Bayley Psychomotor Development Index (PDI) and the Mental Development Index (MDI) to measure psychomotor and mental development in children aged 21 to 33 months. The indices, with a mean value of 100 and a standard deviation of 15.0, were derived from the scores obtained on the Bayley psychomotor and mental scales: scores of 115 or more are indicative of accelerated performance; scores between 114 and 85 reflect a normal performance; scores between 84 and 70 reflect a mildly delayed performance; and scores of ≤ 69 reflect a significantly delayed performance. As shown in Table C.6.16, there was no difference in Bayley PDI or MDI scores between children born following PGD/PGS, ICSI or natural conception, either based on univariate analysis or multivariate analyses. In addition, similar proportions of children were classified as mildly delayed, normal or accelerated across the three groups. The authors conclude that “conception after embryo biopsy in the case of PGD and PGS has no impact on the mental and psychomotor development of 2-year old children when compared with ICSI and natural conception children.”

It should be noted that only singletons were included in this study due to the fact that prematurity and low birth weight are more common in multiple births and are linked to developmental outcome. This may limit the generalisability of these results to the broader population of children born following PGD, if this includes a substantial number of multiple births.

Table C.6.16 Mental and psychomotor development following PGD – Level III evidence (Nekkebroeck et al, 2008a)

Outcome	Age	PGD/PGS Mean ± SD [N] %	ICSI Mean ± SD [N] (%)	NC Mean ± SD [N] (%)	P value Uni- variate	P value Multi- variate
<i>Nekkebroeck 2008a</i>						
Bayley PDI	2 y	103.4 ± 9.91 [60]	101.8 ± 8.1 [66]	104.4 ± 8.4 [65]	0.224	NS <sup>a</sup>
Mildly delayed		3.3	1.5	1.5	0.886	
Normal		88.3	92.4	89.2		
Accelerated		8.3	6.1	9.2		
Bayley MDI	2 y	106.3 ± 10.1 [69]	105.7 ± 8.1 [69]	107.6 ± 7.5 [69]	0.433	NS <sup>a</sup>
Normal		85.5	85.5	87.0	0.961	
Accelerated		14.5	14.5	13.0		

Abbreviations: ICSI, intracytoplasmic sperm injection; MDI, Mental Development Index; NC, natural conception; NS, not statistically significant; PDI, Psychomotor Development Index; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening; SD, standard deviation; y, years

<sup>a</sup> Adjusted for age at assessment, educational level of fathers, age of the mothers at the birth of their child, age of the fathers at child assessment, employment percentage of mothers and fathers, gestational age, marital status, attendance at a day-care centre

Nekkebroeck et al (2008b) assessed socio-emotional and language development in the same group of children included in the cohort described in Nekkebroeck et al (2008a). Three scales were used to measure outcomes in the children: (i) the Child Behaviour Checklist (CBCL) which is used to measure emotional and behavioural problems; (ii) the Short Temperament Scale for Toddlers (STST) which is used to measure temperament; and (iii) the Dutch version of the McArthur Communicative Development Inventories which detects communications problems. As per the study by Nekkebroeck et al (2008a), only singleton children were included in this study.

The results of the analyses are shown in Table C.6.17. In the univariate analyses there was no difference in mean CBCL scores elicited from the mother or father between PGD/PGS, ICSI or natural conception. However, the multivariate analysis, adjusting for a number of potential confounders, showed that mothers in the PGD/PGS and ICSI groups reported fewer total problems than mothers in the natural conception group, while fathers in the ICSI group reported fewer total problems than fathers in the PGD/PGS and natural conception groups. Based on univariate analyses, there was no significant difference in mean temperament scores in children following PGD/PGS, ICSI or natural conception, as rated by mothers or fathers, nor were there any differences in the classification of children into easy, average or difficult temperament. Finally, there was no difference across groups in language comprehension or production scores, and the mean ages according to language comprehension and production were similar across groups. The authors concluded that “PGD/PGS conception does not adversely affect children’s socio-emotional and language development at age 2.”

Table C.6.17 Socio-emotional and language development following PGD – Level III evidence (Nekkebroeck et al, 2008b)

Outcome	Age	PGD/PGS Mean ± SD [N] (%)	ICSI Mean ± SD [N] (%)	NC Mean ± SD [N] (%)	P value Uni- variate <sup>a</sup>	P value Multi- variate <sup>b</sup>
<i>Nekkebroeck 2008b</i>						
CBCL Total – Mother Above threshold	2 y	46.8 ± 8.6 [38] 2.6	46.4 ± 8.9 [33] 6.1	50.0 ± 9.0 [53] 9.4	0.11	0.02
CBCL Total – Father Above threshold	2 y	46.2 ± 9.3 [29] 0	44.1 ± 9.0 [26] 3.8	47.9 ± 9.5 [34] 2.9	0.30	0.02
STST Total – Mother Easy Average Difficult	2 y	3.0 ± 0.5 [38] 21.1 76.3 2.6	2.9 ± 0.4 [34] 26.5 73.5 0	2.9 ± 0.6 [52] 40.3 55.8 3.8	0.11 0.21	-
STST Total – Father Easy Average Difficult	2 y	3.1 ± 0.6 [29] 17.2 75.9 6.9	2.9 ± 0.4 [26] 34.6 65.4 0	2.9 ± 0.6 [51] 29.4 49.2 1.9	0.30 0.28	-
Language comprehension Age	2 y	56.8 ± 30.7 [34] 27.0 ± 4.1 mo	53.6 ± 30.1 [33] 26.9 ± 3.7 mo	59.8 ± 29.3 [46] 27.4 ± 3.3 mo	0.66 0.82	-
Language production Age	2 y	49.0 ± 32.4 [34] 26.1 ± 4.3 mo	52.7 ± 28.4 [33] 27.5 ± 2.5 mo	53.1 ± 29.0 [46] 27.2 ± 2.7 mo	0.82 0.16	-

Abbreviations: CMCL, Child Behavioural Checklist; ICSI, intracytoplasmic sperm injection; mo, months; NC, natural conception; NS, not statistically significant; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening; SD, standard deviation; y, years

<sup>a</sup> The publication's description of the statistical methodology and the results table suggest that these analyses were not adjusted, however the text reports that these results were adjusted for potential confounders.

<sup>b</sup> Adjusted for gender, birth order, mother tongue, age at assessment, educational level of mothers and fathers, age of the mothers at the birth of their child, age of the fathers at child assessment, employment percentage of mothers and fathers, gestational age, birth weight, Apgar score, marital status, attendance at a day-care centre.

Winter et al (2014) used the Wechsler Preschool and Primary Scale of Intelligence III (WPSSI) and the Movement ABC (M ABC) scales to assess the cognitive and psychomotor development of 5 to 6 year olds following PGD, ICSI and natural conception. This is the only one of the included Level III studies which specifically assesses PGD only (i.e. without PGS). As shown in Table C.6.18, there was no significant difference between PGD and natural conception children in terms of intelligence. With regards to motor development, natural conception children performed best overall, and performed significantly better than ICSI children. While there were statistically significant differences across the three conception groups, the authors note that there was no significant difference between PGD children and either control group. They conclude that their study supports the safety of PGD, although they do point out the limited generalisability given the children were all Caucasian and singletons.



Table C.6.18 Physical and motor development following PGD – Level III evidence (Winter et al, 2014)

Outcome	Age	PGD only Mean ± SD [N]	ICSI Mean ± SD [N]	NC Mean ± SD [N]	P value Uni- variate analysis	P value Multi- variate analysis
<i>Winter 2014</i>						
WPSSI Full	5–6 y	117.2 ± 13.3 [47]	115.6 ± 14.4 [49]	118.9 ± 12.7 [48]	-	0.65 <sup>a</sup>
VIQ		116.8 ± 11.6	113.4 ± 13.0	115.6 ± 11.0	-	0.26 <sup>a</sup>
PIQ		115.6 ± 10.6	114.3 ± 14.1	114.3 ± 14.1	-	0.63 <sup>a</sup>
M ABC Total	5–6 y	7.51 ± 4.99 [47]	9.85 ± 5.21 [49]	7.03 ± 3.94 [48]	-	0.03 <sup>a</sup>
Manual dexterity		4.57 ± 3.04	5.19 ± 2.47	4.76 ± 2.30	-	0.87 <sup>a</sup>
Ball skill		1.17 ± 1.32	1.88 ± 2.03	1.14 ± 1.61	-	0.06 <sup>a</sup>
Balance skill		1.76 ± 2.49	2.87 ± 2.88	1.09 ± 1.63	-	0.004 <sup>a</sup>

Abbreviations: ICSI, intracytoplasmic sperm injection; M ABC, Motor ABC; mo, months; NC, natural conception; NS, not statistically significant; PGD, preimplantation genetic diagnosis; PIQ, Performance Intelligence Score; SD, standard deviation; VIQ, verbal intelligence score; y, years  
<sup>a</sup> Adjusted for gender, age, mother's age at birth and educational level of both mother and father

One study provided level IV data on mental and motor development (via the Developmental Quotient; DQ) in PGD children aged 2 months to 7.5 years (Thomaidis et al, 2012). The DQ was calculated using the Bayley Scales of Infant Development and either the Griffiths Scales for Mental Development or the Athina Test for children aged under 3 years.

Based on the General DQ score, 81% of children had at least normal development, while 13% had mild developmental delay and 6% had significant developmental delay (Table C.6.19). Similar proportions were also seen for the Mental DQ score. The authors note that 23% of the 31 children had Motor DQ scores suggesting mildly delayed motor development. In addition, 6% of children had scores suggesting significantly delayed motor development. It is important to note that 26% of the clinical pregnancies included in this series for PGD were for twins or triplets, who are more at risk of prematurity and low birth weight, which has been linked to developmental delay.

Table C.6.19 Mental and motor development following PGD – Level IV evidence

Outcome	Age	PGD only n/N (%)
<i>Thomaidis 2012</i>		
General DQ score	2 mo to 7.5 years	
>115		1/31 (3.2)
86–115		24/31 (77.4)
65–85		4/31 (12.9)
<65		2/31 (6.4)
Mental DQ score	2 mo to 7.5 years	
>115		1/31 (3.2)
86–115		25/31 (80.6)
65–85		2/31 (6.4)
<65		3/31 (9.7)
Motor DQ score	2 mo to 7.5 years	
>115		1/31 (3.2)
86–115		21/31 (67.7) <sup>a</sup>
65–85		7/31 (22.6)
<65		2/31 (6.5)

Abbreviations: DQ, Development Quotient; mo, months; NC, natural conception; PGD, preimplantation genetic diagnosis; PSI, Parental Stress Index; y, years

<sup>a</sup> Percentage corrected from publication (6.8%)

In addition, developmental delays were reported in children born in the following level IV studies:

- Keymolen et al (2012) – one child had neurodevelopmental delay; work-up showed major malformations (cerebellar vermis hypoplasia and mega cisterna magna) which were not tested for at the time.
- De Rademaeker et al (2009) – three children showed developmental delay: one child with galactosemia had a developmental delay of 6 months at 2 years, and two children had a mild transient language delay.
- Strom et al (2000) – one case of developmental delay was reported in a twin delivered at 36 weeks without perinatal complications. This twin had a 6-month speech delay.

### **Quality of life**

No included studies assessed quality of life in children born following PGD.

### **Functional status**

No included studies assessed functional status in children born following PGD.

### **C.6.3. PICO 3**

There was no comparative evidence determining whether PGD is as accurate as prenatal diagnosis. The absolute accuracy of PGD is difficult to estimate since it is impossible to confirm the diagnosis in every embryo. Access for reanalysis is available either during pregnancy (prenatal diagnosis) or after birth (postnatal diagnosis); however, a large number of embryo transfers do not result in pregnancy and confirmatory testing is done on only a proportion of non-transferred embryos (as discussed below) (Dreesen et al, 2008; Goossens et al, 2008b; Dreesen et al, 2014).

Misdiagnosis rates have been estimated based on reporting of the ESHRE membership centres. Table C.6.20 and Table C.6.21 summarises the misdiagnoses rates as reported by the ESHRE PGD Consortium between 1997 and December 2009 (data collection I to XII). Confirmation of diagnosis was performed prenatally in approximately 34% (3380/9813) of fetal sacs (Table C.6.20), and/or postnatally in approximately 28% (2742/9813) of births (Table C.6.21). The rate of misdiagnosis for single gene disorders diagnosed via PCR was estimated at approximately 1.3% prenatally and 0.4% postnatally. The rate of misdiagnosis for chromosomal abnormalities diagnosed via FISH was estimated at approximately 0.2% prenatally and 0.1% postnatally.

Table C.6.20 Summary of misdiagnosis from ESHRE PGD Consortium data I to XII, prenatal diagnosis

Study ID	Misdiagnosis rate per fetal sac tested (after FISH)	Misdiagnosis rate per fetal sac tested (after PCR)	Prenatal diagnosis rate
Geraedts 1999 (Data collection I)	0/42 (0.0%)	1/61 (1.6%)	103/110 (93.6%)
Geraedts 2000 (Data collection II)	0/66 (0.0%)	3/50 (6.0%)	116/224 (51.8%)
Sermon 2002 (Data collection III)	1/122 (0.8%)	1/65 (1.5%)	187/426 (43.9%)
Sermon 2005 (Data collection IV)	1/114 (0.9%)	1/22 (4.5%)	136/387 (35.1%)
Harper 2006 (Data collection V)	0/230 (0.0%)	0/91 (0.0%)	321/476 (67.4%)
Sermon 2007 (Data collection VI)	0/217 (0.0%)	0/40 (0.0%)	257/564 (45.6%)
Harper 2008 (Data collection VII)	1/254 (0.4%)	2/63 (3.2%)	317/665 (47.7%)
Goossens 2008 (Data collection VIII)	0/327 (0.0%)	2/47 (4.3%)	374/837 (44.7%)
Goossens 2009 (Data collection IX)	0/466 (0.0%)	0/80 (0.0%)	546/1529 (35.7%)
Harper 2010 (Data collection X)	0/342 (0.0%)	0/99 (0.0%)	441/1609 (27.4%)
Goossens 2012 (Data collection XI)	0/320 (0.0%)	0/66 (0.0%)	386/1395 (27.7%)
Moutou 2014 (Data collection XII)	1/106 (0.1%)	0/90 (0.0%)	196/1591 (12.3%)
Cumulative data	4/2606 (0.2%)	10/774 (1.3%)	3380/9813 (34.4%)

Source: ESHRE PGD Consortium, data I-XII

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; FISH, fluorescence in situ hybridisation; PCR, polymerase chain reaction; PGD, preimplantation genetic diagnosis

Rate of prenatal diagnosis was defined as the number of fetal sacs (concepti) tested per total number of fetal sacs

Table C.6.21 Summary of misdiagnosis from ESHRE PGD Consortium data I to XII, postnatal diagnosis

Study ID	Misdiagnosis rate per birth (after FISH)	Misdiagnosis rate per birth (after PCR)	Postnatal diagnosis rate
Geraedts 1999 (Data collection I)	0/4 (0.0%)	0/13 (0.0%)	17/110 (15.5%)
Geraedts 2000 (Data collection II)	0/7 (0.0%)	0/17 (0.0%)	24/224 (10.7%)
Sermon 2002 (Data collection III)	0/23 (0.0%)	0/16 (0.0%)	39/426 (9.2%)
Sermon 2005 (Data collection IV)	0/115 (0.0%)	1/13 (7.7%)	128/387 (33.1%)
Harper 2006 (Data collection V)	0/144 (0.0%)	0/29 (0.0%)	173/476 (36.3%)
Sermon 2007 (Data collection VI)	1/224 (0.4%)	0/29 (0.0%)	253/564 (44.9%)
Harper 2008 (Data collection VII)	0/253 (0.0%)	1/24 (4.2%)	277/665 (41.7%)
Goossens 2008 (Data collection VIII)	1/289 (0.3%)	0/48 (0.0%)	337/837 (40.3%)
Goossens 2009 (Data collection IX)	0/323 (0.0%)	0/75 (0.0%)	398/1529 (26.0%)
Harper 2010 (Data collection X)	0/297 (0.0%)	0/104 (0.0%)	401/1609 (24.9%)
Goossens 2012 (Data collection XI)	0/288 (0.0%)	0/58 (0.0%)	346/1395 (24.8%)
Moutou 2014 (Data collection XII)	0/228 (0.0%)	0/121 (0.0%)	349/1591 (21.9%)
Cumulative data	2/2195 (0.1%)	2/547 (0.4%)	2742/9813 (27.9%)

Source: ESHRE PGD Consortium, data I-XII

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; FISH, fluorescence in situ hybridisation; PCR, polymerase chain reaction; PGD, preimplantation genetic diagnosis

Rate of postnatal diagnosis was defined as the number of babies born tested per total number of births

Table C.6.22 summarises the outcomes of misdiagnosis as reported by ESHRE PGD Consortium. Overall, there were a total of 16 misdiagnoses; nine (56%) ended in

termination, six (38%) were born resulting in the birth of affected children, and one (5.6%) was miscarried.

**Table C.6.22 Summary of misdiagnosis from ESHRE PGD Consortium data I to XII (no misdiagnosis reported for data V, X and XI)**

Indication	Method used	PND-postnatal	Outcome	ESHRE report number
<i>Single gene disorders</i>				
Myotonic dystrophy type I	PCR	PND	TOP	I
Cystic fibrosis	PCR	PND	Born	II
B-thalassaemia	PCR	PND	TOP	II
Familial amyloid polyneuropathy	PCR	PND	Born	IV
Cystic fibrosis (1 of twins)	PCR	Post	Born	IV
Charcot-Marie-Tooth (CMT1A) (twins)	PCR	PND	TOP of both twins	VII
B-thalassaemia	PCR	PND	TOP	VIII
Fragile X	PCR	PND	Born	VIII
<i>X-linked disease</i>				
46 XY in Duchene muscular dystrophy twin	PCR	PND	TOP of one twin	III
45, X, Haemophilia A	FISH	PND	TOP	IV
46 XY retinitis pigmentosa	PCR	PND	Born	IV
45, XY, Haemophilia A	FISH	Post	Born	VIII
<i>Chromosomal abnormalities</i>				
47,XX, + der(22)t(11.22) (q23.3;q11.2)mat	FISH	PND	TOP	III
Trisomy 13 after 45,XY,der(13;14)(q10;q10)	FISH	Aborted spontaneously	Aborted spontaneously	VI
46,XY,der(15)t(13;15) (q25.1;q26.3)pat	FISH	PND	TOP	VII
46,XY,der(17)t(5;17)(p13;p13)mat	FISH	PND	TOP	XII

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; FISH, fluorescence in situ hybridisation; PCR, polymerase chain reaction; PGD, preimplantation genetic diagnosis; PND, prenatal diagnosis; TOP, termination of pregnancy.

There were a total of 65 TOPs reported by the ESHRE data collection reports between 1997 and December 2009. According to the data presented in Table C.6.22 above, 14% of TOPs (9/65) were due to misdiagnosis. Other TOPs were due to various reasons such as: complications in pregnancy, acrania, severe growth retardation, agensis corpus callosum, limb body wall defect, neural tube defect, cystic hygroma, encephalocele, tetralogy of Fallot, other ultrasound abnormalities (cardiopathy, enlarged lateral ventricle), trisomy 13, trisomy 21, hydrocephaly and social reasons (e.g. divorce).

Overall, the rates of misdiagnosis reported by the ESHRE PGD Consortium appear to be very low; however, this is dependent on the quality of reporting and whether misdiagnosis is underreported by the participating PGD centres.

### **Misdiagnosis rates as reported by non-ESHRE membership centres**

Five out of the 33 studies included for PICO 1 were not listed under the centres that provided clinical outcome data after PGD to the ESHRE (Cieslak et al, 1999; Ginsburg et al, 2011; Kuliev et al, 2011; Chang et al, 2013; Tan et al, 2013), and thus their data would not be included in the ESHRE dataset. Only one study (Kuliev et al, 2011) reported a single misdiagnosis observed after 395 PGD cycles (95 unaffected children were born). The authors reported a 99.7% accuracy for transfer; or 99% accuracy per

birth. Chang et al (2013) reported that all of the genotyping results of prenatal diagnosis were consistent with PGD without misdiagnosis. The studies by Tan et al (2013), Ginsburg et al (2011) and Cieslak et al (1999) did not report on misdiagnosis.

### Rate of successful diagnosis

The RCT by Goossens et al (2008b) determined the proportion of embryos that could be diagnosed per cycle after the removal of one or two blastomeres using both PCR and FISH techniques for PGD. The results are presented in Table C.6.23. The percentage of diagnosed embryos using the FISH-PGD technique remained similar whether one or two cells were removed (98.2% and 97.5% in group I and II, respectively;  $P=0.838$ ). The percentage of diagnosed embryos using the PCR-PGD technique was 88.6% in the one-cell biopsy group and 96.4% in the two-cell biopsy group ( $P=0.008$ ).

Table C.6.23 Proportion of diagnosed embryos of PCR and FISH-PGD cycles

Description	No. of cycles	No. of embryos biopsied	No. (%) of transferable embryos	No. (%) of not-transferred embryos	No. (%) of abnormal embryos	No. (%) of embryos with no diagnosis
<i>One-cell biopsy</i>	-	-	-	-	-	-
PCR-PGD	52	330	161 (47.9)	121 (36.2)	13 (4.5)	35 (11.4)
FISH-PGD	43	259	90 (33.5)	47 (21.1)	117 (43.6)	5 (1.8)
<i>Two-cell biopsy</i>	-	-	-	-	-	-
PCR-PGD	54	329	188 (58.5)	118 (35.6)	10 (2.3)	13 (3.6)
FISH-PGD	35	177	66 (41.8)	36 (19.5)	71 (36.2)	4 (2.5)

Source: Goossens et al (2008b)

Abbreviations: FISH, fluorescence in situ hybridisation; PCR, polymerase chain reaction; PGD, preimplantation genetic testing.

The ESHRE PGD Consortium data demonstrate an upward trend in the proportion of embryos with a successful diagnosis following testing for monogenic PCR. In earlier data sets, successful diagnosis was achieved in approximately 82% of embryos analysed, whereas in the most recent data collection for cycles performed in 2009, diagnosis was achieved in over 90% of embryos (Geraedts et al, 1999; Moutou et al, 2014).

### Validity of PCR-based PGD methods

There were three studies that validated PCR-based PGD by comparing results of biopsy at the time of PGD with the results of the embryo follow-up analyses in a large cohort of samples ( $N= 1,721$  embryos). Table C.6.24 presents a summary of the results of validation of the PGD-PCR analysis by the three publications.

The study by Dreesen et al (2014) was a multi-centre embryo follow-up study, facilitated by the ESHRE PGD Consortium, which aimed to retrospectively evaluate the validity of PCR-based PGD protocols. Embryos selected for reanalysis were those that were unsuitable for transfer or cryopreservation due to: genetic unsuitability based on PGD-derived genotype (affected); poor developmental capacity and morphology; and couples' decision that their supernumerary embryos were not required for further reproductive treatment cycles. The study was conducted between October 2009 and May 2010, and included data from six centres (total of 940 reanalysed embryos) that met the inclusion and data integrity criteria. The PGD genotyped blastomeres and corresponding reanalysed embryos were compared. Moreover, comparison on the validity was made for the biopsy of one versus two blastomeres, and for singleplex versus multiplex PCR. Overall, there were five false negative diagnostic outcomes (0.76%), which were all

attributed to mosaicism. There were 54 (19.1%) false positives, 54% of which were contributed to mosaicism.

The authors reported that the sensitivity, specificity, and accuracy of PCR-based PGD protocols applied to diagnose single gene disorders were high (99.2%, 80.9%, and 93.7% respectively) (Table C.6.24). The high sensitivity reflects the significantly low risk of adverse misdiagnosis. This is important as adverse misdiagnosis may have severe consequences for couples, such as the birth of an affected child (Wilton et al, 2009).

With respect to the number of biopsied cells (i.e. one-cell versus two cells) that underwent PCR-based PGD, the analysis showed that two-cell biopsy exhibits significant advantages in terms of diagnostic accuracy compared with one-cell biopsy (96.7% versus 91.6%,  $P=0.001$ ) (Table C.6.24). The authors also noted that specificity was significantly different amongst the participating centres owing to the differences in the false positive rate. This could be attributed to the general trend to overestimate the affected status when interpreting the PCR-based PGD results, in order to preclude transfer of any affected embryos. Further, the biopsy of a second blastomere improves the positive predictive value, lowering the misdiagnosis rate (Table C.6.24) (Dreesen et al, 2014).

In an earlier smaller study, Dreesen et al (2008) reanalysed a total of 422 embryos and reported a misdiagnosis rate of 7.1% and a false negative rate of 3.1% (Table C.6.24). The two blastomere biopsies revealed a significantly higher positive predictive value, lowering the misdiagnosis rate, whereas the negative predictive value remained the same.

The RCT by Goossens et al (2008b) presented the false positive rate per embryo reanalysed for the PCR cycles as a secondary outcome, with reanalysis of 359 embryos. Results of the post-PGD-PCR reanalysis showed six false positives in 97 embryos (6.2%) in the two-cell biopsy group and none in the one-cell biopsy group (91 embryos reanalysed). No false negatives were found in either groups (Table C.6.24).

Table C.6.24 Results of validation of the PGD-PCR analysis compared with embryo reanalysis, one-cell versus two-cell biopsy

Study ID	No of embryos	Sensitivity (%)	False negative (%)	Specificity (%)	False positive (%)	Accuracy (%)	Misdiagnosis (%)	LR (positive test)	LR (negative test)	Negative PV (%)	Positive PV (%)
Dreesen 2014	Total group (N=940)	652/657 (99.2)	5/657 (0.76)	229/283 (80.9)	54/283 (19.1)	881/940 (93.7)	59/940 (6.3)	5.2	0.01	229/234 (97.9)	652/706 (92.3)
-	One blastomere (n=534)	337/340 (99.1)	3/340 (0.88)	152/194 (78.3)	42/194 (21.6)	489/534 (91.6)	45/534 (8.4)	4.6	0.01	152/155 (98.1)	337/379 (88.9)
-	Two blastomere (n=389)	300/302 (99.3)	2/302 (0.66)	76/87 (87.4)	11/87 (12.6)	376/389 (96.7)	13/389 (3.3)	7.9	0.01	76/78 (97.4)	300/311 (96.5)
Dreesen 2008	Total group (N=422)	218/225 (96.9)	7/225 (3.1)	174/197 (88.3)	23/197 (11.7)	392/422 (92.9)	30/422 (7.1)	8.3	0.04	174/181 (96.1)	218/241 (90.5)
-	One blastomere (n=176)	76/78 (97.4)	2/78 (2.6)	84/98 (85.7)	14/98 (14.3)	160/176 (90.9)	16/176 (9.1)	6.82	0.03	84/86 (97.7)	76/90 (84.4)
-	Two blastomere (n=246)	142/147 (96.6)	5/147 (3.4)	90/99 (90.9)	9/99 (9.1)	232/246 (94.3)	14/246 (5.7)	10.63	0.04	90/95 (94.7)	142/151 (94.0)
Goosens 2008b	One blastomere (n=154) <sup>a</sup>	63/63 (100)	0/63 (0.0)	91/91 (100)	0/91 (0.0)	154/154 (100)	0/154 (0.0)	-	0.00	-	-
-	Two blastomere (n=168) <sup>a</sup>	71/71 (100)	0/71 (0.0)	91/97 (93.8)	6/97 (6.2)	162/168 (96.4)	6/168 (3.6)	16.1	0.00	-	-

Abbreviations: LR, likelihood ratio; PCR, polymerase chain reaction; PGD, preimplantation genetic diagnosis; PV, predictive value

The sensitivity was defined as the proportion of affected/aberrant embryos diagnosed correctly by PGD (true positive rate). The specificity was defined as the proportion of unaffected embryos diagnosed correctly by PGD (true negative). The accuracy was defined as the proportion of all embryos, affected/aberrant as well as unaffected, diagnosed correctly by PGD. The misdiagnosis rate was defined as the proportion of false negative and -positive. The diagnostic value was expressed by positive and negative predictive values. The positive predictive value was defined as the proportion of PGD analysis that predicted embryos correctly as affected/aberrant, and the negative predictive value was defined as the proportion of PGD analysis that predicted embryos correctly as unaffected. The positive likelihood ratio was defined as the probability of a positive test in those with disease, compared to the probability of a positive test in those without disease. The negative likelihood ratio was defined as the probability of a negative test in those with disease, compared to the probability of a negative test in those without disease.

<sup>a</sup> There were 36 and 21 embryos that failed reanalysis in Group I (one-cell biopsy, n=190) and Group II (two-cell biopsy, n=189) respectively.

The study by Dreesen et al (2014) performed analysis of the PCR-PGD protocols applied (that is multiplex versus singleplex PCR) and showed that multiplex protocols perform statistically significantly better than singleplex protocols in terms of sensitivity (99.8% versus 97.9%,  $P=0.03$ ). However, no significant difference was detected in specificity and diagnostic accuracy ( $P=0.352$  and  $P=0.547$ , respectively) (Table C.6.25).

**Table C.6.25 Results of validation of the PGD-PCR analysis compared with embryo reanalysis, singleplex versus multiplex**

Study ID	PCR-PGD protocol	Sensitivity (%)	False negative (%)	Specificity (%)	False positive (%)	Accuracy (%)	Misdiagnosis (%)
Dreesen 2014	Singleplex	192/196 (98.0)	4/196 (2.0)	45/59 (76.3)	14/59 (23.7)	237/255 (92.9)	18/255 (7.1)
-	Multiplex	460/461 (99.8)	1/461 (0.2)	184/224 (82.1)	40/224 (17.9)	644/685 (94.0)	41/685 (6.0)
-	Singleplex one-cell	67/70 (95.7)	3/70 (4.3)	21/29 (72.4)	8/29 (27.6)	88/99 (88.9)	11/99 (11.1)
-	Singleplex two cells	118/119 (99.2)	1/119 (0.8)	24/29 (82.8)	5/29 (17.2)	142/148 (95.9)	6/148 (4.1)
-	Multiplex one-cell	270/270 (100)	0/270 (0.0)	131/165 (79.4)	34/165 (20.6)	401/435 (92.2)	34/435 (7.8)
-	Multiplex two cells	182/183 (99.5)	1/183 (0.5)	52/58 (89.7)	6/58 (10.3)	234/241 (97.1)	7/241 (2.9)

Source: Dreesen et al (2014)

Abbreviations: PCR, polymerase chain reaction; PGD, preimplantation genetic diagnosis

The sensitivity was defined as the proportion of affected/aberrant embryos diagnosed correctly by PGD (true positive). The specificity was defined as the proportion of unaffected embryos diagnosed correctly by PGD (true negative). The accuracy was defined as the proportion of all embryos, affected/aberrant as well as unaffected, diagnosed correctly by PGD. The misdiagnosis rate was defined as the proportion of false negative and false positive.

The study by Dreesen et al (2014) also investigated the combined diagnostic efficiency of PCR-based PGD strategies (that is, the molecular method and biopsy protocol) by comparing the following subgroups: Singleplex one cell (S1cell), Singleplex two cells (S2cell), Multiplex 1 cell (M1cell), and Multiplex 2 cells (M2cell) biopsy (Table C.6.25). A statistically significant difference was observed between the S1 cell and M1 cell for the sensitivity ( $P=0.048$ ), whereas there was no significant difference detected for sensitivity in the remaining pairwise comparisons (Dreesen et al, 2014). In terms of diagnostic accuracy, multiplex PGD with two cells appeared to identify the status of embryos with significantly greater accuracy compared with singleplex PGD with one cell (97.1% versus 88.9%,  $P=0.024$ ). Likewise, a marginally higher diagnostic accuracy was detected in multiplex PGD with two cells compared with multiplex PGD with one cell (97.1% versus 92.1%,  $P=0.066$ ). There were no studies that evaluated the diagnostic accuracy of other relevant test methods.

Overall, these studies demonstrated that the PGD-PCR procedure is a valid diagnostic test with good diagnostic value. However, it should be noted that for the majority of the embryos used for ET (where reanalysis was not possible), the diagnostic outcome will remain unknown.



## Validity of FISH-based PGD testing methods

There was one study that investigated the diagnostic accuracy of the FISH-PGD technique in reanalysing 558 embryos (Scriven et al, 2013). There were 46 (8%) false positive results and no false negative results. The diagnostic accuracy was estimated to be 92% (512/558), with 100% (375/375) sensitivity and 75% (137/183) specificity (see Table C.6.26).

Table C.6.26 Summary of results of validation of the PGD-FISH analysis

Study ID	Sensitivity	False negative	Specificity	False positive	Accuracy	Misdiagnosis
Scriven 2013	375/375 (100.0%)	0/375 (0.0%)	137/183 (74.9%)	46/183 (25.1%)	512/558 (91.8%)	46/558 (8.2%)

Source: Scriven et al (2013)

## C.7. Interpretation of the clinical evidence

Very little comparative evidence was found to allow a comparison between PGD and the comparators: prenatal testing for PICO 1 and PICO 3, and ICSI alone (without embryo biopsy) for PICO 2. The majority of evidence available for PGD comes from single arm studies and case series. The exception was for PICO 2 (safety and effectiveness of PGD in offspring), where a number of observational studies were available which compared children's outcomes following PGD and IVF, natural conception, or both. No evidence was found in the target populations for PICO 4 and PICO 5.

There were a number of RCTs identified and included in this assessment. However, these compared different PGD methodologies with one other, not PGD with the comparators or no PGD. Thus, it was not even possible to perform additional literature searches in order to conduct a formal indirect comparison between PGD and prenatal testing.

Due to the lack of comparative clinical evidence available, it is not possible to verify the clinical claim that PGD has a similar diagnostic accuracy compared with prenatal diagnosis. Likewise, due to lack of comparative evidence, it is not possible to verify and confirm the claims that the use of PGD reduces the time to an unaffected live birth, or reduces parental psychological trauma due to a reduction in pregnancy terminations, compared with prenatal testing.

There is a small amount of Level III evidence available that suggests that PGD, and in particular the biopsy component of the procedure, does not lead to harms in the offspring of couples undergoing PGD.

Data from single arm studies and case series were included in the clinical evaluation to provide support for the safety and effectiveness of PGD in the target population. Where appropriate, this data has been applied to the PGD arm in the economic model and the financial analysis. Additional literature searches and/or data analysis (outlined in Section D) was used to identify corresponding estimates for the prenatal testing arm.

# Section D. Translating the clinical evaluation to the economic evaluation

## D.1. Identification of issues to be addressed

This section presents each of the translation issues identified to move from the clinical evidence discussed in Section C to the economic evaluation presented in Section D. Applicability, extrapolation and transformation issues were considered to identify each of the issues presented in Table D.1.1. In each instance, a focused analytical plan is presented prior to presenting the results of the pre-modelling study and the relationship between these and the economic evaluation presented in Section D.

Table D.1.1 Translation issues identified in preparing the economic evaluation

Translation issue	Comments	Section C subsection
<i>Applicability issues</i>		
	-	-
Population and circumstances of use	There is a scarcity of publications that directly compare PGD with the Protocol-defined comparators, in the population that would be eligible for public funding under the proposed listing. Nonetheless, the link between the population of the requested listing and the economic model presented in Section D is discussed	Section D.2
<i>Extrapolation issues</i>		
	-	-
Downstream impacts related to affected live births	The ultimate aim of both PGD and prenatal testing is to avoid the potential consequence of conception between parents carrying single gene disorders or chromosomal rearrangements; that is, birth of an affected child. This impacts on both quality of life and healthcare costs. Estimates of the downstream costs are sourced and discussed in this pre-modelling study to ensure they are adequately applied to the model presented in Section D	Section D.3
<i>Transformation issues</i>		
	-	-
Modelling the natural history of pregnancy and the IVF cycle	Although the focus of the analysis is on the birth of a child, an understanding of conception rates, miscarriage rates and the rate at which terminations occur in fetuses with abnormalities was a crucial step in the development of a cost-utility model	Section D.4
Utility weights applied to the economic model	To undertake the cost-utility modelling presented in Section D, it was necessary to source utility weights to be applied to the health states included in the economic model. As discussed, these needed to account for live births affected by abnormalities and those unaffected, as well as miscarriages, terminations and failure to conceive	Section D.5
Healthcare resource use and associated costs	The economic model required costs to be calculated for a variety of health states and events related to the use of IVF and ongoing pregnancy. In doing so, the incremental differences between the model arms could be better estimated	Section D.6

Abbreviations: IVF, in vitro fertilisation; PGD, preimplantation genetic diagnosis

## D.2. Issue 1: Population and circumstances of use

As discussed in earlier sections, there is a scarcity of clinical evidence in the target population that directly compares the effectiveness, diagnostic accuracy and safety of PGD with the comparators defined in the PICO criteria. Nonetheless, the link between

the population who would be eligible for public funding of PGD services and the economic model presented in Section D is discussed in the section below.

### **D.2.1. Focused analytical plan**

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 (offered until February 2005, but since suspended).

The current application proposes that a 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:

- (3) Single gene disorders (SGDs), and
- (4) Chromosomal rearrangements (e.g. translocations)

To compare the population and the circumstances of use in the economic model presented in Section D with the requested listing described in Section A, the following factors were considered:

- Age
- Reason for seeking PGD
- PGD methodology

### **D.2.2. Results of the pre-modelling studies**

Table D.2.1 compares the key features of the requested listing and the population/circumstances of use applied to the economic model presented in Section D.

Table D.2.1 Population and circumstances of use

Translation issue	Proposal for public funding	Application in the economic model	Comment
Age	No restriction applied.	Age is not explicitly considered in the economic model, as the model is short-term in nature without inclusion of background mortality.	Mortality is not considered in the economic model, since there are no reasons to expect a difference in the various arms of the model. As such, it would not impact on the results.  While it may have been relevant to consider age in the case of a broader listing for PGD which includes advanced maternal age, this is not part of the proposed listing.
Reasons for seeking PGD	<p>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.</p> <p>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.</p>	<p>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.</p> <p>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.</p>	<p>The population applied to the economic evaluation is the same as that of the requested listing. As discussed in Section A, the data used to inform the economic model were sourced to match this population as well as possible.</p> <p>The economic evaluation is inclusive of all serious genetic disorders rather than focussing on any particular genetic disorder. A sensitivity analysis incorporates the cost of management of cystic fibrosis for illustrative purposes only. Where available, data specifically relating to the proposed population has been sourced from the literature or from the Applicant.</p>
PGD methodology	No restriction applied in terms of embryo biopsy (e.g. blastocyst, blastomere, polar body) or genetic test method.	No restriction applied in terms of embryo biopsy (e.g. blastocyst, blastomere, polar body) or genetic test method.	Where available, Australian data sources were used in the economic model. Sensitivity analyses were undertaken around estimates that may not reflect the Australian experience (e.g. clinical pregnancy rates and misdiagnosis may arguably be lower in Australia due to the use of blastocyst biopsy).

Abbreviations: PGD, preimplantation genetic diagnosis

### D.2.3. Relationship of the pre-modelling study to the economic evaluation

The economic evaluation presented in Section D was designed with the factors presented above in mind. This is further discussed within Section C, and in Section D below.

Where there was uncertainty around any of these issues, sensitivity analyses presented in Section D.6 examined the impact that varying assumptions had on the estimated incremental cost-effectiveness.

## D.3. Issue 2: Downstream impacts related to affected live births

The ultimate aim of diagnosing abnormalities, either through PGD or prenatal testing, is avoiding the birth of children affected by SGDs and chromosomal rearrangements. Births affected by such abnormalities have important consequences in terms of health-related quality of life (HRQoL), life expectancy and downstream healthcare costs. The applicability of these is considered in this section.

### **D.3.1. Focused analytical plan**

Recognising the importance of downstream impacts equates to recognising the importance of adequately representing the impact of quality of life, life expectancy and downstream healthcare costs. To address these issues and ensure that they are appropriately handled in the economic model, they are each considered in turn.

In the case of quality of life, the model was appropriately structured as a cost-utility study. As discussed in greater detail in Section D, the model adopted the perspective of the couple attempting abnormality-free pregnancy, rather than that of the child. This perspective is appropriate for a multitude of reasons, the most compelling of which is that it is the couple who are seeking pregnancy and, ultimately, the birth of a child. There is, however, no guarantee that a live birth will occur (there may be no successful conception, or other events preventing a birth may occur such as a miscarriage or a termination of the pregnancy). It is therefore appropriate to take the perspective of the couple seeking to have an unaffected child, rather than that of the child, to ensure the incremental effects are adequately captured.

As will be discussed in Section D.5, the utility weights applied to the various health states of the model are able to adequately represent the long-term nature of the health states (such as birth of an unaffected child, birth of an affected child, the effect of miscarriage, etc.). As such, it is possible to extrapolate health preferences over the long term. Therefore, no further consideration of this as a pre-modelling study is required.

With regards to life expectancy, it is important to note once more that it is the life expectancy of the parent that the model would consider when extrapolated over the long term; although the child may have a reduced life expectancy, his/her perspective is not considered in the model.

Modelling the life expectancy of this patient population is an extremely complex undertaking. The range of reasons for which PGD may be sought by such couples comprises an extraordinarily broad range. To argue that any estimate of the average life expectancy of this cohort was reasonably certain would be misleading. Life expectancy was omitted from the model. As such, no further consideration of this as a pre-modelling study was undertaken.

In terms of the downstream cost impact, again there is an untenable degree of uncertainty inherent in this estimation. The broad range of SGDs and chromosomal rearrangements that may cause a couple to seek PGD would have an equally broad range of downstream cost implications. Nonetheless, inclusion of an estimate of some kind was deemed important. Consequently, a literature search was undertaken to provide a proxy estimate that would be used in sensitivity analyses presented in Section D.6 to ascertain the potential impact of downstream costs on the incremental cost-effectiveness.

On the basis of Table 4 of the Final Protocol, an estimate of the total cost of cystic fibrosis was sought. Cystic fibrosis was identified by the Applicant's analysis of gene disorders commonly tested for at their centre as the single most common genetic disease for which PGD is sought (19.5% of all PGD cycles initiated tested for cystic fibrosis). Since treatment of cystic fibrosis is costly, applying this to the model would likely represent an upper limit treatment cost.

### D.3.2. Results of the pre-modelling studies

A study by the Centre for Health Economics Research and Evaluation (CHERE, 2011) was identified through a search of the literature. The study reports the total lifetime healthcare costs associated with cystic fibrosis in Australia. Both mean and median values were reported at a discount rate of 0%, 5% and 10% per annum. The costs were expected to apply over a 38-year period of life expectancy. The majority of these costs are incurred in the inpatient hospital sector (58%), followed by pharmaceuticals (29%), medical services (10%), complications (2%), and diagnostic tests (1%).

The lifetime treatment costs of cystic fibrosis, as estimated by CHERE, are provided in Table D.3.1.

Table D.3.1 Translation issues identified in preparing the economic evaluation

	Discounted at 0% per annum	Discounted at 5% per annum	Discounted at 10% per annum
Mean lifetime treatment cost	\$897,063	\$334,820	\$168,246
Median lifetime treatment cost	\$585,532	\$199,552	\$90,525

### D.3.3. Relationship of the pre-modelling study to the economic evaluation

The mean lifetime treatment cost, discounted at 5% per annum in accordance with MSAC Guidelines, was applied to a sensitivity analysis of the economic model in Section D.6. The inherent uncertainty of any such estimate, as well as its questionable relevance for the entire spectrum of affected children born to parents with SGDs or chromosomal rearrangements, means that it was unsuitable for inclusion in the base case analysis. To include such a cost in the base case analysis would be to introduce unreasonable uncertainty to the analysis and to misrepresent the analysis in favour of PGD.

Similarly, neither downstream quality of life nor life expectancy was included in the base case analysis. As described above, estimating life expectancy in a meaningful way was not possible. With regards to downstream quality of life, while possible, this would have magnified any uncertainty that is inherent in quality-adjusted life year (QALY) weights and the magnification would favour PGD unreasonably. The utility weights discussed in Section D.5 were applied over a long-term version of the model in a sensitivity analysis with the lifetime treatment cost. See Section D.6 for further detail.

## D.4. Issue 3: Modelling the natural history of pregnancy and the IVF cycle

Although the focus of the analysis is on the birth of a child, an understanding of conception rates, miscarriage rates and the rate at which terminations occur in fetuses with abnormalities was a crucial step in the development of a cost-utility model. This section considers each of these in turn.

### D.4.1. Focused analytical plan

The probability of conception was not an explicit consideration in the PGD arm of the economic model. As will be further discussed in Section D, the model cycle length of 20 weeks allows for repeated IVF attempts if necessary. The model assumed that all women using PGD with IVF would become pregnant within the first 20-week cycle. Although

this may require multiple attempts of IVF, the costs applied to the model have accounted for this by costing the average number of attempts required for all women.

In the case of successful conception in the natural conception arms (with and without prenatal testing), the Protocol claims that 20% of attempts at pregnancy using natural conception will be successful. This is similar to the rate used by Davis et al. 2010 (25% for women less than 35 years of age, 15% for women aged 35-40 years and 5% for women greater than 40 years of age).

The model also required an estimate for the proportion of women who will undergo an elective termination following detection of abnormalities. It is important to note that this variable plays a greater role in the natural conception with prenatal testing arm than it does in the PGD arm, as there are expected to be far fewer abnormalities detected in women that conceive via PGD (both due to the accuracy of PGD and the low use of prenatal testing). No women that conceive via natural conception with no subsequent prenatal testing would seek TOP within the model, since abnormalities are not detected during pregnancy.

Since the rate of terminations is mostly an issue in the natural conception with prenatal testing arm, a conservative approach was adopted by setting the termination rate high. Using a high estimate is conservative and serves to avoid any potential bias in favour of PGD.

The rate of miscarriage is the most complex of the variables considered here. Miscarriages are more likely to occur in the early stages of pregnancy and the model must account for this. Additionally, the rate of miscarriage has been historically thought to be higher among those who undergo prenatal testing (procedure-related miscarriages). For this reason, a search of the literature was conducted to determine the most applicable rates to apply to the various arms of the model and at the various stages of pregnancy. Both the literature search and a discussion of the results are presented in Appendix 4.

#### D.4.2. Results of the pre-modelling studies

As discussed above, the rate of natural conception per fertility cycle has been estimated as 20% (ASRM, 2012 Patient Information Fact Sheet). Considering the length of the model cycle in the economic evaluation presented in Section D, which is 20 weeks, this equates to five fertility cycles and five potential attempts for natural conception. This was accounted for in the model to calculate a cumulative pregnancy rate when using natural conception. This is presented in Table D.4.1. The cumulative pregnancy rate was applied to the economic model to ensure the pregnancy rate of a 20-week cycle was adequately accounted for.

Table D.4.1 Pregnancy rate with natural conception per 20-week model cycle

Fertility cycle	Pregnancy rate per fertility cycle	Proportion remaining not pregnant at beginning of cycle	Pregnancies per cycle	Cumulative pregnancy rate
1	0.2	1	0.2	0.2
2	0.2	0.8	0.16	0.36
3	0.2	0.64	0.128	0.488
4	0.2	0.512	0.1024	0.5904
5	0.2	0.4096	0.0819	0.6723

Source: American Society for Reproductive Medicine, 2012 Patient Information Fact Sheet, page 4

With regards to the rate of terminations following a positive prenatal test, a rate of 99% was applied on the basis of data supplied by the Applicant. This approach was conservative and avoids any potential for bias in favour of PGD.

The miscarriage rates sourced from the literature search and the associated evaluation, which were applied to the economic model, are presented in Table D.4.2.

**Table D.4.2 Miscarriage rates applied to the economic model**

Model arm	Description of miscarriage type	Rate of miscarriage
PGD arm	Miscarriage among those who have received PGD but have not yet decided whether they will undergo prenatal testing (i.e. 'early' miscarriage)	0.0990
-	Miscarriage among those who have received PGD and have undergone prenatal testing (i.e. 'late' miscarriage)	0.0122
-	Miscarriage among those who have received PGD and have decided against prenatal testing (i.e. 'late' miscarriage)	0.0122
Natural conception with prenatal testing arm	Miscarriage among those who have conceived naturally but have not yet undergone prenatal testing (i.e. 'early miscarriage')	0.2259
-	Miscarriage among those who have conceived naturally and have undergone prenatal testing (i.e. 'late' miscarriage)	0.0324
Natural conception arm	Miscarriage among those in the natural conception arm of the model and who are in the first half of pregnancy (i.e. early miscarriage)	0.2259
-	Miscarriage among those in the natural conception arm of the model and who are in the second half of pregnancy (i.e. late miscarriage)	0.0324

Source: Appendix 4  
Abbreviations: PGD, preimplantation genetic diagnosis

### D.4.3. Relationship of the pre-modelling study to the economic evaluation

The natural conception rate discussed above was applied to the first cycle of the natural conception arm as well as the natural conception with prenatal testing arm of the model. To limit the number of attempts of natural conception to a realistic number, the possibility of natural conception was limited to the first three cycles of the model in the base case. This equates to up to 15 consecutive fertility cycles in which pregnancy is attempted, at which approximately 96% of couples would achieve pregnancy. The limit is tested in sensitivity analyses presented in Section D.6.

The termination rate was applied to all pregnancies in which an abnormality was detected via prenatal testing. This was a once-only probability and, as discussed above, applied to the natural conception with prenatal testing arm of the model only. The impact of the estimate applied to the model was tested in sensitivity analyses presented in Section D.6.

The miscarriage rates presented in Table D.4.2 were applied as per the descriptions provided in the table. The impact of the estimates used on the results of the base case analysis was tested in sensitivity analyses, as reported in Section D.6.



## D.5. Issue 4: Utility weights applied to the economic model

The economic model presented in Section D relies on the transformation of the HRQoL associated with pregnancy, through IVF or otherwise, into QALYs. In order to do so, the model requires utility weights differentiated by the various health states/events associated with the pregnancy cycle.

The following section presents the pre-modelling study aimed at sourcing appropriate utility weights to apply to the economic model.

### D.5.1. Focused analytical plan

The economic evaluation presented in Section D considers the impact of a live birth on the utility of the woman seeking pregnancy. While accounting for the differential impact of a live birth affected by a single gene disorder or chromosomal abnormality versus that which is unaffected is clear, there was also need to account for other events in the pregnancy/IVF cycle. In particular, there are also HRQoL impacts arising from a failure to conceive, from pregnancy termination and from miscarriage. Each of these required estimates for inclusion in the economic evaluation are presented in Section D.

A literature review was conducted to source utility weights to appropriately represent the health states of the economic model. The search strategy is presented in Appendix 4, in conjunction with the exclusion criteria that were applied and a summary of the process used to identify relevant utility studies.

A list of the health states requiring utility weight estimates is provided in Table D.5.1. Due to the range of health states, a concerted effort was made to minimise the number of sources. That is, to minimise any potential bias due to inter-study variance, there was an *a priori* preference to source utility weights from as few studies as possible.

Table D.5.1 Health states in the economic evaluation requiring utility weights

Health state	Description
Unaffected live birth	Birth to an infant who is unaffected by either single gene disorders or chromosomal rearrangements
Affected live birth	Birth to an infant who is affected by either single gene disorders or chromosomal rearrangements
Affected live birth following an incorrect diagnosis	Birth to an infant, following an incorrect negative diagnostic test, who is affected by either single gene disorders or chromosomal rearrangements
Termination of pregnancy	Termination of a pregnancy due to information indicating the fetus is affected by either a single gene disorder or chromosomal rearrangements
Miscarriage (including procedure-related)	Miscarriage of fetus following a prenatal test to diagnose single gene disorders or chromosomal rearrangements, possibly procedure-related
Miscarriage	Miscarriage of fetus in cases in which there has been no prenatal test to diagnose single gene disorders or chromosomal rearrangements and the miscarriage is definitively not procedure-related
Failed IVF cycle	Failed IVF cycle/transfer an embryo. This could be due to either a cancelled cycle, failed biopsy or failure to harvest abnormality-free embryo(s)
No pregnancy	Failure to conceive naturally, or failure to conceive via IVF for reasons other than those included in the 'Failed IVF cycle' health state described above

Abbreviations: IVF, in vitro fertilisation

### D.5.2. Results of the pre-modelling studies

As detailed in Appendix 4, 12 studies were identified as potentially relevant. These are summarised in Table D.5.2, with a discussion of their appropriateness following.

Table D.5.2 Studies evaluated to source utility weights for the economic model

Study	Study description	Results derived from the study	Comments
Chan et al, 2006	An interviewer-administered survey was conducted in Hong Kong in 67 women who presented to an obstetric clinic for booking visits and 69 women who presented for fetal Down syndrome. The standard gamble was used to elicit preferences for Down-syndrome-affected birth compared to invasive test-related miscarriage.	Down syndrome birth = 0.20 Procedure-related miscarriage = 0.55	Median utility scores were presented rather than mean scores. Cultural considerations may mean the results are not applicable to the Australian context. The authors note that the estimates are much lower than that reported in the Caucasian population (see Kuppermann et al (2000) and Grobman et al (2002)).
Chan et al, 2009	An interviewer-administered survey was conducted in 276 women in China using the standard gamble approach. The aim was to elicit a utility estimate of miscarriage. The health states comprised two alternatives: (1) a screening tests with 90% detection rate and (2) a diagnostic test with 100% accuracy and a finite risk of abortion.	The disutility of miscarriage was estimated to be 0.011	The study population was a homogenous group who were ethnic Chinese and with above average levels of education and income. This has the potential to bias the results. Additionally, cultural considerations may mean the results are not applicable to the Australian context.
Feeny et al, 2000	HRQoL was assessed in 126 women participating in a Canadian RCT to determine utility weights associated with the effects of CVS and amniocentesis.	N/A	This is the Working Paper version of the study presented in Feeny et al (2002) below and presents the same results.
Feeny et al, 2002	A sample of 126 women participating in a Canadian RCT were assessed in interviews at week 8, 13, 18 and 22 of their pregnancy to determine the HRQoL effects of CVS and genetic amniocentesis. To estimate utility values, a standard gamble approach was taken. Direct utility values were estimated for only a portion of health states; utility scores for the remainder were imputed using an equation estimating the relationship between measured utility and measured value (see Feeny et al, 2000).	PND – abnormality detected – abortion at 11th week = 0.85 PND – abnormality detected – abortion at 20th week = 0.74 PND – abnormality detected – abortion – false positive = 0.45 No PND – miscarriage weeks 10-16 = 0.87 PND – miscarriage likely due to test = 0.75 PND – miscarriage after week 20 – unlikely due to test = 0.79 PND – no abnormality detected – Down syndrome birth = 0.45 No PND – Down syndrome birth = 0.55 Down syndrome = 0.28 High risk – choose no pregnancy = 0.79	The chronic health states included here were assumed to be 40 years in duration, meaning that the utility weights were assumed to apply for the entirety of this duration.

Study	Study description	Results derived from the study	Comments
Grobman et al, 2002	An interviewer-assisted survey was administered to 186 pregnant women receiving antepartum care. Utility weights for the birth of a child with Down syndrome and miscarriage were estimated, stratified by patient characteristics. Utilities were elicited using the standard gamble paradigm.	Mild Down syndrome = 0.78 Moderate Down syndrome = 0.72 Severe Down syndrome = 0.65 Weighted average of Down syndrome = 0.73 Miscarriage = 0.76	The study population was predominantly white and college educated, although the authors point to the results being consistent with other studies. Mean values (presented here) are consistently lower than the median values, thereby indicating that the means may be affected by low outlier values.  It is not clear that there was any effort in the study to link miscarriage risk to the diagnostic test(s). As such, it would appear that the estimate does not include procedure-related miscarriage.
Harris, 2001	A decision analysis was undertaken, using preference scores obtained from pregnant women, to determine whether current guidelines maximise the HRQoL of these women.	N/A	While the study presents utility estimates for a number of health states, these were derived from another source (Kuppermann et al, 1999). On this basis, as well as it being referred to in other studies presented in this section, that study was included for further review. The present study, however, was excluded from further consideration.

Study	Study description	Results derived from the study	Comments
Kuppermann et al, 1999	A cross-sectional study of 72 San Franciscan women seeking genetic counselling was undertaken to determine how they valued the outcomes of testing. This was achieved with the standard gamble method.	<p>Unaffected child from current pregnancy, following first-trimester test = 0.96</p> <p>Unaffected child from current pregnancy, following second-trimester test = 0.96</p> <p>Unaffected child from current pregnancy, following first-trimester test, uncertain results, second-trimester test = 0.96</p> <p>Unaffected child from a future birth, following miscarriage after first-trimester = 0.93</p> <p>Unaffected child from a future birth, following miscarriage after second-trimester = 0.93</p> <p>Unaffected child from a future birth, following elective abortion after first-trimester test = 0.93</p> <p>Unaffected child from a future birth, following elective abortion after second-trimester test = 0.91</p> <p>Child with a limb defect following first-trimester test = 0.90</p> <p>No child (pregnancy loss without a future birth), following miscarriage after first-trimester test = 0.86</p> <p>No child (pregnancy loss without a future birth), following miscarriage after second-trimester test = 0.86</p> <p>No child (pregnancy loss without a future birth), following elective abortion after first-trimester test = 0.85</p> <p>No child (pregnancy loss without a future birth), following elective abortion after second-trimester test = 0.84</p> <p>Child with Down syndrome, following false negative results = 0.71</p> <p>Child with Down syndrome, following no prenatal testing = 0.69</p>	<p>The study population was somewhat homogenous and tended to be well educated and affluent, though this may be representative of women who undergo prenatal diagnosis.</p> <p>As acknowledged by the authors, the standard gamble may not be sensitive to small differences in quality of life, even when such differences may be important to individuals deciding which test to undergo.</p>

Study	Study description	Results derived from the study	Comments
Kuppermann et al, 2000	Preferences for procedure-related miscarriage and the birth of an infant affected by Down syndrome were assessed in 534 women from the San Francisco Bay area using the standard gamble and TTO metrics.	<u>TTO results</u> Procedure-related miscarriage = 0.76 Down-syndrome-affected birth = 0.67 <u>Standard gamble results</u> Procedure-related miscarriage = 0.92 Down-syndrome-affected birth = 0.81	Study participants were on average older, better educated and to be white or black and than non-participants.
Kuppermann et al, 2004	Preferences for 12 potential prenatal testing outcomes were estimated using the TTO method and standard gamble method in a cross-sectional study of 584 pregnant women from San Francisco Bay Area practices aged 16 to 47 years.	<u>TTO results</u> No testing – unaffected birth = 0.92 Amniocentesis – negative – unaffected birth = 0.92 Amniocentesis – miscarriage – future unaffected birth = 0.87 Amniocentesis – positive – abortion – future unaffected birth = 0.84 Amniocentesis – miscarriage – future birth not specified = 0.76 Amniocentesis – miscarriage – no future birth = 0.70 Amniocentesis – positive – abortion – no future birth = 0.69 No testing – Down syndrome birth = 0.67 Amniocentesis – positive – Down syndrome birth = 0.69 <u>Standard gamble results</u> Amniocentesis – miscarriage – future birth not specified = 0.90 No testing – Down syndrome birth = 0.81	There is no reason to expect that the results of this study are specific to women receiving amniocentesis, as the health states can be thought of as being overwhelmingly chronic in nature (as per Feeny et al (2002)). Mean values (presented here) are consistently lower than the median values, thereby indicating that the means may be affected by low outlier values. The paper notes that these estimates were presented previously in Kuppermann et al (2000). On the basis of this, as well as reference to that study in other studies discussed in this section, that study was included for further review.
Lubinga et al, 2013	The EQ-5D was used to assess utility weights among 139 women in Uganda (70 with abortion complications; 69 receiving routine obstetric care).	Routine obstetric visit = 0.89 Abortion complications = 0.77	Abortion is illegal in Uganda except to save the life of the mother and so illegally-induced abortions are often carried out in unsafe conditions. These present a significant burden on women and the healthcare system. It can also be expected that these abortions may be associated with more severe disutility. This may mean that the estimate provided here is not applicable in the Australia context.

Study	Study description	Results derived from the study	Comments
Rowley et al, 1998	Decision analysis was performed to conduct an economic evaluation of prenatal screening for cystic fibrosis carriers. As part of the economic evaluation, a TTO study was undertaken to assess the utility of individuals with CF, mothers of individuals with CF and fathers of individuals with CF. The TTO was conducted in teenage children by asking them the TTO question. In the case of younger children, the question was asked to parents with the instruction that they adopt the child's point of view. Additionally, all parents were asked about the effect of having a child with CF on their own quality of life.	Utility of cystic fibrosis: In individuals with CF = 0.70 In mothers of individuals with CF = 0.90 In fathers of individuals with CF = 0.95	The estimates assume a constant value over the whole course of the disease, rather than illness-stage-specific values. The approach, therefore, is somewhat crude. The sample size of the population in which TTO was undertaken is not clear.
Ryan et al, 1997	A utility study using conjoint analysis was conducted to estimate willingness to pay and utility weights with regards to management of miscarriage. The survey was mailed to 600 randomly selected women in Scotland, with two reminders sent. A total of 196 usable questionnaires were received. Two scenarios were compared: (1) Where there is no difference in the attributes of surgical and medical management. (2) Where medical management leads to more pain and complications than surgical management.	N/A	The results generated were not applicable to the health states of the model presented in Section D. The study was, therefore, excluded from further consideration.

Abbreviations: CF, cystic fibrosis; EQ-5D, European Quality of Life – Five Dimensions questionnaire; HRQoL, health-related quality of life; N/A, no applicable; PND, prenatal diagnosis; RCT, randomised clinical trial; TTO, time trade off

Two Chinese studies aimed at eliciting utility estimates were identified. Chan et al (2006) was a relatively small study of 67 Hong Kong women, which used the standard gamble method to estimate HRQoL associated with procedure-related miscarriage and giving birth to a child with Down syndrome. Compared with estimates generated in other studies discussed below, the utility weights were low. This is noted by the authors, who acknowledge the estimates are “much lower” than that reported in the Caucasian population included in Kuppermann et al (2000) and Grobman et al (2002). This comment acknowledges the possibility that the study may not be applicable to the Australian context due to cultural considerations. Consequently, the estimates reported in Chan et al (2006) were not considered further for inclusion in the economic evaluation. A similar conclusion was drawn in relation to Chan et al (2009), which used the standard gamble method in 276 women to estimate the disutility of miscarriage. Again, the estimate varied considerably from that reported in other studies, indicative of a mismatch due to cultural considerations. As such, the study was not given further consideration for inclusion in the economic evaluation.

Both Feeny et al (2000) and Feeny et al (2002) report the same study of 126 women from a Canadian RCT to estimate HRQoL associated with the effects of CVS and amniocentesis. The study used the standard gamble method to estimate a range of temporary and chronic health states associated with pregnancy and pregnancy outcomes. It is the chronic health states that are of greatest interest here. Table D.5.3 presents the full range of utility weights estimated for the chronic health states (assumed by the authors to be 40 years in duration, thereby capturing the long-term effects of potentially life-changing events).

**Table D.5.3 Utility weights reported in Feeny et al (2000) and Feeny et al (2002)**

Health state	Utility estimate
Abnormality detected; pregnancy terminated in the 11 <sup>th</sup> week	0.85
Abnormality detected; pregnancy terminated in the 20 <sup>th</sup> week	0.74
Abnormality reported; pregnancy terminated; told results were incorrect	0.45
Miscarriage in weeks 10-16; no test	0.87
Miscarriage; suspect due to test	0.75
Pregnancy loss after week 20; unlikely due to test	0.79
Test reported normal; birth of Down syndrome baby – test results incorrect	0.45
No test available; birth of Down syndrome baby	0.55
Risk of abnormality; choose not to become pregnant	0.79

The range of utility weights estimated by Feeny and colleagues is comprehensive. TOP is accounted for, as is miscarriage. That said, both of these was estimated with finer granularity in the study relative to the economic model in Section D; the study accounted for the time at which these events took place and, in the case of miscarriage, whether the miscarriage was likely to be procedure-related or not (as opposed to possibly). The study also estimated the HRQoL associated with an affected live birth, using the proxy of a birth to a child with Down syndrome. Affected live births were further disaggregated to consider those due to an incorrect diagnostic test and those that occurred in the case of no test being administered. In all, the health states estimated by Feeny and colleagues matched those of the economic model reasonably well. Further, no serious methodological concerns were identified.

Grobman et al (2002) presents the results of an interviewer-assisted survey administered to 186 pregnant women receiving antepartum care. The standard gamble approach was used to elicit utility weight estimates of giving birth to a child with Down syndrome and experiencing a miscarriage. The study made no attempt to relate the outcome of a Down syndrome birth to the reason for it occurring (as in the case of Feeny et al (2002), for example). Additionally, it is not clear that the study took any steps to link miscarriage to the use of diagnostic tests. As such, it can only be assumed that the estimate does not include procedure-related miscarriage. Note also that the mean values reported in the study were consistently lower than the median values, thereby indicating that they may be influenced by extreme low outliers. This would limit their usefulness in the economic evaluation.

Harris et al (2001) presents a decision analysis, relying on preference scores obtained in pregnant women, to determine whether guidelines maximise such women's HRQoL. The paper, however, does not present results of an original utility study. Instead, it uses utility weights estimated by another source (Kuppermann et al, 1999), which was included for review on this basis. This is discussed below.

Kuppermann et al (1999) reports results from a cross-sectional study of 72 women seeking genetic counselling to determine how they valued the outcomes of testing. The standard gamble method was used. The study population was somewhat homogenous and tended to be well educated and affluent. Additionally, the health states included for utility weight estimation focussed heavily on the final outcome (birth of an unaffected or affected child in either the current pregnancy or a future pregnancy, or no birth either in the current pregnancy or thereafter), making it difficult to isolate the utility impact of the intermediate events (such as miscarriage or termination). As such, the study was of limited use in the context of the economic evaluation.

Kuppermann et al (2000) reports preferences for procedure-related miscarriage and the birth of an infant affected by Down syndrome on the basis of a study in 534 women. Both standard gamble and time trade off (TTO) were used in this study. Non-procedure-related miscarriage was not considered, nor was TOP.

A final study by Kupperman and colleagues (2004) presents standard gamble and TTO results for 12 prenatal testing outcomes elicited from 584 pregnant women aged 16-47 years. As in the case of Kuppermann et al (1999), however, the health states were designed in a way that focussed heavily on the final birth outcomes (affected/unaffected and current/future). As described above, this renders it difficult to isolate the HRQoL impact of the intermediate events such as miscarriage and even TOP, and thus makes it difficult to reconcile with the model structure presented in Section D.

The EQ-5D was used in a study reported by Lubinga et al (2013) to assess utility weights for obstetric visits and abortion complications among 139 Ugandan women. The health states were a poor match for those required by the economic model and were underpinned by factors, both cultural and legal, which made them unsuitable for use in the evaluation.

Decision analysis was undertaken in a study reported by Rowley et al (1998) to determine the cost-effectiveness of prenatal screening for cystic fibrosis. As part of the evaluation, a TTO study was conducted to elicit the utility of individuals with the disease as well as that of their mothers and fathers. The sample size of the population in which the TTO was conducted, however, is not clear. Additionally, it was difficult to reconcile the utility



weight results with the current application's stated aim to minimise the possibility of inter-study variance due to sourcing values from a range of sources.

A conjoint analysis was used in the study reported by Ryan et al (1997) to determine willingness to pay and utility with regards to management of miscarriage. The study considered and compared two scenarios (where there is no difference between the attributes of surgical and medical management, and whether medical management leads to more pain and complications than surgical management). The results generated were not applicable to the health states of the model presented in Section D.

### D.5.3. Relationship of the pre-modelling study to the economic evaluation

The utility weights estimated by Feeny et al (2000 and 2002) were the most suitable for application to the economic evaluation presented in Section D. Additionally, as stated previously, there is a considerable advantage to sourcing all utility estimates required from a single source. In doing so, there is a minimisation of potential bias resulting from using disparate sources that are not internally consistent (i.e. from different study populations using heterogeneous methods).

Table D.5.4 presents a summary of the utility weights applied to the economic model and their source values.

Table D.5.4 Utility weights applied to the economic evaluation

Health state	Value	Source	Notes
Unaffected live birth	1.00	Assumption	
Affected live birth	0.55	Feeny et al (2002) estimate for the birth of an infant with Down syndrome in cases in which no test was administered	
Affected live birth following an incorrect diagnosis of abnormality free	0.45	Feeny et al (2002) estimate for the birth of an infant with Down syndrome in cases in which a test was administered leading to a false negative result	
Termination of pregnancy	0.55	Feeny et al (2002) estimate for TOP following detection of an abnormality; termination in the 11 <sup>th</sup> week	Alternative value associated with a termination after detection of an abnormality; termination in the 20 <sup>th</sup> week is tested in sensitivity analysis
Miscarriage (including procedure-related)	0.75	Feeny et al (2002) estimate for miscarriage suspected to be due to diagnostic test	Alternative value associated with pregnancy loss after week 20 but unlikely to be test related is tested in sensitivity analysis
Miscarriage	0.87	Feeny et al (2002) estimate for miscarriage in cases in which no test was administered	
Failed IVF cycle	0.79	Assumption	Based on Feeny et al (2002) estimate for the utility of the choice to not become pregnant due to the risk of abnormality
No pregnancy	0.79	Based on Feeny et al (2002) estimate for the utility of the choice to not become pregnant due to the risk of abnormality	

Abbreviations: IVF, in vitro fertilisation; TOP, termination of pregnancy

Of the utility weight estimates presented in Table D.5.4, that associated with miscarriage which may be procedure-related is perhaps the most uncertain. It considers a time factor (at week 11), while the economic model presented in Section D is not structured to

consider the timing of the miscarriage. Feeny et al (2002) also estimated the utility of pregnancy loss after week 20, which is unlikely to be procedure-related. Although this may also be applicable to the health state, this value was deemed inappropriate for application to the base case of the model presented in Section D for several reasons. The most important of these is that, in the event of a pregnancy loss after diagnostic testing, the parent is likely to perceive that the miscarriage was procedure-related even when this was not the case. The HRQoL would be impacted by this perception, rendering the alternative utility estimate redundant. Nonetheless, sensitivity analyses considering the impact of this estimate were conducted and are discussed in Section D.6. Moreover, the estimates applied in the base case for a range of health states were varied in sensitivity analyses.

## **D.6. Issue 5: Healthcare resource use and associated costs**

To accurately assess the incremental cost-effectiveness of PGD relative to natural conception with prenatal testing and natural conception alone, a comprehensive assessment of all relevant costs is required. While the costs associated with IVF are considerable, and the importance of PGD costs obvious, other downstream costs associated with the pregnancy must also be accounted for. Estimation of all relevant costs is the focus of this section.

### **D.6.1. Focused analytical plan**

To accurately estimate the true cost associated with each arm of the model, a number of events were identified for costing (see Table D.6.1).

Table D.6.1 Modelled events requiring cost estimates

Row	Event	Description
A	IVF cycles to embryo transfer, biopsy and genetic testing (PGD)	PGD and successful IVF cycle enabling embryo transfer. This event comprises: Initial and follow-up visit with genetic counsellor for referral to fertility specialist <sup>a</sup> PGD test design and validation Planning and management for artificial insemination Assisted reproductive technologies superovulated treatment cycle proceeding to oocyte retrieval IVF related medications Oocyte retrieval Intracytoplasmic sperm injection Embryo biopsy <sup>b</sup> Embryo genetic analysis Freezing of excess embryos for later use
B	PGD with incomplete IVF cycle	PGD with the IVF cycle being incomplete due to oocyte retrieval process being cancelled. This event comprises: Initial and follow-up visit with genetic counsellor for referral to fertility specialist <sup>a</sup> PGD test design and validation Planning and management for artificial insemination Assisted reproductive technologies superovulated treatment cycle that is cancelled before oocyte retrieval
C	PGD without successful biopsy	PGD with the IVF cycle being incomplete due to failure to undertake successful biopsy. This event comprises: Initial and follow-up visit with genetic counsellor for referral to fertility specialist <sup>a</sup> PGD test design and validation Planning and management for artificial insemination Assisted reproductive technologies superovulated treatment cycle proceeding to oocyte retrieval IVF related medications Oocyte retrieval Intracytoplasmic sperm injection
D	Transfer of embryos	Transfer of embryos to attempt pregnancy. This event comprises: First transfer of embryos Preparation of frozen embryos for transfer in subsequent attempts to impregnate after failure to do so (2.4 times on average) Transfer of frozen embryos in subsequent attempts to impregnate after failure to do so (2.4 times on average)
E	Prenatal testing	Prenatal testing, conducted in either the PGD arm in those who choose to undergo such testing or the natural conception with PNT arm. This event comprises: Specialist consultation Ultrasound dating CVS or amniocentesis (use distributed among individuals) Study of whole of every chromosome on any tissue or fluid except blood (chromosomal rearrangements only) Analysis of one or more regions on all chromosomes for specific genetic abnormalities of fresh tissue (SGDs only)
F	Miscarriage	Miscarriage of pregnancy, regardless of whether PGD or PNT has taken place
G	TOP	Elective TOP following a positive prenatal test result indicative of abnormality
G	Live birth	Live birth, regardless of whether the child is affected or unaffected by genetic abnormality

Abbreviations: CVS, chorionic villus sampling; IVF, in vitro fertilisation; PGD, preimplantation genetic diagnosis; PNT prenatal testing; SGDs, single gene disorders; TOP, termination of pregnancy

<sup>a</sup> Applied also to the natural conception with PNT arm. Always applied as a once-only cost, not applied in cases of re-attempts at pregnancy.

<sup>b</sup> Assumed to be a once-only fee for all embryos biopsied within a single IVF cycle.

To estimate the costs associated with the events listed in row A through C of Table D.6.1, it was first necessary to estimate the frequency with which these events apply to the average patient undergoing PGD with IVF.

From ESHRE data (see Appendix 4), it is known that couples with SGDs will require an average of 1.31 IVF cycles before a successful biopsy and subsequent attempt to transfer an embryo. In the case of couples with chromosomal rearrangements, the same data reveal that the average number of cycles is 1.59. Since all are assumed to end with a transfer attempt, there are 0.31 and 0.59 unsuccessful cycles in the case of SGDs and chromosomal rearrangements, respectively.

This means that, in order to successfully reach the point at which embryos can be transferred to attempt pregnancy, the average patient will use all resources shown in row A of Table D.6.1 as well as the resources presented in row B and row C a total of 0.31 or 0.59 times on average. Table D.6.2 calculates how often the resources associated with unsuccessful attempts are required on average in the case of both SGDs and chromosomal rearrangements

**Table D.6.2 Distribution of cycles required prior to embryo transfer, average per patient**

Row	Parameter	SGDs	Chromosomal rearrangements	Reference
A	IVF cycles to biopsy and embryo transfer	1.31	1.59	ESHRE (Appendix 4)
B	Complete cycles required	1	1	Assumption
C	Incomplete cycles required	0.31	0.59	Row C = row A - row B
D	Proportion of failed IVF cycles due to unsuccessful oocyte retrieval	0.0009	0.0009	Calculated from Protocol <sup>a</sup>
E	Proportion of failed IVF cycles due to unsuccessful biopsy	0.9991	0.9991	Calculated from Protocol <sup>a</sup>
F	Attempts ending with cancelled oocyte retrieval	0.0003	0.0005	Row F = row C x row D
G	Attempts ending with failure to successfully undertake biopsy	0.3097	0.5895	Row G = row C x row E

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; SGD, single gene disorders

<sup>a</sup> According to Genea PGD cycle data 2010-2011, 0.02% of oocyte retrieval cycles are cancelled prior to retrieval. Additionally, approximately 22.5% of all attempted cycles end with an unsuccessful attempt to undertake biopsy.

The data from Table D.6.2 can be superimposed on the events presented in Table D.6.1 to present the average frequency of these events. This is presented in Table D.6.3. The weighted average was calculated on the basis of 65% of the population comprising couples with SGDs, while the remainder are those with chromosomal abnormalities (five most recent years of ESHRE data collection; see Appendix 4).

**Table D.6.3 Average frequency of events required prior to embryo transfer**

Event	Frequency in couples with SGDs	Frequency in couples with chromosomal rearrangements	Weighted average frequency <sup>a</sup>
IVF cycles to biopsy, genetic testing (PGD) and embryo transfer	1	1	1
PGD with incomplete IVF cycle due to unsuccessful oocyte retrieval	0.0003	0.0005	0.0004
PGD without successful biopsy	0.3097	0.5895	0.4076

Abbreviations: IVF, in vitro fertilisation; PGD, preimplantation genetic diagnosis; SGD, single gene disorder

<sup>a</sup> Calculated on the basis of 65% of the population comprising single gene disorders

A similar approach was taken with regards to the transfer of embryos, the difference being that the approach was applied to the individual components of the event. Table D.6.4 presents the details of this.

**Table D.6.4 Average frequency of resource use required for successful embryo transfer**

Event	Frequency in couples with SGDs	Frequency in couples with chromosomal rearrangements	Weighted average frequency	Reference
Proportion of population	0.65	0.35	1	See Appendix 4
Attempts required to transfer embryos and achieve pregnancy	3.39	3.54	3.44	ESHRE (see Appendix 4)
First transfer of embryo	1	1	1	Convention
Preparation of frozen embryos for transfer in subsequent attempts to impregnate	2.39	2.54	2.44	Calculated
Transfer of frozen embryos in subsequent attempts to impregnate	2.39	2.54	2.44	Calculated

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; SGD, single gene disorders

The average frequency of miscarriage, TOP and live births was not necessary to consider at this stage. As described elsewhere, the frequency of these events was determined by transition probabilities (see Section D.4).

The unit costs associated with the resources presented in Table D.6.1 are presented in Table D.6.5 through Table D.6.9. Although not captured in the resource use estimates, other fees may be relevant (e.g. Pathology Episode Initiation and Bulk Billing).

**Table D.6.5 Requested fees associated with PGD**

Parameter	Unit cost	Reference
PGD Stage 1: Genetic test design and validation	\$1736.00	Applicant
PGD Stage 2: Embryo biopsy	\$115.00 <sup>a</sup>	Applicant
PGD Stage 3: Embryo genetic analysis	\$635.00	Applicant

Abbreviations: PGD, preimplantation genetic diagnosis

<sup>a</sup> The Applicant has requested this fee per embryo tested. For the base case it has been applied as a single fee (applies to all embryos biopsied in a single cycle) but for the sensitivity analysis it has been applied on a per embryo basis.

**Table D.6.6 Unit cost of MBS items used in the economic analysis**

Parameter	Unit cost	Reference
Genetic counselling (initial consultation)	\$263.90	MBS 132
Genetic counselling (subsequent consultation)	\$132.10	MBS 133
Planning and management for artificial insemination	\$84.70	MBS Item 13209
Assisted reproductive technologies superovulated treatment cycle proceeding to oocyte retrieval - initial cycle in a single calendar year	\$3110.75	MBS Item 13200
Assisted reproductive technologies superovulated treatment cycle proceeding to oocyte retrieval - subsequent cycle in a single calendar year	\$2909.75	MBS Item 13201
Assisted reproductive technologies superovulated treatment cycle that is cancelled before oocyte retrieval	\$465.55	MBS Item 13202
Oocyte retrieval for assisted reproductive technologies	\$354.45	MBS Item 13212
Intracytoplasmic sperm injection	\$417.95	MBS Item 13251
Transfer of embryos	\$111.10	MBS Item 13215
Preparation of frozen or donated embryos or oocytes for transfer	\$793.55	MBS Item 13218
Specialist consultation	\$85.55	MBS Item 104
Ultrasound dating	\$60.00	MBS Item 55700
CVS	\$121.85	MBS Item 16603
Amniocentesis	\$63.50	MBS Item 16600
Study of whole of every chromosome on any tissue or fluid except blood	\$394.55	MBS Item 73287
Analysis of one or more regions on all chromosomes for specific genetic abnormalities	\$230.95	MBS Item 73293

Abbreviations: CVS, chronic villus sampling; MBS, Medicare Benefits Schedule

**Table D.6.7 Unit cost of miscellaneous resources used in the economic analysis**

Parameter	Unit cost	Reference
IVF related medications	\$1620.00	Pharmaceutical Benefits Branch, Department of Health and Ageing, Independent Review of ART, 2006
Freezing and cryopreservation of embryos for up to one year	\$770.00	Genea <sup>a</sup>

Abbreviations: ART, assisted reproductive technologies; IVF, in vitro fertilisation  
<sup>a</sup> <http://www.genea.com.au/my-fertility/i-need-help/costs-payments> (Accessed March 10, 2015)

**Table D.6.8 Unit cost of terminations of pregnancy and miscarriage**

Parameter	Unit cost	Reference
Termination of pregnancy	\$2241.00	AR-DRG O05Z
Miscarriage of pregnancy	\$1780.00	AR-DRG O63Z

Source: National Hospital Cost Data Collection Australian Public Hospitals Cost Report 2011-2012, Round 16

Table D.6.9 Unit cost of live births

AR-DRG code	Separations	Total cost	Weighted cost
O01A	4358	\$18,248.17	\$369.92
O01B	11571	\$12,369.55	\$665.77
O01C	45608	\$10,061.30	\$2,134.51
O02A	1638	\$10,763.56	\$82.01
O02B	4915	\$7,525.90	\$172.06
O60A	16408	\$8,006.76	\$611.10
O60B	102438	\$5,127.26	\$2,443.14
O60C	28044	\$3,827.76	\$499.33
Average	-	-	\$6977.84

Abbreviations: AR-DRG, Australian Refined Diagnosis-Related Group

The cost data presented in Table D.6.5 through Table D.6.9 were used in conjunction with resource use data to estimate the unit costs associated with each event described in Table D.6.1. The results are presented in Section D.6.2

### D.6.2. Results of the pre-modelling studies

The frequency of events, resource use frequency and unit costs presented in Section D.6.1 were used to calculate the costs associated with the events listed in Table D.6.1.

Table D.6.10 presents the calculated cost of each type of cycle leading to a successful IVF cycle with biopsy enabling embryo transfer (rows A through C of Table D.6.1). Table D.6.11 presents the average cost incurred per patient by the time embryos are biopsied and ready for transfer.

Table D.6.10 Total average cost of genetic testing, IVF cycles and biopsy

Resource	Unit cost	Frequency per event	Cost per event
<i>IVF cycles to embryo transfer, biopsy and genetic testing (PGD)</i>			
	-	-	-
Genetic counselling (initial visit)	\$263.90	1	\$263.90
Genetic counselling (subsequent visit)	\$132.10	1	\$132.10
PGD Stage 1: genetic test design and validation	\$1,736.00	1	\$1736.00
Planning and management for artificial insemination	\$84.70	1	\$84.70
Assisted reproductive technologies superovulated treatment cycle proceeding to oocyte retrieval	\$3,110.75	1	\$3110.75
IVF related medications	\$1,620.00	1	\$1620.00
Oocyte retrieval	\$354.45	1	\$354.45
Intracytoplasmic sperm injection	\$417.95	1	\$417.95
PGD Stage 2: Embryo biopsy	\$115.00	1	\$115.00
PGD Stage 3: Embryo genetic analysis	\$635.00	1	\$635.00
Freezing of excess embryos	\$770.00	1	\$770.00
<i>Subtotal</i>	-	-	<i>\$9239.85</i>
<i>PGD with incomplete IVF cycle</i>			
	-	-	-
Genetic counselling (initial visit)	\$263.90	1	\$263.90
Genetic counselling (subsequent visit)	\$132.10	1	\$132.10
PGD Stage 1: genetic test design and validation	\$1,736.00	1	\$1736.00
Planning and management for artificial insemination	\$84.70	1	\$84.70
Assisted reproductive technologies superovulated treatment cycle that is cancelled before oocyte retrieval	\$465.55	1	\$465.55
<i>Subtotal</i>	-	-	<i>\$2682.25</i>
<i>PGD without successful biopsy</i>			
	-	-	-
Genetic counselling (initial visit)	\$263.90	1	\$263.90
Genetic counselling (subsequent visit)	\$132.10	1	\$132.10
PGD Stage 1: genetic test design and validation	\$1,736.00	1	\$1736.00
Planning and management for artificial insemination	\$84.70	1	\$84.70
Assisted reproductive technologies superovulated treatment cycle proceeding to oocyte retrieval - subsequent cycle in a single calendar year	\$2,909.75	1	\$2,909.75
IVF related medications	\$1,620.00	1	\$1,620.00
Oocyte retrieval	\$354.45	1	\$354.45
Intracytoplasmic sperm injection	\$417.95	1	\$417.95
<i>Subtotal</i>	-	-	<i>\$7518.85</i>

Abbreviations: IVF, in vitro fertilisation; PGD, preimplantation genetic diagnosis



Table D.6.11 Average per patient cost of events leading to embryo IVF cycles to embryo transfer, biopsy and genetic testing

Event	Cost per event	Events per patient	Average cost per patient
IVF cycles to biopsy, genetic testing and embryo transfer,	\$9239.85	1	\$9239.85
PGD with incomplete IVF cycle	\$2682.25	0.0004	\$0.97
PGD without successful biopsy	\$7518.85	0.4076	\$3064.71
<i>Total</i>	-	-	<i>\$12,626.50</i>

Abbreviations: IVF, in vitro fertilisation; PGD, preimplantation genetic diagnosis

Table D.6.12 presents the total average cost of successfully transferring embryos and achieving pregnancy.

Table D.6.12 Average per patient cost of successful embryo transfer and impregnation

Event	Unit cost	Resources per patient	Average cost per patient
First transfer of embryos	\$111.10	1	\$111.10
Preparation of frozen embryos for transfer in subsequent attempts to impregnate	\$793.55	2.44	\$1938.25
Transfer of frozen embryos in subsequent attempts to impregnate	\$111.10	2.44	\$271.71
<i>Total</i>			<i>\$2320.71</i>

Table D.6.13 sums the results of Table D.6.11 and Table D.6.12 to present the total average cost of achieving pregnancy via IVF after PGD.

Table D.6.13 Total average cost of successful pregnancy with IVF and PGD

Event	Cost per event	Events per patient	Average cost per patient
IVF cycles to embryo transfer, biopsy and genetic testing	\$9239.85	1	\$9239.85
PGD with incomplete IVF cycle	\$2682.25	0.0004	\$0.97
PGD without successful biopsy	\$7518.85	0.4076	\$3064.71
Successful transfer of embryos leading to pregnancy	\$2320.71	1	\$2320.71
<i>Total</i>	-	-	<i>\$14,626.50</i>

Abbreviations: IVF, in vitro fertilisation; PGD, preimplantation genetic diagnosis

Table D.6.14 presents the average cost of prenatal testing, accounting for the split of SGDs and chromosomal rearrangements described above. It was assumed that the rates of CVS versus amniocentesis was the same among the SGD and chromosomal abnormality groups.

**Table D.6.14 Average cost of prenatal testing**

Event	Unit cost	Frequency per patient	Average cost per patient
Specialist consultation	\$85.55	1	\$85.55
Ultrasound dating	\$60.00	1	\$60.00
CVS <sup>a</sup>	\$121.85	0.372	\$45.33
Amniocentesis <sup>a</sup>	\$63.50	0.628	\$39.88
Analysis of one or more regions on all chromosomes for specific genetic abnormalities of fresh tissue	\$230.95	0.65	\$150.12
Study of whole of every chromosome on any tissue or fluid except blood	\$394.55	0.35	\$138.09
<i>Total</i>	-	-	<i>\$518.97</i>

Note: Genetic counselling was also applied in the natural conception with PNT arm to reflect the need for these consultations to be costed

Abbreviations: CVS, chorionic villus sampling

<sup>a</sup> Calculated from MBS data 2014 (Items 16603 and 16600) – see Appendix 4

The healthcare resource use and associated costs from this pre-modelling study are presented in Table D.6.15.

**Table D.6.15 Costs applied to events included in the economic evaluation**

Event	Unit cost	Cross reference
IVF cycles to embryo transfer, biopsy and genetic testing	\$12,626.50	Table D.6.11
Successful transfer of embryos to achieve pregnancy	\$2320.71	Table D.6.12
Prenatal testing	\$518.97	Table D.6.14
Miscarriage	\$1780.00	Table D.6.8
Termination of pregnancy	\$2241.00	Table D.6.8
Live birth	\$6977.84	Table D.6.9

Abbreviations: IVF, in vitro fertilisation; PGD, preimplantation genetic diagnosis

### **D.6.3. Relationship of the pre-modelling study to the economic evaluation**

The costs presented in Table D.6.15 were applied to the economic model, as described in Section D.4. In the case of prenatal testing, miscarriage and live births, these were applied according to the transition probabilities described in Section D.4. The unit costs of the other events were applied to all individuals in the PGD with IVF arm, as they represent the total average cost of achieving pregnancy in this manner.

The impact of the costs presented in Table D.6.15 on the results of the economic evaluation are explored and discussed in Section D.6.

# Section E. Economic evaluation for the main indication

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## E.1. Overview of the economic evaluation

As described previously in this Assessment Report, public funding of PGD is being requested for couples who carry a specific mutation(s) for a serious genetic disorder which is at high risk of being passed onto their offspring. The absence of public funding for PGD at this time means that costs are currently covered by the facility providing the test or by the couple planning a pregnancy.

This section presents an economic evaluation of the Applicant's proposal 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. The evaluation relates to the proposal for a three-stage diagnostic procedure comprising:

1. Genetic test design and validation;
2. Embryo biopsy; and
3. Embryo analysis.

The economic evaluation reflects the Applicant's claim that PGD is as effective in identifying genetic disorders as prenatal diagnosis. More importantly, however, it also reflects the claim that the time delay associated with prenatal diagnosis and the inflated risk of abnormalities in the population of interest, makes PGD a superior outcome for couples at high risk of having a child with a genetic disorder.

## E.2. Population and circumstances of use reflected in the economic evaluation

The population and circumstances of use were described previously in Section C.2. The population comprises:

1. Couples who carry a specific mutation(s) for a serious 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 at high risk of causing unbalanced genetic content leading to miscarriage, stillbirth, serious congenital abnormality or a genetic disorder in their offspring.

For simplicity, as described elsewhere in this Assessment Report, the model focuses on the female attempting to become pregnant for its perspective. Specifically, this is the perspective with respect to the accrual of utility weights over the duration of the model. As discussed in Section D.3, this has no impact on the incremental utility weights calculated, nor the final cost-utility ratio.

No key differences were identified between the requested listing and the economic evaluation presented here.

Where uncertainty around key inputs or assumptions was identified, the impact of these is tested in sensitivity analyses presented in Section D.6.

### **E.3. Structure and rationale of the economic evaluation**

The structure of the model used in the current economic evaluation was informed by the health economics literature. In particular, studies presenting economic evaluations of diagnostic testing (with IVF or not) and screening among couples with an elevated risk of passing on chromosomal abnormalities were considered. The primary focus of examining such studies was to garner information that could be used to inform the structure of the current evaluation. A summary of the studies considered is presented in Table E.3.1 below. These studies were identified via a literature search which is presented in Appendix 4.

Table E.3.1 Published economic evaluations considered to inform the model structure

Study	Analysis	Model type	Comments
Harris et al, 2001	Comparison of the choice of CVS, amniocentesis and no testing for women who are deciding whether or not to undergo prenatal testing.	Decision analytic model to assess preferences (utilities). The model does not consider costs.	<p>Model considered several outcomes related to diagnostic testing decisions, including:</p> <ul style="list-style-type: none"> <li>• birth of child with no chromosomal disorder</li> <li>• birth of child with chromosomal disorder</li> <li>• birth of child with limb abnormality</li> <li>• miscarriage</li> <li>• elective TOP</li> <li>• test performance characteristics</li> <li>• whether future birth occurs after pregnancy loss</li> </ul> <p>False negative and false positive results were accounted for. Due to the scope of the research question, it did not consider unsuccessful attempts at pregnancy.</p>
Harris et al, 2004	Prenatal testing (CVS and amniocentesis) versus no invasive testing in women who, through screening, have been shown to be at high risk of giving birth to an infant with a chromosomal abnormality.	Decision analytic model to assess cost-utility.	<p>Model considered several outcomes related to diagnostic testing decisions, including:</p> <ul style="list-style-type: none"> <li>• birth of child with no chromosomal disorder</li> <li>• birth of child with chromosomal disorder</li> <li>• miscarriage</li> <li>• elective TOP following positive diagnostic test result</li> <li>• whether future birth occurs after pregnancy loss</li> </ul> <p>False negative and false positive results were accounted for. The model followed from the tenth week of pregnancy through to mortality of the woman. Due to the scope of the research question, it did not consider unsuccessful attempts at pregnancy.</p>
Mersereau et al, 2007	Comparison of IVF alone versus IVF with PGS to prevent aneuploidy births in women with advanced maternal age.	Decision analytic model to assess the cost per healthy infant.	<p>The model considered a number of health states/events related to attempts to give birth to a healthy child, including:</p> <ul style="list-style-type: none"> <li>• whether there will be enough embryos to transfer with additional embryos for cryopreservation</li> <li>• whether there will be enough embryos to transfer without additional embryos for cryopreservation</li> <li>• whether there are not enough embryos to transfer</li> <li>• failure to impregnate</li> <li>• miscarriage</li> <li>• termination of the pregnancy owing to the diagnosis of aneuploidy</li> </ul> <p>False negative and false positive results were accounted for. The model allowed scope for repeated attempts at IVF or IVF with PGS for up to two fresh cycles with up to one frozen cycle per fresh cycle.</p>

Study	Analysis	Model type	Comments
Tur-Kaspa et al, 2010	Comparison of IVF with PGD versus natural conception to explore the benefits relating to avoidance of cystic fibrosis born to carrier couples.	Cost-benefit analysis using a decision analytic model.	<p>The model considered several outcomes related to diagnostic testing decisions, pregnancy and birth, including:</p> <ul style="list-style-type: none"> <li>• birth of a child free of cystic fibrosis</li> <li>• birth of a child with cystic fibrosis</li> <li>• miscarriages</li> <li>• terminations owing to positive diagnostic test results</li> </ul> <p>False negative and false positive results were accounted for. The model allowed for repeated attempts in the event of unsuccessful IVF cycles.</p>
Davis et al, 2010	Comparison of PGD in carrier couples of cystic fibrosis compared with natural conception followed by prenatal testing and termination of affected pregnancies.	Cost-benefit analysis using a Markov model simulating a cohort of 1000 couples who are both cystic fibrosis carriers.	<p>The model considered a range of possible outcomes, including:</p> <ul style="list-style-type: none"> <li>• no pregnancy</li> <li>• miscarriage</li> <li>• elective abortion</li> <li>• birth of a healthy baby</li> <li>• birth of a baby affected by cystic fibrosis</li> <li>• birth of twins (each normal or affected by cystic fibrosis)</li> </ul> <p>False negative and false positive results were accounted for. The model allowed for repeated attempts at conceiving with PGD. The analysis started with the decision to conceive and therefore included consideration of failed attempts to do so. By applying lifetime medical costs and earning, the model took a lifetime perspective.</p>
Ohno et al, 2013	Comparison of non-invasive prenatal testing that did not require amniocentesis for diagnosis of Down syndrome versus screening with non-invasive prenatal testing which would require amniocentesis.	Decision analytic model to assess the incremental cost-utility of screening.	<p>The model considered a range of possible outcomes, including</p> <ul style="list-style-type: none"> <li>• live birth of a normal child</li> <li>• live birth of a child affected by Down syndrome</li> <li>• elective termination</li> <li>• miscarriage</li> </ul> <p>False negative and false positive results were accounted for. Due to the scope of the research question, it did not consider unsuccessful attempts at pregnancy. By applying lifetime costs of treating Down syndrome, the model took a lifetime perspective.</p>

Abbreviations: CVS, chorionic villus sampling; IVF, in vitro fertilisation; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening; TOP, termination of pregnancy

In all, the published models did not correspond well with the research question 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.

It was clear from these studies that a variety of outcomes and events were relevant for consideration in the current evaluation. These included:

- birth of a child unaffected by chromosomal disorders;
- birth of a child affected by chromosomal disorders;
- miscarriage during the course of the pregnancy; and
- elective termination in the event of a positive diagnosis of genetic abnormality.

The studies also highlighted the importance of diagnostic accuracy, which was considered in all of the economic models. Accounting for false negative results, in particular, was shown to have important consequences in terms of final outcomes.

Additionally, the impact of allowing for repeated attempts at conception, either via IVF or natural conception was considered important. Tur-Kaspa et al (2010) allowed for up to six attempts at IVF; Davis et al (2010) ran a broad range of attempts, including (i) natural conception and IVF being repeated until completion (theoretically an unlimited number of cycles until birth) with no requirement for patients to stop attempting conception or switching method of conception; (ii) limiting the number of cycles in the IVF arm between one and six; and (iii) an analysis limiting the number of IVF cycles before women switch to reliance on natural conception.

Although 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 (see Davis et al. 2010 for the best example of this).

Together, these studies informed the structure presented in Figure E.1 through Figure E.3, which provide simplified schematics of the three arms considered in the economic model:

1. PGD;
2. Natural conception with prenatal testing (PNT); and
3. Natural conception with no diagnostic testing.

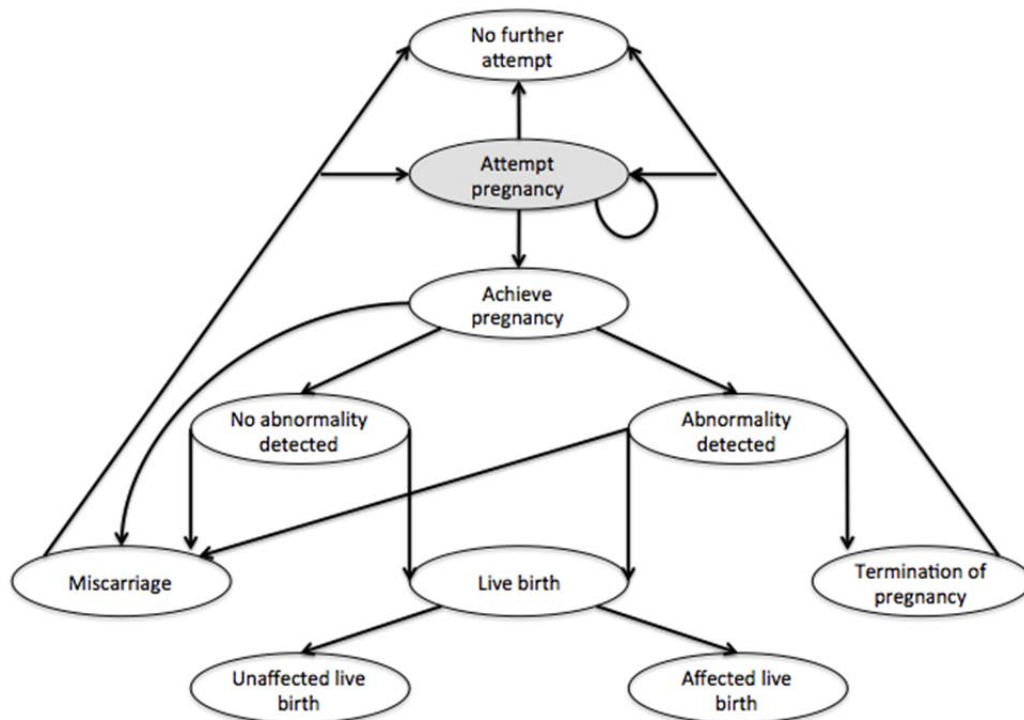
The cost-effectiveness of PGD is assessed against both other arms of the model. While it is acknowledged that some couples may not be able to conceive naturally and would need to undergo IVF even if PGD is not available, for simplicity, this small, specific patient group has not been included in the economic analysis.

A cost-utility approach was adopted for the economic evaluation. 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. This is similar to the cost-utility studies presented in Table E.3.1. While the birth of an unaffected child, or otherwise, will 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.





Figure E.2 Simplified schematic of the model arm representing natural conception with prenatal testing



In the arm capturing natural conception with PNT (Figure E.2), there are a number of differences relative to the PGD arm discussed above.

The first difference is that not all women achieve pregnancy within the first cycle of the model. Although the model applies 20-week cycles, thereby allowing multiple attempts, some will fail to conceive over the course of this period (see Section D.4). Those who do not conceive may continue with further attempts at conception or choose to not pursue a pregnancy at this time.

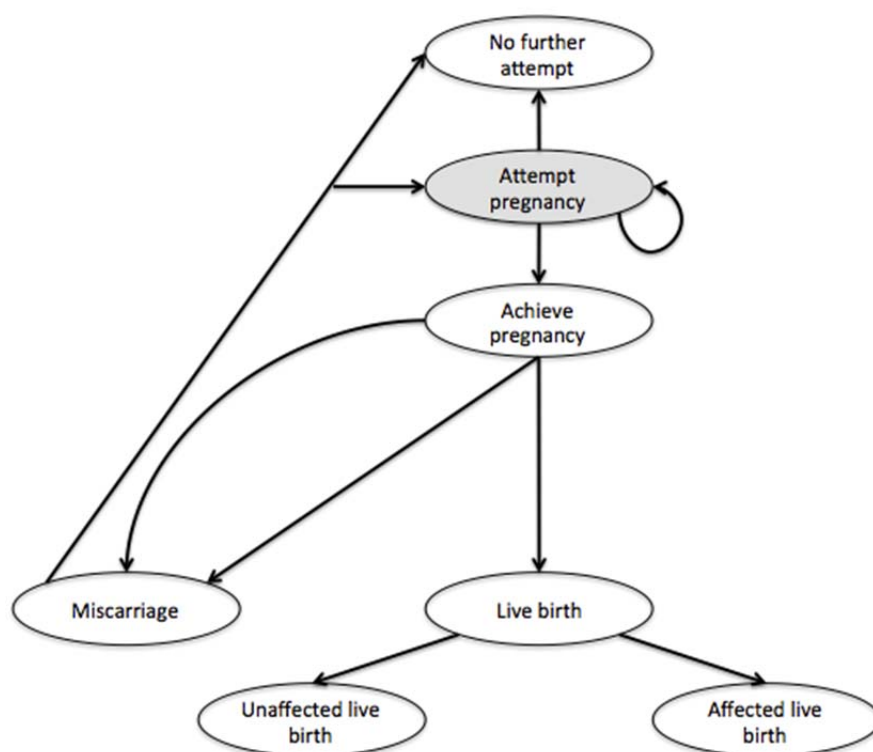
Those who do become pregnant, as in the case of the PGD arm, are at risk of miscarriage for the duration of the pregnancy.

Over the course of the pregnancy, all women in this arm of the model will undergo prenatal testing with either CVS or amniocentesis. This differs from the PGD arm, in which prenatal testing occurs in a proportion of women who seek confirmation of their PGD result. Prenatal testing will lead to abnormalities being detected in some fetuses, while the majority are abnormality free. As in the case of the PGD arm, those who have abnormalities detected may choose to terminate the pregnancy at this time. If not, or if no abnormality is detected, the pregnancy will result in a live birth if not interrupted by miscarriage.

Live births can be categorised as either affected or unaffected to account for the possibility that false negative results can occur in prenatal tests.

Similar to the PGD arm, those who fail to give birth due to either a miscarriage or due to a TOP will choose to either attempt pregnancy once more or to not attempt conception, as determined by probabilities applied to the model.

Figure E.3 Simplified schematic of the model arm representing natural conception with no diagnostic testing



The structure of the natural conception with no diagnostic testing arm of the model is similar to that presented in Figure E.2. In the absence of diagnostic testing, however, there is no way to identify abnormalities. Consequently, TOP is not considered within this arm of the model. All pregnancies result in either miscarriage or in a live birth. The latter are categorised as either unaffected or affected live births.

The model takes the form of a state-transition Markov model with non-constant transition probabilities applied where appropriate (e.g. the probability of re-attempting conception after failure to do so was reduced over time, as described in Section D.4, 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 model was run for 10 cycles of 20 weeks each in the base case. This represents a highly conservative approach, since it accounts for all costs associated with conception, pregnancy and birth but limits the accrual of utility to a short-term period even though utility weights, as discussed in Section D.5, are 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 is tested in sensitivity analyses presented in Section D.6, as is the impact of including long-term costs associated with ongoing medical interventions and therapy required in children born with genetic abnormalities (which has implications for the National Disability Insurance Scheme).

All costs and outcomes were discounted at 5% per annum, in accordance with MSAC Guidelines. TreeAge Pro 2014 was used for all modelling.

## E.4. Variables in the economic evaluation

The variables applied to the economic model, and the assumptions made in relation to these, are discussed in turn in the section below. The variables comprise healthcare resource use/unit costs applied as well as clinical variables.

Where variables were discussed comprehensively as part of Section C, the discussion below is brief and cross-references what was presented previously.

Where simplifying assumptions were used, these are discussed and, where appropriate, tested in sensitivity analyses presented in Section D.6.

### E.4.1. Healthcare resource use and unit costs

Unit costs applied to the economic evaluation were presented previously in Table D.6.6 through Table D.6.9. Additionally, the costs associated with healthcare resource use at various points in the economic model were calculated and discussed at length in Section D.6, with the final estimates presented in Table D.6.15. Nonetheless, these are repeated in Table E.4.1 for transparency.

Table E.4.1 Costs applied to events included in the economic evaluation

Event	Unit cost	Cross reference
IVF cycles to embryo transfer, biopsy and genetic testing	\$12,626.50	Table D.6.11
Successful transfer of embryos to achieve pregnancy	\$2320.71	Table D.6.12
Prenatal testing	\$518.97	Table D.6.14
Miscarriage	\$1780.00	Table D.6.8
Termination of pregnancy	\$2241.00	Table D.6.8
Live birth	\$6977.84	Table D.6.9

Abbreviations: IVF, in vitro fertilisation; PGD, preimplantation genetic diagnosis

As described in Section D.6, the total average cost associated with successful IVF/biopsy of embryos and successful transfer was applied to all patients in the PGD arm of the model.

Prenatal testing was applied to all in the natural conception with PNT arm of the model and a proportion of the cohort in the PGD arm who elect to undergo prenatal testing.

The costs associated with miscarriage and live births were applied probabilistically to all three arms of the model.

The cost associated with termination was applied probabilistically to the PGD arm and the natural conception with PNT arm of the model. Since no terminations occur in the natural conception only arm of the model, this cost was not applied in that part of the model.

The model did not consider any other costs that may be associated with ongoing pregnancy. Although it is expected that pregnant women will undergo continued monitoring and ongoing consultations, these costs are negligible in relation to the other costs included in the economic model. They would have no impact on the final

conclusions of the economic evaluation. Additionally, inclusion of these costs is likely to favour PGD, since the total number of pregnancies is lowest in that arm of the model (see Section E.5.2). These considerations, and a preference for simplicity, means a conservative approach was taken by omitting these from the economic model.

Similarly, as described in Section D.3, downstream medical treatment costs associated with affected births were not included in the base case analysis. Although these costs may be substantial in some cases, they are subject to considerable uncertainty. This fact, along with the fact that their inclusion is likely to favour PGD relative to the comparators, means they were omitted from the base case. Instead, the impact of such costs was examined in sensitivity analyses reported in Section D.6.

#### E.4.2. Diagnostic accuracy of PGD and prenatal testing

It was essential to consider the diagnostic accuracy of both PGD and prenatal testing to reliably estimate the likelihood of giving birth to an unaffected child. If, for example, there were evidence that false negative results were common, one would expect a proportion of births to be affected by SGDs and chromosomal rearrangements even in the presence of testing.

As discussed in Appendix 4, in the case of PGD it is appropriate to assume a very low rate of false negative results (see Table E.4.3 for detail).

Due to the nature of the research question and the scope of the model, it was not necessary to consider the possibility of false positive results with PGD. In the event of such results, which would likely be rare, the embryo would not be transferred and alternative embryos would be used to impregnate.

In the case of prenatal testing with no prior PGD, 48.2% of results would indicate the presence of abnormality (Genea PGD cycle data 2010-2011), while the remaining 51.8% would give a negative result indicating no abnormality. As discussed in Appendix 4, it is also appropriate in the natural conception with PNT arm to assume that there were very few false negative results and that the vast majority of negative results were correct (see Table E.4.3 for detail). With regards to the negative results of prenatal testing without PGD, there is evidence to indicate that 0.03% of negative results using CVS are incorrect. Table E.4.2 presents the calculation of the false negative rate applied to the natural conception with PNT arm of the model.

Table E.4.2 Calculation of false negative rates applicable to prenatal testing with no PGD

Row	Parameter	Value	Reference
A	False negative rate with CVS	0.0003	ESHRE (see Appendix 4)
B	False negative rate with amniocentesis	0.0000	ESHRE (see Appendix 4)
C	Proportion of population using CVS	0.3720	See Appendix 4
D	Proportion of population using amniocentesis	0.6280	XXXSee Appendix 4
E	Average false positive rate of prenatal testing	0.0001	Row E = (row A x row C) + (row B x row D)

Abbreviations: CVS, chorionic villus sampling; ESHRE, European Society of Human Reproduction and Embryology

The diagnostic accuracy rates applied to the economic evaluation are presented in Table E.4.3, with descriptions of how they are applied to the model.

Table E.4.3 Diagnostic accuracy rates applied to the economic model

Name in model	Description	Value	Reference
p_Prenatal_PGD_Abn	Probability of an abnormality being detected with prenatal testing in cases in which PGD has been used  Applied to those who in the PGD arm who undergo prenatal testing  Assumes that PGD is associated with some false negative results	0.00079	ESHRE (see Appendix 4)
p_Affected_PGD	Probability of abnormality being detected in an embryo transferred following PGD in the case of no prenatal testing  Applied to those who are in the PGD arm but choose not to undergo prenatal testing  Assumes that PGD is associated with some false negative results	0.00079	ESHRE (see Appendix 4)
p_Affected_Abn	Probability of a live birth being affected by abnormality in cases in which abnormality was detected via prenatal testing  Applied to those who have had prenatal testing in the PGD arm and in the natural conception with PNT arm  Assumes that prenatal testing has no false positives	1.0000	Assumption
p_Affected_NoAbn	Probability of a live birth being affected by abnormality in cases in which no abnormality was detected via prenatal testing  Applied to those who have had prenatal testing in the PGD arm and the natural conception with PNT arm  Assumes that prenatal testing is associated with some false negative results	0.0001	Table E.4.2

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; PGD, preimplantation genetic diagnosis; PNT, prenatal testing

The impact of the misdiagnosis rates presented in Table E.4.3 was tested in sensitivity analyses presented in Section D.6.

### E.4.3. Transition probabilities

The diagnostic accuracy rates presented in Table E.4.3 also served as transition probabilities by governing how the cohort moved through various stages of each model arm.

In addition to those, the model also required transition probabilities to determine the incidence of pregnancy in the case of natural conception, miscarriage and TOP. These probabilities were previously discussed at length in Section D.4.

For transparency, all transition probabilities applied to the economic model are collated and presented in Table E.4.4. Note that all of these are equivalent to event rates; the structure of the model did not require mathematical modification of the rates in order for them to be applicable to the model.

Beyond the transition probabilities dealt with previously, the model also required estimates of the likelihood of women in the PGD arm undergoing prenatal testing and

the likelihood of women re-attempting pregnancy following a miscarriage or a termination of their pregnancy.

In the case of women undergoing both PGD and prenatal testing, it was estimated that 12.3% of women would do so. In lieu of reliable Australian data, this was sourced from the ESHRE PGD Consortium (Data collection XII; Moutou et al, 2014).

With regards to the likelihood of re-attempting pregnancy, the mean of probabilities from those who experience miscarriage and TOP from Harris et al (2001), which is taken from Kuppermann et al (1999) and Brandenburg et al (1992)) show that 71.65% of women would do so. This was applied to the economic model.

**Table E.4.4 Summary of transition probabilities applied to the economic model**

Name in model	Description	Value	Reference
p_Abn	Probability of abnormality detected in prenatal testing (no PGD preceding)	0.4820	Genea PGD cycle data 2010-2011 <sup>a</sup>
p_Affected	Probability of live birth being affected in cases in which no testing has taken place	0.4820	Genea PGD cycle data 2010-2011 <sup>s</sup>
p_Affected_Abn	Probability of live birth being affected by abnormality in cases in which abnormality was detected via prenatal testing	1.0000	Assumption
p_Affected_NoAbn	Probability of live birth being affected by abnormality in cases in which abnormality was not detected via prenatal testing	0.0001	Table E.4.2
p_Affected_PGD	Probability of abnormality being detected in an embryo transferred following PGD in the case of no prenatal testing Applied to those who are in the PGD arm but choose not to undergo prenatal testing	0.00079	See Appendix 4
p_Misc_NC_Early	Probability of miscarriage applied to the first cycle of natural conception arm of the model	0.2259	Table D.4.2
p_Misc_NC_Late	Probability of miscarriage applied to the second cycle of natural conception arm of the model	0.0324	Table D.4.2
p_Misc_PGD_Early	Probability of miscarriage applied to the first cycle of pregnancy in the PGD arm (before opportunity for PNT)	0.0990	Table D.4.2
p_Misc_PGD_Late	Probability of miscarriage applied to the second cycle of pregnancy in the PGD arm (after choice about PNT)	0.0122	Table D.4.2
p_Misc_PNT_Early	Probability of miscarriage applied to the first cycle of pregnancy in the PNT arm (before opportunity for PNT testing)	0.2259	Table D.4.2
p_Misc_PNT_Late	Probability of miscarriage applied to the second cycle of pregnancy in the PGD arm (after PNT)	0.0324	Table D.4.2
p_Nat_Preg	Probability of natural pregnancy (per model cycle)	0.6732	Table D.4.1
p_PregIVF	Probability of pregnancy via IVF in any model cycle, once embryo free of abnormality is identified. Multiple attempts are possible if required	1.0000	Assumption (see Section D.4)
p_Prenatal_PGD	Probability an individual undergoes prenatal testing following PGD	0.1230	ESHRE DATA (Data collection XII; Moutou et al 2014)
p_Prenatal_PGD_Abn	Probability of a abnormality being detected with prenatal testing in cases in which PGD has been used  Assumes that any false negatives after PGD are identified via PNT	0.00079	See Appendix 4

Name in model	Description	Value	Reference
p_Reattempt_IVF	Probability of re-attempting IVF after failure to conceive after repeated attempts in the first cycle	1	Assumption <sup>b</sup>
p_Reattempt_NC	Probability couples will continue to attempt pregnancy for another model cycle after failing to conceive through natural conception	If first three cycles of the mode, then 1.0000; otherwise 0.0000	Assumption that couples will try for pregnancy via natural conception for the first time in the model for up to three cycles (60 weeks)
p_Reattempt_Preg	Probability of re-attempting pregnancy (via either new IVF cycle or natural conception) following miscarriage or TOP	0.7165	Mean of probabilities for miscarriage and TOP from Harris et al, 2001 (taken from Kuppermann et al (1999), and Brandenburg et al (1992))
p_TOP_Abn	Probability of termination of pregnancy after abnormality is detected via prenatal testing	0.99	Assumption

Abbreviations: ESHRE, European Society for Human Reproduction and Embryology; IVF; in vitro fertilisation; PGD, preimplantation genetic diagnosis; PNT, prenatal testing; TOP, termination of pregnancy

<sup>a</sup> Genea PGD cycle data 2010-2011 show that the average rate of unaffected embryos is 51.2%.

<sup>b</sup> Note this probability only applies in sensitivity analyses where the probability of conception via IVF over first cycle is set to less than 1.

The impact of the transition probabilities presented in Table E.4.4 was examined in a series of sensitivity analyses. Key sensitivity analyses are reported in Section D.6.

#### E.4.4. Quality-adjusted life years

A comprehensive literature search to source utility weights applicable to the model was presented in Section D.5.

The literature search comprised two steps. Initially, a search was conducted to identify published studies that derive utility weights using a recognised approach. As described in greater detail in Appendix 4, electronic searches of PubMed and the Cochrane Library were conducted using the approach discussed previously. Exclusion criteria were applied, leaving ten studies plus a further two studies which were identified manually. These were further considered for application to the model.

Of the identified studies, Feeny et al (2002) provided the strongest estimates of utility weights associated with diagnostic testing and pregnancy outcomes. Furthermore, as discussed in Section D.5, the study also provided considerable advantage in that it enabled all utility weights to be sourced from one single study. In doing so, there was a minimisation of potential bias resulting from using disparate sources that are not internally consistent (i.e. from different study populations using heterogeneous methods).

Table E.4.5 repeats the utility weights presented in Table D.5.4 and summarises the utility weights applied to the economic model and their source values. The impact of these values on the results of the model was assessed in a range of sensitivity analyses, which are reported in Section D.6.

Table E.4.5 Utility weights applied to the economic evaluation

Health state	Value	Source	Notes
Unaffected live birth	1.00	Assumption	-
Affected live birth	0.55	Feeny et al (2002) estimate for the birth of an infant with Down syndrome in cases in which no test was administered	-
Affected live birth following an incorrect diagnosis of abnormality free	0.45	Feeny et al (2002) estimate for the birth of an infant with Down syndrome in cases in which a test was administered leading to a false negative result	-
Termination of pregnancy	0.55	Feeny et al (2002) estimate for TOP following detection of an abnormality; termination in the 11 <sup>th</sup> week	Alternative value associated with a termination after detection of an abnormality; termination in the 20 <sup>th</sup> week is tested in sensitivity analysis
Miscarriage (including procedure-related)	0.75	Feeny et al (2002) estimate for miscarriage suspected to be due to diagnostic test	Alternative value associated with pregnancy loss after week 20 but unlikely to be test related is tested in sensitivity analysis
Miscarriage	0.87	Feeny et al (2002) estimate for miscarriage in cases in which no test was administered	-
Failed IVF cycle	0.79	Assumption	Based on Feeny et al (2002) estimate for the utility of the choice to not become pregnant due to the risk of abnormality
No pregnancy	0.79	Based on Feeny et al (2002) estimate for the utility of the choice to not become pregnant due to the risk of abnormality	-

Abbreviations: IVF, in vitro fertilisation; TOP, termination of pregnancy

## E.5. Results of the economic evaluation

The results of the economic analysis is presented below. Section E.5.1 presents the disaggregated average costs per patient, while Section E.5.2 presents the disaggregated health outcomes in terms of QALYs. The base case incremental cost-effectiveness ratios (ICERs) are presented in Section D.5.3. Sensitivity analyses follow in Section E.6.

### E.5.1. Disaggregated average costs

Table E.5.1 presents a summary of the disaggregated costs of PGD versus natural conception with PNT. Costs are disaggregated by health state.



Table E.5.1 Disaggregated cost results of the economic evaluation, per couple (PGD versus natural conception with PNT)

Health state	PGD arm	Natural conception with PNT arm	Incremental
Attempt pregnancy	\$15,811.14	\$1,564.33	\$14,246.81
Early stage pregnancy	\$0.00	\$0.00	\$0.00
Ongoing pregnancy after abnormality detected with prenatal testing	\$0.05	\$0.00	\$0.05
Ongoing pregnancy after no abnormality detected with prenatal testing	\$62.15	\$0.00	\$62.15
Ongoing pregnancy with no prenatal test administered	\$0.00	0	\$0.00
Affected live birth	\$4.72	\$32.58	-\$27.86
Affected live birth after false negative test result	\$0.09	\$0.39	-\$0.30
Unaffected live birth	\$6708.95	\$3500.94	\$3208.00
No further attempt at pregnancy	\$0.00	\$0.00	\$0.00
No further attempt at pregnancy after failed IVF	\$0.00	0	\$0.00
No further attempt at pregnancy after termination	\$0.06	\$303.50	-\$303.44
No further attempt at pregnancy after late (post-test) miscarriage	\$0.74	\$8.56	-\$7.82
No further attempt at pregnancy after miscarriage without test	\$59.29	\$150.22	-\$90.93
<i>Total</i>	<i>\$22,647.18</i>	<i>\$5,560.52</i>	<i>\$17,086.66</i>

Abbreviations: PGD, preimplantation genetic diagnosis; PNT, prenatal testing; IVF, in vitro fertilisation

Note: The use of transition rewards/costs in TreeAge means that some costs in the table above may appear in health states that precede that in which they are incurred.

Table E.5.2 presents a summary of the disaggregated costs of PGD versus natural conception without PNT. Costs are disaggregated by health state.

Table E.5.2 Disaggregated cost results of the economic evaluation, per couple (PGD versus natural conception)

Health state	PGD arm	Natural conception only arm	Incremental
Attempt pregnancy	\$15,811.14	\$347.61	\$15,463.53
Early stage pregnancy	\$0.00	\$0.00	\$0.00
Ongoing pregnancy after abnormality detected with prenatal testing	\$0.05	0	\$0.05
Ongoing pregnancy after no abnormality detected with prenatal testing	\$62.15	\$0.00	\$62.15
Ongoing pregnancy with no prenatal test administered	\$0.00	\$0.00	\$0.00
Affected live birth	\$4.72	\$2709.17	-\$2704.46
Affected live birth after false negative test result	\$0.09	0	\$0.09
Unaffected live birth	\$6708.95	\$2911.52	\$3797.43
No further attempt at pregnancy	\$0.00	\$0.00	\$0.00
No further attempt at pregnancy after failed IVF	\$0.00	0	\$0.00
No further attempt at pregnancy after termination	\$0.06	0	\$0.06
No further attempt at pregnancy after post-test miscarriage	\$0.74	0	\$0.74
No further attempt at pregnancy after miscarriage without test	\$59.29	\$137.54	-\$78.25
<i>Total</i>	<i>\$22,647.18</i>	<i>\$6,105.83</i>	<i>\$16,541.34</i>

Abbreviations: PGD, preimplantation genetic diagnosis; IVF, in vitro fertilisation

Note: The use of transition rewards/costs in TreeAge means that some costs in the table above may appear in health states that precede that in which they are incurred.

The largest cost in both comparisons is the total cost of attempting pregnancy in the PGD arm of the model. This represents the vast majority of the incremental cost in both comparisons. Other notable cost differences relate to the cost of affected and unaffected births. The higher number of unaffected births sees a higher cost in the PGD arm, while the reverse is also true. The contribution of other costs to the incremental value in both comparisons is negligible.

### E.5.2. Disaggregated health outcomes

Total average QALYs, inclusive of live births of unaffected and affected children, the impact of miscarriages and terminations and re-attempts at pregnancy, are presented in Table E.5.3 and Table E.5.4 for PGD versus natural conception with PNT and natural conception alone, respectively.

Table E.5.3 Disaggregated QALY results of the economic evaluation, per couple (PGD versus natural conception with PNT)

Health state	PGD arm	Natural conception with PNT arm	Incremental
Attempt pregnancy	0.18	0.45	-0.27
Early stage pregnancy	0.33	0.40	-0.07
Ongoing pregnancy after abnormality detected with prenatal testing	0.00	0.15	-0.15
Ongoing pregnancy after no abnormality detected with prenatal testing	0.04	0.16	-0.12
Ongoing pregnancy with no prenatal test administered	0.26	0	0.26
Affected live birth	0.00	0.01	0.00
Affected live birth after false negative test result	0.00	0.00	0.00
Unaffected live birth	2.47	1.12	1.35
No further attempt at pregnancy	0.00	0.36	-0.36
No further attempt at pregnancy after failed IVF	0.00	0	0.00
No further attempt at pregnancy after termination	0.00	0.17	-0.17
No further attempt at pregnancy after post-test miscarriage	0.00	0.01	-0.01
No further attempt at pregnancy after miscarriage without test	0.08	0.19	-0.10
<i>Total</i>	<i>3.36</i>	<i>3.01</i>	<i>0.35</i>

Abbreviations: PGD, preimplantation genetic diagnosis; PNT, prenatal testing; IVF, in vitro fertilisation

Table E.5.4 Disaggregated QALY results of the economic evaluation, per couple (PGD versus natural conception)

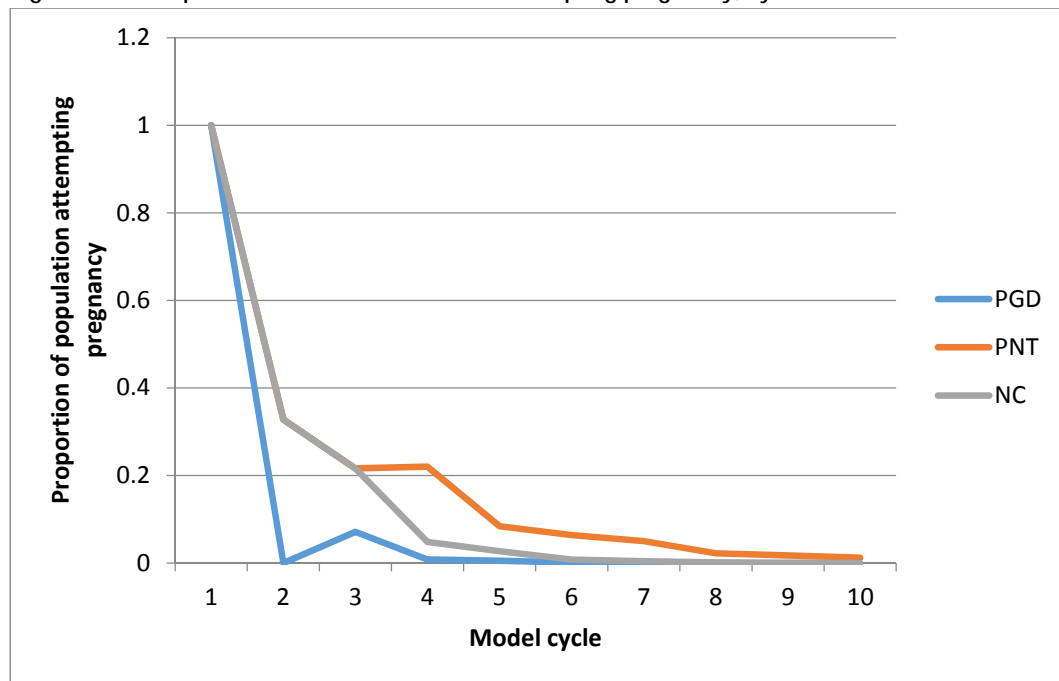
Health state	PGD arm	Natural conception only arm	Incremental
Attempt pregnancy	0.18	0.34	-0.16
Early stage pregnancy	0.33	0.33	0.00
Ongoing pregnancy after abnormality detected with prenatal testing	0.00	0.00	0.00
Ongoing pregnancy after no abnormality detected with prenatal testing	0.04	0.00	0.04
Ongoing pregnancy with no prenatal test administered	0.26	0.25	0.01
Affected live birth	0.00	0.52	-0.52
Affected live birth after false negative test result	0.00	0.00	0.00
Unaffected live birth	2.47	1.02	1.46
No further attempt at pregnancy	0.00	0.19	-0.19
No further attempt at pregnancy after failed IVF	0.00	0.00	0.00
No further attempt at pregnancy after termination	0.00	0.00	0.00
No further attempt at pregnancy after post-test miscarriage	0.00	0.00	0.00
No further attempt at pregnancy after miscarriage without test	0.08	0.19	-0.10
<i>Total</i>	<i>3.36</i>	<i>2.84</i>	<i>0.52</i>

Abbreviations: PGD, preimplantation genetic diagnosis; IVF, in vitro fertilisation

In both cases, the greatest contribution to the incremental QALY is in the affected live birth health state, which favours PGD over both of the comparators. This result is expected.

By examination of the disaggregated results generated by the model, it is also possible to show that the duration of the model is appropriate, in that it captures the vast majority of pregnancy attempts. Figure E.4 below shows the proportion of couples attempting pregnancy in each model cycle. This indicates that any further extrapolation of the model would favour PGD by extrapolating the benefits with virtually no additional costs being incurred.

Figure E.4 Proportion of the modelled cohort attempting pregnancy, by model arm



Abbreviations: NC, natural conception arm; PGD, preimplantation genetic testing arm; PNT, natural conception with prenatal testing arm

The line in Figure E.4 capturing the PGD arm makes intuitive sense. We see the rate of couples seeking to become pregnant falls to zero in the second cycle. This is in line with the assumption that all couples successfully become pregnant with IVF, using repeated attempts if necessary, in the first cycle. The rate of attempted pregnancies becomes non-zero again in the third cycle as a proportion of couples seek to conceive with IVF once more following miscarriage. The rate of attempted pregnancy remains non-zero for a further three cycles for a similar reason before settling on zero in the seventh cycle.

In the case of natural conception without PNT, a steep reduction in the proportion of couples seeking conception can be observed until the third cycle. Beyond this, since re-attempts among those who have not yet become pregnant are precluded due to the assumption of up to three consecutive cycles of attempting pregnancy for the first time (up to 60 weeks), there is a more gentle approach to zero. In this period, re-attempts comprise couples that have experienced a miscarriage and are re-attempting pregnancy once again. By the tenth cycle of the model, none of the cohort is re-attempting pregnancy.

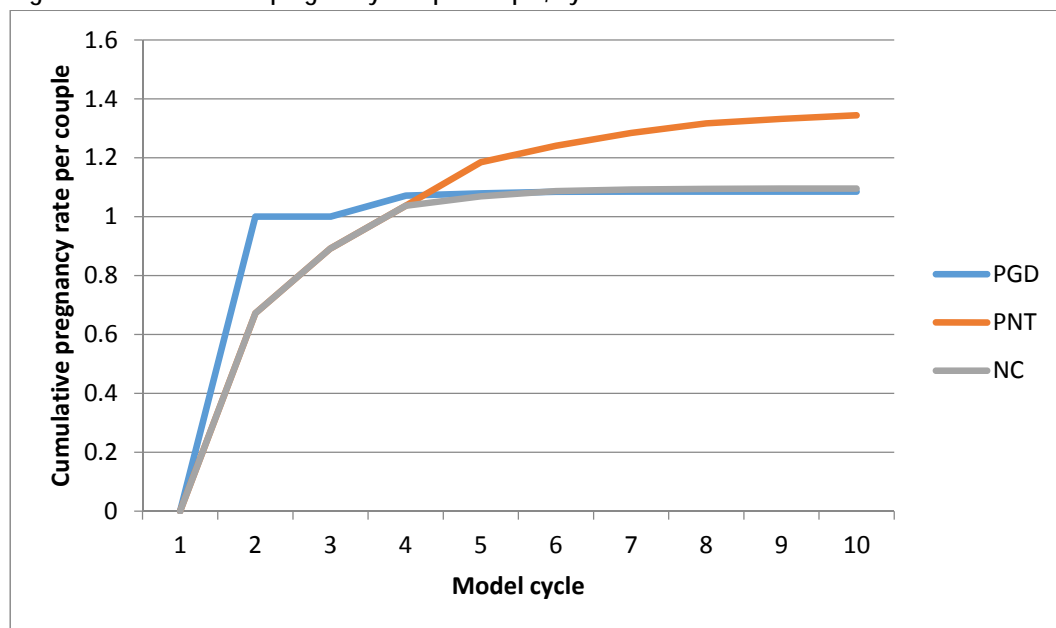
The rate of re-attempts is marginally higher when natural conception is accompanied by prenatal testing. This is due to the presence of terminations in the case of positive prenatal test results. The rate of re-attempted pregnancies behaves as expected, however, and by the final cycle of the model, just 0.2% of the cohort is attempting pregnancy again following a termination or miscarriage.

Together, these results strongly demonstrate that extrapolation of the model beyond this timeframe would not change the conclusions to be drawn from the results. Furthermore, it may lead to an overestimate of the value offered by PGD, as costs would continue to rise (marginally) in the comparator arms but not the PGD arm, thereby reducing the incremental cost of PGD.

Figure E.5 presents the cumulative pregnancy rate by model arm. As expected, the pregnancy rate jumps from zero to one in the case of the PGD arm by the second cycle. From here, it remains somewhat flat with additional pregnancies only occurring in cases in which miscarriages are followed by subsequent attempts. Since the miscarriage rate is relatively low, the cumulative pregnancy rate remains low with an average of 1.085 pregnancies per couple.

The cumulative pregnancy rate in both comparator arms trace one another in the early stages of the model. A difference begins to occur once terminations play a role in the arm with prenatal testing. This leads to a greater amount of pregnancies which do not end in birth and a greater number of re-attempts leading to subsequent pregnancy. As a result, the cumulative pregnancy rate is highest in the arm with prenatal testing at 1.34 per couple by the last cycle. The cumulative rate in the natural conception alone arm is 1.1 per couple in the final cycle of the model. The difference between the cumulative pregnancy rate in the natural conception arm and the PGD arm is driven by the lower miscarriage rate in the case of couples conceiving with PGD.

Figure E.5 Cumulative pregnancy rate per couple, by model arm



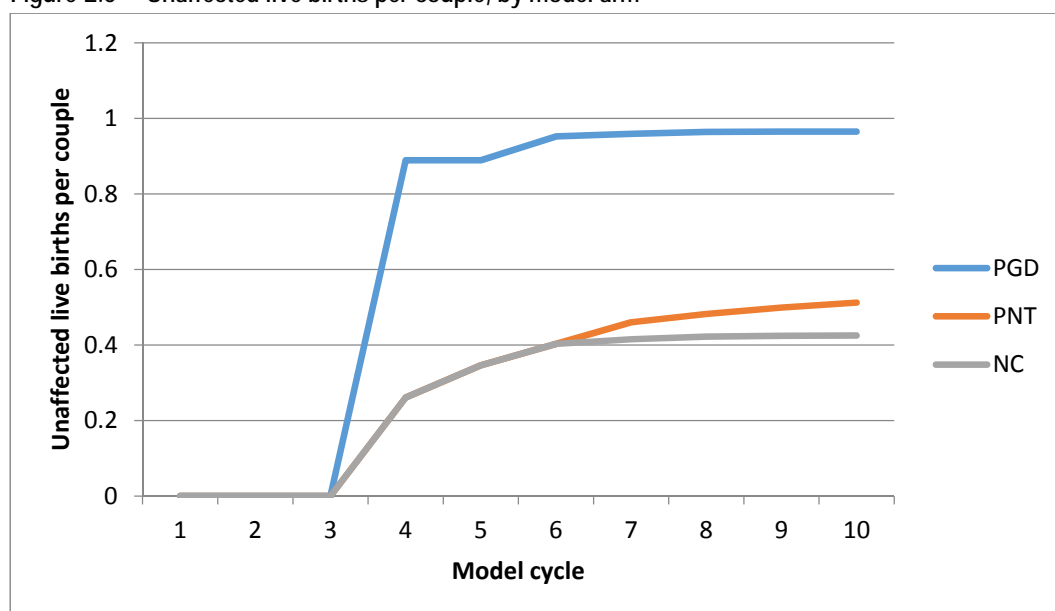
Abbreviations: NC, natural conception arm; PGD, preimplantation genetic testing arm; PNT, natural conception with prenatal testing arm

Extending the duration of the model would increase costs in the comparator arm, potentially biasing the model in favour of PGD.

From the data used to generate Figure E.5, the time until which there is an average of one pregnancy per couple can also be calculated. In the case of the PGD arm, all couples do so within 20 weeks (as per the assumptions of the model). In the case of the natural conception with PNT arm and the natural conception alone arm, it takes 75 weeks until there is an average of one pregnancy for each couple. Note, however, that since 67.2% of couples using natural conception become pregnant within the first model cycle, the median time to pregnancy in all three arms of the model is less than 20 weeks.

Figure E.6 presents the average number of unaffected live births for each of the arms of the model over its duration. As expected, the number of unaffected live births is greatest in the PGD arm (0.965 per couple). This is facilitated by a combination of the diagnostic accuracy and the success of IVF. In the case of natural conception with PNT, the average remains high at 0.512 per couple. The diagnostic accuracy contributes to this, although it is lower than in the PGD arm due to the lower success rate of conception relative to when IVF is used. The rate is lowest in the natural conception arm (0.425) due to the absence of diagnostic testing to prevent affected live births.

Figure E.6 Unaffected live births per couple, by model arm



Abbreviations: NC, natural conception arm; PGD, preimplantation genetic testing arm; PNT, natural conception with prenatal testing arm

### E.5.3. Incremental cost-effectiveness ratio

On the basis of the total costs and QALYs presented in Table E.5.1 and Table E.5.3, respectively, Table E.5.5 presents the base case ICER in terms of the QALY gain offered by PGD relative to natural conception with PNT.

Table E.5.5 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
<i>Incremental cost per QALY</i>	-	-	<i>\$48,875</i>

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

Table E.5.6 presents the base case ICER in terms of the QALY gain offered by PGD relative to natural conception alone.

**Table E.5.6 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
<i>Incremental cost per QALY</i>	-	-	<i>\$31,620</i>

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

Table E.5.7 presents the results of an analysis of the incremental cost per unaffected live birth for PGD relative to natural conception with PNT. The results of a similar analysis, but for PGD versus natural conception only, are presented in Table E.5.8.

**Table E.5.7 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
<i>Incremental cost per unaffected live birth</i>	-	-	<i>\$37,719</i>

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

**Table E.5.8 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
<i>Incremental cost per unaffected live birth</i>	-	-	<i>\$30,632</i>

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

## E.6. Sensitivity analyses

As discussed throughout Section C and Section D, many of the variables applied in the base case analysis are subject to uncertainty. The possibility of uncertainty has been discussed several times previously, but its impact has not been presented thus far. Table E.6.1 presents a series of sensitivity analyses aimed at better understanding the impact of uncertainty around key variables and assumptions. Where these are shown to have a meaningful impact on the results, this is discussed below.

For simplicity, sensitivity analyses are only reported in the case of PGD versus natural conception with PNT in Table E.6.1. Additional analyses are reported versus natural conception only in Table E.6.2.

Table E.6.1 Sensitivity analyses, PGD versus natural conception with PNT

Analysis	Incremental cost	Incremental QALY	Result
<i>Base case</i>	\$17,087	0.35	\$48,875
<i>Model specifications</i>	-	-	-
Attempts at pregnancy increased in the comparator arm from three cycles of trying in the base case to unlimited	\$16,202	0.34	\$48,195
Model duration increased from 10 cycles of 20 weeks to 20 cycles of 20 weeks	\$16,989	0.72	\$23,730
Success rate of IVF reduced from absolute over 20 weeks to 80% over 20 weeks	\$20,806	0.33	\$63,184
Probability of re-attempting pregnancy (via either new IVF cycle or natural conception) following miscarriage or TOP reduced from 0.7165 to 0.5	\$17,021	0.40	\$42,944
Probability of re-attempting pregnancy (via either new IVF cycle or natural conception) following miscarriage or TOP increased from 0.7165 to 1.0	\$17,117	0.28	\$61,044
Discount rate set to 0%	\$16,970	0.38	\$44,290
Discount rate set to 3%	\$17,042	0.36	\$47,027
Discount rate set to 10%	\$17,189	0.32	\$53,574
<i>Clinical probabilities and diagnostic accuracy</i>	-	-	-
Probability of natural conception over 20 weeks increased from 0.67232 to 0.75	\$16,756	0.34	\$49,404
Probability of natural conception over 20 weeks increased from 0.67232 to 1.0	\$15,833	0.31	\$50,765
Additional risk of miscarriage in those receiving PNT to represent potential procedure-related miscarriage (0% in base case, increased to 1.03% additional risk) <sup>a</sup>	\$17,103	0.35	\$48,588
Risk of miscarriage in first half of pregnancy in the PGD arm increased from 9.9% to 20% (in light of McArthur et al, 2008)	\$18,297	0.33	\$56,220
Probability of TOP among those with abnormality detected decreased from 0.99 to 0.83 (Davis et al, 2010)	\$16,898	0.38	\$44,432
Probability of TOP among those with abnormality detected decreased from 0.99 to 0.786 (Harris et al, 2001)	\$16,849	0.39	\$43,358
Probability of false negatives in the case of PNT increased from 0.0001 to 0.005	\$17,087	0.35	\$48,570
Probability of false negatives in the case of PGD set equal to that of PNT (0.0001)	\$17,085	0.35	\$48,867
Probability of false negatives in the case of PGD increased from 0.00079 to 0.0016	\$17,087	0.35	\$48,987
<i>Utility weights</i>	-	-	-
Utility of affected birth increased from 0.55 to 0.65 <sup>b</sup>	\$17,087	0.35	\$48,754
Utility of affected birth reduced from 0.55 to 0.45 <sup>b</sup>	\$17,087	0.35	\$48,997
Utility of choosing to no longer attempt pregnancy after not conceiving increased from 0.79 to 0.90	\$17,087	0.30	\$57,184
Utility of no further pregnancy after termination increase from 0.55 to 0.74 (equivalent to utility weight of termination in the 20 <sup>th</sup> week)	\$17,087	0.29	\$58,482
Utility of no further pregnancy after post-test miscarriage increased from 0.75 to 0.79 (equivalent to pregnancy loss after week 20, but unlikely due to test)	\$17,087	0.35	\$48,929
Disutility associated with miscarriages and terminations removed (utility weights set equivalent to baseline weight of 0.79)	\$17,087	0.36	\$47,625
<i>Costs</i>	-	-	-



Analysis	Incremental cost	Incremental QALY	Result
Total cost of achieving pregnancy with PGD and IVF increased by 25%	\$20,902	0.35	\$59,790
Total cost of achieving pregnancy with PGD and IVF reduced by 25%	\$13,271	0.35	\$37,960
Requested fees associated with PGD increased by 10%	\$17,433	0.35	\$49,866
Requested fees associated with PGD reduced by 10%	\$16,740	0.35	\$47,884
Unit cost of embryo biopsy applied 3.4 times (i.e. once per embryo, as opposed to once only in the base case)	\$19,039	0.35	\$54,461

Abbreviations: PGD, preimplantation genetic diagnosis; PNT, prenatal testing; IVF, in vitro fertilisation; QALY, quality-adjusted life year; TOP, termination of pregnancy

a For simplicity, applied in the natural conception with PNT arm only. Not applied in the PGD arm due to the low use of prenatal testing

b For simplicity, applied to affected live birth only; not applied to cases of affected live birth after an incorrect diagnosis

A number of the sensitivity analyses reported in Table D.6.1 warrant discussion.

It can be seen that increasing the duration of the model improves the cost-effectiveness of PGD relative to natural conception with PNT. This result is expected, as it extrapolates the benefits of PGD's impact on unaffected live births while keeping costs stable (remembering that downstream healthcare costs were not applied in the base case). While an interesting result, it is anticipated the base case analysis would be most helpful for decision-making purposes, as it avoids the risk of making decisions based on a magnification of the inherent uncertainty of the utility weight estimates and avoids any potential bias in favour of PGD.

Reducing the rate of pregnancy via IVF from 100% over 20 weeks to 80% over 20 weeks increases the ICER from \$48,875 to \$63,184. 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. 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 increase 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 couples re-attempt pregnancy following miscarriage or termination will worsen the ICER. An increase in this probability gives couples using natural conception with PNT 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 in to the model (including analysis examining the utility of affected live births, which is uncertain due to the use of a utility weight representative of Down syndrome specifically). Additionally, an analysis exploring the average cost of embryo biopsy was included, given that the item description proposed by PASC states that the cost applies to the biopsy of multiple embryos, while the cost proposed by the Applicant is applied per embryo biopsied (see Section B.3.1 for further details). It is shown in Table E.6.1 that applying the cost of biopsy per embryo has a limited impact on the ICER.

In addition to the sensitivity analyses reported in Table E.6.1, 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. As could be expected from the results exploring the impact of miscarriage rates reported in Table E.6.1, adjusting for the rate of miscarriages in the natural conception arm of the model has very little impact on the conclusions to be drawn when comparing PGD against natural conception only.

**Table E.6.2 Secondary sensitivity analyses, PGD versus natural conception only**

Analysis	Incremental cost	Incremental QALY	Result
<i>Base case</i>	\$16,541	0.52	\$31,620
<i>Model specifications</i>	-	-	-
Risk of miscarriage in the natural conception arm reduced from 22.59% in early pregnancy to 14.4% and from 3.24% in late pregnancy to 1.87% (considers rates estimated using single gene disorders only)	\$16,333	0.53	\$30,769
Risk of miscarriage in the natural conception arm increased from 22.59% in early pregnancy to 37.8% and from 3.24% in late pregnancy to 7.75% (considers rates estimated using chromosomal rearrangements only)	\$17,007	0.51	\$33,546

Abbreviations: PGD, preimplantation genetic diagnosis; QALY, quality-adjusted life year

a For simplicity, applied in the natural conception with PNT arm only. Not applied in the PGD arm due to the low use of prenatal testing.

A further analysis was undertaken to examine the impact of broadening the perspective of the model to include downstream impacts. As discussed previously, the base case model did not include the downstream medical costs associated with treating conditions arising from affected live births. Nor did the base case analysis include consideration of long-term impacts on quality of life.

As discussed in Section D.3, CHERE (2011) provides an estimate of the lifetime costs associated with cystic fibrosis. Over a 38-year life expectancy, it was estimated that the lifetime cost would equate to \$334,820 (discounted at 5% per annum).

This lifetime cost was applied to the model using 110 cycles (38 years equates to approximately 98 cycles, though extra cycles were included to account for conception and the pregnancy period). In this analysis, the utility weights were also considered over this period to ensure the estimated cost per QALY was correctly estimated. Note that the utility weights applied to the model were said to be chronic in nature and applicable for a 40-year period (Feeny et al, 2002).

**Table E.6.3 Incremental cost per QALY ratio of PGD versus natural conception with PNT, including downstream impacts**

Parameter	PGD arm	Natural conception with PNT arm	Incremental
Cost	\$22,878	\$7273	\$15,605
QALY	18.01	15.85	2.16
<i>Incremental cost per QALY</i>	-	-	\$7234

Abbreviations: PGD, preimplantation genetic diagnosis; PNT, prenatal testing; QALY, quality-adjusted life year

Note: Rounding may impact on some figures

Table E.6.4 Incremental cost per QALY ratio of PGD versus natural conception only, including downstream impacts

Parameter	PGD arm	Natural conception only arm	Incremental
Cost	\$22,878	\$136,156	-\$113,277
QALY	18.01	14.47	3.53
<i>Incremental cost per QALY</i>	-	-	<i>PGD offers superior outcomes at a lower average cost</i>

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

Applying downstream costs associated with affected births, while simultaneously extrapolating the utility weights applied to the model has a profound impact on the results in both cases. The result, however, is unexpected given that both modifications have a strongly positive impact on the PGD arm relative to the comparators. While the results demonstrate the degree to which the case for PGD may benefit from inclusion of such downstream impacts, they should be treated with caution. The downstream cost that was applied is likely to be an upper limit; by applying the cost associated with cystic fibrosis, it is very likely this represents an overestimate when considering the broad range of abnormalities PGD may help avoid. Additionally, there is considerable uncertainty in applying utility weights over such a long duration without some modification to reduce the incremental benefits of unaffected births relative to the other health states. Again, the analyses reported here represent a best-case scenario. Consequently, the results presented in Table E.6.3 and Table E.6.4 should be interpreted with caution.

# Section F. Estimated utilisation and financial implications

## F.1. Justification of the selection of sources of data

An electronic workbook <1165\_Section E estimates and data sources.xls> accompanies this Assessment Report.

Consistent with the economic evaluation, the financial estimates consider two populations:

- couples that choose to conceive via PGD; and
- couples that choose to conceive via natural conception with prenatal testing.

Estimation of the number of couples that choose to conceive via natural conception without prenatal diagnosis is fraught with uncertainty; as such, this population is not taken into consideration in the utilisation and financial estimates. It is possible that couples who currently choose this option may attempt PGD if public funding became available, as they may be adverse to pregnancy termination and see PGD as an attractive option.

Key assumptions and sources of data used for the financial estimates are presented in Table F.1.1. The approach used to estimate the utilisation of the proposed medical service in the financial analysis is mainly dependent on Australia and New Zealand Assisted Reproduction Database (ANZARD) and the Applicant's internal data. Further, MBS utilisation data were used to estimate the relative use of CVS and amniocentesis. Estimates from the ESHRE PGD Consortium dataset were only used in the absence of Australian data due to the prevalent use of blastomere biopsy (which is not common practice in Australia).

Table F.1.1 Key assumptions and data sources used for the financial estimates

Assumption	Reference	Justification
<b>Assumptions relating to PGD</b>		
Total number of PGD cycles in Australia	Projection based on ANZARD collection	Australian data. Best available. ANZARD collect data on the number of PGD fresh cycles and the number of live deliveries resulting from PGD in Australia on an annual basis.
Proportion of all PGD cycles initiated for the proposed population Base case: 45%	Final Protocol (p9), based on internal data from Genea	Australian data. Best available but data not available for verification. Estimate is tested in a sensitivity analysis.
Estimated increase in PGD uptake due to public reimbursement Base case: 50% in Year 1, 25% in Year 2, 15% in Year 3, 10% thereafter	Estimate for first five years of public reimbursement, based on stakeholder, Applicant and ANZARD data (Final Protocol, p9),	The Applicant assumes that the largest rate of growth is in the first year of public reimbursement, plateauing over time to 10% (allowing for population growth). Highly uncertain. Estimate is tested in a sensitivity analysis.
Mean number of PGD cycles per couple Base case: 1.4	VARTA Annual Report 2014 (p32);	Australian data but may not be generalisable. VARTA reported 108 women in Victoria with 159 PGD cycles for known genetic risk; and 399 women in Victoria with 520 PGD cycles for numerical chromosome abnormalities. Data not available from ANZARD.
Proportion of PGD cycles that are cancelled prior to oocyte retrieval	Applicant estimate from Genea PGD cycle data 2010-2011 (Final	Australian data. Best available but data not available for verification. Rates are low and not

Assumption	Reference	Justification
Base case: 0.02%	Protocol, decision analytic, p34)	worthwhile testing in sensitivity analysis.
Proportion of PGD cycles that progress to oocyte retrieval Base case: 99.98%	Applicant estimate from Genea PGD cycle data 2010-2011 (Final Protocol, decision analytic, p34)	Australian data. Best available but data not available for verification.
Proportion of PGD cycles (with oocytes) without embryo biopsy Base case: 22.5%	Applicant estimate from Genea PGD cycle data 2010-2011 (Final Protocol, decision analytic, p34)	Australian data. Best available but data not available for verification.
Proportion of PGD cycles (with oocytes) with embryo biopsy Base case: 77.5%	Applicant estimate from Genea PGD cycle data 2010-2011 (Final Protocol, decision analytic, p34)	Australian data. Best available but data not available for verification.
Proportion of PGD cycles with biopsied embryos that undergo genetic testing Base case: 100%	Assumption, based on Applicant decision analytic which leads from cycles with biopsy to embryos with/without abnormality (Final Protocol, p34)	No Australian data available.
Proportion of all PGD cycles that result in embryo transfer Base case: 68.1%	ANZARD data 2007-2012 (Final Protocol, Table 2, p9)	Australian data. Best available.
Mean number of transferred embryos required before successful pregnancy Base case: 3.44	ESHRE PGD Consortium publications 1999 to 2014, weighted for relative proportions of SGD and chromosomal rearrangements (calculated in Appendix 4 using ESHRE data)	Best available data but not Australian. Constitutes 12 data reports covering all applications of PGD from a large number of fertility centres worldwide.
Assumptions relating to prenatal diagnosis after PGD		
Proportion of PGD pregnancies with prenatal diagnosis: Base case: 12.3%	Taken from ESHRE Data collection XII; Moutou et al (2014).	Best available data but not Australian. Only most recent data used because rates of prenatal diagnosis have decreased over time, perhaps reflecting increased confidence in the diagnostic accuracy of PGD.
Proportion of PGD pregnancies with CVS Base case: 37.2%	Medicare Australia data for MBS items 16603 and 16600 in 2014	Australian data. Best available but MBS usage does not specifically relate to PGD population.
Proportion of PGD pregnancies with amniocentesis Base case: 62.8%	Medicare Australia for MBS items 16603 and 16600 in 2014	Australian data. Best available but MBS usage does not specifically relate to PGD population.
Assumptions relating to pregnancy outcome after PGD		
Proportion of PGD pregnancies that end in miscarriage Base case: 11.12%	ESHRE PGD Consortium data collection VIII-XII (calculated in Appendix 4)	Best available data but not Australian. Taken from five most recent publications. Similar rates were reported in other individual studies shown in Section B.6.1.
Proportion of pregnancies that end in termination Base case: $0.079\% \times 0.0116\% = 0.000009\%$	ESHRE PGD Consortium for misdiagnosis (false negative test) for PGD (see Appendix 4) Published literature for misdiagnosis (false negative test) for prenatal diagnosis (see Appendix 4)	Best available sources but not Australian. Only applied to pregnancies where prenatal diagnosis is undertaken after PGD. Calculated using false negative rates for PGD and prenatal diagnosis.
Proportion of embryo transfers affected by the genetic disorder of the parents Base case: 0.079%	ESHRE PGD Consortium (see Appendix 4)	Best available sources but not Australian. Relates to false negative rate for PGD. Only applied to pregnancies where prenatal diagnosis is not undertaken after PGD.
Assumptions relating to natural conception with prenatal diagnosis		
Proportion of couples that switch from natural conception with prenatal diagnosis to PGD Base case: 25%	Assumption	No data available. Highly uncertain. Estimate is tested in a sensitivity analysis.
Number of CVS and amniocentesis services	Medicare Australia data for MBS 16603 from 2010-2014, assuming % change in services for 2014 to 2015 is same as 2013 to 2014. Assumes no further decrease in services thereafter.	Australian data. Best available but MBS usage does not specifically relate to natural conception population. Services have been decreasing over time. Calculations assume a plateau in service numbers using a crude approach.

Assumption	Reference	Justification
Proportion of CVS and amniocentesis services for single gene disorders and chromosomal rearrangements Base case: 15.1% for CVS, 3.7% for chromosomal rearrangements	South Australian Birth Defects Register, Women's and Children's Hospital, Adelaide, South Australia (see 'PND in SA' worksheet)	Australian data. Best available source although it is from South Australia and may not be generalisable.
Proportion of prenatal tests with genetic abnormality Base case: 48.2%	Applicant estimate Genea PGD cycle data 2010-2011 (Final Protocol, decision analytic, p34)	Australian data. Best available but data not available for verification.
Proportion of prenatal tests with abnormality that end in termination Base case: 99%	Assumption from Applicant (Final Protocol, decision analytic, p34)	Assume that couples who undergo prenatal diagnosis intend on acting upon the information received. Uncertain.
Proportion of natural conception pregnancies that end in early miscarriage, prior to prenatal diagnosis Base case: 22.6%	Calculated from the literature (see Appendix 4)	A literature search was conducted to identify relevant evidence. Best available data but not Australian.
Proportion of pregnancies affected by the genetic disorder of the parents Base case: 0.0116%	False negative rate from prenatal diagnosis calculated from the literature (see Appendix 4)	A literature search was conducted to identify relevant evidence. Best available data but not Australian.

Abbreviations: ANZARD, Australia and New Zealand Assisted Reproduction Database; CVS, chorionic villus sampling; ESHRE, European Society of Human Reproduction and Embryology; MBS, Medicare Benefits Schedule; NC, natural conception; PGD, preimplantation genetic diagnosis; PND, prenatal diagnosis; SA, South Australia; VARTA, Victorian Assisted Reproductive Treatment Authority.

The cost of postnatal diagnosis is not factored into the calculations. There are no reliable data to inform the use of postnatal testing after the birth of a child. It is likely that that rates if postnatal testing may be similar for couples that conceive via PGD or via natural conception with prenatal diagnosis.

Consistent with Section D, the financial analysis did not consider any other costs that may be associated with ongoing pregnancy. Although it is expected that pregnant women will undergo continued monitoring and ongoing consultations, these costs are negligible in relation to the other costs included in the calculations.

Similarly, downstream medical intervention and therapy costs associated with affected births were not included in the financial analysis. Although these costs may be substantial in some cases, they are subject to considerable uncertainty due to the large range of serious genetic conditions that are relevant to the proposal for public funding.

Out-of-pocket costs have not been captured in the financial estimates; likewise, the impact of the Extended Medicare Safety Net (EMSN) has not been factored into any of the calculations. An EMSN cap applies to the IVF services that are relevant to PGD, as well as fetal sampling methods for prenatal diagnosis.

## **F.2. Estimation of use and costs of the proposed medical service**

### **F.2.1. Estimated number of PGD services**

The estimated number of PGD services for the first five years of proposed public funding is presented in Table F.2.1. This was estimated by projections of current ANZARD data on the total number of PGD cycles, as well as factoring in the Applicant's estimates that 45% of current PGD cycle numbers are initiated for single gene disorders and gene rearrangements associated with a serious medical condition.

The Applicant estimates that in the event of successful public funding of PGD services, there will be a 50% increase in the uptake of PGD in the first year of listing (taken to be 2016 in the estimates shown in Section E), 25% increase in the second year, and 15% increase in the third year. Thereafter, the Applicant estimates that growth will settle at around 10% allowing for population growth in Australia. However, these estimates are highly uncertain. ANZARD data published in 2012 showed that there was a 93% increase in the number of PGD cycles from 2011 to 2012. Given this sharp increase in the number of PGD cycles, it is difficult to reliably predict future use of PGD, regardless of whether or not the service is publicly funded.

**Table F.2.1 Estimated number of PGD services with public funding (proposed)**

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
PGD Stage 1: genetic test design and validation	2033	2541	2923	3215	3536
PGD Stage 2: embryo biopsy	2206	2757	3171	3488	3836
PGD Stage 3: embryo analysis	2206	2757	3171	3488	3836

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

As already discussed in Section A, PGD is currently provided by private fertility and assisted conception clinics to couples who are concerned about carrying genetic conditions, and are prepared to undergo IVF. However, PGD is not publicly funded and costs are met through a range of pathways including funding assistance programs, self-funding, funding by the facility conducting the PGD service, or through a combination of these mechanisms. In the event that the request for public funding is not successful, PGD will continue to be used, albeit at a lower rate than that shown in Table F.2.1. Estimates for the number of PGD services in the absence of public funding is presented in Table F.2.2.

**Table F.2.2 Estimated number of PGD services without public funding (current)**

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
PGD Stage 1: genetic test design and validation	1577	1798	2019	2241	2462
PGD Stage 2: embryo biopsy	1710	1951	2191	2431	2671
PGD Stage 3: biopsy diagnosis	1710	1951	2191	2431	2671

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

## F.2.2. Estimated cost of PGD services

On the basis of the utilisation estimates presented in Table F.2.1, Table F.2.3 presents the cost of the three proposed services for PGD. These costs are based on the fees proposed by the Applicant (see Section A.3). No cost indexing has been applied over time.

Table F.2.3 Estimated cost of PGD services with public funding (proposed)

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
PGD Stage 1: genetic test design and validation	\$3,529,629	\$4,412,036	\$5,073,842	\$5,581,226	\$6,139,348
PGD Stage 2: embryo biopsy	\$253,641	\$317,052	\$364,609	\$401,070	\$441,177
PGD Stage 3: biopsy diagnosis	\$1,400,541	\$1,750,677	\$2,013,278	\$2,214,606	\$2,436,067
<b>Total</b>	<b>\$5,183,812</b>	<b>\$6,479,765</b>	<b>\$7,451,729</b>	<b>\$8,196,902</b>	<b>\$9,016,592</b>

Source: Excel Section E workbook, <Cost of PGD items - Proposed>  
Abbreviations: PGD, preimplantation

## F.3. Estimation of changes in use and cost of other medical services

### F.3.1. Cost of MBS services relating to PGD, proposed funding arrangements

Table F.3.1 through Table F.3.4 present the estimated cost to the MBS of the associated services that relate to PGD, over the first five years of public funding.

Some of these costs, particularly those relating to anaesthesia for CVS, amniocentesis and miscarriage, are uncertain. Furthermore, although oocyte retrieval and embryo transfers are often performed in hospital with the administration of anaesthesia, the cost of anaesthesia has not been factored into the financial estimates because the MBS item descriptors for oocyte retrieval and embryo transfer do not specify an associated anaesthesia attendance. In this case, however, MBS item 21997 (for the initiation of management of anaesthesia associated with a procedure which has not been identified as attracting an anaesthetic rebate and where the clinical need for anaesthesia was demonstrated) may be applicable. Alternately, the cost of hospitalisation and anaesthesia may be worn by the couple seeking PGD services or by a private health fund.



**Table F.3.1 Estimated cost of other MBS services relating to PGD: proposed funding arrangements**

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
PGD planning and management (for couples)					
Referral from genetic counsellor	\$456,148	\$570,185	\$655,712	\$721,283	\$793,412
Planning and management for artificial insemination	\$146,390	\$182,988	\$210,436	\$231,479	\$254,627
<b>Total</b>	<b>\$602,538</b>	<b>\$753,172</b>	<b>\$866,148</b>	<b>\$952,763</b>	<b>\$1,048,039</b>
PGD with harvesting of embryos, biopsy, and genetic testing					
Cost of assisted reproductive technologies superovulated treatment cycle proceeding to oocyte retrieval	\$6,688,081	\$8,360,101	\$9,614,117	\$10,575,528	\$11,633,081
Cost of oocyte retrieval	\$586,353	\$732,941	\$842,882	\$927,170	\$1,019,887
Cost of intracytoplasmic sperm injection	\$783,641	\$979,552	\$1,126,485	\$1,239,133	\$1,363,046
<b>Total</b>	<b>\$8,058,075</b>	<b>\$10,072,594</b>	<b>\$11,583,483</b>	<b>\$12,741,832</b>	<b>\$14,016,015</b>
PGD with cancelled IVF cycle					
Cost of assisted reproductive technologies superovulated treatment cycle that is cancelled before oocyte retrieval	\$225	\$282	\$324	\$356	\$392
<b>Total</b>	<b>\$225</b>	<b>\$282</b>	<b>\$324</b>	<b>\$356</b>	<b>\$392</b>
PGD without successful biopsy					
Cost of assisted reproductive technologies superovulated treatment cycle proceeding to oocyte retrieval	\$1,941,701	\$2,427,126	\$2,791,195	\$3,070,315	\$3,377,346
Cost of oocyte retrieval	\$170,231	\$212,789	\$244,708	\$269,178	\$296,096
Cost of intracytoplasmic sperm injection	\$227,509	\$284,386	\$327,044	\$359,748	\$395,723
<b>Total</b>	<b>\$2,339,441</b>	<b>\$2,924,302</b>	<b>\$3,362,947</b>	<b>\$3,699,241</b>	<b>\$4,069,166</b>
Cost of transfer of embryos to attempt pregnancy					
Cost of first transfer of embryos	\$47,001	\$58,751	\$67,564	\$74,320	\$81,752
Cost of preparation of frozen oocytes for transfer in subsequent attempts to impregnate	\$983,986	\$1,229,983	\$1,414,480	\$1,555,928	\$1,711,521
Cost of transfer of frozen oocytes in subsequent attempts to impregnate	\$114,683	\$143,353	\$164,856	\$181,342	\$199,476
<b>Total</b>	<b>\$1,145,670</b>	<b>\$1,432,087</b>	<b>\$1,646,900</b>	<b>\$1,811,590</b>	<b>\$1,992,749</b>

Source: Excel Section E workbook, <Cost of associated services - Proposed>  
 Abbreviations: IVF, in vitro fertilisation; PGD, preimplantation genetic diagnosis

Table F.3.2 Estimated cost of MBS services relating to prenatal diagnosis: proposed funding arrangements

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Referral from genetic counsellor	\$15,561	\$19,451	\$22,369	\$24,606	\$27,066
Specialist consultation	\$5,046	\$6,307	\$7,254	\$7,979	\$8,777
Ultrasound for dating	\$4,162	\$5,202	\$5,982	\$6,581	\$7,239
Initiation of patient episode by collection of a specimen	\$472	\$590	\$678	\$746	\$820
<b>Total</b>	<b>\$25,240</b>	<b>\$31,550</b>	<b>\$36,282</b>	<b>\$39,911</b>	<b>\$43,902</b>
<b>CVS</b>					
Chorionic villus sampling	\$2,358	\$2,948	\$3,390	\$3,729	\$4,102
Initiation of management of anaesthesia for CVS	\$1,533	\$1,916	\$2,203	\$2,423	\$2,666
Anaesthesia time unit	\$383	\$479	\$551	\$606	\$666
<b>Total</b>	<b>\$4,274</b>	<b>\$5,343</b>	<b>\$6,144</b>	<b>\$6,758</b>	<b>\$7,434</b>
<b>Amniocentesis</b>					
Amniocentesis	\$2,076	\$2,594	\$2,984	\$3,282	\$3,610
Initiation of patient episode by collection of a specimen	\$2,587	\$3,234	\$3,719	\$4,091	\$4,500
Anaesthesia time unit	\$647	\$809	\$930	\$1,023	\$1,125
<b>Total</b>	<b>\$5,310</b>	<b>\$6,637</b>	<b>\$7,633</b>	<b>\$8,396</b>	<b>\$9,236</b>
<b>Genetic test</b>					
Weighted cost for prenatal genetic test	\$16,994	\$21,243	\$24,429	\$26,872	\$29,560
<b>Total</b>	<b>\$16,994</b>	<b>\$21,243</b>	<b>\$24,429</b>	<b>\$26,872</b>	<b>\$29,560</b>

Source: Excel Section E workbook, <Cost of associated services - Proposed>

Abbreviations: CVS, chorionic villus sampling; PGD, preimplantation genetic diagnosis

**Table F.3.3 Estimated cost of MBS services relating to pregnancy loss and live birth: proposed funding arrangements**

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Termination of pregnancy					
Specialist consultation	\$0	\$0	\$0	\$0	\$0
Termination by curette after CVS (<12 weeks)	\$0	\$0	\$0	\$0	\$0
Anaesthesia for termination	\$0	\$0	\$0	\$0	\$0
Anaesthesia time unit ≤15 min	\$0	\$0	\$0	\$0	\$0
Termination by induction after amniocentesis	\$0	\$0	\$0	\$0	\$0
Anaesthesia for termination	\$0	\$0	\$0	\$0	\$0
Anaesthesia time unit 26-30 min	\$0	\$0	\$0	\$0	\$0
<b>Total</b>	<b>\$0</b>	<b>\$0</b>	<b>\$0</b>	<b>\$0</b>	<b>\$0</b>
Miscarriage					
Counselling by GP	\$4,803	\$6,004	\$6,905	\$7,595	\$8,355
Curettage of the uterus for incomplete miscarriage	\$9,874	\$12,342	\$14,194	\$15,613	\$17,174
Anaesthesia for incomplete miscarriage	\$3,725	\$4,656	\$5,354	\$5,890	\$6,479
Anaesthesia time unit ≤15 min	\$931	\$1,164	\$1,339	\$1,472	\$1,620
<b>Total</b>	<b>\$19,333</b>	<b>\$24,166</b>	<b>\$27,791</b>	<b>\$30,570</b>	<b>\$33,627</b>

Source: Excel Section E workbook, <Cost of associated services - Proposed>

Abbreviations: CVS, chorionic villus sampling; GP, General Practitioner; PGD, preimplantation genetic diagnosis

**Table F.3.4 Estimated total cost to the MBS of associated PGD services: proposed funding arrangements**

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Cost of MBS services relating to PGD	\$12,145,949	\$15,182,437	\$17,459,802	\$19,205,782	\$21,126,361
Cost of MBS services relating to prenatal testing	\$51,818	\$64,773	\$74,489	\$81,937	\$90,131
Cost of MBS services relating to pregnancy loss and live birth	\$19,333	\$24,166	\$27,791	\$30,570	\$33,627
<b>Total cost to the MBS</b>	<b>\$12,217,100</b>	<b>\$15,271,375</b>	<b>\$17,562,082</b>	<b>\$19,318,290</b>	<b>\$21,250,119</b>

Abbreviations: MBS, Medicare Benefits Schedule; PGD, preimplantation genetic diagnosis

### **F.3.2. Cost of MBS services relating to PGD, current funding arrangements**

Table F.3.5 through Table F.3.8 present the estimated cost to the MBS of the associated services that relate to PGD, over the next five years under current funding arrangements.

Table F.3.5 Estimated cost of MBS services relating to PGD: current funding arrangements

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
PGD planning and management (for couples)					
Referral from genetic counsellor	\$353,748	\$403,397	\$453,047	\$502,696	\$552,346
Planning and management for artificial insemination	\$113,527	\$129,461	\$145,395	\$161,329	\$177,263
<b>Total</b>	<b>\$467,275</b>	<b>\$532,858</b>	<b>\$598,442</b>	<b>\$664,025</b>	<b>\$729,608</b>
PGD with harvesting of embryos, biopsy, and genetic testing					
Cost of assisted reproductive technologies superovulated treatment cycle proceeding to oocyte retrieval	\$5,186,686	\$5,914,651	\$6,642,616	\$7,370,582	\$8,098,547
Cost of oocyte retrieval	\$454,723	\$518,545	\$582,367	\$646,188	\$710,010
Cost of intracytoplasmic sperm injection	\$607,723	\$693,019	\$778,314	\$863,610	\$948,906
<b>Total</b>	<b>\$6,249,133</b>	<b>\$7,126,215</b>	<b>\$8,003,297</b>	<b>\$8,880,380</b>	<b>\$9,757,462</b>
PGD with cancelled IVF cycle					
Cost of assisted reproductive technologies superovulated treatment cycle that is cancelled before oocyte retrieval	\$175	\$199	\$224	\$248	\$273
<b>Total</b>	<b>\$175</b>	<b>\$199</b>	<b>\$224</b>	<b>\$248</b>	<b>\$273</b>
PGD without successful biopsy					
Cost of assisted reproductive technologies superovulated treatment cycle proceeding to oocyte retrieval	\$1,505,812	\$1,717,157	\$1,928,502	\$2,139,846	\$2,351,191
Cost of oocyte retrieval	\$132,016	\$150,545	\$169,074	\$187,603	\$206,132
Cost of intracytoplasmic sperm injection	\$176,436	\$201,199	\$225,962	\$250,725	\$275,489
<b>Total</b>	<b>\$1,814,264</b>	<b>\$2,068,901</b>	<b>\$2,323,538</b>	<b>\$2,578,175</b>	<b>\$2,832,812</b>
Cost of transfer of embryos to attempt pregnancy					
Cost of first transfer of embryos	\$36,450	\$41,566	\$46,682	\$51,797	\$56,913
Cost of preparation of frozen oocytes for transfer in subsequent attempts to impregnate	\$763,093	\$870,195	\$977,297	\$1,084,399	\$1,191,501
Cost of transfer of frozen oocytes in subsequent attempts to impregnate	\$88,938	\$101,420	\$113,903	\$126,386	\$138,868
<b>Total</b>	<b>\$888,480</b>	<b>\$1,013,181</b>	<b>\$1,137,882</b>	<b>\$1,262,582</b>	<b>\$1,387,283</b>

Source: Excel Section E workbook, <Cost of associated services - Current>  
Abbreviations: IVF, in vitro fertilisation; PGD, preimplantation genetic diagnosis

Table F.3.6 Estimated cost of MBS services relating to prenatal testing for PGD: current funding arrangements

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Referral from genetic counsellor	\$12,068	\$13,761	\$15,455	\$17,149	\$18,843
Specialist consultation	\$3,913	\$4,462	\$5,012	\$5,561	\$6,110
Ultrasound for dating	\$3,227	\$3,680	\$4,133	\$4,586	\$5,039
Initiation of patient episode by collection of a specimen	\$366	\$417	\$468	\$520	\$571
<b>Total</b>	<b>\$19,574</b>	<b>\$22,321</b>	<b>\$25,068</b>	<b>\$27,816</b>	<b>\$30,563</b>
<b>CVS</b>					
Chorionic villus sampling	\$1,829	\$2,086	\$2,342	\$2,599	\$2,856
Initiation of management of anaesthesia for CVS	\$1,189	\$1,355	\$1,522	\$1,689	\$1,856
Anaesthesia time unit	\$297	\$339	\$381	\$422	\$464
<b>Total</b>	<b>\$3,315</b>	<b>\$3,780</b>	<b>\$4,245</b>	<b>\$4,710</b>	<b>\$5,175</b>
<b>Amniocentesis</b>					
Amniocentesis	\$1,610	\$1,836	\$2,061	\$2,287	\$2,513
Initiation of patient episode by collection of a specimen	\$2,007	\$2,288	\$2,570	\$2,851	\$3,133
Anaesthesia time unit	\$502	\$572	\$642	\$713	\$783
<b>Total</b>	<b>\$4,118</b>	<b>\$4,696</b>	<b>\$5,274</b>	<b>\$5,852</b>	<b>\$6,429</b>
<b>Genetic test</b>					
Weighted cost for prenatal genetic test	\$13,179	\$15,029	\$16,879	\$18,729	\$20,578
<b>Total</b>	<b>\$13,179</b>	<b>\$15,029</b>	<b>\$16,879</b>	<b>\$18,729</b>	<b>\$20,578</b>

Source: Excel Section E workbook, <Cost of associated services - Current>

Abbreviations: CVS, chorionic villus sampling; PGD, preimplantation genetic diagnosis

Table F.3.7 Estimated cost of MBS services relating to pregnancy loss and live birth for PGD: current funding arrangements

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Termination of pregnancy					
Specialist consultation	\$0	\$0	\$0	\$0	\$0
Termination by curette after CVS (<12 weeks)	\$0	\$0	\$0	\$0	\$0
Anaesthesia for termination	\$0	\$0	\$0	\$0	\$0
Anaesthesia time unit ≤15 min	\$0	\$0	\$0	\$0	\$0
Termination by induction after amniocentesis	\$0	\$0	\$0	\$0	\$0
Anaesthesia for termination	\$0	\$0	\$0	\$0	\$0
Anaesthesia time unit 26-30 min	\$0	\$0	\$0	\$0	\$0
<b>Total</b>	<b>\$0</b>	<b>\$0</b>	<b>\$0</b>	<b>\$0</b>	<b>\$0</b>
Miscarriage					
Counselling by GP	\$3,725	\$4,248	\$4,771	\$5,293	\$5,816
Curettage of the uterus for incomplete miscarriage	\$7,657	\$8,732	\$9,807	\$10,881	\$11,956
Anaesthesia for incomplete miscarriage	\$2,889	\$3,294	\$3,699	\$4,105	\$4,510
Anaesthesia time unit ≤15 min	\$722	\$823	\$925	\$1,026	\$1,128
<b>Total</b>	<b>\$14,993</b>	<b>\$17,097</b>	<b>\$19,201</b>	<b>\$21,306</b>	<b>\$23,410</b>

Source: Excel Section E workbook, <Cost of associated services - Current>

Abbreviations: CVS, chorionic villus sampling; GP, General Practitioner; PGD, preimplantation genetic diagnosis

Table F.3.8 Estimated total cost to the MBS of associated PGD services: current funding arrangements

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Cost of MBS services relating to PGD	\$9,419,152	\$10,741,156	\$12,063,159	\$13,385,162	\$14,707,165
Cost of MBS services relating to prenatal testing	\$40,186	\$45,826	\$51,466	\$57,106	\$62,746
Cost of MBS services relating to pregnancy loss and live birth	\$14,993	\$17,097	\$19,201	\$21,306	\$23,410
<b>Total cost to the MBS</b>	<b>\$9,474,506</b>	<b>\$10,804,278</b>	<b>\$12,134,050</b>	<b>\$13,463,822</b>	<b>\$14,793,594</b>

Abbreviations: MBS, Medicare Benefits Schedule; PGD, preimplantation genetic diagnosis

### F.3.3. Cost of MBS services relating to natural conception followed by prenatal testing, proposed funding arrangements

Table F.3.9 through Table F.3.11 present the approximate cost to the MBS of the associated services for couples who know that they carry a serious genetic disorder and who conceive naturally followed by prenatal diagnosis. These financial estimates are based on the assumption that 25% of couples who know that they carry a serious genetic disorder and are at high risk of passing it onto their offsprings would choose PGD over

natural conception with prenatal diagnosis if PGD was funded by the Government. However, this estimate remains highly uncertain.

**Table F.3.9 Estimated cost of MBS services relating to natural conception with prenatal diagnosis: proposed funding arrangements**

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Referral from genetic counsellor	\$46,077	\$43,772	\$41,926	\$40,400	\$38,768
Specialist consultation	\$14,941	\$14,194	\$13,595	\$13,100	\$12,571
Ultrasound for dating	\$12,323	\$11,706	\$11,213	\$10,804	\$10,368
Initiation of patient episode by collection of a specimen	\$1,397	\$1,327	\$1,271	\$1,225	\$1,175
<b>Total</b>	<b>\$74,738</b>	<b>\$71,000</b>	<b>\$68,004</b>	<b>\$65,529</b>	<b>\$62,882</b>
<b>CVS</b>					
Chorionic villus sampling	\$15,487	\$15,295	\$15,102	\$14,910	\$14,717
Initiation of management of anaesthesia for CVS	\$10,065	\$9,940	\$9,815	\$9,690	\$9,565
Anaesthesia time unit	\$2,516	\$2,485	\$2,454	\$2,422	\$2,391
<b>Total</b>	<b>\$28,069</b>	<b>\$27,720</b>	<b>\$27,371</b>	<b>\$27,022</b>	<b>\$26,673</b>
<b>Amniocentesis</b>					
Amniocentesis	\$1,712	\$1,323	\$1,031	\$807	\$561
Initiation of patient episode by collection of a specimen	\$2,135	\$1,649	\$1,286	\$1,007	\$700
Anaesthesia time unit	\$534	\$412	\$321	\$252	\$175
<b>Total</b>	<b>\$4,380</b>	<b>\$3,385</b>	<b>\$2,638</b>	<b>\$2,066</b>	<b>\$1,436</b>
<b>Genetic test</b>					
Weighted cost for prenatal genetic test	\$50,322	\$47,805	\$45,788	\$44,121	\$42,339
<b>Total</b>	<b>\$50,322</b>	<b>\$47,805</b>	<b>\$45,788</b>	<b>\$44,121</b>	<b>\$42,339</b>

Source: Excel Section E workbook, <Cost of NC+PNT associated services - Proposed>  
Abbreviations: CVS, chorionic villus sampling; PGD, preimplantation genetic diagnosis

Table F.3.10 Estimated cost of MBS services relating to pregnancy loss and live birth after natural conception with prenatal diagnosis: proposed funding arrangements

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Termination of pregnancy					
Specialist consultation	\$7,130	\$7,737	\$7,239	\$6,840	\$6,408
Termination by curette after CVS (<12 weeks)	\$13,220	\$15,222	\$14,580	\$14,049	\$13,482
Anaesthesia for termination	\$4,803	\$5,530	\$5,297	\$5,104	\$4,898
Anaesthesia time unit ≤15 min	\$1,201	\$1,383	\$1,324	\$1,276	\$1,224
Termination by induction after amniocentesis	\$4,944	\$3,820	\$2,977	\$2,331	\$1,621
Anaesthesia for termination	\$1,019	\$787	\$613	\$480	\$334
Anaesthesia time unit 26-30 min	\$509	\$394	\$307	\$240	\$167
<b>Total</b>	<b>\$32,825</b>	<b>\$34,873</b>	<b>\$32,337</b>	<b>\$30,321</b>	<b>\$28,133</b>
Miscarriage					
Counselling by GP	\$4,858	\$4,582	\$4,394	\$4,239	\$4,073
Curettage of the uterus for incomplete miscarriage	\$9,985	\$9,418	\$9,033	\$8,714	\$8,373
Anaesthesia for incomplete miscarriage	\$3,767	\$3,553	\$3,408	\$3,287	\$3,158
Anaesthesia time unit ≤15 min	\$942	\$888	\$852	\$822	\$790
<b>Total</b>	<b>\$19,551</b>	<b>\$18,441</b>	<b>\$17,686</b>	<b>\$17,061</b>	<b>\$16,394</b>

Source: Excel Section E workbook, <Cost of NC+PNT associated services - Proposed>

Abbreviations: CVS, chorionic villus sampling; GP, General Practitioner; PGD, preimplantation genetic diagnosis

Table F.3.11 Estimated total cost to the MBS of associated natural conception services: proposed funding arrangements

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Cost of MBS services relating to prenatal diagnosis	\$157,509	\$149,909	\$143,801	\$138,738	\$133,331
Cost of MBS services relating to pregnancy loss and live birth	\$52,376	\$53,313	\$50,024	\$47,382	\$44,527
<b>Total cost to the MBS</b>	<b>\$209,885</b>	<b>\$203,223</b>	<b>\$193,825</b>	<b>\$186,120</b>	<b>\$177,858</b>

Abbreviations: MBS, Medicare Benefits Schedule; PGD, preimplantation genetic diagnosis

#### F.3.4. Cost of MBS services relating to natural conception followed by prenatal diagnosis, current funding arrangements

Table F.3.12 through Table F.3.14 present the approximate cost to the MBS of the associated services for couples who know that they carry a severe genetic disorder and who conceive naturally followed by prenatal diagnosis, in the event where PGD services are not successfully listed.



Table F.3.12 Estimated cost of MBS services relating to natural conception with prenatal diagnosis:  
current funding arrangements

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Referral from genetic counsellor	\$62,331	\$59,820	\$57,671	\$55,775	\$53,796
Specialist consultation	\$20,212	\$22,811	\$21,991	\$21,268	\$20,514
Ultrasound for dating	\$16,670	\$15,998	\$15,423	\$14,916	\$14,387
Initiation of patient episode by collection of a specimen	\$1,889	\$1,813	\$1,748	\$1,691	\$1,631
<b>Total</b>	<b>\$101,101</b>	<b>\$100,442</b>	<b>\$96,833</b>	<b>\$93,650</b>	<b>\$90,327</b>
<b>CVS</b>					
Chorionic villus sampling	\$20,120	\$19,531	\$19,089	\$18,750	\$18,377
Initiation of management of anaesthesia for CVS	\$13,076	\$12,693	\$12,406	\$12,185	\$11,943
Anaesthesia time unit	\$3,269	\$3,173	\$3,101	\$3,046	\$2,986
<b>Total</b>	<b>\$36,466</b>	<b>\$35,397</b>	<b>\$34,596</b>	<b>\$33,981</b>	<b>\$33,305</b>
<b>Amniocentesis</b>					
Amniocentesis	\$2,749	\$2,523	\$2,297	\$2,071	\$1,845
Initiation of patient episode by collection of a specimen	\$3,427	\$3,145	\$2,864	\$2,582	\$2,300
Anaesthesia time unit	\$857	\$786	\$716	\$645	\$575
<b>Total</b>	<b>\$7,033</b>	<b>\$6,455</b>	<b>\$5,877</b>	<b>\$5,299</b>	<b>\$4,721</b>
<b>Genetic test</b>					
Weighted cost for prenatal genetic test	\$68,073	\$65,330	\$62,983	\$60,913	\$58,752
<b>Total</b>	<b>\$68,073</b>	<b>\$65,330</b>	<b>\$62,983</b>	<b>\$60,913</b>	<b>\$58,752</b>

Source: Excel Section E workbook, <Cost of NC+PNT associated services - Current>  
Abbreviations: CVS, chorionic villus sampling; PGD, preimplantation genetic diagnosis

Table F.3.13 Estimated cost of MBS services relating to pregnancy loss and live birth after natural conception with prenatal diagnosis: current funding arrangements

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Termination of pregnancy					
Specialist consultation	\$9,645	\$9,256	\$8,924	\$8,630	\$8,324
Termination by curette after CVS (<12 weeks)	\$17,175	\$16,672	\$16,294	\$16,005	\$15,686
Anaesthesia for termination	\$6,240	\$6,057	\$5,920	\$5,815	\$5,699
Anaesthesia time unit ≤15 min	\$1,560	\$1,514	\$1,480	\$1,454	\$1,425
Termination by induction after amniocentesis	\$7,937	\$7,284	\$6,632	\$5,980	\$5,328
Anaesthesia for termination	\$1,635	\$1,501	\$1,366	\$1,232	\$1,098
Anaesthesia time unit 26-30 min	\$818	\$750	\$683	\$616	\$549
<b>Total</b>	<b>\$45,009</b>	<b>\$43,034</b>	<b>\$41,299</b>	<b>\$39,731</b>	<b>\$38,108</b>
Miscarriage					
Counselling by GP	\$6,571	\$6,306	\$6,080	\$5,880	\$5,671
Curettage of the uterus for incomplete miscarriage	\$13,507	\$12,963	\$12,498	\$12,087	\$11,658
Anaesthesia for incomplete miscarriage	\$5,095	\$4,890	\$4,715	\$4,560	\$4,398
Anaesthesia time unit ≤15 min	\$1,274	\$1,223	\$1,179	\$1,140	\$1,099
<b>Total</b>	<b>\$26,448</b>	<b>\$25,382</b>	<b>\$24,471</b>	<b>\$23,666</b>	<b>\$22,826</b>

Source: Excel Section E workbook, <Cost of NC+PNT associated services - Current>

Abbreviations: CVS, chorionic villus sampling; GP, General Practitioner; PGD, preimplantation genetic diagnosis

Table F.3.14 Estimated total cost to the MBS of associated services for natural conception with prenatal diagnosis: current funding arrangements

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Cost of MBS services relating to prenatal diagnosis	\$212,672	\$207,624	\$200,289	\$193,843	\$187,105
Cost of MBS services relating to pregnancy loss and live birth	\$71,456	\$68,417	\$65,770	\$63,397	\$60,935
<b>Total cost to the MBS</b>	<b>\$284,128</b>	<b>\$276,041</b>	<b>\$266,059</b>	<b>\$257,241</b>	<b>\$248,040</b>

Abbreviations: MBS, Medicare Benefits Schedule; PGD, preimplantation genetic diagnosis

## F.4. Estimated financial implications on the MBS

As shown in Table F.4.1, the availability of public funding for PGD will lead to an increase in costs to the MBS. This is attributed to the fees for the three PGD items (assuming that there will be a change to legislation to allow PGD on the MBS) and the expected increase in uptake of PGD and 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 F.4.1 Total MBS costs for PGD, with and without public funding of PGD**

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Proposed funding arrangement					
Total cost of PGD services <sup>a</sup>	\$5,183,812	\$6,479,765	\$7,451,729	\$8,196,902	\$9,016,592
Total cost of MBS services related to PGD	\$12,217,100	\$15,271,375	\$17,562,082	\$19,318,290	\$21,250,119
Total cost to the MBS	\$17,400,912	\$21,751,140	\$25,013,811	\$27,515,192	\$30,266,711
Current funding arrangement					
Total cost of PGD services	\$0	\$0	\$0	\$0	\$0
Total cost of MBS services related to PGD	\$9,474,506	\$10,804,278	\$12,134,050	\$13,463,822	\$14,793,594
Total cost to the MBS	\$9,474,506	\$10,804,278	\$12,134,050	\$13,463,822	\$14,793,594
Total net financial impact to the MBS of public funding for PGD <sup>a</sup>	\$7,926,406	\$10,946,862	\$12,879,761	\$14,051,370	\$15,473,117

Source: Excel Section E workbook <Incremental costs-PGD>

Abbreviations: MBS, Medicare Benefits Schedule; PGD, preimplantation genetic diagnosis

a The inclusion of the cost of the proposed PGD service items assumes that they will become available on the MBS rather than through another funding model.

In the event of public funding for PGD services, it was assumed that 25% of couples who would otherwise choose to conceive naturally followed by prenatal diagnosis, would instead choose to conceive via PGD. The financial estimates shown in Table F.4.2 indicate that this switch will result in cost savings.

**Table F.4.2 Total MBS costs for natural conception with prenatal diagnosis, with and without public funding for PGD**

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Proposed funding arrangement					
Total cost to the MBS	\$209,885	\$203,223	\$193,825	\$186,120	\$177,858
Current funding arrangement					
Total cost to the MBS	\$284,128	\$276,041	\$266,059	\$257,241	\$248,040
Total net financial impact to the MBS of public funding for PGD	-\$74,243	-\$72,818	-\$72,234	-\$71,121	-\$70,182

Source: Excel Section E workbook <Incremental costs-NC+PNT>

Abbreviations: MBS, Medicare Benefits Schedule; PGD, preimplantation genetic diagnosis

Table F.4.3 presents the total incremental cost of the proposed and associated services to the MBS in the event of public funding for PGD. These estimates assume that PGD services will become available on the MBS (rather than through another funding model).

**Table F.4.3 Total net financial impact of public funding 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	\$7,852,163	\$10,874,044	\$12,807,527	\$13,980,249	\$15,402,935

Source: Excel Section E workbook <Total incremental cost>

Abbreviations: MBS, Medicare Benefits Schedule; PGD, preimplantation genetic diagnosis

## **F.5. Estimated financial implications for Government health budgets**

Current legislation governing MBS funding prevents subsidy of PGD under the Medicare Benefits Scheme. Thus, public funding of the proposed PGD services would require a change to the legislation or the establishment of an alternate funding mechanism. Although Section E.4 captures the cost of the three PGD service items within the MBS budget, these costs may ultimately fall within other Department of Health budgets.

Couples who undertake PGD are likely to receive IVF related medications, which are funded on the Pharmaceutical Benefits Schedule (PBS) and available to couples undergoing ART services on the MBS. Thus, any increase in the use of IVF due to increased uptake of PGD in the event of public funding, will impact on the PBS. The estimated PBS expenditure for an average ART intervention was \$1,620 according to the Independent Review of ART (2006) for the Department of Health and Ageing. This crude estimate was factored into the economic evaluation in Section D but has not been factored into the financial estimates.

As mentioned in Section E.2, oocyte retrieval and embryo transfer is usually performed in a hospital or clinic as a day procedure. These costs have not been calculated in Section E but are most likely an expense for the patient or private health insurer.

Downstream medical intervention and therapy costs associated with affected births have not been included in the financial analysis. A reduction in the number of affected births will have implications for the National Disability Insurance Scheme. As mentioned in Section F.1, although the reduction in downstream medical costs may be substantial in some cases, these costs are subject to considerable uncertainty due to the large range of serious genetic conditions that are relevant to the proposal for public funding.

## **F.6. Identification, estimation and reduction of uncertainty**

A series of sensitivity analyses were undertaken around the key uncertainties in the financial estimates, which primarily relate to the number of PGD cycles for the proposed population and the proportion of couples who would switch from natural conception with prenatal diagnosis to PGD if public funding became available. As discussed in Section E.2.1, ANZARD data published in 2012 showed a 93% increase in the number of PGD cycles from 2011 to 2012. Given this sharp increase in the number of PGD cycles, it is difficult to reliably predict future use of PGD, regardless of whether or not the service is publicly funded. It is expected that PGD services will increase with public funding; however, there may be capacity constraints given that there are currently only a few IVF centres in Australia that offer PGD services.

The results of sensitivity analyses are presented in Table F.6.1.

**Table F.6.1 Total net financial impact of public funding for PGD on the MBS: sensitivity analyses**

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
<i>Base case analysis</i>	\$7,852,163	\$10,874,044	\$12,807,527	\$13,980,249	\$15,402,935
No of PGD cycles assumed increase by 93% again between 2012 and 2013	\$11,458,453	\$15,684,615	\$18,293,920	\$19,771,213	\$21,620,453
Increase in uptake due to public funding increased from 50% to 75% in the first year, 25% to 50% in the second year, and 15% to 25% in the third year	\$10,751,026	\$19,568,454	\$25,849,142	\$28,326,026	\$31,183,290
Proportion of total PGD cycles for the proposed population increased from 45% to 70%	\$12,262,469	\$16,960,107	\$19,967,747	\$21,791,981	\$24,005,049
Proportion of total PGD cycles for the proposed population decreased from 45% to 15%	\$2,559,796	\$3,570,769	\$4,215,263	\$4,606,170	\$5,080,399
Couples switching from natural conception with prenatal testing to PGD increased from 25% to 50%	\$7,782,202	\$10,806,303	\$12,742,919	\$13,918,209	\$15,343,649
Couples switching from natural conception with prenatal testing to PGD decreased from 25% to 12.5%	\$7,887,144	\$10,907,915	\$12,839,831	\$14,011,269	\$15,432,578
Couples switching from natural conception with prenatal testing to PGD decreased from 25% to 0%	\$7,922,125	\$10,941,785	\$12,872,135	\$14,042,289	\$15,462,221
Proportion of PGD pregnancies with prenatal diagnosis increased from 12.3% to 50%	\$7,925,042	\$10,956,794	\$12,904,559	\$14,086,236	\$15,519,628
Proportion of PGD pregnancies with prenatal diagnosis decreased from 12.3% to 5%	\$7,838,052	\$10,858,021	\$12,788,738	\$13,959,726	\$15,380,340

Source: Excel Section E workbook

Abbreviations: MBS, Medicare Benefits Schedule; PGD, preimplantation genetic diagnosis

## Section G. Options to present additional relevant information

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### G.1. Issues relating to equity principles

Given the specialised nature of the service, complexity of the procedure and time constraints for genetic testing of blastocyst tissue, PGD is currently performed in IVF clinics across Australia. However, because specialist genetic expertise is required at all three stages, it is not available in all IVF clinics. Currently couples seeking PGD may have to travel to major towns and cities across Australia to access IVF clinics. As not all genetics laboratories can do all tests, the genetic material is then couriered to centralised genetic laboratories for testing. Patients with particular genetic disorders may be limited to certain clinics or laboratories.

In their response to the Consultation Protocol, the Applicant claimed that the key factor causing inequity of access is not physical access to PGD services, but rather the cost of PGD services. Public consultation feedback indicated that government funding of PGD services would ensure equity of access for all Australians and not limit it to those of higher socioeconomic status. At present, some couples may not be informed of PGD services as clinicians and counsellors assume they cannot afford it.

In their response to the Consultation Protocol, the Applicant noted that the cost of upgrading public hospitals to deliver IVF and PGD services would be significant and there are many recognised and accepted factors that limit PGD services being available at public hospitals.

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Winter, C., F. Van Acker, et al. (2014). "Cognitive and psychomotor development of 5- to 6-year-old singletons born after PGD: A prospective case-controlled matched study." *Human Reproduction* 29(9): 1968-1977.

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# Appendix 1. Health Expert Standing Panel and Assessment Group

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## Health Expert Standing Panel

**Name**

Associate Professor Bruce Bennetts

Dr Michael Gattas

Professor Robert Norman

Mrs Catherine Smith

Professor Finlay Macrae

Associate Professor Sheryl De Lacey

## Assessment Group

**Name**

**Organisation**

Dr Suzanne Campbell

HealthConsult Pty Ltd

Dr Diah Elhassen

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Dr Kristina Coleman

HealthConsult Pty Ltd

Dr Lisa Fodero

HealthConsult Pty Ltd

Mr Joe Scuteri

HealthConsult Pty Ltd

Mr Paul Mernagh

Subcontractor for HealthConsult Pty Ltd



## Appendix 2. Search strategies

### PICO 1–4

A broad literature search was conducted to identify evidence relating to PGD that may be relevant to PICO 1, PICO 2, PICO3 and PICO 4. The search terms for Embase, Medline and the Cochrane Library are shown below.

EMBASE.com (includes Embase and Medline), searched 25 September 2014

#	Query	No. of citations
#1	Preimplantation AND ('diagnosis'/exp OR diagnosis).ab	2,982
#2	Preimplantation And genetic and testing.ab	505
#3	#1 or #2	3,027
#4	#3 AND [Humans]/lim AND [English]/lim	2,088
#5	#4 AND 'article'	1,284

Cochrane Library-preimplantation genetic diagnosis, searched 16 January 2015

#	Query	No. of citations
#1	Preimplantation genetic diagnosis	68
#2	Preimplantation diagnosis	83
#3	Preimplantation genetic testing	30
#4	#1 or #2 or #3	85

### PICO 5

PICO 5 relates to the comparator (couples choosing natural conception with prenatal testing and subsequent decision to terminate the pregnancy) rather than couples choosing PGD. As such, a separate literature search was required to identify literature relating to the psychological impact and physical harms to the mother of the decision to terminate a pregnancy that tested positive on prenatal testing. The search terms for PubMed and the Cochrane Library are shown below.

PubMed, searched 19 September 2014

#	Query	No. of citations
#1	"Chorionic Villi Sampling/adverse effects"[Mesh] OR "Chorionic Villi Sampling/psychology"[Mesh] OR ("Amniocentesis/adverse effects"[Mesh] OR "Amniocentesis/psychology"[Mesh])	1,404
#2	#1 AND [Humans]/lim AND [English]/lim	1,179

Cochrane Library, searched 19 September 2014

#	Query	No. of citations
#1	"prenatal diagnos*"	452
#2	"prenatal test*"	45
#3	amniocentesis	254
#4	chorionic villus sampling	94
#5	fetal blood sampling	45
#6	foetal blood sampling	2
#7	#1 or #2 or #3 or #4 or #5 or #6	686

Due to lack of relevant evidence in the population of interest, a subsequent search was conducted to identify high level evidence on psychological impact and safety of

pregnancy termination after prenatal diagnosis in couples who know that they carry a severe genetic disorder and are at high risk of passing it onto offspring. The PubMed search terms are shown below.

PubMed, searched 16 January 2015

#	Query	No. of citations
#1	termination of pregnancy"[Title/Abstract] OR abortion[Title/Abstract] OR abort[Title/Abstract]	46,126
#2	psychological OR "mental health" OR psychiatric OR harm OR harms OR "side effects" OR complications OR physical	4,806,315
#3	"meta-analysis" OR "systematic review" OR "pooled analysis" OR systematic	939,810
#4	#1 and #2 and #3. Filters: English	423

## Appendix 3. Studies excluded due to small size

### Studies excluded following full text review based on the number of cycles (<200 cycles)

Study	Publications	Number of cycles
<i>PGD overall</i>	-	-
Chen et al 2014	Chen HF, Chang SP, Wu SH, Lin WH, Lee YC, Ni YH, Chen CA, Ma GC, Ginsberg NA, You EM, Tsai FP, Chen M. Validating a rapid, real-time, PCR-based direct mutation detection assay for preimplantation genetic diagnosis. <i>Gene</i> . 2014 Sep 15;548(2):299-305.	20 cycles 15 couples
Srebnik et al 2014	Srebnik N, Margalioth EJ, Rabinowitz R, Varshaver I, Altarescu G, Renbaum P, Levi-Lahad E, Weintraub A, Eldar-Geva T. Ovarian reserve and PGD treatment outcome in women with myotonic dystrophy. <i>Reprod Biomed Online</i> . 2014 Jul;29(1):94-101.	
Rechitsky et al 2011	Rechitsky S, Pomerantseva E, Pakhalchuk T, Pauling D, Verlinsky O, Kuliev A. First systematic experience of preimplantation genetic diagnosis for de-novo mutations. <i>Reprod Biomed Online</i> . 2011 Apr;22(4):350-61.	151 cycles
Zachaki et al 2011	Zachaki S, Vrettou C, Destouni A, Kokkali G, Traeger-Synodinos J, Kanavakis E. Novel and known microsatellite markers within the beta-globin cluster to support robust preimplantation genetic diagnosis of beta-thalassemia and sickle cell syndromes. <i>Hemoglobin</i> . 2011;35(1):56-66.	38 cycles
Renwick et al 2010	Renwick P, Trussler J, Lashwood A, Braude P, Ogilvie CM. Preimplantation genetic haplotyping: 127 diagnostic cycles demonstrating a robust, efficient alternative to direct mutation testing on single cells. <i>Reprod Biomed Online</i> . 2010 Apr;20(4):470-6.	127 biopsy cycles (PGD cycles not reported) 101 couples
Escriba et al 2008	Escribá MJ, Zulategui JF, Galán A, Mercader A, Remohí J, de los Santos MJ. Vitrification of preimplantation genetically diagnosed human blastocysts and its contribution to the cumulative ongoing pregnancy rate per cycle by using a closed device. <i>Fertil Steril</i> . 2008 Apr;89(4):840-6.	40 couples 40 embryos transferred
Kakourou et al 2008	Kakourou G, Dhanjal S, Mamas T, Gotts S, Doshi A, Fordham K, Serhal P, Ranieri DM, Delhanty JD, Harper JC, SenGupta SB. Preimplantation genetic diagnosis for myotonic dystrophy type 1 in the UK. <i>Neuromuscul Disord</i> . 2008 Feb;18(2):131-6.	22 cycles 17 couples
Colls et al 2007	Colls P, Escudero T, Cekleniak N, Sadowy S, Cohen J, Munné S. Increased efficiency of preimplantation genetic diagnosis for infertility using "no result rescue". <i>Fertil Steril</i> . 2007 Jul;88(1):53-61.	100 cycles
Ye et al 2004	Ye YH, Xu CM, Jin F, Qian YL. Identification of embryonic chromosomal abnormality using FISH-based preimplantation genetic diagnosis. <i>J Zhejiang Univ Sci</i> . 2004 Oct;5(10):1249-54	NR 10 couples
Joris et al 2003	Joris H, De Vos A, Janssens R, Devroey P, Liebaers I, Van Steirteghem A. Comparison of the results of human embryo biopsy and outcome of PGD after zona drilling using acid Tyrode medium or a laser. <i>Hum Reprod</i> . 2003 Sep;18(9):1896-902.	NR 59 OR
Pickering et al 2003	Pickering S, Polidoropoulos N, Caller J, Scriven P, Ogilvie CM, Braude P. Strategies and outcomes of the first 100 cycles of preimplantation genetic diagnosis at the Guy's and St. Thomas' Center. <i>Fertil Steril</i> . 2003 Jan;79(1):81-90	100 cycles
Harper et al 2002	Harper JC, Wells D, Piyamongkol W, Abou-Sleiman P, Apeessos A, Ioulianos A, Davis M, Doshi A, Serhal P, Ranieri M, Rodeck C, Delhanty JD. Preimplantation genetic diagnosis for single gene disorders: experience with five single gene disorders. <i>Prenat Diagn</i> . 2002 Jun;22(6):525-33.	14 cycles 8 couples
Platteau et al	Platteau P, Sermon K, Seneca S, Van Steirteghem A, Devroey P, Liebaers I. Preimplantation genetic diagnosis for fragile Xa syndrome: difficult but not	11 couples

Study	Publications	Number of cycles
2002	impossible. Hum Reprod. 2002 Nov;17(11):2807-12.	13 embryo transferred
Hanson et al 2001	Hanson C, Jakobsson AH, Sjögren A, Lundin K, Nilsson L, Wahlström J, Hardarson T, Stevic J, Darnfors C, Janson PO, Wikland M, Hamberger L. Preimplantation genetic diagnosis (PGD): the Gothenburg experience. Acta Obstet Gynecol Scand. 2001 Apr;80(4):331-6.	36 cycles
Rechitsky et al 2001	Rechitsky S, Verlinsky O, Amet T, Rechitsky M, Kouliev T, Strom C, Verlinsky Y. Reliability of preimplantation diagnosis for single gene disorders. Mol Cell Endocrinol. 2001 Oct 22;183 Suppl 1:S65-8.	114 cycles
Verlinsky et al 1999	Verlinsky Y, Rechitsky S, Verlinsky O, Ivachnenko V, Lifchez A, Kaplan B, Moise J, Valle J, Borkowski A, Nefedova J, Goltsman E, Strom C, Kuliev A. Prepregnancy testing for single-gene disorders by polar body analysis. Genet Test. 1999;3(2):185-90.	50 cycles 28 couples
Grifo et al 1998	Grifo JA, Giatras K, Tang YX, Krey LC. Successful outcome with day 4 embryo transfer after preimplantation diagnosis for genetically transmitted diseases. Hum Reprod. 1998 Jun;13(6):1656-9	NR 7 couples
Verlinsky et al 1997	Verlinsky Y, Rechitsky S, Cieslak J, Ivachnenko V, Wolf G, Lifchez A, Kaplan B, Moise J, Walle J, White M, Ginsberg N, Strom C, Kuliev A. Preimplantation diagnosis of single gene disorders by two-step oocyte genetic analysis using first and second polar body. Biochem Mol Med. 1997 Dec;62(2):182-7.	32 embryos transferred
Harper 1996	Harper JC. Preimplantation diagnosis of inherited disease by embryo biopsy: an update of the world figures. J Assist Reprod Genet. 1996 Feb;13(2):90-5.	197 cycles (65 cycles for SGD) 149 couples
Soussis et al 1996	Soussis I, Harper JC, Handyside AH, Winston RM. Obstetric outcome of pregnancies resulting from embryos biopsied for pre-implantation diagnosis of inherited disease. Br J Obstet Gynaecol. 1996 Aug;103(8):784-8.	58 cycles 33 couples
Grifo et al 1994	Grifo JA, Tang YX, Munné S, Alikani M, Cohen J, Rosenwaks Z. Healthy deliveries from biopsied human embryos. Hum Reprod. 1994 May;9(5):912-6.	11 couples
<i>Single gene disorders</i>	-	-
Kakourou et al 2010	Kakourou G, Dhanjal S, Mamas T, Serhal P, Delhanty JD, SenGupta SB. Modification of the triplet repeat primed polymerase chain reaction method for detection of the CTG repeat expansion in myotonic dystrophy type 1: application in preimplantation genetic diagnosis. Fertil Steril. 2010 Oct;94(5):1674-9.	14 cycles 7 couples
Pecina et al 2010	Peciña A, Lozano Arana MD, García-Lozano JC, Borrego S, Antiñolo G. One-step multiplex polymerase chain reaction for preimplantation genetic diagnosis of Huntington disease. Fertil Steril. 2010 May 1;93(7):2411-2.	7 cycles
Wang et al 2010	Wang W, Yap CH, Loh SF, Tan AS, Lim MN, Prasath EB, Chan ML, Tan WC, Jiang B, Yeo GH, Mathew J, Ho A, Ho SS, Wong PC, Choolani MA, Chong SS. Simplified PGD of common determinants of haemoglobin Bart's hydrops fetalis syndrome using multiplex-microsatellite PCR. Reprod Biomed Online. 2010 Nov;21(5):642-8.	8 couples
De Rademaeker et al 2009	De Rademaeker M1, Verpoest W, De Rycke M, Seneca S, Sermon K, Desmyttere S, Bonduelle M, Van der Elst J, Devroey P, Liebaers I. Preimplantation genetic diagnosis for myotonic dystrophy type 1: upon request to child. Eur J Hum Genet. 2009 Nov;17(11):1403-10.	205 cycles to OR 78 couples
Keymolen et al 2007	Keymolen K, Goossens V, De Rycke M, Sermon K, Boelaert K, Bonduelle M, Van Steirteghem A, Liebaers I. Clinical outcome of preimplantation genetic diagnosis for cystic fibrosis: the Brussels' experience. Eur J Hum Genet. 2007 Jul;15(7):752-8.	90 cycles 47 couples
Malcov et al 2007	Malcov M, Naiman T, Yosef DB, Carmon A, Mey-Raz N, Amit A, Vagman I, Yaron Y. Preimplantation genetic diagnosis for fragile X syndrome using	15 cycles

Study	Publications	Number of cycles
	multiplex nested PCR. <i>Reprod Biomed Online</i> . 2007 Apr;14(4):515-21.	6 patients
Chan et al 2006	Chan V, Ng EH, Yam I, Yeung WS, Ho PC, Chan TK. Experience in preimplantation genetic diagnosis for exclusion of homozygous alpha degrees thalassemia. <i>Prenat Diagn</i> . 2006 Nov;26(11):1029-36.	13 cycles 9 couples
Burlet et al 2005	Burlet P, Frydman N, Gigarel N, Bonnefont JP, Kerbrat V, Tachdjian G, Frydman R, Munnich A, Steffann J, Ray PF. Improved single-cell protocol for preimplantation genetic diagnosis of spinal muscular atrophy. <i>Fertil Steril</i> . 2005 Sep;84(3):734-9.	10 cycles 6 couples
Kuliev et al 2005	Kuliev A, Rechitsky S, Verlinsky O, Tur-Kaspa I, Kalakoutis G, Angastiniotis M, Verlinsky Y. Preimplantation diagnosis and HLA typing for haemoglobin disorders. <i>Reprod Biomed Online</i> . 2005 Sep;11(3):362-70.	197 cycles 114 couples
Malcov et al 2005	Malcov M, Ben-Yosef D, Schwartz T, Mey-Raz N, Azem F, Lessing JB, Amit A, Yaron Y. Preimplantation genetic diagnosis (PGD) for Duchenne muscular dystrophy (DMD) by triplex-nested PCR. <i>Prenat Diagn</i> . 2005 Dec;25(13):1200-5.	18 cycles 5 couples
Kyu Lim et al 2004	Kyu Lim C, Hyun Jun J, Mi Min D, Lee HS, Young Kim J, Koong MK, Kang IS. Efficacy and clinical outcome of preimplantation genetic diagnosis using FISH for couples of reciprocal and Robertsonian translocations: the Korean experience. <i>Prenat Diagn</i> . 2004 Jul;24(7):556-61.	70 cycles 49 couples
Monni et al 2004	Monni G, Cau G, Usai V, Perra G, Lai R, Ibba G, Faà V, Incani F, Rosatelli MC. Preimplantation genetic diagnosis for beta-thalassaemia: the Sardinian experience. <i>Prenat Diagn</i> . 2004 Dec 15;24(12):949-54.	42 cycles 23 couples
Moutou et al 2004	Moutou C, Gardes N, Viville S. New tools for preimplantation genetic diagnosis of Huntington's disease and their clinical applications. <i>Eur J Hum Genet</i> . 2004 Dec;12(12):1007-14.	39 cycles 17 couples
Vrettou et al 2004	Vrettou C, Traeger-Synodinos J, Tzetzis M, Palmer G, Sofocleous C, Kanavakis E. Real-time PCR for single-cell genotyping in sickle cell and thalassemia syndromes as a rapid, accurate, reliable, and widely applicable protocol for preimplantation genetic diagnosis. <i>Hum Mutat</i> . 2004 May;23(5):513-21.	6 cycles
Goossens et al 2003	Goossens V, Sermon K, Lissens W, De Rycke M, Saerens B, De Vos A, Henderix P, Van de Velde H, Platteau P, Van Steirteghem A, Devroey P, Liebaers I. Improving clinical preimplantation genetic diagnosis for cystic fibrosis by duplex PCR using two polymorphic markers or one polymorphic marker in combination with the detection of the DeltaF508 mutation. <i>Mol Hum Reprod</i> . 2003 Sep;9(9):559-67.	22 cycles 16 couples
Kahraman et al 2003	Kahraman S, Findikli N, Berkil H, Bakircioglu E, Donmez E, Sertyel S, Biricik A. Results of preimplantation genetic diagnosis in patients with Klinefelter's syndrome. <i>Reprod Biomed Online</i> . 2003 Oct;7(3):346-52.	8 couples
Ulug et al 2003	Ulug U, Bener F, Akman MA, Bahceci M. Partners of men with Klinefelter syndrome can benefit from assisted reproductive technologies. <i>Fertil Steril</i> . 2003 Oct;80(4):903-6.	12 couples
de Vos et al 2003	De Vos A, Sermon K, De Rijcke M, Goossens V, Henderix P, Van Ranst N, Platteau P, Lissens W, Devroey P, Van Steirteghem A, Liebaers I. Preimplantation genetic diagnosis for Charcot-Marie-Tooth disease type 1A. <i>Mol Hum Reprod</i> . 2003 Jul;9(7):429-35.	13 cycles 5 couples
Chamayou et al 2002	Chamayou S, Alecci C, Ragolia C, Giambona A, Siciliano S, Maggio A, Fichera M, Guglielmino A. Successful application of preimplantation genetic diagnosis for beta-thalassaemia and sickle cell anaemia in Italy. <i>Hum Reprod</i> . 2002 May;17(5):1158-65.	9 cycles 7 couples
Loeys et al 2002	Loeys B, Nuytinck L, Van Acker P, Walraedt S, Bonduelle M, Sermon K, Hamel B, Sanchez A, Messiaen L, De Paepe A. Strategies for prenatal and preimplantation genetic diagnosis in Marfan syndrome (MFS). <i>Prenat Diagn</i> . 2002 Jan;22(1):22-8.	9 couples
Daniels et al 2001	Daniels G, Pettigrew R, Thornhill A, Abbs S, Lashwood A, O'Mahony F, Mathew C, Handyside A, Braude P. Six unaffected livebirths following preimplantation diagnosis for spinal muscular atrophy. <i>Mol Hum Reprod</i> . 2001 Oct;7(10):995-1000.	5 couples

Study	Publications	Number of cycles
Kanavakis et al 1999	Kanavakis E, Vrettou C, Palmer G, Tzetis M, Mastrominas M, Traeger-Synodinos J. Preimplantation genetic diagnosis in 10 couples at risk for transmitting beta-thalassaemia major: clinical experience including the initiation of six singleton pregnancies. <i>Prenat Diagn.</i> 1999 Dec;19(13):1217-22.	11 cycles 10 couples
Sermon et al 1998	Sermon K, De Vos A, Van de Velde H, Seneca S, Lissens W, Joris H, Vandervorst M, Van Steirteghem A, Liebaers I. Fluorescent PCR and automated fragment analysis for the clinical application of preimplantation genetic diagnosis of myotonic dystrophy (Steinert's disease). <i>Mol Hum Reprod.</i> 1998 Aug;4(8):791-6.	10 cycles 9 couples
Sermon et al 1998	Sermon K, Goossens V, Seneca S, Lissens W, De Vos A, Vandervorst M, Van Steirteghem A, Liebaers I. Preimplantation diagnosis for Huntington's disease (HD): clinical application and analysis of the HD expansion in affected embryos. <i>Prenat Diagn.</i> 1998 Dec;18(13):1427-36.	9 cycles 5 couples
Sermon et al 1997	Sermon K, Lissens W, Joris H, Seneca S, Desmyttere S, Devroey P, Van Steirteghem A, Liebaers I. Clinical application of preimplantation diagnosis for myotonic dystrophy. <i>Prenat Diagn.</i> 1997 Oct;17(10):925-32.	8 couples
Ao et al 1996	Ao A, Ray P, Harper J, Lesko J, Paraschos T, Atkinson G, Soussis I, Taylor D, Handyside A, Hughes M, Winston RM. Clinical experience with preimplantation genetic diagnosis of cystic fibrosis (delta F508). <i>Prenat Diagn.</i> 1996 Feb;16(2):137-42.	18 cycles 12 couples
Ray et al 1996	Ray PF, Winston RM, Handyside AH. Reduced allele dropout in single-cell analysis for preimplantation genetic diagnosis of cystic fibrosis. <i>J Assist Reprod Genet.</i> 1996 Feb;13(2):104-6.	18 cycles 12 couples
<i>Chromosomal abnormalities</i>	-	-
Chen et al 2014	Chen CK, Wu D, Yu HT, Lin CY, Wang ML, Yeh HY, Huang HY, Wang HS, Soong YK, Lee CL. Preimplantation genetic diagnosis by fluorescence in situ hybridization of reciprocal and Robertsonian translocations. <i>Taiwan J Obstet Gynecol.</i> 2014 Mar;53(1):48-52.	38 cycles 17 couples
Ko et al 2013	Ko DS, Cho JW, Lee HS, Kim JY, Kang IS, Yang KM, Lim CK. Preimplantation genetic diagnosis outcomes and meiotic segregation analysis of Robertsonian translocation carriers. <i>Fertil Steril.</i> 2013 Apr;99(5):1369-76.	120 cycles 62 couples
Brodie et al 2012	Brodie D, Beyer CE, Osborne E, Kravetski V, Rasi S, Osianlis T. Preimplantation genetic diagnosis for chromosome rearrangements - one blastomere biopsy versus two blastomere biopsy. <i>J Assist Reprod Genet.</i> 2012 Aug;29(8):821-7.	170 cycles 114 couples
Chang et al 2012	Chang EM, Han JE, Kwak IP, Lee WS, Yoon TK, Shim SH. Preimplantation genetic diagnosis for couples with a Robertsonian translocation: practical information for genetic counselling. <i>J Assist Reprod Genet.</i> 2012 Jan;29(1):67-75.	66 cycles 34 couples
Loh et al 2012	Loh SF, Wong PC, Jiang B, Yeo GH, Tan AS, Prasath EB, Mathew J, Chan ML, Tan WC, Choolani M, Yap CH, Chong SS. Preimplantation genetic diagnosis of chromosome translocations by analysis of polymorphic short tandem repeats. <i>Singapore Med J.</i> 2012 Oct;53(10):648-54.	6 cycles 5 couples
Alfarawati et al 2011	Alfarawati S, Fragouli E, Colls P, Wells D. First births after preimplantation genetic diagnosis of structural chromosome abnormalities using comparative genomic hybridization and microarray analysis. <i>Hum Reprod.</i> 2011 Jun;26(6):1560-74.	20 cycles 16 couples
Rius et al 2011	Rius M, Obradors A, Daina G, Ramos L, Pujol A, Martínez-Passarell O, Marquès L, Oliver-Bonet M, Benet J, Navarro J. Detection of unbalanced chromosome segregations in preimplantation genetic diagnosis of translocations by short comparative genomic hybridization. <i>Fertil Steril.</i> 2011 Jul;96(1):134-42.	6 couples
Fiorentino et al 2010	Fiorentino F, Kokkali G, Biricik A, Stavrou D, Ismailoglu B, De Palma R, Arizzi L, Harton G, Sessa M, Pantos K. Polymerase chain reaction-based detection of chromosomal imbalances on embryos: the evolution of preimplantation genetic diagnosis for chromosomal translocations. <i>Fertil Steril.</i> 2010 Nov;94(6):2001-11, 2011.e1-6.	27 cycles 27 couples

Study	Publications	Number of cycles
Ko et al 2010	Ko DS, Cho JW, Park SY, Kim JY, Koong MK, Song IO, Kang IS, Lim CK. Clinical outcomes of preimplantation genetic diagnosis (PGD) and analysis of meiotic segregation modes in reciprocal translocation carriers. <i>Am J Med Genet A</i> . 2010 Jun;152A(6):1428-33.	133 cycles 65 couples
Traversa et al 2010	Traversa MV, Carey L, Leigh D. A molecular strategy for routine preimplantation genetic diagnosis in both reciprocal and Robertsonian translocation carriers. <i>Mol Hum Reprod</i> . 2010 May;16(5):329-37.	28 cycles 29 couples
Otani et al 2006	Otani T, Roche M, Mizuike M, Colls P, Escudero T, Munné S. Preimplantation genetic diagnosis significantly improves the pregnancy outcome of translocation carriers with a history of recurrent miscarriage and unsuccessful pregnancies. <i>Reprod Biomed Online</i> . 2006 Dec;13(6):869-74.	No of cycles NR 33 couples
Alves et al 2002	Alves C, Sousa M, Silva J, Barros A. Preimplantation genetic diagnosis using FISH for carriers of Robertsonian translocations: the Portuguese experience. <i>Prenat Diagn</i> . 2002 Dec;22(12):1153-62.	7 cycles 6 couples
Emiliani et al 2002	Emiliani S, Gonzalez-Merino E, Van Den Bergh M, Delneste D, Englert Y, Abramowicz M. Correlation between fluorescence in-situ hybridization analyses and in-vitro development to blastocyst stage of embryos from Robertsonian translocation (13;14) carriers. <i>Hum Reprod</i> . 2002 Nov;17(11):2957-62.	9 cycles 5 couples
Fridstrom et al 2001	Fridström M, Ahrlund-Richter L, Iwarsson E, Malmgren H, Inzunza J, Rosenlund B, Sjöblom P, Nordenskjöld M, Blennow E, Hovatta O. Clinical outcome of treatment cycles using preimplantation genetic diagnosis for structural chromosomal abnormalities. <i>Prenat Diagn</i> . 2001 Sep;21(9):781-7.	43 cycles 18 couples
Munne et al 2000	Munné S, Sandalinas M, Escudero T, Fung J, Gianaroli L, Cohen J. Outcome of preimplantation genetic diagnosis of translocations. <i>Fertil Steril</i> . 2000 Jun;73(6):1209-18.	47 cycles 35 couples
<i>Diagnostic accuracy</i>	-	-
Christofidou et al 2009	Christofidou C, Sofocleous C, Vrettou C, Destouni A, Traeger-Synodinos J, Kekou K, Palmer G, Kokkali G, Mavrou A, Kitsiou S, Kanavakis E. PGD for X-linked and gender-dependent disorders using a robust, flexible single-tube PCR protocol. <i>Reprod Biomed Online</i> . 2009 Sep;19(3):418-25.	2 couples
Gigarel et al 2007	Gigarel N, Frydman N, Bulet P, Kerbrat V, Tachdjian G, Fanchin R, Antignac C, Frydman R, Munnich A, Steffann J. Preimplantation genetic diagnosis for autosomal recessive polycystic kidney disease. <i>Reprod Biomed Online</i> . 2008 Jan;16(1):152-8.	3 couples
Salvado et al 2004	Salvado CS, Trounson AO, Cram DS. Towards preimplantation diagnosis of cystic fibrosis using microarrays. <i>Reprod Biomed Online</i> . 2004 Jan;8(1):107-14.	10 DNA samples
Blake et al 2001	Blake DL, Dean NL, Knight C, Tan SL, Ao A. Direct comparison of detection systems used for the development of single-cell genetic tests in preimplantation genetic diagnosis. <i>J Assist Reprod Genet</i> . 2001 Oct;18(10):557-65.	Donated blastomeres from one couple
Ray et al 1998	Ray PF, Ao A, Taylor DM, Winston RM, Handyside AH. Assessment of the reliability of single blastomere analysis for preimplantation diagnosis of the delta F508 deletion causing cystic fibrosis in clinical practice. <i>Prenat Diagn</i> . 1998 Dec;18(13):1402-12.	15 cycles 112 embryos

# Appendix 4. Additional economic information

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The following section includes detailed information on the literature searches and calculations that have informed the economic model. The findings presented here have been summarised in Section D and Section E.

## G.2. Identifying risk probabilities for the economic model

In order to incorporate into the economic model appropriate risk and cost data associated with PGD, prenatal testing or natural conception, it is first necessary to identify the proportions of two variables:

1. Couples undergoing PGD who are at risk of having a child affected by a single gene disorder versus those at risk of having a child affected by a chromosomal abnormality.
2. Prenatal testing procedures carried out via amniocentesis versus chorionic villus sampling (CVS).

Each will be considered in turn.

### G.2.1. Proportion of single gene disorders versus chromosomal rearrangements

The ESHRE PGD Consortium data collection does not explicitly provide this information; however, a reasonable proxy can be derived using the relative proportion of all PGD cycles and pregnancies relating to single gene disorders and chromosomal abnormalities. To this end, the five most recent publications from the ESHRE PGD Consortium data collection were examined to determine the proportion of cycles to oocyte retrieval, cycles to embryo transfer and clinical pregnancies that were attributed to single genetic disorders versus chromosomal abnormalities. As shown in Table App4.1, across the three different outcome measures the relative proportions of single gene disorder to chromosomal abnormalities were consistent. The results show that in the earlier years presented here (2005 and 2006) the proportions were approximately 50% each while in the later years the proportions were approximately 65% single gene disorders to 35% chromosomal abnormalities.

*Thus, in lieu of other data, we have assumed that 65% of the eligible population has a single gene disorder and 35% of the eligible population has a chromosomal abnormality.*



Table App4.1 Summary of ESHRE PGD Consortium data to determine relative proportion of single gene disorders and chromosomal abnormalities

	Single gene disorders		Chromosomal abnormalities		Total
	n	%	n	%	N
<i>Cycles to OR</i>	-	-	-	-	-
Goossens 2008	500	49	520	51	1020
Goossens 2009	931	53	812	47	1743
Harper 2010	1203	62	729	38	1932
Goossens 2012	1363	64	774	36	2137
Moutou 2014	1597	65	870	35	2467
<i>Cycles to ET</i>	-	-	-	-	-
Goossens 2008	405	55	328	45	733
Goossens 2009	724	59	493	41	1217
Harper 2010	952	68	450	32	1402
Goossens 2012	1031	68	488	32	1519
Moutou 2014	1221	68	572	32	1793
<i>Clinical pregnancies</i>	-	-	-	-	-
Goossens 2008	109	54	94	46	203
Goossens 2009	237	63	141	37	378
Harper 2010	298	66	152	34	450
Goossens 2012	321	68	151	32	472
Moutou 2014	368	66	187	34	555

Abbreviations: ESHRE, European Society of Human Reproduction and Embryology; ET, embryo transfer; OR, oocyte retrieval; PGD, preimplantation genetic diagnosis

Note: PGD for chromosomal abnormalities includes Robertsonian translocation (male and female carrier), reciprocal translocation (male and female carrier), sex chromosome aneuploidy, deletion, and inversion.

### ***Proportion of amniocentesis vs CVS***

The proportion of invasive prenatal testing that is undertaken using amniocentesis compared with CVS was calculated from MBS data from Medicare Australia for 2014. As shown in Table App4.2, the split of amniocentesis to CVS is 62.8% versus 37.2%, respectively.

It should be noted that this data represents all amniocentesis and CVS claims in Australia, regardless of indication, and as such is not specific to the population of interest in this assessment. *However, in lieu of more appropriate data, it is assumed that the proportion of invasive testing conducted in the assessment population is 68.2% for amniocentesis and 37.2% for CVS.*

Table App4.2 MBS data for amniocentesis and CVS, Jan-Dec 2014

Test	Services	Proportion
MBS 16600 (Amniocentesis)	3,578	62.8%
MBS 16603 (CVS)	2,118	37.2%
<i>Total</i>	<i>5,696</i>	-

Source: Medicare Australia, accessed 03 March 2015

Abbreviations: CVS, chorionic villus sampling; MBS, Medicare Benefits Schedule

### ***Risk of miscarriage***

According to Wilcox (2010), the overall risk of miscarriage in the general population (including both those at high and low risk) is reported to be 11% to 14%, with the majority of miscarriages caused by aneuploidy and other chromosomal abnormalities. The majority of miscarriages occur in the first 20 weeks of pregnancy with the peak miscarriage rate occurring from weeks 10 to 12. The risk of miscarriage after week 20 is 1/1000 per week.

In order to populate the model, it is necessary to identify the risk of miscarriage in the following situations:

1. For the *PGD arm* in early pregnancy or prior to prenatal testing;
2. For the *PGD arm* in late pregnancy or following prenatal testing;
3. For the *natural conception arm* in early or late pregnancy;
4. For the *natural conception with PNT arm* prior to prenatal testing; and
5. For the *natural conception with PNT arm* following prenatal testing.

Each of these will be considered in turn. However, it is first necessary to determine the additional risk of miscarriage associated with prenatal testing using amniocentesis and CVS so that this procedure-related risk can be applied to the baseline miscarriage risk following PGD and natural conception.

To identify if there is an increased risk of miscarriage associated with prenatal testing, PubMed was searched using terms related to amniocentesis, CVS and miscarriage. The search terms and number of citations identified are shown in Table App4.3.

**Table App4.3 Literature search terms for miscarriage risk due to prenatal testing**

Database	Query	No. of citations
PubMed (searched 6 Mar 2015)	(amniocentesis[Title] OR "chorionic villus"[Title] OR cvs[Title]) AND (miscarriage[Title] OR "pregnancy loss"[Title] OR "fetal loss"[Title] OR "foetal loss"[Title])	74

After applying exclusion criteria, a total of 12 citations were included. The reasons for exclusion are presented in Table App4.4.

**Table App4.4 Summary of the process used to identify relevant studies reporting miscarriage risk due to prenatal testing**

	PubMed
<i>Number of citations retrieved by search</i>	74
<b>Number of citations excluded after title/abstract review:</b>	-
Published prior to 2005	27
Not assessing risk of miscarriage	21
Wrong indication	1
Wrong intervention	1
Wrong outcome	1
< 2000 subjects	2
Not in English	2
<b>Total excluded</b>	<b>55</b>
<i>Number of citations screened by full text review</i>	19
<b>Number of citations excluded after full text review:</b>	
Wrong/no comparison	7
Twin pregnancies	3
<b>Total excluded</b>	<b>10</b>
<i>Number of citations included from database search</i>	9
Number of citations identified manually	3
<i>Total number of citations included for further consideration</i>	12

A summary of the results of the included studies is shown in Table App4.5. In the studies that included a population that is considered to be at high risk of miscarriage, there was no significantly increased risk of miscarriage associated with either amniocentesis or CVS with the exception of one study that showed an increased risk associated with amniocentesis within 2 days of the test, and within 3 days to 3 weeks of the test. However, no adjustment for population differences between the intervention and control group (ultrasound) were made so this result may be due to underlying differences in risk between the groups. In studies in which the risk of miscarriage was mixed (i.e. the included population was not only women/couples considered to be at high risk), a number of univariate analyses suggested an increased risk of miscarriage associated with CVS (one study) or a decreased risk of miscarriage associated with CVS/amniocentesis (two studies). However, when multivariate analyses were performed in which analyses were adjusted for potential confounders, there was no increased risk of miscarriage associated with either prenatal test, and a decreased risk (OR 0.4; 95% CI 0.3, 0.7) associated with amniocentesis in one study.

*Based on these findings, the additional risk of miscarriage related to prenatal testing for the base case will be set at 0%.*

It should be noted that the literature regularly describes a procedure-related risk of miscarriage of 0.5-1% for amniocentesis and 1-2% for CVS. As presented above, MBS data shows that for 2014, 62.8% of prenatal tests were performed via amniocentesis and 37.2% were performed via CVS, resulting in a weighted additional procedure-related miscarriage risk of 1.03%. *Thus, a weighted PNT procedure-related miscarriage risk of 1.03% may be appropriate to incorporate into a sensitivity analysis.*

Table App4.5 Summary of the results of studies assessing the additional miscarriage risk associated with prenatal testing

Study ID	Study type	Country	Years	Population	Outcome	Amnio n/N (%)	CVS n/N (%)	No amnio/CVS	Difference (unadjusted)	Adjustment for confounders?
Akolekar 2015	Meta-analysis (7 observational studies) <sup>a</sup>	Various	Various	No age restriction Not limited to singleton pregnancy	Up to 24 weeks	324/42716 (0.81)		942/138657 (0.67)	0.11% (p=0.14)	Not in meta-analysis. Unclear if adjustments made in individual included studies. No details on difference in intervention and control populations for individual studies or groups within studies.
-	Meta-analysis (3 observational studies)	Various	Various	No age restriction Not limited to singleton pregnancy	Up to 24 weeks	-	207/8899 (2.18)	534/37388 (1.79)	0.22% (p=0.64)	
<i>High risk population</i>										
Pitukkiyornnakom 2011	Retrospective case-control	Thailand	1997-2006	≥ 35 years Singleton pregnancy Those who had procedure vs those who declined procedure (similar higher risk of miscarriage between populations)	16-24 weeks	11/2990 (0.37)	-	3/1495 (0.20)	0.17% (p=0.49)	No adjustment for potential confounders. Intervention and control from same high risk base population. No significant differences between population in age and length of gestation to abortion. Statistical trends between groups in terms of birth gestation and parity.
-	-	-	-	-	16-28 weeks	41/2990 (1.37)	-	13/1495 (0.87)	0.50% (p=0.28)	
Kozlowski 2008	Retrospective cohort study	Germany	1997-2005	≥ 35 years History of disorders Increased risk on screening < 5% Those who had amniocentesis vs those who had ultrasound (difference in underlying miscarriage risk between groups)	Up to 27 weeks	217/20460 (1.1)	-	59/11017 (0.5)	p≥0.05	No adjustment for potential confounders. Control group had ultrasound and had different characteristics (i.e. at lower risk).
-	-	-	-	-	Within 2 days of test	25 (0.12)	-	3 (0.03)	0.09% (p<0.01)	

Study ID	Study type	Country	Years	Population	Outcome	Amnio n/N (%)	CVS n/N (%)	No amnio/CVS	Difference (unadjusted)	Adjustment for confounders?
-	-	-	-	-	3 days to 3 weeks after test	95 (0.46)	-	12 (0.11)	0.35% (p<0.005)	-
-	-	-	-	-	4 weeks after test to 27 weeks	97 (0.47)	-	44 (0.40)	0.07% (p≥0.05)	-
Mazza 2007	Retrospective cohort study with historical control	Italy	1997-2003	Considered to be increased risk Singleton pregnancy Historical control	Up to 40 weeks	40/4917 (0.81)	-	32/4917 (0.65) <sup>p</sup>	0.16% (p≥0.05)	No adjustment for potential confounders. Historical control used so intervention and control groups not from the same base population.
-	-	-	-	-	Up to 24 weeks	33/4917 (0.67)	-	-	-	-
Towner 2007	Retrospective cohort study	US	1995-2001	Abnormal serum screen Singleton pregnancy Normal ultrasound Those who had procedure vs those who declined procedure (similar higher risk of miscarriage between populations)	Up to 24 weeks	69/15005 (0.46)		90/17045 (0.53)	-0.07% (p≥0.05)	No adjustment for potential confounders. No significant differences in variables associated with miscarriage between those having amniocentesis and those declining.
-	-	-	-	-	Within 2 weeks of prenatal diagnosis evaluation	17 (0.11)		33 (0.19)	-0.08% (p≥0.05)	-
Kong 2006	Retrospective cohort study with historical control	Hong Kong	1997-2004	Advanced maternal age , abnormal screening test, known genetic disorder or previous child with abnormality Singleton or twin pregnancy Historical control	Up to 24 weeks	53/3505 (1.51)		13/1125 (1.16)	0.35% (NR)	No adjustment for potential confounders. Substantial difference between intervention and historical controls groups in terms of age and level of risk.

Study ID	Study type	Country	Years	Population	Outcome	Amnio n/N (%)	CVS n/N (%)	No amnio/CVS	Difference (unadjusted)	Adjustment for confounders?
<i>Mixed risk</i>										
Theodora 2014	Retrospective cohort study	Greece	1996-2010	No age restriction Singleton or multiple pregnancy Those who had amniocentesis vs those who had ultrasound (difference in underlying miscarriage risk between groups)	Up to 24 weeks	155/12413 (1.25)	-	NR	0.6% (p≥0.05)	No adjustment for potential confounders.
Corrado 2012	Retrospective case-control	Italy	2001-2009	No age restriction Singleton or twin pregnancy Those who had amniocentesis vs those who did not (difference in underlying miscarriage risk between populations)	Up to 24 weeks	30/2990 (1.0)		4/487 (0.8)	0.2% (p=0.80)	No adjustment for potential confounders.
Akelokar 2011	Prospective cohort study	UK	2006-2009	No age restriction Singleton pregnancy Those who had CVS vs those who did not (difference in underlying miscarriage risk between populations)	-	-	44/2396 (1.84)	360/31460 (1.14)	0.7% (p=0.003)	Adjusted for the following potential confounders: maternal history, pregnancy characteristics and components of first-trimester screening. OR not reported due to lack of statistical significance.

Study ID	Study type	Country	Years	Population	Outcome	Amnio n/N (%)	CVS n/N (%)	No amnio/CVS	Difference (unadjusted)	Adjustment for confounders?		
Odibo 2008a	Retrospective cohort study	US	1990-2006	No age restriction Singleton pregnancy Those who had CVS vs those who did not (difference in underlying miscarriage risk between populations)	Up to 24 weeks	-	138 (2.7)	161 (3.3)	-0.7% (p≥0.05)	Prediction model showed the following variables associated with fetal loss (delivery before 24 weeks) following CVS: African American race, two or more aspirations/insertions, heavy bleeding during CVS, maternal age < 25 years and gestational age > 13 weeks. However, the risk model was only moderately accurate.		
			1990-2006	≥ 35 years	Up to 24 weeks		121/4531 (2.7)	103/2114 (4.9)	-2.2 (p<0.01)			
			1990-2006	< 35 years	Up to 24 weeks		17/617 (2.7)	46/2689 (1.7)	1.0 (p=0.1)			
			2000-2006	No age restriction Singleton pregnancy	Up to 24 weeks		35/1208 (2.9)	73/2606 (2.8)	0.1 (p=0.92)			
Odibo 2008b	Retrospective cohort study	US	1990-2006	No age restriction Singleton pregnancy Those who had amniocentesis vs those who did not (difference in underlying miscarriage risk between populations)	Up to 24 weeks	113/11695 (0.97)	-	335/39594 (0.84)	0.13% (p≥0.05)	Adjusted for the following potential confounders found to be significant in univariate analyses: maternal age, race, smoking or alcohol use, abnormal serum screen for aneuploidy, prior fetal loss, prior child with abnormal chromosomes and presence of any fetal anomaly or chromosomal abnormality. OR 1.1 (0.9, 1.4) <sup>c</sup>		
			-	≥ 35 years	Up to 24 weeks		69/7642 (0.91)	-	72/9157 (0.79)		0.12% (p≥0.05)	OR 1.2 (0.9, 1.7)
			-	< 35 years	Up to 24 weeks		44/4053 (1.1)	-	263/30437 (0.86)		0.24% (p≥0.05)	OR 1.03 (0.7, 1.5)

Study ID	Study type	Country	Years	Population	Outcome	Amnio n/N (%)	CVS n/N (%)	No amnio/CVS	Difference (unadjusted)	Adjustment for confounders?
Eddleman 2006	RCT-based cohort	US	1999-2002	No age restriction Singleton pregnancy Those who had amniocentesis vs those who did not (difference in underlying miscarriage risk between populations)	Up to 24 weeks	31/3096 (1.00)	-	300/31907 (0.94)	0.06% (p≥0.05)	Adjusted for the following potential confounders found to be significant in univariate analyses: maternal age, BMI, diabetes, previous pregnancy, previous fetus with problems (i.e. miscarriage, abortion, preterm delivery, chromosomally abnormal, genetic disorder), Down screen status, threatened abortion, maternal use of alcohol or medications. OR 0.4 (0.3, 0.7; p<0.01) <sup>d</sup>
-	-	-	-	≥ 35 years	Up to 24 weeks	(1.06)	-	(1.92)	-0.86% (p<0.05)	-
-	-	-	-	< 35 years	Up to 24 weeks	(0.89)	-	(0.75)	0.14% (p≥0.05)	-

Abbreviations: CVS, chorionic villus sampling; RCT, randomised controlled trial

a Includes controlled studies only.

b Expected spontaneous fetal loss in the study population based on data from a 2005 publication.

c Only increased risk for amniocentesis seen in women who had a normal serum screen for aneuploidy (OR 1.4; 1.03, 1.8).

d The authors note that following adjustment, there is a lower risk of fetal loss following amniocentesis compared with no amniocentesis. They note this is because aneuploidy is so closely related to miscarriage – by identifying and likely terminating the majority of cases with aneuploidy, you avoid a substantial number of downstream miscarriages.



## 1. Risk of miscarriage following PGD – in early pregnancy or prior to prenatal testing.

The risk of miscarriage following PGD is estimated using data from the ESHRE PGD Consortium, originally presented in Section C.6.1, and represented in greater detail below.

It should be noted that in the ESHRE publications, miscarriage rate has been calculated by dividing the number of miscarriages by the number of clinical pregnancies (minus lost to follow-up). However, by convention, the miscarriage rate is generally calculated as the number of miscarriages per the total number of miscarriages, stillbirths and live births (Wilcox et al. 2010). Appropriate data is not available within the ESHRE publications<sup>10</sup> and thus the miscarriage rates presented in Table App4.6 are likely slight overestimates because twin and triplet pregnancies are not being taken into account. The average rate of miscarriage from the most recent five publications from the ESHRE data collection was 11% for both single gene disorders and chromosomal abnormalities.

**Table App4.6 Summary of ESHRE data relating to rates of miscarriage for single genetic disorders and chromosomal abnormalities**

Study	PGD Consortium report number and period	Single gene disorders Miscarriage rate <sup>a</sup> n/N (%)	Chromosomal abnormalities Miscarriage rate n/N (%)
Goossens et al 2008	VIII (Jan to Dec 05)	9/104 (8.7)	12/93 (12.9)
Goossens et al 2009	IX (Jan to Dec 06)	23/235 (9.8)	14/140 (10.0)
Harper et al 2010	X (Jan to Dec 07)	37/290 (12.8)	18/138 (13.0)
Goossens et al 2012	XI (Jan to Dec 2008)	26/293 (8.9)	13/146 (8.9)
Moutou et al 2014	XII (Jan to Dec 2009)	48/352 (13.6)	19/169 (11.2)
<i>Cumulative data</i>	<i>VIII-XII</i>	<i>143/1274 (11.2)</i>	<i>76/686 (11.1)</i>

Abbreviations: CP, clinical pregnancies; LFU, lost to follow-up

Note: PGD for single gene disorders includes X-linked, autosomal recessive and autosomal dominant conditions, as well as human leukocyte antigen compatibility. PGD for chromosomal abnormalities includes Robertsonian translocation (male and female carrier), reciprocal translocation (male and female carrier), sex chromosome aneuploidy, deletion, and inversion. 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.

<sup>a</sup> Numerator = number of miscarriages. Denominator = number of clinical pregnancies, excluding those lost to follow-up

Data regarding miscarriage was also extracted from individual studies that reported outcomes from 200 or more PGD cycles, and is presented in Section C.6.1. A large proportion of this data would have been included in the ESHRE PGD Consortium data collection and so has not been replicated here. The rates of miscarriage in these studies was generally in the range of 10% to 15%.

One identified publication outlined the miscarriage rates in a study conducted at a single IVF clinic in Australia based on data collected between 1999 and 2003 for blastomere biopsies, and 2003 and 2006 for blastocyst biopsies (McArthur et al. 2008). This data has been included in the ESHRE data collection. Given blastocyst biopsy is used exclusively in at least one centre in Australia (data from Applicant), and blastomere and polar body biopsy are the dominant biopsy types used in the ESHRE data, it is important to

<sup>10</sup> Data regarding stillbirths and live births are presented in supplementary data tables in the ESHRE publications but those numbers apply to PGD + PGS, not the PDG categories reported here.

consider whether a different biopsy technique might influence the miscarriage rate should PGD be reimbursed in Australia.

The miscarriage rates in the study from McArthur et al (2008) are much higher than those seen across the ESHRE data collection and the majority of other identified studies (Table App4.7). While blastocyst biopsy had a lower miscarriage rate (16%) compared to blastomere biopsy with Day 5 transfer (21%) for single gene disorders, blastocyst biopsy led to a higher miscarriage rate (52%) than blastomere biopsy with Day 5 transfer (29%) for translocations.

The authors' comment on the particularly high rate of miscarriage seen in cases with translocation and note the following:

“We have not seen a similar improvement in viable pregnancies for late biopsies among chromosomal translocation PGD cases, which in our hands (although numbers are comparatively small and the series 3 data were influenced by one particular family with repeated unsuccessful attempts) continue to exhibit rates of miscarriage of well over 20%, irrespective of the stage of development of the embryo at biopsy. Several authors have drawn attention to the higher rates of mosaic states and aneuploidy for chromosomes other than those involved in a balanced reciprocal translocation (Iwarsson et al. 2000; Findikli et al. 2003; Munn et al. 2005), which have not been looked for in the present series. Otherwise, the reason for this comparatively disappointing outcome for these translocations is not clear yet. The data suggest that we should make use of the multicelled nature of trophoctoderm biopsies to screen one or more additional chromosomes for aneuploidy and mosaicism, especially when reciprocal translocations are present, whereas this might be unnecessary for Robertsonian translocations. We found that reciprocal and Robertsonian translocations were equally likely to be associated with chaotic chromosome complements (defined as different signal patterns among at least three cells, prevalence 24%, data not shown) or mosaicism (two or more cells with two signal patterns, prevalence 37%, data not shown).”

**Table App4.7 Summary of Australian data relating to rates of miscarriage for single genetic disorders and translocations (McArthur et al. 2008)**

Miscarriage rate	Single gene disorders <sup>a</sup> -		Translocations <sup>a</sup> -	
	Blastomere n/N (%)	Blastocyst n/N (%)	Blastomere <sup>a</sup> n/N (%)	Blastocyst n/N (%)
Overall	5/24 (20.8%)	9/58 (15.5%)	4/14 (28.6%)	11/21 (52.4%) <sup>b</sup>
Robertsonian	-	-	0/3 (0)	2/8 (25) <sup>c</sup>
Balanced reciprocal	-	-	3/10 (30)	8/12 (67)
Chromosomal inversion	-	-	1/1 (100)	0/1 (0) <sup>d</sup>

Note: The analysis was restricted to embryos that were transferred fresh during the egg retrieval cycle and excluded subsequent pregnancies from additional diagnosed blastocysts that have been cryostored.

a Only the first cycle for each couple was included in the study.

b The numbers reported in Table 2 of McArthur 2008 for miscarriages following blastocyst biopsy for translocations do not tally with those reported in the text for specific translocation types.

c Two pregnancies ongoing at time of data collection.

d Ongoing pregnancy at time of data collection.

Based on the findings of the ESHRE data collections, and supported by the majority of the other large studies included in Section C.6.1, it is proposed that the general miscarriage rate for both single gene disorders and chromosomal abnormalities be set at 11%. As noted previously, the majority of miscarriages occur prior to 20 weeks (and

most occur at 10-12 weeks) and thus an assumption has been made that the proportion of all miscarriages that occur in early pregnancy is 90%.

*Thus, the miscarriage rate prior to prenatal testing for the PGD arm to be used in the economic model is estimated at 9.90% for both single gene disorders and chromosomal rearrangements, and thus the overall miscarriage rate for the PGD arm, in early pregnancy or prior to prenatal testing, is 9.90%. In light of the higher miscarriage risk seen in the Australian study by McArthur et al (2008) and higher miscarriage rate of 20% will be tested in a sensitivity analysis.*

## **2. Risk of miscarriage following PGD – late pregnancy or after prenatal testing**

Based on the fact very few miscarriages occur after 20 weeks, and that data presented previously suggesting there is no increased risk of miscarriage associated with prenatal testing using amniocentesis and CVS, it is expected that the miscarriage rate in late pregnancy reflects the risk remaining after the rate in early pregnancy is taken into account. *This equates to a miscarriage rate in late pregnancy or following prenatal testing for the PGD arm of 1.22%.*

## **3. Risk of miscarriage following natural conception – early pregnancy or late pregnancy**

The majority of data available on miscarriage rates following natural conception either relate to advanced maternal age (and hence increased risk of aneuploidy) or chromosomal rearrangements, both of which are associated with increased rates of miscarriage. In their decision analysis of prenatal testing for chromosomal disorders, Harris et al 2001 used miscarriage risk estimates of approximately 3% for unaffected fetuses and 29% for affected fetuses (average 16%). In their study of miscarriage following PGD for translocations, Fischer et al 2010 quote rates of miscarriage for translocations (without PGD) of 26%, 36% and 65% (average 42%).

*For the purpose of this assessment, the following miscarriage rates will be used for the natural conception arm: 16% for single gene disorders and 42% for chromosomal rearrangements. Based on a split of 65% of the eligible population having a single gene disorder, and 35% having a chromosomal abnormality, a weighted miscarriage rate of 25.1% will be used. Given the majority of miscarriages occur in the first 20 weeks, a rate of 22.59% will be used for early pregnancy in the natural conception arm. Taking into account the number of at-risk pregnancies remaining after 20 weeks, a miscarriage rate of 3.24% will be used for late pregnancy in the natural conception arm.*

## **4. Risk of miscarriage following natural conception – prior to prenatal testing**

As noted above, the miscarriage rate in early pregnancy following natural conception is estimated to be 22.59%. *Thus, a miscarriage rate of 22.59% will be applied to the natural conception plus prenatal testing arm, prior to prenatal testing.*

## **5. Risk of miscarriage following natural conception – after prenatal testing**

As noted above, the miscarriage rate in late pregnancy following natural conception is estimated to be 3.24%. *Thus, based on the assumption that prenatal testing does not increase the risk of miscarriage, a miscarriage rate of 3.24% will be applied to the natural conception plus prenatal testing arm, following prenatal testing.*

## **Literature search for misdiagnoses**

In the case of testing for genetic abnormalities, misdiagnosis can manifest in two ways: (i) embryos or fetuses that test positive may not actually have the disease (false positive) or

(ii) embryos or fetuses that test negative may actually have the disease (false negative). The downstream effects of these misdiagnoses are both adverse: false positive results may result in an unaffected embryo being destroyed, or an unaffected fetus terminated, while false negative results may result in the transfer of an affected embryo, and hence the birth of an affected child. This assessment will incorporate a false negative rate for PGD and prenatal testing into the economic model, as the birth of an affected child after actively trying to prevent that occurring by undergoing PGD or prenatal testing would have a significant negative impact on a family's quality of life, as well as a significant cost burden. A false positive rate has not been incorporated into the model as it is unlikely that false positives would be identified if termination or miscarriage material is not routinely tested; thus, parents are unlikely to know and it will not impact on their quality of life.

### **PGD**

Table App4.8 presents the misdiagnoses related to single gene disorders, chromosomal abnormalities, and sex-linked disorders that were presented in the ESHRE PGD Consortium data collection. As not all ESHRE publications present misdiagnosis data, some data has come from a review of ESHRE reported misdiagnoses by Wilton et al (2009). According to Wilton et al (2009), the misdiagnosis rate varies substantially across different indications and different methods of diagnosis. For example, the misdiagnosis rates for sexing for X-linked disease are 0.25% using FISH and 3.08% using PCR. The rate for single gene disorders is 0.40% and the rate for chromosomal abnormalities using FISH is 0.12%. The data from ESHRE and Wilton et al (2009) has been reanalysed for this assessment for two reasons: (i) Wilton et al (2009) presents data up to only data collection VIII (the published data is now up to data collection XII); and (ii) the denominator used in the Wilton publication is the number of PGD/PGS cycles. In order to calculate a false negative rate for the economic model, a more appropriate denominator is the number of embryos transferred, as these are embryos that were diagnosed as negative via PGD (i.e. being without the disease/abnormality of interest), and it is the proportion of embryos that are actually positive in this group (i.e. false negatives) that will potentially lead to an affected birth.

As shown in Table App4.8, the rate of false negatives has generally declined as the size of the data collection has increased. It is also possible that increased experience with, and improvement in, PGD techniques over time have also reduced the number of embryos being wrongly diagnosed. In three of the last four years of published data collection (2006-2008) there were no misdiagnoses reported, while there was only one in 2009. While it is acknowledged that misdiagnosis may be underreported in this series, it does appear that the rate of misdiagnosis is very low. For the purpose of this assessment, an average rate of misdiagnosis was calculated across all years of the data collection.

*The estimated false negative rate for PGD to be used in the economic model is 0.079%.*

**Table App4.8 False negative misdiagnoses for single genetic disorders, chromosomal abnormalities and sex-linked disorders**

Study	Timeframe	Indication	Method	Diagnosis method	Outcome	False negative rate n/N <sup>a</sup> (%)
Geraedts 1999 <sup>b</sup>	I: 1997-1998	Myotonic dystrophy type 1	PCR	PNT	TOP	1/297 (0.34)
Geraedts 2000 <sup>b</sup>	II: May 2000	B-thalassemia	PCR	PNT	TOP	2/NR <sup>c</sup>
		Cystic fibrosis	PCR	PNT	Born	
Sermon 2002 <sup>b</sup>	III: May 2001	46 XY, in Duchene muscular dystrophy	PCR	PNT	TOP	2/602 (0.33)
		47,XX,+der(22)t(11;22)(q23.3;q11.2)mat	FISH	PNT	TOP	
Sermon 2005 <sup>b</sup>	IV: 2001	Cystic fibrosis (1 of twins)	PCR	Postnatal	Born	4/811 (0.49)
		Familial amyloid polyneuropathy	PCR	PNT	Born	
		46XY in retinitis pigmentosa	PCR	PNT	Born	
		45 XO, haemophilia A	FISH	PNT	TOP	
Harper 2006 <sup>b</sup>	V: 2002	None	-	-	-	0/992 (0)
Sermon 2007 <sup>b</sup>	VI: 2003	T13 after 45,XY,der(13:14)(q10;q10)	FISH	Miscarriage	Miscarriage	0/1166 (0) <sup>d</sup>
Harper 2007	VII: 2004	CMT Type 1	PCR	PNT	TOP	2/1395 (0.14)
		46,XY,der(15)t(13;15)(q25.1;q26.3)pat	FISH	PNT	TOP	
Goossens 2008	VIII: 2005	B-thalassemia	PCR	PNT	TOP	3/1255 (0.24)
		Fragile X	PCR	PNT	Born	
		46,XY, haemophilia A	FISH	Postnatal	Born	
Goossens 2009	IX: 2006	None	-	-	-	0/2157 (0)
Harper 2010	X: 2007	None	-	-	-	0/2341 (0)
Goossens 2012	XI: 2008	None	-	-	-	0/2520 (0)
Moutou 2014	XII: 2009	Reciprocal translocation	FISH	PNT	TOP	1/2952 (0.034)
<b>TOTAL</b>						<b>13/16488 (0.079)</b>

Abbreviations: CMT, Charcot-Marie-Tooth disease; FISH, fluorescence in situ hybridisation; PCR, polymerase chain reaction; PNT, prenatal testing; Postnatal, postnatal diagnosis; TOP, termination of pregnancy

<sup>a</sup> Assumes all misdiagnoses identified via PNT are born; denominator is number of embryos transferred for single gene disorders and chromosomal abnormalities.

<sup>b</sup> Data from Wilton et al (2009)

<sup>c</sup> Number of transferred embryos for single gene disorders and chromosomal abnormalities not reported. Not included in calculations.

<sup>d</sup> Misdiagnosis picked up via miscarriage. Not included in calculation of false negatives as this misdiagnosis would not have resulted in an affected birth.

It should be noted that Section C.6.3 includes misdiagnosis data from a number of diagnostic studies that validated PCR-based PGD by comparing results obtained at the time of PGD with the results of the embryo follow-up analysis in a large cohort of samples (N= 1,721 embryos). In these studies, embryos that were considered unsuitable for transfer (due to being positive for the disease of interest, having poor developmental capacity and morphology, or a couple's decision that they are not required for further reproductive attempts) were retested. The false negative rates in these studies were 0.76% for Dreesen et al (2014), 3.1% for Dreesen et al (2008) and 0% for Goossens et al (2008). When assessed in greater detail, the study by Dreesen et al (2014) showed false negative rates ranging from 0% for a single cell/multiplex PCR protocol to 4.3% for a single cell/singleplex PCR protocol.

These studies only consider the false negative rate relating to embryos, and do not follow up to PNT or birth. Thus, they are likely to overestimate the false negative rate, as a certain proportion of these embryos would miscarry in the early stages of pregnancy and so would not be picked up by either PNT or at birth. For this reason, these results have not been used to estimate the false negative rate for the economic model.

### ***Prenatal testing***

A literature search was conducted to identify studies providing false negative rates relating to prenatal testing using amniocentesis and CVS. The search strategy is shown in Table App4.9. Only the Cochrane Library was searched as the aim was to identify a systematic review of prenatal testing with amniocentesis and CVS. A total of 95 citations were identified by the search.

**Table App4.9 Prenatal testing diagnostic search (searched 25 February 2015)**

Database	Query	No. of citations
Cochrane Library (searched 2 Mar 2015)	#1: amniocentesis or "chorionic villus":ti,ab,kw	283
	#2: MeSH descriptor: [Prenatal Diagnosis] explode all trees	954
	#3: #1 AND #2	173
	#4: randomised or randomized:ti,ab,kw	373716
	#5: #3 AND #4	95 <sup>a</sup>

<sup>a</sup> Includes 9 citations from the Cochrane Database of Systematic Reviews and 86 citations from the Cochrane Clinical Trials Register.

Following the identification of potentially relevant citations, the titles and abstracts of each publication were reviewed. Studies were excluded at this stage if they were:

- Not a diagnostic accuracy study
- Superseded by a more recent study
- Not published in English.

Any studies not excluded at this stage were reviewed in full. One of the identified studies was a Cochrane Review assessing the safety and accuracy of amniocentesis and CVS (Alfirevic et al, 2003). Studies that provided data on false negatives were identified from this review and included. In addition, the retrieved citations were searched for studies published since the Cochrane Review search was undertaken. Exclusion criteria for full text review included:

- Data was not included in the Cochrane Review (if published prior to the review search date)
- Duplicate data.

A total of eight studies were identified for inclusion (including the Cochrane Review).

**Table App4.10 Summary of the process used to identify relevant PNT diagnostic studies**

	Cochrane Library
Number of citations retrieved by search	95
Number of citations excluded after title/abstract review:	
• Not a diagnostic accuracy study	72
• Superseded by a more recent study	2
• Not in English	1
<b>Total excluded</b>	<b>76</b>
Number of citations screened by full text review	20
Number of citations excluded after full text review:	
• No misdiagnosis data included in Cochrane Review	9
• Duplicate data	3
<b>Total excluded</b>	<b>12</b>
Number of citations included	8

Data regarding false negative rates as extracted from the included studies are presented in Table App4.11. After pooling results across the studies, the false negative rates associated with CVS and amniocentesis were 0.03% and 0%, respectively. It should be noted that the population included in these studies does not exactly match the population of interest in this assessment, as the indication for prenatal testing was largely advanced maternal age, and hence detection of aneuploidy. However, in lieu of more appropriate data these rates have been used to calculate a weighted false negative rate for prenatal testing.

*Based on an assumption that 62.8% of women have amniocentesis and 37.2% have CVS (from MBS data above), the weighted false negative rate for prenatal testing to be used in the economic model is 0.0116%.*

Table App4.11 Misdiagnoses following CVS and amniocentesis

Study	Study type	Population	Country	N	CVS type	TP	FP	TN	FN	Amnio type	TP	FP	TN	FN	Notes
MRC (Finland) 1993 <sup>a</sup>	RCT	Advanced maternal age	Finland	800	TC	23	1	368	0	Mid	16	1	365	0	Outcome after birth
CEMAT 1998 <sup>b</sup>	RCT	Advanced age or <5% risk of chromosomal abnormality	Canada	4107	TC	41		2066	1	Mid	33		1966	0	Excludes sex determination
Canada 1992 <sup>c</sup>	RCT	Advanced age or indications for PND	Canada	2391	TC	21	19	820	3	Mid	20	2	945	0	Including sex-related misdiagnoses
-	-	-	-	-	TC	40		823	0	Mid	22		945	0	Excluding sex-related misdiagnoses
Lieden 1998 <sup>d</sup>	RCT <sup>e</sup>	Advanced maternal age	The Netherlands	117	TA	0	1	49		E	1	0	53		Excludes mosaicism
King's 1996 <sup>e</sup>	RCT	Advanced maternal age or family history of chromosomal abnormality	UK	488	TA	8	0	242	0	E	5	0	233	0	Outcome after birth
MRC 1991 <sup>f</sup>	RCT	Advanced maternal age	UK, Finland, Switzerland	2553	Any	56	1	1044	1	Mid	38	1	962	0	Outcome after birth
Philip 2004 <sup>g</sup>	RCT	Advanced age, previous trisomy or positive screening	US	3775	TA	34	0	1878	0	E	38	0	1820	0	Excluding sex-related misdiagnoses
Total								6421	2				4238	0	
FN rate									0.03%					0%	

Abbreviations: AC, amniocentesis; CVS, chorionic villus sampling; E, early; FN, false negative; FP, false positive; Mid, midtrimester; RCT, randomised controlled trial; TA, transabdominal; TC, transcervical; TN, true negative; TP, true positive  
 Note: Only results shown in shading included in calculations. Results including sex-related misdiagnoses excluded; results in early amniocentesis excluded.

a Included in Alfirevic 2003. Recalculated from Åmmälä 1993; b Included in Alfirevic 2003. Recalculated from Winsor 1999; c Included in Alfirevic 2003. Recalculated from Lippman 1992; d Included in Alfirevic 2003. Recalculated from Nagel 1998; e Included in Alfirevic 2003. Recalculated from Nicolaidis 1994; f Included in Alfirevic 2003. Recalculated from MRC 1991; g Not included in Alfirevic 2003.



## Literature search for utility weights

A literature search was conducted to identify primary studies eliciting utility weights relevant to the health states in the economic model. The search strategy is shown in Table App4.12.

Table App4.12 Utility weight literature search terms and results (searched on 25 February 2015)

Database	Query	No. of citations
PubMed (searched 25 Feb 2015)	#1: (((("Abortion, Spontaneous"[Mesh]) OR "Fetal Death"[Mesh]) OR "Embryo Loss"[Mesh]) OR (miscarriage[Title/Abstract] OR miscarriages[Title/Abstract] OR (pregnancy NEAR/5 loss)[Title/Abstract])) OR "Abortion, Induced"[Mesh]) OR (abortion[Title/Abstract] OR abortions[Title/Abstract] OR (pregnancy NEAR/5 termination)[Title/Abstract])	81800
-	#2: (((((((("Quality-Adjusted Life Years"[Mesh]) OR "Quality of Life"[Mesh]) OR ("cost utility"[Title/Abstract] OR "cost-utility"[Title/Abstract] OR costutility[Title/Abstract])) OR ("standard gamble"[Title/Abstract] OR "time trade off"[Title/Abstract] OR "time tradeoff"[Title/Abstract])) OR (tto NOT "tobacco retrotransposon" NOT ("tea tree oil"[Title/Abstract] OR "teatree oil"[Title/Abstract])) OR (qaly[Title/Abstract] OR "quality adjusted life"[Title/Abstract] OR "quality-adjusted life"[Title/Abstract])) OR ("preference weights"[Title/Abstract] OR "preference based health related"[Title/Abstract] OR "preference-based health related"[Title/Abstract] OR "preference based hrqol"[Title/Abstract] OR "preference-based hrqol"[Title/Abstract])) OR ("cost utilities"[Title/Abstract] OR "utility weight"[Title/Abstract] OR "utility weights"[Title/Abstract] OR "utility value"[Title/Abstract] OR "utility values"[Title/Abstract] OR "multiattribute utility"[Title/Abstract] OR "health utility"[Title/Abstract] OR "health utilities"[Title/Abstract])) OR (sf6d[Title/Abstract] OR aqol[Title/Abstract] OR "australian quality of life"[Title/Abstract] OR "assessment of quality of life instrument"[Title/Abstract] OR euroqol[Title/Abstract] OR eq5d[Title/Abstract] OR "short form 6d"[Title/Abstract] OR "hui 3"[Title/Abstract] OR "hui-3"[Title/Abstract] OR "hui iii"[Title/Abstract] OR "hui-iii"[Title/Abstract])) OR ((utility[Title/Abstract] OR utilities)[Title/Abstract] AND "quality of life"[Title/Abstract])	133150
-	#3: #1 AND #2	333
Cochrane Library (searched 25 Feb 2015)	#1: MeSH descriptor: [Abortion, Spontaneous] explode all trees OR MeSH descriptor: [Fetal Death] explode all trees OR MeSH descriptor: [Embryo Loss] explode all trees OR MeSH descriptor: [Abortion, Induced] explode all trees OR miscarriage or miscarriages or (pregnancy near/5 loss):ti,ab,kw OR abortion or abortions or (pregnancy near/5 termination):ti,ab,kw	3456
	#2: MeSH descriptor: [Quality-Adjusted Life Years] explode all trees OR MeSH descriptor: [Quality of Life] explode all trees OR "cost utility" or "cost-utility" OR costutility:ti,ab,kw OR "standard gamble" OR "time trade off" OR "time tradeoff":ti,ab,kw OR tto not "tobacco retrotransposon" not ("tea tree oil" OR "teatree oil"):ti,ab,kw OR qaly OR "quality adjusted life" OR "quality-adjusted life":ti,ab,kw OR "preference weights" OR "preference based health related" OR "preference-based health related" OR "preference based hrqol" OR "preference-based hrqol":ti,ab,kw OR "cost utilities" OR "utility weight" OR "utility weights" OR "utility value" OR "utility values" OR "multiattribute utility" OR "health utility" OR "health utilities":ti,ab,OR sf6d OR aqol OR "australian quality of life" OR "assessment of quality of life instrument" OR euroqol or eq5d OR "short form 6d" OR "hui 3" OR "hui-3" OR "hui iii" OR "hui-iii":ti,ab,kw OR (utility or utilities) AND "quality of life":ti,ab,kw	20248
	#3: #1 AND #2	17 <sup>a</sup>

<sup>a</sup> Includes seven citations from the NHS Economic Evaluation Database and 10 citations from the Cochrane Clinical Trials Register.

Following the identification of potentially useful citations, the titles and abstracts for each publication was reviewed. Studies were excluded at this stage if:

- the study did not report utility weights (*exclusion criterion 1*)

- the indication was incorrect (i.e. not assessing utility weights for the outcomes of prenatal testing including miscarriage, TOP, affected live birth and unaffected live birth) (*exclusion criterion 2*)

Any studies not excluded at this stage were reviewed in full. The reference lists of these studies were also checked for other potentially included studies. In addition to the exclusion criteria described above, studies were also excluded at this stage if:

- the study did not derive utility weights (i.e. used weights reported in other studies) (*exclusion criterion 3*)

A summary of the exclusion process is shown in Table App4.13. Of the 29 identified studies reviewed in full, 21 were excluded from further consideration on the basis of the full text review. An additional three studies were identified from the search of the reference lists of full review studies, resulting in a total of 11 studies being subsequently considered further as potential sources of utility weights to be applied to the model.

**Table App4.13 Summary of the process used to identify relevant utility studies**

	PubMed	Cochrane Library
Number of citations retrieved by search	333	17
Number of citations excluded after title/abstract review:	-	-
• Duplicate	1	13
• Not a utility study	295	3
• Wrong indication: not miscarriage or termination of pregnancy	9	0
Total excluded	305	16
Number of citations screened by full text review	28	1
Number of citations excluded after full text review:	-	-
• Not a utility study	13	0
• Wrong indication: not miscarriage or termination of pregnancy	1	0
• Not an original study	6	0
Total excluded	20	0
Number of citations included from individual database searches	8	1
Number of citations included from combined database searches	9	-
Number of citations identified manually	3	-
Total number of citations included for further consideration	12	-

A list of the studies included for consideration is presented in Table App4.12. Section D.5 presents further discussion of each of these studies, with a focus on their appropriateness for inclusion in the economic evaluation.

**Table App4.14 Utility studies considered for use in the economic model**

Citation
Chan, Y. M., T. N. Leung, et al. (2006). "The utility assessment of Chinese pregnant women towards the birth of a baby with Down syndrome compared to a procedure-related miscarriage." <i>Prenat Diagn</i> 26(9): 819-824.
Chan, Y. M., D. S. Sahota, et al. (2009). "Miscarriage after invasive prenatal diagnostic procedures: how much risk our pregnant women are willing to take?" <i>Prenat Diagn</i> 29(9): 870-874.
Feeny, D., M. Townsend, et al. (2000). Assessing health-related quality-of-life in prenatal diagnosis comparing chorionic villi sampling and amniocentesis: a technical report, McMaster University Centre for Health Economics and Policy Analysis Research. Working Paper 00-04, May 2000.
Feeny, D., M. Townsend, et al. (2002) Health-related quality-of-life assessment of prenatal diagnosis: chorionic villi sampling and amniocentesis. <i>Genet Test</i> 6, 39-46.
Grobman, W. A., S. L. Dooley, et al. (2002). "Preference assessment of prenatal diagnosis for Down syndrome: is 35 years a rational cutoff?" <i>Prenat Diagn</i> 22(13): 1195-1200.
Harris, R. A., A. E. Washington, et al. (2001). "Decision analysis of prenatal testing for chromosomal disorders: what do the preferences of pregnant women tell us?" <i>Genet Test</i> 5(1): 23-32.
Kuppermann, M., D. Feeny, et al. (1999). "Preferences of women facing a prenatal diagnostic choice: long-term outcomes matter most." <i>Prenat Diagn</i> 19: 711-716.
Kuppermann, M., R. F. Nease Jr, et al. (2004). "How do women of diverse backgrounds value prenatal testing outcomes?" <i>Prenat Diagn</i> 24(6): 424-429.
Kuppermann, M., R. F. Nease, et al. (2000). "Procedure-related miscarriages and Down syndrome-affected births: implications for prenatal testing based on women's preferences." <i>Obstet Gynecol</i> 96(4): 511-516.
Lubinga, S. J., G. A. Levine, et al. (2013). "Health-related quality of life and social support among women treated for abortion complications in western Uganda." <i>Health Qual Life Outcomes</i> 11: 118.
Rowley, P. T., S. Loader, et al. (1998). "Prenatal screening for cystic fibrosis carriers: an economic evaluation." <i>Am J Hum Genet</i> 63(4): 1160-1174.
Ryan, M. and J. Hughes (1997). "Using conjoint analysis to assess women's preferences for miscarriage management." <i>Health Econ</i> 6(3): 261-273.

### Cycles to embryo transfer

To estimate the costs associated with reaching the embryo transfer stage, it was first necessary to estimate the frequency with which these events apply to the average patient undergoing PGD with IVF. The average number of IVF cycles to embryo transfer was estimated using data from the 12 years of data collection from the ESHRE PGD Consortium. As shown in Table App4.15, the average number of IVF cycles to embryo transfer for SGDs and chromosomal abnormalities was 1.31 and 1.59, respectively. *Using a split between SGD and chromosomal abnormalities of 65% versus 35%, the average number of IVF cycles to embryo transfer was 1.41.*

Table App4.15 Average number of IVF cycles to embryo transfer

Study	Year	SGD			CA			Weighted no. of cycles to ET
-	-	Cycles to OR	Cycles to ET	No. of cycles to ET	Cycles to OR	Cycles to ET	No. of cycles to ET	-
Geraedts 1999	1998	132	103	1.28	40	27	1.48	1.35
Sermon 2002	2000	200	161	1.24	172	131	1.31	1.27
Sermon 2005	2001	252	181	1.39	340	237	1.43	1.41
Harper 2006	2002	335	228	1.47	474	283	1.67	1.54
Sermon 2007	2003	516	335	1.54	529	282	1.88	1.66
Harper 2007	2004	520	402	1.29	559	359	1.56	1.39
Goossens 2008	2005	500	405	1.23	520	328	1.59	1.36
Goossens 2009	2006	931	724	1.29	812	493	1.65	1.41
Harper 2010	2007	1203	952	1.26	729	450	1.62	1.39
Goossens 2012	2008	1363	1031	1.32	774	488	1.59	1.41
Moutou 2014	2009	1597	1221	1.31	870	572	1.52	1.38
Pooled		7549	5743	1.31	5819	3650	1.59	1.41

Abbreviations: CA, chromosomal abnormality; ET, embryo transfer; IVF, in vitro fertilisation; OR, oocyte retrieval; SGD, single gene disorders. Note: PGD for single gene disorders includes X-linked, autosomal recessive and autosomal dominant conditions, as well as human leukocyte antigen compatibility. PGD for chromosomal abnormalities includes Robertsonian translocation (male and female carrier), reciprocal translocation (male and female carrier), sex chromosome aneuploidy, deletion, and inversion.

### Embryo transfer cycles to clinical pregnancy

To estimate the costs associated with reaching the clinical pregnancy stage, it was first necessary to estimate the frequency with which these events apply to the average patient undergoing PGD with IVF. The average number of ET cycles to clinical pregnancy was estimated using data from the 12 years of data collection from the ESHRE PGD Consortium. As shown in Table App4.16, the average number of ET cycles to clinical pregnancy for SGDs and chromosomal abnormalities was 3.39 and 3.54, respectively. *Using a split between SGD and chromosomal abnormalities of 65% versus 35%, the average number of IVF cycles to embryo transfer was 3.44.*

Table App4.16 Average number of IVF cycles to clinical pregnancy

Study	Year	SGD			CA			Weighted ET cycles to CP
		Cycles to ET	CP	ET cycles to CP	Cycles to ET	CP	ET cycles to CP	
Geraedts 1999	1998	103	24	4.29	27	7	3.86	4.14
Sermon 2002	2000	161	36	4.47	131	32	4.09	4.34
Sermon 2005	2001	181	47	3.85	237	45	5.27	4.35
Harper 2006	2002	228	63	3.62	283	66	4.29	3.85
Sermon 2007	2003	335	90	3.72	282	67	4.21	3.89
Harper 2007	2004	402	103	3.90	359	90	3.99	3.93
Goossens 2008	2005	405	109	3.72	328	94	3.49	3.64
Goossens 2009	2006	724	237	3.05	493	141	3.50	3.21
Harper 2010	2007	952	298	3.19	450	152	2.96	3.11
Goossens 2012	2008	1031	321	3.21	488	151	3.23	3.22
Moutou 2014	2009	1221	368	3.32	572	187	3.06	3.23
Pooled		5743	1696	3.39	3650	1032	3.54	3.44

Abbreviations: CA, chromosomal abnormality; CP, clinical pregnancy; ET, embryo transfer; SGD, single gene disorders.

Note: PGD for single gene disorders includes X-linked, autosomal recessive and autosomal dominant conditions, as well as human leukocyte antigen compatability. PGD for chromosomal abnormalities includes Robertsonian translocation (male and female carrier), reciprocal translocation (male and female carrier), sex chromosome aneuploidy, deletion, and inversion. Clinical pregnancies are defined as the presence of one or more fetal hearts at six weeks of gestation.

## Literature search for economic evaluations

A literature search was conducted to identify existing economic evaluations of PGD to help inform the structure of the economic model developed for this assessment. The search strategy is shown in Table App4.17.

Table App4.17 Utility weight literature search terms and results (searched on 25 February 2015)

Database	Query	No. of citations
PubMed (searched 25 Feb 2015)	#1: (("Preimplantation Diagnosis"[Mesh]) OR ((preimplantation[Title/Abstract] OR "pre-implantation"[Title/Abstract] OR "pre implantation")[Title/Abstract] AND genetic[Title/Abstract] AND (diagnosis[Title/Abstract] OR diagnoses[Title/Abstract] OR diagnostic)[Title/Abstract]))	62,888
-	#2: (((((((("Costs and Cost Analysis"[Mesh])) OR "Quality-Adjusted Life Years"[Mesh]) OR ("cost effectiveness"[Title/Abstract] OR "cost-effectiveness"[Title/Abstract] OR "costeffectiveness"[Title/Abstract])) OR "economic evaluation"[Title/Abstract] OR "health economics"[Title/Abstract] OR ("cost minimization"[Title/Abstract] OR "cost-minimization"[Title/Abstract] OR "costminimization"[Title/Abstract] OR "cost minimisation"[Title/Abstract] OR "cost-minimisation"[Title/Abstract] OR "costminimisation"[Title/Abstract])) OR ("cost utility"[Title/Abstract] OR "cost-utility"[Title/Abstract] OR "costutility"[Title/Abstract]) OR "quality adjusted life"[Title/Abstract] OR qaly[Title/Abstract] OR "life year"[Title/Abstract])	204,129
-	#3: #1 AND #2	26
Cochrane Library (searched 25 Feb 2015)	#1: MeSH descriptor: [Preimplantation Diagnosis] explode all trees OR (preimplantation OR "pre-implantation" OR "pre implantation") AND genetic AND (diagnosis OR diagnoses OR diagnostic):ti,ab,kw	70
	#2: MeSH descriptor: [Costs and Cost Analysis] explode all trees OR MeSH descriptor: [Quality-Adjusted Life Years] explode all trees OR "cost effectiveness" OR "cost-effectiveness" OR costeffectiveness:ti,ab,kw OR "economic evaluation":ti,ab,kw OR "health economics":ti,ab,kw OR "cost minimization" OR "cost-minimization" OR costminimization:ti,ab,kw OR "cost minimisation" OR "cost-minimisation" OR costminimisation:ti,ab,kw OR "cost utility" OR "cost-utility" OR costutility:ti,ab,kw OR "quality adjusted life" OR qaly:ti,ab,kw OR "life year":ti,ab,kw	29,379
	#3: #1 AND #2	4 <sup>a</sup>

a Includes 2 citations from the NHS Economic Evaluation Database and 2 citations from the Health Technology Assessment database.

Following the identification of potentially useful citations, the titles and abstracts for each publication was reviewed. Studies were excluded if they did not present the findings of an economic analysis of PGD. It should be noted that an economic analysis of PGS was also included as it may provide information relevant to the consideration of PGD.

A summary of the exclusion process is shown in Table App4.18. Of the three identified studies reviewed in full, none were excluded from further consideration on the basis of the full text review. An additional study was identified manually, resulting in a total of four studies being subsequently considered in Section D.

Table App4.18 Summary of the process used to identify relevant economic analyses

	PubMed	Cochrane Library
Number of citations retrieved by search	26	4
Number of citations excluded after title/abstract review:	-	-
• Duplicate	0	2
• Not an economic analysis	23	0
• Not in English	0	2 <sup>a</sup>
Total excluded	23	4
Number of citations screened by full text review	3	0
Number of citations excluded after full text review:	-	-
• Not an economic analysis	0	-
Total excluded	23	4
Number of citations included from database searches	3	-
Number of citations identified manually	1	-
Total number of citations included for further consideration	4	

<sup>a</sup> Both excluded analyses were in Spanish.<sup>11</sup>

A list of the economic analyses considered in Section D is presented in Table App4.19. These are discussed further in E.3.

Table App4.19 Economic analyses considered in Section D

Citation
Davis, L. B., S. J. Champion, et al. (2010). "A cost-benefit analysis of preimplantation genetic diagnosis for carrier couples of cystic fibrosis." <i>Fertil Steril</i> 93(6): 1793-1804.
Mersereau, J. E., B. A. Plunkett, et al. (2008). "Preimplantation genetic screening in older women: a cost-effectiveness analysis." <i>Fertil Steril</i> 90(3): 592-598.
Tur-Kaspa, I. (2012). "Cost effective prevention of inherited disease by IVF and PGD." <i>Reproductive BioMedicine Online</i> 24(Suppl 2): S38.
Tur-Kaspa, I., G. Aljadeff, et al. (2010). "PGD for all cystic fibrosis carrier couples: novel strategy for preventive medicine and cost analysis." <i>Reprod Biomed Online</i> 21(2): 186-195.

<sup>11</sup> Callejo-Velasco, D. (2014) Economic evaluation of preimplantation genetic diagnosis (PGD) for screening (Structured abstract). Health Technology Assessment Database.

López-Pedraza, M. J., M. T. Hernández-Menéndez, et al. (2012) Systematic Review of the efficacy, effectiveness, safety and cost of Preimplantational Genetic Screening (Structured abstract). Health Technology Assessment Database.

# Attachment A

## Best practice guidelines for PGD

Table AttA.1 presents a summary of the ESHRE PGD Consortium best practice guidelines for amplification-based PGD.

Table AttA.1 ESHRE PGD consortium best practice guidelines for amplification-based PGD, 2011

PGD method	Recommendations
General uses of DNA amplification-based tests	Amplification-based tests can be used for the diagnosis of monogenic defects at the DNA level (Sermon et al. 2002; Thornhill and Snow 2002). This includes specific diagnosis for X-linked disease, as well as diagnosis of autosomal recessive and dominant diseases.
	Owing to the risk of contamination and allele drop-out (ADO), it is recommended that DNA amplification protocols include the use of linked or unlinked markers in addition to the disease locus (Sermon et al. 2002; Thornhill and Snow 2002).
	For X-linked diseases, analysis of the mutation and linked markers allows for the transfer of unaffected males as well as the exclusion of carrier females, if the patient is so inclined.
	When sexing only is performed for X-linked diseases <sup>a</sup> by DNA amplification, it is recommended that several loci are included to monitor contamination and preclude misdiagnosis owing to ADO (Renwick et al. 2006; Renwick and Ogilvie 2007).
PCR-based amplification	Fluorescent PCR is an efficient way to significantly reduce ADO (Sermon et al. 1998).
	Other PCR design factors leading to better specificity, higher PCR efficiency and low ADO rates are smaller amplicon size (<350 bp) and appropriate primer design using primer software tools together with BLAST (Basic Local Alignment Search Tool, <a href="http://blast.ncbi.nlm.nih.gov/Blast.cgi">http://blast.ncbi.nlm.nih.gov/Blast.cgi</a> ) searches and single nucleotide polymorphism detection to ensure specificity (Piyamongkol et al. 2003).
	DNA degradation and the choice of DNA polymerases also have an impact on efficiency and ADO of single-cell PCR (Piyamongkol et al. 2003).
	The co-amplification of polymorphic marker(s), linked or unlinked, with the mutation of interest in a multiplex PCR is recommended as it allows a more accurate diagnosis and simultaneously reveals the presence of ADO and contamination (Pickering et al. 1994).
	When no linked markers are available, or the couple is not informative for available markers, or the set-up of a reliable multiplex PCR proves to be too difficult, the biopsy and testing of two cells is an acceptable alternative. Their subsequent independent analysis will help in identifying ADO, which will be seen as a discrepancy in genotype between the cells.
	Multiplex PCR in one round likely reduces the chances for contamination and tube transfer errors compared with (hemi)-nested PCR protocols. (Hemi)nested PCR protocols are acceptable as long as they are reliable and accurate (Stern et al. 2002).
Multiplex PCR	It is recommended to include at least two flanking markers in indirect mutation PCR-multiplex protocols.
	Analysis of at least two loci closely linked to the gene underlying the disease will reduce the risk of unacceptable misdiagnosis (i.e. transfer of an affected embryo) owing to ADO (presumed to be around 5%) to a minimum (<1%).
	More than two markers will make the test more robust: an assay with just one marker at each side of the mutation will yield 'no diagnosis' when one marker fails to amplify. Therefore, two upstream and two downstream markers are preferably applied.

Source: ESHRE PGD consortium best practice guidelines for amplification-based PGD (Harton et al. 2011a)

Abbreviations: ADO, allele drop-out; DNA, deoxyribonucleic acid; PCR, polymerase chain reaction.

<sup>a</sup> Not in the scope of this assessment

## Other recommendations for PGD

The Human Fertilisation and Embryology Authority (HFEA), which is the UK's independent regulator overseeing the use of gametes and embryos in fertility treatment and research, publishes guidance notes intended to help fertility centres comply with the



Human Fertilisation and Embryology Act (the Act 1990). According to Guideline 10 of the Code of Practice (HFEA 2009), PGD can be carried out for a heritable condition only in two circumstances:

- Where there is a particular risk that the embryo to be tested may have a genetic, mitochondrial or chromosomal abnormality and will have or develop a serious disability, illness or medical condition, or
- Where there is a particular risk that any resulting child will have or develop a gender related serious disability, illness or medical condition. A condition is gender related if the Authority is satisfied that it affects only one sex, or affects one sex significantly more than the other.

In the first situation, PGD may be carried out to establish whether the embryo has the suspected abnormality; in the second, PGD may be carried out to establish the sex of the embryo.

Table AttA.2 presents a summary of recommendations for PGD from the American Society for Reproductive Medicine and the Society of Obstetricians and Gynaecologists of Canada.

**Table AttA.2 Committee opinions for PGD indications and recommendations**

	Intended population	Recommendations
Preimplantation genetic testing: a Practice Committee Opinion (2008), American Society for Reproductive Medicine (ASRM 2008)	Couples at risk for transmitting a specific genetic disease or abnormality to their offspring. Individuals who carry a balanced chromosomal translocation, inversion, or other structural chromosomal rearrangement, where there is an increased risk that their gametes will have an unbalanced genetic composition due to excess or missing genetic material.	Before PGD is performed, genetic counselling must be provided to ensure that patients fully understand the risk for having an affected child, the impact of the disease on an affected child, and the limitations of available options that may help to avoid the birth of an affected child. PGD can reduce the risk for conceiving a child with a genetic abnormality carried by one or both parents if that abnormality can be identified with tests performed on a single cell. Prenatal diagnostic testing to confirm the results of PGD is encouraged strongly because the methods used for PGD have technical limitations that include the possibility for a false negative result.
Preimplantation genetic diagnosis, SOGC Technical Update (Audibert et al. 2009) <sup>a</sup>	Carriers of single gene disorders, dominant or recessive, autosomal, or X-linked. Carriers of structural chromosome abnormalities, including reciprocal or Robertsonian translocations, inversions, and others.	Before PGD is performed, genetic counselling must be provided to ensure that patients fully understand the risk of having an affected child, the impact of the disease on an affected child, and the benefits and limitations of all available options for preimplantation and prenatal diagnosis. (III-A) Couples should be informed that PGD can reduce the risk of conceiving a child with a genetic abnormality carried by one or both parents if that abnormality can be identified with tests performed on a single cell. (II-2B) Invasive prenatal testing to confirm the results of PGD is encouraged because the methods used for PGD have technical limitations that include the possibility of a false negative result. (II-2B)

Abbreviations: ASRM, American Society for Reproductive Medicine; PGD, preimplantation genetic diagnosis, SOGC, Society of Obstetricians and Gynaecologists of Canada

<sup>a</sup> Recommendations were made according to guidelines developed by the Canadian Task Force on Preventive Health Care.

# Attachment B

## Therapeutic Goods Administration (TGA) classification of IVD medical devices

*Version 1.1 November 2011<sup>12</sup>*

*The medical devices regulatory framework has a separate classification system for in vitro diagnostic medical devices (IVDs). Under this system, IVD medical devices are classified according to the risk posed to the health of the public or an individual, and relates to the risk of an incorrect result arising from the use of the IVD.*

*The detailed legislation describing the classification of IVDs can be found in:*

- *Regulation 3.1 of the Therapeutic Goods (Medical Devices) Regulations 2002 (the Regulations);*
- *Subregulations 3.2 (2) and 3.3 (2) of the Regulations;*
- *Schedule 2A of the Regulations.*

*IVDs are classified according to subregulation 3.3 (2) as follows:*

*Class 1 IVD no public health risk or low personal risk*

*Class 2 IVD low public health risk or moderate personal risk*

*Class 3 IVD moderate public health risk or high personal risk*

*Class 4 IVD high public health risk*

*The same classification rules apply to both commercial IVDs and in-house IVDs.*

**Table AttB.1 Classification Rule 1.3 – Detection of transmissible agents or biological characteristics posing a moderate public health risk or a high personal risk**

1. An IVD is classified as Class 3 IVD medical devices or a Class 3 in-house IVD if it is intended for any of the following uses:
a. detecting the presence of, or exposure to, a sexually transmitted agent;
b. detecting the presence in cerebrospinal fluid or blood of an infectious agent with a risk of limited propagation;
c. detecting the presence of an infectious agent where there is a significant risk that an erroneous result would cause death or severe disability to the individual or foetus being tested;
d. prenatal screening of women in order to determine their immune status towards transmissible agents;
e. determining infective disease status or immune status where there is a risk that an erroneous result will lead to a patient management decision resulting in an imminent life-threatening situation for the patient;
f. the selection of patients; <ul style="list-style-type: none"> <li>i. for selective therapy and management; or</li> <li>ii. for disease staging; or</li> <li>iii. in the diagnosis of cancer;</li> </ul>
g. human genetic testing;
h. to monitor levels of medicines, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in an immediate life-threatening situation for the patient;
i. the management of patients suffering from a life-threatening infectious disease;
j. screening for congenital disorders in the foetus.

<sup>12</sup> Available from the TGA website, accessed 20<sup>th</sup> March 2015

*IVDs captured by this rule present a moderate public health risk or a high individual risk, where an erroneous result could lead to a patient management decision resulting in a significant impact on patient outcome. These IVDs usually provide the critical or sole determinant for correct diagnosis.*

*All tests used for human genetic testing are Class 3 IVDs, for example tests for detecting the Philadelphia chromosome, Huntington's disease or cystic fibrosis.*

*Class 3 IVDs used for screening for congenital disorders include pre- and postnatal tests for trisomy 13, trisomy 18, trisomy 21 or Klinefelter's syndrome; tests for alpha-fetoprotein (AFP) when used in the detection of foetal open neural tube defects.*

# Attachment C

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## Laboratory Accreditation Standards and Guidelines for PGD

As an IVD medical device, PGD is regulated by the National Pathology Accreditation Advisory Council (NPAAC) and is classified as a Level 2 DNA test.

Table AttC.1 Levels of DNA testing, 2013

Type of DNA test for an inherited genetic disorder	Explanatory notes <sup>a</sup>
Level 1 DNA test (standard)	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 (.i.e. 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.

Source: NPAAC 2013. Requirements for Medical Testing of Human Nucleic Acids (Appendix A)

a 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.

# Attachment D

## G.3. National Health and Medical Research Council regulatory framework for ART

### G.3.1. Table AttD.1 NHMRC regulatory framework for ART clinical practice and research in Australia, 2007

Legislation	Clinical practice, research and all other activities referred to in these guidelines must comply with: (1) relevant national legislation, including the PHCR Act, the RIHE Act and the <i>Privacy Act 1988</i> ; and (2) relevant state and territory legislation, including privacy legislation.
NHMRC licensing arrangements	Activities that require a licence are specified under the RIHE Act and must comply with the conditions of the licence and these guidelines.
Professional and accreditation standards	Clinical practice, research and all other related activities referred to in these guidelines must conform to standards established by the relevant professional and accreditation bodies, including certification and maintenance of appropriate professional standards, and maintenance of quality management systems for laboratory and clinical work.
NHMRC guidelines	Clinical practice, research and all other related activities using ART are to adhere to these ethical guidelines as follows: <ul style="list-style-type: none"> <li>• they must comply with all relevant legislation relating to the activities described in these guidelines;</li> <li>• they must conform with ethical principles outlined in Parts B and C of the guidelines; and</li> <li>• they should follow the practical guidelines provided in Parts B and C to ensure conformity with ethical principles.</li> </ul> Research using ART should also conform to the most recent editions of other relevant NHMRC guidelines, including: <ul style="list-style-type: none"> <li>• the National Statement;</li> <li>• Values and Ethics: Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research; and</li> <li>• Australian Code for the Responsible Conduct of Research.</li> </ul>
Human research ethics committee	Activities that require a licence and all proposals for human research must be approved by an HREC. Other activities, such as some quality assurance and innovative practices, may also need to be considered and approved by an HREC.
Monitoring	Research institutions have the responsibility for monitoring all human research.

Source: National Health and Medical Research Council, 2007

Abbreviations: ART, Assisted Reproductive Technology; HREC, human research ethics committee; PHCR, Prohibition of Human Cloning and Reproduction; RIHE, Research involving Human Embryos

- ANZARD Australian and New Zealand assisted reproduction database annual reports.
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- Harton, G. L., J. C. Harper, E. Coonen, et al. (2011b). ESHRE PGD Consortium best practice guidelines for fluorescence in situ hybridization-based PGD. *Human reproduction* 26(1): 25-32.
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