Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1165.1 (CA) - Preimplantation Genetic Diagnosis Assessment

Applicant: **Genea**

Date of MSAC consideration: **MSAC 69th Meeting, 6-7 April 2017**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

A resubmission requesting three new Medicare Benefits Schedule (MBS) listings for Preimplantation Genetic Diagnosis (PGD) was received from Genea by the Department of Health (the Department).

2. MSAC's advice to the Minister

After considering the evidence presented in relation to safety, clinical effectiveness and cost-effectiveness, MSAC supported public funding of pre-implantation genetic diagnosis, but considered that it was not appropriate for usual listing on the MBS. The committee acknowledged that there will be significant and complex implementation issues, particularly to elaborate the gatekeeper role of the requester of the service and in monitoring implementation to ensure that it is not rendered in sub-optimal circumstances.

MSAC requested the Department investigate the implementation issues and provide further information to the MSAC Executive in order to develop more informed advice.

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

This resubmission requested public funding for PGD. MSAC noted that three separate items were requested, reflecting the three stages of PGD: 1) genetic test design and validation; 2) embryo biopsy; and 3) embryo genetic analysis in order identify a specific genetic and/or chromosomal disorder prior to implantation. Importantly, MSAC recognised that the purpose of PGD testing is not to reduce the number of individuals deemed costly to society, nor to degrade society's willingness to care for those born with a genetic abnormality. MSAC acknowledged the important clinical need for PGD in providing couples with information to guide reproductive decision-making.

An application requesting MBS listing of PGD was considered by MSAC in July 2015. MSAC deferred the application and requested the following information be provided to aid its decision making:

- the best estimate of how many healthy babies would be delivered/pregnancy using PGD compared with current practice without PGD (acknowledging that significant variables may not be incorporated into the analysis);
- the best estimate of the associated costs across this comparison, and thus an estimate of the incremental cost per extra live healthy birth (acknowledging that significant variables may not be incorporated into the analysis);
- a re-calculation of the annual financial implications to the MBS;
- examples of the costs and health consequences associated with babies with significant disability and/or ill-health; and
- comments from the applicant on the revised MBS item descriptors and on implementation strategies to minimise using PGD in less severe medical conditions.

MSAC noted that, in general, the resubmission appropriately addressed these areas as requested.

MSAC accepted at its July 2015 meeting that PGD is at least no worse in terms of safety or effectiveness than other available options to reduce the risk of a live-born affected child. MSAC acknowledged the additional information provided in the resubmission regarding the medical and psychological consequences of terminating a pregnancy.

MSAC noted that, as requested, the resubmission provided an estimate of clinical effectiveness based on the number of healthy babies delivered with PGD compared with current practice without PGD. The incremental cost per unaffected live birth was estimated at $32,727. MSAC noted that this estimate was driven by the assumption that 48.2% of embryos would have an abnormality, which MSAC considered to be high and uncertain, noting that higher rates of abnormality would result in a higher estimate of unaffected live births compared with current practice. MSAC also considered that there was some uncertainty regarding the *in vitro* fertilisation (IVF) success rates in this population, noting that lower rates of success are likely to marginally increase the incremental cost-effectiveness ratio.

MSAC noted that the revised economic model calculated the incremental cost per extra live birth associated with PGD. MSAC considered that these estimates were reasonably robust, although sensitive to the cost of IVF. MSAC noted that the estimates may also be sensitive to the proportion of embryos tested with an abnormality. MSAC considered the contents of the Genea document, Supplementary Information for ESC 2016, provided to the Department in December 2016. MSAC noted that this document was not made available to ESC for consideration at the February 2017 ESC meeting. This document provided additional information regarding downstream lifetime costs and quality of life information for several conditions, further supporting the cost-effectiveness of PGD. MSAC acknowledged that in conditions with high lifetime costs, PGD was likely to be cost-effective or cost-saving. However, ESC advised that costs vary substantially by condition, emphasising the need to ensure that its use is limited to those conditions where it is most likely to be cost-effective.

MSAC noted the revised financial estimates provided in the resubmission with an estimated net cost to the MBS of $3.9 million in year one and $6.8 million in year five. Where the cost of IVF is included, these estimates increase to $9.3 million in year one and $16.1 million in year five. MSAC noted the predicted uptake of 954 cycles in year one, increasing to 1660 in year five. MSAC considered that the uptake estimates for PGD are highly uncertain and likely to be a considerable underestimate of the actual uptake. MSAC noted that the MBS cost offsets presented were also highly uncertain.

Overall, MSAC concluded that there was a clinical need for PGD. While recognising that uncertainties remain in some areas, MSAC acknowledged that the evidence presented

suggested acceptable safety, clinical effectiveness and acceptable cost-effectiveness in conditions associated with high lifetime costs. As such, MSAC recommended that PGD should be publicly funded. However, MSAC advised that several major implementation issues make PGD unsuitable for usual inclusion on the MBS. The outstanding implementation issues discussed by MSAC were:

- Current legislation governing the MBS does not allow subsidy of PGD under the Medicare Benefits Scheme.
- PGD would best be managed by a program with an accountable and independent committee.
- A gate-keeper function will be required to limit use to conditions for which there is acceptable evidence of clinical benefit and cost-effectiveness.
- IVF clinics providing PGD need accreditation and oversight to avoid inappropriate use of PGD.
- Patients should have access to counselling.
- Current out of pocket costs for patients remain a major equity concern.

MSAC noted that under the current legislation governing the MBS, PGD does not qualify for funding and advised that an alternate funding mechanism is required to fund the service.

In considering the need for a mechanism to determine and review conditions suitable for PGD, MSAC acknowledged the applicant's preference for use of the WHO International Classification of Functioning, Disability and Health criteria (ICF). However, MSAC advised that this was unlikely to be a practical option for determining eligibility. MSAC discussed the possibility of establishing a set of criteria to guide eligibility for PGD, however this was considered to be impractical. MSAC determined that this implementation issue could best be addressed by establishing an independent gate-keeper. MSAC considered that important guiding principles for a gate-keeper function would be to consider limiting eligibility for use of PGD to conditions:

- that cause significant disability;
- that have a high level of penetrance; and
- where no curative treatment options are available.

MSAC also identified the need for an arrangement to provide accreditation and oversight of IVF clinics providing PGD services.

MSAC discussed the current arrangements in place in the United Kingdom (UK) for PGD funding. The National Health Service (NHS) Clinical Commissioning Policy outlines the arrangements for funding of PGD in England. It specifies the conditions under which PGD will be routinely funded by the NHS in order to reduce variation in access to PGD and ensure its use in conditions where there is acceptable evidence of clinical benefit and cost-effectiveness. MSAC noted it also specifies mandatory criteria for those wishing to undergo PGD.

The Human Fertilisation and Embryology Authority (HFEA) is the body responsible for licensing and monitoring fertility clinics and all research involving human embryos in the UK. This body is responsible for approving indications for PGD. MSAC suggested that the arrangements used in the UK could be explored and adapted for the Australian system of reimbursement. MSAC noted the importance of accountability and transparency in such arrangements. MSAC advised that input from ethicists and independence from the IVF industry is necessary to avoid the potential for managing significant conflicts of interest in this area.

MSAC also noted the outstanding consumer issues of ensuring that patients have appropriate access to counselling and addressing the high out of pocket costs for both PGD and IVF that are likely to impact on patient access and equity.

After considering the evidence presented in relation to the safety, clinical effectiveness and cost-effectiveness MSAC supported public funding of PGD, but considered it was not appropriate for usual MBS listing. The committee acknowledged there will be significant and complex implementation issues, particularly in regards to adequately delineating the gatekeeper role of service requester and in monitoring implementation to ensure that it is not rendered in sub-optimal circumstances. MSAC requested the Department investigate the implementation issues and provide further information to the MSAC Executive in order to develop more informed advice.

4. Background

Application 1165 was considered at the July 2015 MSAC meeting. MSAC deferred the application to obtain further information to address the following issues:

- the best estimate of how many healthy babies would be delivered/pregnancy using PGD compared with current practice without PGD (acknowledging that significant variables may not be incorporated into the analysis);
- the best estimate of the associated costs across this comparison, and thus an estimate of the incremental cost per extra live healthy birth (acknowledging that significant variables may not be incorporated into the analysis);
- a re-calculation of the annual financial implications to the MBS;
- examples of the costs and health consequences associated with babies with significant disability and/or ill-health; and
- comments from the applicant on the revised MBS item descriptors and on implementation strategies to minimise using PGD in less severe medical conditions. (At this time the Department are satisfied that the implementation strategies will be addressed at a later date).

5. Prerequisites to implementation of any funding advice

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

The assessment report noted that IVF and PGD services are performed in specialist centres that provide access to trained medical professionals and counsellors. Specialised equipment for services such as blastocyst biopsy and cryostorage will normally be located at the centre or clinic. IVF clinics that perform PGD have specialist staff who manage PGD and IVF cycles, that include fertility specialists, geneticists, genetic and/or fertility counsellors, nurses, embryologists and molecular geneticists.

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

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

Fertility clinics that perform IVF are currently located in most cities and many regional areas of Australia, providing for the needs of most couples. However, PGD requires a higher level of expertise, technology and quality assurance than IVF and is currently available in only a few IVF clinics in Australia. Biopsy material (DNA) obtained at other clinics would need to be transferred to one of these specialist clinics for analysis. Transfer of biopsy material may incur additional costs which are not expected to be large (there is no cold chain required). In this circumstance the Approved Pathology Practitioner who receives the biopsy material can raise a "specimen referred fee" covered under the MBS, subject to P.19.1 of the MBS - '*Rules for Interpretation of the Pathology Services Table*,' relating to specimen referred fees.

With PGD services provided privately in a small number of fertility clinics, it is not expected that additional equipment or quality assurance for testing platforms would be required by these facilities. Increased demand may put pressure on output capabilities and so upgraded equipment with larger/faster output capacity may be required to meet this demand. Alternatively, more clinics may provide the service. Ethical guidance could be required if testing platforms such as whole genome testing and microarrays are used. However, these provide more information than is necessary for a PGD service, and additional data and findings may give rise to complications regarding management.

6. Proposal for public funding

The application proposed that public funding be made available for couples:

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

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.

7. Summary of Public Consultation Feedback/Consumer Issues

Consumers noted concerns about limited data and access to genetic counselling.

8. Proposed intervention's place in clinical management

In the July 2015 PSD for Application 1165, MSAC agreed with the proposed clinical management algorithm.

9. Comparator

In the July 2015 PSD for Application 1165, MSAC considered that pregnancy via natural or IVF conception with prenatal testing and the option of termination of pregnancy (TOP) is an appropriate technical comparator. However, it is not an appropriate overall comparator due to non-medical considerations, such as psychological, ethical and social issues, regarding management of genetic risk. MSAC advised that a mixed comparator – including natural pregnancy or IVF conception with prenatal testing, natural pregnancy or IVF conception with

postnatal testing, and choosing not to have biological children – may be more appropriate to account for the risks and consequences.

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 (which is rarely used in Australia). 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.

Parents may also 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.

PGD is therefore provided in addition to other services already being utilised. Should the service be publically funded, 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.

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.

10. Comparative safety

Although evidence suggests that amniocentesis, CVS, and TOP are reasonably safe procedures when undertaken by experienced operators in an appropriate clinical setting, there remains a small risk of serious complications, which is avoided using preimplantation rather than prenatal diagnosis. Further, some women who undergo TOP for fetal anomaly experience anxiety, post-traumatic stress and depression, which decreases over time but may still remain in some women at 12 months post procedure.

PGD efficiency data shows that the rate of affected births following PGD (false negative rate) is very low. For couples that choose natural (or IVF) conception with no prenatal testing, there is a 1 in 2 or a 1 in 4 risk of having a child with a serious genetic disorder or unbalanced genetic content (chromosomal rearrangement). The birth of an affected child results in costs to the parents and health care system as well as negative health consequences for the child and parents.

11. Comparative effectiveness

MSAC previously considered data provided on the analytical validity of the assay for PGD, which showed a small but significant false negative rate (0.0722% based on updated data from the ESHRE PGD Consortium).

From the studies that assessed the diagnostic accuracy of amniocentesis for the detection of single gene defects, the pooled false negative rate was 0.52%. Studies that performed early amniocentesis prior to 14 weeks' gestation were excluded from analysis since the safety and accuracy of early amniocentesis is less clear and is not common practice in Australia.

No firm conclusions can be drawn about the comparative diagnostic validity of PGD versus prenatal testing. However, on the basis of poor quality, non-comparative evidence, the false negative rate for PGD appears to be small and similar to that of prenatal testing.

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.

There is evidence that couples undergoing prenatal testing experience anxiety (albeit transient) while waiting for a test result and during decision-making. However, there is also evidence that some women experience anxiety at some time points during PGD, particularly at the time of embryo transfer. While PGD can theoretically reduce the time taken to achieve pregnancy and birth, no studies were identified that have directly measured the time difference.

MSAC also requested information on studies that provided information on fear as a factor limiting family size, or estimates of uptake or changes in family size with PGD or prenatal testing to assess reduction in frequency of affected babies. No relevant studies were identified by the evaluation that address these issues.

Clinical Claim
The clinical claim is that PGD is as effective in identifying genetic disorders as prenatal diagnosis. In addition, PGD offers superior safety for couples due to (1) the absence of the requirement of TOP due to fetal anomaly and its associated psychological trauma, or (2) possible reduction in negative outcomes due to not having a child with a serious genetic disorder.

12. Economic evaluation

The economic evaluation was modified in response to the MSAC request for information from Application 1165.

While the previous iteration of the model considered the cost-utility and cost-effectiveness of PGD relative to either natural conception with prenatal testing, or natural conception without prenatal testing, MSAC requested that the revised model considers the cost-effectiveness of PGD relative to a mixed comparator.

Table 1 Summary of the economic evaluation

Perspective	Health care payer
Comparator	Mixed: natural conception with prenatal testing; IVF conception with prenatal testing; natural conception with postnatal diagnosis; IVF conception with postnatal diagnosis. The model results also factor in a proportion of women who elect to not have biological children (i.e. accrue no costs or outcomes)
Type of economic evaluation	Cost-effectiveness
Sources of evidence	Systematic review
Time horizon	200 weeks (10 cycles)
Outcomes	Incremental cost per unaffected live birth
Methods used to generate results	Markov model
Health states	Attempt pregnancy, Achieve pregnancy, Miscarriage, Abnormality detected, No abnormality detected, Termination of pregnancy, Live birth, Unaffected live birth, Affected live birth
Cycle length	20 weeks
Discount rate	5% per annum
Software packages used	TreeAge Pro

Abbreviations: IVF, in vitro fertilisation.

Table 2 presents the base case incremental cost-effectiveness ratio (ICER) in terms of the incremental cost per unaffected live birth for PGD versus the mixed comparator.

Table 2 Incremental cost per unaffected live birth (PGD versus the mixed comparator), per person

Parameter	PGD arm	Mixed comparator arm	Incremental
Cost	$23,593	$6692	$16,901
Unaffected live births	0.967	0.451	0.516
Incremental cost per unaffected live birth	-	-	*$32,727*

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

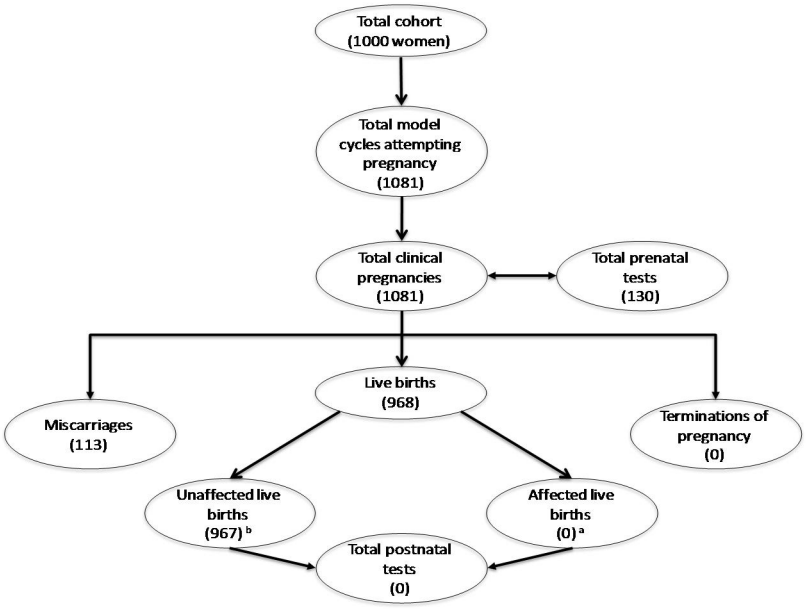
Consideration of the identified costs in the context of the mean lifetime health system cost of managing of an affected individual (estimated at approximately $335,000 for an individual with cystic fibrosis in 2011)[1] indicated that PGD results in a significant saving in healthcare costs.

However, from an economic perspective this should be interpreted with caution as the analysis does not take into account the value associated with clinical outcomes; that is, life, affected or otherwise. Furthermore, the genetic disorders for which PGD funding is proposed are diverse; lifetime treatment costs vary significantly depending on life expectancy and severity. Nonetheless, the cost of disability care to the patient, family, carers, healthcare system and the economy can be substantial, and there are also social, emotional and psychological impacts that are not captured in the economic evaluation.

To provide clarity on how PGD compares against the mixed comparator in terms of health outcomes beyond unaffected live births in the economic evaluation, flowcharts are presented below to report key outcomes of interest.

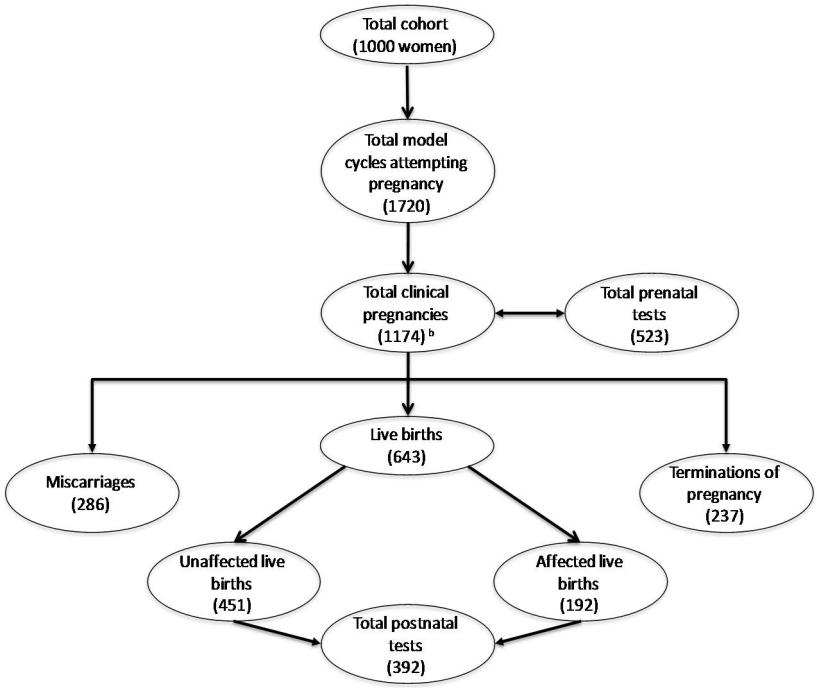
[1] Estimate from CHERE (2011), using 5% discount rate. Mean annual costs for cystic fibrosis patients with severe disease, defined on the basis of lung function, were reportedly three times higher than those for patients with mild disease.

Figure 1 Flowchart reporting cumulative health outcomes and events for 1000 women (PGD arm)



a The number of affected live births in a cohort of 1000 women is non-zero, but less than 1
b Sum of unaffected and affected live births appears to not sum to total live births in figure due to rounding

Figure 2 Flowchart reporting cumulative health outcomes and events for 1000 women (mixed comparator)



a Calculated from distribution data presented.
b Greater than the sum of miscarriages, live births and terminations, since there are a number of ongoing pregnancies at the termination of the model.

Over the 200 weeks of the model in the PGD arm, there were a total of 1411 IVF cycles to achieve 968 live births. Similarly, to achieve the 968 live births, there were 3400 instances of embryo biopsy (Stage 2 PGD item) and embryo DNA analysis (Stage 3 PGD item) in the cohort of 1000 women.

Among those in the comparator arm who used IVF, there was a total of 131 IVF cycles attempted. Accounting for the cohort size and the relative use of IVF in the mixed comparator, this translates to an average of 0.055 IVF cycles per woman over the duration of the model.

13. Financial/budgetary impacts

The estimated number of PGD services and costs for the first five years of public funding is presented in Table 3. The number of Stage 1 services reflects the estimated number of women undergoing PGD. To put this number into perspective, the Victorian Assisted Reproductive Treatment Authority (VARTA) Annual Report for 2014-15, reported 128 women in Victoria who underwent PGD.[2]

Table 3 Estimated number of PGD services and cost for PGD services with public funding

	Year 1 2018	Year 2 2019	Year 3 2020	Year 4 2021	Year 5 2022
Estimated number of services					
PGD Stage 1: genetic test design and validation	873	1092	1255	1381	1519
PGD Stage 2: embryo biopsy	954	1193	1371	1509	1660
PGD Stage 3: embryo analysis	954	1193	1371	1509	1660
Estimated cost for PGD services					
PGD Stage 1: genetic test design and validation	$1,516,012	$1,895,015	$2,179,267	$2,397,194	$2,636,913
PGD Stage 2: embryo biopsy	$373,047	$466,309	$536,255	$589,881	$648,869
PGD Stage 3: biopsy diagnosis	$2,059,869	$2,574,836	$2,961,061	$3,257,167	$3,582,884
Total	**$3,948,928**	**$4,936,160**	**$5,676,584**	**$6,244,242**	**$6,868,666**

Abbreviations: PGD, preimplantation genetic diagnosis.

In addition to the cost of the three proposed PGD items, there are other costs associated with PGD, which are currently funded on the MBS. These include costs related to IVF, confirmatory prenatal testing (in a proportion of women who opt for this), and miscarriage. The total cost, inclusive of these associated services, is shown in Table 4.

Table 4 Estimated total cost with public funding of PGD

	Year 1 2018	Year 2 2019	Year 3 2020	Year 4 2021	Year 5 2022
Total cost of PGD services[a]	$3,948,928	$4,936,160	$5,676,584	$6,244,242	$6,868,666
Total cost of MBS services related to PGD	$5,329,627	$6,662,059	$7,661,367	$8,427,504	$9,270,255
Total	**$9,278,555**	**$11,598,218**	**$13,337,951**	**$14,671,746**	**$16,138,921**

Abbreviations: MBS, Medicare Benefits Schedule; PGD, preimplantation genetic diagnosis.

If PGD is publicly funded, it is expected that a proportion of women who would otherwise choose natural (or IVF) conception with or without prenatal testing, will instead opt for PGD. In the base case, the proportion who switch is assumed to be 25% (tested in sensitivity analyses). Table 5 shows the total net cost of public funding for PGD, taking into consideration the expected decrease in services for those who would switch to PGD if it was publicly funded. These estimates are highly uncertain as it is difficult to reliably estimate the number and relative proportion of couples that are currently choosing to have a child via natural (or IVF) conception.

[2] The number of women who underwent Preimplantation Genetic Screening was 503.

Table 5 Total net financial impact of public funding for PGD

	Year 1 2018	Year 2 2019	Year 3 2020	Year 4 2021	Year 5 2022
Total incremental cost to the MBS of public funding for PGD on the MBS[a]	$5,684,638	$7,769,255	$9,242,119	$10,289,541	$11,448,833
Total incremental cost to the MBS of public funding for PGD through an alternative funding model	$1,735,710	$2,833,096	$3,565,535	$4,045,299	$4,580,167

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.

The net financial impact to the MBS must be considered in light of the substantial downstream costs and health consequences that are avoided through the use of PGD. For couples that undergo either PGD or prenatal testing, the estimated number of affected live births over the five-year time period is zero, due to the low false negative rates associated with these tests. For couples that choose to conceive via natural or IVF conception and not undergo prenatal testing, the estimated number of affected live births is substantial (approximately 250 affected births per year in the current scenario and 100 affected births per year in the proposed scenario, assuming that 25% of couples with switch to PGD if listed on the MBS).

The cost to the health system of managing an affected individual is highly variable, given the large range in life expectancy, age of disease onset, and rate of disease progression across the range of genetic disorders for which PGD can be used. An Australian study estimated that the mean annual healthcare cost for managing an individual with cystic fibrosis is over $22,000 (over $55,000 for the most severe disease category).

Therefore, the financial costs associated with PGD could at least be partially offset by reduced costs of care for affected individuals (especially in light of recent developments with the National Disability Insurance Scheme) as well as broader, less tangible savings.

14. Key issues from ESC for MSAC

A request for MBS listing of PGD was originally considered by MSAC in July 2015. MSAC deferred the application and requested additional information be provided for reconsideration of the application. ESC considered how these requests are addressed in the reapplication.

ESC noted ongoing concerns regarding leakage into populations with less severe conditions and the ongoing issue around the definition of 'serious' in this context. ESC considered the appropriate eligibility criteria and the method to identify eligible couples or individuals. ESC acknowledged that a list of eligible conditions is limiting, particularly for rare conditions. Despite this ESC considered that a list may be required, particularly to provide guidance for disorders which are of borderline severity, or if the genetic condition has a lower level of penetrance therefore causing variation in the underlying risk of developing the condition. ESC noted that any list of eligible conditions would need to be subject to timely and flexible review by an expert committee, and should not rely on modification of the item description.

ESC noted that applying the International Classification of Functioning, Disability and Health (ICF) criteria, as suggested by the applicant, is another possible approach.

In previous considerations it was noted that the definition of the eligible population could be improved by clarifying the definition of 'rare' so that it aligned with other Government guidance, such as the definition provided in the Therapeutic Goods Regulation 1990 '…a disease, or condition, likely to affect not more than 2,000 individuals in Australia at any time.' However, ESC noted that this definition may now be out-dated, and ESC would not restrict any definition to the number of individuals with the condition in Australia, due to the rarity of most genetic conditions.

MSAC requested the use of a mixed comparator including:

a) not having biological children;
b) pregnancy (natural or IVF) with postnatal testing; or
c) prenatal testing with the option of termination of pregnancy (the previous comparator).

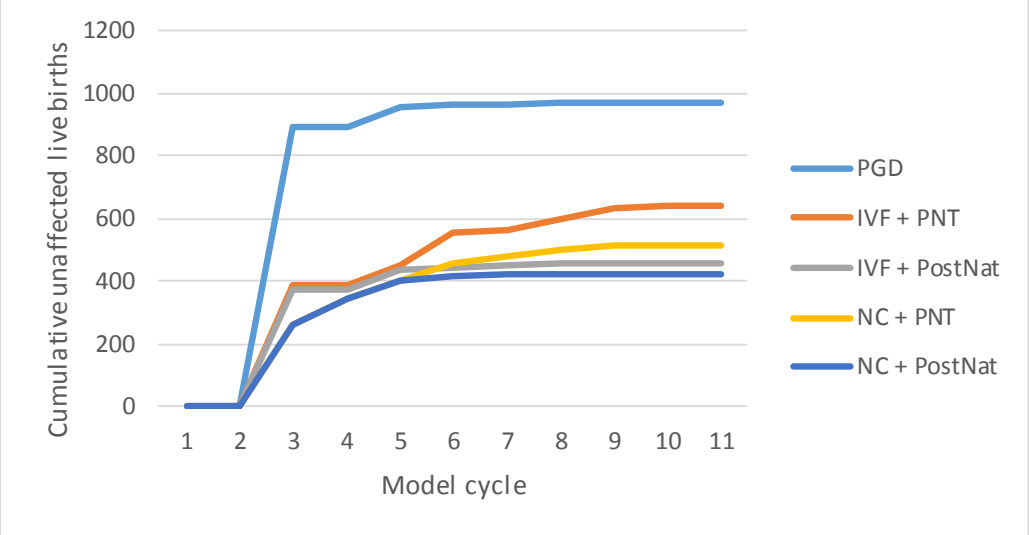
ESC considered that the mixed comparator used in the reapplication is appropriate. However ESC noted that there is still considerable uncertainty regarding the proportion of patients who would choose not to have biological children, and the proportion that would choose to undergo PGD.

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

ESC noted that information from five Cochrane reviews was considered as not being directly relevant to the population under consideration. However, ESC considered that although the evidence is not in an identical population, it is informative if conservatively applied to this application. ESC noted that an additional four studies also provide evidence that termination of pregnancy may be associated with potential psychological impacts and mental health problems. ESC noted costs of care for mental and psychological impact of termination of pregnancy are not included in the model.

MSAC requested that the reapplication provide the best estimate of how many healthy babies would be delivered with PGD compared with current practice without PGD. ESC considered that this request was addressed appropriately and noted Figure 3 (Figure 13, p183 of the assessment report) which shows the cumulative unaffected births for each treatment arm.

Figure 3 Cumulative unaffected live births, by treatment arm (for a cohort of 1000 women)



Abbreviations: PGD, preimplantation genetic diagnosis; PNT, prenatal testing; PostNat, postnatal testing; IVF, in vitro fertilisation.

ESC noted that the calculations indicate that for every 1000 women in the PGD arm there would be an additional 516 unaffected live births compared with the mixed comparator arm. ESC questioned the number of additional unaffected live births, which is largely driven by the assumption that 48.2% of embryos would have an abnormality. ESC noted that this assumption is based on Genea PGD cycle data that shows that the average rate of unaffected embryos is 51.2%. ESC suggested that this rate is high because it is based on an enriched subgroup and questioned whether abnormality rates would be lower in an unselected population. ESC also noted that this assumption was not tested in sensitivity analyses and that this would be useful information for decision making.

ESC noted that an 'unaffected' live birth does not necessarily equate to a healthy baby and acknowledged that this is more complex to determine. ESC noted that, as shown in the figure above, unaffected live births in the PGD arm is close to 100%.

In previously considering the cost-effectiveness of PGD, MSAC requested that the reapplication provide the best estimate of the associated costs across the comparators, and thus an estimate of the incremental cost per extra live healthy birth. ESC noted that the ICER is calculated at $32,727 per unaffected live birth. ESC noted that compared with the estimated lifetime health system cost for treating an affected individual (eg. $335,000 for cystic fibrosis) this suggests significant savings in health system costs. This may be a conservative estimate as there are other more severe diseases where management requires ongoing use of high cost drugs. ESC also noted that the ICER does not take into account the costs associated with mental health conditions or other societal costs.

ESC noted that although the assessment report provides a significant amount of information to justify the model assumptions, many assumptions are layered and lack clear evidence which introduces substantial uncertainty. ESC considered that the sensitivity analyses indicate fairly robust results but uncertainty in IVF success rates could influence cost-effectiveness. ESC noted that overall a conservative approach was taken to the economic model.

In considering the financial impact of PGD for the original submission MSAC requested that a reapplication provide recalculation of the annual financial implications to the MBS. ESC noted the revised financial impacts of $9.3 million total net cost in year one and $16.1 million in year 5. ESC considered uptake of the service may be underestimated if MBS funding

increases the overall number of parents who choose to conceive but this is difficult to predict. ESC noted that some prenatal and postnatal testing is still likely to occur after PGD. ESC also advised that downstream medical intervention and therapy costs for affected births are not considered in the financial impact estimates. Omission of these costs is appropriate, but favours the comparator arm of the evaluation.

ESC noted equity concerns given the current out of pocket costs for patients accessing PGD which are estimated at $16,000 to $22,000. ESC also noted concerns regarding access to genetic counselling, which while not specifically covered in the MBS, will be required in all patients accessing PGD. The economic evaluation used MBS item specialist consultation items 132 ($263.90) for the initial clinical visit and item 133 ($132.10) for subsequent visits. These items may not be claimed by a genetic counselor without other specialist qualifications.

ESC discussed whether the proposed item for stage 1 of the service (genetic test design and validation) is a process that is required for prenatal diagnosis of genetic and/or chromosomal disorder. ESC noted expert advice that given the small number of cells removed at the embryo stage in PGD, there is a risk that with subsequent amplification the mutation segment will be lost (allele drop-out). Flanking markers are looked for as well as the gene mutation to reduce the false-negative rate, increasing the complexity of the genetic test design. Development of a prenatal test is for the mutation only. Linkage analysis is not required to control for allele drop out because a CVS or amniotic fluid sample contains a greater quantity of DNA which does not have to be copied.

MSAC requested comments from the applicant on the revised MBS item descriptors. ESC noted that the applicant rejected the suggestion to apply a single fee for stage 2 of the item descriptor rather than a fee per embryo and acknowledged that this is likely to be appropriate. ESC also noted the applicant's suggestion to change the wording within item descriptors to 'couple or gamete recipients' so as not to exclude an individual who is at risk of having a child with a genetic disorder.

ESC noted consumer support for listing of the service in reducing current out of pocket costs and increasing equity of access for PGD. ESC also noted consumer concerns regarding access to genetic counselling. ESC acknowledged important ethical considerations for consumers around this service and its possible impacts.

ESC noted that current legislation governing MBS prevents subsidy of PGD assessment under the MBS and that this is a matter for the policy area to address as part of implementation.

15. Other significant factors

Nil

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

Genea is very pleased with the support of MSAC for public funding of PGD. With regard to the outstanding implementation issues discussed by MSAC:

- We note that there may be an alternate funding model outside of the MBS scheme which would provide a subsidy of PGD outside of the current legislation enabling an expedited implementation.
- Management by a committee should not be unnecessarily cumbersome, but permit expeditious treatment for patients.

- A gatekeeper function should similarly permit expeditious treatment. Throughout our submission we strongly contested the application of a list of diseases. However, the evaluation subcommittee was concerned about opening a flood gate of trivial uses. A list of the most common serious diseases would potentially fast-track the service for the most common diseases tested. There would need to be an efficient process for timely and flexible review, including for serious but very rare diseases, for which there may not currently be known families in Australia, but that could be diagnosed in the future.
- Accreditation - Clinic accreditation of IVF is already performed by RTAC. We concur that the cost effectiveness will be influenced by success rate. There is a very wide range of success rates for IVF reported in ANZARD. PGD should not be offered in clinics with low success rates. The new listing of in-house IVDs with the TGA (effective 1/7/2017) requires compulsory NATA accreditation of all diagnostic PGD laboratories.
- We concur that it is vital that couples must have access to genetic counselling.
- 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 separate items have been proposed so that the payer only pays for the exact service provided to the patient. Both the Stage 2 and Stage 3 fees are per embryo biopsied and there is no upper limit proposed on the number of embryos biopsied per cycle. It is most cost-effective to test all suitable embryos from a stimulated IVF cycle.

Public funding will permit greater equity of access to this reproductive option to the broader Australian community, reducing the cost of care of individuals affected by serious genetic conditions as well as important intangible benefits to the families.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
visit the MSAC website