Australian Government
Medical Services Advisory Committee
Protocol Advisory Sub-committee

Feedback Survey:

Application 1165 - Consultation protocol to guide the assessment of Pre-implantation Genetic Diagnosis

Thank you for taking the time to complete this feedback form on a draft protocol to consider the options by which a new intervention might be subsidised through the use of public funds. You are welcome to provide feedback from either a personal or group perspective for consideration by the Protocol Advisory Sub-Committee (PASC) of MSAC when the draft protocol is being reviewed.

The data collected will be used to inform the MSAC assessment process to ensure that when proposed healthcare interventions are assessed for public funding in Australia, they are patient focused and seek to achieve best value.

This feedback form should take 10-12 minutes to complete.

You may also wish to supplement your responses with further documentation or diagrams or other information to assist PASC in considering your feedback.

Responses are be provided to the MSAC , its subcommittees and the applicant with responses identified unless you specifically request deidentification.

While stakeholder feedback is used to inform the application process, you should be aware that your feedback may be used more broadly by the applicant.

Please reply to the HTA Team

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Email: HTA@health.gov.au

Your feedback is requested by 21 March 2014 to enable the collation of responses to be given to PASC.

PERSONAL AND ORGANISATIONAL INFORMATION

1. What is your name? Clare Stuart
2. Is the feedback being provided on an individual basis or by a collective group?

Collective group.

What is the name of the organisation you work for (if applicable)? The Australasian Tuberous Sclerosis Society (ATSS)

4. What is your e-mail address? clare@atss.org.au
5. Are you a:

Consumer

What is the highest level of qualification you have completed? Bachelor's Degree

MEDICAL CONDITION (DISEASE) - (Refer to page 6 of the protocol)

Feedback Survey:

A proposal requests MBS listing of Preimplantation Genetic Diagnosis (PGD) for couples who carry a specific mutation(s) for a serious genetic disorder (and know the exact nature of that mutation) which is at high risk of passing on to their offspring.

The proposal requests three items to cover the procedures encompassed by PGD:

Item 1. PGD test design and validation for a known specific genetic mutation(s)

Item 2. PGD embryo biopsy

Item 3. PGD embryo analysis

PROPOSED INTERVENTION - (Refer to page 6 of the protocol)

Pre-implantation genetic diagnosis (PGD) of cells harvested from embryos created *in vitro* is being proposed as a three stage process, being: (1) genetic test design and validation, (2) embryo biopsy, and (3) embryo analysis. Currently, PGD is provided by private fertility clinics and assisted conception clinics to couples who are concerned about carrying genetic conditions, and are prepared to undergo *in vitro* fertilization (IVF). 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. The population to which PGD is currently offered is broader than that for which the funding is sought. The proposal requests that subsidy for PGD be offered to:

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

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

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

CLINICAL NEED AND PUBLIC HEALTH SIGNIFICANCE

1) Describe your experience with the medical condition (disease) and/or proposed intervention relating to the draft protocol?

The Australasian Tuberous Sclerosis Society is made up of people affected the genetic condition Tuberous Sclerosis Complex (TSC), their families, friends, health professionals and researchers. We provide education and support services to people living with TSC and are in regular contact with hundreds of families living with the disease. The committee of ATSS is made up of people with TSC and parents of a person with TSC (and some are both). Clare Stuart (author of this submission) is the sibling of a person with TSC.

TSC is an autosomal dominant genetic disease with estimated incidence of up to 1 in 5,800. It causes tumours to grow in various organs of the body resulting in a chronic and complex health condition. There is a wide spectrum of severity in how an individual may be affected by TSC and neither genotype nor other biomarkers have any predictive value for an individual diagnosed with the condition. Although approximately 70% of cases of TSC occur when there is no family history of the disease, at least 30% are inherited from one parent. In many cases a child who inherits TSC from a parent will be more severely affected by TSC than their parent.
TSC is a leading cause of epilepsy, autism, developmental delay, and intellectual disability. It can also cause kidney disease, lung disease, mental health challenges and disfiguring skin conditions.
Genea data (obtained from the protocol) indicate that people affected with TSC make up 2.5% of current PGD services. The alternative pre-natal diagnosis is either by genetic testing (e.g. CVS) or diagnosis of clinical signs via foetal ultrasound and/or MRI.

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2) What do you see as the benefits of this proposed intervention for the person involved and/or their family and carers?

PGD provides more people living with TSC an option to use to avoid conceiving a child with TSC. The proposal partially addresses the inequity in the current situation.
Current services offered by IVF providers are expensive and this is prohibitive for some people. My understanding of the proposal is that this cost barrier would be reduced, which we see as a positive step in improving equity.

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3) What do you see as the disadvantages of this proposed intervention for the person involved and/or their family and carers?

- This proposal is for the PGD specific services. From our understanding there would still be significant out of pocket costs for the IVF services required to access PGD. Some families in regional and remote areas would still have a barrier to access that should be considered by the committee.
- With the increasing availability of this technology a subtle pressure is applied to those living with the condition to pursue those options. Given the very personal nature of the ethical issues involved in this technology (e.g. destruction of embryos in PGD/IVF, termination of pregnancy in pre-natal testing) it is important that we consider it a valid choice to not use such technologies to prevent the birth of a child with a genetic condition.
- It is also important to retain and improve support (e.g. health and disability services, education) for those that do have a genetic condition and to continue to fund research. Many genetic conditions are not inherited so could not be 'prevented' by genetic technologies. This is the case with approximately 70% of cases of TSC.
- For up to 30% of people with TSC a disease causing mutation cannot be identified. Therefore PGD would not be an option for them. This scenario should be considered by the committee.

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4) How do you think a person's life and that of their family and/or carers can be improved by this proposed intervention?

For those living with TSC that are able to access PGD, they may be avoided the additional psychological stress involved in pre-natal testing as a way to avoid passing on TSC to their children.
For those who may not use pre-natal testing for ethical reasons, the ability to avoid having a child with TSC will remove the potential caring burden. There are no comprehensive studies on the impact of TSC on the family, however approximations could be used from related disorders such as Autism, Epilepsy and intellectual disability.

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5) What other benefits can you see from having this proposed intervention publicly funded on the Medicare Benefits Schedule (MBS)?

No comments on this question.

INDICATION(S) FOR THE PROPOSED INTERVENTION AND CLINICAL CLAIM

6) Flowchart of current management and potential management with the proposed intervention for this medical condition **(Refer to figure 1, page 22 of the protocol).** Do you agree or disagree with the eligible population for the proposed intervention as specified in the proposed management flowchart? **(refer to pages 11-13, and figure 1 of the protocol)**

❑ Agree

Why or why not?

As a starting point, this definition of the population is appropriate. **ATSS supports a more comprehensive consultation process to elaborate on this definition.** My response below is intended to highlight some challenges in defining this criteria and therefore why a more in depth consultation regarding the criteria should be undertaken.

For example, Tuberous Sclerosis is a highly variable condition. A parent may have only mild symptoms such as reduced kidney function, some skin manifestations and an anxiety disorder. However any child they have with TSC may have much more severe symptoms. The geneticist would need to quantify the risk of the child having a more severe manifestation of TSC – would they consistently evaluate this as 'high'? In the case of a highly variable condition, a simple evaluation of risk based on 1 in 2 or 1 in 4 may not be appropriate.

We note in the proposal that two options are being explored for defining the population. We suggest that only option 2 (the use of a non-disease specific checklist) would allow equity for those living with rare conditions.

The proposal suggests criteria of "'untreatable, apart from symptomatic care, and unable to be prevented". This is a reasonable definition however the example of Tuberous Sclerosis highlights the grey area in these criteria. Recently TGA approved (and PBS listed) mTOR inhibitor medication (Everolimus) for Tuberous Sclerosis may not be considered symptomatic care. It has been shown to shrink some tumours in some people living with TSC. So very strictly, TSC is not untreatable. However We expect that the

majority of clinicians familiar with the disease would identify it as a serious disease that warrants publicly funded PGD services.

We would also like clarification on the setting of this clinical genetics evaluation. ATSS suggests that it is appropriate to have this evaluation done by a publicly funded genetics service rather than within the IVF provider.

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7) Do you agree or disagree with the comparator for the proposed intervention as specified in the current management flowchart? **(Refer to page 23, and figure 1 of the protocol)**

The proposed comparator for PGD in couples is pregnancy by natural conception or IVF followed by prenatal diagnosis and the option of termination of the pregnancy (TOP). Prenatal diagnosis may be performed using either free foetal DNA (performed at 8-10 weekd using a blood smaple from the mother; not currently subsidized), chorionic villus sampling (CVS; suitable at 10-12 weeks pregnancy), amniocentesis (suitable at 14-16 weeks pregnancy), or foetal blood sampling (FBS; rarely used). PGD could be used in place of, or in combination with prenatal testing.

The comparators for the assessment of diagnostic accuracy are diagnosis using PGD, compared with prenatal diagnosis. In addition, comparison of accuracy of PGD testing methods should be undertaken.

Should PGD prove to be more accurate than prenatal diagnosis, the rate of change in management will be assessed by comparing PGD stage 3 (embryo genetic analysis followed by selective implantation) and prenatal diagnosis by genetic analysis followed by possible termination of pregnancy. The decision to terminate is likely to be the major change in management.

❑ Disagree

Why or why not?

There are different ethical considerations at play in a couple deciding to use PGD or pre-natal testing. A second comparator should be considered: ‘wait and see’. Some couples may elect to proceed with a pregnancy if termination is not an option for ethical reasons. In a highly variable condition such as TSC this may be a lottery the couple is willing to take.

PGD, as it involves a different ethical dilemma (destruction of embryos rather than late termination of a pregnancy) may be an option.

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8) Do you agree or disagree with the clinical claim (outcomes) made for the proposed intervention?

We are not sure what clinical claim is being made.

❑ Strongly agree
❑ Agree
❑ Disagree
❑ Strongly disagree

Why or why not?

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9) Have all associated intervention been adequately captured in the flowchart?

❑ Yes
❑ No

If not, please move any misplaced interventions, remove any superfluous intervention, or suggest any missing interventions to indicate how they should be captured on the flowcharts. Please explain the rationale behind each of your modifications.

The flowchart should include explicitly the role of genetic counselling and in what setting this would be provided (by IVF provider or by public genetics services). We think this would add clarity to the flowchart's decision points and identify any impacts on public genetics services.

ADDITIONAL QUESTIONS FOR PASC SPECIFIC TO THIS PROPOSAL.

1. Defining the population

There are two different options being considered as a means of defining the relevant populations who may seek Commonwealth funded PGD. Option 1 is having a list of approved severe disorders, although this may restrict access to rare and severe disorders, or severe disorders for which mutations are identified for in the future. Option 2 is defining 'severe' by use of a checklist. The concern with this option is that it may allow scope creep, given the difficulties and subjectivity in defining a severe disease. Please provide input on which option would be more appropriate.

Please also refer to our comments for question 6. **Specifically that this question is deserving of a more thorough consultation process.**
Both options have concerns.
Option 1 may make the process more straightforward for the majority of PGD parents. It should have less overhead than a case by case checklist evaluation. Could this be implemented alongside a review process to consider conditions outside the list? The review process would need to be quick to ensure that couples can seek approval within a reasonable timeframe.
Option 2 would be a more equitable for rarer genetic conditions as they would be assessed in a similar way to more common conditions. Most of these conditions would not have data (such a specific quantification of impact on quality of life) to support a definition of severe. The checklist in Appendix C is highly subjective with the assessor being asked to evaluate severity with little guidance.

2. PGD item descriptors

The nature of some serious genetic disease mutations may warrant a more complex and/or intensive analysis than others. Therefore, are tiered item numbers warranted for Item 1 proposed in the application – for example one item for rare mutation test design and validation; and one for common/known mutations (for which a test is likely to have been designed before); or one item for complex and one for simple test designs; or one item for standard time one item for extended time required to test and validate? What is the best way to stratify the descriptor?

We have limited technical expertise in this area. The statement in the protocol:

"it would be expedient if information provided by testing in this stage was made accessible to those requiring it in the future and not be treated as intellectual property by the clinic that performed the test."
It is not clear whether this approach is feasible or if it has been discussed with the laboratories that would be doing this work?

3. Access questions
Would parents be given the right to choose a carrier free embryo? Would this be a clinician's choice only?
Is it appropriate to limit the number of claims for Stages 2 and 3?
This is not relevant for Tuberous Sclerosis as it is a dominant condition.
Given a limited health budget, we would see avoiding certain disease as a higher priority than avoiding carrier status.
We also recommend the committee investigate cases where genotypes historically termed as 'carriers' may not be asymptomatic. E.g. Fragile X tremor ataxia, Fabry carrier symptoms. Thus the distinction between disease free embryo and carrier free embryo may be blurred.

4. Issues associated with clinical pathway
Although the starting population for PGD are those couples who know they carry a genetic disorder and who at high risk of passing this on, there may be prior steps that occur and incur costs eg a geneticist consultation may be required to classify the couple as high risk. It is also possible that some screening of couples is undertaken to determine their genetic disorder. Is this the case and if so, would an equivalent level of screening be performed for the comparator arm? How different are the tests for prenatal testing and preimplantation testing that patients would undergo in clinical setting?

ADDITIONAL COMMENTS

10) Do you have any additional comments on the proposed intervention and/or medical condition (disease) relating to the proposed intervention?

- Whilst we agree with the intent of the proposal, **it should be considered within the broader context of clinical genetics services.** In our experience, genetics services in Australia are a patchwork of state funded services which can be inconsistent, inequitable, involve long waiting periods and significant out of pocket costs. On top of this, they do not appear to be well positioned to accommodate technological advancement such as free-fetal DNA testing. Several attempts have been made to review and improve these services (e.g. the Genetics Services Working Group); the consumers we represent have seen little progress.

- We urge the committee to consider whether this proposal may compound the challenges of current genetics services. For example, could demand for genetic services increase as more people with genetic conditions approach state run services for advice and referrals. Or, if private genetic counselling services are utilized more as a result of this proposal what the implications are for the availability of consistent, high quality, integrated genetic services for consumers.

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11) And finally, do you have any comments on this feedback form and process? Please provide comments or suggestions on how this process could be improved.

Feedback Survey:

- Reading the protocol was very helpful in understanding the issues and the basis of the economic evaluation. Thank you for making this detail available.
- A proposal like this requires consultation with a very broad range of consumers. We understand that it is a challenge to identify and communicate with so many different organisations. We feel the committee could have done more to encourage a diverse range of consumer input.
- Timeframes for input are consistently too short. Many consumer organisations, particularly for rare diseases, are volunteer run. Volunteers (many living with a chronic condition or with significant caring responsibilities) are stretched just keeping their small organisations running. Thus longer timeframes would increase the likelihood of getting feedback from these smaller organisations and rare disease consumers.
- The technical nature of the protocol was very difficult to understand. This questionnaire was also difficult to complete. This may have prevented many consumers from making a submission.

Thank you again for taking the time to provide your valuable feedback.

If you experience any problems completing this on-line survey please contact the HTA Team

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