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MSAC Application 1637

Expanded Reproductive Carrier Screening of couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires in order to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: [hta@health.gov.au](mailto:hta@health.gov.au)

Website: [www.msac.gov.au](http://www.msac.gov.au/)

# PART 1 – APPLICANT DETAILS

## Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): Murdoch Children’s Research Institute

Corporation name: Murdoch Children’s Research Institute

ABN: 21006566972

Business trading name: Murdoch Children’s Research Institute

**Primary contact name: REDACTED**

Primary contact numbers

Business: **REDACTED**

Email: **REDACTED**

**Alternative contact name: REDACTED**

Alternative contact numbers

Business: **REDACTED**

Mobile: **REDACTED**

Email: **REDACTED**

## (a) Are you a consultant acting on behalf of an Applicant?

Yes

No

## (a) Are you a lobbyist acting on behalf of an Applicant?

Yes

No

## If yes, are you listed on the Register of Lobbyists?

Yes

No

# PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

## Application title

Application for funding of pre-conception or early pregnancy expanded Reproductive Carrier Screening of couples for joint carrier status in a large number of genes associated with autosomal recessive and X-linked conditions.

## Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Autosomal and X-linked recessive conditions that affect children usually cannot be cured, and the affected children and their family will be impacted by these conditions physically, financially and psychologically. Although these conditions are identified as rare diseases 1, they are not collectively rare and affect millions of people globally 2, accounting for 1 in 10 cases of infant mortality and 1 in 5 paediatric hospitalisations 3. One study estimates that more than 1 in 400 children will be born with one of these conditions in Australia 4. A study by Bell et al (2011) demonstrated that over 97% (101/104) of people were carriers of a severe condition; however, in reality this is likely to be closer to 100% as Bell et al (2011) only analysed 448 genes 5

If both parents are carriers of the same autosomal recessive condition, their children will have a 25% chance of being affected by the condition. With respect to X-linked conditions, if the mother is a carrier, their male offspring have a 50% chance of being affected, their female offspring are usually not affected but have a 50% chance of also being a carrier 7.

## Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

Whilst screening was initially conducted for one or few conditions, it is now possible to screen for over 1000 genes using massively parallel sequencing (MPS) (also known as next generation sequencing (NGS)). This is called expanded carrier screening (ECS). The proposed medical service is reproductive carrier screening to identify the carrier status of couples for autosomal recessive conditions and of women for X-linked recessive conditions, at pre-conception or early pregnancy. The eligible couples will have biological samples taken from them (usually blood or a mouth swab) from which DNA is extracted for analysis.

Carrier screening for over 1000 genes associated with autosomal recessive and X-linked conditions will be performed using different techniques (Table 1). The list of genes condition list was determined using a rigorous review process 8. A combined result will be issued indicating whether the couple has a low or high risk of having a child with a genetic condition.

Table 1: Examples of testing methods for recessive conditions

| **Condition** | **First Tier Testing** | **Second Tier Testing** |
| --- | --- | --- |
| Autosomal Recessive and X-Linked conditions | * Exome * NGS targeted panel   Variant detection - SNPs and small in/del variants & limited CNV analysis | For certain genes, MLPA as required to validate CNV identified (e.g. DMD deletions and duplications) |
| Fragile X syndrome\* | * TP-PCR / other PCR based method   FMR1 CGG repeat sizing | FMR1 AGG interruption analysis |
| Spinal muscular atrophy | * SMN1 – real-time PCR * MLPA |  |

CNV = copy number variation; DMD = Duchenne muscular dystrophy; FMR1 AGG = fragile X mental retardation 1 AGG trinucleotide repeat; FMR1 CGG = fragile X mental retardation 1 CGG trinucleotide repeat; MLPA = Multiplex ligation-dependent probe amplification; NGS = next generation sequencing; PCR = Polymerase chain reaction; SMN = Spinal muscular atrophy; TP = triplet repeat primed.

## ****(a) Is this a request for MBS funding?****

Yes

No

## ****If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?****

Amendment to existing MBS item(s)

New MBS item(s)

## ****If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:****

Not applicable

## ****If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?****

Not applicable

## ****If a new item(s) is being requested, what is the nature of the change to the MBS being sought?****

1. **A new item which also seeks to allow access to the MBS for a specific health practitioner group**
2. **A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)**
3. **A new item for a specific single consultation item**
4. **A new item for a global consultation item(s)**

## ****Is the proposed service seeking public funding other than the MBS?****

Yes

No

## ****If yes, please advise:****

## What is the type of service:

Therapeutic medical service

Investigative medical service

Single consultation medical service

Global consultation medical service

Allied health service

Co-dependent technology

Hybrid health technology

## For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

1. To be used as a screening tool in asymptomatic populations
2. Assists in establishing a diagnosis in symptomatic patients
3. Provides information about prognosis
4. Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
5. Monitors a patient over time to assess treatment response and guide subsequent treatment decisions
6. A service that tests for heritable mutations in clinically affected individuals to make a genetic diagnosis.

## Does your service rely on another medical product to achieve or to enhance its intended effect?

Pharmaceutical / Biological

Prosthesis or device

No

## (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

Yes

No – Not applicable

## If yes, please list the relevant PBS item code(s):

Not applicable

## If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

Yes (please provide PBAC submission item number below)

No – Not applicable

## If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Not applicable

## (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

Yes

No – Not applicable

## If yes, please provide the following information (where relevant):

Billing code(s): Not applicable

Trade name of prostheses: Not applicable

Clinical name of prostheses: Not applicable

Other device components delivered as part of the service: Not applicable

## If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

Yes

No – Not applicable

## Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

Yes

No – Not applicable

## If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

Not applicable

## Please identify any single and / or multi-use consumables delivered as part of the service?

All single use consumables are included in the item fee and include:

* Saliva kit
* Educational material

# PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

## (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: in-vitro diagnostic test

Manufacturer’s name: Not applicable

Sponsor’s name: Not applicable

## Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

Class III

AIMD

N/A Not applicable

## (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

Yes (If yes, please provide supporting documentation as an attachment to this application form)

No

## If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

Yes (if yes, please provide details below)

No- Not applicable

ARTG listing, registration or inclusion number: Not applicable – the relevant laboratories would have their in-vitro diagnostic tests listed on the TGA but do not have a specific number for each test.

TGA approved indication(s), if applicable: Not applicable

TGA approved purpose(s), if applicable: Not applicable

## If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

Not applicable

## If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

Not applicable

# PART 4 – SUMMARY OF EVIDENCE

## Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

|  | Type of study design\* | Title of journal article or research project (including any trial identifier or study lead if relevant) | Short description of research (max 50 words)\*\* | Website link to journal article or research (if available) | Date of publication\*\*\* |
| --- | --- | --- | --- | --- | --- |
| 1. | Observational study | The Israeli national population program of genetic carrier screening for reproductive purposes  Zlotogora et al., 2016 9 | The population-wide reproductive carrier screening program is carried out in Israel, where multiple recessive diseases are screened for 60-70,000 citizens a year, launched in January 2013. The national population genetic carrier screening is aimed toward providing couples with knowledge of the existing options for the prevention of serious genetic conditions when it is relevant for them. | <https://www.nature.com/articles/gim201555#t1> | 2015, April |
| 2. | Observational study | Prenatal screening for cystic fibrosis  Mennie et al., 1992 10 | Eligible enrolled women were offered screening in a prenatal setting (n=3165). When a women was found to be a CF carrier her partner was also tested. There were 4 carrier couples, and 1 pregnancy with an affected fetus by prenatal diagnosis was terminated. By providing time for couples to discuss the possibility of screening and by offering the test at a point (the antenatal booking clinic) at which most pregnant women are seen, this approach has advantages, provided that counselling is readily available. | <https://www.sciencedirect.com/science/article/pii/014067369290476J> | 1992, July |
| 3. | Observational study | Population-based carrier screening for cystic fibrosis in Victoria: the first three years’ experience.  Massie et al., 2009 11 | A total of 3200 individuals were screened (3000 females). 106 carriers were identified. All carrier partners were screened, and nine carrier couples identified. Of the nine carrier couples, six were pregnant at the time of screening and all had CVS. Two fetuses were affected, three were carriers and one was not a carrier. Termination of pregnancy was undertaken for the affected fetuses. Carrier screening for CF, largely ordered by obstetricians and general practitioners by cheek swab sample, can be successfully undertaken prior to pregnancy or in the early stages of pregnancy. | <https://www.ncbi.nlm.nih.gov/pubmed/19780730> | 2009, October |
| 4. | Cluster randomised trial | Effectiveness of earlier antenatal screening for sickle cell disease and thalassaemia in primary care: cluster randomised trial  Dormandy et al., 2010 12 | Practices were randomised to three groups for seven months, including primary care parallel, primary care sequential and midwife care. Anonymised data on all pregnant women attending participating practices during a six month period before randomisation and a seven month period after randomisation. This included 1708 eligible women. There were 25 UK general practices from inner city areas. The main finding was that offering sickle cell disease and thalassaemia screening in primary care was effective. | <https://www.bmj.com/content/341/bmj.c5132> | 2010, August |
| 5. | Observational study | Offering preconceptional cystic fibrosis carrier couple screening in the absence of established preconceptional care services.  Henneman et al., 2003 13 | In this pilot study, CF carrier screening was targeted to couples who were considering a pregnancy in the future, in the mid-western region of the Netherlands. To reach target group, over 38,000 individuals at the age of 20–35 years were invited by a personal letter to participate in a CF carrier screening program if they had a partner with whom they were planning to have children. This study demonstrated that carrier testing offered to couples planning a pregnancy is feasible. Satisfaction among the participants was high; 95% would make the decision to be tested again, 88% would recommend testing to others, and 89% supported the implementation of the routine offer of preconception CF carrier screening. | <https://www.ncbi.nlm.nih.gov/pubmed/12748433> | 2003, June |
| 6. | Observational study | Evaluation of a multi-disease carrier screening programme in Ashkenazi Jewish high schools  Ioannou et al., 2010 14 | This paper investigated screening for carrier status for seven autosomal recessive conditions in Jewish high schools in Australia. The results indicated that the main reasons for choosing to have screening were desire to know carrier status and convenience. Knowledge level decreased and negative feelings increased compared with screening for Tay-Sachs disease alone | <https://www.ncbi.nlm.nih.gov/pubmed/20597919> | 2010 |
| 7. | Observational study | Tay Sachs disease in Australia: reduced disease incidence despite stable carrier frequency in Australian Jews.  Lew et al., 2012 15 | This paper describes the results of screening high school students in the Ashkenazi Jewish population for Tay-Sachs disease and describes that no children affected with Tay-Sachs were born to parents who had been screened for Tay-Sachs carrier status. On the other hand, children with Tay-Sachs were born in Australia to unscreened couples, which includes non-Ashkenazi Jewish individuals. The paper calls for carrier screening for Tay-Sachs disease to be expanded to the whole population. | <https://www.ncbi.nlm.nih.gov/pubmed/23230938> | 2012 |
| 8. | Observational study | Reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome, and spinal muscular atrophy in Australia: outcomes of 12,000 tests  Archibald et al., 2018 16,17 | This paper described the results of carrier screening 12,000 individuals for three recessive diseases: cystic fibrosis, fragile X syndrome and spinal muscular atrophy. The results identified 610 carriers for one of the three diseases and that 88% of these carriers had no family history of the diseases. | <https://www.ncbi.nlm.nih.gov/pubmed/29261177> | 2018 |
| 9. | Observational study | GP-provided couple-based expanded preconception carrier screening in the Dutch general population: who accepts the test-offer and why?  Schuurmans et al., 2020 18 | This paper describes the acceptability of couple-based screening to couples and found that sparing a child a life with a severe genetic condition was the most important reason for couples to choose to use carrier screening. | <https://www.ncbi.nlm.nih.gov/pubmed/31570785> | 2020 |
| 10. | Observational study | Feasibility of couple-based expanded carrier screening offered by general practitioners.  Schuurmans et al., 2019 19 | This paper identified that couple-based carrier screening could be offered through general practitioners and argued that couple-based screening was the way to offer expanded carrier screening in a population health program. | <https://www.ncbi.nlm.nih.gov/pubmed/30742054> | 2019 |
| 11. | Observational study | Measuring the impact of genetic knowledge on intentions and attitudes of the community towards expanded preconception carrier screening'  Ong et al., 2018 20 | This study of attitudes towards carrier screening in the West Australian population identified that two-thirds of nearly 1,000 respondents would use carrier screening if it was available, 10% would not and the remainder were unsure. | <https://www.ncbi.nlm.nih.gov/pubmed/30068663> | 2018 |

*\* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

*\*\*Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*

*\**\*\* *If the publication is a follow-up to an initial publication, please advise.*

## Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

|  | Type of study design\* | Title of research (including any trial identifier if relevant) | Short description of research (max 50 words)\*\* | Website link to research (if available) | Date\*\*\* |
| --- | --- | --- | --- | --- | --- |
| 1. | Observational study- Prospective cohort | The Use of Digital Genetic Assistant (DGA) for Expanded Carrier Screening | This study aims to enrol 600 participants (Couples (Male + Female) that plan to have children together) to estimate the change in the number of post-test face-to-face/telephone genetic counselling sessions in patients willing to undergo expanded preconception carrier screening (Carrier Scan Screening Test). | <https://clinicaltrials.gov/ct2/show/NCT04014114> | **REDACTED** |
| 2. | Pivotal study:  Observational study- Prospective cohort | Mackenzie's Mission: The Australian Reproductive Carrier Screening Project | This study will investigate reproductive genetic carrier screening (RGCS) in 10,000 couples across Australia. Carrier screening for approximately 1300 genes associated with severe, childhood-onset, X-linked and autosomal recessive conditions will be performed on each member of the couple. A combined result will be issued indicating whether the couple has a 'low' or 'increased' risk of having a child with a genetic condition. | <https://clinicaltrials.gov/ct2/show/NCT04157595> | **REDACTED** |
| 3. | Pilot study | Results from offering a reproductive carrier screening test in Western Australia | This pilot study of couple-based preconception carrier screening in Western Australia used gene panel-based sequencing for 474 genes and separate analyses for spinal muscular atrophy and fragile X syndrome. Of 201 couples screened, 7 were shown to be high risk. This is 1:28, or 3.5% of couples, a higher number than expected. The study demonstrated that carrier screening could be performed using existing components of the WA Department of Health including the state genetic service, Genetic Services WA and the Health Department pathology laboratory service PathWest. |  | November 2020 |

*\* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

*\*\*Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

*\**\*\**Date of when results will be made available (to the best of your knowledge).*

# PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

## List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):

The relevant professional bodies include:

* The Australian Genomics Health Alliance
* Australian Genomics Health Futures Mission
* The Royal Australian College of General Practitioners (RACGP)
* The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)
* The Royal College of Pathologists of Australasia (RCPA)
* Human Genetics Society of Australasia (HGSA)
  + The Australasian Society of Genetic Counsellors (ASGC)
  + The Australasian Society of Diagnostic Genomics (ASDG)
* Royal Australasian College of Physicians (RACP)

## List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):

The relevant professional bodies include:

* The Australian Genomics Health Alliance
* The Royal Australian College of General Practitioners (RACGP)
* The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)
* The Royal College of Pathologists of Australasia (RCPA)
* Human Genetics Society of Australasia (HGSA)
* Royal Australasian College of Physicians (RACP)

## List the relevant consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):

* Genetic Alliance Australia (GA)
* Genetic Support Network Victoria (GSNV)
* The Genetic and Rare Disease Network (GaRDN)
* Rare Voices Australia (RVA)

## List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:

* Carrier screening is provided by multiple commercial providers; for an example list of providers see: <https://www.mackenziesmission.org.au/other-options-for-carrier-screening/>

## Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):

**REDACTED**

*Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.*

# PART 6 – POPULATION (AND PRIOR TESTS), INDICATION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

## Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:

Genetic conditions are one of the major causes of death and chronic illness in children. It has been estimated that over one million people in Australia are affected directly or indirectly by a genetic condition. The impacts on families cannot be overstated, with grief and loss due to a child’s disability and sometimes premature death having profound, long-term effects on the child and the child’s parents and other family members. Diagnosis and treatment of genetic conditions require substantial funding from government, including but not limited to hospital care, the costs of specialised treatments, disability services, special education, loss of productivity of parents and income support for carers.

Autosomal recessive conditions occur when a mutation in the same gene is inherited from each parent. In other words, if the child only has one copy of a gene mutation inherited from one parent, he or she will not be affected but will be a carrier. If the parents are both carriers for a mutation in the same gene which is associated with an autosomal recessive condition (i.e. both of them have one normal copy and one copy of the gene with a mutation), their children will have 1 out of 4 chance of being affected by the condition. For many conditions, there are multiple different associated genes but in almost all cases, the parents must carry variants in the same gene for there to be an increased chance of having an affected child. In X-linked conditions the gene with the mutation is located on the X chromosome. Thus, if the mother is a carrier, her male offspring have a 50% chance of being affected. Female offspring have a 50% chance of inheriting the copy of the gene with the mutation, but are generally either not affected by the condition or are more mildly affected than a male with the mutation (6); thus the overall chance of having an affected child is close to 1 in 4. The father is not tested for X-linked conditions in the context of screening because he would be expected to be affected if he had a mutation in a gene on the X chromosome.

Autosomal and X-linked recessive conditions are identified as rare diseases according to the European Union 1 which puts prevalence at less than 1 out of 2,000 per condition; however, collectively they affect millions of people globally 2, accounting for approximately 1 in 10 infant deaths and 1 in 5 paediatric hospitalisations 3. One study estimates that 1-2% of couples have an increased chance of having a child affected by an autosomal or X-linked recessive condition. In other words, more than 1 in 400 children will be born with one of these conditions 4. A study by Bell et al (2011) demonstrated that over 97% (101/104) of people were carriers of a severe condition; however, in reality this is likely to be closer to 100% as Bell et al (2011) only analysed 448 genes 5. In Australia, the three most common conditions for which screening is offered are cystic fibrosis (CF), spinal muscular atrophy (SMA), and fragile X syndrome (FXS) (22) (Table 2).

Table 2: Characteristics of CF, FXS, and SMA and details about genetic testing

| **Condition** | **Type** | **Prevalence** | **Carrier frequency** | **Description** | **Life expectancy** |
| --- | --- | --- | --- | --- | --- |
| Cystic fibrosis | Autosomal recessive | 1/2500 | 1/25 | Most common life-threatening autosomal recessive condition affecting Australian children | Mid-30s |
| Fragile X syndrome | X-linked | 1/4,000 males 1/5,000-1/8,000 females | 1/250 | Most common cause of inherited intellectual disability | Normal |
| Spinal muscular atrophy | Autosomal recessive | 1/10,000 | 1/50 | Most frequent genetic cause of infant mortality | Type 1: <2 years; Type 2: 2 years to 3rd/4th decade; Type 3: normal |

## Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

Couples who are planning to become pregnant or in early stage of pregnancy will be eligible for carrier screening. In most cases the ‘couple’ will include a male and female partner. In some instances (such as same sex couples and couples with infertility), a donor gamete or embryo may be planned to be used/may have been used to conceive a pregnancy. In these circumstances the carrier screening test would be performed on the ‘genetic contributors’ to that pregnancy/planned pregnancy. If the ‘genetic contributors’ are embryo/gamete donors, the donors would need to be available and willing to undergo carrier screening by providing a DNA sample.

Pre-test and post-test genetic counselling should be available to assist in facilitating the screening test as required.

Given the nature of the test, the test can be offered by different healthcare providers, including; general practitioner, obstetrician, midwife, nurse, fertility specialist, or genetics health professional. The applicants request that these providers would be able to offer the test; however, MSAC/PASC may wish to consider what level of qualification would be appropriate.

## Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

A woman (either with their partner or by themselves) who is planning to become pregnant or is in early stage of pregnancy would access health care in relation to her planned or current pregnancy. Their health care provider would provide preconception or early pregnancy care.

RACGP guidelines recommend that all woman of reproductive age should be considered for preconception care, this includes the opportunity for carrier screening of genetic conditions 21.

PART 6b – INFORMATION ABOUT THE INTERVENTION

## Describe the key components and clinical steps involved in delivering the proposed medical service:

A woman (either with their partner or by themselves) who is planning to become pregnant or is in early stage of pregnancy would access health care in relation to her planned or current pregnancy. Their health care provider would provide preconception or early pregnancy care. As part of that care the clinician would provide information with regards to carrier screening for recessive genetic conditions (21). The health care provider can obtain a sample (if both genetic contributors are present at the health care interaction), provide sample kits or advise on how to access sample kits.

There is no consensus on which autosomal and X-linked recessive conditions should be included in the screening panel for reproductive health 22. The inclusion criteria, where reported in the literature, are that the condition should have a well-defined phenotype and a serious impact on the affected individual and their family, be able to be diagnosed prenatally, and that screening for the condition is perceived to be acceptable to the target population and the community 22. With regards to this application, a condition list that was applicable to the Australian population has been decided upon, using rigorous scientific methods and based on that “the condition should be life-limiting or disabling, with childhood onset, such that couples would be likely to take steps to avoid having an affected child; and/or be one for which early diagnosis and intervention would substantially change outcome”. Strong evidence for gene-phenotype relationship was required. Candidate genes were identified from OMIM and via review of 23 commercial and published gene lists. Genes were reviewed by 16 clinical geneticists using a standard operating procedure, in a process overseen by a multidisciplinary committee which included clinical geneticists, genetic counsellors, an ethicist, a parent of a child with a genetic condition and scientists from diagnostic and research backgrounds” (see attached manuscript in confidence).



Figure 1: Preconception or early pregnancy

## Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

Not applicable

## If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

Not applicable

## If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

One limitation is failed samples (though these are rare). If failed samples were identified during the analysis, further sample collection would be required.

## If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:

There are no other additional medical services that would need to be delivered in addition to the test; however, information is likely to be provided about the screening test at the same time as another health care provider interaction.

## If applicable, advise which health professionals will primarily deliver the proposed service:

As the service can be provided by several types of health care professional, the applicant request that the following providers would be able to offer the test; however, MSAC/PASC may wish to consider what level of qualification would be appropriate:

* General practitioner
* Obstetrician
* Midwife
* Nurse
* Genetic councillor
* Fertility specialist
* Genetics health professional

## If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

Depending on MSAC/PASC decision re 33 above testing could be delegated to appropriately trained midwife or other allied health professional operating under the supervision of the doctor responsible for the patient’s care.

## If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

Not applicable

## If applicable, advise what type of training or qualifications would be required to perform the proposed service as well as any accreditation requirements to support service delivery:

Not applicable

## (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select all relevant settings):

Inpatient private hospital

Inpatient public hospital

Outpatient clinic

Emergency Department

Consulting rooms

Day surgery centre

Residential aged care facility

Patient’s home

Laboratory

Other – please specify below

See (b) below

1. **Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:**

The offer of the test will be in general practice clinics, outpatient clinics, consulting rooms, inpatient private hospital, inpatient public hospital. The test procedure (buccal swabs) can be performed in people’s homes. The rational for making the test available to the patient’s home, is that the genetic partner may not be available for test sampling at the interaction with the health care professional. The buccal swab is a simple procedure that can be carried out with ease by the patient. The service (the screening test) will be provided in the laboratory setting.

## Is the proposed medical service intended to be entirely rendered in Australia?

Yes

No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

## Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

Both RACGP and RANZCOG/HGSA suggest that some form of carrier screening should be offered to women either planning to have or are in early pregnancy 21,23.

Currently, several pathology services offer carrier screening on a user pays basis (except for haemoglobinopathies for which testing is funded), which can be ordered by a health care provider or can be ordered directly by the consumer (eg: eugenelabs.com). Depending on the test provider:

* Screening may look for a limited number of conditions (e.g. CF, fragile X syndrome [FXS], spinal muscular atrophy) or screen for an expanded range of conditions (i.e. >100)
* Genetic counselling may or may not be available.

However, carrier screening is not available through the Medicare Benefits Schedule (MBS). So, the usual practice comparator for this application would be pregnancy with no genetic testing. Typically, without routine screening, the couple will only find out that they are carriers of the same genetic condition if they have a child born with that genetic condition. Some recessive conditions may not be evident at birth, but clinical symptoms develop, and diagnosis occurs during childhood or adulthood.

Of note, an application for carrier screening for cystic fibrosis, spinal muscular atrophy and fragile X syndrome is currently underway by MSAC (MSAC Application 1573). This has yet to be reviewed by MSAC so an outcome on listing has yet to be made 24.

Therefore, the appropriate comparator for this reproductive carrier screening is “Usual practice without genetic carrier screening” with a near market comparator of “Carrier screening for cystic fibrosis, spinal muscular atrophy and fragile X syndrome”.

## Does the medical service that has been nominated as the comparator have an existing MBS item number(s)?

Yes (please provide all relevant MBS item numbers below)

No- Not applicable

## Define and summarise the current clinical management pathways that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards including health care resources):

Not applicable

## (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

Yes

No

## If yes, please outline the extent of which the current service/comparator is expected to be substituted:

The proposed medical service (reproductive carrier screening) will be added as a new medical service to be provided to couples both pre-conception and in early pregnancy.

## Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service including variation in health care resources (Refer to Question 39 as baseline):



Figure 2: Clinical management pathways

IVF = Invitro fertilisation; PGT = Pre-implantation genetic testing

\* Routine pregnancy management could include IVF, PGT, amniocentesis, etc. but is likely to be at a lower rate than in patents that are identified as high risk.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

## Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

Reproductive carrier screening has superior effectiveness in detecting carrier couples than the current pathways and is an important screening test to help couples make clear and informed decisions about family planning. When implemented, reproductive carrier screening reduces the incidence of autosomal and X-linked recessive genetic disorders. Reproductive carrier screening is a safe procedure.

## Please advise if the overall clinical claim is for:

Superiority

Non-inferiority

## Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

**Safety Outcomes:**

There are no safety concerns associated with the test procedure; however, the following post-test outcomes will be explored:

Psychological harms from positive test results

Adverse events from follow on testing and procedures (e.g.: CSV/Amniocentesis, IVF, pregnancy termination)

Outcomes from false negative results

**Clinical Effectiveness Outcomes:**

The total number of affected births averted;

The total number of affected pregnancies;

The total number of terminated pregnancies;

Quality-adjusted life years (QALYs);

**Cost effectiveness outcomes:**

Total cost of the screening program per patient

Cost per affected births avoided

Cost per QALY.

# PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

## Estimate the prevalence and/or incidence of the proposed population:

A total of 309,142 births were registered in Australia in 2017, resulting in a total fertility rate (TFR) of 1.74 babies per woman. 25 While individually rare, collectively recessive conditions occur relatively frequently with approximately 1-2% of couples at high risk of having an affected child, equating to more than 1 in 400 children being born with one of these conditions. 4 Screening for some conditions, such as cystic fibrosis (CF), fragile X syndrome (FXS) and spinal muscular atrophy (SMA), is already available on a user-pays basis. However, these currently available tests suffer from limitations, including inequity of access due to costs and lack of awareness of the tests among medical practitioners and the public 26-28. Nonetheless, there is already evidence that this form of screening is highly cost-effective 29. In the future, as costs of genetic sequencing fall and costs of treatments rise, screening will become even more cost-effective. For example, there are approved expensive treatments for several recessive conditions including spinal muscular atrophy and some lysosomal storage disorders.

See Table 3 for calculations on the number of couples eligible for genetic carrier screening. The number of future births was derived from Series B projection of the ABS Australian Population Projections. Series B reflects current trends in fertility and birth 30.

Historical birth and confinement data were used to estimate the number of women who give birth. Confinements count labour periods which results in at least one live birth 31. Confinements were used instead of births because confinements do not double count multiple births. Using data from 2010 to 2018, it was estimated that there were 1.01 births per confinement.

The number of women starting a family (primiparous) was calculated by dividing number of confinements by the average number of children per parous woman. The average number of children per parous woman was calculated by dividing the fertility rate by the proportion of women who have children (85%) 31. Fertility rates were derived from population projections for the forecast years and historic fertility data for past years 30,32. For the base case, the series B projection estimated a fertility rate of 1.8 births per woman.

## Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

It is proposed that the reproductive carrier screening test would be performed once in a lifetime to couples either pre-conception or in early pregnancy (though an individual may have multiple analyses of data from a single test if they proceed to have children with different partners).

## How many years would the proposed medical service(s) be required for the patient?

This should be a once in a lifetime test, while the characteristics of the exome are likely to be updated regularly, it is unlikely that couples would return to have additional testing (though an individual may have multiple analyses of the data from a single test if they proceed to have children with different partners). As the list of genes is expanded based on new findings, some targeted panels may need to be retested. However, this is likely to be a small number of patients as most couples will have completed their reproductive period in a short period of time and not need additional panel screening.

## Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

In 2015, the AIHW estimated that only 50% of mothers had a antenatal visit within the first 11 weeks of gestation 33. For our calculations it was assumed that women who were likely to visit their health care professional prior to pregnancy would be contained in those that presented in the first 11 weeks of gestation. In a recent study in WA only over two thirds of patients said they would undergo prenatal carrier screening if it was available 20. Given that these are likely to change with increased awareness, changes in practice, etc, the effect of these will be explored in the Applicant developed assessment report (ADAR). Table 3 provides an estimate of the population that would avail of the service given the current information. The pivotal study (NCT04157595) will inform the true estimates in an Australian population for uptake rates.

Table 3: Estimated population for carrier screening

|  | **Parameter** | **Source/Calculation** | **2020** | **2021** | **2022** | **2023** | **2024** | **2025** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| A | Confinements | ABS population projection Series B (Births)/1.01 a | 325,430 | 331,928 | 338,038 | 343,716 | 348,944 | 353,712 |
| B | % women who never give birth | 2011 and 2016 Census  females 45-49 years | 15% | 15% | 15% | 15% | 15% | 15% |
| C | Fertility rate | ABS population projection Series B (fertility rate) | 1.8 | 1.8 | 1.8 | 1.8 | 1.8 | 1.8 |
| D | Births per parous woman | C/(1-B) | 2.11 | 2.11 | 2.11 | 2.11 | 2.11 | 2.11 |
| E | primipara women starting a family | A/D | 141,914 | 144,748 | 147,412 | 149,888 | 152,168 | 154,248 |
| F | Parous women eligible for first screening | (A-E)  Ft-1\*(1/D) | 174,796 | 82,747 | 39,172 | 18,544 | 8,778 | 4,156 |
| G | Population eligible for screening based on presentation ≤ 11 weeks gestation | (E+F)\*0.5 | 165,964 | 121,386 | 100,942 | 91,865 | 88,111 | 86,826 |
| H | Population who would undergo screening if offered | H\*0.675 | 112,026 | 81,935 | 68,136 | 62,009 | 59,475 | 58,608 |
| I | Final number tested | Assumed Uptake rate based on awareness of population and health care provider 60% rising to 100% in year 4 | 67,216 | 57,355 | 54,509 | 55,808 | 59,475 | 58,608 |

## Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of ‘leakage’ to populations not targeted by the service:

The anticipated uptake for the screening program in year 3 after listing is estimated to be 67,000 couples in first year of listing reducing to about 58,000 couples once parous women are screened. The Reproductive carrier screening is currently offered by a number of pathology services. Depending on the uptake rate there may be some constraints in supply if uptake is exceeded in the early years of implementation. Given that the indicated population is specific, the applicant does not foresee any major risk of leakage to populations not indicated for the proposed service.

# PART 8 – COST INFORMATION

## Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

It is anticipated that the procedure would cost approximately $**REDACTED** and the screening where one or both genetic contributors have previously been tested to be approximately $**REDACTED**. However, a time and motion study will be conducted during the pivotal study (**REDACTED**) to estimate the true cost of the procedure and presented in the ADAR.

## Specify how long the proposed medical service typically takes to perform:

The amount of time to collect a sample is very short (<5 mins). However, there is a need to read the accompanying material and package and post the sample to the laboratory. Once received in the laboratory, test results would be available within 4 weeks.

## If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

Category 6 (Pathology Services) – Group P7 Genetics

Proposed item descriptor:

Non-invasive expanded carrier screening testing of an asymptomatic couple (or genetic contributors to a pregnancy), either pre-pregnancy or prenatal, to determine their autosomal recessive and X-linked recessive single gene carrier status for conditions identified by the Australian Reproductive Genetic Carrier Screening Project.

Fee: To be determined

Category 6 (Pathology Services) – Group P7 Genetics

Proposed item descriptor:

Non-invasive expanded carrier screening testing of an asymptomatic couple (or genetic contributors to a pregnancy), either pre-pregnancy or prenatal, to determine their autosomal recessive and X-linked recessive single gene carrier status of conditions identified by the Australian Reproductive Genetic Carrier Screening Project, where one or both genetic contributors have previously been tested.

Fee: To be determined

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