



Australian Government

Department of Health

MSAC Application 1671

Targeted carrier testing for severe monogenic 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

Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):

Corporation name: The Royal College of Pathologists of Australasia

ABN **REDACTED**

Business trading name: The Royal College of Pathologists of Australasia

Primary contact name: REDACTED

Alternative contact numbers

Business **REDACTED**

Mobile: **REDACTED**

Email: **REDACTED**

Alternative contact name: REDACTED

Alternative contact numbers

Business: **REDACTED**

Mobile: **REDACTED**

Email: **REDACTED**

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

- Yes
 No

(b) If yes, are you listed on the Register of Lobbyists?

- Yes
 No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Targeted carrier testing for severe monogenic conditions.

4. 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)

Carriers of autosomal recessive disorders such as cystic fibrosis (CF) and spinal muscular atrophy (SMA) are relatively common in the Australian population, with a recent Australian population screening study conducted in Victoria finding that of 12,000 individuals screened for CF, SMA and fragile X (FXS), 1:20 were carriers.¹ However, there are > 7,000 rarer monogenic diseases that contribute significantly to morbidity, mortality and healthcare costs, and, as a group, affect 1 in 50 individuals.² Many of these disorders are especially common in certain ethnic groups who identify with a particular geographical heritage, such as β -thalassaemia in people with a Mediterranean or Chinese heritage.³ Although relatively uncommon in the Australian population as a whole, there are a number of severe monogenetic conditions that are highly prevalent in certain ethnic groups, where individuals would be considered to have a >10% personal risk of being a heterozygous carrier. This means that, even though their risk of being a genetic carrier is far higher than CF, SMA or FXS in the general population, there is no publicly funded genetic testing for the majority of these conditions.

The exemplar population in Australia would be individuals of Ashkenazi Jewish (AJ) ancestry, who originated from Central and Eastern Europe.³ A small number of recessive genetic conditions are responsible for significant morbidity and mortality in this sub-population, with some of these conditions being almost exclusive to the AJ population (e.g. familial dysautonomia), some of which are more common (e.g. Tay Sachs disease) and some are as common as in the general population (e.g. cystic fibrosis).⁴ A 2013 population screening study reported that 30.2 per cent of individuals with Ashkenazi Jewish ancestry were carriers for at least one condition, but 10.1 and 2.5 per cent were carriers for two and three conditions, respectively.⁵ So, although individual conditions may be rare in themselves, about 1 in 5 (20%) AJ individuals screened with a relatively small gene panel will be carriers for one or more of these conditions, including: Tay Sachs disease (variants in the *HEXA* gene), CF (*CFTR*), Canavan disease (*ASPA*), familial dysautonomia (*ELP1 [IKBKAP]*), Niemann Pick disease type A (*SMPD1*), Bloom syndrome (*RECQL3*), mucopolysaccharidosis Type IV (*MCOLN1*), glycogen storage type 1A (*G6PC*), Fanconi anaemia type C (*FANCC*), SMA (*SMN1*) and Gaucher disease (*GBA*).^{4,6} Given the prevalence of the conditions, and current state of the evidence base this application will consider *HEXA*, *CFTR* and *SMN1* as exemplar genes.

Although genetic testing could, in principle, be performed through either preconception or antenatal intervention points, there are important practical considerations as to why offering only one route rather than both would be suboptimal and might result in poorer healthcare outcomes. Access only via antenatal genetic testing may raise ethical and/or religious issues that may cause some not to access the service. Due to adherence to traditional beliefs, some individuals who identify with ancestral heritage highly associated with these disorders might be less likely to take up antenatal screening, although they would be likely to take up the same testing on a pre-conceptual basis. Preconception testing also provides a wider range of reproductive options to at risk individual and couples, as some of those options are necessarily ruled out if the couple is already pregnant. Finally, antenatal testing necessitates strict requirements on turn-around time (“TAT”) for test results, placing stress on the healthcare system and often resulting in higher testing costs, and occasionally in failure to complete testing within the time available for intervention. The ideal framework for access to testing would be a combination of opportunistic preconception testing for these conditions in the primary care setting, with supplementary antenatal testing for those who had not availed themselves of the preconception testing opportunity. This would ensure equitable access to this subpopulation. For this reason, item numbers for both opportunistic

^a The majority of Jewish Australians are of Ashkenazi Jewish ancestry, with populations originating Central and Eastern Europe.⁴ HGSA (2015). *Ashkenazi Jewish Population Screening*, Alexandria, NSW <https://www.hgsa.org.au/documents/item/6092..>

preconception testing, as well as antenatal testing are being requested. For those tests that are conducted during pregnancy, testing of both parents should be conducted concurrently and without delay to minimise the risk of failure to complete testing within the limited time available for intervention and utilisation of the test results, should this be requested or required.

5. 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)

- i. Testing of asymptomatic individuals of reproductive age for the presence of a pathogenic heterozygous variant(s) for a clinically significant monogenic disorder in order to ascertain their genetic carrier status, in a panel of genes that would include *CFTR*, *SMN1* and testing for FXS (triplet repeat)^b regardless of the individual's ancestry. Additional genes would be included in the panel depending on the patient's family history and ethnic heritage/risk, drawn from published, publicly accessible lists of pathogenic genetic variants and associated disorders. For example, a gene panel relevant to reproductive risk in the exemplar AJ population may include the following additional genes that are in common use in this clinical scenario: *HEXA*, *ELP1 [IKBKAP]*, *SMPD1*, *ASPA*, *ELP1*, *FANCC*, *RECQL3*, and *MCOLN1*, requested by a medical practitioner or a genetics healthcare practitioner who manages the treatment of the patient.⁶

To ensure that the medical service is appropriately targeted, tested, individuals must have a >10% *a priori* aggregate personal risk of being a heterozygous genetic carrier of a clinically significant disorder associated with pathogenic or likely pathogenic variants of the genes in the testing panel. The genes included in the relevant gene panels would need to have been validated for clinical relevance and utility to meet this 10% threshold as part of the normal NATA laboratory accreditation process of pathology laboratories.

One test per lifetime.

- ii. Testing, requested by a medical practitioner or a genetics healthcare practitioner, of a pregnant female for the presence of a pathogenic heterozygous variant(s) for a clinically significant monogenic disorder in order to ascertain their genetic carrier status, in a panel of genes that would include *CFTR*, *SMN1* and testing for FXS (triplet repeat), regardless of the individual's ancestry. As above, additional genes would be included in the panel depending on the patient's family history and ethnic heritage/risk, drawn from published, publicly accessible lists of pathogenic genetic variants and associated disorders. For the exemplar AJ population, genes relevant to determining reproductive risk that are in common use in this clinical scenario include: *HEXA*, *ELP1 [IKBKAP]*, *SMPD1*, *ASPA*, *ELP1*, *FANCC*, *RECQL3*, and *MCOLN1*.

To ensure that the medical service is appropriately targeted, tested, individuals must have a >10% *a priori* aggregate personal risk of being a heterozygous genetic carrier of a clinically significant disorder associated with pathogenic or likely pathogenic variants of the genes in the testing panel. The genes included in the relevant gene panels would need to have been validated for clinical relevance and utility to meet this 10% threshold as part of the normal NATA laboratory accreditation process of pathology laboratories.

One test per lifetime.

- iii. Concurrent prenatal genetic testing of the male reproductive partner of (ii) above, regardless of his pre-test risk, of a pregnant female partner who has a >10% *a priori* aggregate personal risk of being a heterozygous genetic carrier of a clinically significant disorders associated with pathogenic or likely pathogenic variants of these genes as described in i or ii, for the purpose of determining the couple's reproductive risk of these conditions.

One test per lifetime.

^b Note that in July 2020, MSAC supported public funding for reproductive carrier testing to detect CF, SMA and FXS pathogenic variants. Once this item number is added to the MBS, then good clinical practice dictates that testing for CF, SMA and FXS should be included in any gene panel testing for other monogenic disorders, especially as CF and SMA are highly prevalent in some ethnic groups, to prevent the need for two tests.

- iv. Cascade screening should be offered to relatives of these genetic carriers. Genetic testing for the relevant genetic variant in a first-degree biological relative of a patient found to be a carrier of a recessive pathogenic variant(s) identified by item i or ii.

Note: iv is required for a transitional period. As at-risk members of the population have accessed testing over the period of a reproductive generation (of the order of 30 years) through i-iii above, then iv would become progressively less frequently, and eventually infrequently used, if at all.

6. (a) Is this a request for MBS funding?

- Yes
 No

(b) 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)

(c) 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:

N/A

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

- i. An amendment to the way the service is clinically delivered under the existing item(s)
ii. An amendment to the patient population under the existing item(s)
iii. An amendment to the schedule fee of the existing item(s)
iv. An amendment to the time and complexity of an existing item(s)
v. Access to an existing item(s) by a different health practitioner group
vi. Minor amendments to the item descriptor that does not affect how the service is delivered
vii. An amendment to an existing specific single consultation item
viii. An amendment to an existing global consultation item(s)
ix. Other (please describe below):

N/A

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

- i. A new item which also seeks to allow access to the MBS for a specific health practitioner group
ii. 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)
iii. A new item for a specific single consultation item
iv. A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

- Yes
 No

(g) If yes, please advise:

N/A

7. 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

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

- i. To be used as a screening tool in asymptomatic populations
- ii. Assists in establishing a diagnosis in symptomatic patients
- iii. Provides information about prognosis
- iv. Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
- v. Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

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

- Pharmaceutical / Biological
- Prosthesis or device
- No

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

N/A

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

N/A

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

N/A

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

N/A

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

N/A

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

N/A

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

N/A

(d) 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

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

N/A

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

Single use consumables: General single use laboratory consumables such as pipette tips, centrifuge tubes etc

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

The National Association of Testing Authorities (NATA) and the Royal College of Pathologists Australasia (RCPA) oversee the regulation of genetic testing for clinical purposes. Laboratories require accreditation by a joint NATA/RCPA process to ISO 15189, and specifically accredited to provide genetic testing. This accreditation process covers the technical aspects of the laboratory sequencing, analysis pipelines, curation (or interpretation) of results and production of the report to a clinical standard. This allows any accredited laboratory to provide equivalent mutational analysis services to a minimum standard. There are no requirements for use of specific manufacturer's reagents, equipment or analysis pipelines.

- 13. (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: N/A

Sponsor's name: N/A

- (b) 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

- 14. (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

- (b) 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

- 15. 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?**

- Yes (please provide details below)
 No

- 16. 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?**

- Yes (please provide details below)
 No

PART 4 – SUMMARY OF EVIDENCE

17. 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	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
Guideline ACMG USA		The American College of Medical Genetics and Genomics' (ACMG) latest guidelines for the screening for autosomal recessive and X-linked conditions during pregnancy and preconception are expected to be published prior to August 2021 in <i>Genetics in Medicine</i>		2021
Guideline RANCOG's Genomics Advisory Working Group & Women's Health Committee Australia	Genetic carrier screening ⁷	Information on carrier screening for other genetic conditions should be offered to all women planning a pregnancy or in the first trimester of pregnancy. Options for carrier screening include screening with a panel for a limited selection of the most frequent conditions (i.e. cystic fibrosis, spinal muscular atrophy and fragile X syndrome) or screening with an expanded panel that contains many disorders (up to hundreds). For individuals of AJ descent, additional screening for Tay Sachs disease, Niemann Pick disease type A, Fanconi anaemia group C, familial dysautonomia, Bloom syndrome, Canavan disease and mucopolidosis type IV should be offered. Consensus-based Recommendations	https://ranzocg.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Genetic-carrier-screening(C-Obs-63)New-March-2019_1.pdf?ext=.pdf	2019
Opinion American College of Obstetricians and Gynecologists' Committee on Genetics USA	Committee Opinion No. 691 Summary: Carrier Screening for Genetic Conditions ⁸	Carrier screening and counselling ideally should be performed before pregnancy because this enables couples to learn about their reproductive risk and consider the most complete range of reproductive options. Conditions with a carrier frequency of 1 in 100 or greater, which corresponds with a disease incidence of 1 in 40,000, is a useful threshold. When only one partner is of Ashkenazi Jewish descent, that individual should be offered screening first. If it is determined that this individual is a carrier, the other partner should be offered screening.	https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/03/carrier-screening-for-genetic-conditions	2017

Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
Position paper Joint Human Genetics Society of Australia, Royal Australian and New Zealand College of Obstetricians and Gynaecologists Prenatal Diagnosis and Screening Committee Australia	Ashkenazi Jewish Population Screening ⁴	All AJ individuals of reproductive age should be made aware of the availability of AJ preconception genetic screening for severe monogenetic conditions and offered access to screening for TSD, CF, FD, FA NPD, BLM, CD and MPLIV. Preconception screening is preferable to antenatal screening. Where screening is conducted during pregnancy, screening of both parents concurrently and without delay is preferred. Where an AJ individual is diagnosed as a carrier for one or more severe monogenetic conditions, their partner should be offered screening for the condition(s) in question, regardless of AJ heritage.	https://www.hgsa.org.au/documents/item/6092	2015
Guidelines American College of Medical Genetics and Genomics USA	Carrier screening in individuals of Ashkenazi Jewish descent ⁹	Recommend that carrier screening for cystic fibrosis, Canavan disease, familial dysautonomia, and Tay-Sachs disease be offered to all Ashkenazi Jews who are pregnant or considering pregnancy. In addition, it is recommended that carrier screening be offered for Fanconi anaemia (Group C), Niemann-Pick (Type A), Bloom syndrome, mucopolysaccharidosis IV, and Gaucher disease. Testing for the specific mutations associated with these disorders will result in a carrier detection rate >95% for most disorders. As a result, even in less common disorders, expected mutation-specific carrier frequencies will be relatively high.	https://www.acmg.net/PDFLibrary/Ashkenazi-Jewish-Carrier-Screening.pdf	2008

Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
<p>Opinion Society of Obstetricians and Gynaecologists of Canada (SOGC) Genetics Committee and the Canadian College of Medical Geneticists (CCMG) Clinical Practice Committee Canada</p>	<p>Joint SOGCeCCMG Opinion for Reproductive Genetic Carrier Screening: An Update for All Canadian Providers of Maternity and Reproductive Healthcare in the Era of Direct-to-Consumer Testing¹⁰</p>	<p>For couples of AJ heritage, routine carrier screening for Tay-Sachs disease; Canavan disease; and familial dysautonomia should be offered, preferably preconception or as early in pregnancy as is possible (II-2A) (GRADE moderate/high).</p> <p>When only one member of a couple is of AJ ancestry, screening should not be offered for familial dysautonomia and Canavan disease because of low carrier frequency in individuals who are not of AJ heritage and concurrent limitations of carrier screening in this situation (III-D) (GRADE moderate/moderate).</p> <p>Additional AJ carrier screening should be offered when a positive family is elicited for one of the conditions known to be present at an increased frequency in this population: Bloom syndrome; Fanconi anaemia group C; Niemann-Pick type A; mucopolidosis type IV; Gaucher disease; glycogen storage disease type 1a; familial hyperinsulinism; maple syrup urine disease; dihydrolipoamide hydrogenase deficiency; CF; Usher syndrome; nemaline myopathy; Joubert syndrome; Walker-Warburg syndrome (III-A) (GRADE moderate/high).</p>	<p>https://pubmed.ncbi.nlm.nih.gov/27638987/</p>	<p>2016</p>
<p>Retrospective diagnostic yield Clinical Utility Israel</p>	<p>Impact of a national genetic carrier-screening program for reproductive purposes¹¹</p>	<p>A total of 919,820 carrier-screening genetic tests were conducted during 2015-2017 for up to 22 prevalent conditions, depending on risk of disease. 34.5% of those tested were AJ. Rates of prenatal diagnosis, pregnancy termination and affected live-born children with selected diseases in 2014-2017 were also reported. There was a 57% decrease in the observed number of SMA-affected children born during 2014-2017, compared with the expected rate. Familial dysautonomia, Canavan and Tay-Sachs diseases yielded a very low prevalence.</p>	<p>https://pubmed.ncbi.nlm.nih.gov/32242916/</p>	<p>2020</p>

Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
Retrospective diagnostic yield Israel	The Israeli national population program of genetic carrier screening for reproductive purposes ¹²	Earlier results than Singer et al (2020). In the 12-months, 2013-14, >62,000 carrier-screening genetic tests were conducted. Carrier rates were 1:45, 1:57, 1:149 and 1:45 for CF, SMA, FXS and TS, respectively.	https://pubmed.ncbi.nlm.nih.gov/25880436/	2016
Comparative Conference abstract USA	Tay-Sachs disease carrier screening: Comparative analysis of NGS-based sequencing and enzyme testing results ¹³	Comparison of carrier screening results for 25,926 individuals in a pan-ethnic population tested by NGS-based HEXA sequencing and enzyme analysis. Individuals heterozygous for pathogenic or likely pathogenic variants were classified as DNA-POS. All others were classified as DNA-NEG, including those carrying variants of uncertain significance. Hexosaminidase A activity was categorised as carrier (ENZ-POS), indeterminate (ENZ-IND), or negative (ENZ-NEG). We detected 6 B1 carriers and 112 individuals with a benign pseudodeficiency (ψ D) allele. Among non-B1, non- ψ D results, 94.7% (24,447) had concordant DNA and enzymes and 0.9% (226) were discordant (all DNA-NEG:ENZ-POS). An additional 4.4% were ENZ-IND (1126 DNA-NEG; 9 DNA-POS). Different cut-offs used by the biochemical reference laboratories yielded different ENZ-IND rates (7.3% vs. 1.8%). Most DNA-NEG:ENZ-IND individuals are truly non-carriers. Rare missense VUSes (b10 alleles in gnomAD) were significantly enriched (14.2%) in DNA-NEG:ENZ-POS individuals, but nearly absent (0.2%) from the ENZ-NEG group and infrequent (1.2%) in ENZ-IND individuals. Enzyme testing has high sensitivity, but the burden of indeterminate and potentially false positive results is significant when used for first-line screening in pan-ethnic populations.		2020

Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
Comparative test accuracy USA	Screening for Tay-Sachs disease carriers by full-exon sequencing with novel variant interpretation outperforms enzyme testing in a pan-ethnic cohort ¹⁴	<p>Combined results of enzyme testing, retrospective computational analysis, and variant reclassification to estimate the respective clinical performance of TSD screening via enzyme analysis and NGS.</p> <p>Clinical sensitivity for carriers was estimated to be 99.9% by NGS and 99.33% by enzyme testing in an AJ cohort, and 98.7% and 95.55% in a pan-ethnic population, respectively. In each population separately, the clinical specificity was estimated to be >99.9% by NGS-based testing and >99.2% by enzyme-based testing. Compared to NGS, the estimated PPV for enzyme analysis was significantly lower in both AJ-only and non-AJ cohorts ($p < 0.05$): among non-AJs, estimated PPV was <50% for enzyme analysis and >98% for sequencing.</p>	https://onlinelibrary.wiley.com/doi/full/10.1002/mgg.3.836	2019
Retrospective diagnostic yield Conference abstract USA	Importance of expanded carrier screening in the Ashkenazi Jewish population ¹⁵	A total of 81 AJ students underwent carrier screening for the 4 strongly recommended AJ genetic conditions, 14 AJ genetic conditions that can be offered, and the genetic diseases that are not specifically mentioned for screening in this population. Of these, 36 (44.4%) were found to be carriers of at least one disease. Out of the 36 patients, 28 were found to be a carrier for one disease, 7 for two diseases, and 1 for three diseases, representing 45 total identified variants. The carrier rate was 7/45 (15.6%) for the 4 recommended AJ genetic diseases, 20/45 (44.4%) for the 14 offered AJ conditions, and 25/45 (55.6%) for genetic diseases that were not recommended in this specific population.		2019

Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
Retrospective diagnostic yield USA	Modeled Fetal Risk of Genetic Diseases Identified by Expanded Carrier Screening ¹⁶	A total of 346,790 individuals self-identified in 15 ethnic groups, underwent carrier screening (targeted genotyping or NGS). Most individuals screened were female. All ethnic groups were screened for CF, SMA, FXS, the ACMG AJ panel (see above), haemoglobinopathies, the Newborn Screening Recommendations and an expanded carrier panel of profound and severe conditions. The number of pregnancies/100,000 expected to be affected for all ethnic groups for the AJ disease panel ranged from 0.5 (Southeast Asian) to 131 (AJ). For CF, SMA and FXS rates ranged from 0.8 to 43.7 (Northern European) [36.2 AJ], 5.3 (African) to 15.1 (Southern European) [7.6 AJ] and 7.0 (Southeast Asian) to 77.8 (Middle East) [54.7 AJ], respectively.	https://pubmed.ncbi.nlm.nih.gov/27533158/	2016
Prospective diagnostic yield USA	Comprehensive population screening in the Ashkenazi Jewish population for recurrent disease-causing variants ¹⁷	2,252 individuals who self-reported 100% AJ ancestry underwent carrier screening using DNA genotyping for 85 variants causative of 29 conditions. An additional 1,390 individuals of AJ ethnicity and at least 6,813 individuals of ethnicities excluding 100% AJ ancestry received carrier screening for 18 of these conditions. Seven conditions had a carrier frequency >1:100, nine between 1:100 and 1:200, and four between 1:200 and 1:500. The combined AJ carrier frequency for 18 relatively prevalent diseases was 1:6, and the risk of AJ individuals to be a carrier couple for one of these 18 diseases as 1:441.	https://pubmed.ncbi.nlm.nih.gov/27415407/	2017
Retrospective diagnostic yield USA	Evaluation of two-year Jewish genetic disease screening program in Atlanta: insight into community genetic screening approaches ¹⁸	685 self-identified AJ individuals and 39 non-AJ partners were screened for at least 17 AJ associated diseases. Both molecular and Hex A enzyme testing were performed for TSD screening. 188 individuals (25.9%) were identified as carriers for at least one disease (21.82% one disease, 4.01% two and 0.14% three), with an overall carrier frequency of 1 in 3.9 for Jewish genetic diseases.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4356671/	2015

Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
Qualitative USA	Knowledge, attitudes, and barriers to carrier screening for the Ashkenazi Jewish panel: A Florida experience ¹⁹	412 AJ individuals (mean age=24.9 years; 54.7 % female) completed the surveys. Participants' level of knowledge increased from pre- to post-intervention (81.4 vs 91.0 %; p<0.0001). Concern about the possibility of being a carrier was significantly higher after an educational, as was the level of concern regarding having an affected. The number of participants who agreed or strongly agreed that the test results would not have any influence on their reproductive behaviour was lower after the session (17.2 vs. 20.8 %). An educational carrier screening program increased knowledge and elucidated awareness of the attitudes and barriers toward carrier screening.	https://pubmed.ncbi.nlm.nih.gov/24415495/	2014
Diagnostic yield USA	Experience with Carrier Screening and Prenatal Diagnosis for Sixteen Ashkenazi Jewish Genetic Diseases ²⁰	Testing for 16 disorders (118 variants) in a prenatal AJ panel in 466 individuals and 574 prenatal screens. Screening among the 100% AJ-descended individuals resulted in ~1 in 3.3 being a carrier for one disease and ~1 in 24 for two diseases. Over 95% of screenees chose to be screened for all possible AJ diseases, including disorders with lower carrier frequencies and/or detectability. Carrier screening identified rare individuals homozygous for disease-causing mutations who had previously unrecognised clinical manifestations.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2970726/	2010
Retrospective diagnostic yield Israel	Carrier frequency of autosomal-recessive disorders in the Ashkenazi Jewish population: should the rationale for mutation choice for screening be reevaluated? ²¹	A total of 10,078 unselected healthy AJ individuals were examined to identify carriers of disease-causing mutations (GD, CF, FD, A1AT, ML4, FAC, CD, NP and BLM). 635 individuals were carriers of one mutation and 30 were found to be carriers of two mutations. GD had the highest carrier frequency (1 : 17) followed by CF (1 : 23), FD (1 : 29), A1AT (1 : 65), ML4 (1 : 67) and FAC (1 : 77). The carrier frequency of CD, NP and BLM was 1 : 82, 1 : 103 and 1 : 157, respectively.	https://pubmed.ncbi.nlm.nih.gov/18264947/	2008

Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
Retrospective diagnostic yield Conference abstract Australia	The Victorian Ashkenazi Jewish secondary school carrier screening program for Tay-Sachs disease and related conditions ²²	A genetic carrier screening program for Year 11 students attending 6 Jewish secondary schools in Melbourne ran from 2003–2015. Screening was initially for TSD, with screening for 6 other genetic conditions introduced in 2008, and an 8 th in 2014. Over this 13-year period, 4,058 Year 11 students were screened, and 325 students were identified as carriers. Eleven of these students were carriers of two conditions, and one was a carrier of three conditions. The frequency of TSD carriers in this population from 2003–2007 was 1 in 33. The carrier frequency for all conditions screened from 2008 to 2015 increased to 1 in 8.5 students. Funding for this program carrier in 2016.		2017
Systematic review Australia	Ashkenazi Jewish population screening for Tay-Sachs disease: the international and Australian experience ²³	In Jewish individuals, DNA-based testing has a carrier detection sensitivity of 93.1–99.1% and is the most cost-effective testing method. The small residual risk relates to other HEXA mutations. Most non-Jewish populations exhibit TSD carrier frequencies of one in 250–300.	https://pubmed.ncbi.nlm.nih.gov/24923490/	2015
Retrospective observational audit Australia	Tay Sachs disease in Australia: reduced disease incidence despite stable carrier frequency in Australian Jews ²⁴	Retrospective audit of infantile and intermediate TSD cases diagnosed in Sydney and Melbourne between 1 January 1995 and 31 December 2011, and carrier frequency among Jewish high school students attending schools participating in TSD screening programs over the same period. The 7,756 Jewish students screened for TSD had a carrier frequency of one in 31. The estimated expected number of TSD-affected births in Melbourne and was 4.1 for Jewish births and 7.4 for other births, with the actual number being 12, of which only two were Jewish. This lower than expected number of Jewish TSD cases coincided with a screening program. No Jewish TSD-affected children were born to parents who were screened previously.	https://pubmed.ncbi.nlm.nih.gov/23230938/	2012

Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
Qualitative evaluation Australia	Evaluation of a multi-disease carrier screening programme in Ashkenazi Jewish high schools ²⁵	710 students who identified as Jewish participated in a carrier screening program for TSD. There was a 67% uptake for testing with a carrier rate of 1 in 28 determined. The level of knowledge of the students following education was high and of relative importance regarding decision making, as were their feelings and attitudes about genetic testing for carrier status. A significant impediment to test uptake was the need for blood sampling, resulting in a recommendation for the introduction of DNA analysis on cheek brush samples.	https://pubmed.ncbi.nlm.nih.gov/20597919/	2010
Qualitative evaluation Australia	High school Tay-Sachs disease carrier screening: 5 To 11-year follow-up ²⁶	Questionnaires were distributed to participants who had TSD screening in high school between 1999 and 2005 (>5years ago). 54 were completed and returned, giving a response of 38.7 % for carriers, 24.6 % for non-carriers, and an overall response of 29.3 %. Most participants (82 %) retained good knowledge of TSD and there was no evidence of a difference in knowledge between carriers and non-carriers. Most participants (83 %) were happy with the timing and setting of screening. There was no difference between carriers and non-carriers in mean scores for the State Trait Anxiety Inventory and Decision Regret Scale.	https://pubmed.ncbi.nlm.nih.gov/23893770/	2014

Type of study design*	Title of journal article or research project	Short description of research (max 50 words)**	Website link to journal article or research	Date of publication***
Qualitative evaluation Australia	Tay-Sachs disease preconception screening in Australia: self-knowledge of being an Ashkenazi Jew predicts carrier state better than does ancestral origin, although there is an increased risk for c.1421 + 1G > C mutation in individuals with South African heritage ²⁷	A total of 4,105 subjects underwent carrier testing for TSD. The majority identified as AJ (78.2%), with 2.8%, 11.8% and 7.2% identifying as Sephardic, mixed or unknown, respectively. Grandparents' birthplace for AJ subjects was also ascertained. AJ ethnicity is a good predictor of being a TSD mutation carrier and students with European ancestry were more likely to be TSD carriers; however, South African ancestry conveyed a fourfold increased likelihood of carrying the mutation c.1421+1G>C (OR, 4.19) compared with other AJ subjects.	https://pubmed.ncbi.nlm.nih.gov/22109873/	2011
Cost-effectiveness Australia	Cost-effectiveness of a school-based Tay-Sachs and cystic fibrosis genetic carrier screening program ²⁸	A model was developed to estimate the cost-effectiveness of the school-based carrier screening program compared to a hypothetical situation in which there is no school-based screening program. The model estimates that, for a "mixed" schools program of 10 schools (4 Jewish, 6 government; each with an average of 100 students in year 11), the screening program will detect an estimated 10.2 TSD carriers and 14 CF carriers per year (24.2 genetic carriers of either disorder). For the same hypothetical cohort of 1,000 students, only 1.3 genetic carriers would be detected without the program. The school screening program detects 23 additional genetic carriers, with an incremental cost-effectiveness of A\$5,834 per additional carrier detected.	https://www.nature.com/articles/gim200596	2005

It should be noted that much of the peer reviewed research describes the use of "expanded carrier screening" for use in both the Ashkenazi Jewish population, and the general population at large. These panels usually include autosomal recessive (including those predominant in the AJ population), autosomal dominant and X-linked disorders, and utilise either whole exome or whole genome sequencing. Expanded carrier screening is not relevant to this application but may indicate the usefulness of carrier screening in discrete populations such as the AJ population.

Retrospective diagnostic yield USA	Lessons learned from expanded reproductive carrier screening in self-reported Ashkenazi, Sephardi, and Mizrahi Jewish patients ²⁹	Over a 2-year period, 6,805 individuals of self-reported Jewish ancestry received carrier screening using a targeted NGS-based panel for 96 diseases. The overall chance of being a carrier for one or more of 96 disease genes tested by NGS was 1 in 1.57 (63.7% of individuals). Approximately 27% of individuals were carriers for multiple diseases, 1253 were carriers of two diseases, 425 of three diseases, and 134 of four or more diseases.	https://pubmed.ncbi.nlm.nih.gov/31880409/	2020
Retrospective diagnostic yield USA	Estimating yields of prenatal carrier screening and implications for design of expanded carrier screening panels ³⁰	Carrier rates for 415 genes associated with severe recessive conditions in 6 ancestries were estimated from 123,136 exome sequencing samples, of which 4,925 were AJ. In AJ, only 28 of the 415 genes had a carrier rate >1%. The cumulative AJ carrier rate across all 415 genes was 62.9%, with 90% of the cumulative carrier rate contributed by the 48 (out of 415) top ranking genes with the highest gene carrier rate. In AJ, 28 genes had a gene carrier rate >1.0%. The at-risk couple rate for all 415 genes was highest for intra-ancestry AJ couples at 252 of 10,000 couples (2.52% would carry a likely pathogenic or pathogenic variant in the same severe recessive disease gene). If only 40 genes with gene carrier rate >1.0% in any ancestry would identify 2.41% of couples as being at risk. Screening 87 genes with gene carrier rate >0.5% would identify 2.50% of couples, and screening the 244 genes with gene carrier rate >0.1% would identify nearly all 2.52% of at-risk couples. Lowering the threshold for genes that should be screened greatly increases the number of genes that would need to be screened, but results in a modest increase in the CCR and a small increase in the ACR.	https://pubmed.ncbi.nlm.nih.gov/30846881/	2019

Retrospective diagnostic yield USA	Lessons learned from expanded reproductive carrier screening in self-reported Ashkenazi, Sephardi, and Mizrahi Jewish patients ²⁹	Over a 2-year period, 6,805 individuals of self-reported Jewish ancestry received carrier screening using a targeted NGS-based panel for 96 diseases. The overall chance of being a carrier for one or more of 96 disease genes tested by NGS was 1 in 1.57 (63.7% of individuals). Approximately 27% of individuals were carriers for multiple diseases, 1253 were carriers of two diseases, 425 of three diseases, and 134 of four or more diseases.	https://pubmed.ncbi.nlm.nih.gov/31880409/	2020
Retrospective diagnostic accuracy USA	A data-driven evaluation of the size and content of expanded carrier screening panels ³¹	Carrier rates and at-risk couple rates were calculated in 56,281 patients who underwent a 176-condition ECS and were evaluated for panels satisfying various criteria. A per-condition carrier rate greater than 1 in 100 has been recommended. A compliant panel would include between 3 and 38 conditions, identify 11-81% fewer at-risk couples, and detect 36-79% fewer carriers than a 176-condition panel. If the carrier rate threshold must be exceeded in all ethnicities, ECS panels would lack prevalent conditions like CF. Simulations suggest that the clinical detection rate remains >84% for conditions with carrier rates as low as 1 in 1000. Therefore 1-in-100 criterion limits at-risk couple detection and should be reconsidered.	https://pubmed.ncbi.nlm.nih.gov/30816298/	2019
Retrospective diagnostic yield USA	Comparing ethnicity-based and expanded carrier screening methods at a single fertility center reveals significant differences in carrier rates and carrier couple rates ³²	A total of 4,232 infertility patients were tested using the ECS panel from the genetic testing laboratory (68.1% females). Self-reported ethnicity was recorded. Carrier rates were determined according to ethnicity-based guidelines or the ECS panel. The ECS panel identified 1,243 carriers (29.4%). For the same population, ethnicity based screening and the ACOG panel would have identified 359 (8.5%) and 659 carriers (15.6%), respectively. In 15 couples (1.2%), both partners carried pathogenic variants for the same genes, 47% of whom would have been missed had screening been ethnicity-based.	https://pubmed.ncbi.nlm.nih.gov/30327537/	2019

Retrospective diagnostic yield USA	Lessons learned from expanded reproductive carrier screening in self-reported Ashkenazi, Sephardi, and Mizrahi Jewish patients ²⁹	Over a 2-year period, 6,805 individuals of self-reported Jewish ancestry received carrier screening using a targeted NGS-based panel for 96 diseases. The overall chance of being a carrier for one or more of 96 disease genes tested by NGS was 1 in 1.57 (63.7% of individuals). Approximately 27% of individuals were carriers for multiple diseases, 1253 were carriers of two diseases, 425 of three diseases, and 134 of four or more diseases.	https://pubmed.ncbi.nlm.nih.gov/31880409/	2020
Retrospective diagnostic accuracy USA	Validation of an Expanded Carrier Screen that Optimizes Sensitivity via Full-Exon Sequencing and Panel-wide Copy Number Variant Identification ³³	NGS preconception carrier screening for 235 genes, including those in the AJ panel described in this application. Clinical impact was modelled using data from a cohort of 36,859 patients, which revealed the impact on fetal disease-risk detection attributable to novel CNVs (9.19% of risk) and technically challenging conditions (20.2% of risk). Of the 7,498 couples screened, 335 were identified as at risk for an affected pregnancy, underscoring the clinical importance of the test. Validation of our ECS demonstrated >99% analytical sensitivity and >99% analytical specificity.	https://pubmed.ncbi.nlm.nih.gov/29760218/	2018
Diagnostic yield USA	Expanded genetic screening panel for the Ashkenazi Jewish population ³⁴	DNA samples collected and sequenced from 128 disease-free AJ individuals. Sequencing identified 2,434 variants, 80 of which were reported as “pathogenic” or “possibly pathogenic”. Those determined to be pathogenic or likely pathogenic were reviewed for clinical utility using a panel of 76 autosomal recessive, 24 autosomal dominant, and 3 X-linked disorders. Screening of all mutations in our expanded panel is expected to detect medically relevant dominant mutations in 28% of patients and prenatal screening for recessive conditions using our expanded panel is expected to affect 3–4% of the couples.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4814352/	2016

Retrospective diagnostic yield USA	Lessons learned from expanded reproductive carrier screening in self-reported Ashkenazi, Sephardi, and Mizrahi Jewish patients ²⁹	Over a 2-year period, 6,805 individuals of self-reported Jewish ancestry received carrier screening using a targeted NGS-based panel for 96 diseases. The overall chance of being a carrier for one or more of 96 disease genes tested by NGS was 1 in 1.57 (63.7% of individuals). Approximately 27% of individuals were carriers for multiple diseases, 1253 were carriers of two diseases, 425 of three diseases, and 134 of four or more diseases.	https://pubmed.ncbi.nlm.nih.gov/31880409/	2020
Retrospective diagnostic yield USA	Carrier screening in the era of expanding genetic technology ³⁵	506 individuals (55% females, 45% males) who had requested carrier screening. The total screened population was composed of AJ individuals (85.55%), individuals with unknown or mixed ancestry (9.51%), and those with other ethnic backgrounds (4.94%) – all self-reported ancestry. 288 (57%) individuals were found to be carriers for a total of 434 pathogenic variants and a carrier of at least one genetic condition. 142 (28%) were carriers of 2 or more conditions, 28 (5%) were carriers of 3 or more, and 4 (1%) were carriers of 4 conditions. Of the 288 individuals identified as a carrier of at least one condition, 52 (18%) would not have been detected without NGS technology.	https://pubmed.ncbi.nlm.nih.gov/27054707/	2016
Diagnostic accuracy USA	Carrier testing for severe childhood recessive diseases by next-generation sequencing ³⁶	NGS preconception carrier screening for 448 severe childhood recessive illnesses. At a resultant 160× average target coverage, 93% of nucleotides had at least 20× coverage, and mutation detection/genotyping had ~95% sensitivity and ~100% specificity for substitution, insertion/deletion, splicing, and gross deletion mutations.	https://pubmed.ncbi.nlm.nih.gov/21228398/	2011

* 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.

18. 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.

None identified

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

- 19. 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):**

Royal College of Pathologists of Australasia (RCPA)

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

The Royal Australian College of General Practitioners (RACGP)

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)

Royal Australasian College of Physicians (RACP)

Australian Medical Association (AMA)

Human Genetics Society of Australasia (HGSA)

Australian Genomics

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

Rare Find Foundation

Rare Voices Australia

Gaucher Association of Australia & New Zealand

Genetic Alliance Australia

Moriah College

Jewish Care

Chinese Australian Services Society

Moriah Jewish College

Reddam House

National Council of Jewish Women of Australia

Wolper Jewish Hospital

Executive Council of Australian Jewry

JewishCare Victoria

Maronite Catholic Eparchy of Australia

Jewish Communal Appeal (JCA)

Co.As.It (Italian community group)

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

Not applicable

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

REDACTED

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

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. 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:

In Australia, many individuals have an ethnically diverse heritage and are likely to have a >10% personal risk of being a heterozygous genetic carrier of the disorders as described in this application. However, the clinical literature predominantly describes genetic testing for these variants in the Ashkenazi Jewish population. Therefore, in the context of this application, the Ashkenazi Jewish population will be used as the “exemplar” population.

A small number of recessive genetic conditions are responsible for significant morbidity and mortality in the Ashkenazi Jewish population. Although some of these conditions are considered rare in themselves, approximately 1 in 5 (20%) of Ashkenazi Jewish individuals who undergo genetic testing will be carriers for one or more of these conditions. The clinical characteristics, mode of inheritance and prevalence of the conditions recommended to be tested for are summarised in Table 1. Given the prevalence of these conditions in the AJ population, and the current state of the evidence base this application will consider *HEXA*, *CFTR* and *SMA* as exemplar genes. It should be noted that *CFTR* and *SMA* are equally prevalent in the non-AJ Australian population, and publicly funded carrier testing for these genes (plus fragile X) have recently been found to be cost-effective by the MSAC (MSAC application 1573).

In February 2015, the Human Genetics Society of Australasia released a position paper on Ashkenazi Jewish Population Screening that recommended that all AJ individuals of reproductive age should be made aware of the availability of AJ preconception genetic testing for severe monogenetic conditions and offered access to testing for TSD, CF, FD, FA NPD, BLM, CD and MPLIV. Preconception genetic testing is preferable to antenatal testing; however, if testing takes place during pregnancy, testing of both parents concurrently without delay should occur. Published studies, as listed in Question 17, have demonstrated successful health outcomes in genetic testing delivered by a combination of high school genetic testing programs, outreach community programs, opportunistic testing by medical practitioners and preconception testing. The partner of an AJ individual who has been identified as a carrier for one or more severe monogenetic conditions should be offered testing for the condition(s) regardless of heritage.⁴

The 2019 good practice note produced by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists recommends that carrier testing of women and their partners, preferably prior to pregnancy, for the common genetic conditions such as CF, SMA, FXS should be conducted. In addition, RANZCOG recommends that for individuals of AJ descent, testing for Tay Sachs disease, Niemann Pick disease type A, Fanconi anaemia group C, familial dysautonomia, Bloom syndrome, Canavan disease and mucopolidosis type IV should also be offered.⁷

Genetic testing for these conditions is currently only available on a user pays basis in Australia.

Table 1 Characteristics of disorders recommended to be tested for in individuals with a >10% personal risk of being a heterozygous genetic carrier.

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency in AJ population	Carrier testing	Detection rate of carrier test
Tay-Sachs disease (TSD), a lysosomal storage disorder ³⁷	Typically appears in infants aged 3-6 months, when normal development slows, and muscles used for movement weaken, resulting in a loss of motor skills such as turning over, sitting, and crawling. Disease progression is a result of neurons in the brain and spinal cord gradually being destroyed, with symptoms including an exaggerated startle reaction to loud noises, seizures, vision and hearing loss, intellectual disability, and paralysis/spasticity. Children with severe infantile form of TSD usually only live into early childhood (<4 years). Although there are other milder, late-onset forms of TSD that may occur in childhood, adolescence, or adulthood, these forms are extremely rare. ³⁷	Autosomal recessive. Carriers typically do not show signs or symptoms of TSD. Caused by variants in the <i>HEXA</i> gene, which is required for the production of beta-hexosaminidase A, a key lysosomal enzyme needed to breakdown GM2 gangliosides. Without functional beta-hexosaminidase A, GM2 gangliosides accumulate to toxic levels causing progressive damage to neurons within the brain and spinal cord. ³⁸ Individuals with TSD have two null alleles with no HEX A enzymatic activity. ³⁹	No cure. Treatment is mostly supportive. Seizures may be controlled using conventional antiepileptic drugs such as benzodiazepines, phenytoins, and/or barbiturates; however, seizures are progressive and can change in type and severity. ³⁹	Incidence in unscreened Jewish populations is 1: 3,900 births ²⁴ Carrier frequency in Ashkenazi Jewish population 1:25 Carrier frequency in general population 1:250 ⁴	More than 120 variants in the <i>HEXA</i> gene described that reduce or eliminate the functional activity of beta-hexosaminidase A, resulting in TSD ³⁸ . Targeted analysis of the 6 most common pathogenic variants: 3 null alleles: p.Tyr427IlefsTer5 c.1421+1G>C c.1073+G>A Adult onset p.Gly269Ser 2 pseudo-deficiency alleles p.Arg247Trp p.Arg249Trp ³⁹	Targeted analysis in the AJ population 92-99% ⁹

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency in AJ population	Carrier testing	Detection rate of carrier test
Cystic fibrosis (CF)	Chronic suppurative lung disease, pancreatic exocrine insufficiency, blocked biliary ducts, elevated sweat electrolytes, poor weight gain, and infertility in males.	Autosomal recessive. Affected individuals have two copies of faulty <i>CFTR</i> gene variants, one inherited from each parent. Greater than 2,000 disease-causing <i>CFTR</i> variants have been identified.	No cure. Advances in treatment have led to increases in life expectancy (median survival is mid-30s) and improvements in quality of life; however, these therapies are not curative. Ivacaftor (Kalydeco) is listed on the PBS (Highly Specialised Drugs Program) for treatment of CF in patients aged 6-years and older who have a G551D mutation in the <i>CFTR</i> gene. Ivacaftor 150 mg tablet, has a base dispensed price (DPMQ) of \$22,500. Since its listing in December 2014, a total of 268 patients have been supplied ivacaftor for CF (lower than predicted, however the number of prescriptions per patient was higher than predicted). The average number of prescriptions per patient per year was 10. The average cost per year was approximately \$50 million. ^c Lumacaftor (Orkambi) has also been added to the PBS, to be used in conjunction with ivacaftor at a DPMQ price of \$18,797, for CF patients homozygous for the F508del mutation in the <i>CFTR</i> gene. Dornase alfa, a recombinant DNase used to reduce the viscosity of sputum in with CF patients was added to the PBS in 1996. The defined daily dose of dornase alfa is 2.5 mg (inhaled). Dornase alfa has a DPMQ of \$1917. Mannitol, added to the PBS in 2012, is indicated	Same prevalence and carrier frequency in the general and AJ populations Birth prevalence in Australia 1 in 3,700 ⁴² Carrier frequency in Australia 1 in 25 ⁴ Most common life-threatening recessive condition affecting Australian children.	Analysis of the <i>CFTR</i> gene using a technology that achieves >95% diagnostic sensitivity for potentially pathogenic variants typically uses a panel of 50 most common pathogenic variants, including the 5T variant. Even higher diagnostic sensitivity can be achieved using genomic technologies.	90%*

^c <http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/2018-02/ivacaftor-for-cystic-fibrosis-february-2018>

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency in AJ population	Carrier testing	Detection rate of carrier test
			<p>for the treatment of CF in both paediatric and adult populations >6-years and above as either an add-on therapy to dornase alfa or in patients intolerant to, or inadequately responsive to, dornase alfa. The defined daily dose of mannitol is 0.8 g inhaled. Mannitol has a DPMQ of \$1,696. In the 12 months from May 2013 to April 2014, 1,570 patients received dornase alfa and 106 patients received mannitol on the PBS. In 2013, PBS expenditure was \$12,426,463 for dornase alfa and \$404,442 for mannitol.^d</p> <p>As the disease progresses, patients require more intensive health care that includes home-based care, medications, more frequent and prolonged hospital admissions, and, in around half of all cases, lung transplantation. A 2013 Australian study estimated the cost of lung Tx as US\$70,000^e plus ongoing treatment with immunosuppressants⁴⁰. 5-year survival rates of lung Tx have been reported as 67%, with 50% of patients living >10 years.⁴¹ In Australia in 2015 a total of 44 CF patients were assessed and accepted onto the lung Tx waiting list, with 30 receiving a Tx. Of these, 15 were aged 18-29 years, and 14 aged >30 years.⁴²</p> <p>In 2015, 17 deaths were reported to the CF registry, compared to 19 deaths in 2014. Of</p>			

^d www.pbs.gov.au/industry/listing/participants/public-release-docs/2014-10/cystic-fibrosis-dornase-mannitol-dusc-prd-10-2014.docx

^e The US\$70,000 was in 2009 prices. Taking into account inflation, this amount would equate to US\$82,366 in 2018 prices, which when converted to Australian dollars, is equivalent to A\$115,971 (as of Oct 22nd 2018)

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency in AJ population	Carrier testing	Detection rate of carrier test
			these, one was aged 12-17 years and eight were 18-29 years. The median age of death was 31.6 years, compared to 27.7 years in 2014. Ten of the 17 deaths reported in 2015 were due to pulmonary causes, 3 due to gastro-intestinal complications, with another 3 cases as a result of post-transplant complications. One cause of death was unknown ⁴²			
Canavan disease (CD)	Neonatal/infantile CD is the most common and most severe form of the condition. Affected infants appear normal for the first few months of life; however, a loss of motor skills begins to develop by 3-5 months. Affected infants have difficulty with turning over, controlling head movement, and sitting without support. Other common features include hypotonia, macrocephaly, and irritability. Feeding and swallowing difficulties, seizures, and sleep disturbances may also develop. ⁴³	Autosomal recessive. Carriers typically do not show signs or symptoms of CD. Caused by variants in the <i>ASPA</i> gene, which codes for aspartoacylase, an enzyme that breaks down N-acetyl-L-aspartic acid (NAA). NAA is found predominantly in neurons in the brain; however, its role is currently unclear. Mutations in the <i>ASPA</i> gene reduce the function of aspartoacylase, preventing the breakdown of NAA, leading to a build-up of NAA and subsequent impairment of enzyme	No cure. The average life expectancy for infants affected with neonatal/infantile CD is 18 months, although some individuals may survive into adolescence or beyond. ⁴ The milder, juvenile form does not usually result in a shortened lifespan. ⁴³ Once diagnosed, patients will usually undergo a brain MRI and neurologic, developmental and ophthalmologic assessments. ⁴⁴ Treatment of neonatal/infantile CD is supportive, aiming to provide adequate nutrition and hydration, managing infectious diseases, and protecting the airway. Physical therapy may minimise contractures and maximise motor function. Seizures can be treated with antiepileptic drugs. ⁴⁴	Prevalence 1 in 6,400 to 13,500 ⁴³ Carrier frequency 1:40 ⁴	In AJ populations, 97% of CD is caused by 2 pathogenic variants in the <i>ASPA</i> gene: Missense mutation c.854A>C (p.Glu285Ala) Nonsense mutation c.693C>A (p.Tyr231ter) ⁴	Targeted analysis in the AJ population 97.4% ⁹

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency in AJ population	Carrier testing	Detection rate of carrier test
		activity. High levels of NAA build up in the neonatal/infantile form of CD, with lower levels in the milder, juvenile form. The build-up of NAA leads to the progressive destruction of existing myelin sheaths, causing malfunction of nerves, which disrupts normal brain development. ⁴³				
Familial dysautonomia	<p>FD affects cells of the autonomic nervous system, responsible for controlling involuntary actions such as digestion, breathing, tear production, and regulation of blood pressure and body temperature. FD also affects the sensory nervous system, which controls activities such as taste and the perception of pain, heat, and cold.⁴⁵</p> <p>FD usually manifests during infancy, with early symptoms including hypotonia, feeding difficulties, poor growth, lack of tears, frequent lung infections, and difficulty</p>	<p>Autosomal recessive. Carriers typically do not show signs or symptoms of FD.</p> <p>Mutations in the <i>ELP1</i> (<i>IKBKAP</i>) gene cause FD. <i>ELP1</i> codes for a protein that is found in a variety of cells throughout the body, including brain cells. Nearly all individuals with FD have 2 copies of the same <i>ELP1</i> variant, which disrupts production of ELP1 protein. Reduced levels of ELP1 protein in the brain disrupts critical</p>	<p>Life expectancy is reduced, with affected individuals living up to 40 years of age. Treatment aims to ameliorate symptoms by providing adequate nutrition; measures to avoid aspiration; treatment of gastroesophageal reflux; daily chest physiotherapy; possible high-frequency chest-wall oscillation; hydration, elastic stockings, leg exercises, counter-manoeuvres to treat orthostatic hypotension; pacemaker for bradyarrhythmia and/or syncope; and artificial tear solutions for corneal healing. An annual spine examination for scoliosis should be conducted, with spinal fusion performed as needed.⁴⁶</p>	<p>Birth prevalence 1 in 3,700⁴⁵</p> <p>Carrier frequency 1:30⁴</p>	<p>In AJ populations, 99% of CD is caused by 2 pathogenic variants in the <i>ELP1</i> (<i>IKBKAP</i>) gene:</p> <p>Major founder variant c.2204+6T>C</p> <p>Rare variant p.Arg696Pro⁴⁶</p>	<p>Targeted analysis in the AJ population >99%⁹</p>

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency in AJ population	Carrier testing	Detection rate of carrier test
	maintaining body temperature. Developmental and motor milestones, such as walking and speech, may be delayed due to hypotonia, with some children experiencing learning disabilities. Increased difficulty with balance and walking may occur with increasing age. By adolescence, 95% of individuals with FD will have some evidence of scoliosis. ⁴⁵ Persons with FD are more likely than the general population to develop end-stage renal disease (at age 25 years FD 19% vs general population 0.1%). ⁴⁶	activities, leading to the signs and symptoms of FD. ⁴⁵				
Niemann Pick disease type A (NPD)	There are 4 main types of NPD, classified based on genetic cause, and signs and symptoms of the condition: Types A, B, C1 and C2. ⁴⁷ Type A is also known as neuronopathic NPD, with death occurring in early childhood. NPD type B is also known as non-neuronopathic. ⁴⁸	Autosomal recessive. Carriers typically do not show signs or symptoms of NPD. NPD types A and B are caused by mutations in the <i>SMPD1</i> gene, which codes for the enzyme acid sphingomyelinase. Acid sphingomyelinase is found in lysosomes, and	NPD-A: Progressive neurologic disease. Physical and occupational therapy to maximise function and to prevent contractures is appropriate. Regular consultation with a dietician should be provided, and the use of nasogastric tube feeding or surgical placement of a feeding tube may be required. Medications for sleep disturbance may be needed. ⁴⁸ NPD-B: Most affected individuals have thrombocytopenia and blood transfusion may be required. Partial splenectomy may be considered	Prevalence Population prevalence estimated to be 1:250,000 ⁴⁸ Carrier frequency 1:80 ⁴	3 founder point variants account for 97% of AJ carriers: c.911T>C p.Leu304Pro c996delC c.1493G>T p.Arg498Leu ⁴	90% ⁴⁸

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency in AJ population	Carrier testing	Detection rate of carrier test
	<p>Infants with NPD type A usually develop hepatosplenomegaly by 3 months and fail to thrive, with psychomotor regression occurring at 12-months. Interstitial lung disease also develops, causing recurrent lung infections leading to respiratory failure.⁴⁷</p> <p>NPD type B usually presents in mid-childhood, with milder symptoms similar to type A, with affected individuals surviving into adulthood. Patients with NPD type B often have hepatosplenomegaly, recurrent lung infections, and thrombocytopenia. They also have short stature, slowed mineralisation of bone, and approximately 1/3 may have neurological impairment.⁴⁷</p> <p>Symptoms of NPD types C1 and C2 can develop at any time but usually become apparent in childhood. Affected individuals may survive into adulthood. Symptoms include ataxia,</p>	<p>converts the lipid, sphingomyelin, into ceramide. Mutations in <i>SMPD1</i> lead to a shortage of acid sphingomyelinase, which results in the reduced break down, and accumulation of, sphingomyelin, in cells. As a result, cells malfunction and eventually die. Over time, cell loss impairs function of tissues and organs including the brain, lungs, spleen, and liver.⁴⁷</p> <p>NPD type C is caused by variants in either the <i>NPC1</i> or <i>NPC2</i> genes. These variants lead to a shortage of functional protein, which prevents movement of cholesterol and other lipids, leading to their accumulation in cells. As a result, many normal cell functions that require these lipids, such as cell membrane formation, are impaired.</p>	<p>for individuals with severe hypersplenism. Total splenectomy should be avoided as the removal of the spleen will exacerbate pulmonary disease. Patients with symptomatic pulmonary disease may require supplemental oxygen. Adults with hyperlipidaemia should be treated to bring the serum concentration of total cholesterol into the normal range. Dietary assessment is indicated in all cases to assure that calorie intake is adequate to prevent growth retardation.⁴⁸</p> <p>Orthotopic liver transplantation in infants with NPD-A and amniotic cell transplantation in several individuals with NPD-B have been attempted with little or no success.⁴⁸</p>		Note that many current-generation diagnostic assays only test for type A. More modern genomic technologies may be able to test for the other types.	

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency in AJ population	Carrier testing	Detection rate of carrier test
	vertical supranuclear gaze palsy, dystonia, severe liver disease, and interstitial lung disease. Affected Individuals also have problems with speech and swallowing that worsen over time, eventually interfering with feeding. In addition, a progressive decline in intellectual function is common, and about 1/3 have seizures. ⁴⁷	The accumulation of lipids as well as the cell dysfunction eventually leads to cell death, resulting in the tissue and organ damage observed in NPD types C1 and C2. ⁴⁷				
Bloom syndrome	<p>Bloom syndrome is characterised by:</p> <ul style="list-style-type: none"> • short stature, with individuals rarely exceeding 5 feet tall in adulthood; • excessive photosensitivity with facial lupus-like skin lesions, characterised by the presence of telangiectasias. Hypopigmentation or hyperpigmentation may occur on skin not exposed to the sun; and • an increased risk of multiple cancers (especially leukaemia and lymphoma), that arise 	<p>Autosomal recessive.</p> <p>Bloom syndrome is caused by mutations in the <i>BLM</i> gene, which codes for the protein RECQL3, a RecQ helicase, required for DNA replication and repair during cell division.⁴⁹</p> <p>In the absence of the BLM protein the frequency of sister chromatid exchange is 10-fold higher than average. Chromosome breakage occurs more frequently in affected individuals, resulting in</p>	<p>A multidisciplinary approach is important in management of these patients. Due to the rarity of this condition and its complexities, there is no consensus for management or treatment.</p> <p>Annual breast, cervix and colon cancer screenings are recommended as adults with cancer may benefit from surgical resection of carcinomas at an early stage. Due to the high risk of chromosomal breakage, radiation exposure should be avoided for both diagnosis (MRI and US instead of CT) and for treatment. In addition, chemotherapy doses should be adjusted to reduce toxicity, which may result in high levels of DNA fragmentation. The mean age of cancer diagnosis in Bloom syndrome patients is 23 years, with death occurring before 30 years of age.⁵⁰</p>	<p>Prevalence Rare</p> <p>Carrier frequency 1:102⁴</p>	<p>A single pathogenic variant in <i>BLM</i> gene, known as BLMash, is responsible for over 90% cases of Bloom syndrome in the AJ population - a 6-bp deletion/7-bp insertion in exon 10 of <i>BLM</i></p> <p>c.2207_2212delinsTAGATTC.⁵¹</p>	<p>Targeted analysis for c.2207_2212delinsTAGATTC</p> <p>In AJ population 93%</p> <p>Non-AJ population 6%.⁵¹</p>

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency in AJ population	Carrier testing	Detection rate of carrier test
	<p>earlier in life than they do in the general population.⁴⁹</p> <p>In addition, individuals with Bloom syndrome have a high-pitched voice and distinctive facial features including a long, narrow face; a small lower jaw; and prominent nose and ears. Learning disabilities, an increased risk of diabetes, chronic obstructive pulmonary disease, and mild immune system abnormalities leading to recurrent infections of the upper respiratory tract, ears, and lungs during infancy, have also been noted. Hypogonadism is also a feature, with males usually infertile. Females have reduced fertility and experience menopause at an earlier age than usual.⁴⁹</p>	<p>gaps and breaks in the DNA. In addition, a lack of DNA repair, especially damage caused by UV light, results in increased sun sensitivity. The high rate of genomic instability leads to cells dividing uncontrollably, leading to cancer.⁴⁹</p>				
Mucopolipidosis Type IV	<p>Mucopolipidosis type IV (95% of cases) is characterised by severe psychomotor delay that usually becomes apparent during the first year of life. Affected individuals have intellectual disability,</p>	<p>Autosomal recessive. Carriers typically do not show signs or symptoms. Mucopolipidosis Type IV is caused by mutations in the <i>MCOLN1</i> gene,</p>	<p>Evaluations following diagnosis:</p> <ul style="list-style-type: none"> • Ophthalmic examination • Brain MRI • Iron studies • Neurologic evaluation, including EEG 	<p>Prevalence 1 in 40,000.⁵²</p> <p>Carrier frequency 1:100.⁴</p>	<p>2 pathogenic variants in the <i>MCOLN1</i> gene account for 95% of all cases of mucopolipidosis</p>	<p>Targeted analysis for pathogenic variants</p>

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency in AJ population	Carrier testing	Detection rate of carrier test
	<p>limited or absent speech, difficulty chewing and swallowing, hypotonia that gradually turns into spasticity and difficulty controlling hand movements. Vision becomes increasingly impaired over time, and by early teens, affected individuals have severe vision loss or blindness caused by a combination of corneal clouding and retinal degeneration.⁵²</p> <p>About 5% of cases have atypical mucopolidosis type IV, associated with milder symptoms.⁵²</p>	<p>coding for the protein mucolipin-1, which is located in the membranes of lysosomes and endosomes. The role of mucolipin-1 is not fully understood; however, a lack of functional mucolipin-1 impairs the transport of lipids and proteins, causing a build up inside lysosomes. Most variants of the <i>MCOLN1</i> gene result in the production of a non-functional protein or prevents protein production.⁵²</p> <p>Mucolipin-1 is important for the development and maintenance of the brain and retina. In addition, this protein is likely critical for normal functioning of the cells in the stomach that produce digestive acids.⁵².</p>	<ul style="list-style-type: none"> • Consultation with a clinical geneticist and/or genetic counsellor <p>Treatment:</p> <ul style="list-style-type: none"> • Speech therapy • Physical therapy & rehabilitation for motor dysfunction (spasticity and ataxia) • Ankle-foot orthotics in individuals with hypotonia and weakness of ankle dorsiflexion • Antiepileptic drugs • Topical lubricating eye drops, artificial tears, gels, or ointments for management of the intermittent ocular irritation seen frequently in younger children • Surgical correction of strabismus.⁵³ 	<p>Most affected individuals are non-AJ⁵³</p>	<p>type IV in the AJ population</p> <p>The splice pathogenic variant c.406-2A>G is 3x more common than the deletion pathogenic variant 6.4 kb del, also known as g.511_6943del.⁵³</p>	<p>In AJ population 95%</p> <p>Non-AJ population 6%-10%.⁵³</p>

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency in AJ population	Carrier testing	Detection rate of carrier test
Glycogen storage type 1A (GSD1)	GSD1 is characterised by the accumulation of glycogen and fat in the liver and kidneys, resulting in hepatomegaly and renomegaly. Untreated neonates may present with severe hypoglycaemia; more commonly, however, untreated infants present at 3-4 months with hepatomegaly, lactic acidosis, hyperuricaemia, hyperlipidaemia, hypertriglyceridaemia, and/or hypoglycaemic seizures. Deposits of cholesterol in the skin (xanthoma) and diarrhoea may be present. Impaired platelet, neutrophil and monocyte function as well as chronic neutropenia is observed. Long-term complications of untreated GSDI include growth retardation resulting in short stature, osteoporosis, delayed puberty, gout, renal disease, pulmonary hypertension, hepatic adenomas with potential for malignant transformation, polycystic ovaries, pancreatitis, and	Autosomal recessive. Carriers typically do not show signs or symptoms. GSD1 is caused by pathogenic variants in 2 genes, <i>G6PC</i> and <i>SLC37A4</i> , coding for the enzyme glucose-6-phosphatase (G6Pase). These variants prevent the breakdown of glucose 6-phosphate to glucose, decreasing available energy to the body. As a result, toxic levels of glycogen and fat builds up within cells, damaging organs and tissues throughout the body, but in particular, the liver and kidneys. ⁵⁵	Medical nutritional therapy to maintain normal blood glucose levels, allopurinol to prevent gout; lipid-lowering medications; citrate supplementation to prevent urinary calculi or ameliorate nephrocalcinosis; ACE inhibitors to treat microalbuminuria; kidney transplantation for end-stage renal disease; surgery or other interventions hepatic adenomas; liver transplantation for those individuals refractory to medical treatment; and treatment with human granulocyte colony-stimulating factor for recurrent infections. Surveillance: > 10 years age annual kidney US, monitor for hepatic adenomas with US, MRI or CT depending on age every 12-24 months; hepatic profile (AST, ALT, albumin, bilirubin, PT/INR, aPTT) and serum creatinine every 6-12 months; complete blood count every 3 months for those on G-CSF; imaging with measurement of the spleen for those on G-CSF; > 10 years age screen for pulmonary hypertension with ECG every 3 years; routine monitoring of vitamin D levels. Diet should be low in fructose and sucrose; galactose and lactose intake should be limited; combined oral contraception should be avoided in women, particularly those with adenomas. ⁵⁴	Prevalence Overall incidence of GSDI is 1: 100,000 Disease prevalence in AJ population is 1: 20,000 ⁵⁴ Carrier frequency 1:64. ¹⁰	Biallelic pathogenic variants in <i>G6PC</i> (GSDIa) (80%) chromosome locus 17q21.31 OR <i>SLC37A4</i> (GSDIb) (20%) chromosome locus 11q23.3. ⁵⁴	Sequence analysis 95%. ⁵⁴

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency in AJ population	Carrier testing	Detection rate of carrier test
	changes in brain function. Most affected individuals live into adulthood. ⁵⁴					
Fanconi anaemia (FA)	<p>Approximately 90% of individuals with FA have impaired bone marrow function leading to aplastic anaemia. This results in fatigue and anaemia, frequent infections due to neutropenia, and thrombocytopenia. Patients with FA may also develop myelodysplastic syndrome, where immature blood cells fail to develop.⁵⁶</p> <p>Individuals with FA also tend to have hypopigmentation, malformed thumbs or forearms and other skeletal problems including short stature; malformed or absent kidneys and other defects of the urinary tract; gastrointestinal abnormalities; heart defects; eye abnormalities such as small or abnormally shaped eyes; and malformed ears and hearing loss. Abnormal genitalia or malformations of the reproductive system are</p>	<p>FA is most often inherited as an autosomal recessive. Can be X-linked (rare).⁵⁶</p> <p>Mutations in at least 15 genes can cause FA, however, 80-90% of cases are due to mutations in one of 3 genes: FANCA (60-70%), FANCC (14%), and FANCG (10%). Proteins produced from these genes are involved in a cell process known as the FA pathway or complex, which is activated when DNA replication is blocked due to DNA damage.</p> <p>Pathogenic variants in any of these genes will produce a non-functional complex, disrupting the FA pathway. As a result, DNA damage is not</p>	<p>Treatments have potential significant toxicity: oral androgens improve blood counts in approximately 50% of individuals with FA; administration of G-CSF improves the neutrophil count in some; haematopoietic stem cell transplantation is the only curative therapy for the haematologic manifestations of FA, but the high risk for solid tumours remains and may increase in those undergoing HSCT.</p> <p>Surveillance: Annual evaluation by endocrinologist; regular blood counts; at least annual bone marrow aspirate/biopsy to evaluate morphology, cellularity, and cytogenetics; for those receiving androgen therapy, monitoring liver function tests and regular US of liver; monitoring for solid tumours.</p> <p>Avoid transfusions of red cells or platelets for persons who are candidates for HSCT; family members as blood donors if HSCT is being considered; blood products that are not leuko-depleted or irradiated; toxic agents that have been implicated in tumorigenesis; unsafe sex practices, which increase the risk of HPV-associated malignancy; radiographic studies in the absence of clinical indications.⁵⁷</p>	<p>Prevalence 1: 160,000⁵⁶</p> <p>Carrier frequency 1:80⁴</p>	<p><i>FANCA</i> 16q24.3</p> <p><i>FANCB</i> Xp22.2</p> <p><i>FANCC</i> 9q22.32</p> <p><i>FANCD2</i> 3p25.3</p> <p><i>FANCE</i> 6p21.31</p> <p><i>FANCF</i> 11p14.3</p> <p><i>FANCG</i> 9p13.3</p> <p><i>FANCI</i> 15q26.1</p> <p><i>FANCL</i> 2p16.1</p> <p><i>FANCM</i> 14q21.2⁵⁷</p> <p>Note that many current diagnostic tests only</p>	<p>Targeted analysis in the AJ population >99%⁹</p>

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency in AJ population	Carrier testing	Detection rate of carrier test
	<p>also observed, resulting in infertility. Hydrocephalus and microcephaly have also been reported.⁵⁶</p> <p>Individuals with FA have an increased risk (10-30%) of developing acute myeloid leukemia or tumours of the head, neck, skin, gastrointestinal system, or genital tract.⁵⁶</p>	<p>repaired efficiently and inter-strand cross-links build up, stalling DNA replication. This ultimately results in</p> <p>i) abnormal cell death due to an inability make new DNA molecules. Cells that are particularly affected are those that divide quickly, such as bone marrow cells and cells of the developing fetus. The death of these cells results in the decrease in blood cells and the physical abnormalities characteristic of FA;</p> <p>or</p> <p>ii) uncontrolled cell growth due to a lack of DNA repair processes. The build-up of errors in DNA leads to uncontrolled cell growth, with affected individuals developing acute myeloid leukaemia or other cancers.⁵⁶</p>			examine for FANCC	

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency in AJ population	Carrier testing	Detection rate of carrier test
<p>Gaucher disease (GD)</p> <p>Note: Carrier testing for Gaucher disease (GD) is not routinely included in all carrier testing programs</p>	<p>GD varies in clinical presentation; however, it is characterised by hepatosplenomegaly, cytopenia, sometimes severe bone involvement and, in some forms, neurological impairment.</p> <p>The clinical presentation of Type 1 is variable, ranging from asymptomatic throughout life to early-onset forms presenting in childhood. Initial symptoms vary considerably, and patients can be diagnosed at any age. Fatigue, growth retardation and delayed puberty are common. Splenomegaly, hepatomegaly and thrombocytopenia is observed in > 90%, 60–80% and 60-90% of patients, respectively.⁵⁸</p> <p>GD types 2 and 3 are characterised by the presence of primary neurologic disease. GD type 2: onset before age 2-years, limited psychomotor development, and a rapidly progressive course with death</p>	<p>Autosomal recessive.</p> <p>There are several types of GD, all caused by a mutation in the beta-glucocerebrosidase (<i>GBA</i>) gene, categorised by the absence (type 1, most common) or presence (types 2 & 3) of neurological impairment. These variants result in the decreased activity of the lysosomal enzyme, glucocerebrosidase (GCCase), which hydrolyses glucosylceramide into ceramide and glucose. A decrease in GCCase leads to an accumulation of glucosylceramide in macrophages, transforming them into Gaucher cells, which then infiltrate bone marrow, the spleen, liver and other organs.⁵⁸</p>	<p>All GD patients require regular monitoring. Enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) are not justified in all cases. However, once it has been initiated, treatment must generally be administered for life. Treatment should commence before the onset of complications, the sequelae of which are disabling or not improved by further treatment, including massive fibrous splenomegaly, secondary osteoarthritis, vertebral compression and other fractures, hepatic fibrosis and lung fibrosis. ERT with intravenous recombinant enzyme products supplies the GCCase lacking in the cells. This strategy supplies sufficient exogenous enzyme to overcome the block in the catabolic pathway, clearing the stored substrate, GL1, and in so doing, reversing haematologic and liver/spleen involvement. There is no evidence that ERT has reversed, stabilised, or slowed the progression of neurological involvement. Therefore, none of the ERTs are indicated for GD2 as treatment has no impact on the rapid progression of its severe neurological symptoms. Specific treatment with ERT should be considered for all GD3 patients, but only for those GD1 patients who have symptomatic clinical or biological abnormalities. SRT aims to reduce excess cell GlcCer by decreasing its production in Gaucher cells. Some SRTs are used as a second-line treatment when ERT can no longer be tolerated.^{58, 59}</p>	<p>Prevalence</p> <p>In general population</p> <p>Type 1 GD 1: 30,000 to 1: 40,000</p> <p>Types 2 and 3 GD < 1: 100,000⁶⁰</p> <p>Incidence in AJ population 1: 850⁵⁸</p> <p>Carrier frequency 1:18¹⁰</p>	<p>More than 300 <i>GBA</i> mutations have been described in the <i>GBA1</i> gene.</p> <p>4 pathogenic variants in the <i>GBA</i> gene account for 90% of all AJ cases and 50-60% of cases in the general population</p> <p>c.84dupG</p> <p>c.115+1G>A</p> <p>p.Asn409Ser</p> <p>p.Leu483Pro⁵⁸</p>	<p>Sequence analysis ~99%</p> <p>Gene-targeted deletion/duplication analysis Unknown, likely <1%⁵⁹</p> <p>Note: Because type I GD can be a less severe disease than others presented in this application, we have provided information on the condition, but are proposing <i>not</i> to require inclusion of <i>GBA</i> testing in the core testing panel.</p>

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency in AJ population	Carrier testing	Detection rate of carrier test
	by age 2-4 years. GD type 3: onset before age 2-years with slower progression and survival into the third or fourth decade. ⁵⁹		Patients should be managed by a multidisciplinary team. For persons not receiving ERT or SRT, symptomatic treatment includes partial or total splenectomy for massive splenomegaly and thrombocytopenia. Supportive care may include: transfusion of blood products for severe anaemia and bleeding; analgesics for bone pain; joint replacement surgery for relief from chronic pain and restoration of function; and anti-bone resorptive agents, calcium, and vitamin D for osteoporosis. The use of anticoagulants in individuals with severe thrombocytopenia and/or coagulopathy should be discussed with a haematologist to avoid the possibility of excessive bleeding. ⁵⁹			
Spinal muscular atrophy (SMA)	<p>Progressive muscle weakness and atrophy. Classified according to maximal functional status achieved.</p> <p>Type 1: never sit unsupported, onset before 6 months, marked weakness and hypotonia, areflexia, tongue fasciculations, life expectancy <2 years from respiratory failure.</p> <p>Type 2: sit independently but never stand or walk, onset between 6 and 18 months, proximal weakness, hand</p>	<p>Autosomal recessive.</p> <p>SMA is due to homozygous deletions of the survival motor neuron gene (SMN1) in 95% of individuals. The remainder are compound heterozygotes for the deletion and an intragenic mutation of SMN1.</p>	<p>No cure.</p> <p>Multidisciplinary management of pulmonary, gastrointestinal, nutritional, and orthopaedic issues.</p> <p>In April 2018, the PBS listed nusinersen (Spinraza) - a disease modifying therapy for SMA for all patients under the age of 18 years. Nusinersen is an antisense oligonucleotide that modifies pre-mRNA splicing to promote exon 7 inclusion in SMN2 mRNA transcripts, resulting in production of more full-length SMN protein. It is administered using intrathecal injections via lumbar puncture.⁶¹ Nusinersen has a DPMQ of \$110,000. It is expected that around 160 patients will receive treatment every year as a result of</p>	<p>Prevalence 1 in 10,000</p> <p>Carrier frequency 1 in 40</p> <p>SMA is the most frequent genetic cause of infant mortality.</p>	Ascertaining SMN1 copy number by MLPA	95%

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency in AJ population	Carrier testing	Detection rate of carrier test
	tremor, scoliosis, life expectancy > 2 years to 3rd/4 th decade. Type 3: stand and walk independently, onset after 18 months, may ultimately require wheelchair, life expectancy similar to unaffected population.**		this listing, costing an estimated \$367,850 per patient, per year (\$58,856,000 per year). ^f Nusinersen is not curative but will improve QoL and increase life expectancy.			

* For Victorian Clinical Genetics Services 38-variant panel, ** In some classification systems type 0 (prenatal onset) and type 4 (adult onset) also delineated.

MLPA = multiplex ligation-dependent probe amplification, MRI = magnetic resonance imaging, US = ultrasound, CT = computed tomography

^f <http://www.health.gov.au/internet/main/publishing.nsf/Content/MC17-021776-SMA>

25. 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:

Using the AJ population as the exemplar, carrier testing should be offered to all individuals who have an *a priori* >10% personal risk of being a heterozygous genetic carrier for a serious inherited disorder as described in Table 1, noting that these disorders are highly prevalent in the AJ population.

The testing laboratory should only proceed with testing if it provides a testing panel that has been validated against a number of pathogenic or likely pathogenic genetic variants, where these variants have an aggregate frequency sufficient to meet the *a priori* 10% threshold. For the AJ exemplar population, the following additional genes *HEXA*, *ELP1* [*IKBKAP*], *SMPD1*, *ASPA*, *ELP1*, *FANCC*, *RECQL3*, and *MCOLN1* are commonly included within commercially available testing panels, noting that additional genes may also be included.

Testing must not be commenced without completion of pre-test education that should be delivered by a qualified health professional or professional health educator, either in person, or via an online medium. Details of conditions screened for including clinical features, mode of inheritance and implications for relatives should be included in the education. Information should be imparted regarding reproductive options for at-risk couples. If an individual is diagnosed as a carrier for one or more of these severe monogenetic conditions, their reproductive partner should be offered screening for the condition(s) in question, regardless of the *a priori* genetic carrier risk of that partner.

Although both should be made available, preconception testing is preferable to antenatal testing due to less pressure of time for completion of testing, and to provide the widest possible range of reproductive options to the individual and the couple. Where testing is conducted during pregnancy, testing of both parents concurrently is preferred and testing without delay is essential.⁴

26. 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):

There is no clinical management pathway for individuals prior to receiving the intervention as defined by this application. Carrier testing is designed to identify “at-risk” individuals.

Carrier testing for conditions such as thalassaemia (although noting that testing for thalassaemia is usually performed by non-genetics proxy means, such as a blood count) prior to conception or in early pregnancy is already an integral part of reproductive care with women and, as necessary, their reproductive partners. Preconception carrier testing is currently recommended as standard practice by:

- RACGP: “Provide opportunity for carrier screening for genetic conditions (e.g. cystic fibrosis, haemoglobinopathies) and referral for genetic counselling based upon risk factors”^g and
- RANZCOG/HGSA: “Information on carrier screening for the more common genetic conditions that affect children (e.g. cystic fibrosis, spinal muscular atrophy, fragile X syndrome) should be offered to all women planning a pregnancy or in the first trimester of pregnancy”^h

In Australia, genetic testing for severe monogenetic disorders, such as those described in this application, is currently accessible to some at-risk individuals in the AJ population via three clearly defined pathways:

- Cohort high school-based pre-conception testing;
- Pre-conception testing prior to marriage (generally only utilised by the religiously very observant); and
- Antenatal testing early in pregnancy.

These programs are well established and are organised by the AJ community itself, funded either by individuals paying fully out-of-pocket expenses, or via charitable organisations within the communities.

^g RACGP <https://tinyurl.com/4dmd6phn>

^h RANCOG <https://tinyurl.com/2wmx3j8u>

Note that the cohort high-school testing programs in the AJ community is only available in NSW, and then only to students in selected high schools, resulting in significant inequity of access to testing.

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

The test requires collection of a sample (usually blood, saliva or buccal/cheek swab) that is referred to a pathology laboratory, where DNA is extracted for genetic analysis.

Ideally, carrier testing should be a whole-of-population approach, with both at-risk males and females of reproductive age being screened prior to marriage/partnering and to provide an informed choice for future reproductive decision-making (Population A in Figure 1). Previous testing programs in Australia were conducted in high schools, which allowed large numbers of students to access carrier screening at the same time of offering an important opportunity to deliver education around the impact of autosomal recessive conditions.^{24, 26} However, if carrier testing for these monogenic disorders is introduced as an MBS funded item, it is likely to be as a 2-step approach that is preferably undertaken in the pre-conception period (Population B in Figure 1). In the first instance, carrier testing of all at-risk women planning a pregnancy should be undertaken. If the woman is confirmed as a heterozygote carrier for any of the conditions, then testing of her partner should be undertaken to fully evaluate the risk of having an affected child, regardless of the pre-test risk of the partner. If the woman is already pregnant (Population C in Figure 1), the couple should receive appropriate advice and counselling regarding the potential consequences before prenatal diagnosis is offered. All identified carriers and their partners should be offered genetic counselling.⁶² **Error! Reference source not found.** outlines the clinical pathway for 2-step carrier testing.

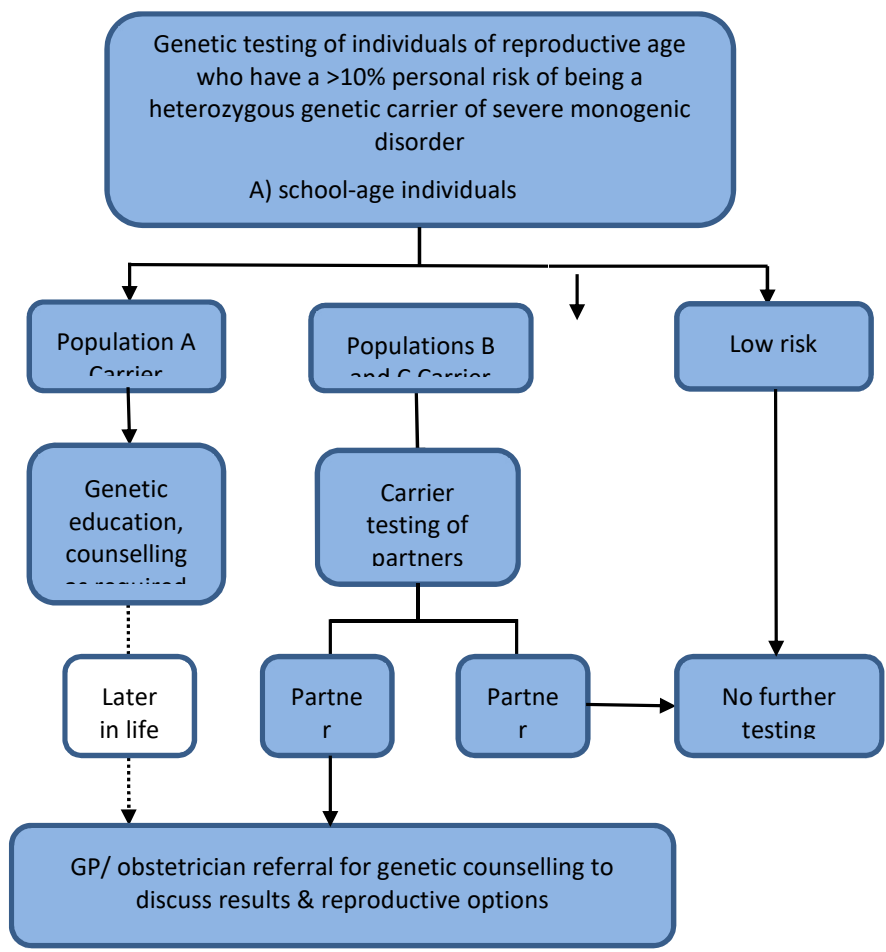


Figure 1 Clinical pathway for 2-step carrier testing

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

N/A

29. 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?

N/A

30. 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):

Once in a lifetime diagnostic test.

31. 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:

Although genetic counselling has been a critical component of genomic testing and is recommended to be offered for all identified carrier couples, the traditional in-person, multi-visit approach to genetic counselling services is increasingly being recognised as insufficient to meet the demands of genetics practice in the age of genomic medicine. Alternative service delivery models are emerging that maintain patients' confidentiality, fit into the healthcare systems' workflows, and are financially viable.

There is no "one model fits all" in genetic counselling and service delivery models need to consider the context in which they operate. We make a distinction between high volume low impact results such as in reproductive carrier screening, versus low volume high impact results such as in predictive genetic testing for untreatable genetic conditions e.g., neurodegenerative disorders. And in reproductive carrier screening, we make a distinction between antenatal testing (where there is pressure of time for results and interpretation) and preconception testing.

Web-based technologies and tele-genetic services are increasingly being used to improve access for patients. General pre-test education videos for patients, results delivered through a secure portal, and access to tele-genetic counselling by telephone are methods that have proven to be efficient in managing large-scale population based genetic screening programs.^{63,64} On line genetic counselling has also been shown to be effective, feasible and cost effective as well as increasing access to care and reduce time and costs for patients and health professionals.⁶⁵ More recently chat-bots have been used for consenting purposes with participants on one study supporting the use of chatbots to consent for genomics research, to interact with healthcare providers for care coordination following receipt of genomic results and to share genetic information with relatives.⁶⁶ Chat-bots can complement genetic counselling both pre and post-test and be incorporated into models of genetic counselling.⁶⁷

Alternative models of service delivery are required for reproductive carrier screening in the Australian context that draw on current evidence and continue to be evaluated. Consideration of a model that includes automated result delivery to individual patients with positive or negative result. Couples who are identified as carriers are contacted directly via phone either the ordering provider or a genetic counsellor to communicate the test results and provide follow up counselling.

The model that has been successfully used in AJ Community Genetics testing programs makes use of pre-test education, and post-test counselling delivered through a selection of these modalities. As described elsewhere in this submission, these programs have achieved high levels of participant and community satisfaction, with 100% health outcomes effectiveness.

For those selected cases requiring more in-depth counselling, it is unlikely that counselling would occur prior to, or at the same time as the genetic test due to long waiting lists. The requesting clinician may triage the patient to counselling at the same time as requesting the genetic test while explaining the test procedure, benefits and limitations, and potential consequences of test results to the individual and/or family members. Alternatively, the requesting clinician may triage the patient to counselling after a definitive genetic diagnosis is obtained.

Note that preconception testing offers a wider range of both counselling modalities and reproductive options than does antenatal testing. However, if a couple is tested antenatally and found to both be carriers of a condition only during pregnancy, after counselling remaining healthcare options include

diagnostic testing of the fetus via amniocentesis or chorionic villus sampling (CVS) with a further option to terminate the pregnancy if a genetic disease is confirmed in the fetus. Some couples may choose to continue with the affected pregnancy and will simply prepare themselves for the birth of an affected child.

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

A pathologist with appropriate Scope of Practice, or an appropriately qualified medical scientist in an accredited and supervised medical pathology laboratory would perform the service and provide the clinical report, including any required interpretation of the results.

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

Pre-test education could be delegated to an appropriately trained health professional operating under the supervision of the doctor responsible for the patient's care.

The testing can only be performed in a NATA accredited pathology laboratory.

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

N/A

35. 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:

Testing would be delivered only by NATA Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered Medical Practitioners in line with other tests in the MBS Pathology Table. Interpretation of results would be provided by approved practising pathologists with appropriate Scope of Practice, or medical scientists under supervision in an accredited medical pathology service.

All women considering pregnancy should be referred for antenatal testing by either their treating General Practitioner or obstetrician.

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL relevant settings):

- Inpatient private hospital (admitted patient)
- Inpatient public hospital (admitted patient)
- Private outpatient clinic
- Public outpatient clinic
- Emergency Department
- Private consulting rooms - GP
- Private consulting rooms – specialist
- Private consulting rooms – other health practitioner (nurse or allied health)
- Private day surgery clinic (admitted patient)
- Private day surgery clinic (non-admitted patient)
- Public day surgery clinic (admitted patient)
- Public day surgery clinic (non-admitted patient)
- Residential aged care facility
- Patient's home
- Laboratory
- Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

N/A

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

- Yes
- No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

- 38. 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):**

The appropriate comparator for the proposed carrier testing is no genetic testing.

For the most common and serious of the genetic conditions affecting the exemplar AJ community, Tay-Sachs disease. Prior to DNA-based genetic testing in the exemplar population, HEXA enzyme testing would have been considered the gold standard for the diagnosis of TSD; however, HEXA enzyme testing is technically complex, requires laboratory expertise and may yield indeterminate, false negative and false positive results. Medications such as the combined oral contraceptive pill may also affect HEXA enzyme concentration.⁴ Since the introduction of DNA-based genetic testing programs Australian pathology laboratories ceased offering HEXA enzyme testing. All testing is now performed exclusively by genetic or genomic DNA-based technologies.

- 39. 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

- 40. 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):**

Prior to genetic testing, most individuals would only have been identified *after* the birth of an affected child. The only condition that is easily screened for in the absence of genetic testing would have been HEXA enzyme testing in order to identify carriers of Tay Sachs disease; however, as mentioned above, HEXA enzyme testing has ceased in Australia with the advent of DNA-based genetic testing.

Couples who are both found to be carriers of the same autosomal recessive disorder, have a one in four (25%) chance of having an affected child (for each pregnancy). Where pre-conception testing has been performed, a full range of options are available. Once informed about the risks of the condition, options for couples to consider would include: prenatal diagnosis, pre-implantation genetic diagnosis, adoption, and in vitro fertilisation (IVF) using a donor egg, sperm, or embryo. Couples may also choose not to have children, or use the information to assist in preparing for the possibility of a child with a genetic condition.⁶⁸

Where only antenatal testing during pregnancy has been performed, some of the potential options will have been ruled out, as the couple is already pregnant by the time of testing. If a couple are found to both be carriers of a condition during pregnancy, remaining options include diagnostic testing of the fetus via amniocentesis or chorionic villus sampling (CVS) with a further option to terminate the pregnancy if a genetic disease is confirmed in the fetus.

In the absence of genetic testing, couples who are both carriers of the same disorder, have a one in four (25%) chance (for each pregnancy) of having an affected child, and this risk repeats itself for each subsequent pregnancy. Diagnosis of an affected child may be immediate or may only occur later in the child's life: for example, it may be made in the first 6-12 months of life or in early childhood by a paediatrician, depending on the disorder. Where the diagnosis is only made later (especially after 3-6 months of age) there is the possibility that the couple might commence a subsequent pregnancy before they knew that their earlier child was affected by the disorder, which means that they then have a 25% risk of having *two* children affected by a serious disorder. As described in Table 1, for many of the disorders, supportive care is the only treatment option available for an affected child, who may be affected by severe disabilities, either requiring life-long care, or else resulting in death.

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

- In addition to (i.e. it is an add-on service)
 Instead of (i.e. it is a replacement or alternative)

(b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:

Comparator is no genetic testing. This application is to fund a service that is currently not provided by an alternative.

42. 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):

The clinical management would be altered by the introduction of this test by offering the test to individuals and couples either prior to conception (preferred) or in early pregnancy. The offer would be made by the individual/couple's GP or obstetrician, or through a formally-structured Community Genetics program under the supervision of a genetics health professional or a medical health professional with expertise in genetics. Couples identified as being at high risk of having an affected child would be referred to a clinical geneticist, maternal-fetal medicine service, a specialist obstetrician, or to a genetics health professional under appropriate medical supervision.

It is likely that the introduction of this service prior to conception would increase the use of services such as IVF and pre-implantation genetic diagnosis, as described in Question 40. However, the introduction of carrier testing for couples who are already pregnant may not impact significantly on the usage of IVF services, and instead would increase services such as CVS or amniocentesis and termination; only after the pregnancy would the resource impact revert to being similar to those utilising preconception testing. For these reasons, although both routes need to be available, preconception testing is preferred to antenatal testing, as the range of options available to the individual and the couple are wider.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

43. 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):

Screening programs should satisfy the World Health Organization's accepted criteria for screening programs. Opportunistic carrier testing for conditions prevalent in the exemplar (AJ) population satisfies many of these conditions. However, criteria such as "there should be an accepted treatment for patients with recognised disease" and "there should be a recognisable latent or early symptomatic stage" are not directly applicable to carrier testing. Unlike cancer screening programs, carrier testing is directed at people who are not likely to develop the disease themselves, but rather to those who are at risk of having children who will be affected by a serious inherited genetic disorder. The goal of carrier testing is to provide information to individuals and couples about the risk of transmitting a clinically significant genetic condition to their offspring with associated morbidity and/or mortality. Providing this information enables informed reproductive choices to be made, in order that pregnancy with a child with a serious incurable childhood-onset disorder may be minimised or avoided. Ultimately, the benefits of screening should outweigh any potential harms.^{62, 69} The goal of reproductive carrier testing is to give couples the opportunity to avoid the birth of a severely affected child. This is in contrast to newborn screening programs which seek to identify affected child at an early to expedite interventions that could modify the course of disease.

As stated in Question 42, the introduction of carrier testing for severe monogenic disorders might result in an increase in the rate of pre-implantation genetic diagnosis, prenatal diagnosis and in vitro fertilisation, with a concomitant reduction in the number of severely clinically affected children born over time. The Australian evidence for preconception testing derives predominantly from the evaluation of school based TSD testing programs in the AJ population. Long term follow-up found that the testing program was acceptable to students and parents with high levels of participation (>98%) and low levels of anxiety associated with diagnosis of TSD carrier status. Over a 17 year evaluation period, no Australian screening program participant has had a TSD affected child, representing 100% disease prevention and

100% health outcomes effectiveness in this cohort.^{4, 24, 26, 70} The reduced incidence of these conditions over time will result in a subsequent reduction in the utilisation of health services associated with the care of affected children including reduced:

- visits to GPs;
- visits to allied health practitioners;
- outpatient visits;
- hospital admissions;
- expenditure on PBS listed drugs; and
- Disability-associated services and support.

There is, of course, an ethical dimension to genetic carrier testing used to enable reproductive choices and family planning based on the risk of having a child with a serious inherited disorder. Any assessment of a carrier testing program should address the four principles of biomedical ethics: autonomy, non-maleficence, beneficence and justice. Providing an informed choice and counselling addresses issues around autonomy. The principles of non-maleficence and beneficence demand that the risks of harm should be outweighed by the probable benefits before a genetic test is accepted into general practice. The RANZCOG recommends that all women who are considering a pregnancy, or who are in early pregnancy, should be offered carrier testing for *common* disorders. The offer must not carry any obligation to have the test, or act in a given way in response to the information provided by the test.⁷ These are not novel considerations and have been widely discussed in the international literature and recognised by clinicians providing antenatal screening for chromosome disorders. Genetic carrier testing should be offered in conjunction with appropriate information to allow informed choice. Formal genetic counselling should also be available for partners who are identified as carriers of the same autosomal recessive condition.¹⁰ Online education and counselling services offered via newer telehealth technologies now enable these activities to be provided effectively at scale.

44. Please advise if the overall clinical claim is for:

- Superiority
 Non-inferiority

45. 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:

Physical and/or psychological harms from genetic testing or no genetic testing, adverse events from testing, Psychological effects of false positives or false negatives

For those women already pregnant – safety issues associated with invasive diagnostic testing (amniocentesis or chorionic villus sampling) following a positive screening test

Clinical Effectiveness Outcomes:

Assessment of diagnostic/test accuracy: sensitivity, specificity, number of false positives, number of false negatives, number of inconclusive results

Clinical utility: the impact on increased decision options for future reproduction, the change in number of children born with severely disabling inheritable diseases, for women already pregnant – the termination of pregnancy rate due to the detection of a variant

Cost-effectiveness outcomes:

Cost of carrier testing versus long-term health system/societal savings from reduction in the number of children affected

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

46. Estimate the prevalence and/or incidence of the proposed population:

The following is based on the Ashkenazi Jewish exemplar population.

In 2016, Australia's total Jewish population was estimated to be 117,903, with the majority identifying as Ashkenazi Jews, whose ancestry originated from Central and Eastern Europe. The overwhelming majority of the Australian AJ population live in the urban centres of Melbourne and Sydney (83.9%). In the 5-years between 2011 and 2016, the recorded Jewish population in Australia only grew by one per cent, a sharp decrease in growth compared to the 5-years between 2006 and 2011, where six per cent growth was recorded.⁷¹ This might be due to changes in population growth, or to changes in self-identification as AJ, or to loss of knowledge of AJ ancestry.

Overall, more than 80 per cent of Australian AJ individuals in the reproductive age group have not had, or no longer have, the opportunity to participate in existing Jewish high school-based screening programs. This is because the school-based program is now only offered in NSW (the Victorian program having ceased operation due to financial constraints), and in NSW, it is now only offered in the six schools of highest numbers of AJ student enrolments. In Australian Jewish communities living outside of Melbourne and Sydney, where no high school-based screening programs were conducted, the proportion of unscreened AJ individuals of reproductive age is likely to be even higher.⁴

See Table 1 for the estimated carrier frequencies and clinical features of the conditions recommended, or likely to be included on the AJ carrier screening gene panel.

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

Once per lifetime testing.

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

Once per lifetime testing.

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

Using the Australian AJ population as the exemplar population.

The 2016 census of the Jewish population in Australia reported that 11 per cent of the population were aged 10-19 years, 10 per cent 20-29 years, 12 per cent were aged 30-39 years and 13 per cent aged 40-49 years. Based on the total 2016 Jewish population of 117,903, this would equate to a total of 54,234 individuals of reproductive age, who may be eligible for carrier screening in the first year.⁷¹ However, this number is likely to be an *overestimate* as it would include a number of individuals who have already participated in the earlier school-based screening programs, or paid out-of-pocket for screening.

If only couples planning a pregnancy were tested, the number of individuals likely to take up the offer of carrier testing would be small and could be estimated by looking at the number of births in the AJ population. In 2016, the total number of births in the Jewish community was 1,224.⁷¹ Therefore 1,224 (mothers) would represent the lower limit in the first year, with 2,448 representing the upper limit (both mothers and fathers being tested, although it is unlikely that all males would require testing).

Of note is that the RCPA conducted a survey, on behalf of the Commonwealth Department of Health, of all Australian laboratories (n=87) known to offer genetic/ genomic tests that yielded results with medical utility during the 2016/17 financial year. During this time, 626 tests using an Ashkenazi Jewish disease genes panel were conducted. As these tests would have been conducted largely in the private sector on a user pays basis, this figure would under represent the true demand for testing in any given year.⁷²

A more detailed estimate is described in [Appendix 1](#).

50. 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:

It is likely that there would be significant uptake of testing in the first year as there is currently a large "prevalent" untested population who may not be able to afford or access testing on a user pays basis. Testing levels are likely to be slightly less in the second and third years of implementation due to the initial surge of testing of the "prevalent" population in year 1 of funding.

A more detailed estimate is described in [Appendix 1](#).

PART 8 – COST INFORMATION

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

Costings will vary from laboratory to laboratory.

Note: Reagent costs shown below are for CFTR, SMN1 and FXS only. As this does not meet the 10% threshold, reagent costs would need to be slightly higher than shown here, to include the additional variants relevant to the individual's particular ancestral background. For the AJ exemplar subpopulation, in the private sector, panel testing is \$510 (9 gene AJ panel, subsidised philanthropically and doesn't include *SMN1* or *FXS*). Approximate costs include:

Equipment and resources	Per test
Kit, probes, reagents, ancillary reagents	\$360.00
Labour medical (consultant pathologist)	\$80.00
Labour scientific	\$60.00
Labour on costs	\$15.00
Depreciation, overheads	\$25.00
Admin, IT	\$10.00
Total	\$550.00

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

Depending on laboratory workflow and capability, test turn-around times (TAT) would typically be in the range 1-8 weeks. For antenatal testing, TAT's should strictly adhere to 1-4 weeks to ensure adequate time to explore options for reproductive partners who are at risk of their offspring developing a recessive condition. In a preconception setting, results of testing are not held to the same time pressures as antenatal reporting and can be carried out over several weeks or even months.

Key steps affecting turn-around times are:

- Specimen receipt and DNA extraction (1-3 days)
- Test preparation e.g. library generation for panel (2-3 days)
- Test process and review (1-10 days)
- Test bioinformatics (1-10 days)
- Interpretation and Reporting (1-10 days)

53. 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.

Item AAAA	Category 6 (Pathology Services) – Group P7 Genetics
<p>Testing of asymptomatic individuals of reproductive age for the presence of a pathogenic or likely pathogenic variant(s) in order to ascertain their carrier status, in a panel of genes that must include variants in the cystic fibrosis transmembrane conductance regulator (<i>CFTR</i>), survival motor neuron 1 (<i>SMN1</i>), fragile X mental retardation 1 (<i>FMR1</i>) genes in addition to <i>at least</i> other genes relevant to the ancestry of that individual, requested by or on behalf of a medical practitioner who manages the treatment of the patient.</p> <p>Individuals must have a >10% personal risk of being a genetic carrier of serious clinical disorders associated with pathogenic or likely pathogenic variants of genes in the testing panel.</p> <p>One test per lifetime.</p> <p>Fee: \$600</p>	
Item BBBB	Category 6 (Pathology Services) – Group P7 Genetics

Testing of a pregnant female for the presence of a pathogenic or likely pathogenic variant(s) in order to ascertain their carrier status, in a panel of genes that must include variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*), survival motor neuron 1 (*SMN1*), fragile X mental retardation 1 (*FMR1*) genes in addition to *at least 3* other genes relevant to the ancestry of that individual, requested by or on behalf of a specialist or medical practitioner who manages the treatment of the patient.

Individuals must have a >10% personal risk of being a genetic carrier of serious clinical disorders associated with pathogenic or likely pathogenic variants of genes in the testing panel.

One test per lifetime.

Fee: \$600

Item CCCC

Category 6 (Pathology Services) – Group P7 Genetics

Concurrent prenatal genetic testing, regardless of pre-test risk, of the male reproductive partner of a pregnant female who has a >10% personal risk of being a heterozygous genetic carrier of serious clinical disorders associated with pathogenic or likely pathogenic variants of genes as described in in BBBB, for the purpose of determining the couple's reproductive risk of this condition. Requested by or on behalf of a specialist or consultant physician who manages the treatment of the patient.

One test per lifetime.

Fee: \$600

Note 1: For individuals of Ashkenazi Jewish ancestry, the panel of genes *must also* include *HEXA* and should also include at least the following genes: *IKBKAP*, *SMPD1*, *ASPA*, *FANCC*, *RECQL3* and *MCOLN1*. Additional genes *may also* be included in the panel using standardised pathology lists of genes ethnic risk.

Note 2: For individuals of Asian, African or Mediterranean ancestry, the panel of genes must at least include genes relevant to the individual's risk for Thalassaemia and haemoglobinopathy. Additional genes may be included in the panel, using standardised pathology lists of genes ethnic risk.

Item DDDD

Category 6 (Pathology Services) – Group P7 Genetics

Genetic testing in a first-degree biological relative of a patient found to be a genetic carrier of an autosomal recessive pathogenic or likely pathogenic variant(s) identified by items AAAA or BBBB, requested by or on behalf of a specialist or consultant physician who manages the treatment of the patient.

One test per lifetime.

Fee: \$100

Item EEEE

Category 6 (Pathology Services) – Group P7 Genetics

Reanalysis of genetic test results arising from testing previously performed under Items AAAA, BBBB or CCCC, for the purpose of identifying previously unreported pathogenic or likely pathogenic variants in any genes included in the gene panel to determine genetic carrier status, where the pathogenicity of these variants might not have been known at the time of the previous analysis.

One test per five years.

Fee: \$ 100

Item FFFF

Interpretation of genetic carrier test results previously performed on two individuals under items AAAA, DDDD or EEEE, for the purpose of determining the couple's reproductive risk of this condition. Requested by, or on behalf of, a medical practitioner.

One test per reproductive couple per five years.

Fee: \$ 100

Appendix 1

1. Hypothetical gene panels to meet 10% threshold risk, demonstrating that an “AJ panel” will differ to an Asian ancestry panel. Provides reassurance that not everyone would qualify with the AJ panel, with each subpopulation requiring its own panel.
2. Simulation of anticipated uptake of preconception, antenatal or both.

Demonstration of how gene panels would work

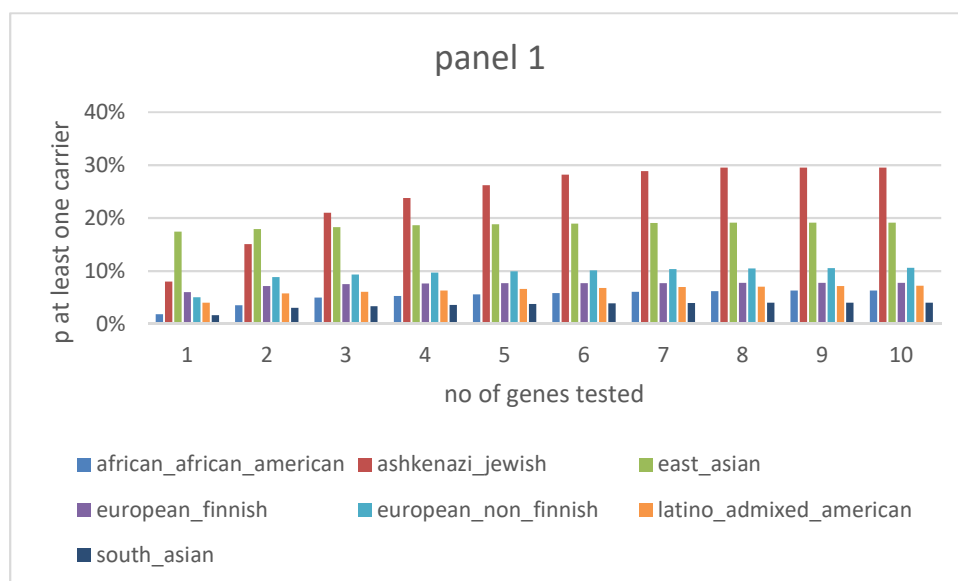
To demonstrate how it is possible to estimate the *a priori* threshold risk of an individual in the AJ subpopulation, as well as to demonstrate that this *a priori* risk will vary with subpopulation so that the chosen gene panel cannot be indiscriminately applied to those of other subpopulations, we prepared the following.

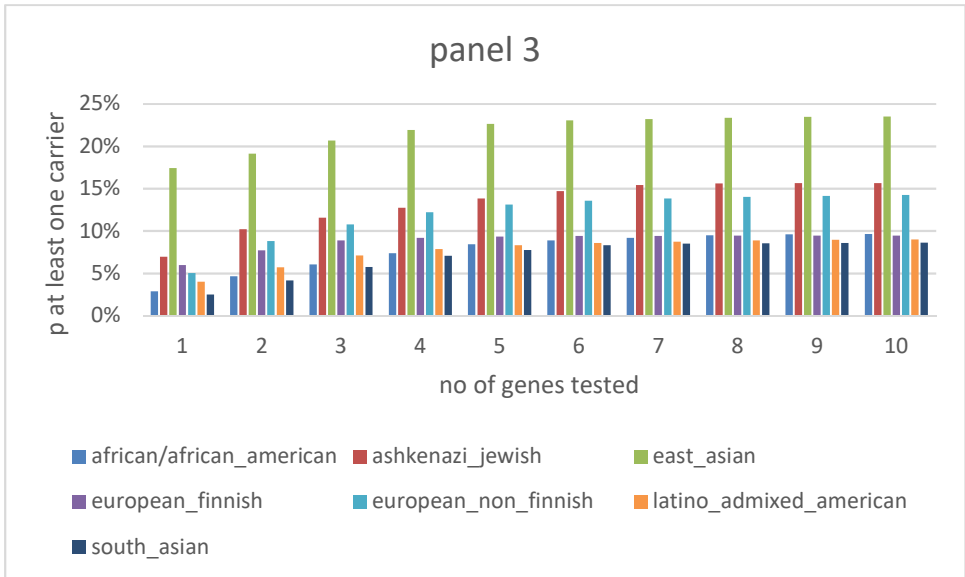
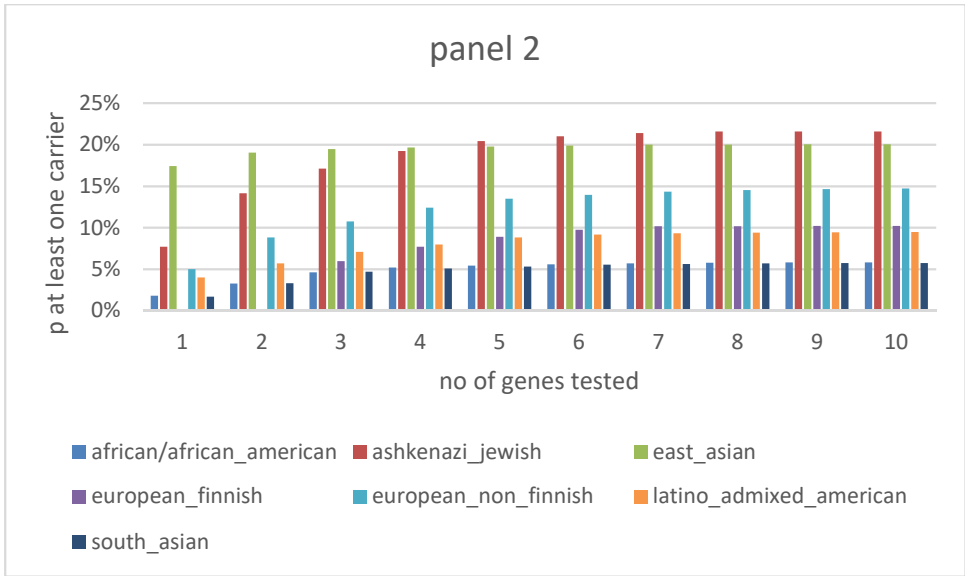
Gene variant frequencies relevant to genetic carrier screening were extracted from standard publicly available datasets such as the genome aggregation database (gnomAD). The gnomAD v2.1 data set contains data from 125,748 exomes and 15,708 whole genomes, gathered from 7 populations (African/African-American, Latino/Admixed American, Ashkenazi Jewish, East Asian, European (Finnish), European (non-Finnish) and South Asian). Data from gnomAD⁷³ can be retrieved programmatically using hail, downloaded in VCF format, or interactively using the gnomAD browser (<https://gnomad.broadinstitute.org>). Data is bioinformatically filtered these so that only ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>) pathogenic or likely pathogenic variants remain.

Three hypothetical gene panels (each consisting of 10 different genes in this example) were selected, based on genes with pathogenic variants that are known to be at elevated frequency in different population groups, as demonstrated by Lazarin et al (2013)⁵ and Nappo et al (2020).⁷⁴ These example panels were selected to demonstrate how three population groups in Australia (Asian, European – non-AJ and European – AJ) have different reproductive genetic risks, based on the genes in each panel. Each graph shows the probability of being a carrier of at least one disorder of clinical significance (with the relevant threshold level being 10%).

Note:

1. Different genes will be relevant to different sub-populations, so that the requirement to meet an *a priori* risk of 10% means that the test can be targeted to those for whom it is relevant, so that it would not be used indiscriminately.
2. It is feasible to select such a panel of genes that will be relevant to particular sub-population groups within the broader Australian population. This means that there will be no barrier for suitably accredited laboratories to be able to offer this test.





Simulation of anticipated annual uptake based on the Ashkenazi Jewish exemplar population

Simulation of anticipated annual uptake of the proposed medical service over 30 years, showing the different profiles for preconception testing (only), antenatal testing (only), or both preconception and antenatal testing routes being available.⁷⁵

Overall Assumptions: (Data taken from Question 49)

AJ population: 117,903

AJ subpopulation of reproductive age: 54,234

Assume annual birth rate is 1/40 of this = (approx.) 1,300 births p.a.

Assume second child born within 2-4 years of first child (no need to test reproductive partner again); assume average family size 2 children.

AJ population aged 10-19: 11% of total =12,969, or 1,297 per year within this cohort (round to 1,300). Assume preconception testing from age 16-18 (as at present)

Model 1: Antenatal testing only (no preconception testing)

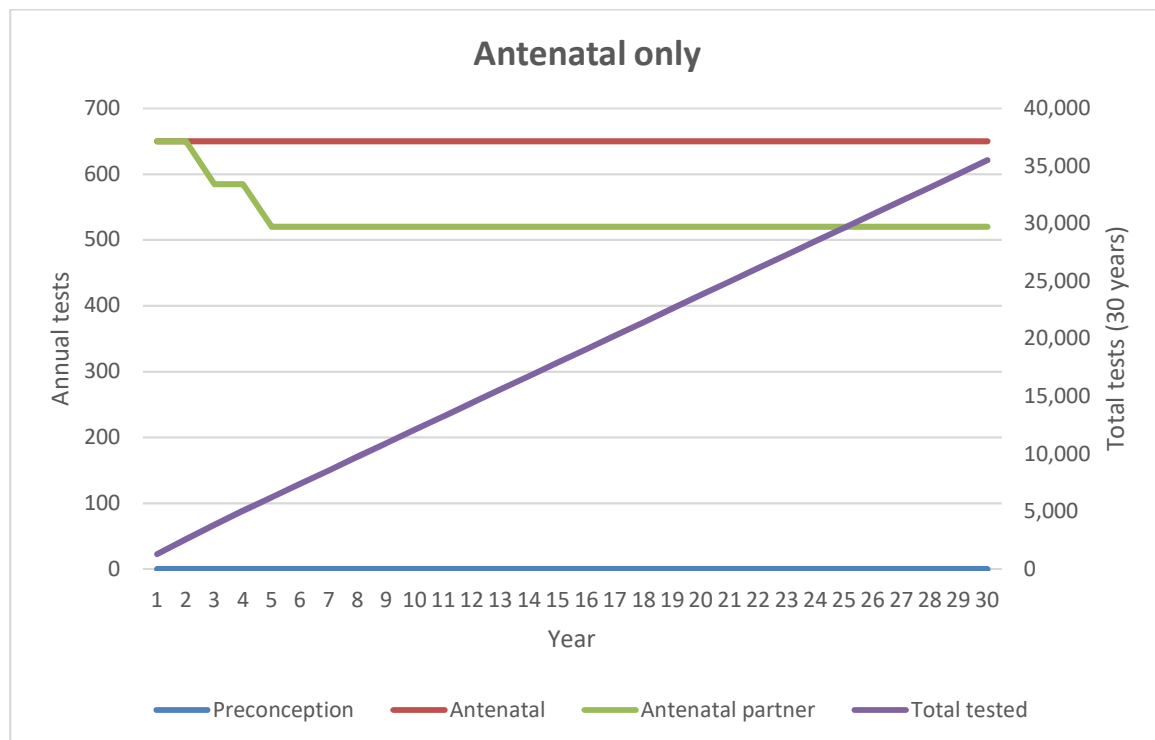
Assumptions: 1,300 births p.a. 50% (650 women) tested each year, plus (initially) 650 male reproductive partners need testing. After year 2, only 90% of male partners require testing (as those couples have a 2nd child); by year 4, only 80% of male partners require testing. After 4 years, assumed childbearing is (on average) complete in a family of 2 children.

Not yet included in modelling: We have assumed 100% uptake. Real-world uptake is likely to be lower, perhaps in the range 40-70%.

30-year test usage: 35,490 services, plus downstream costs

Downstream costs: Every couple will need genetic counselling. ~6-10% will require CVS/Amniocentesis 1st pregnancy (1); and 5-6% will require CVS/Amnio in subsequent pregnancies (1); ~ 1.5-3% will elect to terminate the pregnancy.

Outcome effectiveness: Not yet known. Short-term outcome effectiveness currently being evaluated as part of Mackenzie’s Mission research study.



Model 2: Preconception testing only (no antenatal testing)

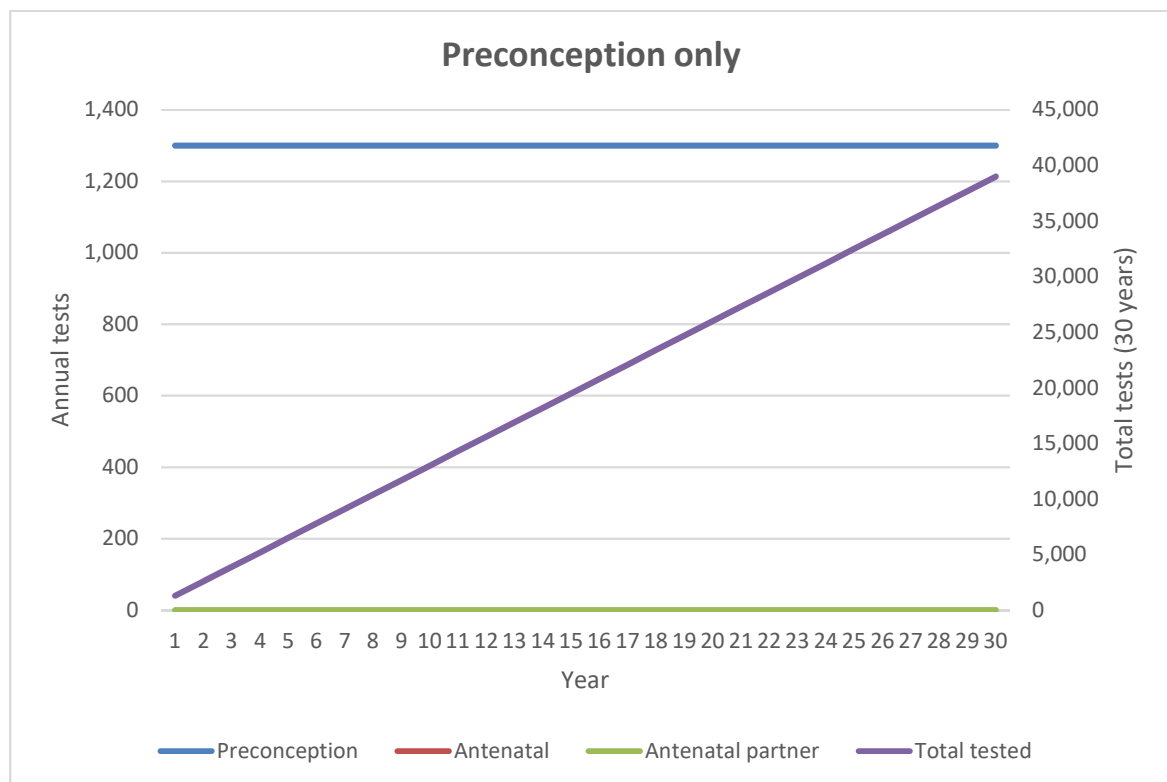
Assumptions: 1,300 young adults tested in annually (entire cohort).

Not yet included in modelling: We have assumed 100% uptake. Real-world uptake is known to be lower, in the range 70-90%.

30-year test usage: 39,000 services, plus downstream costs.

Downstream costs: Every couple will need a GP consultation at some point to review their joint results. Approx 5-6% will go on to require genetic counselling (1). A proportion of these may seek IVF or may proceed to pregnancy with CVS/Amnio.

Outcome effectiveness: Long-term 100% effective based on 15-year health outcome follow-up for Tay-Sachs disease testing (Australian data; consistent with results from overseas studies)²⁴



Model 3: Both preconception and antenatal testing

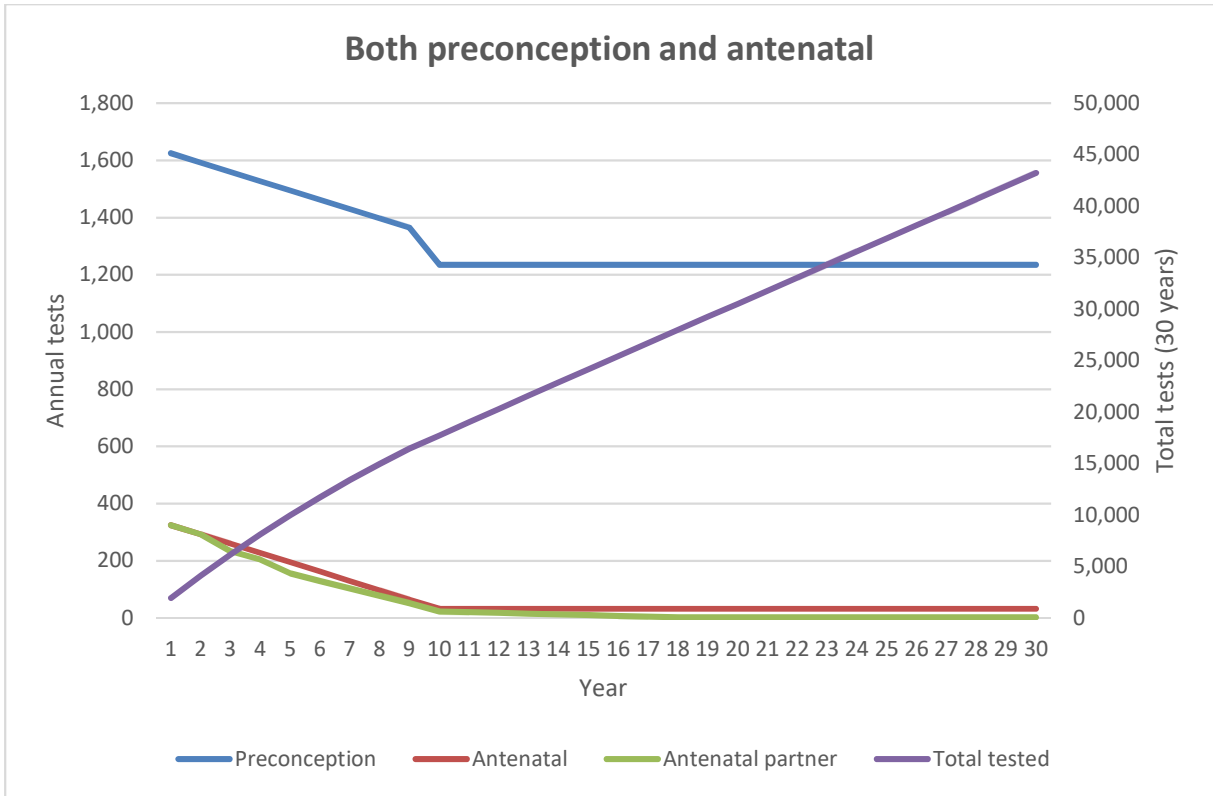
Assumptions: 1,300 young adults tested annually (entire cohort). For the first 10 years, older adults who did not have previous access to preconception testing: 50% access preconception; and 50% access antenatal in year 1, decreasing 10% per annum until year 10. From year 10, all testing is preconception, except for 10% who are assumed to access antenatal because they might have missed preconception opportunities. Reproductive partner testing assumed to be initially as for of Model 1 but decline over time as male partners progressively have been tested preconceptionally; 10% of 10% residual remain.

Not yet included in modelling: As two routes of access are provided, real-world uptake is likely to be higher than either Model 1 or Model 2. We have assumed 100% uptake.

30-year test usage: 43,327 services, plus downstream costs.

Downstream costs: Approximating that for Model 2 (preconception), but with a proportion of costs as for Model 1 (antenatal) in initial years, then decreasing for 1st 10 years.

Outcome effectiveness: Likely to be at least as good as preconception (100%), so we would anticipate maximum utility and effectiveness with this model.



References

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