



Australian Government

Department of Health

Application Form

**Carrier screening for cystic fibrosis, spinal muscular atrophy and
fragile X syndrome**

Requests for Public Funding)

(Version 2.4)

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.

Phone: +61 2 6289 7550

Fax: +61 2 6289 5540

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: 52 000 173 231

Business trading name: The Royal College of Pathologists of Australasia

In partnership with: Australian Pathology and Public Pathology Australia

Primary contact name: <Redacted>

Primary contact numbers

Business: <Redacted>

Mobile: <Redacted>

Email: <Redacted>

Alternative contact name: <Redacted>

Alternative contact numbers

Business:

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

Reproductive carrier screening for fragile X syndrome, spinal muscular atrophy and cystic fibrosis.

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)

RANZCOG recommend carrier screening of women and their partners, preferably prior to pregnancy, for specific mutations in genes that result in common genetic conditions including cystic fibrosis (CF), spinal muscular atrophy (SMA) and fragile X syndrome (FXS).¹ Many children affected by these conditions are born to families with no history of disease due to the rare nature of the conditions and patterns of inheritance.

CF is one of the most common autosomal recessive disorders, characterised by the build-up of thick, sticky mucus that results in progressive damage to the respiratory system and chronic digestive system problems.² Although the average life expectancy has increased with improved treatment regimens, there is no cure for CF.

SMA belongs to the family of motor neuron disorders, with the most common form being an autosomal recessive (95% of cases) caused by a homozygous deletion or mutation of the survival motor neuron 1 (*SMN1*) gene. SMA remains one of the most common genetic causes of infant mortality.^{3, 4}

FXS is inherited as a X-linked dominant disorder with variable penetrance and expression that causes a range of developmental problems including learning disabilities and cognitive impairment, with males usually more severely affected than females.⁵ It is the most common inherited cause of intellectual disability worldwide.

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)

Carrier screening of asymptomatic couples with no family history of CF, SMA or FXS, and who are planning or in the early stages of pregnancy, for heterozygous mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*), survival motor neuron 1 (*SMN1*), and fragile X mental retardation 1 (*FMR1*), genes. That is, to identify couples at approximately 25% risk of having a child with CF, SMA or fragile X syndrome in order to provide them with reproductive options that may prevent the birth of an affected child.

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):

(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:

The applicant recognises that the MBS need not be the only mechanism for funding this screening test, but submits that the MBS may be the best vehicle.

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
- vi. A service that tests for heritable mutations in clinically affected individuals to make a genetic diagnosis and thus estimate their variation in (predisposition for) future risk of further disease and, when also appropriate, cascade testing of family members of those individuals who test positive for one or more relevant mutations, to make a genetic diagnosis and thus estimate each family member's variation in (predisposition for) future risk of developing the clinical disease

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?

- Yes
- No

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

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

- Yes (please provide PBAC submission item number below)
 No

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

Trade name:

Generic name:

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

- Yes
 No

N/A

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

Billing code(s):

Trade name of prostheses:

Clinical name of prostheses:

Other device components delivered as part of the service:

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

- Yes
 No

(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):

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

Single use consumables: Laboratory consumables used to conduct quantitative polymerase chain reaction, such as primers, reaction tubes and laboratory pipette tips.

Multi-use consumables: Nil

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

ARTG listing, registration or inclusion number:

TGA approved indication(s), if applicable:

TGA approved purpose(s), if applicable:

- 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

Date of submission to TGA:

Estimated date by which TGA approval can be expected:

TGA Application ID:

TGA approved indication(s), if applicable:

TGA approved purpose(s), if applicable:

- 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

Estimated date of submission to TGA:
Proposed indication(s), if applicable:
Proposed purpose(s), if applicable:

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 (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication ***
Cystic fibrosis (CF)					
1.	Population screening Australia	Population-based carrier screening for cystic fibrosis in Victoria: The first three years experience ⁶	CF carrier screening was offered to women and couples planning a pregnancy, or in early pregnancy. 12 CFTR gene mutations were tested. A total of 3,200 individuals were screened (3,000 females). 106 carriers were identified. All carrier partners were screened, and 9 carrier couples identified (total carriers 115). Of the nine carrier couples, six were pregnant at the time of screening. Two fetuses were affected, three were carriers and one was not a carrier. Termination of pregnancy was undertaken for the affected fetuses.	https://obgyn.onlinelibrary.wiley.com/doi/pdf/10.1111/j.1479-828X.2009.01045.x	2009
2.	Population screening Italy	A 10-year large-scale cystic fibrosis carrier screening in the Italian population ⁷	A semi-automated reverse-dot blot assay was used to identify 47 of the most common CFTR gene mutations followed by DGGE/dHPLC analysis. 57,999 individuals with no prior family history of CF were screened Of these, 25,104 were couples and 7,791 singles. CFTR mutations were found in 1,879 carriers (frequency 1/31), with ΔF508 being the most common (42.6%).	https://tinyurl.com/y8vowbkt	2010

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication ***
3.	Population screening USA	Cystic fibrosis testing 8 years on: Lessons learned from carrier screening and sequencing analysis ⁸	Review of population-based CF carrier screening database. We queried the database containing approximately 3 million CF screening tests, 1,300 prenatal diagnostic tests, and 2,400 CF sequencing analyses. An overall CF carrier frequency of 1:37.6 individuals in the pan-ethnic tested population, with a detection rate of 77%, giving an estimated US pan-ethnic carrier frequency of 1:29. In total, 119 affected fetuses were identified by prenatal diagnoses, a ratio of 1 affected fetus per 25,000 carrier screens.	https://www.nature.com/articles/gim9201129.pdf	2011
4.	Population screening - comparative Italy	Cystic fibrosis carrier screening effects on birth prevalence and newborn screening ⁹	CF carrier screening was performed in eastern region (ER) and not in the western region (WR). In 10-years, the total number of screened neonates was 1,112,620 (685,575 in the ER; 427,045 in the WR). A total of 259 newborns with CF were detected through NBS (145 in the ER, 114 in the WR). In the ER, 150 carrier couples were found. Mean annual percentage of birth prevalence decrease was 9% per 10,000 (P = 0.002) and was greater in the ER (15%, P = 0.0008; WR 1%, P = ns). The WR estimated birth prevalence was 1/3,589 in 1993 and 1/3,870 in 2013; in the ER it was 1/2,730 in 1993 and 1/14,200 in 2013. The ER birth prevalence correlated inversely with the number of carrier couples (P = 0.0032).	http://www.nature.com.proxy.library.adelaide.edu.au/articles/gim201568	2016

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication ***
5.	Systematic review	Population-based carrier screening for cystic fibrosis: a systematic review of 23 years of research ¹⁰	A total of 85 references met the inclusion criteria for data extraction. 31 (37%) were from the UK, 21 (25%) were from the US, and 8 (9%) were from Australia. 64 (75%) articles involved offering CF screening, with 34 (40%) focusing on prenatal screening and 26 (31%) on preconception screening. The remaining 25 (29%) offered CF screening to the general population regardless of pregnancy status.	https://www.nature.com/articles/gim2013125.pdf	2014
6.	Cost-effectiveness Australia	Cost-effectiveness of carrier screening for cystic fibrosis in Australia ¹¹	Screening reduced the annual incidence of CF births from 34 to 14/100,000 births (an aggregate number of CF births of 100.9 and 41.9 respectively). In initial pregnancies, costs in the screening arm (A\$16.6 million/100,000 births) exceed those in the non-screening arm (A\$13.4 million/100,000 births). The incremental cost per CF birth in initial pregnancies is therefore approximately A\$150,000. However, this was reversed for subsequent pregnancies, in that the pre-collected information reduces the incidence of CF in subsequent pregnancies at low additional costs. When aggregated, the results suggest screening is likely to be cost-saving.	https://www.cysticfibrosisjournal.com/article/S1569-1993(12)00016-1/pdf	2012

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication ***
7.	Economic assessment Australia	Understanding the Costs of Care for Cystic Fibrosis: An Analysis by Age and Health State ¹²	Using data from 3 waves of the Australian Cystic Fibrosis Australia Data Registry, the annual costs of CF care by age and health state were estimated. The mean annual health care cost for treating CF is US \$15,571. Costs for patients with mild, moderate, and severe disease are US \$10,151, US \$25,647, and US \$33,691, respectively. Lifetime health care costs are approximately US \$306,332 (3.5% discount rate). The majority of costs are accounted for by hospital inpatients (58%), followed by pharmaceuticals (29%), medical services (10%), complications (2%), and diagnostic tests (1%).	https://ac.els-cdn.com/S1098301512042684/1-s2.0-S1098301512042684-main.pdf?_tid=2c8f7357-d3ee-4e77-93b6-e09296a49db3&acdnat=1539566102_f648671ad07ca8f7428ac27098253312	2013
Spinal muscular atrophy (SMA)					
8.	Case series USA	Newborn and Carrier Screening for Spinal Muscular Atrophy ¹³	Women or couples, referred to 2 perinatal centres in Ohio for genetic counselling and consultation with a maternal fetal medicine specialist, were offered SMA carrier screening. Carrier testing was performed on 500 pre-conceptual or pregnant women. DNA testing detected 16 carriers for a carrier frequency of approximately 1 in 31. Among the 16 carriers, 14 had their partners tested and all partners tested negative for carrier status.	https://onlinelibrary.wiley.com/doi/pdf/10.1002/ajmg.a.33474	2010

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication ***
9.	Population screening Taiwan	Carrier Screening for Spinal Muscular Atrophy (SMA) in 107,611 Pregnant Women during the Period 2005–2009: A Prospective Population-Based Cohort Study ¹⁴	Prospective population-based cohort study of 107,611 pregnant women from 25 counties in Taiwan. A 3-stage screening program was used: (1) pregnant women tested for SMA heterozygosity; (2) if the mother was determined to be heterozygous for SMA (carrier status), the paternal partner was tested; (3) if both partners were SMA carriers, prenatal diagnostic testing was performed. A total of 2,262 SMA carriers with one copy of the SMN1 gene were identified among the 107,611 screened pregnant women (carrier rate of 1/48, 2.10%). In addition, 2,038 spouses were determined to be SMA carriers. Among those individuals, 47 couples were determined to be at high risk for having offspring with SMA. Prenatal diagnostic testing was performed in 43 pregnant women and SMA was diagnosed in 12 fetuses.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3045421/pdf/pone.0017067.pdf	2011
10.	Population screening USA	Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72 400 specimens ¹⁵	Clinical laboratory data were reviewed for 72,453 individuals and 121 fetal samples referred for SMN1 copy number analysis over a 12-month time period. Approximately 95% of the 72,453 individuals referred for carrier testing had no family history of SMA. The calculated <i>a priori</i> carrier frequency of SMA is 1/54 with a detection rate of 91.2%, and the pan-ethnic disease incidence is calculated to be 1/11 000. Carrier frequency and detection rates provided for 6 major ethnic groups in the US range from 1/47 and 94.8% in the Caucasian population to 1/72 and 70.5% in the African American population, respectively.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3234503/pdf/ejhg2011134a.pdf	2012

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication ***
11	Meta-analysis Canada	SMA carrier testing: a meta-analysis of differences in test performance by ethnic group ¹⁶	Systematic review and meta-analysis of SMA genotype frequency, carrier frequency, and carrier test performance in different ethnic groups determined from 169,000 individuals in 14 published studies (5 studies conducted in North America, 4 in Europe, 2 in Asia, 2 in the Middle East, and one in Australia). Pooled estimates were calculated for each ethnic group using a random effects meta-analysis. The detection rate of SMA screening in the non-Black population was 87-95%; however, detection rates fell to 71% among the Black population. The negative predictive value of SMA testing ranged from 99.2% to 99.9%.	https://obgyn.onlinelibrary.wiley.com/doi/pdf/10.1002/pd.4459	2014
12.	Cohort USA	The next generation of population-based spinal muscular atrophy carrier screening: comprehensive pan-ethnic SMN1 copy-number and sequence variant analysis by massively parallel sequencing ¹⁷	A novel method called paralogous gene copy number analysis by ratio and sum for SMA carrier testing based on short-read NGS data validated in a clinical setting using 6,738 pan-ethnic samples and compared to results generated by MLPA or qPCR. The sensitivity of the test to detect SMA carriers with one copy of SMN1 was 100% and specificity was 99.6%. This comprehensive approach yielded SMA carrier detection rates of 90.3–95.0% in 5 ethnic groups studied.	https://www.nature.com/articles/gim2016215.pdf	2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication ***
13	Population screening Israel	Large-scale population screening for spinal muscular atrophy: Clinical implications ¹⁸	A total of 6,394 individuals without family history of SMA underwent genetic screening by multiplex ligation-dependent probe amplification, designed to detect SMN1 exon 7 and exon 8 copy number. Results: One hundred fifty-nine individuals carried an SMN1 heterozygous exon 7 deletion, yielding a carrier frequency of 1:40. It is estimated that the SMA carrier detection rate is about 90%.	https://www.nature.com/articles/gim9201121.pdf	2011
Fragile X					
14.	Case series Hong Kong	Identification of fragile X pre-mutation carriers in the Chinese obstetric population using a robust FMR1 polymerase chain reaction assay: implications for screening and prenatal diagnosis ¹⁹	Cross-sectional survey in prospectively recruited pregnant Hong Kong women without a family history of fragile X syndrome. A specific FMR1 polymerase chain reaction assay was performed on peripheral blood to determine the CGG repeat number of the FMR1 gene. In 2,650 Chinese pregnant women, two individuals with pre-mutation alleles (0.08%, 1:1325) and one asymptomatic woman with full mutation (0.04%, 1:2650) alleles were identified. The overall prevalence of pre-mutation and full mutation alleles was 0.11% (1:883). Furthermore, 30 (1.1%) individuals with intermediate alleles were detected.	http://www.hkmj.org/abstracts/v23n2/110.htm	2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication ***
15.	Population screening USA	FMR1 premutation carrier frequency in patients undergoing routine population-based carrier screening: Insights into the prevalence of fragile X syndrome, fragile X-associated tremor/ataxia syndrome, and fragile X-associated primary ovarian insufficiency in the United States ²⁰	A previously validated triplet-primed PCR was used to detect pre-mutation and full mutation alleles in an unselected series of 11,759 consecutive CF carrier screening samples and 2,011 samples submitted for screening for genetic diseases prevalent among the Ashkenazi Jewish population. Pre-mutations were identified in 48 cystic fibrosis screening samples (1:245) and 15 samples (1:134) from the Ashkenazi Jewish population. Adjusted for the ethnic mix of the US population and self-reported ethnicity in our screening population, the estimated female pre-mutation carrier frequency in the US was 1:178. The calculated frequency of full mutation alleles was 1:3,335 overall, and the calculated permutation frequency in males was 1:400.	https://www.nature.com/articles/gim920117.pdf	2011
16.	Retrospective cohort Korea	Frequency of FMR1 premutation carriers and rate of expansion to full mutation in a retrospective diagnostic FMR1 Korean sample ²¹	10,241 pre-conceptional or pregnant women underwent FMR1 mutation analysis. Ninety-five of 10,241 patients had a positive family history. Among the 10,241 women tested, 13 were pre-mutation carriers. The estimated frequencies of carrier and pre-mutation alleles was 1:788 and 0.0006, respectively. In 95 individuals with a positive family history, one pre-mutation carrier was identified. 75 intermediate mutation carriers were detected, yielding an IM carrier frequency of 1 in 137.	https://onlinelibrary.wiley.com/doi/pdf/10.1111/cge.12195	2014

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication ***
17.	Population screening (retrospective) USA	FMR1 premutation frequency in a large, ethnically diverse population referred for carrier testing ²²	Retrospective study estimating the Fragile X pre-mutation carrier frequency in a large, ethnically diverse population of 134,933 women referred for routine carrier screening. The pan-ethnic pre-mutation carrier frequency was 1 in 201. Only the Asian group differed significantly from this frequency. Using the carrier frequency of 1 in 201, a conservative pan-ethnic risk estimate for a male fetus to have FXS can be calculated as 1 in 2,412. This risk is similar to the highest ethnic-based fetal risks for CF and SMA, for which population-wide screening is currently recommended.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6001625/pdf/AJMG-176-1304.pdf	2018
CF, SMA and fragile X					
18.	Population screening Australia	Reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome, and spinal muscular atrophy in Australia: outcomes of 12,000 tests ²³	Simultaneous genetic carrier screening for CF, fragile X syndrome, and SMA in 12,000 individuals, 88% of whom had no family history. A total of 610 carriers (5.08%; 1 in 20) were identified: 342 CF, 35 FXS, 241 SMA (8 carriers of 2 conditions). 94% of CF and SMA carriers' partners were tested. Fifty couples (0.42%; 1 in 240) were at increased risk of having a child with one of the conditions (14 CF, 35 FXS, and 1 SMA) with 32 pregnant at the time of testing. Of these, 26 opted for prenatal diagnosis revealing 7 pregnancies affected (4 CF, 2 FXS, 1 SMA).	https://www.nature.com/articles/gim2017134.pdf	2018

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication ***
19.	Population screening Israel	The Israeli national population program of genetic carrier screening for reproductive purposes. ²⁴	The Israeli population carrier screening program tests for CF, fragile X syndrome, and SMA. During the first 12-months more than 62,000 individuals were screened. Among the in 62,444 individuals for whom data were available, the SMA carrier rate was 1:57. Among the 59,644 individuals for whom data were available, the CF carrier rate was 1:45. Among the 44,592 women for whom data were available, the FXS carrier rate was 1:149.	http://www.nature.com.proxy.library.adelaide.edu.au/articles/gim201555	2016

* 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.

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
1.					
2.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
3.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
4.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
5.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
6.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
7.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
8.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date
9.	Insert study design	Insert title of research	Insert description	Insert website link	Insert date

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

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

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

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

- 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)

Australian Medical Association (AMA)

Australian Pathology

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

Fragile X Association of Australia

Cystic Fibrosis Australia

Spinal Muscular Atrophy Australia

- 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):**

Name of expert 1: Prof Graeme Suthers

Telephone number(s): <Redacted>

Email address: <Redacted>

Justification of expertise: Director of Genetics, Sonic Healthcare (Australia). Professor Suthers is a clinical geneticist and a genetic pathologist, and one of Australia's most respected experts in the field of genetics. Professor Suthers is nationally and internationally recognised for his expertise in genetic disorders, testing and clinical service provision. Professor Suthers is a former member of the MSAC.

Name of expert 2: Professor John Wilson AM

Telephone number(s): <Redacted>

Email address: <Redacted>

Justification of expertise: In addition to being the President –elect of the RACP, Professor Wilson is Head of the Cystic Fibrosis Service at the Alfred Hospital, Melbourne. Professor Wilson has extensive experience in the implementation of clinical practice guidelines and has worked with the Clinical Pathways Working Group at the Alfred hospital on the integration of clinical and cost effectiveness evidence and CPGs into health service delivery in respiratory medicine.

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

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, 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:

The clinical characteristics, mode of inheritance and prevalence of CF, SMA and FXS are summarised in Table 1.

Many children affected by CF, SMA or FXS are born to families with no history of disease and no awareness of their carrier status due to the rare nature of the conditions and patterns of inheritance.

RANZCOG's good practice note states that pre-conception screening is preferable to antenatal screening for heritable genetic conditions as this potentially allows more options for carrier couples, including use of donor gametes and pre-implantation genetic diagnosis (PGD). As such, RANZCOG recommends carrier screening of women and their partners, preferably prior to pregnancy, for mutations in genes that result in common genetic conditions including CF, SMA, FXS.¹ The American College of Obstetricians and Gynecologists recommends that CF and SMA carrier screening should be offered to all women who are considering pregnancy or are currently pregnant.²⁵ Carrier screening is currently offered by several providers in the private sector in Australia on a user pays basis.^a

Carrier screening programs offer genetic screening to individuals who do *not* have a known family history and are therefore *not* considered to be at an increased risk of being a carrier of deleterious inherited conditions such as CF, SMA, and FXS. Ascertaining the carrier status provides individuals and couples with information about their risk of having a child with CF, SMA or FXS, and as such, enables an informed reproductive choice for couples. Reproductive options may include the use of donor gametes, PGD, prenatal diagnosis, adoption, or using the information to assist in preparing for the possibility of a child with a genetic condition.²⁶

In an Australian population where the majority of individuals are without a family history of all three conditions, there is a relatively high carrier frequency rate. A recent Australian population screening study conducted in Victoria found that of 12,000 individuals screened for CF, SMA and FXS, 1:20 were carriers (n=610, 5.08%). Of these, 342 were carriers of CF, 241 were carriers of SMA and 35 carriers of FXS, whilst a small number (n=8) were carriers of two conditions. The majority of carriers were pregnant at the time of testing (58.69%, 358/610). When carrier screening was then conducted on the partners of these women, 50 couples (0.42%; 1 in 240) were at increased risk of having a child with one of the conditions (14 CF, 1 SMA, 35 FXS). Of these at-risk couples, 32 (64%) of the women were pregnant at the time of testing, and of these 26 (9 CF, 1 SMA, 22 FXS), opted for prenatal diagnosis which found that seven pregnancies were affected (4 CF, 1 SMA, 2 FXS).²⁷

Couples who are both carriers for either CF or SMA, who are unaware of their carrier status, have a 25% chance of having an affected child, and a 50% chance that their child will also be a carrier. Children of either gender born to women who carry the fragile X pre-mutation gene have a 50% chance of inheriting the affected gene, with sons being a greater risk of being affected than daughters.

^a See Sonic genetics <https://www.sonicgenetics.com.au/tests/carrier-screening-panel-cf-sma-fragile-x/>
http://www.wdp.com.au/Portals/0/PDF/PatientBrochure/GD17%20Genetic%20Carrier%20Screen%20for%20GPs_WDP_2_LR.pdf

See Victorian Clinical Genetics Services (VCGS) <https://www.vcgs.org.au/tests/prepair>

Table 1 Characteristics of cystic fibrosis, spinal muscular atrophy and fragile X syndrome²³

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency	Carrier testing	Detection rate of carrier test
Cystic fibrosis	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 CFTR gene variants, one inherited from each parent. Greater than 2,000 disease-causing CFTR 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. ^b 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	1 in 2,500 1 in 25 Most common life-threatening recessive condition affecting Australian children.	Analysis of the <i>CFTR</i> gene for 50 most common mutations, including the 5T variant.	90%*

^b See Pharmaceutical Benefits Scheme (PBS) <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	Carrier testing	Detection rate of carrier test
			<p>(inhaled). Dornase alfa has a DPMQ of \$1917. Mannitol, added to the PBS in 2012, is indicated 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.^c</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^d plus ongoing treatment with immunosuppressants.¹² 5-year survival rates of lung Tx have been reported as 67%, with 50% of patients living >10 years.²⁸ 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.²⁹</p>			

^c See Pharmaceutical Benefits Scheme (PBS) www.pbs.gov.au/industry/listing/participants/public-release-docs/2014-10/cystic-fibrosis-dornase-mannitol-dusc-prd-10-2014.docx

^d 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	Carrier testing	Detection rate of carrier test
			In 2015, 17 deaths were reported to the CF registry, compared to 19 deaths in 2014. Of 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. ²⁹			
Spinal muscular atrophy	<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 tremor, scoliosis, life expectancy > 2 years to 3rd/4th decade.</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.³⁰ Nusinersen has a DPMQ of \$110,000. It is expected that around 160 patients will receive treatment every year as a result of this listing, costing an estimated \$367,850 per patient, per year (\$58,856,000 per year).^e</p>	<p>1 in 10,000</p> <p>1 in 40</p> <p>SMA is the most frequent genetic cause of infant mortality.</p>	<p>Ascertaining SMN1 copy number by MLPA</p>	<p>95%</p>

^e See The Department of Health <http://www.health.gov.au/internet/main/publishing.nsf/Content/MC17-021776-SMA>

Condition	Clinical features	Mode of inheritance and cause of condition	Treatment and/or management	Prevalence and carrier frequency	Carrier testing	Detection rate of carrier test
	Type 3: stand and walk independently, onset after 18 months, may ultimately require wheelchair, life expectancy similar to unaffected population.**		Nusinersen is not curative but will improve QoL and increase life expectancy.			
Fragile X syndrome	<p>Developmental delay, intellectual disability, speech delay, autistic-like behaviours, anxiety, ADHD, epilepsy, macrocephaly, large ears, long face.</p> <p>Features of FXS vary from mild to severe with males more likely to be severely affected than females.</p>	<p>X-linked.</p> <p>Caused by the expansion of the CGG triplet repeat region of the FMR1 gene. Full mutation (≥ 200 CGG repeats) is associated with fragile X syndrome.</p> <p>A carrier result conveys both reproductive risk and implications for the health of the individual screened. Female full mutation and pre-mutation carriers are at risk of having an affected child. Female pre-mutation carriers are at risk of fertility problems and early menopause and male and female carriers are at risk of fragile X-associated tremor/ataxia syndrome.</p>	<p>No cure.</p> <p>Management through early intervention, occupational and speech therapy to address sensory defensiveness, hyperarousal, and attention problems. Tailored educational interventions. Pharmacological treatments for ADHD, anxiety, aggression, and mood instability. Clinical trials are under way for a number of drug therapies.</p>	<p>1 in 4000 to 1 in 6000</p> <p>1 in 250</p> <p>Most common known cause of inherited intellectual disability</p>	<p>Sizing and triplet repeat primed PCR to detect expansion of the CGG repeat region in the 5' region of FMR1 gene.</p>	>99%

* For Victorian Clinical Genetics Services 38-variant panel, ** In some classification systems type 0 (prenatal onset) and type 4 (adult onset) also delineated.
ADHD = attention deficit hyperactivity disorder, MLPA = multiplex ligation-dependent probe amplification

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:

All women considering pregnancy should undergo carrier screening testing, preferably prior to conception, to ascertain their carrier status. In addition, partners of women found to be carriers of SMA or CF should undergo testing.

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):

Carrier screening prior to conception or in early pregnancy has been an integral part of reproductive care for decades. Clinicians routinely screen red cell parameters of women and, as necessary, their partners to identify carriers of thalassaemia. (Carrier screening for thalassaemia using red cell parameters and Hb studies is already rebated by the MBS). The principles of education, autonomy, confidentiality, and expedited post-test referral (if indicated) are not new principles for clinicians.

Preconception carrier screening is currently recommended as standard practice by

- RACGP: “Provide opportunity for carrier screening for genetic conditions (eg cystic fibrosis, haemoglobinopathies) and referral for genetic counselling based upon risk factors” (See the Royal Australian College of General Practitioners (RACGP) <https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/red-book/preventive-activities-prior-to-pregnancy>)
- 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” (See the Royal Australian and New Zealand College of Obstetrics and Gynaecology (RANZCOG) https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Prenatal-screening.pdf?ext=.pdf)

The guidance regarding the use of reproductive carrier screening is in place. Resources to assist clinicians in pre-test counselling are already available, and will continue to be developed by professional bodies, public health services, and laboratories providing 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 a venepuncture to be performed on individuals for the collection of a blood sample that is referred to a pathology laboratory, where DNA is extracted for genetic analysis:

- Cystic fibrosis: analysis of the *CFTR* gene for 50 most common mutations, including the 5T variant. 50 mutations is the minimum number to provide the requisite sensitivity.
- Spinal muscular atrophy: ascertaining *SMN1* copy number by multiplex ligation-dependent probe amplification (MLPA) or by quantitative PCR.
- Fragile X syndrome: sizing and triplet repeat analysis to detect expansion of the CGG repeat region in the 5' region of *FMR1* gene.
 - Women with less than 45 triplet repeats are unaffected and are not at risk of having an affected child.
 - Women with 45-54 repeats are not at risk of FXS-associated disease, but the number of repeats may increase when the gene is passed to the woman's child
 - Women with between 55-200 triplet repeats have a pre-mutation. They have a normal intellect but may exhibit fragile X-associated tremor/ataxia syndrome or *FMR1*-related premature ovarian failure.
 - Individuals with >200 repeats have the full mutation that results in the full expression of FXS in males and variable expression in females.²⁵

Population carrier screening should be a 2-step approach that is preferably undertaken in the pre-conception period. In the first instance, population carrier screening of all women planning a pregnancy should be undertaken. If the woman is confirmed as a heterozygote carrier for CF or SMA, then screening of her partner should be undertaken to fully evaluate the risk of having a child with SMA or CF. If the woman is identified as a carrier of FXS alone there is no need for her partner to undergo screening due to the X-linked mode of inheritance. If the woman is already pregnant, 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.²⁶

Figure 1 outlines the clinical pathway for 2-step population carrier screening.

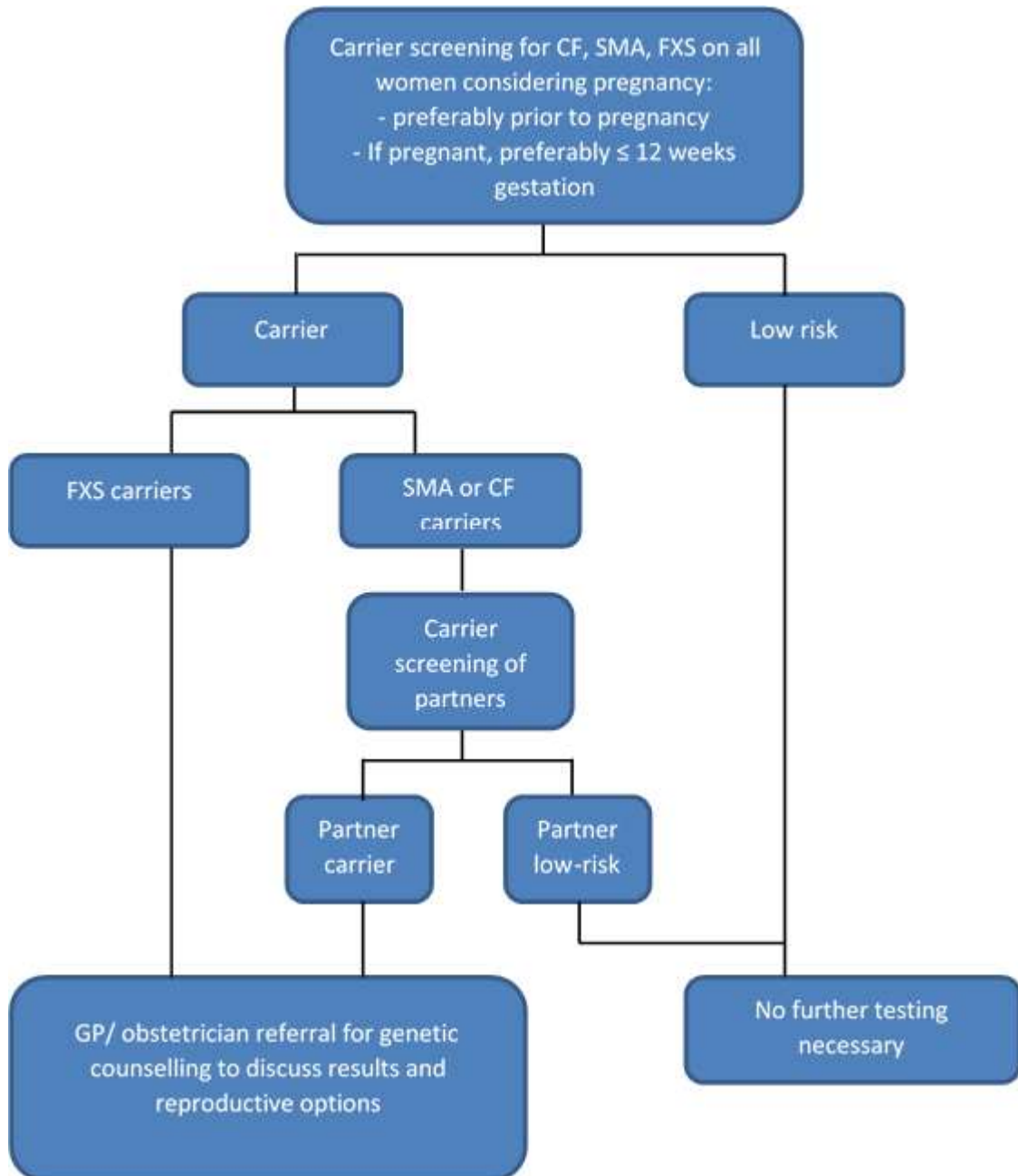


Figure 1 Clinical pathway for 2-step carrier screening

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):

N/A

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:

As noted above (26), the principles underlying reproductive carrier screening are already in routine use for screening for carriers of thalassaemias. Additional resources have been developed by professional societies, public education services, and labs providing testing.

The post-test genetic management of couples identified as being at high risk of having an affected child will require access to genetic counselling services in the public or private sector (See Human Genetics Society of Australasia and Sonic Genetics www.hgsa.org.au/asgc/find-a-genetic-counsellor and www.sonicgenetics.com.au/counsellingservices, respectively).

The need for genetic counselling in association with genetic tests has been identified in a number of PSDs from MSAC, but there remains no rebate for genetic counselling in the MBS. There are rebates for counselling in pregnancy provided by other allied health practitioners. It is not the purpose of this application to address this issue.

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

All women considering pregnancy should be referred for screening by either their treating General Practitioner or obstetrician, which will then be carried out in a NATA approved laboratory.

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

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

The testing would only be performed in an 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 Approved Practising Pathologists in Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered Medical Practitioners (non-pathologists) in line with other tests in the MBS Pathology Table.

All women considering pregnancy should be referred for screening 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
- Inpatient public hospital
- Outpatient clinic
- Emergency Department
- Consulting rooms
- Day surgery centre
- 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:

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):

In the absence of population carrier screening, women would only be tested for their carrier status as part of cascade screening, that is, as a consequence of having either a family member or a child affected by CF, SMA or FXS.

CF: Carrier testing for CF has only recently been approved for MBS funding for individuals with a close family history of a known mutation in the CFTR gene. This rebated test can only be ordered by a medical specialist. This test was only added to the MBS in July 2018, and so it is too soon to have any data re the impact of this listing on the reproductive practice. Hence the appropriate comparator for carrier screening for CF is “no carrier screening for CF, irrespective of family history”. A small proportion of fetuses affected with CF will be identified prenatally with echogenic gut; since July 1, genetic testing to identify the genetic basis of echogenic have been listed on the MBS.

The comparator involves the diagnosis of an affected fetus identified as having CF due to the development of echogenic gut during pregnancy. After birth, there will be diagnoses, either through diagnostic testing or by newborn screening (in most jurisdictions). There are then the direct costs of therapy for CF, and the indirect costs of care of children with this disorder.

SMA: Diagnostic and carrier testing for SMA is not listed on the MBS, despite there being an SMA-specific therapy recently listed on the PBS. Hence the appropriate comparator for carrier screening for SMA is “no carrier screening for SMA, irrespective of family history”. There are no antenatal indicators of a fetus being affected with SMA.

The comparator involves the diagnosis through diagnostic testing or by newborn screening (in NSW). There are then the direct costs of therapy for SMA, and the indirect costs of care of children with this disorder.

FXS: Diagnostic and carrier testing for FXS has been listed on the MBS for many years. In contrast to CF carrier testing, this test can be requested by any medical practitioner. The uptake of carrier screening in families in which a child has been diagnosed with FXS will be incomplete; the degree of uptake has not been evaluated using Australian MBS data. Hence the appropriate comparator for carrier screening for FXS is “no carrier screening in the absence of family history (with appropriate recognition of incomplete uptake of carrier screening among those with a family history)”. There are no antenatal indicators of a fetus being affected with FXS.

The comparator involves diagnosis of an affected child with developmental delay, with carrier identification among relatives. After birth, there will be diagnoses in other children, with through a failure of uptake of the offer carrier screening or due to there being no affected child identified to trigger carrier screening. There are then the indirect costs of care of children with this disorder.

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

Item number 16600: AMNIOCENTESIS, diagnostic. Fee: \$63.50

Item number 16603: CHORIONIC VILLUS SAMPLING, by any route. Fee: \$121.85

In July 2018, **diagnostic testing** to identify the presence of mutations in the *CFTR* gene in patients **with a family history or considered to be at high-risk** of cystic fibrosis was added to the MBS:

Item number 73345: Testing of a patient for pathogenic cystic fibrosis transmembrane conductance regulator variants for the purpose of investigating, making or excluding a diagnosis of cystic fibrosis or a cystic fibrosis transmembrane conductance regulator related disorder when requested by a specialist or consultant physician who manages the treatment of the patient, not being a service associated with a service to which item 73347, 73348, or 73349 applies. The patient must have clinical or laboratory

findings suggesting there is a high probability suggestive of cystic fibrosis or a cystic fibrosis transmembrane conductance regulator related disorder. Fee \$500

Item number 73346: Testing of a pregnant patient whose carrier status for pathogenic cystic fibrosis transmembrane conductance regulator variants, as well as their reproductive partner carrier status is unknown, for the purpose of determining whether pathogenic cystic fibrosis transmembrane conductance regulator variants are present in the fetus, in order to make or exclude a diagnosis of cystic fibrosis or a cystic fibrosis transmembrane conductance regulator related disorder in the fetus when requested by a specialist or consultant physician who manages the treatment of the patient, not being a service associated with a service to which item 73350 applies. The fetus must have ultrasonic findings of echogenic gut, with unknown familial cystic fibrosis transmembrane conductance regulator variants. Fee \$500

Item number 73347: Testing of a prospective parent for pathogenic cystic fibrosis transmembrane conductance regulator variants for the purpose of determining the risk of their fetus having pathogenic cystic fibrosis transmembrane conductance regulator variants. This is indicated when the fetus has ultrasonic evidence of echogenic gut when requested by a specialist or consultant physician who manages the treatment of the patient, not being a service associated with a service to which item 73345, 73348, or 73349 applies. Fee \$500

Item number 73348: Testing of a patient with a laboratory-established family history of pathogenic cystic fibrosis transmembrane conductance regulator variants, for the purpose of determining whether the patient is an asymptomatic genetic carrier of the pathogenic cystic fibrosis transmembrane conductance regulator variants that have been laboratory established in the family history when requested by a specialist or consultant physician who manages the treatment of the patient, not being a service associated with a service to which item 73345, 73347, or 73349 applies. The patient must have a positive family history, confirmed by laboratory findings of pathogenic cystic fibrosis transmembrane conductance regulator variants, with a personal risk of being a heterozygous genetic carrier of at least 6%. (This includes family relatedness of: parents, children, full-siblings, half-siblings, grand-parents, grandchildren, aunts, uncles, first cousins, and first cousins once-removed, but excludes relatedness of second cousins or more distant relationships).

Item number 73349: Testing of a patient for pathogenic cystic fibrosis transmembrane conductance regulator variants for the purpose of determining the reproductive risk of the patient with their reproductive partner because their reproductive partner is already known to have pathogenic cystic fibrosis transmembrane conductance regulator variants requested by a specialist or consultant physician who manages the treatment of the patient, not being a service associated with a service to which item 73345, 73347, or 73348 applies. Fee \$500

Item number 73350: Testing of a pregnant patient, where one or both prospective parents are known to be a genetic carrier of pathogenic cystic fibrosis transmembrane conductance regulator variants for the purpose of determining whether pathogenic cystic fibrosis transmembrane conductance regulator variants are present in the fetus in order to make or exclude a diagnosis of cystic fibrosis or a cystic fibrosis transmembrane conductance regulator related disorder in the fetus, when requested by a specialist or consultant physician who manages the treatment of the patient, not being a service associated with a service to which item 73346 applies. The fetus must be at 25% or more risk of cystic fibrosis or a cystic fibrosis transmembrane conductance regulator related disorder because of known familial cystic fibrosis transmembrane conductance regulator variants. Fee \$250

Since 2003, *diagnostic testing* to identify the presence of mutations in the *FMRI* gene in patients *with a family history or considered to be at high-risk* of fragile X syndrome was added to the MBS:

Item number 73300: Detection of mutation of the FMR1 gene where:

(a) the patient exhibits intellectual disability, ataxia, neurodegeneration, or premature ovarian failure consistent with an FMRI mutation; or

(b) the patient has a relative with a FMR1 mutation. Fee \$101.30

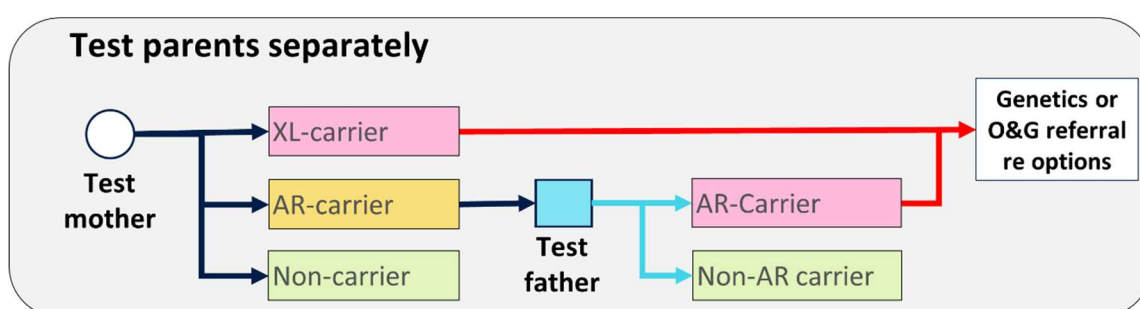
Item number 73305: Detection of mutation of the FMR1 gene by Southern Blot analysis where the results in item 73300 are inconclusive. Fee \$202.65

In addition, a number of drugs listed on the PBS:

- For CF: Ivacaftor (PBS code [10170G](#) and [10175M](#), Kalydeco, Highly Specialised Drugs Program). Ivacaftor 150 mg tablet, has a base dispensed price (DPMQ) of \$22,500. Lumacaftor (PBS code [11463H](#) and [11466L](#), Orkambi) at a DPMQ price of \$18,797. Dornase alfa (PBS codes [5704F](#) and [6120D](#)) has a DPMQ of \$1,917. Mannitol (PBS codes [2008Q](#) and [2015C](#)) has a DPMQ of \$1,696
- For SMA: Nusinersen has a DPMQ of \$110,000 (PBS code [11363C](#), [11370K](#), [11378W](#), [11470Q](#), [11472T](#), [11476B](#))

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):

The following Figure summarises the care pathway for a woman found to be a carrier of an X-linked or autosomal recessive disorder:



If the woman is not a carrier of FXS (X-linked) or of SMA or CF (both autosomal recessive), then no further action is required.

If she is a carrier for FXS, then her partner's status is on no consequence, and she would be referred to a clinical genetics service or feto-maternal medicine service in the public or private sector.

If she is a carrier for one of the autosomal recessive disorders, her reproductive partner would be tested for those conditions. If he is not a carrier, then no further action is required. If he is a carrier for the same condition as his partner, the couple should be referred to genetics/FMF as above.

The triage process would need to be reviewed (but not re-test the subjects) should either partner have a different reproductive partner in the future.

This care pathway does not address the options that could be considered by the couple once they have been referred to a clinical geneticist or FMF service. These options could include reproductive options such as prenatal diagnosis, pre-implantation genetic diagnosis, adoption, and in vitro fertilisation (IVF) using a donor egg, sperm, or embryo, or using the information to assist in preparing for the possibility of a child with a genetic condition.

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

- Yes In addition to
 No Instead of

1. If **yes** in addition to, please outline the extent of which the current service/comparator is expected to be substituted:

Outline service/comparator substitution here

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):

This application does not address the situation in which a couple are known to have a close family history of CF, SMA, or FXS. Such couples should receive genetic assessment, counselling, and testing through

established channels. The applicants recognise that there are issues with the funding of services in this situation (CF carrier screening must be requested by a specialist, while FXS carrier testing can be order by a GP; there is no diagnostic or carrier test funded for SMA), but addressing these issues lies outside the scope of this application.

For couples in whom there is no family history of these disorders, there is no rebated testing to determine their carrier status for these disorders. The first indication that there may be a problem would be the finding of echogenic gut by ultrasound during the second trimester. Rebated testing to determine whether this represents fetal CF is now available, and so this scenario is not considered further. This rebated testing includes determining the carrier status of the parents.

The situation for the majority of affected children (and their parents) will be that the diagnosis is made in the first month of life by newborn screening (CF), or in the first year of life by a paediatrician (SMA), or in early childhood by a paediatrician or child development specialist (FXS).

The clinical management would be altered by the introduction of this test by offering the test to couples either prior to conception (preferred) or in early pregnancy. The offer would be made by the couple's GP or obstetrician. Couples identified as being at high risk of having an affected child would be referred to a clinical geneticist or FMF service as outlines above. This would potentially preclude the diagnosis and consequences of CF, SMA, or FXS outlined in the preceding paragraph.

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):

Population-based screening programs in Australia are funded by a variety of mechanisms. The Australian Government currently funds three stand-alone population-based screening programs for cancer (bowel, breast and cervical). The Australian Government also funds carrier screening for thalassaemia, and antenatal screening for chromosome abnormalities such as Down syndrome. Being embedded in Medicare, these tests do not constitute a formal program as outcomes are not directly linked to testing and outcomes are not audited. In addition, State and Territory Governments fund standalone screening programs for antenatal testing for chromosome abnormalities (some jurisdictions) and newborn screening (all jurisdictions).

This is a proposal for funding of reproductive carrier screening through Medicare. The applicant has chosen to frame the application in this way because it would align carrier screening with the current Medicare funding of thalassaemia screening and chromosome disorders. However, we recognise that MSAC may recommend that a standalone national carrier screening program be created. Whether such activity be funded by Medicare or other means, some of the data which would inform that decision has been derived from population-wide studies.

Screening programs should satisfy the World Health Organization's accepted criteria for screening programs. Population carrier screening for CF, SMA and fragile X syndrome 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 applicable to reproductive carrier screening. Unlike cancer screening programs, carrier screening is directed at people who are not likely to develop the disease themselves. The goal of screening is to provide couples with the option to avoid a pregnancy with a child who will have a serious incurable childhood-onset disorder. As such, reproductive carrier screening for CF, SMA and FXS satisfies the following screening program criteria:

- the condition should be clinically significant – in this case a significant impact on the affected individual and their family;
- the condition should be relatively common - in this case, a high carrier frequency;
- the natural history of the condition, including development from latent to declared disease, should be adequately understood;
- there should be a suitable test or examination that has a high level of accuracy with good detection rates (sensitivity and specificity – consideration must be given to the number of false positives and false negatives);
- the test should be acceptable to the population;
- there should be an agreed policy on whom to treat as patients;
- facilities for diagnosis and treatment should be available; and
- the cost of screening (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

Ultimately, the benefits of screening should outweigh any potential harms.^{26, 31, 32}

Population carrier screening programs offer genetic screening to individuals who do not have a known family history and are therefore not considered to be at an increased risk of being a carrier of deleterious inherited conditions such as CF, SMA, or FXS. Ascertaining the carrier status provides individuals and couples with information about their risk of transmitting a clinically significant genetic condition to their offspring with associated morbidity and/or mortality, and as such, enables an informed reproductive choice for couples. Reproductive options may include prenatal diagnosis, PGD, adoption, and in vitro fertilisation (IVF) using a donor egg, sperm, or embryo, or using the information to assist in preparing for the possibility of a child with a genetic condition.²⁶

The goal of reproductive carrier screening is to give couples the opportunity to avoid the birth of an 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. Newborn screening program

in Australia tests for CF, and that NSW recently added SMA testing to the NBS. Newborn screening aims to identify affected individuals to allow early access to treatments that may slow progression of disease.

The introduction of population carrier screening should 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 affected children born over time. A recent retrospective review of the CF carrier screening program in Israel reported a marked decrease in the rate of CF from 14.5 in 1990 to six per 100,000 live births in 2011. From 2004–2011, 387 couples carrying 2 mutations opted for invasive pre-natal diagnosis with an annual mean rate of 48.3 ± 8.8 . During this period, a total of 87 pregnancies were terminated at an annual mean rate of 11 ± 3.4 . Between 2009 and 2013, population carrier screening was utilised by a total of 276,452 couples or $55,290 \pm 3055$ annually. Although no data was available, it was estimated that couples only undergo screening once. A total of 95 children were born with CF in the period between 2004 and 2011. The parents of 22 of the 95 children born with CF had undergone carrier screening, and in 5 cases, no mutation was found when the mother was screened, and therefore the partner was not tested. In the other 17 cases, both parents were found to carry CFTR mutations.³³ The reduced prevalence of the three conditions over time will result in a subsequent reduction in the utilisation of health services associated with the treatment of CF, SMA and fragile X syndrome affected children. For all three conditions, this will include reduced:

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

Initially rates of pre-natal diagnosis and terminations may increase.

There is, of course, an ethical dimension to carrier screening. As recommended by RANZCOG, all women who are considering a pregnancy, or who are in early pregnancy, should be offered carrier screening 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. These are not novel considerations, and they are already recognised by clinicians providing antenatal screening for chromosome disorders. These issues have already been widely discussed in the international literature.³⁴ The fact that there are ethical considerations does not preclude funding of carrier screening by a national program or by Medicare

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

Clinical Effectiveness Outcomes:

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

Cost effectiveness outcomes:

Cost of population screening 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:

Rates of prevalence will vary depending on an individual's ethnic background.

CF is the most common severe autosomal recessive condition in those of Northern European ancestry, with a prevalence of 1 in 2,500–3,500 live births and a carrier frequency of 1 in 25.^{10,35}

SMA has a reported prevalence of approximately 1–2 per 100,000 persons and incidence around 1 in 10,000 live births.³⁶

The reported prevalence of the FXS *FMR1* alleles varies. Frequencies of the *FMR1* FM in males have ranged from 1 in 2,633 to 1 in 6,209. Reported rates of the pre-mutation in females ranged from 1 in 154 in Israel to 1 in 549 in Canada, with rates of 1 in 178 and 1 in 209 reported in the USA.³⁷

One of the private Australian laboratories offering carrier screening quote the following carrier frequencies and incidence.^f

	CARRIER FREQUENCY	NUMBER OF LIVE BIRTHS
Cystic Fibrosis	1 in 25	1 in 2,500
Fragile X	1 in 150	1 in 4,000 males (1 in 8,000 females)
Spinal Muscular Atrophy	1 in 40	1 in 6,000 – 10,000

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

The test only needs to be delivered once in a woman's, and if necessary in her reproductive partner's, life. If the reproductive partner changes, testing may need to be repeated for the new partner.

More specifically, if either partner is a carrier for an autosomal recessive disorder (CF or SMA), then their new reproductive partner should be screened for the relevant disorder so that revised reproductive advice can be given.

If the woman is a carrier of an X-linked recessive disorder (FXS), the risk of her having an affected child is independent of her reproductive partner (assuming the partner is unaffected).

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

One test per person during their reproductive years.

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

There are a number of factors which make it difficult to predict the uptake of testing.

- The cost of screening for these three disorders has dropped in the last few years.
- There is growing awareness of the benefit of carrier screening among clinicians providing pre-natal services.

^f See Western Diagnostic Pathology

www.wdp.com.au/Portals/0/PDF/PatientBrochure/GD17%20Genetic%20Carrier%20Screen%20for%20GPs_WDP_2_LR.pdf

- Women are becoming more aware of the availability of screening tests during pregnancy, as can be seen in the rapid acceptance of non-invasive prenatal testing among mothers at low risk of having a chromosomally abnormal fetus.
- There has been intense publicity regarding the potential for carrier screening and wide interest in Mackenzie’s Mission, the MRFF-funded pilot of population screening for hundreds of different disorders.

In 2016, the ABS recorded a total of 311,104 births registered in Australia.^g Based on the increase in the number of births from 2015 to 2016 of 1.87%, it is estimated that in 2019 there would be 328, 884 births (using an annual increase of 1.87%). The public and private laboratories which provide carrier screening may be able to provide data regarding the recent uptake (and acceleration of uptake) that would inform an estimate of the proportion of these mother who would accept an offer of reproductive carrier screening.

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:

For the first year of carrier testing, the number of services required would equate to the number of births for the first year, assuming that no women had been tested (although a small proportion would have a known family history). In 2016 in Australia, 42.9% of mothers had their first baby, with 35.1% having their second, 13.8% their third, 4.86% their fourth and 3.34% had more than four babies.³⁸ Therefore the number of primipara births each year would give an estimate of the number of carrier tests required. In the second and subsequent years, this would be approximately 43% of the total number of births (Table 2). This figure may reflect a maximum value, however, as currently only 80% of women accept antenatal screening for Down syndrome.

Table 2 Estimated number of primipara women who would be tested (based on 2016 ABS data^h)

Year	Estimated number of births each year*	Estimated number of primipara women who would be tested**
2019	328, 884	328,884
2020	335, 034	144,064
2021	341, 299	146,758
2022	347,681	149,502

* Estimates based on an increase in the number of births from 2015 to 2016 of 1.87%

** 100% of women giving birth for the first year, with 43% of all births in each subsequent year

^g See Australian Bureau of Statistics <https://tinyurl.com/y884gkwj>

^h See Australian Bureau of Statistics <https://tinyurl.com/y884gkwj>

PART 8 – COST INFORMATION

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

In the private sector, panel testing for mutations in the three genes costs between \$345 to \$400 (Sonic Genetics, Victorian Clinical Genetics Services, and Primary Healthcare).

An estimated breakdown of costs would be:

Equipment and resources	Per test
Kit, probes, reagents, ancillary reagents	\$260.00
Labour medical (consultant pathologist)	\$50.00
Labour scientific	\$40.00
Labour on costs	\$15.00
Depreciation, overheads	\$25.00
Admin, IT	\$10.00
Total	\$400.00

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

Estimated 10 day turnaround from taking test sample to results.

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.

Category 6 (Pathology Services) – Group P7 Genetics
<p>Proposed item descriptor:</p> <p>Testing of an asymptomatic woman to identify heterozygous mutations 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 for the purpose of determining the reproductive risk of these conditions. Limited to people with no known family history of these conditions, one test per lifetime.</p> <p>Fee: \$400</p>

Category 6 (Pathology Services) – Group P7 Genetics
<p>Proposed item descriptor:</p> <p>Testing of the asymptomatic reproductive partner of a woman who has been found to be a carrier of a heterozygous mutation in the cystic fibrosis transmembrane conductance regulator (<i>CFTR</i>) gene or survival motor neuron 1 (<i>SMN1</i>) gene for the purpose of determining the couple's reproductive risk of these conditions. Limited to people with no known family history of these conditions, one test per lifetime.</p> <p>Fee: \$400</p>

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