Australian Government

Department of Health

Application Form

(New and Amended Requests for Public Funding)

(Version 2.5)

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.

The application form will be disseminated to professional bodies / organisations and consumer organisations that have will be identified in Part 5, and any additional groups that the Department deem should be consulted with. The application form, with relevant material can be redacted if requested by the Applicant.

Should you require any further assistance, departmental staff are available through 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: MSAC Website

PART 1 – APPLICANT DETAILS

1. **Applicant details (primary and alternative contacts)**

Corporation / partnership details (where relevant):
Corporation name: Roche Diagnostics Australia Pty Ltd
ABN: **REDACTED**
Business trading name:

Primary contact name: REDACTED

Primary 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 consultant acting on behalf of an Applicant?**

☐ Yes

☒ No

(b) If yes, what is the Applicant(s) name that you are acting on behalf of?

Insert relevant Applicant(s) name here.

3. **(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

4. Application title

Non-invasive prenatal testing for common trisomies (21, 18 and 13)

5. 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)

Trisomy 21 (Down syndrome) is a condition that occurs when an extra chromosome 21 originates in the development of either the sperm or the egg, and is the most frequently occurring clinically significant genetic condition in newborns. It can cause delays in physical and intellectual development. Prenatal testing for Down syndrome is the standard of care, and most women undergo some form of testing. Down syndrome occurs in approximately 1/300 pregnancies and 1/550 newborns.

Trisomy 18 (Edwards syndrome) is due to an extra copy of chromosome 18. It is associated with a high rate of miscarriage. Infants born with Edwards syndrome may have various medical conditions and a shortened lifespan. Edwards syndrome occurs in approximately 1/1,100 pregnancies and 1/5,500 newborns.

Trisomy 13 (Patau syndrome) is due to an extra chromosome 13 and is also associated with a high rate of miscarriage and various abnormalities in surviving fetuses. Expected lifespan of infants with trisomy 13 is extremely reduced. Trisomy 13 occurs in approximately 1/3,000 pregnancies and 1/10,000 newborns.

References: www.betterhealth.vic.gov.au/health/conditionsandtreatments/trisomy-disorders, brochures.mater.org.au/brochures/mater-mothers-hospital

6. 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)

Non-Invasive Prenatal Testing (NIPT) that assesses the risk of fetal aneuploidy (specifically trisomies 21, 18, and 13) using an assay of cell-free DNA (cfDNA) in maternal plasma which documents 1) the presence of sufficient cfDNA from the fetus to do an analysis, and 2) the likelihood of fetal aneuploidy. The measurement, reporting and incorporation of fetal fraction into the final probability score is a quality control metric underlying the testing.

7. (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:

Insert relevant MBS item numbers here

(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):

Insert description of 'other' amendment here

(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:

Insert description of other public funding mechanism here

8. **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

9. **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. ☐ Is for genetic testing for heritable mutations in clinically affected individuals and, when also appropriate, in family members of those individuals who test positive for one or more relevant mutations (and thus for which the Clinical Utility Card proforma might apply)

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

☐ Pharmaceutical / Biological

☐ Prosthesis or device

☒ No

11. **(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):**

Insert PBS item code(s) here

(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

Insert PBAC submission item number here

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

Trade name: Insert trade name here

Generic name: Insert generic name here

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

☐ Yes

☐ No

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

Billing code(s): Insert billing code(s) here

Trade name of prostheses: Insert trade name here

Clinical name of prostheses: Insert clinical name here

Other device components delivered as part of the service: Insert description of device components here

(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):**

Insert sponsor and/or manufacturer name(s) here

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

Single use consumables:

NIPT analyses a maternal blood sample drawn by standard phlebotomy as per current combined first trimester screening (FTS). If the blood draw for the NIPT occurs at the same time as FTS then no additional needles are required.

NIPT requires two cfDNA collection tubes. These are similar to standard blood collection tubes but with a solution to prevent cell lysis (breakdown), thereby improving the yield of fetal cfDNA.

Multi-use consumables: Insert description of multi use consumables here

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

14. **(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: Insert description of single use consumables here

    Manufacturer's name: Insert description of single use consumables here

    Sponsor's name: Insert description of single use consumables here

    (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

15. **(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

16. **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

17. **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: December 2016. The Harmony Prenatal Testing reagents are currently a Research Use Only (RUO) product. Pathology laboratories who perform the testing are responsible for registering the test as an inhouse IVD.(Attachment 1)

    Roche Diagnostics Australia is in the process of collating the regulatory information from this submission and will submit an application to the TGA as soon as all the documents are received. We also plan to register the Software with the TGA at this time.

    The cfDNA collection tubes are already registered with TGA. (Certificate number 270396)

PART 4 – SUMMARY OF EVIDENCE

18. **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***
As a matter of principle relating to good laboratory practice, we propose that the descriptor require confirmation of sufficient fetal cfDNA for analysis prior to assessment of the risk of fetal trisomy. Without limiting the generality of the application, we note that there are only two tests currently available in Australia fulfilling that requirement, Harmony and Panorama. For this reason, the summary below includes: 1) studies of Harmony and Panorama that have assessed diagnostic accuracy for the detection of T21, T18 and/or T13; and 2) meta-analyses of all NIPTs (these may include studies that are not relevant to the application, due to the type of NIPT or outcomes assessed).					
Meta-analyses (all NIPTs)					
1.	Meta-analysis	Taylor-Phillips 2016	Systematic review and meta-analysis of 41 case–control studies (≥15 trisomy cases) or cohort studies (≥50 pregnant women) given NIPT and a reference standard to measure test accuracy of NIPT for T21, T18 and T13 using cfDNA, and identify factors affecting accuracy. Outcomes: sensitivity, specificity.	http://bmjopen.bmj.com/content/6/1/e010002.full	18 January 2016
2.	Meta-analysis	Mackie 2016	Systematic review and meta-analysis of 118 cohort studies reporting cfDNA-based NIPT performance in singleton pregnancies to determine accuracy for all conditions and evaluate influence of other factors on test performance. Outcomes: sensitivity, specificity.	http://onlinelibrary.wiley.com/doi/10.1111/1471-0528.14050/full	31 May 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***
3.	Meta-analysis	Gil 2015	Meta-analysis of 37 studies reporting cfDNA results in relation to fetal karyotype from invasive testing or clinical outcome, to determine the performance of cfDNA testing in screening for aneuploidies. Outcomes: sensitivity (detection rate), false-positive rate.	http://onlinelibrary.wiley.com/doi/10.1002/uog.14791/abstract	1 February 2015
Harmony NIPT					
General pregnancy population					
4.	Prospective blinded cohort	Norton 2015	NIPT evaluated alongside FTS. Participants and physicians blind to NIPT result. N = 18,955 (Canada, Europe, US). Outcomes: Area under the ROC curve (T21).	http://www.nejm.org/doi/full/10.1056/NEJMoa1407349	23 April 2015
5.	Clinical experience	Willems 2014	Clinical experience. N = 3000 (Belgium, Netherlands). Outcomes: Sensitivity, specificity, false-negative rate, false-positive rate.	http://www.fvvo.be/archive/volume-6/number-1/facts/the-first-3000-non-invasive-prenatal-tests-nipt-with-the-harmony-test-in-belgium-and-the-netherlands/	March 2014
6.	Prospective cohort	Nicolaides 2012	Blood collected at FTS. NIPT evaluated after invasive testing. Lab staff blind to trisomy status. N = 2,049 (UK). Outcomes: Sensitivity (detection rate), false-positive rate (risk cut-off 1%) (T21, T18).	http://www.ajog.org/article/S0002-9378(12)00913-1/abstract	November 2012
7.	Case control	Ashoor 2013	Blood collected at FTS (controls) or after invasive testing (cases). N = 1,949 (UK, US). Outcomes: false-positive rate (risk cut-off 1%) (T13).	http://onlinelibrary.wiley.com/doi/10.1002/uog.12299/abstract	23 November 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***
8.	Prospective cohort	Del Mar Gil 2013	Blood collected at FTS. NIPT evaluated as per practice (prior to determining need for invasive test). Participant and physician unblinded to NIPT result. N = 1,005 (UK). Outcomes: false-positive rate (risk cut-off 1%) (T21, T18, T13).	http://onlinelibrary.wiley.com/doi/10.1002/uog.12504/abstract	7 June 2013
9.	Case control	Sparks 2012a	Compared 'average-risk' women (no invasive testing at time of blood collection) with confirmed cases. N = 298 (US). Outcomes: Z-statistics (risk cut-off not reported) (T21, T18).	http://onlinelibrary.wiley.com/doi/10.1002/pd.2922/abstract	6 January 2012
10.	Retrospective chart review	Fairbrother 2013	Comparing NIPT and FTS. Actual practice with NIPT implementation. N = 289 (US). Outcomes: Negative and positive rates (risk cut-off not reported) (T21, T18, T13).	http://onlinelibrary.wiley.com/doi/10.1002/pd.4092/abstract	15 March 2013
11	Retrospective and prospective	Del Mar Gil 2014	NIPT evaluated after invasive test result, using blood collected at FTS, and NIPT as per actual practice. N = 275 (UK). Outcomes: Sensitivity (detection rate), false-positive rate (risk cut-off 1%) (T21, T18, T13 in twins).	http://www.karger.com/Article/FullText/356495	June 2014
12.	Prospective cohort	Stokowksi 2015	NIPT evaluated after invasive test result or karyotyping at birth. N = 799 (Sweden, UK, US). Outcomes: Sensitivity (detection rate), specificity (T21, T18, T13).	http://www.karger.com/Article/FullText/356495	June 2014
Trisomy high-risk population					
13.	Prospective cohort	Norton 2012	Blood collected prior to invasive testing. NIPT evaluated after invasive test. Lab staff blind to invasive test result. N = 3,228 (Netherlands, Sweden, US). Outcomes: Sensitivity, specificity (by risk cut-off) (T21, T18).	http://www.ajog.org/article/S0002-9378(12)00584-4/abstract	August 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***
14.	Prospective consecutive cohort	Verweij 2013	Blood collected prior to invasive testing. NIPT evaluated after invasive test. Lab staff blind to invasive test result. N = 520 (Netherlands, Sweden). Outcomes: Sensitivity, specificity, false-negative rate, false-positive rate, accuracy (risk cut-off 1%) (T21).	http://onlinelibrary.wiley.com/doi/10.1002/pd.4182/abstract	21 July 2013
15.	Nested case-control	Ashoor 2012	Blood collected prior to invasive testing. NIPT evaluated after invasive test. Lab staff blind to invasive test result. Each case matched to 3 controls for length of sample storage. N = 400 (Netherlands, Sweden, US). Outcomes: Sensitivity, specificity (risk cut-off not reported) (T21, T18).	http://www.ajog.org/article/S0002-9378(12)00060-9/abstract	April 2012
16.	Prospective	Sparks 2012b	Lab staff not blind (training set) or blind (validation set) to invasive test result. N = 338 (UK). Outcomes: Sensitivity, specificity (by risk cut-off) (T21, T18).	http://www.ajog.org/article/S0002-9378(12)00061-0/abstract	April 2012
17.	Case control	Nicolaides 2014	Blood collected prior to invasive testing. NIPT evaluated after invasive test result. Lab staff blind to invasive test result. N = 177 (UK). Outcomes: Sensitivity (detection rate), false-positive rate (risk cut-off 1%) (SCA).	http://www.karger.com/Article/FullText/357198	February 2014
18.	Case control	Hooks 2014	Blood sample collected prior to invasive testing. NIPT evaluated after invasive test. Lab staff blind to invasive test result. N = 432 (UK). Outcomes: Sensitivity (detection rate), false-positive rate (risk cut-off not reported) (SCA).	http://onlinelibrary.wiley.com/doi/10.1002/pd.4338/abstract	20 February 2014
Panorama NIPT					

	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***
General pregnancy population					
19.	Prospective cohort	Nicolaides 2013	Blood collected before CVS. NIPT evaluated after invasive testing. Lab staff blind to trisomy status. N = 242 (UK). Outcomes: Sensitivity (detection rate), specificity), false-positive rate (risk cut-off not reported) (T21, T18, T13).	http://onlinelibrary.wiley.com/doi/10.1002/pd.4103/abstract	24 April 2013
20.	Prospective cohort	Pergament 2014	Blood samples collected at various stages (FTS, invasive testing, birth/termination). Lab staff blinded to ~50% samples. N = 1,064 (international). Outcomes: Sensitivity (detection rate), specificity, false-negative rate, false-positive rate (risk cut-off not reported) (T21, T18, T13).	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4144440/	1 August 2015
21.	Case control	Ryan 2016	Blood sample and blinding information not reported. N = 587 (US). Outcomes: Sensitivity (detection rate), specificity (T21, T18, T13)	http://www.karger.com/Article/FullText/442931	31 March 2016
22.	Case control	Zimmermann 2012	Blood samples drawn prior to invasive testing (euploid) or after (most aneuploid). Lab staff unblinded. N = 166 (US). Outcomes: Sensitivity (detection rate), specificity, accuracy (T21, T18, T13).	http://onlinelibrary.wiley.com/doi/10.1002/pd.3993/abstract	30 October 2012
Other relevant Australian studies					
23.	Cost-effectiveness model	Ayres 2014	Cost-effectiveness analysis of different strategies of NIPT for trisomy 21 screening in comparison with current practice	http://onlinelibrary.wiley.com/doi/10.1111/ajo.12223/full	8 September 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***
24.	Review	Hui 2013	Review of the basis of NIPT, literature describing the effectiveness of NIPT in screening for T21, and the potential methods by which NIPT could be incorporated into current screening strategies	http://onlinelibrary.wiley.com/doi/10.1111/ajo.12117/abstract	31 July 2013
25.	Expert survey	Hui 2015	Survey on the use and clinical implementation of NIPT by all members of the Australian Association of Obstetrical and Gynaecological Ultrasonologists, during its first year of local availability	http://onlinelibrary.wiley.com/doi/10.1111/ajo.12306/abstract	29 April 2015
26.	Retrospective analysis	Maxwell 2016	Analysis of screen-positive and detection rates for T21 by FTS risk cut-off, and analysis of the implications for the introduction of NIPT in a contingent screening model	http://onlinelibrary.wiley.com/doi/10.1111/ajo.12428/abstract	8 January 2016
27.	Prospective study	McLennan 2016	Review of NIPT data at three private practices specialising in obstetric ultrasound and prenatal diagnosis to assess detection rates for T21, T18 and T13 and compare outcomes for 3 screening models	http://onlinelibrary.wiley.com/doi/10.1111/ajo.12432/abstract	27 January 2016
28.	Cost-effectiveness model	O'Leary 2013	Cost-effectiveness decision tree analysis of introducing NIPT for women found to be at high-risk following FTS, assessing the reduction in invasive tests and procedural-related fetal losses, additional T21 cases confirmed, and cost per T21 case confirmed	http://onlinelibrary.wiley.com/doi/10.1111/ajo.12136/abstract	1 October 2013

	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***
29.	Retrospective analysis	Robson 2015	Assessment of reduction in invasive testing by comparing amniocentesis/CVS numbers before and during the FTS era, and before and after the introduction of NIPT	http://onlinelibrary.wiley.com/doi/10.1111/ajo.12380/abstract	11 August 2015

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.*

19. **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.	Model	Diagnostic performance and costs of contingent screening models for trisomy 21 incorporating non-invasive prenatal testing.	Australian-based analysis of the performance and cost-effectiveness of contingent screening models using different threshold risks categorising women as being at low, intermediate, or high risk of fetal trisomy 21.	Not available	Manuscript in preparation

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

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

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

    The Royal College of Pathologists of Australasia (RCPA)

    Human Genetics Society of Australia (HGSA)

    The Royal Australian College of General Practitioners (RACGP)

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

    See above

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

    We have recently contacted Prenatal Diagnosis Support Australia (http://www.pdsaustralia.org) and Downs Syndrome Australia and will provide an update on their support as soon as possible.

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

    This application is being submitted by Roche Diagnostics Australia, suppliers of the Harmony NIPT. The application is generic, being delimited by attributes of test performance, not by the distributer.

24. **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: **REDACTED**

    Telephone number(s): **REDACTED**

    Email address: **REDACTED**

    Justification of expertise: **REDACTED**

    Name of expert 2: **REDACTED**

    Telephone number(s): **REDACTED**

    Email address: **REDACTED**

    Justification of expertise: **REDACTED**

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

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

__PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION__

25. **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:**

    Down syndrome is a condition that occurs when an extra chromosome 21 originates in the development of either the sperm or the egg. Down syndrome is the most frequently occurring, clinically significant genetic condition in newborns. It can cause delays in physical and intellectual development. Other complications include increased risks of heart defects, leukaemia, infectious diseases, dementia, sleep apnea and obesity. Down syndrome occurs in 1/380 pregnancies and 1/901 newborns, and is associated with a higher than average mortality; however, patients can live to 60 years on average (Abeywardana et al 2008).

    Trisomy 18 is due to an extra copy of chromosome 18. Trisomy 18 known clinically as Edwards syndrome and is associated with a high rate of miscarriage. Infants born with Edwards syndrome have various medical conditions and a shortened lifespan. The clinical presentation of Edwards syndrome is characterised by antenatal growth deficiency, specific craniofacial features, major system malformations and marked psychomotor and cognitive developmental delay. Edwards syndrome occurs in 1/1,480 pregnancies 1/5,000 newborns (Abeywardana et al 2008). A study in England and Wales estimated that for live births with non-mosaic Edwards' syndrome, the median survival time is 14 days, with 3-month and 1-year survival rates of 20% and 8%, respectively (Wu et al 2013).

    Trisomy 13, Patau syndrome, is due to an extra chromosome 13 and is associated with a high rate of miscarriage. Trisomy 13 occurs in 1/3,846 pregnancies and 1/16,667 newborns (Abeywardana et al 2008). A study in England and Wales estimated that for live births with non-mosaic Patau syndrome, the median survival time is 10 days, with 3-month and 1-year survival rates of 18% and 8%, respectively (Wu et al 2013).

26. **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:**

    <u>Characteristics of patients</u>

    For pregnant women the risk of fetal trisomy involving chromosomes 21, 18, and 13 rises markedly with maternal age. Prenatal screening is the term used to define the noninvasive tests carried out during pregnancy that give an indication for the possible presence of a fetal aneuploidy. These include serum markers and ultrasound test currently listed on the MBS, as well as the NIPT test proposed as a contingent test in this application. These tests are not diagnostic and require invasive testing to confirm the result. The first approach to prenatal screening for trisomy 21 was to offer amniocentesis and fetal cytogenetic studies to women aged 35 years or more. This maternal-age threshold corresponded to a risk of approximately 1:300 at birth, and became a de facto definition of the threshold risk at which invasive testing is warranted.

    The introduction of biochemical screening of maternal plasma, initially in the second trimester and subsequently in the first trimester, together with first trimester ultrasound studies, improved the performance of screening programs for fetal trisomies. These programs achieved sensitivities of 80-90% for trisomy 21, and specificities of 95-97% (i.e. low positive predictive value).

    Experience with these screening programs documented the risk of fetal loss as a consequence of amniocentesis or chorionic villus biopsy. These programs also demonstrated that the chromosome status of the placenta and fetus could be discordant, with ~1:3,000 normal fetuses having an aneuploid placenta, and ~1:100 trisomic fetuses having a normal placenta (Grati et al 2014).

NIPT is based on the analysis of fetal cfDNA that is present in maternal plasma. As most of this cfDNA is in fact derived from the placenta/trophoblast strictly speaking, the term "fetal cfDNA" is incorrect, but it has wide currency and will be used in this application. Analysis of fetal cfDNA has the potential to identify trisomic fetuses, subject to the biological discordances noted above.

cfDNA is a highly variable analyte (Breitbach et al 2012, Dwivedi et al 2012, Haghiac et al 2012, Tug et al 2015). In non-pregnant subjects, the concentration of cfDNA rises 10-fold with exercise, inflammation or obesity and can return to baseline levels within 90 minutes. In a pregnant woman, such a rise would reduce the corresponding proportion of cfDNA derived from the fetus and render assessment of fetal aneuploidy impossible. In the presence of sufficient fetal cfDNA for analysis, NIPT is highly sensitive and specific. The specificity of NIPT potentially allows a risk-based approach to testing for trisomies that is broader than the maternal-age-related threshold of 1:300.

Currently, Australian clinical guidelines fail to clearly define the place of NIPT. RANZCOG (2015) suggests that: 1) the uptake of this particular aspect of screening should be optional where possible; 2) if a woman has received a normal/low risk result from a cfDNA screening test, an additional risk calculation for aneuploidy by FTS is not recommended as this will increase the false positive rate without substantially improving the detection rate; 3) presence of a fetal structural anomaly remains an important indication for invasive prenatal testing, even in the presence of a prior normal/low risk cfDNA result.

The International Society for Prenatal Diagnosis (ISPD) considers the use of cfDNA to be appropriate within the following protocols: 1) a primary screening test offered to all pregnant women; 2) secondary to a high risk assessment based on serum and ultrasound screening protocols; or 3) contingently offered to a broader group of women ascertained as having high or intermediate risks by conventional screening Methods. The American College of Medical Genetics and Genomics also released updated guidelines for the use of cfDNA for screening. These guidelines recommend that all pregnant women are Informed that NIPS is the most sensitive screening option for traditionally screened aneuploidies.

Proposed model for patient eligibility

The sponsor proposes a contingent testing model for the implementation of NIPT. This model categorises pregnant women into one of three categories (low risk, intermediate risk, high risk of fetal trisomy) based on FTS. Women at 'intermediate risk' are offered NIPT. Women at 'high risk' would be recommended invasive testing as per current practice, and women at 'low risk' would undergo no further testing, as per current practice. Women at 'intermediate risk' would be referred by their general practitioner (GP) or obstetric specialist for NIPT to potentially avoid unnecessary invasive testing and the associated risk of miscarriage.

It is proposed that the risk cut-offs used to define low and high risk (with intermediate risk being between these categories) would be explored as part of the assessment. The base case low- and high-risk cut-offs would be <1:1000 and >1:10, respectively. Hui et al (2013) estimate that 0.5% of women would be considered 'high risk' and 86.5% considered 'low risk' at these thresholds.

• the use of NIPT only in 'high risk' pregnancies, takes advantage of the negative predictive value of NIPT to reducing invasive testing in high-risk women (and associated testing costs and miscarriage risks), but it would not improve the overall sensitivity of testing relative to FTS alone (Hui et al 2013).

• the low risk threshold could eventually be reduced to a level where all women are offered NIPT, irrespective of the FTS risk assessment, thereby negating the utility of FTS as a triage tool prior to NIPT. Of note there may be other benefits in retaining FTS for detection of conditions other than fetal trisomies 21, 18 and 13.

Recent clinical studies have demonstrated the benefits of NIPT as a primary testing tool in the general pregnancy population (see Part 4 above). The Royal Australian and New Zealand College of Obstetrics and Gynecology (RANZCOG) released a statement in March 2015 (C-Obs 59) recognising the value of NIPT as an optional test alongside current FTS (RANZCOG 2015). This document is currently under revision.

27. **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):**

The approach to FTS for T21 and T18 recommended by RANZCOG (2015) is presented below. The same approach is also used to test for T13 and other chromosomal abnormalities.

Pregnant women are offered an initial risk assessment (FTS) based on their age, biochemical blood analysis, and an ultrasound. Women with a risk of 1:300 or higher for T21 (Down syndrome) are then offered diagnostic testing via either chorionic villus sampling (CVS) or amniocentesis. Women confirmed by invasive testing as carrying a trisomic fetus are then offered the option of terminating their pregnancy.

As shown in Diagram 1 (**Attachment 2**), FTS currently consists of:

1. maternal age;
2. ultrasound measurement of fetal nuchal translucency (NT), where available.
3. blood collected at 9 weeks – 13 weeks 6 days for biochemical analysis of:
   - pregnancy associated placental protein-A (PAPP-A)
   - free βhCG; and

Under this proposal, NIPT would be offered to women considered to be at 'intermediate risk' of trisomies based on their FTS and other factors (**contingent testing model – see part 6a/25 above**).

Another option would be to provide NIPT as a first-line testing option (**primary testing model**). It is expected that NT ultrasound and current FTS biochemistry (maternal serum) screening would continue to be offered for the detection of conditions other than the fetal trisomies 21, 18 and 13 (thus outside the scope of this application for NIPT).

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

The NIPT would be ordered by a GP or obstetric specialist, similar to current FTS tests

NIPT can be delivered in many clinical settings, such as GP offices, obstetric clinics, public or private hospitals, in vitro fertilisation (IVF) centres, ultrasound centres, and radiology centres.

As a simple blood draw, no additional equipment, personnel or experience is necessary other than access to phlebotomy. A trained phlebotomist is required to draw maternal blood as routinely occurs for FTS currently. Two tubes of maternal blood are collected for analysis. The blood is collected via a standard phlebotomy procedure and sent to a certified laboratory for analysis.

All NIPT laboratories should only issue a report if the fetal cfDNA fraction is documented to be sufficient to detect fetal trisomy in the sample received. Multiple studies have now verified the importance of fetal fraction and it is becoming recognized as an essential laboratory quality control metric. In 1-2% of cases a repeat sample is required due to low fetal fraction of cfDNA. Clinical studies demonstrate fetal fraction to vary positively with gestational age, negatively with maternal weight, and improve on blood redraw (Wang et al 2013).

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

Several private institutions offer an NIPT using cfDNA to analyse risk for common trisomies. Each company uses a unique technology and requires independent clinical validation.

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

Not applicable

31. **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):**

As described above, NIPT can be delivered in the same clinical settings where FTS is currently delivered, and no additional equipment, personnel or experience is necessary other than access to phlebotomy. Therefore, there are no limitations on accessibility compared with current FTS.

32. **If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:**

Under the contingent testing model, the NIPT would be delivered subsequent to current combined FTS, which includes an NT scan (MBS Item 55700) and first trimester biochemistry (MBS Item 66750) as part of the consultation, for those women considered to be at 'intermediate risk' as a result of combined FTS.

Under the primary testing model, the NIPT would be delivered as a first-line testing option. It is expected that NT ultrasound and FTS biochemistry (maternal serum screening) would continue to be performed for the detection of conditions other than fetal trisomies 21, 18 and 13 (thus outside the scope of this application for NIPT).

Similar to the current protocol with FTS, genetic counselling may be offered to women with an 'intermediate risk' result for FTS, and/or 'high risk' result for NIPT (not covered by the MBS).

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

The NIPT would be ordered by a GP or obstetric specialist, similar to current FTS tests. The NIPT results would be interpreted and used by the GP, specialist, midwife or genetic counsellor.

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

Not applicable

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

The NIPT can be offered, and the referral made, by an obstetric specialist or GP. The NIPT testing should be performed by a NATA accredited Pathology laboratory.

36. **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:**

Requesting doctor: the pre-test counselling requirements are similar to those already required for FTS i.e. this is a screening for test for potentially serious abnormality. The test is not diagnostic and, in the event of an abnormal screen, confirmatory testing would be required.

Phlebotomist: no additional training.

Laboratory staff: training and supervision as per NCAAP requirements for an accredited test.

37. **(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

Specify further details here

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

NIPT is run in a laboratory, but the blood draw can occur in a number of settings including an outpatient office or pathology blood collection site. This is the same situation as for the blood samples collected for biochemical analysis as part of FTS. The consultation with the GP or obstetrician would occur in a consulting room or outpatient clinic.

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

☒ Yes

☐ No – please specify below

Specify further details here

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

39. 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):

As agreed by PASC in December 2014, the comparator for NIPT is current combined FTS (i.e. biochemical and NT screening without NIPT). However, NIPT would not replace current combined FTS (see paragraph below), but would augment it, either by being offered subsequently after triage following FTS for women at intermediate risk (contingent testing model) or additional to current NT ultrasound or FTS biochemistry which would be used to detect conditions other than fetal trisomies 21, 18 and 13 (primary testing model).

Theoretically, NIPT can be used instead of FTS for the detection of fetal trisomies 21, 18, or 13. However, under either testing model, first trimester biochemistry would also still be of use to determine the risk for other obstetric conditions. PaPP-A levels for example can help to determine the risk of fetal loss, preterm birth, intrauterine growth restriction and pre-eclampsia, and the detection of aneuploidies other than trisomies 21, 18 and 13 (outside the scope of this application for NIPT). Ultrasound is still advised for correct dating, diagnosis of multiple pregnancies, and chorionicity and anatomy assessment (fetal anomalies and physical deformities).

The reference standard is CVS or amniocentesis, which provide confirmatory diagnosis following FTS or NIPT, but with an increased cost and associated risk of miscarriage.

40. 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

The MBS item numbers relevant to the comparator (FTS) are:

• NT scan (MBS Item 55700)

• First trimester biochemistry (MBS Item 66750)

41. **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):**

Currently, following FTS (without NIPT), women deemed to be at an increased risk (≥1:300) of trisomies are recommended to undergo invasive diagnostic testing (Diagram 1 - Attachment 2). Women not deemed to be at an increased risk generally are not recommended any further testing.

Women recommended and opting to undergo diagnostic testing receive pre-test counselling and information, and undergo either CVS or amniocentesis. There is a risk of miscarriage associated with either procedure. Women diagnosed with having a fetus affected by trisomy based on invasive testing, are offered further counselling and termination of pregnancy. Women who do not opt for termination would require further support to assist with managing the trisomic birth (as would false-negatives from the FTS).

With such a program, the sensitivity is ~80-90%, but the specificity is only 95-97%. When applying this performance to the average risk of Down Syndrome in the Australian pregnancy population we achieve a positive predictive value of only 3-5%. As a result, many invasive diagnostic tests are required to diagnose each affected pregnancy, and these tests carry the risk of procedure-related loss of chromosomally normal fetuses.

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

☐ Yes

☒ No

(b) **If yes, please outline the extent of which the current service/comparator is expected to be substituted:**

It is expected that with the introduction of NIPT, current combined FTS would continue to be performed.

Although NIPT has the potential to replace FTS, it is expected that current biochemistry screening would continue to be performed for the detection of other conditions outside the scope of this NIPT application. Similarly, NT ultrasound would still be required for correct dating, diagnosis of multiple pregnancies, and chorionicity and anatomy assessment (fetal anomalies and physical deformities). Of note RANZCOG (2015) recognise the value of NIPT as an optional test alongside current FTS.

The introduction of NIPT within a contingent or primary testing model would reduce the number of invasive tests, and associated risk of miscarriage.

43. **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 proposed clinical management pathway with NIPT (current pathway with NIPT introduced) is presented in the Diagram 2 and 3 (Attachment 2) and below.

In the contingent testing model, NIPT is offered prior to invasive diagnostic testing with CVS or amniocentesis for women determined by FTS to be at 'intermediate risk'. This would reduce the number of invasive procedures and associated risks of miscarriage, whilst providing a similarly and more accurate diagnosis of T21, T18 or T13.

Women indicated by NIPT to be at 'high risk' would be offered invasive confirmatory testing (CVS or amniocentesis). Therefore, fewer of the following invasive tests would be performed overall:

- Chorionic villus sampling (MBS Item 16603)
- Amniocentesis (MBS Item 16600)
- Consultation (MBS Item 104)
- Cytogenetics/karyotyping (MBS Item 73287)

Notably, Robson et al (2015) report that following the introduction of NIPT, the number of amniocenteses performed in Australia fell by 51% between the first quarter of 2013 and the final quarter of 2014 (p < 0.005), and the total number of CVS fell by 37% over the same period (p < 0.005). This represents the largest annual decrease in invasive procedures during the previous 20 years (e.g., compared to the introduction of combined FTS circa 2000).

Under a contingent testing model (Diagram 2 – Attachment 2), there may be an increased demand for genetic counselling (not funded under the MBS) among women recommended NIPT due to an 'intermediate risk' result with FTS. However, NIPT would reduce the demand for pre/post-invasive test counselling. The net impact on genetic counselling is ambiguous and would be determined in the Assessment.

Under a primary screening model (Diagram 3 – Attachment 2), NIPT due to its superior performance in detecting trisomies 21, 18 and 13 would be performed as first-line test. However it is not expected to replace either NT ultrasound or biochemistry screening performed as part of current FTS, since those tests are required to detect other fetal conditions, including fetal growth restriction, preeclampsia and rare genetic syndromes (see responses to questions 26, 31 and 38).   However, with first line testing by NIPT there may nevertheless be a reduction in traditional FTS for two reasons.

First, traditional screening tests have several limitations:

• Serum proteins and ultrasound use indirect and non-specific markers to assess trisomy risk.
• Measurements must be taken during specific time periods (first trimester bloods and NT between 11-13 weeks and second trimester bloods between 15-19 weeks).
• Ultrasound assessment typically requires referral to a specialist.
• These screening tests produce false positive rates of up to 5% for trisomies 21, 18 and 13 and fail to identify up to 30% of Down syndrome cases.

Second, NT screening requires a skilled user to provide an accurate scan, and there is variation in the experience of operators. In some regional/rural areas, access is limited or not available. If a high quality NT scan is not readily accessible, NIPT may be used instead.

NIPT may therefore reduce the utilisation of:
• First trimester biochemistry (MBS Item 66750)
• Second trimester biochemistry (MBS item 66751)
• NT scan (MBS Item 55700).

Under a primary testing model, the number of genetic counselling consultations is expected to decrease in line with the demand for invasive testing. Pre/post-test counselling for NIPT is expected to be combined with FTS counselling.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

44. 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):

Traditional first-line screening for Down syndrome involves the measurement of serum proteins via a blood draw and ultrasound assessment. The limitations of serum proteins and ultrasound assessment are outlined in the response to question 42 above.

These screening tests also produce false positive rates of up to 5% for potential chromosome conditions and fail to identify 10-30% of Down syndrome fetuses. This means 1 in 20 women are given a false positive result which leads to maternal anxiety and unnecessary further testing with invasive procedures such as amniocentesis that can cause miscarriage (see below).

Invasive diagnostic tests (CVS, amniocentesis) are typically offered to women who receive positive FTS screening results (including false positives) and to women with other 'high risk' criteria (age ≥35 years, previous pregnancy with trisomy, etc.). While such tests provide confirmatory diagnosis, they are highly invasive and associated with a miscarriage risk, which varies depending on the skill of the operator and the number of procedures performed. Miscarriage risks of up to 0.5% with amniocentesis and up to 1% with CVS (additional to background miscarriage risks) have generally been reported, with more recent evidence suggesting weighted pooled procedure-related risks of miscarriage for amniocentesis and CVS of up to 0.11% and 0.22%, respectively (Avolekar et al 2016, Wulff et al 2016).

Therefore, 15,000 women per year can be unnecessarily alarmed through a false positive result with traditional methods, and 150 normal foetuses potentially lost each year as a result of unnecessary invasive procedures (based on 300,000 pregnancies in Australia per year – see question 46). The potential benefits of NIPT are in lowering the risk of miscarriage and healthcare costs by avoiding unnecessary invasive testing.

The benefits of NIPT as compared to traditional FTS screening methods for Down syndrome are highlighted below for the Harmony NIPT.

	NIPT (Gil et al 2015, Mackie et al 2016, Taylor-Phillips et al 2016)	Traditional FTS (Norton et al 2015)
Analyte	**Direct:** Fetal cfDNA	**Indirect:** Serum proteins, ultrasound measurements
Accuracy (sensitivity)	>99%	70-90%
False positive rate	0.09%	4-5%
Workflow	Standard blood draw	May require multiple visits, specialist referral

Under a contingent (or primary) testing model, NIPT is expected to reduce the number of invasive tests in normal fetuses and subsequently reduce the associated complications such as miscarriage.

The fundamental purpose of any prenatal test, including NIPT, is to provide the pregnant woman with a reliable result that can be the basis for her informed decision-making. If a woman's primary testing result is confirmed by diagnostic testing the options available to her include continuing the pregnancy and termination of the pregnancy. These options carry different costs subsequent to the prenatal diagnosis, and the proportions of women choosing different options will impact on the overall outcome of the screening process, whether that is measured by the incidence of trisomy at term, cost per prenatal diagnosis, or quality of life for the mother.

45. **Please advise if the overall clinical claim is for:**

☒ Superiority

☐ Non-inferiority

46. **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

The primary safety outcome will be number of miscarriages associated with amniocentesis/CVS.

NIPT provides an analysis of maternal venous blood collected using a standard phlebotomy procedure. Therefore, there are no potential risks to the mother (or fetus) from the technology, other than the minor side effects of bruising and inflammation (phlebitis) associated with a standard blood draw.

Clinical Effectiveness Outcomes

The primary effectiveness outcomes proposed for the Assessment are:

- trisomy (T21, T18 and T13) cases detected;

- invasive procedures avoided.

'Trisomy cases detected' is consistent with the primary outcomes of the clinical studies, which report sensitivity (detection rate), specificity and other measures of diagnostic accuracy. Detection provides a woman with a greater reproductive choice.

Trisomies 21, 18, and 13 account for up to 80% of the chromosome abnormalities documented at term. Some of the remaining 20% of pregnancies with a non-trisomic chromosome abnormality are incidentally detected by FTS. Such events do not represent the primary purpose of FTS and the performance of FTS in detecting such pregnancies is not well characterised. In general NIPT is not intended to replace FTS for identification of fetal conditions other than trisomy 21, 18 and 13.

Secondary effectiveness outcomes include the consequences of identifying trisomies and avoiding invasive procedures (the primary effectiveness outcomes), including:

- reduced incidence of undetected trisomy (T21, T18 and T13) at term;

- euploid fetal losses (miscarriages of healthy foetuses, due to CVS or amniocentesis) prevented.

These outcomes are further expected to improve quality of life for the pregnant population, by reducing the number of false-positive (and false-negative) results and associated anxiety for pregnant women, and reducing the need for invasive testing and associated discomfort and impact of related fetal losses. However, quality of life is not proposed as an effectiveness outcome for the Assessment due to an expected absence of data.

Economic Outcomes

Previously, PASC indicated that the economic analysis should be a cost-effective analysis, exploring (Item 7: 1396 - Final Ratified PASC Meeting Outcomes, December 2014):

- cost per trisomic fetus detection;

- cost per miscarriage avoided;

- costs of testing, counselling, miscarriage, termination and Down syndrome births (including false positives and false negatives).

A reduction in the birth incidence of trisomies would reduce the costs of such medical and supportive care as might have been required.

Question 51 details a number of cost-effectiveness studies which could be utilised in exploring the economic outcomes of NIPT.

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

Under a contingent testing model, expected utilisation requires the proportion of women at 'intermediate risk' to be applied to the general pregnancy population. A detailed estimation will be undertaken in the Assessment, and is partly dependent on the proposed risk cut-offs.

A proxy for the number of women at gestational age ≥10 weeks each year in Australia is the number of mothers giving birth in Australia, which was 297,126 women in 2011, including live births and stillbirths (due to miscarriage or termination) from 20 weeks gestation (Li et al 2013). This number is projected to be ~300,000 women at present.

This slightly underestimates the number of eligible women by the numbers who miscarry or elect to terminate during gestational weeks 10-19. In 2011, 166 women in South Australia underwent termination for fetal reasons (Scheil et al 2013). Assuming these terminations all occurred between gestational weeks 10-19 then, compared with 20,043 women giving birth in South Australia, the estimated degree of underestimation in prevalence is only 0.083% (166 ÷ 20,043).

Based on 'low risk' and 'high risk' cut-offs of 1:1000 and 1:10, respectively, approximately 13% of pregnant women would be considered to be at 'intermediate risk' (Hui et al 2013), i.e. 39,000 women (13% × 300,000).

Under a primary testing model, the expected utilisation of NIPT can be estimated by simply multiplying the number of women at gestational age ≥10 weeks each year in Australia (~300,000) by expected uptake.

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

The NIPT would be delivered once per pregnancy in a woman's first trimester, unless a retest is required due to an indeterminate result. Realistically, therefore, NIPT would be offered up to two times per year. Currently, some providers provide a re-test at no extra charge

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

An NIPT may be accessed at any point during a woman's child-bearing age, typically defined as 15 to 44 years of age, in the years she is carrying a fetus from 10 weeks gestational age.

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

Among 32,478 women undergoing FTS in Western Australia in 2005–06, the uptake of invasive testing among women with a high-risk result from FTS was 75% (O'Leary et al 2013). This suggests that ~29,000 women would receive NIPT under a contingent testing model (75% × 39,000). However, uptake of NIPT is likely is likely to be higher than for invasive testing due to its relative ease and no risk of miscarriage.

Up ~230,000 women would use NIPT in the first full year under a primary testing model, based on the uptake of first trimester serum screening being 77% (83% total uptake × 93% of uptake in first trimester) in 2013 among pregnant women in Victoria, Australia (Hui et al 2016) (77% × 300,000 = 230,000).

51. **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:**

Utilisation expected to grow at a CAGR of 17.5% over the period 2014-2022 and then stabilise to increase in accordance with population growth among women aged 15-44 years.

No constraints in the health system in meeting the needs of the proposed population are expected. On the contrary, the reduction in invasive testing represents a reduction in demand on the health system. Under a contingent testing model, there may be utilisation of NIPT by women at low or high risk (as defined by the risk cut-offs). However women in low or high risk categories would not be eligible for Medicare reimbursement under the proposed MBS descriptor.

PART 8 – COST INFORMATION

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

The current private market cost of NIPT, for which testing is providing within Australia, is $395 to $550 (depending on the laboratory and provider).

NIPT implementation could bring not only substantial clinical benefit but also cost reduction. Cost savings with NIPT are mainly driven from fewer unnecessary invasive procedures, replacement of traditional screening test costs, and driving utilisation of primary care physicians while reducing specialist referrals. A reduction in the birth incidence of trisomies would reduce the costs of such medical and supportive care as might have been required.

There have been a number of published analyses of the cost-effectiveness of including NIPT in prenatal testing programs which support this application and outline models to explore the economic outcomes:

- *Cuckle et al. (2013)* found that the main factor in the economic evaluation was the unit cost of NIPT. They concluded that a contingent policy whereby 10% to 20% women selected during conventional first trimester screening undergo NIPT to be more cost-efficient than primary screening.

- *O'Leary et al. (2013)* developed a health economic model to compare the costs and benefits of the performance of noninvasive prenatal testing for high-risk pregnancies following first-trimester screening compared with current practice. They found that the implementation of NIPT would reduce the number of invasive diagnostic tests and the number of procedure-related fetal losses by 88%. While an increase in the cost was determined over a two year period, sensitivity analysis considered the impact of variation in a number of model parameters, including the cost and uptake of NIPT. The unit cost of NIPT has decreased since this study was published.

- *Ayres et al (2014)* published a cost-effectiveness analysis comparing different strategies to implement NIPT for Down syndrome (DS) screening in comparison with current practice in Australia. The number of DS cases detected and procedure-related losses (PRL) were compared between strategies. The incremental cost per case detected was the primary measure of cost effectiveness. They found that the strategy of offering NIPT as a second investigation following 'high-risk' CFTS stratification (> 1/300) was cost saving, more effective in avoiding PRL, however slightly less effective for DS detection than the current practice. It is implicit that modifying the thresholds of this strategy more in line with the suggested contingent model would increase the number of DS detected.

  Suthers and O'Leary (manuscript in preparation – see question 18: study 1) compared the performance and cost-effectiveness of contingent testing models using different threshold risks to a base model with sensitivity equivalent the current cFTS. They determined that thresholds of 1:10 (high risk) and 1:1000 (Low risk) had a 1% increase in the cost per diagnosis from the base model with an 8% increase in sensitivity and a 13 fold increase in diagnosis per fetal loss. The current private market cost of NIPT, for which testing is providing within Australia, is $395 to $550 (depending on the laboratory and provider).

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

The medical service can be described in two stages:

1. Pre-service: blood collection and cfDNA extraction (blood collection, test requisition, blood sample transportation, plasma preparation, cfDNA extraction);
2. Intra-service: analysis and reporting (library preparation [pre-PCR laboratory], detection of library products [post-PCR laboratory], microarray imager, analysis, patient report).

The time to complete stage 1 depends on the time required for the standard blood draw and collection of samples, transportation (location of the collection site relative to the laboratory, up to 4 business days), cfDNA extraction method (~1 day), and batching of samples.

The time to complete stage 2 depends on the specific NIPT test. Turnaround times are reported by NIPT providers to be approximately 3 to 10 business days.

54. 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
Proposed item descriptor: Non-invasive prenatal testing to assess the risk of fetal trisomy of chromosomes 21, 18, and 13 by quantification of fetal fraction and analysis of cell-free DNA in maternal plasma.   Eligibility for MBS funding: Categorised as intermediate risk in a contingent testing model   Fee: $ To be determined as part of the Assessment

PART 9 – FEEDBACK

The Department is interested in your feedback.

55. How long did it take to complete the Application Form?

Five days

56. (a) Was the Application Form clear and easy to complete?

☒ Yes

☐ No

(b) If no, provide areas of concern:

Describe areas of concern here

57. (a) Are the associated Guidelines to the Application Form useful?

☒ Yes

☐ No

(b) If no, what areas did you find not to be useful?

Insert feedback here

58. (a) Is there any information that the Department should consider in the future relating to the questions within the Application Form that is not contained in the Application Form?

☒ Yes

☐ No

(b) If yes, please advise:

Question 41 should be reworded to avoid confusion, and/or the yes/no response changed to other response options.

27 | P a g e
A p p l i c a t i o n   F o r m
N e w   a n d   A m e n d e d   R e q u e s t s   f o r   P u b l i c   F u n d i n g

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Attachment 1

Exemption from the regulatory requirements of the Therapeutic Goods Act 1989 supporting documentation

NIPT is currently performed in Australia by laboratories as an in-house IVD test.

The reagents and consumables supplied to laboratories performing NIPT are currently supplied by commercial companies as Research Use Only and therefore are exempt from registration with the TGA by the commercial company.

It is the responsibility of the laboratory performing this NIPT to comply with in-house IVD directives. Details of these directives can be found at TGA website.

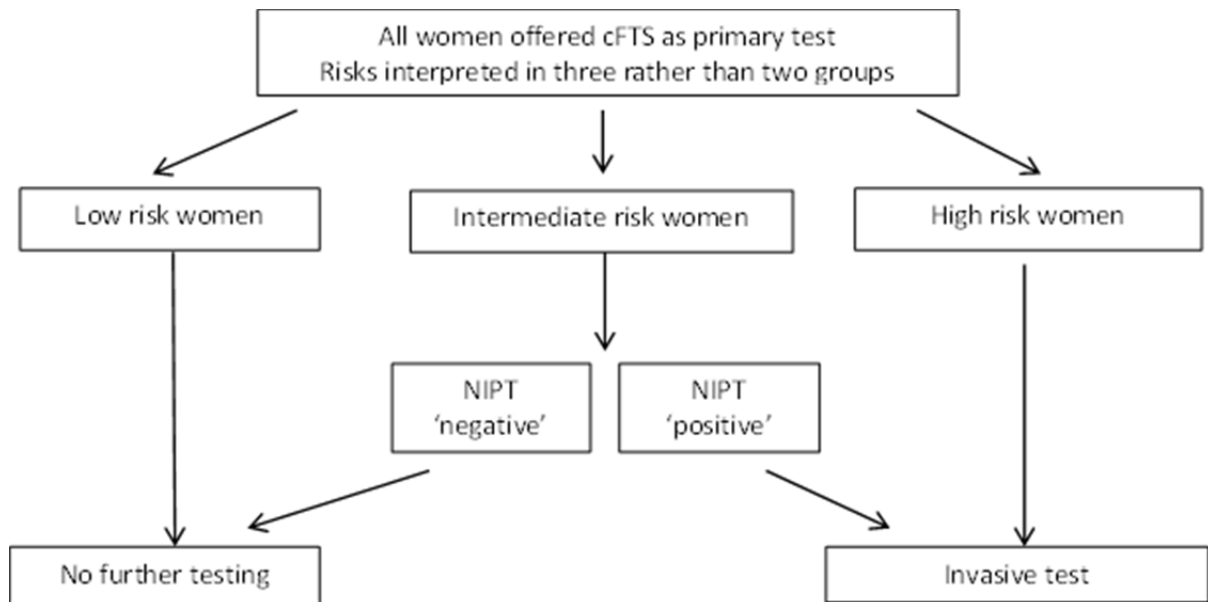# Attachment 2

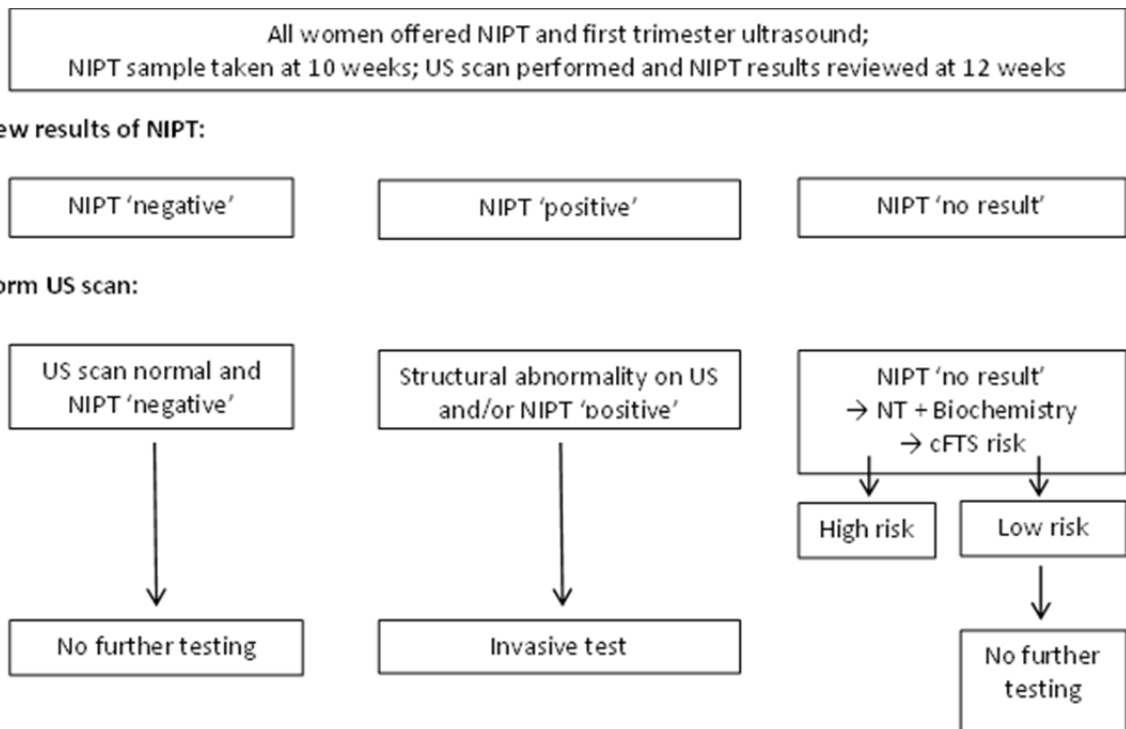**Diagram 1.**   <u>Current first trimester testing pathway</u>
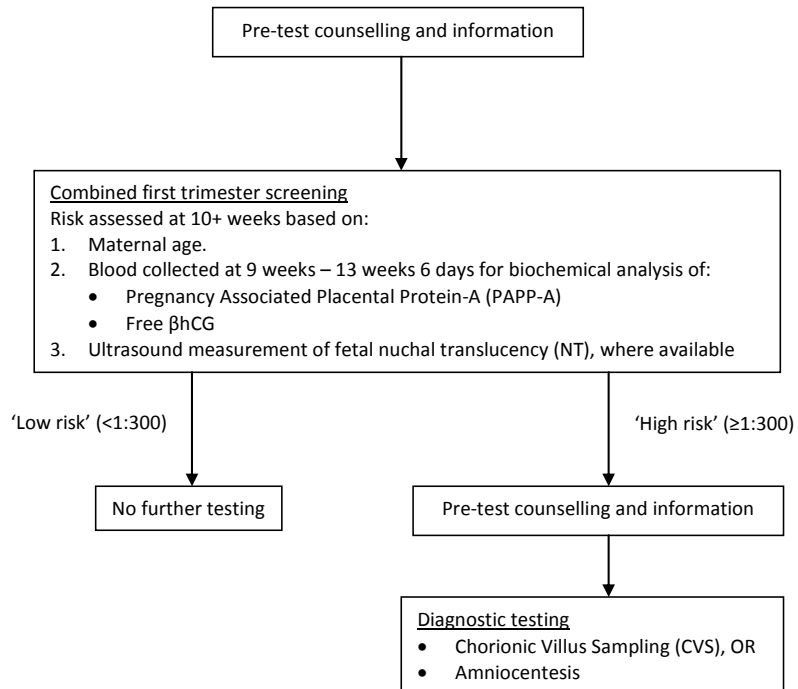
Diagram 2. Proposed prenatal testing pathway with NIPT funded under a contingent testing model

Source: Hui et al (2013), specific risk thresholds removed

Note: under specific thresholds for 'low risk' and 'high risk' the contingent testing model is identical to the general testing model (below) since all women would be within the risk range recommended to receive an NIPT

Diagram 3. Proposed prenatal testing pathway with NIPT funded under a primary testing model

Source: Hui et al (2013), specific risk thresholds removed