



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: The Royal College of Pathologists of Australasia

ABN: **redacted**

Business trading name: The Royal College of Pathologists of Australasia

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 (NIPT)

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)

The medical conditions relevant to the proposed service are conditions such as Down syndrome, Edward syndrome, Patau syndrome and Turner syndrome that arise where the number of chromosomes present in the patient is abnormal (aneuploidy).

Prenatal screening is a routine medical service for a pregnant woman to evaluate her personal risk of fetal aneuploidy. These aneuploidies include but are not limited to; trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome), trisomy 13 (Patau syndrome) and monosomy X (Turner syndrome).

This application is for Non-Invasive Prenatal Testing for the detection of fetal aneuploidies to be supported by public funding through the Medicare Benefit Schedule.

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 through the analysis of cell free fetal DNA is a major technological advancement in testing for fetal aneuploidy.¹⁻¹⁷

Until recently, obtaining tissue of fetal origin for genetic testing could only be obtained by invasive techniques such as amniocentesis (amniotic fluid samples containing fetal cells mostly of epithelial origin) or chorionic villus sampling (placental samples containing mesodermal connective tissue and trophoblastic cells of the placenta). However DNA from the fetus is found in circulating in maternal blood in intact fetal cells or after the breakdown of cells (mostly placental) as cell free DNA. Only 10-15% of cell free DNA circulating in maternal blood is fetal in origin but this fetal fraction can now be detected and measured.

In NIPT, cell free fetal DNA (cffDNA) is analysed by next generation sequencing (NGS) to detect quantitative differences in the number of DNA fragments of different chromosomes to distinguish fetal aneuploidies from unaffected pregnancies.

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:

Several assays are available for NIPT and all require single use consumables such as laboratory pipette tips.

This application does not endorse any one specific commercial product. A detailed listing of all products and their consumables is beyond the scope of this application. It should be noted that new products will continue to be developed using the same scientific principles.

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: In-vitro diagnostic test

Manufacturer's name: Various

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

ARTG listing, registration or inclusion number:

ARTG licence numbers for IVDs including but not limited to:

Human genetics-related IVDs

Abbott Australasia Pty Ltd Molecular Division 197099

In Vitro Technologies Pty Ltd 248555

Inborn/inherited genetic disorder IVDs

Abbott Australasia Pty Ltd Molecular Division 207725, 211695, 212778

Diagnostic Solutions Pty Ltd 201693

Emergo Asia Pacific Pty Ltd T/a Emergo Australia 262500

ESL Biosciences Australia 2012 Pty Ltd 214427

PerkinElmer 233472

Roche Diagnostics Australia Pty Limited 234007

TGA approved indication(s), if applicable: Insert approved indication(s) here

TGA approved purpose(s), if applicable: Insert approved purpose(s) here

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

Date of submission to TGA: Insert date of submission here

Estimated date by which TGA approval can be expected: Insert estimated date here

TGA Application ID: Insert TGA Application ID here

TGA approved indication(s), if applicable: If applicable, insert description of TGA approved indication(s) here

TGA approved purpose(s), if applicable: If applicable, insert description of TGA approved purpose(s) here

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: Insert date of submission here

Proposed indication(s), if applicable: If applicable, insert description of proposed indication(s)

Proposed purpose(s), if applicable: If applicable, insert description of proposed purpose(s) here

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***
1.	Clinical practice guidelines	Caramins M, Chopra M: Non-invasive prenatal testing, Common Sense Pathology. Surry Hills, NSW, Royal College of Pathologists Australasia (RCPA), Australian Doctor with funding from the Australian Government Department of Health., 2014	Australian clinical practice guidelines written by the Royal College of Pathologists of Australasia to support General Practitioners in providing counselling and guidance to patients and to inform appropriate decision-making regarding NIPT.	link to journal article	Feb 2014
2.	Observational study	Fairbrother G, Johnson S, Musci TJ, et al: Clinical experience of noninvasive prenatal testing with cell-free DNA for fetal trisomies 21, 18, and 13, in a general screening population. Prenat Diagn 33:580-3, 2013	US study of 289 pregnant women screened prenatally for fetal trisomy (30 Jul - 1 Dec 2012). NIPT was offered to all patients in addition to first trimester combined screening (FTS). The study concluded that NIPT has the potential to be a highly effective screening method as a standard test for risk assessment of fetal trisomies 21, 18, and 13 in general pregnant populations.	link to journal article	15 Mar 2013
3.	Observational study	Jiang F, Ren J, Chen F, et al: Noninvasive Fetal Trisomy (NIFTY) test: an advanced noninvasive prenatal diagnosis methodology for fetal autosomal and sex chromosomal aneuploidies. BMC Medical Genomics 5:1-11, 2012	A study of 903 pregnant women comparing NIFTY results with full karyotyping. The results demonstrated NIFTY had 100% sensitivity and 99.9% specificity for autosomal aneuploidies and 85.7% sensitivity and 99.9% specificity for sex chromosomal aneuploidies. The test was more accurate and robust for the detection of both fetal autosomal and sex chromosomal aneuploidies.	link to journal article	1 Dec 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***
4.	Clinical practice guidelines	Woolcock J, Grivell R: Noninvasive prenatal testing. Australian Family Physician 43:432-434, 2014	Australian clinical practice guidelines written by the Royal Australian College of General Practitioners (RACGP) to assist in making informed decisions about the use of NIPT. The guidelines indicated a high level of accuracy for the detection of Down Syndrome, the risks of insufficient counselling and the prohibitive costs for many women and their families.	link to journal article	Jul 2014
5.	Retrospective audit	Hui L, Teoh M, da Silva Costa F, et al: Clinical implementation of cell-free DNA-based aneuploidy screening: perspectives from a national audit. Ultrasound in Obstetrics & Gynecology 45:10-15, 2015	An Australian national audit of 1839 NIPT referrals by Australian Association of Obstetrical and Gynaecological Ultrasonologists (AAOGU). The results reported the accuracy of NIPT and the effects of its introduction on antenatal care in the private health sector.	link to journal article	2 Jan 2015
6.	Cost-benefit study	Gyselaers W, Hulstaert F, Neyt M: Contingent non-invasive prenatal testing: an opportunity to improve non-genetic aspects of fetal aneuploidy screening. Prenat Diagn 35:1347-52, 2015	Belgian study using national data to model the medical and economic impact of NIPT. The study reported that contingent NIPT screening would maintain current live birth prevalence of Down syndrome (LBPD) with an 11% reduction in costs. Lowering the screening threshold or increasing sensitivity could reduce LBPD with minimal increase of overall costs. It concluded that NIPT is both clinically and economically beneficial.	link to journal article	27 Oct 2015

	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.	Cost-benefit study	Fairbrother G, Burigo J, Sharon T, et al: Prenatal screening for fetal aneuploidies with cell-free DNA in the general pregnancy population: a cost-effectiveness analysis. J Matern Fetal Neonatal Med 29:1160-4, 2016	US cost-benefit study modelled on a cohort of 4 million pregnant women comparing NIPT to first trimester combined screening (FTS). The study demonstrated that compared to FTS NIPT identified 15% more trisomy cases, reduced invasive procedures by 88%, reduced iatrogenic fetal loss by 94% and is more economical at a NIPT unit cost of U\$550 with 85% screening adherence.	link to journal article	22 May 2015
8.	Cost-benefit study	Benn P, Curnow KJ, Chapman S, et al: An Economic Analysis of Cell-Free DNA Non-Invasive Prenatal Testing in the US General Pregnancy Population. PLoS One 10:e0132313, 2015	US cost-benefit study modelled on the general pregnancy population comparing conventional screening with NIPT. The results indicated that NIPT would reduce invasive procedures by 60.0% and the number of procedure-related euploid fetal losses by 73.5%. The study concluded that universal application of NIPT can be economically justified if provided for \leq \$744 and that offering NIPT to all pregnant women is associated with substantial prenatal healthcare benefits.	link to journal article	9 Jul 2015
9	Study of diagnostic accuracy	Cuckle H, Benn P, Pergament E: Cell-free DNA screening for fetal aneuploidy as a clinical service. Clin Biochem 48:932-41, 2015	US review of cell free DNA (cfDNA) screening for fetal aneuploidy. The study reported that the efficacy of cfDNA for common autosomal trisomies far exceeds conventional screening. The study concluded that a Primary cfDNA test has the highest performance but is expensive, while a Contingent test can achieve high performance at a relatively low cost.	link to journal article	4 Mar 2015

	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***
10.	Cost-benefit study	Non-invasive Prenatal Testing: A Review of the Cost Effectiveness and Guidelines. Rapid Response Report: Summary with Critical Appraisal. Ottawa ON, Canadian Agency for Drugs and Technologies in Health., 2014	A Canadian economic study providing information on the cost-effectiveness of NIPT and to describe evidence-based guidelines for its use.	link to journal article	10 Feb 2014
12.	Observational study	McLennan A, Palma-Dias R, da Silva Costa F, et al: Noninvasive prenatal testing in routine clinical practice - An audit of NIPT and combined first-trimester screening in an unselected Australian population. Aust N Z J Obstet Gynaecol 56:22-8, 2016	Australian study assessing the implementation of NIPT as first and second line screening for fetal aneuploidy (5267 pregnant women). The study demonstrated that NIPT achieved 100% trisomy 21 detection and had a higher detection rate for all aneuploidies when used as a first-line test. It concluded that NIPT is an advanced screening test, rather than a diagnostic test that benefits from additional CFTS.	link to journal article	29 Jan 2016
13.	Cost-benefit study	Morris S, Karlsen S, Chung N, et al: Model-based analysis of costs and outcomes of non-invasive prenatal testing for Down's syndrome using cell free fetal DNA in the UK National Health Service. PLoS One 9:e93559, 2014	UK study of the cost-benefits of NIPT compared with current screening for Down Syndrome (DS) in the National Health Service (NHS). The study concluded that if the NHS cost was at the lower end of the £400-£900 private sector price range with screening risk cut-off of 1:150, NIPT as contingent testing would be cost-neutral or cost-saving compared with current DS screening.	link to journal article	10 Apr 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***
14.	Study of diagnostic accuracy	Zhang H, Gao Y, Jiang F, et al: Non-invasive prenatal testing for trisomies 21, 18 and 13: clinical experience from 146,958 pregnancies. Ultrasound Obstet Gynecol 45:530-8, 2015	NIPT was performed on 146,958 samples. Aneuploidy was confirmed in 720 of 781 T21-positive cases, 167 of 218 T18-positive cases, and 22 of 67 T13-positive cases. The overall sensitivity of NIPT was 99.17% for T21, 98.24% for T18, and 100% for T13, and the specificity was 99.95% for T21, 99.95% for T18, and 99.96% for T13.	link to journal article	May 2015
15.	Cost benefit study	Ayres AC, Whitty JA, Ellwood DA. A cost-effectiveness analysis comparing different strategies to implement noninvasive prenatal testing into a Down syndrome screening program. Australian and New Zealand Journal of Obstetrics and Gynaecology. 54(5):412-7, 2014.	An Australian study to evaluate the cost-effectiveness of different strategies of NIPT for Down Syndrome (DS) screening compared with current practice on a theoretic cohort of 300,000 pregnancies. Benefits of universal screening were identified as 18% increase in DS detection and 89% decrease in invasive procedures. The study concluded that the cost of NIPT needs to decrease significantly if it is to replace current practice.	link to journal article	2014
16.	Observational study	Nicolaidis KH. First trimester diagnosis of chromosomal defects. In: The 11-13 ⁺⁶ weeks scan. London Fetal Medicine Foundation; 2004.	A summary of factors involved in first trimester pregnancy diagnosis of chromosomal defects and the calculation of individual risk.	link to journal article	2004

	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.	Observational study	Taneja PA, Snyder HL, de Feo E, et al: Noninvasive prenatal testing in the general obstetric population: clinical performance and counseling considerations in over 85 000 cases. Prenatal Diagnosis 36:237-243, 2016	US study of demographics and test metrics for 86,658 NIPT clinical cases (aneuploidy for chromosomes 21, 18, or 13). Of the 1360 (1.6%) cancellations, only 101 (0.1%) were for technical reasons. Overall positive predictive value (PPV) was 83.5% (608/728); observed PPVs for trisomies 21, 18, and 13 ranged from 50.0 to 92.8%. Data was used to develop a chart for counselling patients on PPV based on maternal age. The report demonstrated that NIPT is a highly accurate screen for fetal aneuploidy in the general obstetric population.	link to journal article	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.

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.	Clinical practice guidelines	The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) review of NIPT	RANZCOG are currently receiving submissions and preparing new guidelines on NIPT.	link to journal article	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.

***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):**

Royal College of Pathologists of Australasia (RCPA)

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

It should be noted that the RCPA provides the comparator services of maternal serum markers (biochemical testing) and karyotyping (genetic testing).

Other professional bodies:

Royal Australian and New Zealand College of Radiologists

Royal Australian and New Zealand College of Obstetricians & Gynaecologists

Royal Australasian College of General Practitioners

Royal Australasian College of Physicians

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

List relevant consumer organisations here

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

Not applicable

- 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:

The medical conditions relevant to the proposed service are conditions such as Down syndrome, Edward syndrome, Patau syndrome and Turner syndrome arising from chromosomal aneuploidy.

Prenatal screening is a routine medical service for a pregnant woman to evaluate her personal risk of fetal aneuploidy. These aneuploidies include but are not limited to; trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome), trisomy 13 (Patau syndrome) and monosomy X (Turner syndrome). Non-invasive prenatal testing (NIPT) through the analysis of cell free fetal (cff)DNA is a major technological advancement in testing for fetal aneuploidy.

Down syndrome is the most common chromosomal cause of intellectual disability in children and adults, occurring with a frequency in the population of approx. 1 in 800. a Maternal age is the most important risk factor for having a child with trisomy 21; approx. 1 in 300 for a maternal age of 35 years and 1 in 100 when aged 40 years. Australia, in common with other developed countries has an increasing frequency of children born to mothers in these age groups and with a corresponding increase in prevalence of trisomy 21. a

With the current prenatal screening program, the rate of Australian babies born with Down syndrome is approximately 1 in 1,100 compared with a worldwide rate of 1 in 700. b Other chromosomal conditions that are screened for include Edwards syndrome (trisomy 18), Patau syndrome (trisomy 13) that are associated with disability, pregnancy loss or death in the newborn. a Trisomies 21, 18 and 13 account for approx. 80% of major chromosome abnormalities detected prenatally.

Edwards syndrome occurs in approx. 1 in 5,000 newborns causing intrauterine growth retardation, low birth weight and multiple life-threatening physical abnormalities so that only 5-10% of affected children survive beyond one year of age. c

Patau syndrome occurs in approx. 1 in 16,000 newborns usually causing severe intellectual disability and life-threatening physical abnormalities so that only 5-10% of affected children survive beyond one year of age. The risk of trisomy 13 increases with maternal age. c

Turner syndrome does not cause intellectual disability but affects physical development and ovarian function. A proportion of affected individuals have heart defects, skeletal abnormalities and renal impairment. c Turner syndrome occurs in approx. 1 in 2,500 newborn girls worldwide c and the risk for Turner syndrome does not increase with maternal age. d

The rate of fetal death is high in Turner, Edwards and Patau syndromes with approx. 80% fetal loss between 12 and 40 weeks of pregnancy. d

Sources:

- a. RANZCOG
- b. Down Syndrome Australia
- c. US National Library of Medicine
- d. Fetal Medicine Foundation

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:

In every pregnancy there is a small risk of a chromosomal abnormality being present in the unborn child.

RANZCOG recommendations include that “*all pregnant women should be provided with information and offered the opportunity to have a discussion about the range of chromosome abnormalities that can be detected and the characteristics of the available prenatal screening and diagnostic tests*” and that “*women should have timely access to tests for risk assessment of chromosomal abnormalities with adequate sensitivity and specificity (defined in table 1). Prenatal screening options should be discussed in the first trimester whenever possible in order to maximise screening options.*”^a

NIPT for the common autosomal trisomies has a greater efficacy than conventional screening. It is currently only available in Australia on a self-funded basis, raising issues of equity for pregnant women and their families.

Possible strategies for the inclusion of publicly funded NIPT in prenatal screening are as a primary or contingent test.

- A **primary** test would be offered universally to all pregnant women. In this scenario, NIPT has the highest performance and would identify fetal aneuploidies undetected in current screening without the risks of invasive testing.^{7,9,12,17}
- A **contingent** test would be offered to pregnant women identified at higher risk of fetal aneuploidy. In this scenario, NIPT could achieve high performance at a relatively low cost^{6,9,13} compared with current testing with reduced use of invasive testing. To determine the patient-specific risk, the background or a priori risk would be evaluated from maternal age and gestation, and multiplied by the likelihood ratios calculated from the results first trimester ultrasound and maternal serum marker testing.^{15,16}

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 clinical management pathway would be equivalent to current practice for management of pregnancy. However, earlier non-invasive testing would be available to pregnant women. The preferred option in this application is for NIPT as a primary test available to all pregnant women. An alternative option would be testing contingent on a patient’s risk for fetal aneuploidy.

Scenario 1. Primary testing

Patient presents to medical practitioner for management of pregnancy. At the initial visit the patient is offered NIPT.

Scenario 2. Contingency testing

Patient presents to medical practitioner for management of pregnancy. Patient is offered the current first or second trimester screen. Where a high risk of fetal aneuploidy (≥ 1 in 300) is identified, the patient is offered NIPT.

High risk of fetal aneuploidy is calculated from factors including but not limited to:

- maternal age equal to or greater than 35 years
- abnormal maternal serum or ultrasound nuchal translucency results
- family history of chromosomal abnormalities

See Appendix A Flowchart

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

Non-Invasive Prenatal Testing (NIPT) detects genetic abnormalities by detecting trophoblastic or fetal DNA circulating in maternal blood.¹ The test requires a venepuncture to be performed on the pregnant woman for the collection of a blood sample that is referred to a pathology laboratory for genetic analysis.

NIPT would be offered as part of routine clinical care, either universally or to women with high risk pregnancies, and provided after 10 weeks gestation.

The NIPT result would be reported to the treating medical practitioner who would advise the patient of the result and provide counselling where required.

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

Various assays are available for NIPT using the same scientific principles and no single commercial or trademark product is endorsed in this application.

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):

NIPT would be utilised once in a pregnancy, either universally or to women with high risk pregnancies, with the possibility of repeat testing in some instances where results are equivocal (1.6%).¹⁷

32. 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:

Counselling by a medical practitioner about the potential results of NIPT is required prior to testing and specialist genetic counselling may be needed when increased risk of fetal aneuploidy is detected.

RANZCOG recommends that *“if an increased risk result is obtained for chromosome anomalies, the woman should have access to genetic counselling services for support during the next decision-making phase and follow-up”*.

Source: [visit RANZCOG website](#)

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

Testing would be provided by Approved Practising Pathologists in line with other tests in the MBS Pathology Table.

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:

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.

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:

Testing would be delivered only by Approved Practising Pathologists in Accredited Pathology Laboratories (as defined in MBS Pathology table).

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:

Describe rationale here

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):

Existing non-invasive prenatal testing for fetal aneuploidy consists of combined first trimester testing (CFTS) at 11⁺⁰ and 13⁺⁶ weeks of pregnancy by calculating the overall risk for trisomy 21 from maternal age, ultrasound measurement of fetal nuchal translucency and maternal serum biochemical marker evaluation (β -human chorionic gonadotrophin (β -hCG) and pregnancy associated plasma protein A (PAPP-A)). While no one of these tests has sufficient sensitivity and specificity on its own, as a combination recommended performance standards for screening are achieved with a sensitivity of 85%, specificity of 95% and a positive predictive value of approx. 7 to 10%.ⁱ Risk results for trisomy 13 and 18 can also be incorporated into the first trimester combined screening algorithm.ⁱ

Currently approx. 80% of pregnant women in Australia receive first trimester antenatal care. However, for those who do not attend a medical practitioner until later in pregnancy, alternative screening is required.

Second trimester screening consists of a maternal serum biochemical quadruple test (alpha-fetoprotein (AFP), β -hCG, unconjugated oestriol, and inhibin A). This screening for trisomy 21 is reported to have a sensitivity of 75%, specificity of 95% and a positive predictive value of approx. 2 to 3%.ⁱ An ultrasound at 18-20 weeks of pregnancy is not recommended as a primary screening test for trisomy 21 due to its relatively poor sensitivity and specificity.ⁱ

Secondary confirmatory genetic testing is required where high risk is identified. This is undertaken on samples obtained from the fetus using invasive techniques; amniocentesis or chorionic villus sampling (CVS) for fetal karyotyping.

Current prenatal testing for fetal aneuploidy:

- a) Ultrasound NT at 11 to 13 completed weeks of pregnancy combined with maternal serum markers at 9 to 13 weeks' gestation.
- b) Option (a) can be extended to include other first trimester serum or sonographic markers. Ultrasound performance needs to be prospectively validated by the centre where the screening is performed.
- c) A contingent test whereby women with borderline risks from option (a) have option (b) at a specialist centre and the risk is subsequently modified.
- d) Four maternal serum markers (quadruple test) at 15 to 19 weeks, for women who first attend after 13 weeks + 6 days gestation.
- e) Combining options (a) and the quadruple test (d) in either a stepwise or contingent protocol – provided that all screening test data are included in the final risk assessment. Integrated screening can be offered when CVS is not available. A serum integrated test when NT measurement is unavailable.
- f) Contingent second trimester ultrasound to modify risks for aneuploidy for women having combinations of the above options

Source: [visit RANZCOG website](#)

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

Non-invasive prenatal tests:

66750 to 66751 – maternal serum total, free and free β -human chorionic gonadotrophin (HCG) and pregnancy-associated plasma protein-A (PAPP-A), unconjugated oestriol (uE3)

55700 to 55727 – ultrasound pelvis or abdomen for nuchal translucency

Invasive prenatal tests:

16600 – amniocentesis

16603 – chorionic villus sampling

Other relevant MBS item codes:

104 – consultation

73287 – karyotyping (cytogenetics)

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):

The clinical management pathway after the comparator medical service (current testing) will depend on the results of each test.

Where an increased risk (≥ 1 in 300) of fetal aneuploidy is indicated after combined first or second trimester screening, invasive testing with amniocentesis or CVS is offered.

Amniocentesis at 14-20 weeks gestation has a 1% higher risk of fetal loss and is associated with an increased risk of respiratory distress syndrome and pneumonia.¹⁶ Amniocentesis at 10-14 weeks gestation has 2% higher risk of fetal loss and has a 1.6% higher risk of talipes equinovarus (club foot) than first-trimester CVS or second trimester amniocentesis.¹⁶

First trimester CVS has a similar risk to second trimester amniocentesis. However CVS must be performed after 10 weeks gestation to avoid other fetal abnormalities (fetal transverse limb abnormalities, micrognathia and microglossia).¹⁶

Where an abnormality is diagnosed women select the option appropriate to their circumstances to either continue the pregnancy or undertake a termination. Historically, termination is selected in 90% of cases when Down syndrome is detected.⁵

Spontaneous fetal loss may occur when fetal aneuploidy is present. Trisomy 21 results in approx. 30% fetal loss between 12 and 40 weeks. Trisomies 18 and 13 and Turner syndrome the rate of fetal loss between 12 and 40 weeks is approx. 80%.¹⁶

See Appendix A Flowchart

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:

Primary screening

Maternal serum (biochemical) testing for chromosomal abnormalities could be replaced totally by universal NIPT (100%).¹⁵

First trimester ultrasound would not be replaced (0%) due to its importance for other pregnancy indicators.

NIPT could reduce invasive pre-natal testing (amniocentesis and CVS) techniques in the range of 60-89%.^{7,15}

Contingency screening

Maternal serum (biochemical) testing would not be reduced (0%) by contingency NIPT.

First trimester ultrasound would not be replaced (0%) due to its importance for other pregnancy indicators.

NIPT could reduce invasive pre-natal testing (amniocentesis and CVS) techniques in the range of 95%.¹⁵

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):

Primary screening

All pregnant women offered NIPT (population risk Trisomy 21 = 1 in 800) instead of current maternal serum markers for fetal aneuploidy.¹⁵ First trimester ultrasound would still be offered due its importance for other pregnancy indicators.

- Where NIPT indicates a low risk of fetal aneuploidy (97.6% are normal results)¹ and there are no other risk factors, pregnancy management would proceed as usual. Many women would be spared the unnecessary distress of a high-risk CFTS result.¹⁵ Most importantly many (up to 89%) would avoid unnecessary secondary invasive diagnostic testing (IDT) with amniocentesis or CVS.¹⁵
- Where NIPT indicates a high risk of fetal aneuploidy (abnormal results), the patient would be referred for secondary fetal karyotyping with secondary invasive diagnostic testing (IDT) with amniocentesis or CVS.¹⁵ The clinical pathway would then proceed according to current patient care.
 - Where fetal aneuploidy is confirmed, the patient is counselled by her treating medical practitioner. The patient then selects the appropriate option for her circumstances; either termination or continuation of pregnancy.
 - Where fetal euploidy (normal karyotype) is indicated and there are no other risk factors, pregnancy management would proceed as usual.

Contingent screening

All pregnant women (population risk Trisomy 21 = 1 in 800) would be offered current CFTS for fetal aneuploidy (as outlined in Q39).

- Where CFTS indicates a low risk (<1 in 300) of fetal aneuploidy¹⁵ and there are no other risk factors, pregnancy management would proceed as usual.
- Where CFTS indicates a high risk result (≥ 1 in 300) of fetal aneuploidy,¹⁵ patient is offered NIPT.
- Where NIPT indicates a low risk of fetal aneuploidy and there are no other risk factors, pregnancy management would proceed as usual. Many would avoid unnecessary secondary invasive diagnostic testing (IDT) with amniocentesis or CVS.¹⁵
- Where NIPT indicates a high risk of fetal aneuploidy (abnormal results), the patient would be referred for secondary fetal karyotyping with secondary invasive diagnostic testing (IDT) with amniocentesis or CVS.¹⁵ The clinical pathway would then proceed according to current patient care.
 - Where fetal aneuploidy is confirmed, the patient is counselled by her treating medical practitioner. The patient then selects the appropriate option for her circumstances; either termination or continuation of pregnancy.
 - Where fetal euploidy (normal karyotype) is indicated and there are no other risk factors, pregnancy management would proceed as usual.

Note:

A minority of women who attend a medical practitioner for the first time after the first trimester will have their risk of fetal aneuploidy assessed as outlined in Q39 and a similar contingent NIPT screening pathway would be offered.

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):

NIPT is superior clinically when compared to CFTS. The comparative benefits are in sensitivity, specificity and scope of chromosomal abnormalities detected. NIPT is superior in comparative harm when compared to IDT with CVS and amniocentesis by reducing risks to pregnancy from procedure-related (iatrogenic) euploid losses.

Primary screening

Primary screening with NIPT would be highly beneficial for pregnant women in Australia. Detection of Down syndrome and other fetal aneuploidies would be improved with an increase in detection in the range of 15% to 18%.^{6,7,15} A reduction in invasive testing with amniocentesis and CVS would reduce iatrogenic euploid losses from invasive testing in the range 74% to 94%.^{7,8,15}

Universal screening of all pregnant women with NIPT would result in a higher detection rate for Down syndrome (Trisomy 21) with decreased iatrogenic euploid losses. In a theoretical population of 300,000, this would equate to detecting 657 Down syndrome cases with only 11 iatrogenic euploid losses.¹⁵

Contingency screening

Contingency screening of all pregnant women with high risk CFTS results with NIPT would result in a detection rate for Down syndrome similar to current screening but with decreased iatrogenic euploid losses. In a population of 300,000, this would equate to detecting 531 Down syndrome cases only five iatrogenic euploid losses.¹⁵

Comparator (current screening)

It is estimated that in the same theoretical population, current screening would detect 534 Down syndrome cases with 101 iatrogenic euploid losses.¹⁵

Comparison of NIPT to current prenatal tests ^{1,15}

	NIPT	Combined first trimester screening (CFTS)	CVS/amniocentesis
Risk to pregnancy	No	No	Yes; 0.5-1%
Detection rate for Down syndrome	High (sensitivity, or true positive $\geq 99.5\%$ or higher)	Moderately high (sensitivity 85%)	Diagnostic test ($\geq 99.9\%$)
False-positive rate	Low (specificity, or true negative $\geq 99.8\%$)	Moderate (specificity 95%)	Diagnostic test ($\geq 99.9\%$)
Ability to detect other chromosomal abnormalities	Currently 13, 18, 21 (+/- X and Y). These account for ~70% of the major chromosomal abnormalities	Targeted to screen for trisomy 13,18, 21	Yes <ul style="list-style-type: none"> • Plain karyotype: all chromosomes to a resolution visible on microscopy (5-10 million DNA base pairs) • Chromosome microarray: all chromosomes to a relatively high submicroscopic resolution (generally less than 250,000 DNA base pairs)

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:

NIPT is equivalent in safety to other pathology tests involving venepuncture for blood sampling.
 NIPT is superior in safety to CVS and amniocentesis with lower risk of iatrogenic fetal losses.

Clinical Effectiveness Outcomes:

NIPT is superior in detecting fetal aneuploidy and has lower false positive results compared with current screening.

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

Population is estimated to be 300,000.

A downward trend has been observed with Australian births decreasing from 308,100 in 2013 to total of 299,700 births registered in Australia in 2014. Therefore 300,000 is a reasonable estimate.

Source: [Australian Bureau of Statistics](#)

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

One test per year, most commonly, but occasionally testing for a second pregnancy would be required within the same year.

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

Two years, most commonly, estimated from number of pregnancies per women of reproductive age. Australia's total fertility rate was 1.8 babies per woman in 2014 down from 1.88 in 2013.

Source: [Australian Bureau of Statistics](#)

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

- Primary testing: 300,000 would be a reasonable estimation for the testing of all pregnancies.
- Contingent testing: High risk pregnancies can be estimated from the proportion of mothers are aged 35 years and over (22%). Therefore 66,000 is a reasonable estimate for contingent testing

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:

Uptake in the next three years is likely to remain the same without an increase in birth rate. However, the proportion of mothers 35 years and over is increasing (from 19% in 2003 to 22% in 2013).

- Primary testing: 300,000 would remain a reasonable estimation of tests in three years' time. Leakage to other populations is not applicable if all pregnant women are offered NIPT.
- Contingent testing: With an increase in maternal childbearing age to 24%, a reasonable estimation in three years' time would be 75,000 tests.

Source: [Australian Bureau of Statistics](#)

PART 8 – COST INFORMATION

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

Non-Invasive Prenatal Testing (NIPT) is likely to cost approx. \$500 based on current fees advertised by various pathology laboratories (Sonic Genetics, Victorian Clinical Genetics Services, SDS/Primary Healthcare, Pathwest and Genea) between \$400 and \$550.

It should be noted that many past cost-benefit studies reported in the literature are based on NIPT at considerably higher costs than these current fees.^{7,8,10,11,15} It should be noted that a recent US study⁷ concludes that NIPT detects more fetal trisomy cases compared with current first trimester screening and is cost-effective with 85% screening adherence at a NIPT unit cost of A\$732 (US\$550).⁷

An estimated breakdown of costs would be:

Equipment and resources	Per test
Kit, probes, reagents, ancillary reagents	\$350.00
Labour medical (consultant pathologist)	\$50.00
Labour scientific	\$40.00
Labour on costs	\$14.00
Depreciation, overheads	\$25.00
Admin, IT	\$10.00
Total	\$489.00

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

A turnaround time of five working days is required for the complete testing process from specimen collection to pathology report.

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.

MBS Pathology Table Category 6, Group P7 -Genetics
<p>Primary testing:</p> <p>Proposed item descriptor: Non-Invasive Prenatal Testing of blood from a pregnant woman for the detection of the more common fetal aneuploidies including but not limited to; trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome), trisomy 13 (Patau syndrome) and monosomy X (Turner syndrome) in trophoblastic or fetal DNA circulating in maternal blood.</p> <p>Fee: \$500</p>
<p>Contingent testing:</p> <p>Proposed item descriptor: Non-Invasive Prenatal Testing of blood from a pregnant woman at high risk for the detection of the more common fetal aneuploidies including but not limited to; trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome), trisomy 13 (Patau syndrome) and monosomy X (Turner syndrome) in trophoblastic or fetal DNA circulating in maternal blood.</p> <p>High risk pregnancy defined as a risk of ≥ 1 in 300 for fetal aneuploidy, calculated from factors including but not limited to:</p> <ul style="list-style-type: none"> • Maternal age of 35 years or greater • Abnormal maternal serum markers • Abnormal first trimester ultrasound nuchal translucency <p>Fee: \$500</p>

PART 9 – FEEDBACK

The Department is interested in your feedback.

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

Seven days

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

Yes

No

(b) If no, provide areas of concern:

Mostly clear and easy to complete but some information on IVDs, clinical management flow charts and others are quite difficult.

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?

The guidelines do not provide any extra information compared with the form. The guidelines would benefit by including an explanation of the application process and schedule.

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:

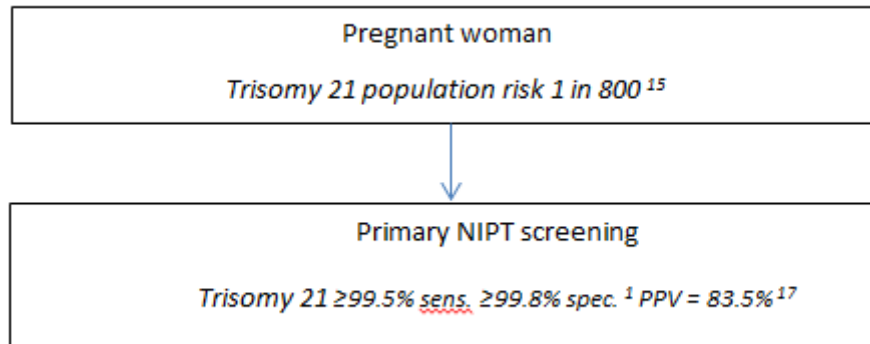
The form could be better tailored for Pathology items that are not technology-specific (i.e. not a single TGA product) and already have established rules in the MBS (Approved Pathology Practitioners; accredited laboratories; referrals by registered medical practitioners).

Appendix A

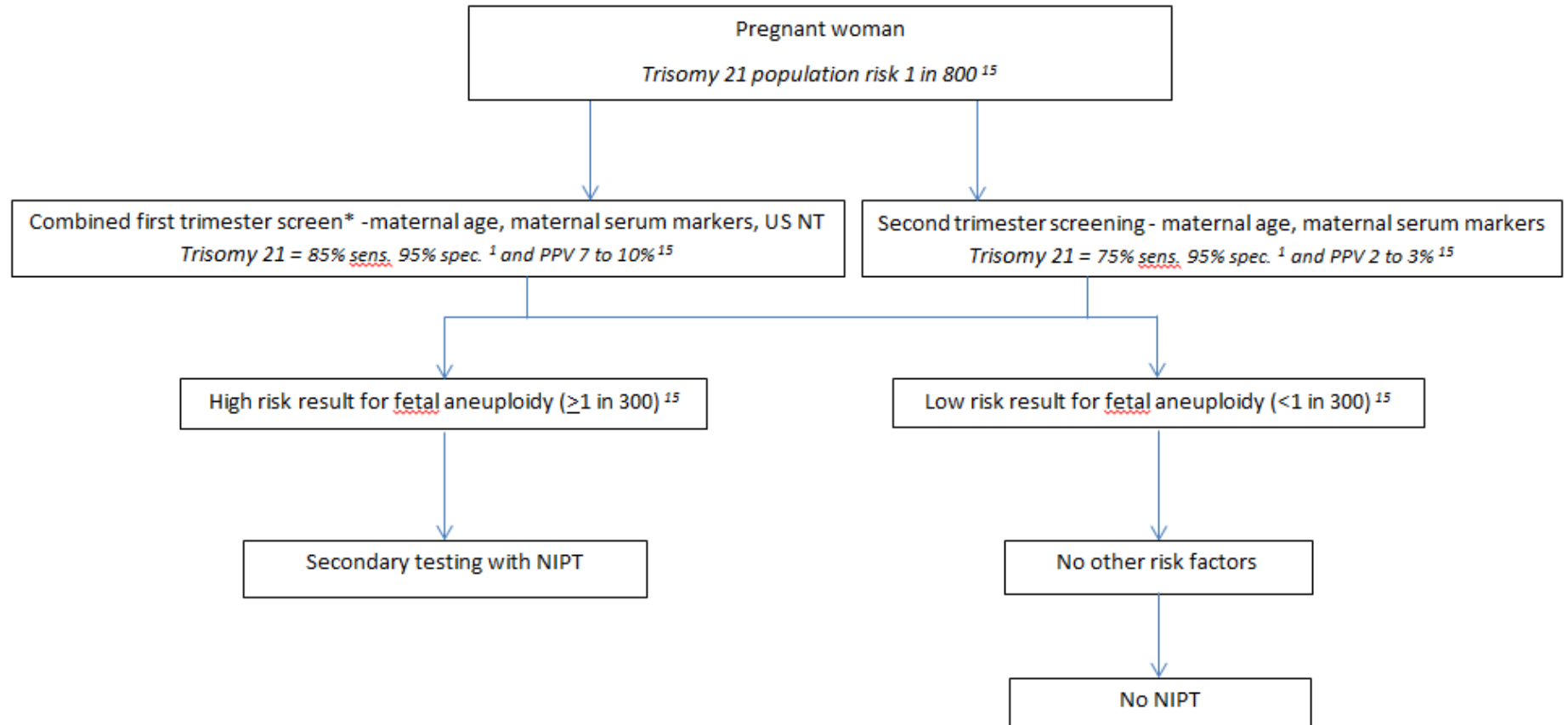
Flowcharts

Q26 Clinical pathway before intervention

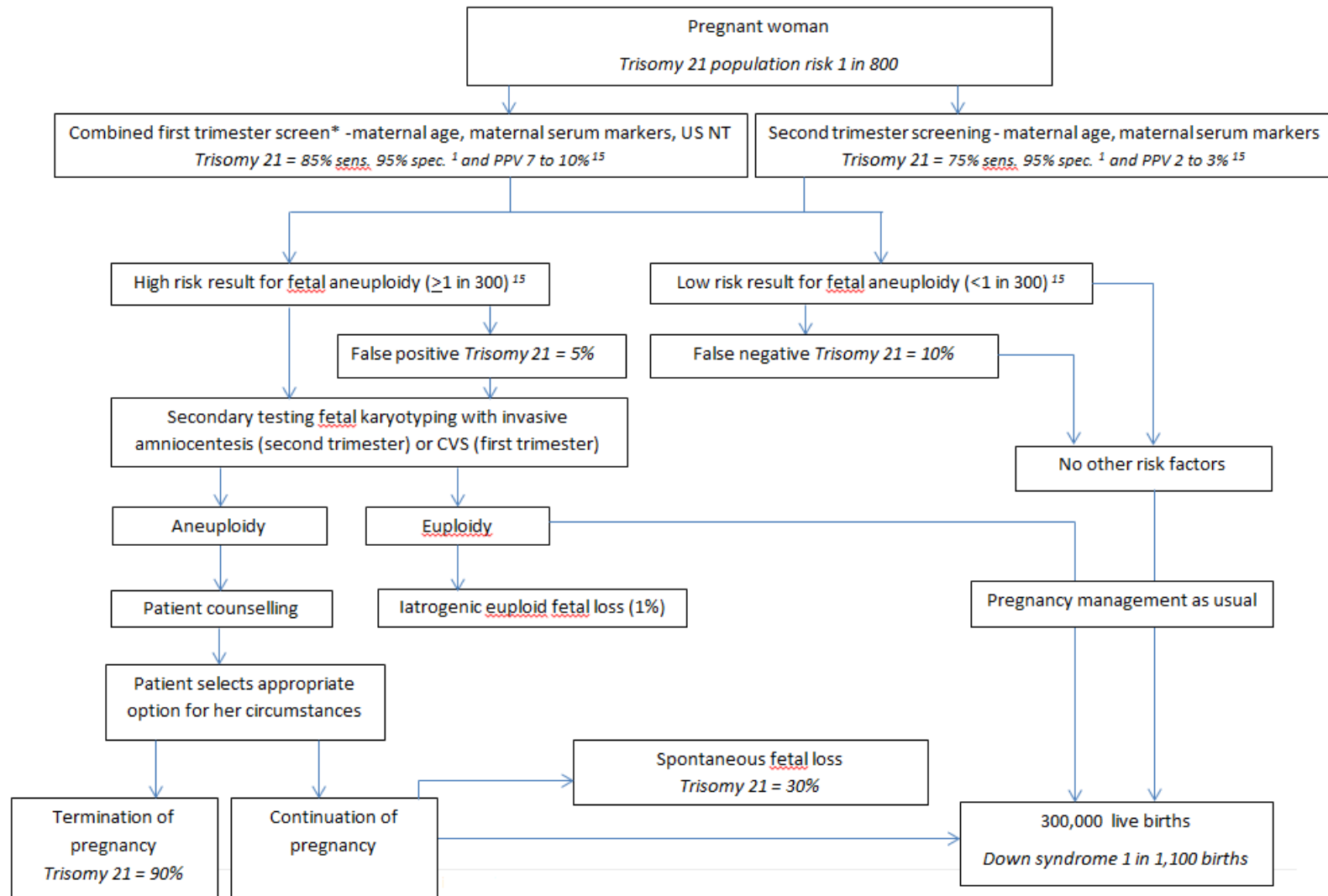
Scenario 1 Primary NIPT screening



Scenario 2 Contingency NIPT screen



Q40 Clinical pathway after comparator



*Approx. 80% of pregnant receive first trimester antenatal care in Australia. Source [AIHW](#)