Australian Government
Department of Health

Application 1461:

Non-Invasive Prenatal Testing For Common Trisomies (21, 18 and 13)

PICO Confirmation

(to guide a new application to MSAC)

(Version 0.1)

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Population 1: Contingent testing

Component	Description
Patients	Pregnant women at intermediate risk of fetal aneuploidy, with risk being categorised following combined first trimester screening (CFTS). • Proposed definition of intermediate risk is between <1:1,000 to >1:10 • Alternative risk thresholds will be explored in the assessment
Prior tests (for investigative medical services only)	CFTS consisting of: • Ultrasound for nuchal translucency (NT) at 11 to 13 completed weeks of pregnancy • Maternal serum biochemical marker evaluation (β-human chorionic gonadotrophin (β-hCG) and pregnancy associated plasma protein A (PAPP-A)) at 9 to 13 completed weeks of pregnancy
Intervention	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. Plus prior tests (CFTS) NIPT is not limited to any specific product, but must include the measurement, reporting and incorporation of fetal fraction into the final probability score as a quality control metric.
Comparator	Prior tests (CFTS) alone (without NIPT)
Outcomes	<u>Safety</u> <u>Efficacy/effectiveness</u> • Sensitivity/specificity/positive predictive value/negative predictive value/ROC area under the curve (AUC) for o Trisomy 21 o Trisomy 13 o Trisomy 18 o Monosomy X o Other genetic conditions which are tested for (e.g. other sex chromosome aneuploidies, microdeletions) • Rate of uninterpretable tests/repeat tests required • Invasive procedures avoided (amniocentesis/CVS)

Component	Description
	• Change in number of genetic consultations • Other changes occurring in ≥10% patients • Quality of life (avoidance of anxiety) • Trisomy cases detected/undetected • Other chromosomal abnormalities detected/undetected (e.g. trisomy 13 & 18, monosomy X) <u>Healthcare resources</u> • Cost of testing • Cost of counselling • Cost of first trimester ultrasound and maternal serum biomarker evaluation • Cost amniocentesis and CVS • Cost of termination • Cost of trisomy 21 birth <u>Cost-effectiveness</u> • Cost per true positive/trisomic fetus detected • Cost per non-trisomic fetus saved <u>Total Australian Government Healthcare costs</u>

Population 2: primary screening

Component	Description
Patients	All pregnant women
Prior tests (for investigative medical services only)	None
Intervention	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. NIPT is not limited to any specific product, but must include the measurement, reporting and incorporation of fetal fraction into the final probability score as a quality control metric.
Comparator	CFTS consisting of:

Component	Description
	• Ultrasound for nuchal translucency (NT) at 11 to 13 completed weeks of pregnancy • Maternal serum biochemical marker evaluation (β-human chorionic gonadotrophin (β-hCG) and pregnancy associated plasma protein A (PAPP-A)) at 9 to 13 completed weeks of pregnancy
Outcomes	<u>Safety</u> <u>Efficacy/effectiveness</u> • Sensitivity/specificity/positive predictive value/negative predictive value/ROC area under the curve (AUC) for o Trisomy 21 o Trisomy 13 o Trisomy 18 o Monosomy X o Other genetic conditions which are tested for (e.g. other sex chromosome aneuploidies, microdeletions) • Rate of uninterpretable tests/repeat tests required • Invasive procedures avoided (amniocentesis/CVS) • Change in number of genetic consultations • Other changes occurring in ≥10% patients • Quality of life (avoidance of anxiety) • Trisomy cases detected/undetected • Other chromosomal abnormalities detected/undetected (e.g. trisomy 13 & 18, monosomy X) <u>Healthcare resources</u> • Cost of testing • Cost of counselling • Cost of first trimester ultrasound and maternal serum biomarker evaluation • Cost amniocentesis and CVS • Cost of termination • Cost of trisomy 21 birth <u>Cost-effectiveness</u> • Cost per true positive/trisomic fetus detected • Cost per non-trisomic fetus saved <u>Total Australian Government Healthcare costs</u>

PICO or PPICO rationale for therapeutic and investigative medical services only

Population

The medical conditions most relevant to the proposed service are Down syndrome, Edwards syndrome and Patau syndrome.

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 apnoea 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 [1].

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 and 1/5,000 newborns [1]. 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[2].

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 [1]. 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[2].

Two patient populations are considered:

1. Contingent testing
   Pregnant women at intermediate risk of fetal aneuploidy who are identified using the current prenatal testing approach (CFTS) and are subsequently offered NIPT.

   CFTS currently consists of:
   - Maternal age;
   - Ultrasound measurement of fetal nuchal translucency (NT), where available.
   - Blood collected at 9 weeks – 13 weeks 6 days for biochemical analysis of:
     - Pregnancy associated placental protein-A (PAPP-A)
     - Free βhCG.

   Intermediate risk of fetal aneuploidy is defined as a base-case as between <1:1,000 and >1:10. Using this definition it is expected that approximately 13% of women would be defined as at intermediate risk [3] which is approximately 39,000 women per year.
   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 low risk threshold could eventually be reduced to a level where all women are offered NIPT, irrespective of the CFTS risk assessment, thereby negating the utility of CFTS as a triage tool for the detection of common trisomies prior to NIPT.

2. Primary screening
   All pregnant women are at risk of fetal aneuploidy, and therefore the second population is to test all women who are pregnant. Currently in Australia this is approximately 300,000 women per year.

Rationale

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 testing 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 [4].

The rationale for patient population 1 (contingent testing) is that it would reduce the number of invasive tests in normal foetuses and subsequently reduce the associated complications such as miscarriage.

The rationale for patient population 2 (primary screening) is that it would reduce the number of invasive tests in normal foetuses and subsequently reduce the associated complications such as miscarriage, while also increasing the detection rate of trisomic fetuses.

Prior tests

Contingent testing – women at intermediate risk of fetal aneuploidy

The prior tests are combined first trimester testing (CFTS) at 11^{+0} to 13^{+6} weeks of pregnancy which includes:

- ultrasound measurement of fetal nuchal translucency (NT) and
- maternal serum biochemical marker evaluation (β-human chorionic gonadotrophin (β-hCG) and pregnancy associated plasma protein A (PAPP-A)).

1. Primary screening – all pregnant women

No prior tests. All pregnant women are eligible.

Intervention

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 [5-7]. 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.

NIPT is not limited to any specific product, but must include the measurement, reporting and incorporation of fetal fraction into the final probability score as a quality control metric.

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.

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.

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.

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.

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.

NIPT is not currently subsidised in Australia by Government or private health insurance. Women may self-fund the test.

Rationale

The applicant has stated that NIPT is used to test for Down syndrome, trisomy 18 and trisomy 13. The submission by the Royal Australian College of General Practitioners (RACGP) raises the concern regarding the use of NIPT for screening for sex chromosome aneuploidies and microdeletions on the basis that:

- The positive predictive values (PPVs) for sex chromosome aneuploidies and microdeletions are low (if known)
- They are unlikely to be reported in the test results
- Therefore decision-making will be based on low-quality information, and these decisions may include non-medical sex selection
- The testing laboratories may add an additional charge for these results.

More broadly, the RACGP calls for PPVs for each condition to be clearly stated both in marketing materials and when reporting laboratory results to assist in decision making, however it would be difficult to ensure that laboratories follow this practice.

Given that this application is for any NIPT product with regulatory approval on the Australian market, and with the knowledge that the technology will continue to evolve, consideration should be given as to how additional information provided by the test may be used, particularly information on sex chromosomes and any other information which may be able to be provided as the technology changes.

Clinical advice is that although the application targets trisomy's, which have low false positive rates, it can currently be used for detecting sex chromosome aneuploidies and microdeletions (7-8 available to be tested in Australia currently). The addition of these conditions increases the complexity of genetic counselling and also increases the false positive rate. NIPT will screen for an ever expanding range of conditions, with the clinical expert describing the technology as "limitless". Consideration of how the test is likely to be used beyond the indication for which funding is sought (common trisomies) should be included in the assessment. This should include consideration of

potential ethical issues and analysis of consumer preferences, including both pregnant women and their partners and the broader community.

Comparator

1. Contingency testing – women at intermediate risk of having a child with a fetal aneuploidy

The comparator tests are CFTS followed by invasive testing (amniocentesis or CVS) in high risk women (risk greater than 1 in 300) (i.e. prior testing alone).

In this population, NIPT is used as a triage test to reduce the use of invasive testing in high-risk women. It is expected that NIPT will better target use of amniocentesis and CVS thus reducing, but not eliminating, their use.

1: Primary screening – all pregnant women

The comparator tests are combined first trimester testing (CFTS) at 11^{+0} to 13^{+6} weeks of pregnancy which includes:

- ultrasound measurement of fetal nuchal translucency (NT) and
- maternal serum biochemical marker evaluation (β-human chorionic gonadotrophin (β-hCG) and pregnancy associated plasma protein A (PAPP-A)).

NIPT is a replacement test for CFTS for prenatal screening for common trisomies.

However, NIPT would not replace current combined FTS, but would be additional to current NT ultrasound or FTS biochemistry which would be used to detect conditions other than fetal trisomies 21, 18 and 13. 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).

Rationale

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.

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.

Outcomes

Patient relevant

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 fetuses, 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. The applicant has not proposed quality of life as an effectiveness outcome for the Assessment due to an expected absence of data, however absence of data is not considered a reason for excluding an outcome in the protocol and it has therefore been listed.

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.

Healthcare system

The introduction of NIPT is not expected to reduce the use of CFTS.

The introduction of NIPT using either scenario is expected to reduce the use of invasive testing. If NIPT were used for primary screening then its introduction would also be expected to reduce the number of births of babies with trisomy's which would affect healthcare resources.

It is not clear what impact either scenario would have on the utilisation of counselling services for pregnant women undergoing screening.

The following outcomes should be explored:

- 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.

Rationale

Diagnostic performance is not a patient relevant outcome but is critical for understanding how the test compares to existing prenatal screening and diagnosis and how clinical practice may change were the test publicly funded.

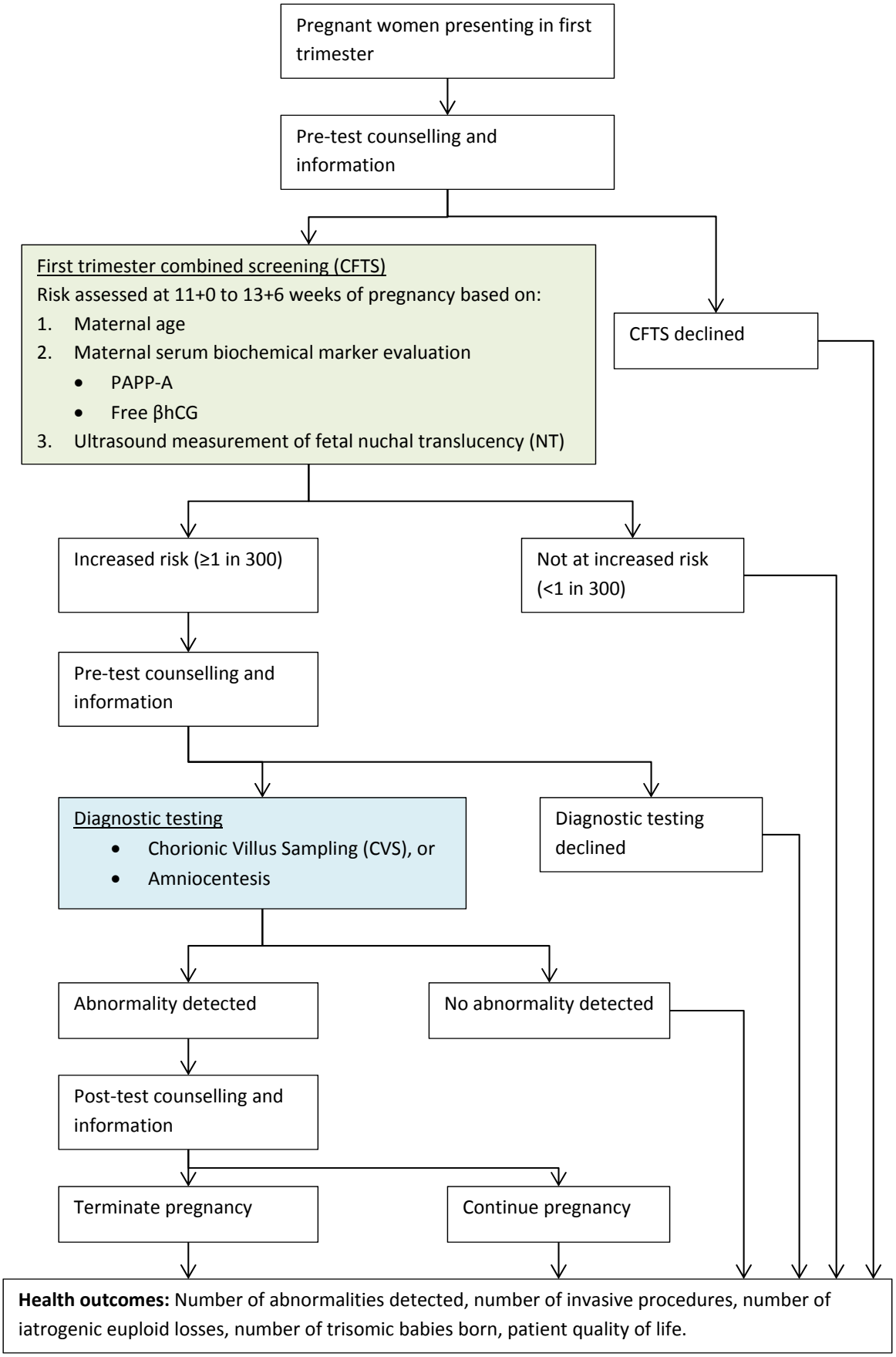
Additional outcomes for both scenarios are listed in the summary of the PPICO. It is important to report, where possible, the actual changes that occur rather than modelled changes based on test performance. For example, a positive NIPT would prompt a woman to be offered an invasive test but not all women will take up this offer, furthermore, some women who have a negative NIPT or do not undergo NIPT, may still elect to have an invasive test.

The importance of the outcomes listed in the PPICO may depend on the perspective taken, for example, the most patient relevant outcomes are likely around pregnant women's quality of care experiences (captured as quality of life in the outcomes table) which may include access to, and ability to understand, information relating to screening and the testing options available, levels of anxiety and participation in decision making.

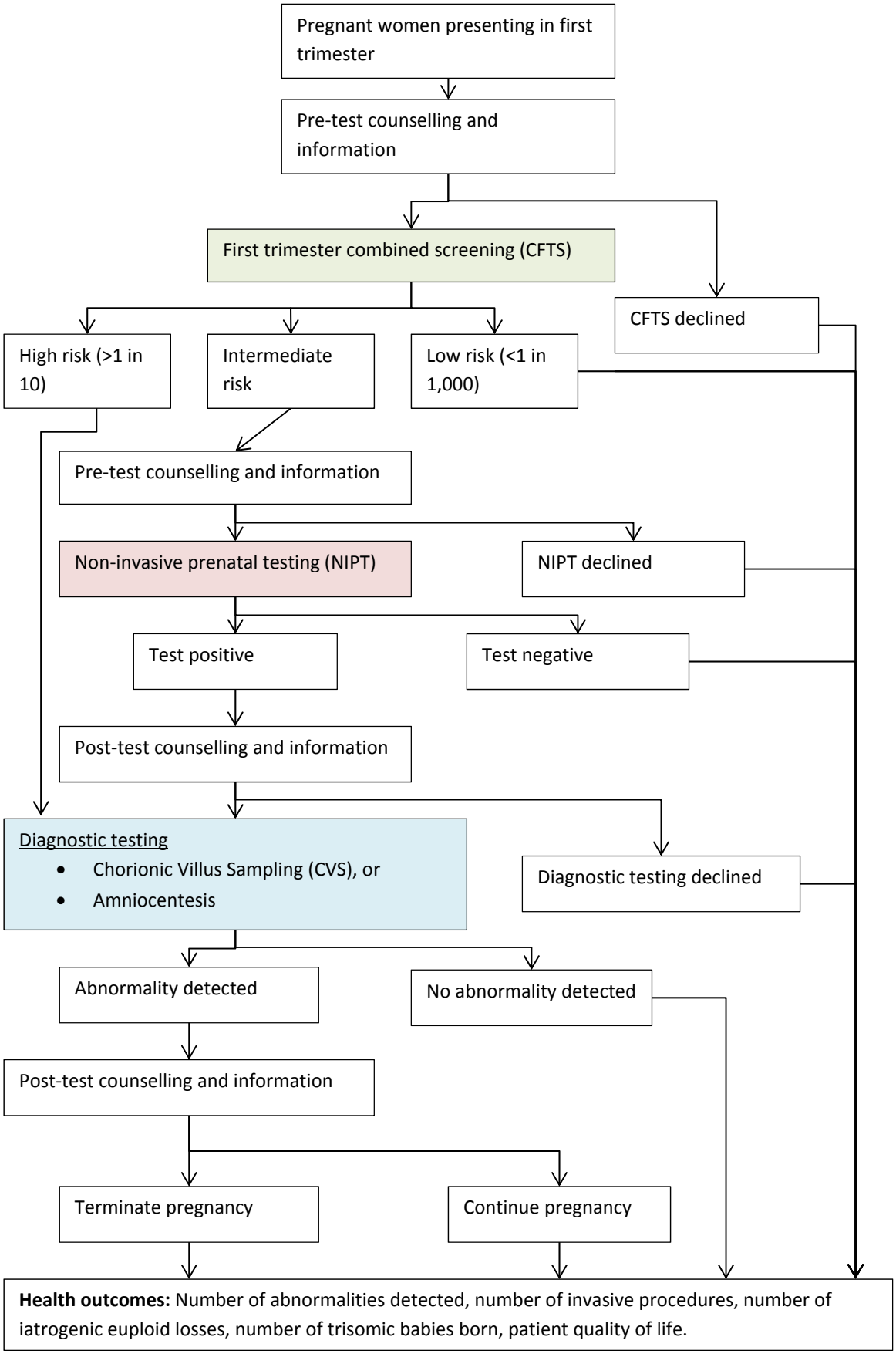
As discussed, NIPT is a technology which can already detect many more conditions than those considered in this application. The test characteristics of some of these (e.g. sex chromosome aneuploidies, microdeletions) are requested as outcomes in the PPICO. The detection of additional conditions by the test will change the overall rates of false positives, the utilisation of downstream services (diagnostic testing and counselling) and the overall economics of the test. The extent to which there will be available data to address these issues and model their impact is unclear. It is also unclear how this would be best incorporated into the assessment.

A case could also be made that this is an application in which consideration of the ethical and societal implications of the technology should be considered and prioritised in the assessment.

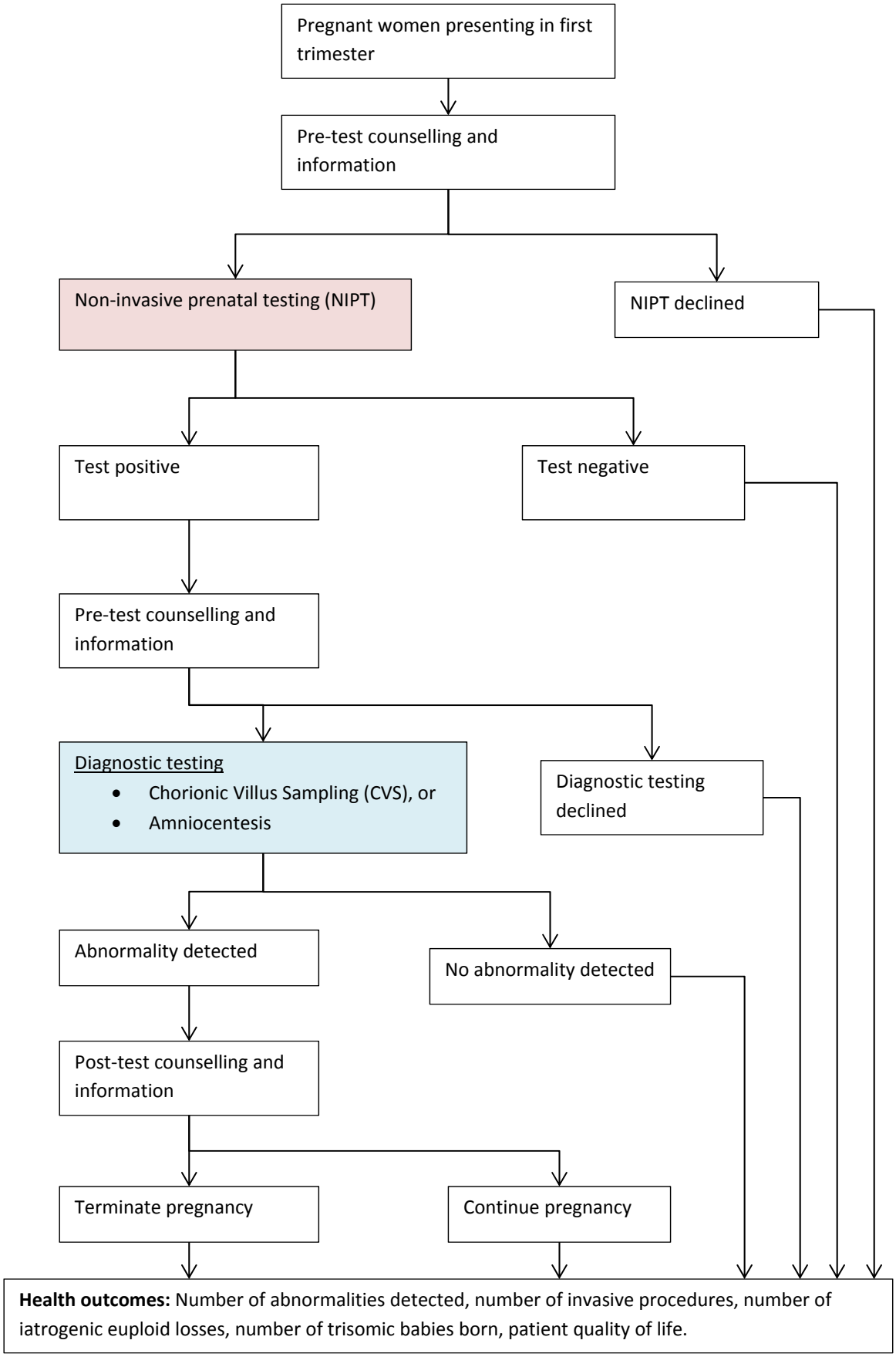
Current clinical management algorithm for identified population



Proposed clinical management algorithm for identified population – contingent testing



Proposed clinical management algorithm for identified population – primary screening



Proposed economic evaluation

The clinical claim is that NIPT is non-inferior in safety and superior in clinical effectiveness to current testing. According to the *Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee: Investigative* the required economic analysis is therefore a cost-utility analysis. However, a cost-consequences analysis would in this assessment be considered helpful and may provide more useful information to the decision maker than aggregated utility values.

Proposed item descriptor

The following item descriptor has been proposed:

Category 6 – Pathology Services
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

References

1. Abeywardana, S. and E.A. Sullivan, *Congenital anomalies in Australia 2002-2003*, in *Birth anomalies series* 2008, AIHW National Perinatal Statistic Unit: Sydney.
2. Wu, J., A. Springett, and J.K. Morris, *Survival of trisomy 18 (Edwards syndrome) and trisomy 13 (Patau Syndrome) in England and Wales: 2004–2011.* American Journal of Medical Genetics Part A, 2013. **161**(10): p. 2512-2518.
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4. Grati, F.R., et al., *Fetoplacental mosaicism: potential implications for false-positive and false-negative noninvasive prenatal screening results.* Genet Med, 2014. **16**(8): p. 620-624.
5. Breitbach, S., S. Tug, and P. Simon, *Circulating Cell-Free DNA.* Sports Medicine, 2012. **42**(7): p. 565-586.
6. Dwivedi, D.J., et al., *Prognostic utility and characterization of cell-free DNA in patients with severe sepsis.* Critical Care, 2012. **16**(4): p. R151.
7. Haghiac, M., et al., *Increased Death of Adipose Cells, a Path to Release Cell-Free DNA Into Systemic Circulation of Obese Women.* Obesity, 2012. **20**(11): p. 2213-2219.