Australian Government
Department of Health

Application 1458:

Non-Invasive Prenatal Testing (NIPT)

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: Primary testing

Component	Description
Patients	All pregnant women
Prior tests (for investigative medical services only)	None
Intervention	Non-invasive prenatal testing (NIPT) to detect genetic abnormalities by detecting trophoblastic or fetal DNA circulating in maternal blood. Not limited to any specific product.
Comparator	Combined first-trimester testing (CFTS) which includes: • 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))
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 21 cases detected/undetected • Other chromosomal abnormalities detected/undetected (Trisomy 13 & 18, monosomy X) <u>Healthcare resources</u>

Component	Description
	• 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 Down syndrome 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: Contingency screening

Component	Description
Patients	Pregnant women at increased risk of fetal aneuploidy, defined as a risk of ≥1 in 300 following combined first trimester testing (CFTS)
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))
Intervention	Non-invasive prenatal testing (NIPT) to detect genetic abnormalities by detecting trophoblastic or fetal DNA circulating in maternal blood. Plus prior tests (CFTS) NIPT is not limited to any specific product.
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

Component	Description
	○ Monosomy X ○ 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 (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 Down syndrome 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 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).

Trisomies 21, 18 and 13 account for approximately 80% of major chromosome abnormalities detected prenatally.

Down syndrome is the most common chromosomal cause of intellectual disability in children and adults, occurring with a frequency in the population of approximately 1 in 800. Maternal age is the most important risk factor for having a child with trisomy 21; approximately 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 with a corresponding increase in the prevalence of trisomy 21.[1]

Edwards syndrome occurs in approximately 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.[2]

Patau syndrome occurs in approximately 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.[2]

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.[2] Turner syndrome occurs in approximately 1 in 2,500 newborn girls worldwide[2] and the risk for Turner syndrome does not increase with maternal age.[3]

The rate of fetal death is high in Turner, Edwards and Patau syndromes with approximately 80% fetal loss between 12 and 40 weeks of pregnancy.[3]

Two patient populations are considered:

<u>1: Primary testing – all pregnant women</u>

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

2. Contingency screening – women at increased risk of having a child with a fetal aneuploidy

Pregnant women at increased risk of fetal aneuploidy are identified using the current prenatal testing approach and are subsequently offered NIPT.

High risk of fetal aneuploidy is considered to be a risk of ≥1 in 300 and 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.

It is estimated that the number of pregnant women in population 2 would be approximately 66,000 (i.e. the number of pregnant women aged >35 years).

Rationale

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 (NT) 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 approximately 7 to 10%.[1] Risk results for trisomy 13 and 18 can also be incorporated into the first trimester combined screening algorithm.[1]

Currently approximately 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 approximately 2 to 3%. [1] 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.[1]

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.

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.[3] 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.[3]

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).[3]

The rationale for patient population 1 (all pregnant women) is that it would increase the detection of fetal aneuploidy with a corresponding reduction in invasive testing, which would reduce iatrogenic euploid losses.

The rationale for patient population 2 (contingency screening) is that it would maintain the current rate of detection of fetal aneuploidy with a corresponding reduction in invasive testing, which would reduce iatrogenic euploid losses. It would also be a cheaper option than patient population 1. The criteria for contingency screening and categorisation of 'high risk' (≥1 in 300) are based on current practice for CFTS and define the population who are currently recommended for invasive testing. Other options for defining this population could be considered (for example, lowering the risk threshold).

Prior tests

1: Primary testing – all pregnant women

No prior tests. All pregnant women are eligible.

2. Contingency screening – women at increased risk of having a child with a 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)).

Note these prior tests are only applicable for women who present to a medical practitioner in the first trimester of pregnancy. For women who present later in pregnancy, the following prior test would be undertaken:

- serum biochemical quadruple test (alpha-fetoprotein (AFP), β-hCG, unconjugated oestriol, and inhibin A).

Women who don't present to a medical practitioner in the first trimester are not considered further in this PICO confirmation and are not included in the clinical algorithm.

Intervention

Non-invasive prenatal testing through the analysis of cell free fetal DNA is a major technological advancement in testing for fetal aneuploidy.

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 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.

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

NIPT would be offered as part of routine clinical care and provided after 10 weeks gestation. It would be offered once per pregnancy, unless a repeat test was required due to test failure (estimated 1.6% [4]).

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

Various assays are available for NIPT using the same scientific principles. The assessment will consider all commercial products and would allow for the use of any product which has regulatory approval on the Australian market. It is anticipated that new products will continue to be developed using the same scientific principles.

NIPT is not currently subsidised in Australia by Government or private health insurance. Women may self-fund the test. The RANZCOG considers that this financial barrier poses major ethical and economic challenges to the successful incorporation of NIPT testing into prenatal care and precludes them from providing universal recommendations. NIPT testing is currently provided to women in Australia from overseas laboratories via local distributors, but it is expected local provision will be available in the future [1].

Rationale

The applicant has stated that NIPT is used to test for fetal aneuploidies "including but not limited to; trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome), trisomy 13 (Patau syndrome) and monosomy X (turner syndrome)." Current CFTS calculates the risk of trisomy 21, 18 and 13 but does not screen for monosomy X. 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. This should include consideration of potential ethical issues and analysis of consumer preferences, both pregnant women and their partners and the broader community.

Comparator

1: Primary testing – 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)).

Note these tests are only applicable for women who present to a medical practitioner in the first trimester of pregnancy. For women who present later in pregnancy, the following comparator test would be undertaken:

- serum biochemical quadruple test (alpha-fetoprotein (AFP), β-hCG, unconjugated oestriol, and inhibin A).

NIPT is a replacement test for CFTS. However, although maternal serum biochemical marker evaluation is expected to be replaced by NIPT, first-trimester ultrasound would not be replaced as it is used for other pregnancy indicators (e.g. dating, morphology, twin pregnancy etc.) and therefore would continue to be undertaken although it would no longer function to screen for trisomy.

2. Contingency screening – women at increased 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.

Rationale

The accuracy of NT ultrasound measurement is highly operator dependent. Operator training and expertise are critical and access to specialised operators maybe variable across the country.

Outcomes

Patient relevant

No specific safety outcomes are listed. NIPT is considered a safe test as it only requires collection of maternal blood, a routine procedure during pregnancy.

1: Primary testing – all pregnant women

The introduction of NIPT is expected to increase the detection of fetal aneuploidies and reduce utilisation of invasive testing (amniocentesis and CVS), which would reduce iatrogenic euploid losses from these tests. Therefore the key patient-relevant health outcomes are:

- trisomy cases detected
- invasive procedures avoided.

2. Contingency screening – women at increased risk of having a child with a fetal aneuploidy

The introduction of NIPT is expected to maintain the current rate of detection of fetal aneuploidies and reduce utilisation of invasive testing (amniocentesis and CVS), which would reduce iatrogenic euploid losses from these tests. Therefore the patient-relevant outcomes are the same as for primary testing using NIPT.

Healthcare system

The introduction of NIPT is not expected to reduce the use of first trimester ultrasound.

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.

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.

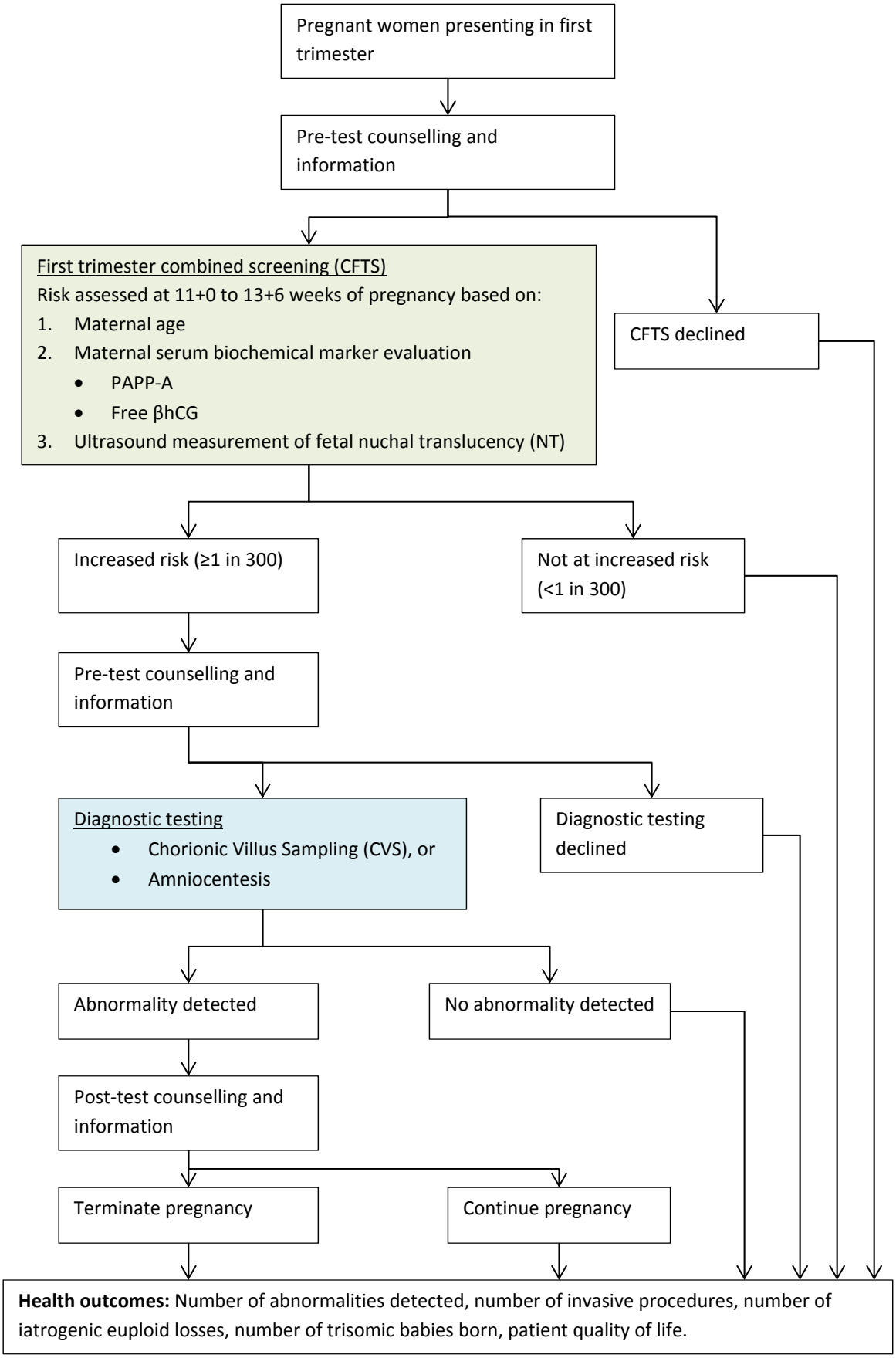
The importance of the outcomes listed in the PPICO may depend on the perspective taken, for example, the most patient relevant outcomes are likely around pregnant women's quality of care experiences (captured as quality of life in the outcomes table) which may include access to, and

ability to understand, information relating to screening and the testing options available, levels of anxiety and participation in decision making.

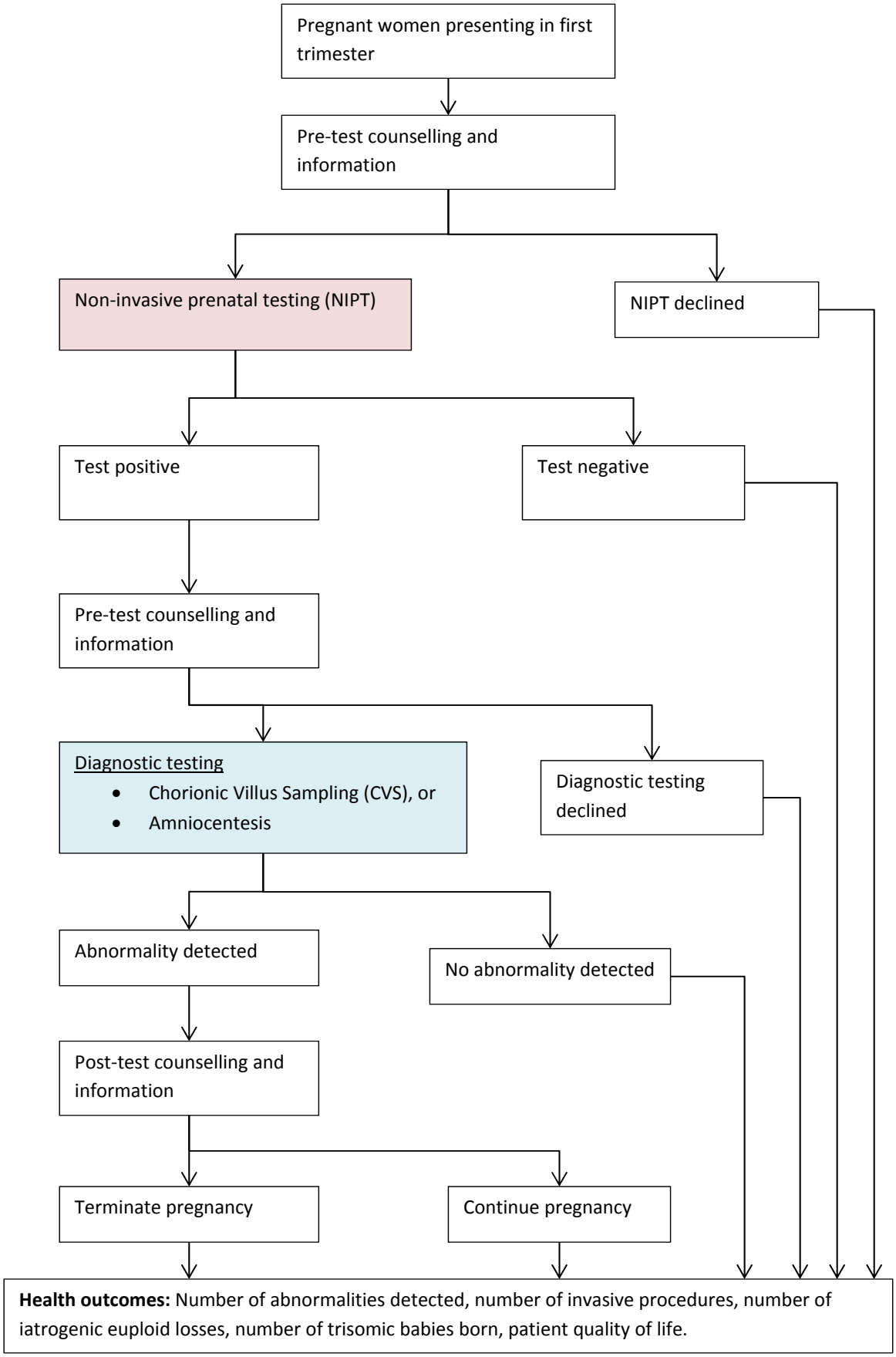
As discussed, NIPT is a technology which can already detect many more conditions than those considered in this application. The test characteristics of some of these (sex chromosome aneuploidies, microdeletions) are requested as outcomes in the PPICO. The detection of additional conditions by the test 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.

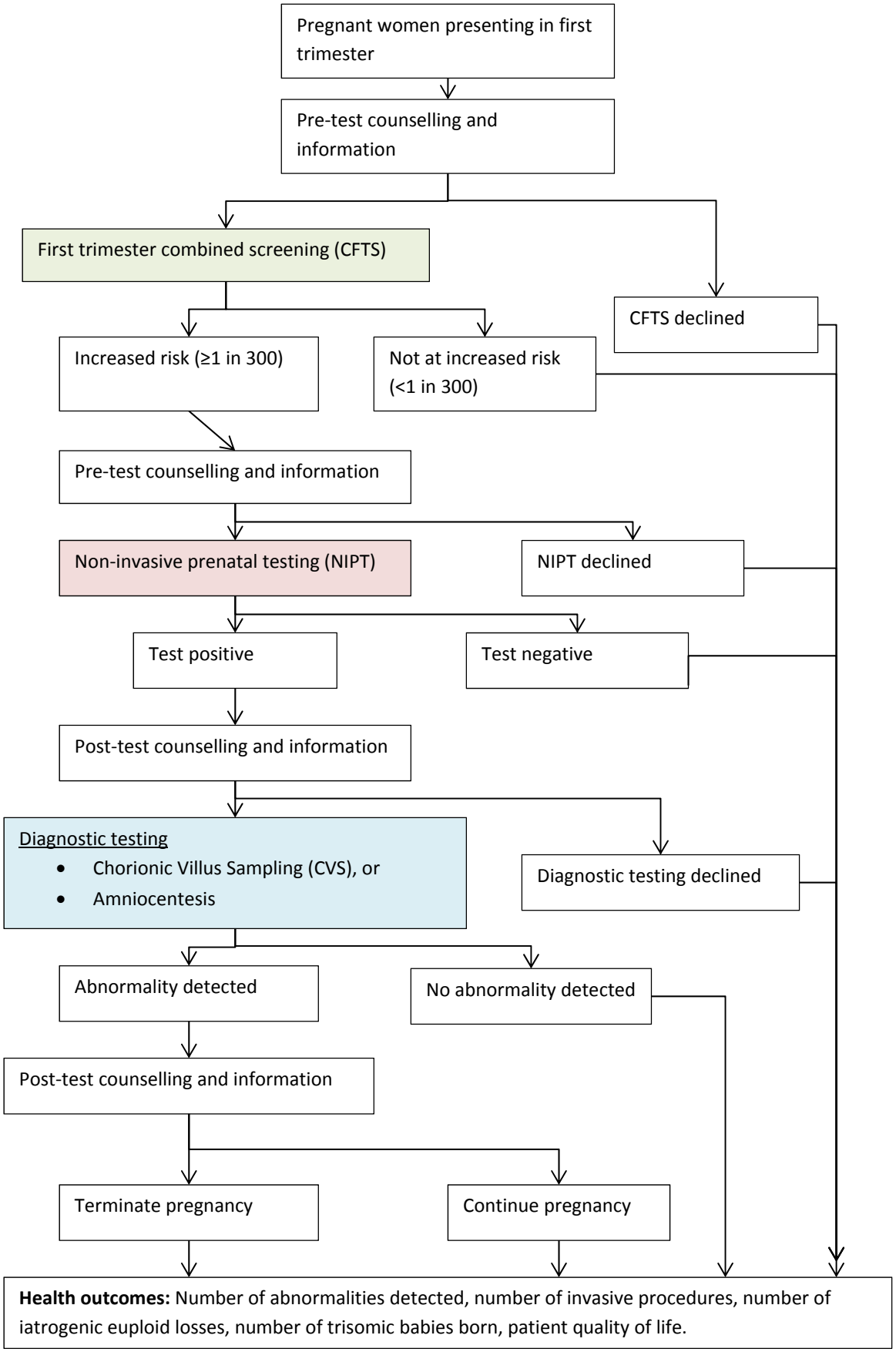
Current clinical management algorithm for identified population



Proposed clinical management algorithm for identified population – Primary screening



Proposed clinical management algorithm for identified population – Contingency 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 is proposed if NIPT were publicly funded for primary testing.

Category 6 (Group P7 Genetics) – Pathology services
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. Fee: $500

The following item descriptor is proposed if NIPT were publicly funded for contingency screening.

Category 6 (Group P7 Genetics) – Pathology services
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. High risk pregnancy defined as a risk of ≥1 in 300 for fetal aneuploidy, calculated from factors including but not limited to: • maternal age of 35 years or greater • abnormal maternal serum markers • abnormal first trimester ultrasound nuchal translucency Fee: $500

References

1. RANZCOG & HGSA *Prenatal screening and diagnosis of chromosomal and genetic conditions in the fetus in pregnancy*. 2015.
2. U.S. National Library of Medicine. *Health Conditions*. 2016 19/10/2016]; Available from: Health Conditions. 2016 19/10/2016.
3. Nicolaides, K.H., *The 11-13^{+6} week scan*. 2004, Fetal Medicine Foundation: London.
4. Taneja, P.A., et al., *Noninvasive prenatal testing in the general obstetric population: clinical performance and counseling considerations in over 85 000 cases.* Prenatal Diagnosis, 2016. **36**(3): p. 237-243.