Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1492 – Non-Invasive Prenatal Testing

Applicant: **Royal College of Pathologists of Australasia (RCPA) and Roche Diagnostics Australia Pty Ltd**

Date of MSAC consideration: **MSAC 73rd Meeting, 26-27 July 2018**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting Medicare Benefit Schedule (MBS) listing for non-invasive prenatal testing (NIPT) for trisomies 21, 18, 13 and monosomy X (Application 1458) was received from the RCPA, while an application also requesting MBS listing for NIPT , to test common trisomies 21, 18 and 13 (Application 1461) was received from Roche Diagnostics.

Due to the similarities between the applications 1458 and 1461, the PICO Advisory Sub-Committee (PASC) advised that these applications should be merged into one MSAC application.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost effectiveness, MSAC deferred its advice on public funding for NIPT for common trisomies (21, 18 and 13) due to significant uncertainty regarding the proposed place of NIPT in the clinical management algorithm. In particular, MSAC was uncertain of how best to define the most suitable population of pregnant women to be eligible for funded testing, including whether and how this could be limited to a high-risk population.

MSAC noted that the application was submitted by the RCPA and Roche Diagnostics as the service providers, and considered that a stakeholder meeting that also included consumers and the service requesters (i.e. general practitioners and obstetricians) would inform the above uncertainties.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that the application was for NIPT for trisomies 21, 18 and 13 using fetal cell free DNA from maternal blood. NIPT may reduce invasive procedures such as amniocentesis and chorionic villus sampling (CVS), thereby minimising the risk of complications, pregnancy loss and anxiety. However, it will not replace amniocentesis and CVS. NIPT also

will not replace the nuchal translucency (NT) scan at 12 weeks, as this scan can detect structural abnormalities in the fetus, or the PAPP-A component, as this is a predictor for adverse pregnancy outcomes.

MSAC noted that NIPT has high sensitivity and specificity, and is superior to combined first trimester screening (CFTS) or second trimester maternal serum screening (2TMSS) in terms of invasive procedures required, unnecessary invasive procedures performed, and trisomy cases undetected. NIPT is well established in Australia and there is high demand for the test in the community. MBS data show that invasive procedures have decreased over recent years, and NIPT is the most likely explanation for this.

MSAC considered that NIPT was safe as it involves collecting a sample of maternal blood.

MSAC considered the clinical management algorithm and noted that the place of NIPT in this algorithm was highly uncertain. MSAC considered whether NIPT should be available for all pregnant women (primary screening) or only those identified as being at high risk after CFTS or 2TMSS (contingent population). If a contingent population was considered appropriate, the risk threshold would need to be defined for this population (e.g. a risk of aneuploidy of 1 in 300 or 1 in 1000). MSAC considered the basis for the risk threshold and whether this should include age as a factor (e.g. women aged over 35 years), obesity or twin pregnancy. MSAC noted that many women become pregnant at an older age, and therefore this 'contingent' population would be a large proportion of the primary population of pregnant women of all ages. It was also noted that current screening programs in older women have been highly successful and most aneuploidies now occur in infants of younger women, creating issues of equity if NIPT is restricted based on age. MSAC was concerned that the time taken to assess the risk for a contingent population, plus the overall decision turnaround time of about three weeks (noting that only a limited number of laboratories in the country currently render this service and it requires interpretation of the test results) leaves little time to intervene to terminate a pregnancy in which a trisomy is detected. MSAC was also concerned that as the risk threshold drops to 1 in 1000 or below in primary screening, the low prevalence will result in increasing likelihood of false positive test results.

MSAC noted expert advice from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists that the risk of fetal aneuploidy is either low or high and that what was proposed as "intermediate risk" was actually "high risk". This should also be reflected in the clinical management algorithm. In addition, MSAC noted that genetic counselling is an important part of the algorithm.

MSAC considered that reducing the fee for NIPT to $400 was appropriate because the cost of NIPT has decreased and is expected to continue this trend, particularly if public listing increases uptake. MSAC noted concerns from ESC that reducing the fee to $400 may mean that laboratories start to charge for repeat tests, which are currently usually provided at no extra cost. However, the applicant advised that additional costs would not be charged as a result of market demand. MSAC also considered that the service should be supported by the required genetic counselling.

Regarding the economic evaluation, the cost-effectiveness of NIPT as a primary screening test compared with CFTS and 2TMSS depended largely on the cost of NIPT, the second NIPT fail rate, NIPT sensitivity and specificity, and rate of procedure-related losses. As a contingent test compared with CFTS and 2TMSS, the cost-effectiveness of NIPT depended largely on the cost of NIPT, the risk threshold, uptake of contingent NIPT, NIPT sensitivity and specificity, and rate of procedure-related losses. MSAC indicated that it would also like

to compare the cost-effectiveness of NIPT across use with a risk threshold of 1 in 1000 and use with a risk threshold of 1 in 300.

MSAC noted the substantial financial implications to the MBS budget of NIPT as a primary screening test of about $110 million per year.

MSAC concluded that stakeholder consultation with the service providers, consumers and service requesters (i.e. general practitioners and obstetricians) was necessary before the application could be resubmitted. This consultation would help to clarify the place of NIPT in the clinical management algorithm and a justification for a nominated risk threshold if appropriate.

MSAC anticipated the following issues would need to be addressed for the MBS item descriptor in the event that a subsequent application is supported:
- whether sex chromosome aneuploids are included
- whether twin or other multiple pregnancies are included
- whether to limit to one test per pregnancy
- whether to report the fetal fractions.

4. Background

MSAC has not previously considered an application for NIPT.

5. Prerequisites to implementation of any funding advice

Multiple tests are marketed and available in Australia, and several tests are registered on the ARTG.

6. Proposal for public funding

All pregnant women are at risk of fetal aneuploidy, and therefore the first population is to test all women who are pregnant. The second population is targeted to pregnant women at high risk of fetal aneuploidy. These women are identified using the current prenatal testing approach and are subsequently offered NIPT. The proposed MBS item descriptors for both patient populations are presented in Table 1 and Table 2.

Table 1 Proposed MBS item descriptor for NIPT primary screening

Category 6 – (Group P7 Genetics) – Pathology services
Non-invasive prenatal screening from the blood of a pregnant woman patient for the detection of the more common fetal aneuploidies, trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome) and trisomy 13 (Patau syndrome) in trophoblastic or fetal DNA circulating in maternal blood.
Fee: $400

Table 2 Proposed MBS item descriptor for NIPT contingent screening

Category 6 – (Group P7 Genetics) – Pathology services
Non-invasive Prenatal screening of blood from a pregnant woman patient at high risk for the detection of the more common fetal aneuploidies, trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome) and trisomy 13 (Patau 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 of including but not limited to: •maternal age of 35 years or greater •abnormal maternal serum markers •abnormal first trimester ultrasound nuchal translucency
Fee: $400

Advice from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) suggested the following MBS item descriptors:

> *Screening using plasma cell-free DNA from a pregnant woman for the detection of the most common autosomal aneuploidies in the fetus; trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome) and trisomy 13 (Patau syndrome).*
>
> *Screening using plasma cell-free DNA from a pregnant woman at high risk for the detection of the most common autosomal aneuploides in the fetus; trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome) and trisomy 13 (Patau syndrome).*
>
> *High risk pregnancy is defined as screen positive on a prior screening test for fetal aneuploidy, including but not limited to:*
>
> - *maternal age of 35 years or greater*
> - *combined first trimester screening (with nuchal translucency and serum markers)*
> - *high risk second trimester maternal serum screening.*

7. Summary of Public Consultation Feedback/Consumer Issues

Feedback was received from a professional organisation which was supportive of using NIPT to screen for common fetal trisomies.

8. Proposed intervention's place in clinical management

NIPT analyses fetal cell free DNA (cfDNA) to detect quantitative differences in the number of DNA fragments of different chromosomes to distinguish fetal aneuploidies from unaffected pregnancies. 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 CVS for fetal karyotyping.

NIPT would be offered as part of routine clinical care and provided after 10 weeks' gestation. It would be offered once for each pregnancy unless test failure required a repeat test. Results would be reported to the treating medical practitioner, midwife or genetic counsellor, who would advise the patient of the result and provide counselling where required.

The current and proposed clinical management algorithms for primary screening and contingent screening in the first and second trimesters are presented in Figure 1, Figure 2, Figure 3 and Figure 4.

Figure 1 Right: Proposed clinical management algorithm for pregnant women presenting in first trimester (primary screening). Left: Current clinical management algorithm of pregnant women presenting in first trimester.

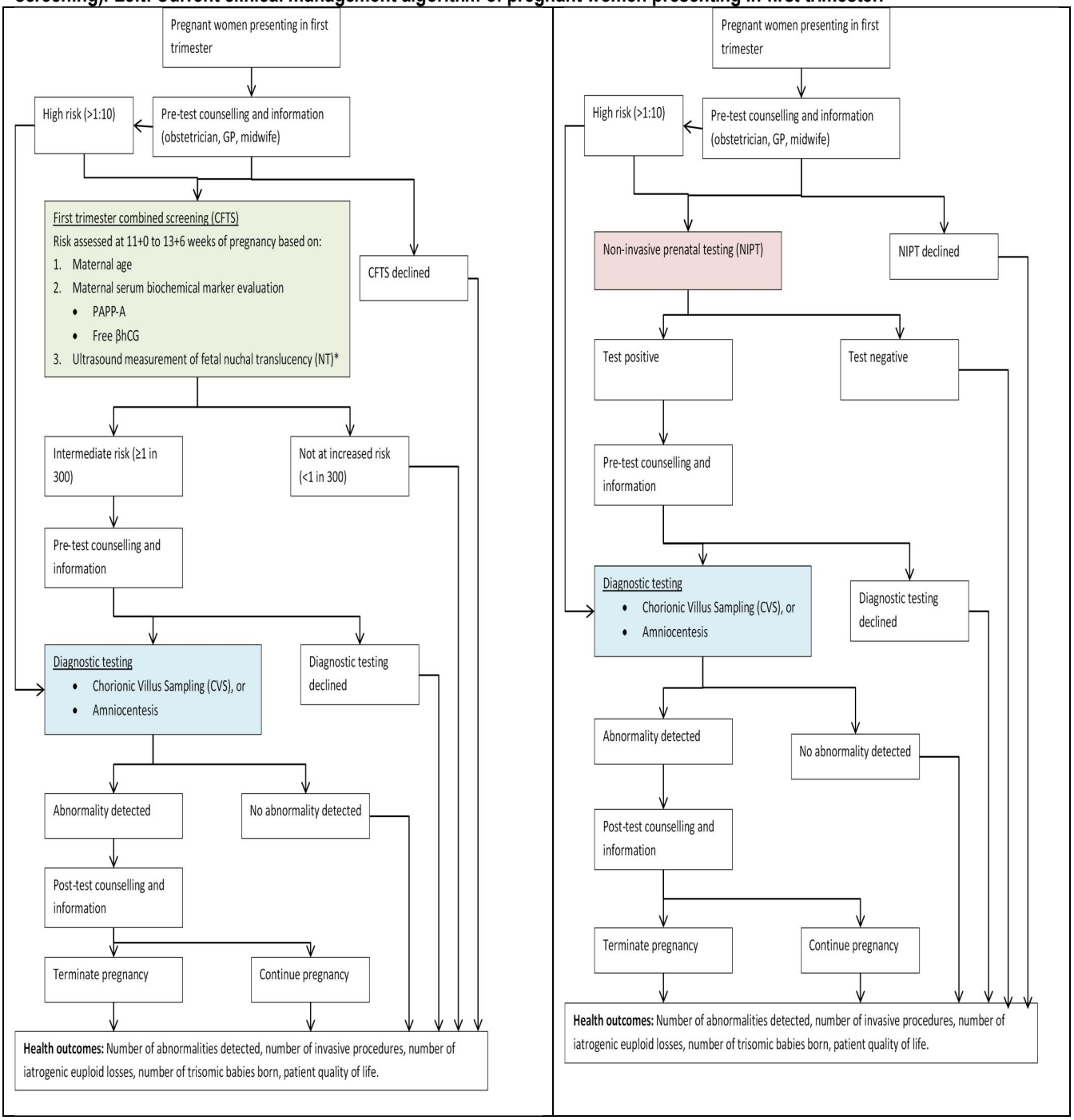


Figure 2 Right: Proposed clinical management algorithm for pregnant women presenting in first trimester (contingent screening). Left: Current clinical management algorithm of pregnant women presenting in first trimester.

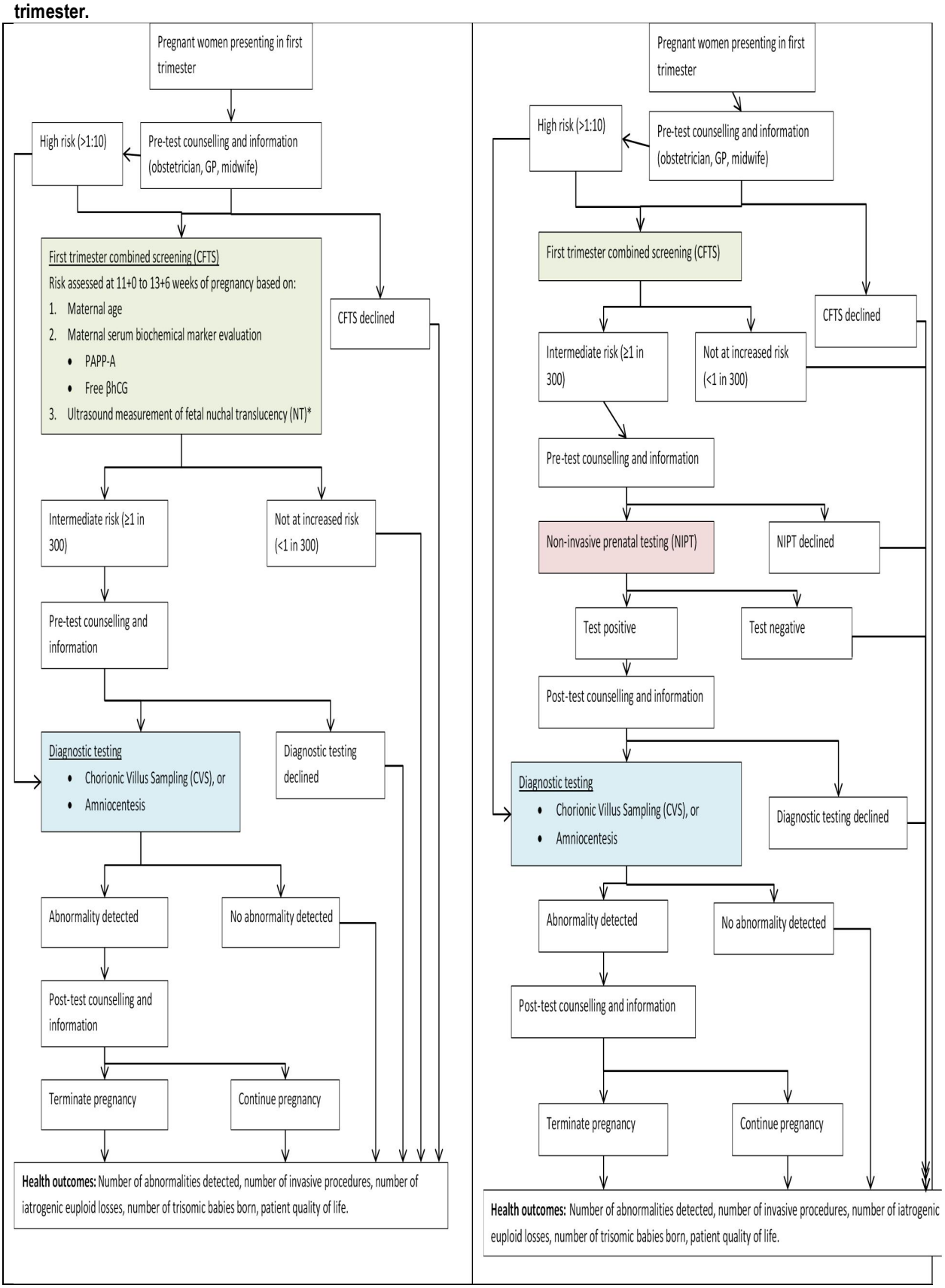


Figure 3 Right: Proposed clinical management algorithm for pregnant women presenting in second trimester (primary screening). Left: Current clinical management algorithm of pregnant women presenting in second trimester.

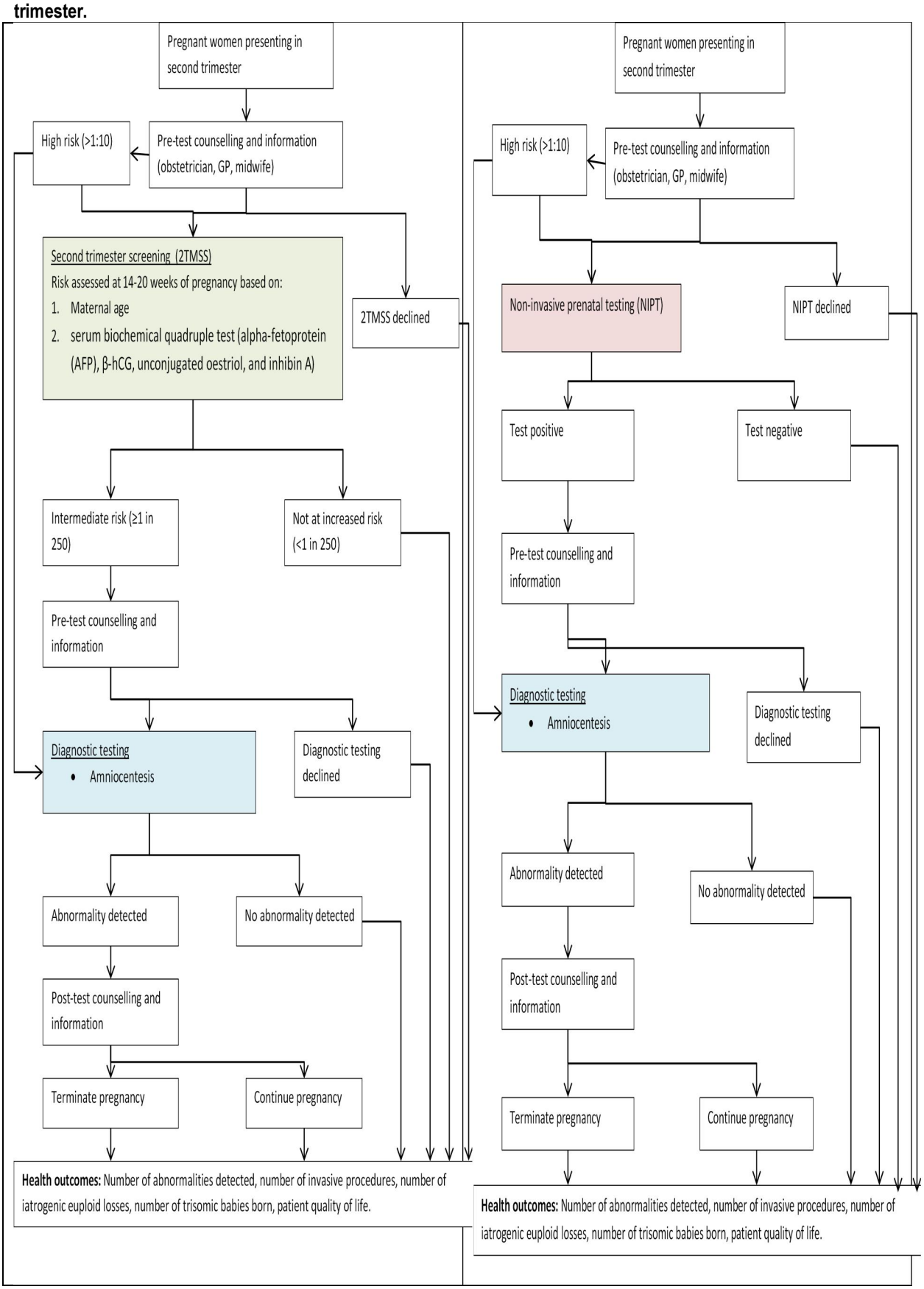
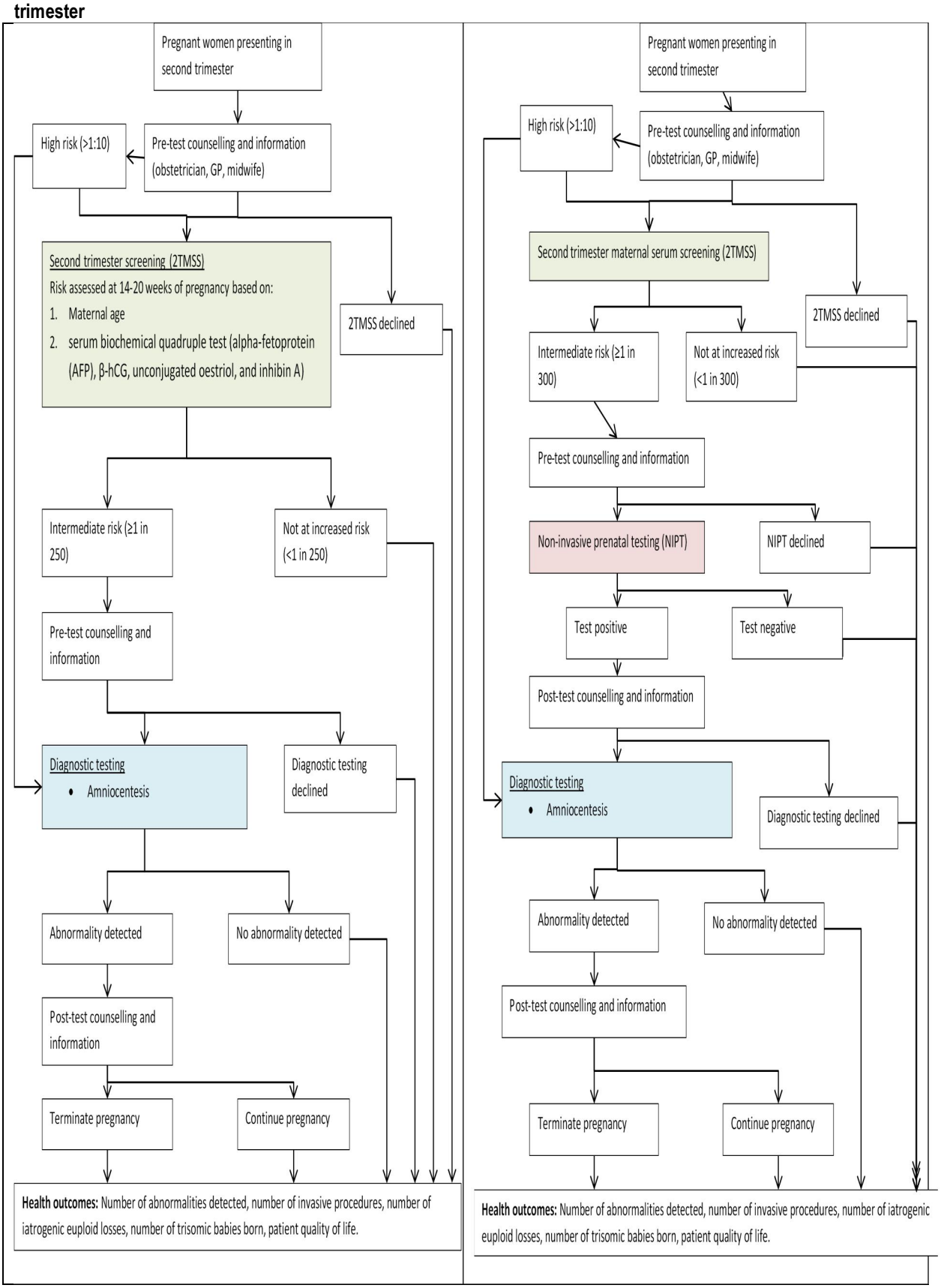


Figure 4 Right: Proposed clinical management algorithm for pregnant women presenting in second trimester (contingent screening). Left: Current clinical management algorithm of pregnant women presenting in second trimester



9. Comparator

For Population 1 (primary screening, all pregnant women) the nominated comparators are:
- CFTS at 11^{+0} to 13^{+6} weeks of pregnancy, which includes consideration of maternal age, ultrasound measurement of fetal NT; and maternal serum biochemical marker evaluation of ß-hCG and PAPP-A; and
- 2TMSS at 14 to 20 weeks of pregnancy, which includes a serum biochemical quadruple test of AFP, ß-hCG, unconjugated oestriol and inhibin A.

For Population 2 (contingent screening; women assessed at high risk) the comparator nominated is:
- CFTS followed by secondary confirmatory invasive genetic testing in high risk women.

10. Comparative safety

NIPT is considered a safe test as it only requires collection of maternal blood, a routine procedure during pregnancy. The application claimed that NIPT is non-inferior in safety compared to CFTS or 2TMSS, for the screening of common fetal trisomies.

11. Comparative effectiveness

Accuracy
Effectiveness from linked evidence from meta-analysis showed that the pooled sensitivity of using NIPT in screening for common fetal trisomies was 98.6% [97.8-99.2] and the pooled specificity was 99.8% [99.8-99.9], indicating a high level of sensitivity and specificity in this population. The pooled sensitivity of using NIPT in screening for common trisomies and monosomy X was 97.5% [96.2-98.4] and the pooled specificity was 99.7% [99.4-99.9]. The application stated that these findings indicate that NIPT is both highly sensitive and highly specific in screening for common trisomies and monosomy X.

Therapeutic efficacy (change management)
Assuming NIPT results would guide clinical decision making regarding invasive procedures, this meta-analysis found that using NIPT to screen for common fetal trisomies compared to CFTS or 2TMSS would result in an 87.9% reduction (0.9% compared to 7.7%) in the number of pregnant women undergoing invasive procedures for the diagnosis of common trisomies, a 76.9% reduction in the number of pregnant women undergoing unnecessary invasive procedures for the diagnosis of common trisomies (21.5% compared to 93.1% of positive results are false positive), and a 26.0% reduction in the number of common fetal trisomy cases undetected (5.2% compared to 7.0%) . The application stated that these findings indicate that NIPT has superior clinical utility to CFTS or 2TMSS in screening for common trisomies.

Therapeutic effectiveness (health benefit from change in management)
On the basis of the evidence profile, the application suggested that, compared to CFTS or 2TMSS, NIPT for the screening of common fetal trisomies has non-inferior safety and superior effectiveness.

Clinical claim

The clinical claim is that NIPT is non-inferior in safety and superior in clinical effectiveness to current testing in that it would increase the detection of fetal aneuploidies and reduce utilisation of invasive testing (amniocentesis and CVS), which would reduce iatrogenic euploid fetal losses from these tests and decrease the number of trisomic cases undetected (at birth). For the contingent population, NIPT would 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.

12. Economic evaluation

The modelled economic evaluation included a cost effectiveness analysis, which was conducted from the perspective of the healthcare payer, including costs related to the provision of health care resources and health outcomes.

The overall costs and outcomes, and incremental costs and outcomes as calculated for NIPT as a contingent test and comparator in the model with the base case assumptions are shown in the tables below.

Table 3 shows the base case results in primary screening for common trisomies.

Table 3 Total and incremental costs ($) and effectiveness (per pregnant woman); primary screening

	Primary NIPT	Usual care	Incremental cost or effectiveness	ICER (per unit of outcome)
Cost (including GP/specialist visits/testing/miscarriages/terminations)	$624	$253	$371	
Total correct diagnoses	0.9923	0.9477	0.04	$8,317
True positives	0.0037	0.0032	0.0005	$767,676
True negatives	0.99	0.94	0.04	$8,408
Invasive procedures [avoided] (number)	0.01	0.04	0.03	$11,082
Procedure-related miscarriages [avoided] (number)	0.00001	0.00006	0.00004	$8,450,856
[Decrease in] the number of trisomy cases missed	0.00003	0.00037	0.00034	$1,092,909

Table 4 shows the base case results in contingent screening for common trisomies.

Table 4 Total and incremental costs ($) and effectiveness (per pregnant woman); contingent screening

	Contingent NIPT	Usual care	Incremental cost or effectiveness	ICER (per unit of outcome)
Cost (including GP/specialist visits/testing/miscarriages/terminations)	$250	$253	$ -2.91	Cost-neutral
Total correct diagnoses	0.9910	0.9477	0.04	NIPT Dominates
True positives	0.0030	0.0032	**-0.0002**	Comparator Dominates
True negatives	0.99	0.94	0.04	NIPT Dominates
Invasive procedures [avoided] (number)	0.002	0.042	0.040	NIPT Dominates
Procedure-related miscarriages [avoided] (number)	0.000003	0.000055	0.00005	NIPT Dominates
[Decrease in] the number of trisomy cases missed (at birth)	0.00040	0.00037	**-0.00003**	Comparator Dominates

Bold font indicates an outcome that favours the comparator – usual care

The cost effectiveness of NIPT as a primary screening test relative to CFTS and 2TMSS depended largely on the cost of NIPT, the second NIPT fail rate, and the NIPT sensitivity and specificity, and the rate of procedure related losses. The cost effectiveness of NIPT as a contingent test relative to CFTS and 2TMSS depended on the cost of NIPT, the uptake of contingent NIPT, and the sensitivity and specificity of NIPT, and the rate of procedure related losses.

13. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of the introduction of NIPT.
The financial implications to the MBS resulting from the proposed listing of NIPT are summarised in Table 5 for the primary population and in Table 6 for the contingent population.

Table 5 Total costs to the MBS associated with NIPT as primary screening test

	2018-19	2019-20	2020-21	2021-22	2022-23
NIPT					
Number of services	*265,397*	*268,154*	*270,503*	*272,434*	*274,030*
Sub-total cost $ (M)	112.8	114.0	115.0	115.8	116.5
Subsequent intervention	-	-	-	-	-
Number of services	-26,795	-27,073	-27,310	-27,505	-27,666
Sub-total cost	-5.13	-5.18	-5.23	-5.26	-5.29
Total services	**245,503**	**248,053**	**250,226**	**252,012**	**253,489**
Total cost $(M)	**107.67**	**108.79**	**109.74**	**110.52**	**111.17**

Source: Critique

Table 6 Total costs to the MBS associated with NIPT in a contingent population

	2018-19	2019-20	2020-21	2021-22	2022-23
NIPT					
Number of services	*12,123*	*12,249*	*12,356*	*12,445*	*12,518*
Sub-total cost $(M)	5.2	5.2	5.3	5.3	5.3
Subsequent intervention	-	-	-	-	-
Number of services	-19,449	-19,651	-19,823	-19,965	-20,082
Sub-total cost $(M)	-5.60	-5.66	-5.71	-5.75	-5.79
Total services	**-7,010**	**-7,083**	**-7,145**	**-7,196**	**-7,238**
Total cost $(M)	**-0.45**	**-0.46**	**-0.46**	**-0.46**	**-0.47**

Source: Critique of CA

14. Key issues from ESC for MSAC

Key issues from ESC to MSAC

ESC Key ISSUES	ESC ADVICE
Poor quality evidence	Need adequate sensitivity analyses to address the clinical effectiveness uncertainty e.g. test failures; potential to overestimate accuracy, ttherapeutic efficacy and therapeutic effectiveness benefits over the comparator).
Uncertain clinical place in therapy	Consultation with obstetricians be undertaken to understand how NIPT will be used in clinical practice i.e. whether it will be an add-on or replace its comparators.
Descriptor proposed by applicant has potential for leakage to populations without evidence	Proposed change to the MBS Item Descriptor is appropriate to reduce leakage to populations for which there is no evidence of benefit of NIPT. If evidence is available to support testing for further fetal aneuploidies, these could be subsequently considered as additional options. Consider an addition to the MBS Item Descriptor to restrict NIPT to once per pregnancy
Proposed fee is not representative of current NIPT cost.	Reduction of fee from $500 to $400 is appropriate
As with all genetic testing, the requirement for pre- and post-test counselling is, at present, an issue of good clinical practice	Ensure adequate funding arrangement to support Genetic counselling
Cost of second NIPT	$0 appears to be the current practice
Fail rate of second NIPT	Repeat testing – the failure rate ranges from 1% to 25%; the wide range introduces uncertainty
Uptake of NIPT	Uptake in the contingent population – savings reduce by around $0.5–1 million as uptake increases.
ESC advised that it is highly recommended that obstetricians, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists and pregnant women are approached for their input before the application comes back to MSAC	

ESC discussion

ESC noted that this item was a merger of items 1458 (RCPA) and 1461 (Roche Diagnostics) due to the similarities of requested listing between the applications.

The submission proposes Medicare Benefits Schedule (MBS) listing of NIPT for trisomies 21 (Down syndrome), 18 (Edwards syndrome) and 13 (Patau syndrome) and monosomy X. With greater awareness that all trisomies are more frequent in older mothers, screening in that population has been very effective. The majority of trisomy births are now in mothers aged in their late teens to early 30s. The proposal addresses the need for a more accurate test for screening.

ESC noted that the application proposed two patient populations:

1. all women who are pregnant; where no prior testing is required; estimated to be approximately 300,000 per year (primary population, comparator CFTS); and
2. pregnant women at high risk of fetal aneuploidy are identified using current screening approaches and are subsequently offered NIPT (contingent population, comparator 2TMSS).

The clinical claim for primary screening is that NIPT has non-inferior safety and superior clinical effectiveness to current SoC. The PICO confirmation, contracted assessment (CA) and critique differed in their definitions of safety and clinical outcomes. The analysis of comparative effectiveness included women of any risk, so was a very heterogeneous population. ESC noted that, although NIPT seems to be sensitive and specific compared to the reference standard, the quality of the evidence was poor. One major issue was that the estimates of diagnostic performance of the comparators were poor quality and varied greatly.

ESC noted that the Song 2013 study comparing NIPT and 2TMSS showed a 45% difference in sensitivity, which was not considered credible due to small numbers. The Bianchi 2014 study showed similar high sensitivity and specificity for NIPT compared to CFTS or 2TMSS.

ESC noted that the CA used estimates of sensitivity pooled across trisomies. However, available studies showed variation in sensitivity for each trisomy. Performance of the test varied according to the disorder (highest for Down syndrome, lower for Edwards syndrome; lowest for Patau syndrome).

ESC considered that small studies and wide variations made it difficult to interpret the true difference between the intervention and the comparator. ESC noted that no discussion of publication bias was presented in the CA, despite a systematic review of largely the same studies finding evidence of bias (Taylor-Phillips 2016). ESC noted that publication bias would likely overestimate test accuracy. Overall, results for accuracy were difficult to interpret due to small difference between NIPT and its comparators. Furthermore, ESC noted that the evidence for the efficacy outcome of change in management was limited and based on many assumptions.

ESC considered estimates of clinical validity (post-test probabilities) to be flawed due to improper calculation or use of inappropriate prevalence rates. Sensitivity and specificity may be more commonly viewed as a measure of test accuracy. In addition, the CA combined studies in women of all risks (no prior risk assessment, low-, intermediate- and/or high-risk) to derive diagnostic accuracy, making it difficult to interpret as to which of the populations the results applied. This is relevant to the economic model.

ESC noted that the clinical claim for the contingent population is that NIPT would maintain the current rate of detection of fetal aneuploidies and reduce the use of invasive testing (amniocentesis and chorionic villus sampling [CVS]). ESC noted that there is very little evidence of change in management as a consequence of testing, and the assumptions in the CA had little evidence to support them. Although it is likely that NIPT offers improvements over CFTS or 2TMSS in terms of referrals for invasive procedures, the magnitude of such an effect is likely to be overestimated and it is unclear what an accurate increment would be. ESC also noted inconsistent modelling of therapeutic effectiveness in the CA.

In terms of the proposed clinical algorithm, ESC noted that NIPT was to replace CFTS which includes biomarker pathology test and an ultrasound fetal translucency scan in the primary population. ESC considered this claim to be uncertain as the CA and Critique failed to consider the real-world implementation of NIPT and obtain comments from obstetricians

who will be the primary requestors of the test. ESC noted that it may replace the pathology testing (items 66750 and 66751), which has a rebate of $33.80; but may not replace the ultrasound scan (item 55707). ESC therefore considered that NIPT will likely to be an add-on test to CFTSS.

ESC noted that the CA did not include data on the current number of screening in first trimester and second trimester which can be obtained from MBS usage database. ESC further noted that while the use of CVS and amniocenteses is relatively low (and not stated in the CA), NIPT does not replace these invasive diagnostic tests. ESC advised that more consultation with obstetricians is necessary to understand the impact of NIPT in clinical practice.

ESC noted that a number of potentially relevant systematic reviews and studies were omitted from the assessment. However, the impact of this was considered to be minimal, as additional results consistently indicated that NIPT had high sensitivity and specificity in detecting common trisomies.

ESC noted that the analyses did not use available MBS data on the number of tests that are actually done, or the number of pregnancies that lead to a live birth. The number of first trimester screening tests has declined since 2013–14 and plateaued, possibly because NIPT has been available for some time. Despite this, most women in Australia have first trimester screening. The number of amniocentesis and CVS procedures under the MBS has declined to about a quarter of previous levels; only 3900 were done in Australia in 2016–17. Including this data in the assessment would have given a better picture of current utilisation.

With regards to the MBS item descriptor, ESC agreed with changes made by the Department (see tables below). ESC agreed that the wording 'including but not limited to' in the MBS item descriptor in relation to the fetal aneuploidies would allow for the reporting of anomalies such as sex chromosome aneuploidies and microdeletions, for which there has been no formal request in the application. ESC therefore agreed that the wording of the MBS item descriptor instead list the three trisomies, with the option for MSAC of adding monosomy X once evidence is available to support this.

ESC further noted that the test is not limited to one per pregnancy and this should be specified in the descriptor. ESC also noted that the test is not just a 'blood test' but also involves next-generation sequencing or microarray. ESC agreed that the fee of NIPT should be reduced to $400 as the cost of NIPT has decreased and is expected to continue this trend over the next few years, especially if a positive listing increases the volume of uptake.

Table 7 ESC revised MBS item descriptor for NIPT primary screening

Category 6 – (Group P7 Genetics) – Pathology services
Non-invasive prenatal screening from the blood of a pregnant ~~woman~~ patient for the detection of ~~the more common~~ fetal aneuploidies~~,~~ trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome) and trisomy 13 (Patau syndrome) in trophoblastic or fetal DNA circulating in maternal blood.
Fee: $400

Table 8 ESC revised MBS item descriptor for NIPT contingent screening

Category 6 – (Group P7 Genetics) – Pathology services
Non-invasive Prenatal screening of blood from a pregnant ~~woman~~ patient at high risk for the detection of ~~the more common~~ fetal aneuploidies~~;~~ trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome) and trisomy 13 (Patau 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 of ~~including but not limited to~~: •maternal age of 35 years or greater•abnormal maternal serum markers•abnormal first trimester ultrasound nuchal translucency.
Fee: $400

ESC noted that the economic evaluation comprised a cost-effectiveness analysis, which was considered appropriate, despite the PICO confirmation suggesting cost-utility or cost-consequences analysis. The evaluation used a decision analytic model. However, the analysis was essentially a list of different outcomes and associated costs – there were no trees or Markov assessments. The time horizon for the evaluation was very clear (until birth).

ESC noted that there is limited information in the CA on the quality adjusted life years (QALYs). ESC noted that there is published literature available for QALYs of trisomy 21; however the CA did not make reference to this. ESC noted that the CA did not include quality of life outputs and there is insufficient evidence to report on quality of life. Furthermore, it was not stated in the CA whether the quality of life of the mother due to reduced anxiety was reported in any study. Due to the insufficient evidence on QALYs, ESC did not make any further comments.

ESC noted the importance of the terminology regarding clinical outcomes. The applicant, CA and PICO confirmation use different terms ('number of trisomy cases missed', 'number of trisomic cases undetected [at birth]', 'number of trisomic babies born', respectively).

ESC noted that the CA used 'counts' of outcomes such as procedures avoided, correct diagnosis and adverse events. ESC further noted the applicant's pre-ESC response stated that the goal is to provide accurate information and not to reduce the number of trisomic births, so the relevant outcome should be 'number of trisomy cases missed'. ESC therefore noted that there is a mix of positive and negative outcomes.

ESC queried whether testing was conducted in Australia or overseas and whether that had any consequences for custodianship of results. The CA did not allude to this issue. The critique noted that there are limited centres of testing in Australia, one of which the applicant advised sends non-standard tests offshore. However, there were no further details and this was not discussed further.

ESC noted that the incremental cost-effectiveness ratio (ICERs) provided in the CA were based on $500 per test. ICERs were dependent on the outcome being considered (correct diagnosis or invasive procedure avoided). For the primary screening population, ICERs were approximately $8000 to $12,000. In the contingent population, ICERs were dominant. In the CA sensitivity analysis, ICERs were lower if the fee per test was $400.

ESC queried who would bear the cost of repeat testing after failed tests if the failure rate is as high as 25%. The applicant indicated that the majority of laboratories will retest the sample for free. One laboratory confirmed this, but another advised that it charges on a case-by-case basis. ESC noted that reducing the NIPT test fee from $500 to $400 may lead to some labs charging for the retest thus increasing the financial impact on the MBS.

ESC agreed it is better to assess financial implications using the lower cost of NIPT. The critique used $400 in only some of the calculations in the sensitivity analysis, but stated that cost decreases for the primary screening population and savings increase for the contingent population. However, the savings were noted to be highly uncertain due to the drivers listed in the CA: NIPT cost, fail rate, accuracy, specificity of comparator, and uptake.

ESC questioned the clinical value of NIPT into the practical setting and advised consultation with obstetricians to better understand the place of NIPT in clinical practice. ESC advised to utilise MBS data to determine the actual population of women in primary and secondary testing. While the quality of clinical evidence is poor, the economic evaluation should be revised using the cost of $400 NIPT fee, noting that this revised cost may lead laboratories to reconsider current practice of a $0 repeat test.

15. Other significant factors

Nil.

16. Applicant's comments on MSAC's Public Summary Document

Roche is concerned that our attempts to inform on this assessment, in particular our response to the ESC report, have not been fully considered or included in PSD. The risk threshold of 1:300 used in the contingent assessment provides the least advantageous evaluation of NIPT, because it represents a flawed model. We suggest, a cost effective analysis assessment is performed over a range of cut offs up to the 1:1000 risk threshold. There has been a substantial change in antenatal care nationally since the introduction of NIPT, funded solely by individual patients who 'can afford to pay'. We respectfully request this submission is expedited back to MSAC for review urgently, so that the current inequity of prenatal care can be addressed.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
visit the MSAC website