Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1492 – Non-invasive prenatal testing (NIPT) for trisomies 21, 18 and 13

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

Date of MSAC consideration: **MSAC 77th Meeting, 28-29 November 2019**

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

1. Purpose of application

Following consideration by MSAC in July 2018, the Department commissioned additional work (second contracted assessment; 2nd CA) on MSAC Application 1492 comprising:

- an updated literature review – using the same search terms as the original search;
- an expansion of the rationale for moving from the previous evidence base to the new basis, particularly regarding the Norton (2015) paper;
- an assessment of how discordant results may influence clinical management; and
- provision of updated financial implications and updated/adjusted utilisation and cost estimates.

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 did not support the public funding of this proposal on cost-effectiveness grounds. MSAC concluded that, largely due to the effectiveness of the existing prenatal testing options, the desirable consequences of augmenting this with the proposed testing, including for improved decision-making by patients and their care-givers, were too small (about 195 extra cases detected across approximately 300,000 women having funded access to this test) to justify the estimated $100 million increase in annual MBS expenditure required.

Consumer summary
Roche Diagnostics Australia Pty Ltd and Royal College of Pathologists of Australasia applied for public funding through the Medicare Benefits Schedule (MBS) for non-invasive prenatal testing to detect whether a foetus has trisomy 21, 18 or 13. A trisomy is a genetic condition where the cells have an extra copy of a chromosome: this causes developmental abnormalities which may either be detected during pregnancy (sometimes called birth defects) or may occur after delivery. Each of the trisomies 21, 18 and 13 can cause particular abnormalities, each of which has varying severity.

Consumer summary

Non-invasive prenatal testing is a genetic test done on a sample from the pregnant woman's blood, so it does not put the foetus at any risk. This is compared to invasive prenatal testing, such as amniocentesis (testing the fluid surrounding the foetus) or chorionic villus sampling (testing the placenta, i.e. where the mother's blood join's the blood of the foetus), which have some risk for the foetus.

Currently, any pregnant woman can have another type of blood test and an ultrasound test, which may indicate her baby may have a trisomy. Some women may have difficulty accessing these tests depending on where they live, and others choose not to have them.

If the current blood and ultrasound tests indicate a positive result suggestive of having a baby with a trisomy, the woman can go on to have the more invasive prenatal tests to confirm whether the foetus has a trisomy or not. With these results, and counselling support, the decision can then be made whether to continue or end the pregnancy.

Non-invasive prenatal testing is more accurate than these current blood and ultrasound tests in detecting these potential genetic conditions when present, and in ruling out the conditions where they are not present. Importantly, it picks up more cases of trisomy, but it is much more expensive than the current tests. MSAC calculated that of the 300 000 women who could be eligible for this test, 195 additional trisomy cases would be detected at a cost of $100 million per year.

MSAC's advice to the Commonwealth Minister for Health

MSAC did not support funding of this test for trisomies. MSAC advised that non-invasive prenatal testing is not cost-effective for picking up additional trisomies compared with current testing.

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

MSAC noted that the purpose of this application was to seek public funding of non-invasive prenatal testing (NIPT) for trisomies 21, 18 and 13 using cell-free fetal DNA from maternal blood. MSAC noted that it had already accepted the clinical efficacy and superiority of NIPT compared to ultrasound plus biochemical tests used in prenatal screening. MSAC noted that stakeholders at a meeting in November 2018 concluded that NIPT would be used in unselected pregnant women – that is, as an opportunistic screening test. Not all stakeholders agreed on this issue. From an efficiency perspective or a financial perspective, it could be argued that NIPT should be restricted to those pregnant women at high-risk for trisomies. However, from an equity of access perspective, it was thought that the test should be available to all pregnant women.

MSAC noted that there is still some uncertainty as to whether NIPT should replace the current biochemical screening tests in pregnancy or whether it would be an additional test. MSAC concluded that it would largely be an additional test. MSAC considered that NITP is proposed to be used once per pregnancy, thus if NIPT is used in the first trimester, the second trimester screening test would still be required to be available, however if NIPT is used in the second trimester, the ultrasound component of first trimester screening tests would still be required to be available, whereas the biochemistry tests may not. MSAC also recalled that the stakeholder meeting in November 2018 suggested that, because the cost of the biochemical tests is low ($35), they could be left on the MBS even if NIPT was added, leaving clinicians to decide which test is most suitable on a case-by-case basis. MSAC advised that, because

ultrasound can detect other abnormalities and the second trimester biochemistry tests also assesses individual risk for abdominal wall defects (AWD) and neural tube defects (NTD), these should not be replaced by NIPT. MSAC also noted that a proportion of women present for their first trisomy test in the second trimester – such women should still be able to determine their risk of trisomies plus AWD and NTD.

MSAC noted that first trimester ultrasounds are not readily available in all rural/regional areas meaning that there may be equity of access issues with the current screening approach. MSAC considered this to have implications for its consideration of NIPT, which may have less equity of access implications because, like other pathology tests based on a blood sample, NIPT is expected to have less consequences for the distances travelled to access this service than ultrasounds. MSAC also noted that, currently, 25–30% of pregnant women are paying for NIPT out of their own pocket because it is acknowledged to be a superior test (identifying 99% of trisomies compared to 85% using current screening approaches) and possibly because they want to avoid unnecessary invasive testing (Norton, 2015).

MSAC noted that a number of factors make it difficult to determine the clinical and economic impact of listing NIPT on the MBS. In seeking to better examine this impact, MSAC specified four categories of patients:

- women who have access to screening and choose to screen
- women with access to biochemical testing but not ultrasound
- women with no access to ultrasound or biochemistry testing
- women who have access to screening but choose to not screen.

MSAC considered that the primary outcome of interest is the number of additional trisomies that NIPT would detect (compared to not having NIPT on the MBS). When considering the numbers of women in all of these four categories and the associated uptake and detection rates, MSAC estimated that NIPT would detect an additional 195 trisomies per year overall (see Table 1). However, it remains uncertain as to whether there is a proportionally higher incidence of trisomies who are born among those women who do not have access to first trimester ultrasound, or any screening at all, and if these could be appropriate populations to have preferential public funding for NIPT.

MSAC then calculated that if all pregnant women had unrestricted access to NIPT, then approximately 300,000 women would be able to access it. Based on data presented in the application from the Victorian Perinatal Linkage Study, 83.4% of women in Victoria underwent at least one form of aneuploidy screening. Based on the uptake rate of current screening of 83% as the upper limit of national uptake if NIPT were to become available, 250,200 out of 300,000 women would potentially avail themselves of testing per year. The MBS expenditure for NIPT in these women would be in the order of $100 million to detect approximately an additional 195 cases of trisomies per year, as compared to the current testing methods. MSAC advised that this was not acceptably cost-effective, and that this conclusion would not be affected by attempting to resolve whether invasive prenatal testing (IPT) rates would change further with the public funding of NIPT for these three trisomies.

Table 1: Estimating the extra number of trisomies 21, 18 and 13 detected per year and cost per extra case detected

	Categories of pregnant women			Total
	Access to screening and choose to undergo screening at least once per pregnancy	Access to second trimester biochemistry, but no ultrasound	No access to ultrasound or biochemistry, or have access to screening, but choose not to screen	
Proportion of pregnancies per year[1]	77.7%	5.3%	17%	100%
Representative number of pregnancies per year	233,100	15,900	51,000	300,000
Combined annual incidence of trisomies 21, 18 and 13[2]	36/10,000	36/10,000	36/10,000	36/10,000
Expected number of pregnancies with trisomies 21, 18 and 13 per year	839	57	184	1080
Current uptake of screening	100%	100%	0%	83%
Current screening diagnostic yield	CFTS = 78%[3a]	2TMSS = 54.4%[3b]	0%	-
Number of pregnancies with trisomies detected by current testing	654 (by CFTS)	31 (by 2TMSS)	0	685
Estimated uptake of NIPT	100%	100%	0%	83%
Screening diagnostic yield with NIPT[4]	98.2%	98.2%	0%	-
Expected number of pregnancies with trisomies detected by NIPT in first trimester	824	56	0	880
Extra pregnancies with trisomies detected by NIPT	170	25	0	195
Cost of NIPT per service	$400	$400	-	-
Cost of NIPT for population	$93,240,000	$6,360,000	-	$99,600,000
Cost per extra trisomy detected	$548,471	$254,400	-	$510,769

1: Source = L. Hui,, A. Lindquist , A. Poulton et al. State-wide performance of traditional and cell-free DNA-based prenatal testing pathways: the Victorian Perinatal Record Linkage (PeRL) study. Sep 2019.
2: Source = Abeywardana S & Sullivan EA 2008. Congenital anomalies in Australia 2002–2003. Birth anomalies series no. 3 Cat. no. PER 41. Sydney: Australian Institute of Health and Welfare National Perinatal Statistics Unit.
3a: Source = CFTS = 85% (Norton 2015)
3b: Source = 2TMSS = 54.5% (Song 2013)
4: Source = NIPT = 98.2% (Norton 2015)
CFTS = combined first trimester screening; 2TMSS = second trimester maternal serum testing; NIPT = non-invasive prenatal testing

MSAC considered that the proportion of women who choose to undergo testing for trisomies would be unlikely to change if NIPT became more widely available. MSAC discussed the difficulty of categorically determining the personal choices in pregnancy management that individuals may make following NIPT, which makes it difficult to determine the cost-effectiveness of the test. Some women will have a termination if the NIPT and IPT detects a trisomy, but they may not make that decision until they have had counselling before and after testing. Other women may have no intention of terminating a pregnancy should the NIPT and/or IPT test be positive, but want the NIPT so that they can prepare for life with a child with a trisomy. MSAC accepted that these women may choose not to proceed to IPT in the event of a positive NIPT test result. Other than this, MSAC was given no clear explanation for why a test with improved detection rates for the three trisomies than current screening would contribute to an overall reduction in IPT rates. MSAC noted that, if the clinical practice were for a positive NIPT result to result directly in termination of pregnancy without IPT confirmation, then this practice would contradict current clinical practice guidelines.

MSAC acknowledged that the 'value of knowing' is important for many consumers, but, currently, this cannot be accurately costed using current health technology assessment methods.

MSAC acknowledged the clinical need for comprehensive access to screening as many women (23%) do not currently have access to, or undertake, first trimester ultrasound assessment. However, MSAC advised that the NIPT listing as proposed would have both unacceptable cost-effectiveness and unacceptable financial impact.

MSAC noted that current screening in the first and second trimester does not solely aim to assess the risk of trisomies. The effect of implementing NIPT on the ascertainment of the other targeted medical conditions with morbidity and mortality remains uncertain.

Given the slightly more favourable cost-effectiveness results in Table 1 for those pregnant women who have access to biochemistry but not to ultrasound and the larger improvement in screening effectiveness for these women, MSAC considered the possibility of an MBS item for NIPT which is limited geographically to women in rural and remote areas who may not have immediate access to ultrasound. MSAC considered that this might be worth pursuing if there is a demonstrated strong association between geographical location and utilisation of the ultrasound MBS items used for combined first trimester screening (CFTS). If this variation could also be shown to be linked to the expectation of lower rates of NIPT being paid for out-of-pocket women in rural and remote areas (for example associated with lower socioeconomic status), then this might strengthen this aspect of a greater benefit from MBS-funded access. The feasibility of implementing an MBS item descriptor targeting such women would also need to be explored.

4. Background

This is the first reconsideration of Application 1492. The original application requested MBS listing of non-invasive prenatal testing (NIPT) for "common" trisomies (21, 18, and 13) from the Royal College of Pathologists of Australasia (RCPA) and Roche Diagnostics.

At its July 2018 meeting, MSAC deferred its advice on public funding for NIPT for 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, if so, how this could be limited to a high-risk population (Application 1492 Public Summary Document [PSD] 2018, p1).

In November 2018, MSAC convened a Stakeholder Meeting where the key objectives were "to seek input from service requesters, providers and consumers on the place of NIPT in the clinical management algorithm, and on the most suitable population of pregnant women who should be eligible for funded testing". In brief, the following was discussed.

- **NIPT target population:** participants agreed that the target population for publicly funded NIPT should be all pregnant women, regardless of risk.
- **NIPT as add-on or replacement:** participants emphasised that NIPT should not replace the current CFTS, which comprises both ultrasound and biochemical testing, but should be an additional service.
- **Timing of NIPT and results:** participants discussed the timing of NIPT, which should be conducted from 10 weeks gestation at the earliest.
- **Potential changes in practice:** participants noted the dramatic reduction in invasive prenatal testing (amniocentesis and chorionic villus sampling) over recent years, with Medicare Benefits Schedule (MBS) funded testing declining from about 10,000 per

year in 2011/12 to about 4000 in 2016/17, and that the advent of privately-funded NIPT is the most likely explanation for this.

- **Education for health professionals, including genetic counselling:** participants noted the importance of education for health professionals about NIPT itself (what it measures, how accurate it is), as well as genetic counselling for women before and after testing, which should already occur with current screening tests.
- **Access, equity and patient choice:** participants noted that NIPT is currently restricted to people who can afford to pay for it.
- **Future NIPT expansion:** participants agreed that the current proposal for NIPT was appropriately limited to the three trisomies 21, 18 and 13, but that future expansions were likely as the necessary evidence becomes available.
- **MBS item descriptor:** participants discussed potential issues for the proposed MBS item descriptor around sex chromosome aneuploidies, multiple pregnancies, number of tests per pregnancy, fetal fractions, and future technologies.

(Final Stakeholder Meeting Minutes, pp 1-7).

5. Prerequisites to implementation of any funding advice

This was unchanged. Refer to Application 1492 PSD 2018, p3.

6. Proposal for public funding

The proposed MBS item descriptor for NIPT of any pregnant woman is presented in Table 2, as modified by ESC. This item descriptor does not include any indication of the order that tests should be performed in pregnancy.

Table 2: Proposed MBS item descriptor for NIPT for trisomies 21, 18 and 13, as modified by ESC in Application 1492

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

Source: Table 7 p14 of Application 1492 Public Summary Document

7. Summary of Public Consultation Feedback/Consumer Issues

This was unchanged. Refer to Application 1492 PSD 2018, p4.

8. Proposed intervention's place in clinical management

The clinical management algorithms for NIPT in any pregnant woman (primary testing) remains relevant for this application. Refer to Application 1492 PSD 2018, Figure 1 (NIPT primary screening in women in first trimester, p5) and Figure 2 (NIPT primary screening in women in second trimester, p7). The possible scenarios are as an add-on test (where positive result on either the existing screening tests or NIPT would lead to referral for IPT), or as replacement for all existing testing (which appears unacceptable), or as replacement of just the biochemistry component of existing testing (which appears acceptable to some but not all stakeholders). Victorian data indicates that, in usual clinical practice, NIPT is being used to replace biochemistry tests (>90% of NIPT were done without CFTS or second trimester maternal serum screening [2TMSS] biochemistry tests, Hui et al. 2019), but not to replace ultrasound (rates of 11-14 week ultrasound continued to rise after NIPT became available, Hui et al. Genet Med 2017).

9. Comparator

The comparator for NIPT to diagnose trisomies in any pregnant woman remained unchanged from the previous application. Refer to Application 1492 PSD 2018, p9:

- combined first trimester screening (CFTS) at 11+0 to 13+6 weeks of pregnancy, which includes consideration of maternal age, ultrasound measurement of fetal nuchal translucency (NT); and maternal serum biochemical marker evaluation of ß-hCG and PAPP-A; and
- second trimester maternal serum screening (2TMSS) at 14 to 20 weeks of pregnancy, which includes a serum biochemical quadruple test of AFP, ß-hCG, unconjugated oestriol and inhibin A.

10. Comparative safety

No specific safety outcomes are listed in original application, nor in the 2nd CA. There are no physical safety concerns from NIPT (obtained from a maternal blood test), and there is potential for reduction in adverse effects from IPT (fetal loss, membrane rupture, bleeding) where a NIPT is negative for trisomies 12, 18 or 13. Of note, a large randomised trial (Malan et al. JAMA 2018) found no difference in miscarriage rate between arms randomised to NIPT +/- IPT (triage) vs IPT alone, indicating that it is possible that NIPT will not reduce iatrogenic euploid fetal losses (however, the low miscarriage rates in this trial means there is considerable uncertainty in the estimated difference between them).

There are potential psychological safety concerns from anxiety and depression after a positive test result, and after pregnancy loss (whether this is spontaneous pregnancy loss, procedure-related pregnancy loss, or voluntary termination). There is no direct evidence on adverse consequences on patient outcomes from false positives and false negatives, and whether these differ for NIPT vs its comparator. There is also no evidence on the consequences of incidental findings on sex chromosome aneuploidies and other conditions which are not being targeted.

11. Comparative effectiveness

A systematic literature search was conducted and no studies were identified which reported on the sensitivity and specificity of a combination of NIPT and CFTS/ 2TMSS. However, the search identified 14 relevant publications, including:

- three systematic reviews and health technology assessments (HTAs)
- eight "paired design" studies comparing NIPT with standard screening for trisomies 21, 18 and 13 (including three publications not considered in the first MSAC 1492 CA versus a reference standard). Chorionic villus sampling (CVS) and amniocentesis was included as the reference standard in all studies, six studies also included neonatal evaluation and two studies additionally included assessment of the products of conception. In the absence of studies reporting the sensitivity and specificity of a combination of NIPT and CFTS/2TMSS, these studies were used to estimate these characteristics.
- one randomised trial (Kagan et al. Ultrasound in Obstetrics and Gynecology 2018; 51:437-444) of NIPT in combination with ultrasound (US) versus current practice of CFTS (i.e. including ultrasound) in women with a normal ultrasound. This trial effectively looked into replacing the serum screening component of current practice
- one additional randomised trial was not identified by the search as a comparison of NIPT + IPT vs IPT alone in high risk women (Malan et al. JAMA 2018; 320:557-565).

Diagnostic performance (sensitivity and specificity) of combination tests

The results of the sensitivity and specificity of each of the individual tests (NIPT and CFTS/2TMSS) and the estimates for the combination of tests are presented in Table 3.

Table 3: Updated results of trials comparing NIPT and CFTS or 2TMSS for trisomies 21, 18 and 13 against the reference standard in unselected population of pregnant women

Study ID	N analysed	Result	NIPT [95%CI]	CFTS [95%CI]	CFTS+NIPT#	Difference*
Nicolaides 2012	1,949	Sensitivity	100% [69, 100]	100% [69, 100]	100%	0%
		Specificity	99.9% [99.9, 100]	95.5% [94, 96]	95.4%	-0.1%
Norton 2015	15,841 (T21;T18) 11,185 (T13)	Sensitivity	98.0% [89, 100] *98.2% [95, 100]***	78.0% [64, 88]	99.6% *99.6%*	+21.6%
		Specificity	99.9% [100, 100] *96.7% [96, 97]***	94.1% [94, 95]	94.0% *91.0%*	-0.1% *-3.1%***
Quezada 2015	2856 (CFTS) 2818 (NIPT)**	Sensitivity	91.5% [80, 98] *100% [100, 100]***	100% [100, 100]	100% *100%*	0%
		Specificity	99.9% [99, 100] *98.2% [98, 99]***	95.6% [94, 95]	95.9% *94.2%*	-0.1% *-1.8%***
Costa 2018^	789	Sensitivity	100 [100, 100]	71% [38, 100]	100%	+28%
		Specificity	100 [100, 100]	93% [92, 95]	93%	0%
Study ID	**N analysed**	**Result**	**NIPT [95%CI]**	**2TMSS [95%CI]**	**2TMSS +NIPT**	**Difference**
Song 2013	1741	Sensitivity	100.0% [100, 100]	54.5% [23, 83]	100%	+45.5%
		Specificity	99.9% [99, 100]	86.0% [84, 88]	85.9%	-0.1%
Study ID	**N analysed**	**Result**	**NIPT [95%CI]**	**CFTS or 2TMSS [95%CI]**	**CFTS/2TMSS +NIPT#**	**Difference**
Bianchi 2014	1912 (SS) 1952 (NIPT)	Sensitivity	100.0% [100, 100]	100.0% [100, 100]	100%	0%
		Specificity	99.8% [99, 100]	98.2% [98, 99]	98.0%	-0.2%
Langlois 2017^	1152	Sensitivity	100.0% [100, 100]	83.3% [54, 100]	100%	+16.7%
		Specificity	99.8% [99, 100]	94.5% [93, 96]	94.3%	-0.2%
Pérez-Pedregosa 2015^	581 (SS) 579 (NIPT)	Sensitivity	100.0% [100, 100]	88.2% [73, 100]	100%	+11.8%
		Specificity	100.0% [100, 100]	96.2% [95, 97]	96.2%	0%

* calculated with respect to standard prenatal screening+NIPT vs standard prenatal screening alone

** based on the recalculated data presented in EUnetHTA (2018) accounting for "no-call" results (test failures, low-quality samples, indeterminate results)

the online calculator does not return 95% CI

^ newly identified studies, not included in first CA

CFTS = combined first trimester screening; 2TMSS = second trimester maternal serum testing; SS=standard screening; CI = confidence interval; NIPT = non-invasive prenatal testing; T21=trisomy 21; T18=trisomy18; T13 = trisomy 13

The 2nd CA stated it appears that a combination of CFTS/2TMSS and NIPT is superior to CFTS/2TMSS in terms of sensitivity but inferior to CFTS/2TMSS in terms of specificity. However, it noted the included studies were low-quality and results should be interpreted with caution.

Implications of the combination of CFTS/2TMSS and NIPT to clinical practice

No studies were identified that reported on the implications of a combination of NIPT and standard screening in an unselected population, with respect to the impact on IPT referrals. On the basis that the stakeholders noted (as per the ratified minutes of this meeting) "… that healthcare providers should be … advised to act on the highest-risk results rather than assume a reduced risk", and the fact that the combination of tests reduces specificity, this should result in an increase in IPT referrals. The base case of the economic evaluation, which is

based on sensitivity and specificity, therefore assumes an increase in IPT referral with the combination of NIPT and standard practice compared with standard practice alone.

However, this contradicts the observed trend of declining rates of IPT over time (based on MBS usage data). Possible explanations for this could be: (i) NIPT may be used as a partial replacement of CFTS/2TMSS (Victorian data indicate >90% NIPTs are done without biochemistry (Hui et al 2019)), or (ii) women may be making decisions on the basis of a positive NIPT result without confirming the diagnosis through IPT (Victorian data indicate only 48.5% of pregnancies with high risk NIPT result had IPT (Hui et al 2019)). There is extensive international and Australian literature that investigates the declining trends in the rate of invasive diagnostic procedures since the introduction of self-funded NIPT. The epidemiological estimates range from 39.6% (based on the State of Victoria data) to over 50% (based on the Canadian and Dutch data). Canada and the Netherlands introduced subsidised NIPT in a high-risk population in 2014 and 2017, respectively. The Netherlands recommended NIPT as a first-line screening test for trisomies 21, 18 and 13 instead of the combined test (Prenatal screening, Health Council of the Netherlands, December 2016), however only women with high risk (>1:200) are fully reimbursed, while the remainder are entitled to a subsidy (Appendix VI). Randomised controlled trial data on the other hand, suggest the expected decline could be over 80%. In the Kagan et al trial (2018), use of NIPT instead of biochemistry tests in women with normal ultrasound led to 84% relative reduction in IPT rate (absolute rates 1.7% vs 0.3%, considerable uncertainty in estimates due to small numbers of IPT). In the Malan et al trial (2018), use of NIPT to triage for IPT led to 89% relative reduction in IPT rates (absolute rates 76.5% vs 8.3%).

The 2nd CA noted there is only indirect evidence that, following MBS listing of NIPT, the rates of referral to IPT would decrease even further in comparison to the currently observed decline. The magnitude of any potential further decline (as proposed by stakeholders) would in part, depend on the number of women who would not self-fund NIPT. It is also possible that NIPT is considered by some to be sufficiently convincing as to substitute for IPT (that is, a diagnostic test rather than a screening test). Clinical guidelines[1] and the Stakeholder Meeting[2] strongly recommend diagnostic testing with IPT prior to any management decisions, however Victorian data indicates that >50% of NIPTs are not confirmed by IPT (Hui et al 2019).

Discordant results and their influence on clinical management

Two comparative studies (Costa 2018 and Langlois 2017; reporting the diagnostic accuracy of NIPT compared with CFTS or CFTS+2TMSS, respectively versus the reference standard) provided primary data on concordance or discordance of results of the NIPT and standard practice. These data were included in the calculation of the observed rate of IPT versus a hypothetical rate of IPT referrals based on positive results of the combination of screening procedures plus the cases where NIPT, even after the second attempt, produced a "no-call" (test failures, low-quality samples, or indeterminate results) outcome. However, the 2nd CA noted the data was insufficient to draw any reliable conclusions about the implications for referrals to IPT and interpreting discordant results between screening procedures.

[1] The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) 2018 Guidelines provide a consensus-based recommendation: "Diagnostic testing with amniocentesis or chorionic villus sampling should be recommended prior to definitive management decisions (e.g. termination of pregnancy) in cases of "increased chance" screening results, including cfDNA-based screening (RANZCOG 2018, p12).

[2] The Stakeholder meeting noted that *"…NIPT does not replace invasive testing – amniocentesis or CVS will still be recommended for women"* (Stakeholder Meeting Minutes Nov 2018, p4).

Pre-MSAC response
Roche stated that a screening model in which both CFTS and NIPT are done simultaneously, with an abnormal result in either being deemed a "positive screen", does not represent clinical practice.

The RCPA stated the 2nd CA should have analysed the more realistic clinical practice scenario where the intervention of NIPT alone (in conjunction with ultrasound [US]) is compared to CFTS alone as the comparator (in conjunction with US). In all studies bar one included in the 2nd CA, the sensitivity and specificity of NIPT alone was superior when compared to CFTS alone. The recent retrospective analysis of Victorian data conducted by Hui et al (2019) reiterates this, reporting a superior sensitivity and specificity for the combined trisomies (T21/13/18) of 100% and 99.9% for NIPT, compared to 89.6% and 97.3% for CFTS, respectively.

12. Economic evaluation

The updated economic evaluation is a cost-consequences analysis (CCA) that utilised the Deloitte model presented in the previous CA (Table 4).

Table 4: Summary of the updated economic evaluation

Perspective	Health care system
Intervention (base case)	A combination of current prenatal screening (CFTS in the first trimester) and NIPT for detecting trisomies 21, 18 or 13
Intervention (scenario analyses)	1. A combination of current prenatal screening (CFTS in the first trimester or 2TMSS in the second trimester) and NIPT 2. NIPT alone 3. A combination of NIPT and ultrasound (for NT) in the first trimester
Comparator (base case)	Current prenatal screening (CFTS in the first trimester)
Comparator (scenario analysis)	1. CFTS in the first trimester or 2TMSS in the second trimester 2. CFTS (including ultrasound) 3. Ultrasound (for NT) in the first trimester
Type of economic evaluation	Cost-consequences analysis
Sources of evidence (base case)	Outcome of the systematic literature search in the 'paired' design studies that administered both types of screening (CFTS in the first trimester) and NIPT in the same cohort of unselected patients (relying on the EUnetHTA recalculations of Norton 2015, which had the largest study population of unselected women, as the main source of evidence)
Time horizon	Pregnancy duration
Outcomes	Number of fetal aneuploidy pregnancies correctly identified (true positive and negative cases, number of invasive procedures avoided, number of fetal aneuploidy cases undetected (at birth); number of procedure-related miscarriages avoided
Methods used to generate results	Cohort-expected value analysis
Discount rate	Not applicable
Software package used	Microsoft EXCEL 2013

The total costs and outcomes, and incremental costs and outcomes with respect to the base case scenario where a combination of CTFS+NIPT in an unselected population was assessed against standard screening (CFTS) as a comparator is presented in Table 5.

Table 5: Results of the updated modelled economic evaluation comparing CFTS+NIPT vs CFTS (Norton, 2015)

	CFTS + NIPT	CFTS	Incremental cost/ effectiveness	ICER (per unit of outcome)
Cost (including GP/specialist visits/testing/miscarriages/terminations)	$765	$337	$427	
Total correct diagnoses	0.90	0.94	-0.04	*CFTS dominates*
True positives	0.0037	0.0029	0.0008	$540,528
True negatives	0.90	0.940	-0.04	*CFTS dominates*
Invasive procedures [avoided]	0.08	0.05	-0.03	*CFTS dominates*
Number of procedure-related miscarriages	0.00011	0.00007	0.00004	*CFTS dominates*
[Decrease in the] Number of trisomy cases missed	0.00001	0.00056	-0.00053	$784,689

The 2nd CA stated that, in terms of the total number of fetal aneuploidies correctly identified and number of invasive procedures avoided (and unlike in the original model), results of the updated model were robust to the variations in the cost of NIPT, the failure rate of the repeat NIPT and the sensitivity and specificity of the comparator tests when univariate sensitivity analysis was performed.

To address uncertainty about the place of NIPT in the clinical pathway, two scenario analyses were conducted:

- In Scenario 1, women from an unselected population have a choice of either NIPT or CFTS and if the result of the test for a woman is positive, invasive testing is offered. The implicit assumption is that NIPT would completely replace CFTS (informed by the model in the previous CA, and consistent with the Norton, 2015 study design). The results indicate that the estimated incremental cost of correctly identifying an additional trisomy case (true positive) would be $113,448 and the estimated incremental cost of not missing one additional trisomy case (false negative) is expected to be $375,065.
- In Scenario 2, all women from an unselected population undergo ultrasound (US) for nuchal translucency (NT), which may or may not be followed by NIPT; if results are positive on either of the tests, an invasive procedure is offered. The results indicate US dominates (is less costly and more effective) for both correctly identifying an additional trisomy case (true positive) and not missing one additional trisomy case (false negative).

Pre-MSAC response

Roche observed the 2nd CA's economic evaluation set the time horizon at delivery. Roche stated it is appropriate that MSAC takes a longer-term view as the birth of a child with major disability constitutes a cost to the community. This is one of the considerations of couples deciding whether to have prenatal testing for genetic disorders.

The RCPA stated that in reality, the option deemed most clinically appropriate for expectant mothers is in fact, Scenario 2: a first trimester US followed by, or in conjunction with, NIPT, with NIPT replacing the biochemistry component of existing testing (Hui et al. 2019). Most guidelines, as stated in the 2nd CA, emphasise the importance of US, which can detect congenital abnormalities other than the trisomies. Unfortunately the 2nd CA only modelled the economic analysis of NIPT and US, compared to US alone, rather than NIPT and US compared to CFTS and US. Whilst the College acknowledged that women in rural and remote communities may have limited access to ultrasound, it noted that the majority of

guidelines recommend that NIPT should only be performed after, or in conjunction with, an US.

13. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of universally funding NIPT for trisomies 21, 18 and 13. Financial implications reflected the assumptions underlying the base case and two scenario analyses in the economic evaluation. Base case results relating to the combined NIPT+CFTS screening tests assumed the uptake of first and second trimester screening was 83% [based on estimates in the literature; Table 6]); the results were sensitive to this assumption.

Table 6: Net cost of a combination of NIPT and CFTS to MBS (based on uptake rate of 83%)

Number of services/ cost	**2017-18**	**2018-19**	**2019-20**	**2020-21**	**2021-22**	**2022-23**	**2023-24**
			Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
CFTS services (68%)	182,758	185,754	188,976	192,372	195,942	199,437	202,722
2TMSS services (32%)	86,004	87,414	88,930	90,528	92,208	93,852	95,398
Number of screening services (uptake rate 83%, Hui (2016)	268,762	273,167	277,906	282,900	288,150	293,289	298,120
Cost of CFTS* ($)	17,049,052	17,328,498	17,629,106	17,945,903	18,278,939	18,604,934	18,911,391
Cost of 2TMSS* ($)	4,038,955	4,105,157	4,176,371	4,251,421	4,330,318	4,407,547	4,480,147
*Total cost of CFTS/2TMSS** ($)	21,088,007	21,433,655	21,805,477	22,197,324	22,609,258	23,012,481	23,391,539
Cost of invasive procedures (IPT*) *constant trend* ($)	1,750,766	1,750,766	1,750,766	1,750,766	1,750,766	1,750,766	1,750,766
Total cost of CFTS/2TMSS+IPT* constant trend* ($)	22,838,773	23,184,421	23,556,244	23,948,090	24,360,024	24,763,248	25,142,305
Cost of NIPT* ($)	91,379,080	92,876,848	94,488,040	96,186,000	97,971,000	99,718,260	101,360,800
Cost of US* in CFTS ($)	15,991,339	16,253,448	16,535,407	16,832,550	17,144,925	17,450,696	17,738,140
Cost of invasive procedures (IPT*) *declining trend* ($)	2,059,725	1,853,753	1,647,780	1,441,808	1,132,849	720,904	411,945
Total cost of NIPT*+US*+2TMSS* +IPT* *declining trend* ($)	113,469,099	115,089,206	116,847,598	118,711,779	120,579,092	122,297,406	123,991,032
Incremental cost of NIPT* to US* +2TMSS*+IPT*, i.e. replacing all biochemistry of CFTS ($)	90,630,326	91,904,785	93,291,354	94,763,688	96,219,068	97,534,159	98,848,727

* 85% of the total

CFTS = combined first trimester screening; 2TMSS = second trimester maternal serum testing; NIPT = non-invasive prenatal testing; US=ultrasound

Source: Tables 21 and 22, pp43-45 of 2nd CA

Note the declining trend relates to the reduction in the rate of invasive diagnostic procedures since the introduction of self-funded NIPT; Although there is no direct evidence of NIPT resulting in decreases in the number of invasive procedures, the estimates range from 39.6% (based on the State of Victoria data) to over 50% (based on the Canadian and Dutch data). (p4, 2nd CA)

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Likely level of NIPT uptake	Using data from Western Australia, South Australia and Victoria, 80–85% appears likely, but is uncertain.
Specificity and sensitivity of the test	The combination of combined first trimester screen (CFTS)/ second trimester maternal serum screening (2TMSS) and non-invasive prenatal testing (NIPT) has superior sensitivity but inferior specificity for trisomy risk assessment and diagnosis compared to CFTS/2TMSS alone (for trisomy risk assessment), which are acceptable for prenatal testing.
Interpretation of NIPT	Results of NIPT need to be communicated in such a way that it is not interpreted as a diagnostic test. Similar to CFTS/2TMSS it should be regarded as a screening test thus requiring referral to invasive prenatal testing (IPT) as necessary to inform clinical decision making.
Cost-effectiveness of the test	In Scenario 1 (screening), the ICERs are $113,000 for correctly identifying an additional trisomy case (true positive) and $375,000 for not missing one additional trisomy case (false negative). In Scenario 2 (ultrasound), ultrasound is dominant.
Uncertainty regarding the budget implications	Considerable uncertainty exists around the financial implications.

ESC noted that the combination of combined first trimester screen (CFTS)/ second trimester maternal serum screening (2TMSS) and non-invasive prenatal testing (NIPT) has superior sensitivity but inferior specificity (compared with CFTS/2TMSS alone). ESC considered superior sensitivity to be more important for a screening test, because the purpose of screening is to minimise false negatives rather than false positives. However, ESC also questioned whether NIPT may be incorrectly interpreted by some parents and clinicians as a diagnostic test (and thus directly informing clinical decision making for the specified trisomies without referral for invasive prenatal testing [IPT] of amniocentesis or chorionic villus sampling). This is in contrast to CFTS/2TMSS which is usually correctly regarded as a screening test sufficient only to report age-adjusted risk of trisomies and thus requiring referral to IPT as necessary to inform clinical decision making.

ESC also considered the effects of NIPT on invasive prenatal testing (IPT) referral rates for trisomies in two scenarios:

1. NIPT replacing CFTS/2TMSS
2. NIPT replacing the first trimester biochemical assays, but retaining the first trimester ultrasound in order to assess the risk of medical conditions other than trisomies.

In the two scenarios, it was assumed that a positive NIPT identifying one of the three trisomies tested for would be followed by a confirmatory IPT.

ESC considered Scenario 1 to be unrealistic, as guidelines and expert opinion do not support replacing ultrasound with NIPT as ultrasound may detect important structural abnormalities that are unrelated to trisomy 21, 18 or 13. The 2TMSS also screens for the risk of abdominal wall and neural tube defects in addition to risk of trisomies and so is not entirely substitutable by NIPT. ESC considered Scenario 2 to be more plausible, as some guidelines and expert advice suggest that NIPT could replace biochemical testing for trisomies 21, 18 and 13.

Data from Victoria, overseas, the stakeholders meeting and randomised controlled trials suggest that introducing NIPT would result in a 40% to 89% reduction in IPT referrals,

although ESC noted the populations for each data source were different. Thus, the predicted reduction in IPT rates remains uncertain.

ESC noted the stakeholders' strong preference for universal NIPT testing over contingent screening, but noted the high incremental financial cost of an NIPT testing program ($93.3–98.8 million each year over 5 years for an assumed uptake rate of 83%, full replacement of the biochemistry component of CFTS, and a declining trend in IPT rates). ESC noted Roche's preference for contingency testing to be included in the application.

ESC noted the two financial impacts presented, and the uncertainty associated with the possible increase in referrals due to MBS listing of NIPT and clinical advice acting on the highest risk result from either of the screening tests. ESC also noted that costs associated with obstetrician consultations, terminations, miscarriages, invasive procedure-related complications or any other medical services were not included in the calculations.

ESC noted the consumer feedback regarding the application, in particular, concern from Down Syndrome Australia and a parent about the ethical issues of universal screening (see Section 15, "Other significant considerations", below).

ESC noted that, overall, this 2nd CA addressed most of MSAC's concerns from the first CA, but considerable uncertainty remains regarding the proposed place of NIPT in the clinical algorithm, the likely extent of NIPT uptake, the extent of reduction in IPT rates and the size of the budget implications.

15. Other significant factors

The health utilities for terminating a pregnancy, having (or not having) a child with one of the trisomies 21, 18 or 13, and the duration of psychological outcomes related to test or pregnancy loss are not known, and so it is difficult to weigh up the relative value of these outcomes. There are significant ethical considerations to prenatal genetic testing that should inform any decision for voluntary termination of a fetus with trisomy 21, 18 or 13. There remains a need for adequate pre- and post-test counselling to ensure the decision is informed and that psychological support is available. There is also the potential for increased stigmatisation of people with trisomies 21, 18 or 13 and their families with the use of NIPT. This concern was based on consumer input from Down Syndrome Australia and a parent.

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

The RCPA had no comment.

Roche is disappointed with the conclusion that the lack of cost-effectiveness precludes funding of non-invasive prenatal testing (NIPT) and is concerned about the implications this has for the equity of care for pregnant women across Australia. MSAC has previously accepted the efficacy and comparative superiority of NIPT when compared with the comparator, ultrasound (US) and biochemical (MSS) tests. MSAC's conclusion regarding cost-effectiveness is based on flawed modelling and does not address the original ratified PICO.

1) MSAC refers to the need for conventional tests to be retained on the MBS despite the use of NIPT, without acknowledging that the reasons for doing so are not related to the purpose of NIPT. If NIPT places a woman at low risk of the trisomies specified in the PICO, there is no clinical indication to perform MSS or US for that purpose; however, there may be reasons

to perform these tests for other purposes. MSAC has gone beyond the scope of the PICO by comparing NIPT to detect three trisomies and conventional tests used for any purpose.

2) The ratified PICO specified that contingent screening be considered, stating that "The intermediate risk threshold of ≥1 in 300 is to be used as a base case, with sensitivity analysis performed using different definitions of low, intermediate and high risk. This sensitivity analysis should include defining intermediate risk as between 1:10". This analysis was not actioned.

Roche has repeatedly raised these and other concerns over the four year duration of this application. The outcome is that MSAC has only assessed the most costly 'universal' model. Roche respectfully requests in view of procedural fairness that MSAC is given the opportunity to assess the models of care and purpose of testing as agreed with the applicants in the ratified PICO.

17. Further information on MSAC

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