



## STAKEHOLDER MEETING MINUTES - FINAL

### NON-INVASIVE PRENATAL TESTING (NIPT) FOR COMMON TRISOMIES (21, 18 AND 13)

Tuesday 6 November 2018

#### Attendees

Meeting attendees included members of the Medical Services Advisory Committee (MSAC); clinicians with experience and expertise in obstetrics and gynaecology, pathology, clinical genetics and genetic counselling; representatives of the applicant; representatives from consumer organisations; and representatives from the Department of Health.

#### 1. Meeting open – welcome and introduction

The MSAC Chair opened the meeting at 1:10 pm.

The Chair thanked participants for attending and clarified that the stakeholder meeting was not an MSAC decision-making forum, but would inform MSAC's reconsideration of the issues raised by MSAC at its July 2018 consideration of Application 1492: non-invasive prenatal testing (NIPT) for common trisomies (21, 18 and 13). MSAC's advice would then be considered by the Government.

The key objective of the meeting was 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.

The Chair reminded participants that this was a confidential discussion. The outcomes of the meeting would be provided to all attendees for input before being published on the MSAC website. The Chair indicated that these minutes would not attribute any of the discussion to any identified individual.

#### Conflicts of interest

The Chair noted the conflicts of interest declared.

#### 2. Background – recent MSAC consideration and key discussion points

At its July 2018 meeting, MSAC deferred its advice 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 (contingent model).

MSAC noted that the application was submitted by the Royal College of Pathologists of Australasia (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 [GPs] and obstetricians) would inform the above uncertainties. The Chair clarified that the analytical and clinical validity of NIPT were not under question.

### **3. Summary of discussion**

#### **Defining the target population**

Participants agreed that the target population for funded NIPT should be all pregnant women, regardless of risk. It was noted that many women become pregnant at an older age, and therefore a ‘contingent’ population based on a maternal age criteria 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.

Contingent testing based on an assessment of high risk from combined first trimester screening (CFTS)<sup>1</sup> was also not favoured, mostly because of inequitable access to the ultrasound scanning that such an approach would rely on, either because of remoteness to an ultrasound facility or high out-of-pocket expenses. Another issue discussed was a concern with current levels of quality assurance with nuchal translucency screening, especially in centres undertaking low numbers of scans outside urban areas.

Contingent testing based on biochemical testing alone was contemplated, but rejected on the grounds that biochemistry alone did not provide the sensitivity required for a triage test.

It was noted that contingent testing involving a step before NIPT would generate a longer total turnaround between start of the testing process and decision-making, and would involve additional anxiety for more patients determined to be at sufficiently high risk for NIPT whilst awaiting the NIPT results.

It was noted that several other countries have implemented universal NIPT or are considering it, including the Netherlands and Canada. Participants expressed a clear preference for universal testing rather than testing for a contingent population.

#### **NIPT as an add-on or a replacement**

Participants emphasised that NIPT should not replace the current CFTS (which comprises both ultrasound and biochemical testing), but should be an additional service. The ultrasound (nuchal translucency scan) can detect the same common trisomies as NIPT, although with lower sensitivity and specificity. The ultrasound is also important to detect anatomical abnormalities in the fetus, whether there are multiple fetuses, whether the fetus is alive, whether the placenta is healthy, and is also used to date the gestation. This information is also useful for interpreting the results of NIPT. Biochemical testing includes pregnancy-associated placental protein-A (PAPP-A), free  $\beta$ -human chorionic gonadotropin (free  $\beta$ -hCG) and placental growth factor (PLGF), and is important to detect other chromosomal abnormalities and early onset pre-eclampsia. One practical issue therefore is that NIPT is proposed to be restricted to three trisomies, but CFTS may be positive for a wider range of anomalies and

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<sup>1</sup> CFTS – is carried out between 11 and 13 weeks + 6 days of gestation and combines ultrasound measurements including nuchal translucency, maternal biochemical analytes (includes free hCG, oestradiol, placental growth factor (PLGF), pregnancy-associated plasma protein A [PAPP-A]) and maternal age to produce a risk score. If the score exceeds a cut-off value the pregnancy is considered high-risk and diagnostic testing should be considered.

hence a negative NIPT result would not provide the necessary assurance to women that invasive testing could be foregone.

Participants agreed that removing the standard CFTS services and replacing them with NIPT alone would have an adverse impact on a range of pregnancy outcomes. In addition, this would likely create inequities in other areas, in that women who could afford to have ultrasound and biochemical testing would pay for these, while others would receive only the funded NIPT. Participants agreed that ultrasound, biochemical testing and NIPT should be considered as a package of services, all of which combine to provide complementary information on a range of measures.

The addition of NIPT to CFTS would add value by substantially increasing sensitivity and specificity to detect common trisomies. As a DNA-based test, NIPT is more accurate than biochemical tests. It was suggested that the cost-effectiveness of the package of CFTS services may need to be re-examined if NIPT is added for all pregnant women. Participants discussed whether any of the biochemical tests could be removed, but considered that the cost of these tests is relatively small, so removing one would be unlikely to make a significant financial impact and would certainly not offset the additional cost of NIPT. It was noted that the original role of the ultrasound was to detect chromosomal abnormalities, but that this may need to be redefined in the context of NIPT as a test for anatomical abnormalities and fetal viability, and to help interpret the NIPT results.

Participants noted that NIPT is not as useful in certain population groups, such as women with obesity who are at greater risk of the NIPT being unable to provide an accurate risk assessment.

### **Timing of NIPT and results**

Participants discussed the timing of NIPT, which should be conducted from 10 weeks gestation at the earliest. Clinicians indicated that patients are aware that NIPT is available from 10 weeks and often present at precisely this time so they can be tested as early as possible. However, it was noted that there may be benefits to delaying NIPT until after 10 weeks to reduce the chance of the test being unable to provide an accurate risk assessment and minimise the time until invasive tests can be done (if required) and definitive results obtained.

It would be easiest for women if NIPT was done at the same visit as CFTS at 12 weeks gestation. As already noted, participants noted that it would be preferable to do the ultrasound first (i.e., also at 12 weeks gestation) to determine fetal viability and whether it is a multiple pregnancy, before performing NIPT. However, due to the already noted inequitable access to ultrasound scanning, the proposed MBS item for NIPT should not be made contingent on prior or concomitant ultrasound scanning.

Regarding the turnaround time for laboratory results from NIPT, participants noted that there are 6 laboratories that can provide NIPT results, and results can be dispatched in around 5 business days. This turnaround for NIPT at 12 weeks gestation allows sufficient time for counselling and decision making before gestation becomes too advanced for a safe termination (if required), and thus reduces patient anxiety.

### **Potential changes in clinical practice**

Participants noted the dramatic reduction in invasive prenatal testing (amniocentesis and chorionic villus sampling [CVS]) 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 CFTS and then NIPT is the most likely explanation for this. Amniocentesis and CVS were used for primary diagnosis before the introduction of CFTS. Implementing universal funded NIPT for all pregnant women would likely further decrease the rates of amniocentesis and CVS. Participants agreed that it was reasonable to estimate that the rate of invasive tests may further decrease by 50% over 5 years after implementing universal NIPT. A similar reduction had been seen in Victoria since NIPT became widely available, and around 1 in 3 women elect to have NIPT and pay for it out of pocket. The meeting noted that the 80% decrease estimated in the model considered by MSAC in July 2018 may be reasonable in a comparison between NIPT and no NIPT rather than the 50% further decrease in a comparison between universal NIPT and current partial uptake of NIPT.

It was noted that NIPT does not replace invasive testing – amniocentesis or CVS will still be recommended for women who screen positive for trisomies or structural abnormalities in the fetus, women who have had fetal abnormalities in the past, and women who want testing for less-common chromosomal abnormalities. Although the number of invasive tests being done due to structural abnormalities will remain constant, introducing NIPT will result in fewer invasive tests being ordered overall based on the mother’s age or results of CFTS, which are less sensitive and less specific than NIPT. This indicates that invasive testing will be more targeted to women who are at higher risk. Although invasive tests may increase for these particular circumstances, these numbers will be small.

Participants noted the lack of data on the true rate of trisomies in women who are not identified as high risk through CFTS, and also the rate of non-trisomy abnormalities that are identified using CFTS. This lack of baseline data may make the impact of NIPT difficult to measure accurately.

### **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. A genetic counsellor commented that whether a woman is offered NIPT often depends on her choice of pregnancy care provider and the provider’s knowledge of NIPT, and that many women miss out on NIPT because their provider did not recommend it.

Education is important for both obstetric specialists and GPs, since GPs will likely be requesting the majority of NIPT tests in the future. A clinician commented that GPs may tell their patients that NIPT is 99% accurate because this is how the test is advertised; however, this implies that NIPT is a diagnostic test rather than a screening test, and prevents women from providing fully informed consent. However, participants emphasised the importance and implications of a high risk NIPT result. This result would mean a woman is offered more invasive diagnostic testing and, if the chromosomal condition is diagnosed prenatally, there is the possibility that the patient may choose termination of pregnancy.

Consumer organisations noted the importance of educating healthcare providers about how to give this information to their patients before the test, and how to provide balanced information with the results. All participants agreed on the importance of pre- and post-test genetic counselling, and noted that this also applies to a range of other genetic services.

When NIPT is offered, it was noted that, in some cases, NIPT is being presented as ‘just another pregnancy blood test’, which can lead to confusion and anxiety when women are faced with making important decisions that they may not have been aware of before the test.

The same considerations have been recognised to apply to CFTS. It was considered important that the healthcare professional requesting NIPT makes it clear to the patient that having the test is a choice, and that some test results may require difficult decisions to be made. It was also noted that the rate of false positives will increase with universal access to NIPT, and that this also needs to be explained to consumers. It was suggested that the MBS reimbursement could be restricted to those who provide evidence of informed consent.

Regarding post-test support, one organisation noted that healthcare providers may advise a woman whose fetus has Down syndrome to terminate the pregnancy to 'save the child from a lifetime of suffering'. However, studies show that people with Down syndrome have high quality of life, and women may be making irreversible decisions based on incomplete information. It was noted that many women do not feel supported by their providers at the time of confirmed diagnosis of a trisomy in a fetus.

Participants agreed that post-test genetic counselling requires a unique and specialised skillset to help women with high-risk pregnancies make decisions about their next steps, and that there should be clear referral pathways to clinical genetic services. Participants strongly supported the use of telehealth to provide this information and support.

Participants also noted that provision of genetic counselling by non-medical personnel is not publicly funded, and some NIPT providers provide this genetic counselling as part of their service. It was suggested that provision of post-test genetic counselling for women with high-risk NIPT results should be included in the MBS item descriptor; however, this would inappropriately tie a clinical service to the delivery of a pathology test. It was also suggested that genetic counselling is part of good clinical practice and that this could be managed through other channels, such as through the colleges, or through education and professional development programs. It was also noted that this applies to a wide range of MBS items, not just NIPT, and the possibility of developing specific MBS items for pre- and post-test genetic counselling was suggested. This may require greater capacity of genetic counsellors, but would also help account for the time required to adequately discuss results of genetic tests that are becoming increasingly complex.

Participants discussed the potential scenario of discordant results; for example, where NIPT is negative but ultrasound indicates high risk. It was suggested that healthcare providers should be educated on how to manage this situation and advised to act on the highest-risk results rather than assume a reduced risk. Healthcare providers also require education on other anomalous results, such as copy number variants.

### **Access, equity and patient choice**

Participants noted that NIPT is currently restricted to people who can afford to pay for it. Even if a healthcare professional recommends NIPT to an individual patient, they may not have the test due to financial barriers. However, there is very high demand for NIPT – clinicians noted that women often ask if they can pay for NIPT on a payment plan in an effort to make it more affordable. Participants also noted that many women cannot afford to attend for a nuchal translucency scan unless it is bulk billed, and NIPT would be the same. Although the fee for NIPT has not yet been decided, participants were concerned that if it is set too low, NIPT would also not be able to be bulk billed, and this would affect access in the same way.

Clinicians noted the high value that patients place on NIPT for its sensitivity and specificity, which provide accurate information on which to base their decisions. The value of reassurance if the test result is normal is also substantial.

Participants noted that although people in rural and remote areas may not have ready access to nuchal translucency scans, the pathology component of CFTS, like NIPT, is readily accessible. NIPT would improve access to a more extensive prenatal screen in rural and remote areas as it does not require access to a specialist for ultrasound and would therefore be more easily available. Universal access to NIPT would mean that women who can access both CFTS and NIPT would maintain an advantage, but that women who can only access NIPT would receive at least some form of first trimester screening. Participants agreed that, in women with no access to ultrasound, NIPT alone would be preferable to biochemical testing alone, due to the substantially higher sensitivity and specificity of NIPT.

NIPT may also improve quality control and standardisation in rural and remote areas, since ultrasounds are not performed as regularly, and NIPT results are generated by only 6 accredited laboratories in Australia. The use of telehealth for pre- and post-test counselling for NIPT could also ensure equity in these areas.

Participants noted that uptake of CFTS is not universal – around 30% of women do not present for CFTS or second trimester screening. This may be due to a range of issues, including long travel distances or ethnic community considerations. Although NIPT is a simpler test that may increase access, participants agreed that uptake would not reach 100% as there will always be women who choose not to be tested.

Participants discussed the potential for gender selection if results for sex chromosomes are reported with NIPT results. Participants agreed that sex chromosomes should not be specified unless medically requested; for example, the report could state ‘there are no abnormalities in chromosomes 21, 18, 13 and sex chromosomes’. It was also noted that, in an estimated 1 in 2000 tests, the NIPT result for the fetus’s sex is different to the results of later gender tests. This may be due to biological, genetic or technical reasons and is difficult to determine.

### **Future NIPT expansion**

Participants agreed that the current proposal for NIPT was appropriately limited to the three common trisomies, but that future expansions were likely as the necessary evidence becomes available. However, the issues discussed above would likely lay a robust platform for consideration of these future developments.

### **MBS item descriptor**

Participants discussed the potential issues for the proposed MBS item descriptor, and agreed the following:

- Sex chromosome aneuploidies – the item descriptor would not need to specify whether sex chromosome aneuploidies are included. As discussed above, results for sex chromosomes should not be reported unless medically indicated.
- Multiple pregnancies – the item descriptor would not need to differentiate singleton and twin pregnancies as most providers have published data regarding performance in both singleton and twin pregnancies. However, there is limited published data regarding the availability or performance of NIPT in triplet or higher order pregnancies.
- One test per pregnancy – participants agreed that the item descriptor should specify one test per pregnancy, noting that if the test fails patients should proceed to invasive testing rather than repeating NIPT.

- Fetal fractions – participants noted that some NIPT samples do not produce a risk assessment and this can be because of low fetal fractions. Participants noted that fetal fractions were part of the laboratory’s quality assurance processes but were not necessarily included in the report, and therefore should not be included in the item descriptor.
- Participants agreed that reporting fetal fractions had uncertain clinical utility– for instance fetal fraction can change with gestational age and maternal weight and with certain fetal chromosomal abnormalities. Also equivalence between assays has not been established, making interpretation and comparison difficult. Participants concluded that it could be left to the discretion of the laboratory as to whether to report fetal fraction, and that this issue could be referred to the college as a matter of professional practice.
- Future technologies – participants agreed that future technologies and tests may require changes to the item descriptor for universal NIPT to accommodate changes, but that needing to change the descriptor in the future would be preferable to a more open descriptor at this point.

#### **4. Meeting close**

The Chair invited each attendee to make any further comment. Participants were then thanked for their valuable insights and it was hoped that they found the meeting informative.

The meeting closed at 4:30 pm.