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RCPA
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Position Statement

Subject: **Non-Invasive Prenatal Testing**
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Review By: Genetics Advisory Committee
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Background

Non-invasive prenatal testing (NIPT) is a highly sensitive and specific screening investigation to identify fetuses with chromosomal aneuploidy of chromosomes 13, 18, and 21, as well as other additional genetic changes. Currently, the most commonly available additional information from various providers includes:

- The detection of sex chromosome aneuploidies,
- The detection of other autosomal chromosome aneuploidies,
- The detection of select microdeletions.

Whilst test performance characteristics (sensitivity and specificity) of NIPT can be very high, and are substantially better than conventional first trimester screening, the test should not be regarded as a diagnostic test. When NIPT is offered in a low-risk population, the lower pre-test probability further reduces positive predictive value, and it is more appropriately considered to be a screening test. Results of NIPT should always be interpreted in the light of other clinical and laboratory data about the pregnancy. Abnormal NIPT results should be confirmed by invasive testing.

There is ongoing interest in NIPT from specialist clinicians, general practitioners, midwives and the general public. The College has welcomed this increasing awareness of the potential for a sophisticated genetic test to be used widely in the management of pregnancies. However, the nature of NIPT and the significant clinical decision-making which can flow from the test result require careful consideration of a number of issues; pre-analytical (including requesting), analytical, and post-analytical (including reporting) contexts.

NIPT is a developing and complex investigation. Its routine use may lead to health professionals finding it less important to inform women about the choices they may face, presenting some risks to patient autonomy and informed choice.

Pre-analytical recommendations:

1) **Appropriate requesting:** Pathology tests, including NIPT, are generally requested by a medical practitioner who is accountable for the selection of the test, communication and interpretation of the result to the patient, and for medical decisions arising from the test. In relation to genetic tests specifically, the NPAAC standard for molecular genetic laboratories [1] notes that "S1.1 The Laboratory must provide medical nucleic acid testing only in the context of a clinical service provided by a medical practitioner". Requests for NIPT must therefore be made by a medical practitioner.

   The RCPA recognises that a woman's antenatal care may be managed in a team environment where midwives or genetic counsellors work under the direct supervision of a medical practitioner who is accountable for the care of the patient. In this context, it is reasonable for a registered midwife or genetic counsellor to make a request for NIPT *on behalf of the clinician* who is accountable for the care of the patient. This is in

keeping with the standard prescribed by NPAAC as the supervising clinician is still responsible for the patient's test results and management.

2) **Appropriate test choice:** Testing is voluntary and should respect patient autonomy. Alternative testing options (such as combined first trimester screening) should be discussed with the patient, allowing informed choice based on individual circumstances. This may include a discussion of test performance characteristics such as sensitivity, specificity, and positive predictive value (PPV).

3) **Appropriate pre-test information provision:** all women should be provided pre-test information by the requesting practitioner. Pre-test information may include:

- **a.** What is being screened for, and the associated clinical features of each condition included in the test.
- **b.** The fact that NIPT is a screening test for targeted abnormalities; false negatives and false positives, while rare, may occur.
- **c.** The management plan depending on the result returned
- **d.** Limitations of testing

Analytical recommendations

Be aware of the complexities associated with test targets other than trisomy 13, 18 and 21 when requesting these (e.g. sex chromosome aneuploidy, microdeletions, and testing for aneuploidy of additional chromosomes). The complexities of testing vary for each of these, as does the clinical phenotype associated with the imbalance (which can be minimal such as for 47,XYY, or highly variable such as 22q11.2 microdeletions). Current Australian and international clinical guidelines do not recommend routine testing for microdeletions or additional chromosomes.

Post-analytical recommendations

1) All patients in whom NIPT results indicate that a chromosome imbalance has been detected should have confirmatory diagnostic testing, either by chorionic villus sampling or amniocentesis with karyotype/microarray of the sampled material. Invasive testing is associated with a small risk of procedure-related miscarriage (1/500-1/1000). CVS testing is performed on a similar biological sample to NIPT and may be subject to similar biological biases (e.g. possible confined placental mosaicism).

2) Patients returning low risk and test failure results may still require further testing based on clinical circumstances. This may be limited to a standard morphology scan at 18-20 weeks. However, if there are other indications of increased risk for a chromosomal or other genetic disorder, then consideration should be given to diagnostic testing.

Further reading and references:

NPAAC standards: Requirements for medical testing of human nucleic acids:
http://www.health.gov.au/internet/main/publishing.nsf/Content/E688964F88F4FD20CA257BF000 1B739D/$File/V0.25%20NAD%20Human%20Genetics.pdf

Joint ESHG/ASHG position statement with recommendations regarding responsible innovation in prenatal screening with NIPT (2015):
http://www.nature.com/ejhg/journal/vaop/ncurrent/full/ejhg201557a.html

ACMG position statement on NIPT (2016):
https://www.acmg.net/docs/NIPS_AOP.pdf

RANZCOG statement: Prenatal screening and diagnostic testing for fetal chromosomal and genetic conditions (C-Obs 59), 2018:
https://www.ranzcog.edu.au/news/Revised-statement-Prenatal-screening-and-diagnosti