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Sullivan Nicolaides PATHOLOGY
Quality is in our DNA

# Fetal fraction – the essential factor in non-invasive prenatal testing

## Dr James Harraway - Pathologist-in-charge, Genetics

Non-Invasive Prenatal Testing (NIPT), the cell-free DNA-based blood test that screens for fetal chromosomal abnormalities, is fast becoming a routine part of obstetric care.

Sullivan Nicolaides Pathology is NATA-accredited to perform the Harmony® test that screens for trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome), as well as abnormalities in sex chromosomes.

Harmony® is one of the most tried and trusted forms of NIPT worldwide and has been used in well over one million pregnancies. A key reason for this is that it is one of the few NIPTs that precisely measures the amount of fetal DNA in the sample – the fetal fraction – and reports this to the clinician. This is essential in achieving an accurate result. If there is insufficient fetal DNA, the result may merely reflect the genetic status of the mother. We report a result only if there is sufficient fetal DNA to be confident of accuracy.

For women who have a high-risk NIPT result we provide follow-up cytogenetic testing on CVS or amniocentesis (karyotype and rapid Fluorescence In Situ Hybridization test) at no charge to the patient.

### NIPT at a glance

- During pregnancy, maternal plasma contains fragments of DNA from the mother and from the placenta (fetal DNA).
- The proportion of DNA fragments from particular chromosomes is usually very stable throughout pregnancy.
- If there is an excess of fetal fragments from one chromosome, the proportion of fragments from that chromosome will be changed.
- If there is sufficient fetal DNA in a test sample, the Harmony® test can either confirm that the proportion of fragments is as expected (low risk result) or detect a change in proportion (indicating that the fetal DNA is high risk for an abnormality).
- In rare instances, the Harmony® test cannot tell whether the fetal DNA is low risk or not, and a result cannot be reported.

### Inconclusive tests

Rarely, a test for trisomy 21,18 and 13 cannot be reported. This occurs in 3% of women tested by Sonic Genetics and is usually because there is insufficient fetal DNA compared with maternal DNA in the mother's plasma. This low fetal fraction can be due to a relative excess of maternal DNA and this can vary over time. It is more common in women with increased body weight, and more likely in the presence of infection and inflammation, or after exercise.

It also occurs if the mother or fetus has some subtle benign variations in chromosome structure (copy number variants) that make estimating the proportion of fragments from a chromosome unreliable. In some instances, the DNA in the sample has degraded during collection and shipping to the laboratory, and the quality is insufficient for a reliable result. These factors interfere with quality control of the test.

Two thirds of women will get a result on re-testing. However, if the second test is inconclusive, it should not be repeated. This occurs in 1% of pregnant women screened. It is also not worth using another form of non-invasive prenatal test. Other tests do not estimate the fetal fraction accurately and may provide false reassurance.

A decision about other test modalities (combined first trimester screen, second trimester serum screen, detailed ultrasonography or invasive genetic testing such as CVS/amniocentesis) should be based on assessment of all identified risk factors and may require specialist consultation.

More rarely (in 0.5 –1% of women) the test reports a result for trisomy 21, 18 and 13 but not for fetal gender and sex chromosome abnormalities. It is unlikely that a repeat test will provide a result. A decision about using fetal ultrasound or invasive genetic testing to document fetal gender should be based on assessment of need and any identified risk factors.

**Please note:** when results are inconclusive, the test is repeated at no charge.

The Sullivan Nicolaides Pathology NIPT laboratory is the largest in Australia and performs all NIPT testing for Sonic's Australian pathology practices. For more information go to sonicgenetics.com.au/nipt/doctors and click on the menu item 'Inconclusive tests'. Patient information is available at 'When there is no result' on the NIPT patient page.

# Female study links low vitamin D and multiple sclerosis risk

## Dr Daman Langguth - Pathologist-in-Charge, Immunology

For some time, it has been recognised that countries closer to the poles have a much greater incidence of multiple sclerosis (MS). It has been thought that vitamin D insufficiency (30-50 nmol/L) or deficiency (<30 nmol/L) was a risk factor, though prospective evidence was lacking.

A Finnish maternity cohort was enrolled in a case-control study showing that vitamin D deficiency and insufficiency increased the risk of MS by 43% and 23% respectively at 9 years. While absolute numbers were low, the morbidity and cost of MS are enormous and this represents an avenue to prevent this disease. The role of vitamin D in the treatment of MS is still under investigation.

**Reference**

Nielsen NM, Munger KL, Koch-Henriksen N, Hougaard DM, Magyari M, Jørgensen KT, et al. Neonatal vitamin D status and risk of multiple sclerosis: A population-based case-control study. Neurology. 2017 January 3, 2017;88(1):44-51.

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# *Clostridium difficile* – new weekly updates now available

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***Clostridium difficile***, no longer just a hospital infection.

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Once regarded as exclusively a hospital infection, *C. difficile* now circulates in the wider community, especially in aged care homes. In the first of what will be a series of weekly reports on infectious diseases, our Microbiology department is monitoring and recording *C. difficile* infections circulating in our area. Visit our website for *C. difficile* reports by age group and origin of sample, along with a comprehensive overview on what it is; who to test; and when to test.

Visit our website for weekly updates on infectious diseases.

# Update – cervical screening program changes

## Why it's important to stop collecting slides and collect only ThinPrep® samples for Pap smears

The Cervical Screening Program transition period, which runs up until December 1, is giving all those collecting cervical samples for Pap smears valuable time to develop techniques to ensure they are collecting satisfactory ThinPrep® samples.

During this transition period, when all samples are still being screened for cytological changes, we have the opportunity to assess the quality of every sample. Recent experience has brought to light that experienced practitioners using slides have unexpectedly had issues with inadequate sampling when changing to ThinPrep® collections. However, with feedback , they are able to quickly overcome this.

Changing to ThinPrep® collections now is a very important step in the transition to CST, as the technique used to apply the sample onto a slide is very different to that used to wash the sample into the ThinPrep® vial. After December 1, when the CST program comes into effect, we expect that about 70% of cervical samples will have only an HPV test performed. Although there is a quality control step that checks human DNA for adequacy of collection, the HPV test does not assess cellularity. Hence, the transition period is important in allowing for evaluation and feedback on collection technique.

### Faster turnaround times

Once the sample is in the laboratory, the ThinPrep® process allows for faster turnaround time.

### New packaging for cervical cytology collection devices

These are being distributed and the old individual devices are no longer available.

### Reminder

After December 1 and the implementation of the CST program, there is no provision in the testing algorithms for conventional smears and there will not be a Medicare rebate.

# Profile – Dr Sarah Sim MBBS FRCPA

Dr Sarah Sim started her pathology training with Sullivan Nicolaides Pathology in 2010 before going on to rotations that included the Royal Brisbane and Womens Hospital, Princess Alexandra Hospital, Mater Hospital, and the Prince Charles Hospital where she developed an interest in lung pathology.

A University of Queensland graduate, while training as a registrar she held a six-month research posting in breast pathology at the UQ Centre for Clinical Research under Professor Sunil Lakhani, contributing to publications during that time.

Now we are delighted to have her back with us in Histopathology at Bowen Hills, Brisbane, where with experience across a broad range of general surgical pathology she is dividing her time between thoracic pathology, haematopathology and skin pathology.

Dr Sim says she feels fortunate to be with Sullivan Nicolaides Pathology 'because the practice is led by doctors and patient care always comes first'. She believes close communications with colleagues across all medical specialities are essential in delivering good patient care and she attends regular interdisciplinary clinical meetings to review and discuss cases. She encourages referring doctors to contact her if they have anything they need to discuss.

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