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PATHOLOGY MATTERS

Bringing you the latest news in clinical testing

First Trimester Combined Screening for Down Syndrome

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Approximately one in every 800 births results in the delivery of a baby with an abnormal number of chromosomes (non-gonosomal aneuploidy). The most frequent of these aneuploidies is trisomy 21 or Down syndrome, and its prevalence in Europe is 22 per 10,000 births[1]. The risk of having a child with Down syndrome was found to correlate with maternal age, which has increased over the last 20 years, and with it an increase in the number of trisomy-affected pregnancies in Europe[1]. Children born with Down syndrome have multiple medical conditions including malformations and cognitive impairment ranges from mild to severe.

Prenatal diagnosis of Down syndrome commonly involves invasive methods, namely chorionic villus sampling (CVS) and amniocentesis, both associated with a risk of miscarriage[2]. Over the last decade, “risk screening” using multiple markers has improved the risk detection for chromosomal abnormalities and therefore has been widely acceptance in routine antenatal care.

Traditional prenatal screening for Down syndrome combines clinical information with ultrasound and biochemical markers that are altered in affected pregnancies. Nuchal translucency (NT) is an established first trimester ultrasound marker: it measures the neck edema that is more pronounced in foetuses with Down syndrome[2]. In addition, altered maternal levels of placental biomarkers have been observed in affected pregnancies such as pregnancy-associated plasma protein A (PAPP-A), human chorionic gonadotropin (hCG) and its free β-subunit (free β-hCG), alpha-fetoprotein (AFP), unconjugated estriol (uE-3) and Inhibin A.

There are different screening approaches based on a combination of clinical history, ultrasound measurements and serum biomarkers analyses. First trimester combined screening is an effective screening option. It is more sensitive than screening in the second trimester (85 – 95% versus 60 – 70%, at 95% specificity)[2] and allows for early identification of pregnancies that are candidates for further investigation[3], thereby sparing healthy pregnancies from the more invasive measures.

Several international guidelines recommend that all pregnant women should be informed during their first visit of the risks and benefits of prenatal tests, and all pregnant women should be offered screening for Down syndrome by end of their first trimester[4]. Several national guidelines recommend the combined test (nuchal translucency, free β-hCG and PAPP-A) during the first trimester[4], particularly between 11 weeks and 13 weeks 6 days of gestation. In women who present later in pregnancy is not possible due to foetal position or raised body mass index, guidelines recommend second trimester screening[4].

Proven and reliable for risk assessment of Down's Syndrome in the 1st Trimester[5]

Precise over the entire measuring range and consistent from lot to lot[5]

Approved by the Fetal Medicine Foundation (FMF) for 1st trimester screening[6]

Elecsys® PAPP-A and free β-hCG reliably support first trimester combined screening for Down's Syndrome

Non-Invasive Prenatal Testing (NIPT)

By Dr. Keith Byron

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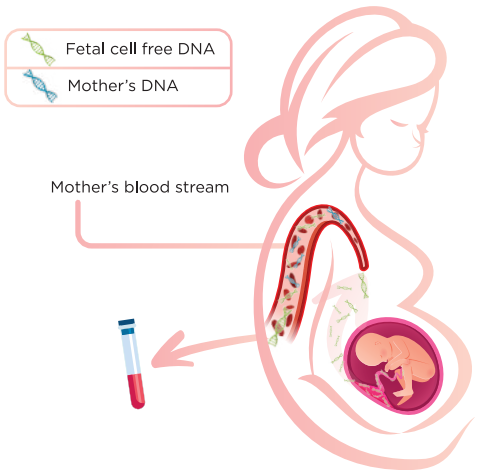
Although the most aneuploidy is Down syndrome trisomy 21, babies can also be born with trisomy 18 (Edward's syndrome) or trisomy 13 (Patau syndrome). These syndromes are associated with high rates of miscarriage or stillbirth with surviving babies have major anatomic abnormalities, intellectual handicaps, and a shortened lifespan. Sex chromosome conditions occur when there is a missing, extra, or incomplete copy of one of the sex chromosomes. There is significant variability in the severity of these conditions with most individuals having mild, if any, physical or behavioural features, but can often have growth and reproductive disorders.

The introduction of non-invasive prenatal testing (NIPT) was made possible by advances in DNA sequencing technology. Today, DNA sequencing determines the order of nucleotides in a DNA fragment and enables millions of DNA fragments to be sequenced simultaneously. The use of massively parallel sequencing to precisely measure the relative abundance of sequences from each chromosome forms the basis of NIPT for aneuploidy screening. Most NIPT methods performed today have a detection rate of over 99% for trisomy 21, 96% for trisomy 18 and 91% for trisomy 13. More importantly, the cumulative false positive rate is less than 0.4%[8].



Short fragments of DNA called cell-free DNA (cfDNA) are released into the plasma from normal cellular turnover which are then rapidly cleared from the circulation.

In a pregnant woman, most of the cfDNA is derived from turnover of maternal cells, however, a small proportion is derived from the placenta, which typically reflects the foetal genotype (Picture on the left). The percentage of plasma cfDNA derived from the placenta is called the 'foetal fraction'.

There is a wide range of foetal fractions found in pregnant women, with a median value at 10 weeks' gestation being approximately 10%[7].

Another important parameter to consider when evaluating NIPT as a screening test is the positive predictive value (PPV), that is, the probability that the foetus is truly affected when the result is positive. The PPV depends partly on the analytical performance of a test (eg: sensitivity and specificity), but also with the prevalence of the condition being screened for in a given population. A low prevalence for a condition will decrease the PPV. NIPT PPV's for a given chromosome and risk group, can range from 50-80%[9]. Although relatively rare, both false positive and false negative results do occur. A potential false negative result, or incomplete result is typically due to the sample being collected too early in the pregnancy or because of maternal obesity, both of which can result in a low foetal fraction.

Traditionally a foetal fraction at or above 4% was required for reliable results, but now with newer methods being available to enrich for the foetal fraction post sample collection, foetal fractions of between 2-3% are now acceptable to generate reliable results. False positive results tend to be due to biological reasons and can be caused by foetal mosaicism, confined placental mosaicism, interference from a vanished twin, maternal chromosome variations or even maternal malignancy.

More recently, NIPT has expanded to screen for a number of select microdeletions (eg: DiGeorge syndrome, 1p36 syndrome, Cri-Du-Chat syndrome, Prader-Willi/Angelman syndrome, and Wolf-Hirschhorn syndrome). Individual microdeletions can present with variable clinical phenotypes and are much rarer than autosomal aneuploidies. As such there is less analytical validation data available regarding NIPT performances for microdeletions. Furthermore, the rarity of these abnormalities will also mean that the PPV will be significantly lower than that for autosomal or sex chromosome aneuploidies, potentially leading to an increased rate of confirmatory invasive testing.

Because of the potential complexities of NIPT as discussed above, it is important that woman considering NIPT be offered both pre-test and post-test genetic counselling.

Tuberculosis in Pregnancy

Article Review from QIAGEN Biotechnology Malaysia

Tuberculosis (TB) is the leading infectious cause of mortality globally[10]. Active TB disease during pregnancy remains associated with a substantially elevated risk for poor maternal and foetal outcomes, including a threefold increase in maternal morbidity (eg, antenatal admission, anemia, and cesarean birth), ninefold increase in miscarriage, twofold increase in preterm birth and low birthweight, and sixfold increase in perinatal death[11,12].

The perinatal period is an important opportunity to screen, diagnose, and treat those at high risk for TB. Adversed maternal and neonatal outcomes are increased with inadequate treatment, advanced disease, and late diagnosis of TB in pregnancy[13]. Professional associations including the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, and the Centers for Disease Control and Prevention (CDC) recommend screening all women who are at high risk for TB at the initiation of antenatal care[14,15].

Pregnant women should be evaluated for TB on initiating antenatal care by assessing symptoms, performing a physical examination, and ascertaining TB risk factors[14]. TB testing is critical even if treatment might be delayed until postpartum to avoid missing a diagnosis in women who do not follow up postpartum[16]. People who have latent TB infection, which is not contagious, but without treatment latent TB infection can progress to active TB disease, most commonly in the first 2 years after infection[17].

TB Blood test (interferon-gamma release assay -IGRA) may be used to test for latent TB in pregnancy[16]. IGRA are the preferred test for people who have received the BCG vaccine for TB and people who may have difficulty returning for a second appointment to be evaluated for a reaction to the skin test[14].

Innoquest Pathology Offers:

Panel Code	Test	Specimen Requirements
FTT	**First Trimester Test (Down Syndrome)** Free β-hCG PAPP A	8ml Plain (Gel-YELLOW) - Maternal blood. 11 weeks - 13 weeks. Need NT & CRL measurement. Please provide name of registered diagnostic medical sonographer.
DWN	**Down Syndrome & NTD (Double Test)** AFP Free β-hCG (Risk factor - Neural tube defect - Down Syndrome)	8ml Plain (Gel-YELLOW). Measure at 14 -19 weeks gestation. ALL relevant details - Maternal weight in kg, Maternal DOD, LMP, gestation determination MUST be on the form. Accurate gestation (preferably by ultrasound) is essential for correct risk assessment.
NC1	**Prenatal NIPT Test** T21, T18, T13 and complete 23 pairs of chromosomes with foetal sex and foetal fraction reporting.	10ml Streck/ PAXgene tube. Immediately invert the tube 5 times each. Please call for collection kit. Store kits and contents at room temperature. Do not freeze or refrigerate.
MR8	**Prenatal NIPT Test + 8 Microdeletions**	
MR2	**Prenatal NIPT Test + 20 Microdeletions**	
QFT	**Mycobacterium tuberculosis** (QuantiFERON TB Gold, an IGRA assay)	Special collection kit. Must be incubated before 16hrs from sample collection.

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