**Revolutionary changes**

“Chromosomal disorders have been, and will always be with us; that is a given. What is changing is our ability to recognize and detect them: detection both in terms of the subtlety of abnormalities, and of the means we can use to find them. Classical cytogenetics has now well and truly given way to ‘molecular karyotyping’, and this has been the extraordinary development of the early 21st century.”

So begins the newly published fifth edition of Chromosome Abnormalities and Genetic Counseling, written by past VCGS Professors Mac Gardner and David Amor (1). The new edition is timely given the major changes in chromosome testing that have occurred in the last decade (figure 1 - view as PDF here). Nowhere have these changes been felt more strongly than in prenatal testing.

**NIPT, CMA & trends in diagnostic testing**

Both non-invasive prenatal testing (NIPT) and chromosome microarray (CMA) have altered the face of prenatal diagnostic testing.

Introduced in 2012, cell-free DNA NIPT has revolutionised antenatal screening for the common chromosome aneuploidies (trisomies 13, 18 and 21).

NIPT, as well as advances in combined first trimester screening (CFTS), have improved our ability to identify pregnancies at risk of these conditions.

This has resulted in a significant reduction in the number of invasive diagnostic procedures being performed. This fall has been continuous since CFTS was first introduced in 2000 and has been accelerated more recently by the incorporation of the measurement of nasal bone into CFTS and the widespread uptake of NIPT (figure 2) (2).

Improved identification of pregnancies at high risk of chromosomal aneuploidy has not surprisingly lead to an increase in detection rate through CVS and amniocentesis diagnostic testing. The most significant recent advance has been the introduction of CMA in 2011 (figure 3) (3).
NIPT @ VCGS

Using a whole genome next-generation sequencing approach, VCGS has further developed NIPT so all 24 chromosomes are analysed. This genome-wide screening approach allows for the detection of trisomies of all chromosomes, as well as larger genetic changes, like deletions and duplications, across the genome. Expanding the scope of NIPT to include all chromosomes enables screening of pregnancies for a significantly broader range of chromosomal conditions.

This has enabled us to screen pregnancies of known translocation carriers, enabling couples access to a non-invasive means of identifying at-risk pregnancies for the first time (5).

Additionally, the whole genome approach has successfully identified many other ‘atypical’ chromosome conditions including isochromosomes, known deletion syndromes and other, more complex genomic imbalances.

CMA @ VCGS

CMA provides a highly sensitive tool for prenatal diagnosis of chromosome conditions and allows for the identification of those caused by genetic changes at the sub-microscopic level. VCGS uses a high resolution single nucleotide polymorphism (SNP) platform.

This adds significant advantage as it also enables the identification of genetic conditions where there is no net loss or gain of genetic material such as Prader-Willi syndrome.

Challenges arising from NIPT & CMA

Whilst these advances have significantly improved screening and diagnosis of chromosomal conditions during pregnancy, they have also created new challenges for health professionals and families.

Although detection and confirmation rates are generally high, it is important that NIPT is considered a screening test.

The most significant drawback of CMA is the potential for uncertain/unknown genetic information.

We all carry genetic changes, but in most cases these do not impact on our health. ‘Variants of uncertain significance’ (VOUS) can be difficult to interpret in the prenatal setting and in some cases, create ongoing uncertainty.

References