VCGS Leaders in Genetic Health

the partumpost

Impact of recent advances in prenatal testing

Volume 2 Issue 1 April 2018

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.

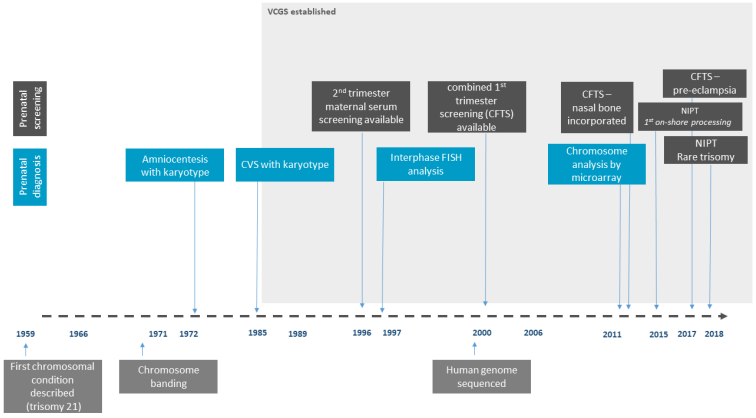

Figure 1. Time line of prenatal screening and diagnostic testing in Victoria, Australia.

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).

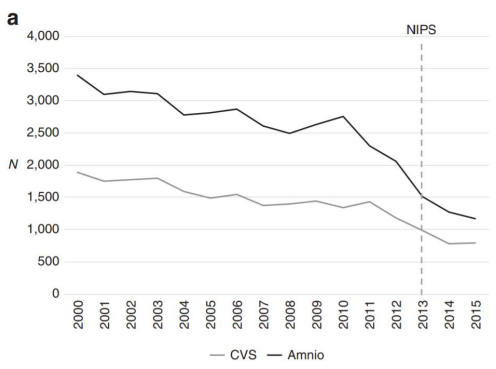

Figure 2. Diagnostic procedures in Victoria, Australia in the past 15 years (Hui et al. 2017)

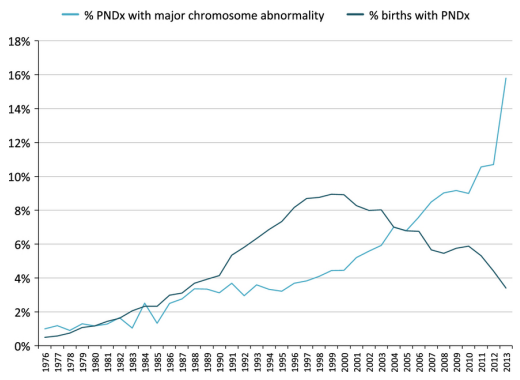

Figure 3. Trends in invasive testing rates and diagnostic yield in Victoria, Australia (Hui et al 2016.)

Victorian Clinical Genetics Services
Murdoch Children's Research Institute
The Royal Children's Hospital
Flemington Road, Parkville VIC 3052
P +61 3 8341 6201 W vcgs.org.au

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.

VCGS uses a strong evidence based approach when reporting genetic changes identified using prenatal CMA by ensuring there is adequate literature to support assessment of pathogenicity.

Genetic changes must be of a size and gene content that warrants further parental investigation. This approach reduces the number of women who experience the anxiety that can be associated with receiving a VOUS result.

Supporting women during screening & testing

Given the challenges arising from these new technologies, it is important that women and their partners are supported in navigating prenatal screening and testing.

While advances in screening have led to a reduction in the proportion of women having prenatal diagnosis, there has been an increase in the complexity of genetic alterations identified requiring expert analysis and interpretation.

VCGS has a fully integrated reproductive genetics team specialising in maternal serum screening, NIPT, diagnostic testing and genetic carrier screening. Performing the full spectrum of screening & diagnostic testing ensures the most appropriate investigations are carried out.

Our clinical team of genetic counsellors and medical geneticists work collaboratively with our laboratory scientists as well as specialist physicians and healthcare providers offering testing. This ensures patients have access to expert information and support.

Research and evaluation of our screening programs enables us to better understand how to tailor our services to the needs of patients, families and healthcare providers.

We are available to provide information and support to patients considering or undergoing any of these tests.

Please email vcgs@vcgs.org.au for any questions, topic suggestions or to subscribe to the partum**post**.

References

1. Gardner, R.M., and Amor, D.J., 2018. Chromosome abnormalities and genetic counseling (5th Edition). OUP USA.
2. Hui, L., Hutchinson, B., Poulton, A. and Halliday, J., 2017. Population-based impact of noninvasive prenatal screening on screening diagnostic testing for fetal aneuploidy. Genetics in Medicine, 19(12), p.1338.
3. Hui, L., Muggli, E.E. and Halliday, J.L., 2016. Population based trends in prenatal screening and diagnosis for aneuploidy: a retrospective analysis of 38 years of statewide data. BJOG: An International Journal of Obstetrics & Gynaecology, 123(1), pp.90-97.
4. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Prenatal screening and diagnosis of chromosomal and genetic conditions in the fetus in pregnancy (C-Obs 59). Sydney: RANZCOG, 2015.
5. Pertile, M.D., Charles, T. and Burgess, T., 2017. Advanced NIPT: detecting unbalanced translocations. partum**post** 1(4).