VCGS Leaders in Genetic Health

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Genome-wide screening using NIPT

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Why screen for segmental imbalances

Segmental imbalances are subchromosomal changes involving deletions or duplications of genetic material. Imbalances visible at the karyotype level of resolution (>10 Mb) include de novo deletions and duplications, unbalanced translocations and other complex changes like ring or marker chromosomes, insertional rearrangements and isochromosomes.

These clinically significant segmental changes can't be detected using standard methods of NIPT and may go unrecognised during pregnancy. Although individually rare, collectively they have a prevalence of about 1 in 2,500 births (1). As *percept* NIPT analyses all 24 chromosomes (2, 3), segmental imbalances ≥ 10Mb in size can be identified using this genome-wide screening approach.

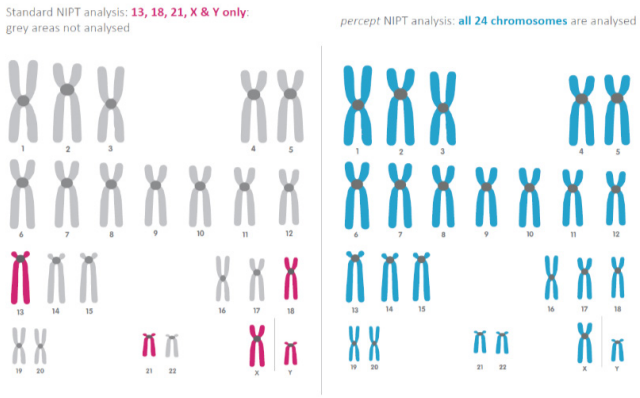

Figure 1. *percept* routinely analyses all 24 chromosomes

A more comprehensive screening test

Recent research suggests women want a more comprehensive prenatal screening test when this is available. In the Netherlands, NIPT has been offered to every pregnant woman since April 2017. As part of the implementation study, women can elect a targeted analysis of only chromosomes 13, 18, and 21, or a genome-wide NIPT where all chromosomes are analysed.

After eight months of study, 80% of women (n=48,234) have elected the genome-wide NIPT option (4). *percept* NIPT offers a similar genome-wide screening approach.

How often are segmental imbalances detected?

Genome-wide analysis of >20,000 *percept* NIPT samples indicates approximately 1 in 612 pregnancies (0.16%) will return an increased risk result involving a segmental imbalance (VCGS data on file). Of increased risk results with outcome data, 53% (19/36 cases) have been confirmed with a pathogenic change in the fetus. This positive predictive value (PPV) is similar to that reported for trisomy 13 following NIPT (5). *percept* test sensitivity (detection rate) for segmental imbalances ≥ 10 Mb is estimated at 78% (95% CI, 49.2 – 95.3) (VCGS data on file).

What segmental imbalances does *percept* NIPT detect?

Pathogenic segmental imbalances can be found in any region of the genome, some of which are associated with known, well-described conditions. Examples of known conditions identified with *percept* NIPT and confirmed after prenatal diagnosis include:

- Wolf-Hirschhorn syndrome (chromosome 4)
- Cri-du-chat syndrome (chromosome 5)
- Miller-Dieker syndrome (chromosome 17)
- Jacobsen syndrome (chromosome 11)
- Emanuel syndrome (chromosome 22)
- Pallister-Killian syndrome (tetrasomy 12p)
- Tetrasomy 9p syndrome
- tetrasomy 18p syndrome

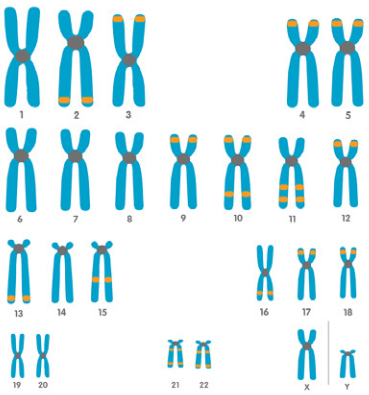

Figure 2. examples of segmental changes found by *percept*

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Other, non-specific pathogenic chromosome deletions and duplications have also been identified, including several de-novo and inherited unbalanced translocations.

Segmental imbalances, confined placental mosaicism, and maternal findings

Not all segmental imbalances identified using genome-wide NIPT are confirmed in the fetus (6). One reason for these discrepancies is that the "fetal" component of the cell-free DNA is derived from the placenta (7). Thus, any segmental imbalance confined to the placenta may cause a false positive result, in the same way that this can occur for the common trisomies analysed with standard NIPT.

Therefore, *invasive prenatal diagnosis is always recommended to confirm increased risk results*. Very rarely, genome-wide screening may identify a maternal mosaic segmental imbalance (that is subclinical). These findings can have serious developmental consequences for the fetus if the rearrangement is passed on in its non-mosaic form (8).

What influences test sensitivity for genome-wide NIPT?

The ability to accurately screen for segmental imbalances is determined by the amount of fetal cell-free DNA in the sample (fetal fraction), the depth of sequencing, the segment size, and the genomic region involved (9). Higher fetal fractions enable improved detection of smaller segmental imbalances, but in general, segmental imbalances will require higher amounts of fetal cell-free DNA to be detected when compared with whole chromosome trisomies.

percept NIPT reports segmental imbalances as additional findings. Therefore, a negative result does not remove the possibility of an unbalanced chromosome condition in the pregnancy. False negative results may occur for smaller imbalances, at lower fetal fractions, or from high levels of normal cells confined to the placenta. For these reasons, genome-wide screening is not a replacement for CVS or amniocentesis, but it can provide additional reassurance compared with standard methods of NIPT.

Reporting of segmental imbalances

When a segmental imbalance is detected, the *percept* NIPT report provides a clear explanation of the findings, the approximate genomic coordinates of the imbalance to facilitate prenatal microarray analysis, and any recommendations for follow-up testing. In some instances, maternal investigations or uniparental disomy (UPD) studies may be recommended.

VCGS can provide follow-up testing for all relevant cytogenomic investigations. Genetic counselling support is available at no charge to patients having *percept* NIPT and credentialed clinical scientists with expertise in genome-wide NIPT and invasive prenatal testing are available to discuss test results with health practitioners as required.

Laboratory accreditation & quality assurance

VCGS holds NATA/RCPA accreditation for genome-wide NIPT and is one of only a small number of services available internationally with extensive experience in this area. This additional screening is performed for every patient at no additional cost.

As Australia's most advanced NIPT, *percept* is a better screening option for couples who seek the reassurance of a more comprehensive prenatal screening test.

See our website for more information about percept:
vcgs.org.au/perceptNIPT

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