Noninvasive prenatal detection of genetic defects

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Curriculum vitae

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Jessica Maria Elisabeth van den Oever werd geboren op 11 mei 1980 te Roosendaal, gemeente Roosendaal en Nispen. In 1997 behaalde zij haar HAVO diploma aan het Gertrudiscollege te Roosendaal, waarna zij in datzelfde jaar startte met de opleiding Biologie en Medisch Laboratorium Onderzoek aan de Hogeschool Brabant, Faculteit Techniek en Natuur te Etten-Leur (tegenwoordig onderdeel van Avans Hogeschool gevestigd te Breda).

Tijdens haar afstudeerstage op de afdeling Klinische Genetica van de Erasmus Universiteit Rotterdam onder supervisie van Dr. Rob Willemsen, deed zij onderzoek naar het fragiele X syndroom. Hiervoor bestudeerde zij het transport van FMRP in een PC12 neuronale cellijn.

Na het behalen van haar diploma, startte zij in 2001 met haar studie Biologie aan de Universiteit Leiden via een HBO-instroom programma. Ter afronding van deze studie werd stage gelopen bij de sectie Moleculaire Biologie van het instituut voor Moleculaire Plantkunde bij de Faculteit Biologie van Universiteit Leiden. Onder begeleiding van Prof. Herman Spaink en Prof. Michael Richardson werd gestart met een pilot studie met vertebraten waarbij er onderzoek gedaan werd naar het expressie patroon van Selenium Binding Protein in zebravissen.

In 2005 begon zij als research analist op het project “Immunomodulatory properties of Mesenchymal Stem Cells” op de afdeling Immunohematologie en bloedtransfusie (IHB) van het Leids Universitair Medisch Centrum (LUMC) onder begeleiding van Prof. Wim Fibbe, Dr. Alma Nauta en Dr. Kirsten Canté-Barrett. Vanaf 2007 was zij tevens werkzaam als research analist op het project “Mechanismen van cytokine-geïnduceerde hematopoietische stam- en progenitorcel mobilisatie” onder begeleiding van Prof. Wim Fibbe en Dr. Melissa van Pel. Daarnaast heeft zij in die periode gewerkt als interim proefdiercoördinator voor de afdeling IHB.

Eind 2008 begon zij als research analist op het project “Gene expression profiling in a chronic restraint stress rat model” bij de afdeling Medische Farmacologie van het Leiden/ Amsterdam Center for Drug Research (LACDR)/ LUMC onder begeleiding van Dr. Nicole Datson en Prof. Ron de Kloet.

In oktober 2010 werd gestart met het promotie onderzoek “Noninvasive prenatal detection of genetic defects” bij de afdeling Klinische Genetica op het Laboratorium voor Diagnostische Genoomanalyse (LDGA) van het LUMC te Leiden. Onder leiding van Dr. Elles Boon en Prof. Bert Bakker werden de experimenten verricht die staan beschreven in dit proefschrift. Van juli t/m september 2015 heeft zij onder supervisie van Prof. Joris Vermeesch gewerkt als interim project manager voor targeted NIPT bij het Centrum Menselijke Erfelijkheid van de Katholieke Universiteit Leuven in België.

Publications and Presentations

Publications

- Brison, N., Van Den Bogaert, K., **van den Oever, J.M.**, Dehaspe, L., Janssens, K., Blaumeiser, B., Peeters, H., Van Esch, H., de Ravel, T., Legius, E., Devriendt, K., Vermeesch, J.R., *Maternal incidental findings during non-invasive prenatal testing for fetal aneuploidies*, submitted.
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- Invited speaker: Prenatal Molecular Diagnostics; Trends, advances & prospects, Lisbon, April 2015.
- *Noninvasive prenatal diagnosis of Huntington disease in the Netherlands*: DHDRN, Amsterdam, mei 2014.
- Invited speaker: Werkgroep prenatale diagnostiek en therapie/ werkgroep foetale

echoscopie: *Gemetyleerd RASSF1A: een universele biomarker ter bevestiging van de aanwezigheid van foetaal DNA in maternaal bloed*; najaarssymposium, Utrecht, oktober 2013.

- *Single Molecule Sequencing of Free DNA from maternal plasma for noninvasive trisomy testing*: Medical Genetics Centre PhD student workshop, Luxemburg, mei 2013
- Invited speaker: *Noninvasive fetal aneuploidy detection using Next Generation Sequencing: towards application in diagnostics*; Integrated Data Analysis meeting organised by the dept. of Epidemiology in collaboration with SASC, LUMC, Leiden, november 2012.
- Invited speaker: *Noninvasive fetal aneuploidy detection using Helicos: Third generation vs Next Generation Sequencing*: NBIC *Next Generation Sequencing meeting,* Leuven, juni 2012.
- *Noninvasive fetal sexing and maternal discrimination tests: a validation study for application and implementation in diagnostics*; NVHG voorjaarssymposium, Veldhoven, maart 2011.

Grants/ Awards:

- VIVA400 Award 2015 nominee in the category “Knappe koppen”.
- Travel grant Stichting Simonsfonds (2014).

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Appendices

Appendix 1: Confined placental mosaicism

Placental villi obtained with CVS can be analyzed by two distinct culturing methods. With a semi-direct method (short-term culture or STC) cells from the invading cytotrophoblast are analyzed. After culture (long-term culture or LTC) cells of the mesenchymal lineage are evaluated. Distinction between these two culturing methods and knowledge of the origin of the cells is very important for interpretation of the outcome of prenatal genetic testing on CVS material, since cells of different embryogenic progenitors are analyzed for chromosomal analysis of the fetus with these two distinct culturing methods (Bianchi *et al.*, 1993). When culturing is successful and sufficient sample is provided, preferably a combination of both STC and LTC should be used to interpret prenatal findings.

In the majority of pregnancies the karyotype of the placental cells is similar to the karyotype of the fetus. However, in ~2% of the pregnancies studied by CVS a cytogenetic abnormality is found, most often a trisomy (Kalousek *et al.*, 1996). The existence of a discrepancy between the karyotype from chorionic tissue and embryonic/fetal tissue is caused by complex developmental events during early embryogenesis. When a trisomy is formed soon after fertilization before the trophoblast and the inner cell mass are differentiated, the discrepancy (or mosaic) can be generalized to both placenta and fetal tissues. When it is formed after the separation of the fetal and placental compartments, the abnormal tissue may be confined to either the placenta (**confined placental mosaicism** or **CPM**) or the fetus, but not necessarily to both tissues (Simoni *et al.*, 1992). Therefore, in case of mosaicism it is very important to distinguish between a true fetal mosaicism (TFM) and CPM and confirmatory karyotyping on amniocytes is required to asses which type of mosaicism is present. Mosaicism can be classified according to the distribution of the abnormal cell line (Table 1) (Grati, 2014).

Type	*Nature*	*Trophoblast (direct)*	*Mesenchyme (culture)*	*Amniocytes*
I	CPM	Abnormal	Normal	Normal
II	CPM	Normal	Abnormal	Normal
III	CPM	Abnormal	Abnormal	Normal
IV	TFM	Abnormal	Normal	Abnormal
V	TFM	Normal	Abnormal	Abnormal
VI	TFM	Abnormal	Abnormal	Abnormal
Evaluated in:		**CVS(STC)/ NIPT**	**CVS (LTC)**	**Amniocentesis**

Table 1: Different types of mosaic outcome: (CPM; confined placental mosaisicm, TFM; true fetal mosaicism) found after chorionic villous and amniocytes karyotyping. Adapted from (GRATI, 2014).

Since cffDNA is derived from trophoblast cells, the presence of a possible CPM can also influence results of noninvasive prenatal testing (NIPT) for common fetal aneuploidies. Due to feto-placental mosaicism potential false positive (CPM type I or III) and false negative (TFM type V) results may occur for mosaics in which the trophoblast is cytogenetically discrepant from the fetus. Even though a discrepancy between karyotypes occurs only in around 2% of the cases, in the majority of cases, the mosaicism is confined to the placenta (i.e. CPM type I, ~35%). CPM type III and TFM type V are found in around 10% and 6% of the cases respectively (Grati, 2014). For NIPT, additional genetic analysis of either amniocytes or a combination of STC and LTC is therefore required to determine fetal karyotype in case of an aberrant result.

Appendix 2: Epigenetic allelic ratio, haplotype ratio analysis and relative mutation dosage.

Analysis of the epigenetic allelic ratio (EAR) is a method to assess copy number of a particular chromosome of interest for fetal aneuploidy detection by determining the ratio of an informative single nucleotide polymorphism (SNP) on fetal alleles. This SNP is present within a fetal specific amplified DNA molecule in a differentially methylated region (DMSR) on the chromosome of interest. Bisulfite converted DNA samples are amplified with methylation specific PCR (MSP). Subsequently, methylation differences are assessed with allele-specific primer extension. This primer extension utilizes internal primers which anneal to a PCR-generated template and terminate immediately 5' adjacent to the informative single base variation (Gonzalgo *et al.*, 1997). Extension of these allele specific primers can distinguish between an allele with a nucleotide that is not affected by the conversion (allele A) and an allele with a polymorphism that is affected by the bisulfite conversion (allele B with an unmethylated cytosine (C) which is converted into a thymidine). The extension reactions are designed to generate products of distinct masses (and thus distinct peaks) when analyzing the alleles with Mass Spectrometry.

In euploid fetuses there are equal amounts of allele A and B. Therefore, the theoretical relative peak frequency of allele A and B is both 50% (or 0.5). The EAR can subsequently be calculated by dividing the relative peak frequency of A by the relative peak frequency of B (1). Hence, for euploid fetuses, the EAR is 1.

In case of a fetus with a trisomy, instead of two alleles, three alleles are present. Moreover, there is an overrepresentation of one of these alleles (e.g. either allele A (AAB) or allele B (ABB)). For AAB, there is twice the amount of A alleles contributing to the total amount of three alleles (e.g. twice as much A compared to B). Therefore, the contribution of A relative to the total amounts of alleles is 2 out of 3 (i.e. 67% or 0.67), while relative the B allele is present in only 1 of the 3 alleles (i.e. a relative peak frequency of 33% or 0.33 for B). Therefore, the EAR for AAB is 2 (i.e. 0.67/0.33). In case a fetal trisomy with only one A allele and two B alleles (i.e. ABB), the relative contribution for A is 0.33 and 0.67 for B, resulting in an EAR for ABB of 0.5 (i.e. 0.33/0.67). An EAR that has deviated from 1 (i.e. euploid fetus) is indicative for a fetal trisomy. Adapted from (Tong *et al.*, 2006).

(1) $$EAR = \frac{Relative\ peak\ frequency\ A}{Relative\ peak\ frequency\ B}$$

Another method for fetal aneuploidy detection is the determination of the **haplotype ratio** (HR). In HR analysis only highly heterozygous tandem SNPs on the chromosomes of interest exhibiting three different alleles (haplotypes) are considered informative (i.e. two different maternal alleles and a third distinctive paternally inherited fetal allele) (**Fig. 1**). In contrast to EAR, for HR it is not required to have SNPs only present in DMR, since this method is not based on differences in methylation.

For HR, first Multiplexed Linear Amplification (MLA) is performed on DNA from maternal buccal swaps. This linear amplification product is used as a template in a "sequence specific" PCR and Cycling Temperature Capillary Electrophoresis (CTCE). When results of the maternal buccal swaps indicate that the maternal tandem SNP status is homozygous, the SNPs are not informative. When the maternal SNPs are heterozygous, maternal plasma can be processed similar to the maternal buccal DNA and analyzed subsequently. Fetal chromosome dosage can

be determined by calculating HR using the area under the curve of the three distinct peaks (p1, p2 and p3) in the electropherogram after CTCE (8). As a control, gDNA from maternal buccal swabs or maternal lymphocytes is analyzed and compared to the mixed profile of both mother and fetus in maternal plasma (**Fig. 1**). The maternal contribution to the fetal haplotype can be (quantitatively) compared to the paternally inherited haplotype (yellow peaks) to determine fetal aneuploidy status. In **Fig. 1**, each peak is schematically represented as a triangle and represents one haplotype; either only from the mother (e.g. no fetal contribution; white), only the fetus (e.g. the paternally inherited haplotype; only yellow) or a shared haplotype between mother and fetus (white and yellow). In a maternal plasma sample from a mother carrying a euploid fetus, the presence of three different alleles are informative (Figure 1 A and B). There is a unique non-shared maternal haplotype (white), a haplotype that is shared between mother and fetus (white and yellow) and a distinct unique paternally inherited haplotype (yellow). In a euploid fetus the paternally inherited peak p3 is equal to the relative difference between p1 and p2, resulting in HR = 1 (2). Both maternal and paternal contribution to the fetal genotype is equal.

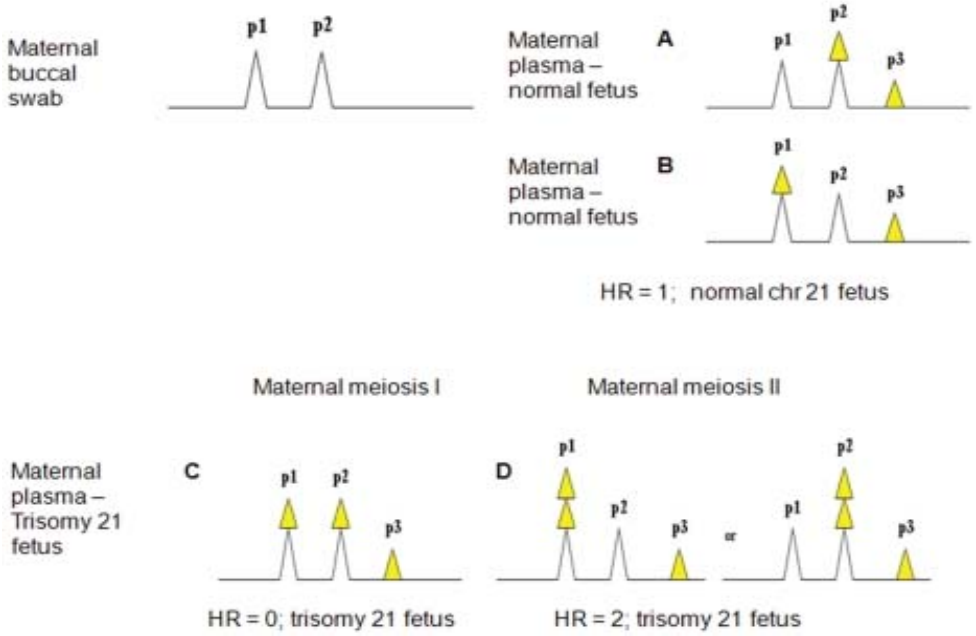

Figure 1: Theoretical CTCE electropherogram output from maternal buccal swab and maternal plasma using tandem SNP analysis. Adapted from (GHANTA et al., 2010).

In case of a plasma sample from a mother carrying a fetus with a trisomy, the CTCE electropherogram shows an uneven contribution between paternal (p3) and maternal haplotypes (p1 and/or p2) of the fetus. Fetal trisomy can be caused either by a familial form (e.g. Robersonian translocation) or, in the majority of cases, by a meiotic nondisjunction event. A normale gamete (ovum or sperm) has one copy of each chromosome, containing 23 chromosomes in total (n). With nondisjunction, chromosomes fail to separate normally, resulting in a gain or loss of a chromosome in a gamete.

(2) $$HR = \frac{(|p1 - p2|)}{p3}$$

Nondisjunction can occur both in mitosis and meiosis. Failure of sister chromatids to separate during mitosis may lead to mosaicism. Failure of a pair of homologue chromosomes to separate in meiosis I (i.e. primary nondisjunction) will result in both members of this homologues pair to be present into the same daughter cell (**Fig. 2 left**) resulting in a fertilized egg with an abnormal number of chromosomes (i.e. aneuploidy). Failure of the sister chromatids to separate during meiosis II (i.e. secondary nondisjunction) will result in both daughter chromosomes going into the same gamete, also resulting in an abnormal number of chromosome in the fertilized cell (**Fig. 2 right**).

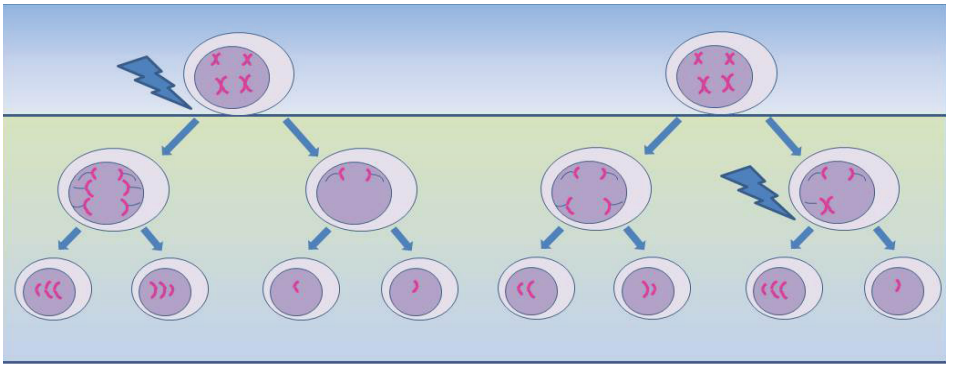

Figure 2: Nondisjunction occurring at meiosis I (left) and meiosis II (right). Nondisjunction in meiosis I will lead to two gametes with an extra chromosome (n+1) and two gametes with a missing chromosome (n-1). After fertilization this will result in a trisomy or monosomy respectively. Nondisjunction in meiosis II will lead to two normal gametes (n) and two abnormal gametes with either an extra chromosome (n+1) or missing one chromosome (n-1).

In case of fetal trisomy, the CTCE plots can also provide information about whether primary or secondary nondisjunction has occurred. When both maternal haplotypes (p1 and p2) are shared in the fetus, nondisjunction occurred during maternal meiosis I. The HR value for maternal meiosis I equals 0 (p1 = p2; therefore the relative difference between p1 and p2 = 0) (Figure 1 C). With secondary maternal nondisjunction, three alleles with different areas are reported whereas p1 or p2 is equal to twice the area of p3, resulting in HR = 2 (Figure 1 D). Adapted from (Ghanta *et al.*, 2010)

In addition to previous described methods used for fetal aneuploidy detection, also digital PCR can be used for fetal aneuploidy detection to determine the relative overrepresentation of a chromosome by calculating relative chromosome dosage (RCD). With RCD the total copy number of a chromosome is assessed in a sample to determine whether this chromosome is overrepresented when compared to a reference chromosome. However, the use of digital PCR is not only restricted to fetal aneuploidy detection in NIPT. Similar to RCD, the principle of digital relative mutation dosage (RMD) can also be applied to NIPD of monogenic diseases. With digital RMD it is no longer required to test only for paternally inherited mutations or fetal sequences that are different (e.g. methylated *RASSF1A*) or absent (e.g. *SRY*) in the mother. With RMD it is possible to compare and measure relative amounts of both the maternal mutant (M) and wild type alleles (N) in maternal plasma to determine the inherited dosage of the mutant allele by the fetus (**Fig. 3**). Therefore, it is no longer necessary to distin-

guish between fetal and maternal sequences. Digital RMD, performed by digital PCR, determines whether the M or N alleles are in balance in maternal plasma (**Fig. 3**). When a pregnant woman and her fetus are both heterozygous for a certain mutation, the amounts of the M allele and N allele are in balance (M=N). When the fetus is homozygous for the mutation, there will be an over-representation of the mutant allele (M>N). When the fetus is wild type, there will be an under-representation of the mutant allele (M<N) in the RMD. Adapted from (Chiu *et al.*, 2009; Lun *et al.*, 2008b).

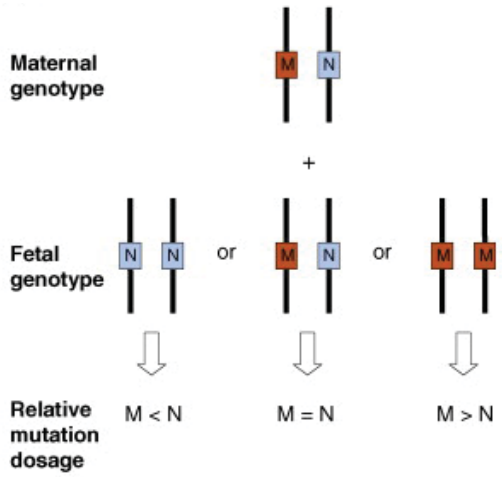

Figure 3: Relative mutation dosage of mutant (M) and normal (N) wild type alleles. Adapted from (Chiu et al., 2009)

Appendix 3: Calculations for trisomy detection

Relative sequence tag density (RSTD):

Shotgun sequencing of numerous of short cfDNA sequences produced after massive parallel sequencing (MPS) are mapped to the chromosome of origin. For each chromosome, these short sequence fragments or reads are counted and summed. In addition, the median of these summed reads from all the autosomes was calculated. To correct for input, for each sample the sum of the reads per chromosome is normalized by dividing this value by the median of all autosomes; the sequence tag density (STD). Male plasma samples or maternal plasma samples from women carrying male euploid fetuses can be used as a reference. STD was also calculated for the controls or reference samples, by first calculating the average of summed tags per chromosome from all reference samples. Subsequently, the median is determined over the values of the autosomes. The average of summed tags per chromosome is normalized by dividing this number by the median value of the autosomes (3). Relative sequence tag density (RSTD) can be determined for each sample by calculating ratios between normalized value per chromosome from each maternal plasma sample and normalized value per chromosome for the controls (4) (Adapted from (Fan *et al.*, 2008).

By determining these ratios, the over- or underrepresentation of any chromosome in maternal plasma contributed by an aneuploidy fetus can be detected. This method does not

require the differentiation between maternal and fetal sequence tags. When a woman carries a healthy fetus, both mother and fetus have 2 copies of each autosome. The RSTD between the normalized value for each autosome as compared to the normalized value of the controls is therefore ~1.

(3) $$Normalized\ chr\ N = \frac{\sum tags\ chr\ N}{median\ autosomes}$$

(4) $$RSTD = \frac{Normalized\ chr\ N_{sample}}{Normalized\ chr\ N_{controls}}$$

A fetus with a trisomy (e.g. trisomy 21) has an additional copy of chromosome 21 as compared to mother. Theoretically, the RSTD of chromosome 21 between mother and this affected fetus would be 1.5 (e.g. the mother has 2 copies of chromosome 21 while the fetus has 3 copies). However, in maternal plasma, the fetal contribution to cfDNA in maternal plasma is only ~10% in the first trimester. Therefore, the RSTD for a plasma sample from a fetus with trisomy 21 is expected to be between 1 and 1.5 due to the relatively small contribution of the additional fetal chromosome 21 as compared to the maternal background (**Table 2**).

Sample	*Fetal DNA content*	*↑ chr 21 (21)*	*↑ chr 21 (fold)*
CVS	100 %	50 %	1.5
Maternal plasma	~10 %	5 %	1.05

Table 2: Theoretical example of fold increase of chromosome 21 in fetal trisomy 21 in gDNA from chorionic villus sampling (CVS) and maternal plasma.

Z-scores:

In fetal trisomy detection, the Z-score refers to the number of standard deviations that the percentage of reads from a particular chromosome in a test sample differs from the mean % of that particular chromosome in a reference data set. Such reference set contains plasma samples from pregnancies of women carrying euploid fetuses. The advantage of a reference set and reference values is that they have to be established only once for a certain run setting. It is therefore no longer required to run control samples together with unknown samples.

For Z-score calculations, first the % representation of unique sequences mapped to a chromosome is calculated by dividing the number of unique count for chromosome N (chr N) by the total counts from that sample (5). Subsequently, the difference between % chr N (x) and the mean % of chr N (μ) in the reference set is determined and divided by the standard deviation (SD; σ) of the % chr N in the reference set to determine the Z score for chromosome N (6). With this Z-score, disease status of the fetus is determined by looking at the overrepresentation of a certain chromosome. For example, a maternal plasma sample with a % chr 21 that is > 3 SD from the mean of the % chr 21 of the euploid reference set is considered to be a fetal trisomy 21 (Adapted from (Chiu *et al.*, 2008) and ISPD preconference NGS Course, 2012).

(5) $$\%\ chr\ N = \frac{Unique\ count\ for\ chr\ N}{Total\ unique\ count}$$

(6) $$chr\ N\ Z-score\ for\ test\ sample = \frac{\%\ chr\ N_{sample} - mean\ \%\ chr\ N_{reference}}{SD\ \%\ chr\ N_{reference}}$$

Or $$Z = \frac{x-\mu}{\sigma}$$

NCV:

Normalized chromosome value (NCV) calculations are based on correction for the intrarun and interrun sequencing variation in the chromosomal distribution of sequence reads. These variations may obscure the effects of fetal aneuploidy on the distribution of mapped sequence sites. For NCV calculations, a chromosome ratio is calculated (7), in which the count of mapped sites for the chromosome of interest is normalized to counts of another predetermined chromosome (or set of chromosomes) of the same sample (8); Modified from (Sehnert *et al.*, 2011).

Sehnert *et al.* used a training set, consisting of pregnancies with unaffected fetuses. For each chromosomes of interest (e.g. chr 13, 18, and 21) they determined the denominator chromosome that minimized the variation of the chromosome ratios within and between the runs (**Table 3**). They also used the training set to determine parameters and boundaries for sample classification (i.e.. mean, SD and NCV classification). An NCV > 4.0 classifies the chromosome as affected (i.e. aneuploidy for that chromosome). An NCV < 2.5 classifies the chromosome as unaffected. Samples with an NCV between 2.5 and 4.0 were classified as "no call". Similar to Z-score calculations, this method does not require additional control sample to be sequenced together with maternal plasma samples when all parameters and boundaries have been established. Adapted and modified from (Sehnert *et al.*, 2011).

(7) $$ratio\ chr\ N = \frac{\#\ reads_{numerator}}{\#\ reads_{denominator}}$$

(8) $$NCV\ chr\ N = \frac{ratio\ chr\ N - mean\ ratio_{trainingset}}{SD\ ratio_{trainingset}}$$

Chromosome of interest	Numerator (chromosome mapped sites)	Denominator (chromosome mapped sites)
21	21	9
18	18	8
13	13	Sum (2-6)

Table 3: Numerator and denominator combinations for noninvasive trisomy detection.

Note: Determination of appropriate control groups and calculation methods that have been addressed in Appendix 3 were used for fetal aneuploidy detection as described in chapters 3 and 4.