CNVs – Copy Number Variations

CNVs – Copy Number Variations: Partial deletions and duplications at a size of 7 million base pairs or more (7 megabases, 7Mb)

Beside free monosomies and trisomies, subchromosomal (partial) structural alterations, so-called (micro-)deletions and -duplications (Copy Number Variations, CNVs), can also influence the development of a fetus or child. PrenaTest® can detect CNVs of all autosomal chromosomes (Chr. 1 – 22) at a size of ≥ 7 Mb.

Positive rate extended NIPT screening, all risk groups*,1,2					
Trisomy 21	Trisomy 18	Trisomy 13	Gonosomal aneuploidies	RAAs	CNVs (≥ 7 Mb)
0.39%	0.13%	0.04%	0.39%	0.34%**	0.10%
total					
0.56%			0.39%	0.44%	

* For gonosomal aneuploidies and RAAs, the positive rates of the different chromosomal aberrations were added together.

** Rare autosomal trisomies only included in the study. The screening positive rate for all RAAs (including monosomies) is therefore probably slightly higher than the rate reported for rare autosomal trisomies.

How accurate is the test?

Sensitivity and specificity for (micro-)deletions and -duplications of ≥7 Mb (CNVs); with known mosaics[3]

	Sensitivity	Specificity
Estimated value (n/N)	74.1 % (20/27)	99.8 % (2000/2004)
2-sided 95% CI	55.3 % 86.8 %	99.49 % 99.92 %

Sensitivity indicates the probability that a present chromosomal disorder will be tested as positive („conspicuous“). Specificity indicates the probability that an absent chromosomal disorder will be tested as negative („inconspicuous“).

What does a positive test result mean?

A positive test result indicates the presence of a CNV. The phenotype depends on the size of the chromosomal region affected as well as on the genes located in this region. It is also possible, especially in the case of smaller CNVs, that no clinical phenotype is formed. The high accuracy of PrenaTest® has been proven in clinical studies. However, in very rare cases false-positive or false-negative results are possible. In case of a positive test result, we recommend (according to §10 of the German Genetic Diagnostics Act (GenDG)) that you consult a specialist in clinical genetics for clarification of the etiology and the clinical impact. In case of discordant results, please contact us.

Please keep in mind:
NIPT is a screening test. It is possible that false-positive as well as false-negative results occur. The probability for a (micro-)deletion or -duplication during pregnancy depends on many factors including clinical and family history of the patient.

1 Pertile MD Genome-wide cell-free DNA-based prenatal testing for rare autosomal trisomies and subchromosomal abnormalities. In: Nonivasive Prenatal Testing, Academic Press 2018, Eds Page-Christiaens and Klein
2 Liang et al. Clinical utility of noninvasive prenatal screening for expanded chromosome disease syndromes. Genetics in Medicine 2019; doi.org/10.1038/s41436-019-0467-4
3 Illumina VeriSeq NIPT Solution v2 Packungsbeilage, Dokument-Nr. 1000000078751 v06 DEU, August 2021

Possible clinical manifestations

CNVs can be associated with

- Neurological disorders (motor and cognitive retardation)
- Dysmorphic features (especially craniofacial dysmorphism and growth retardation a. o.)
- Malformations of internal organs (especially cardiac malformations)

Please keep in mind that a negative test result does not necessarily exclude a clinical manifestation. Depending on the disorder, the size of the critical region whose deletion or duplication leads to the clinical manifestation may also be < 7 Mb. CNVs or microdeletions/-duplications <7 Mb (with the exception of Di-George syndrome***) are not detected by PrenaTest®.

The following disorders, among others, have been described in connection with CNVs:

- Prader-Willi syndrome
- Angelman syndrome
- Cri-du-chat syndrome
- Wolf-Hirschhorn syndrome
- Trisomy 9q
- Trisomy 10q

CNVs are not necessarily clinically significant or associated with a particular syndrome. They may be clinically inconspicuous. A literature search can help to better understand and evaluate the clinical significance of individual CNVs.

Limitations

- PrenaTest® can only detect CNVs at a size of ≥7 Mb
- Balanced translocations are not detected
- Gonosomal CNVs are not detected
- Maternal CNVs may influence the result

In addition, the general limitations of NIPT apply. For further information please visit our website (https://lifecodexx.com/en/for-physicians/limitations/).

*** Testing for Di-George syndrome (22q11.2 microdeletion) can be requested separately and is not part of the CNV analysis. For more information, please refer to the 22q11.2 microdeletion fact sheet.

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