

Clinician Guide to Results: Aneuploidy

Trisomy 21, Trisomy 18, Trisomy 13, Monosomy X, Triploidy/Vanishing Twin



Panorama® is a non-invasive prenatal screening test (NIPT) that uses single nucleotide polymorphism (SNP)-based technology to analyze cell-free DNA (cfDNA) fragments in maternal blood to provide a fetal risk score for common chromosomal aneuploidies and select microdeletion syndromes. This guide is meant to assist clinicians in interpreting results for aneuploidies. For additional assistance, you are encouraged to contact a LifeLabs genetic counsellor at **1-844-363-4357**, ask.genetics@lifelabs.com or www.lifelabsgenetics.com.

Fetal Fraction (FF)

Fetal fraction is the measurement of the amount of cfDNA in a sample that is from the pregnancy. The average FF at the time of NIPT is ~10%. FF is a critical component for accurate risk assessment, as indicated by ACOG and other sources.¹ FF is included on each report, and is factored into the risk score provided.

Risk Score

Results for aneuploidies are reported as a personalized risk score, which reflects the confidence level of the call. The risk calculation combines the SNP data with the patient's prior risk based on maternal and gestational ages. The majority of risk scores are at the maximum confidence level: >99/100 for high risk, and <1/10,000 for low risk. Intermediate risk scores reflect a reduced confidence call (1/100 to 99/100).

Positive Predictive Value (PPV)

PPV is the likelihood that diagnostic testing will confirm a high risk result. This value is dependent on many factors: the incidence of the condition based on maternal and gestation ages, sensitivity and false positive rate of the test, and the type of chromosome abnormality. The table below is included on all high risk aneuploidy reports, and provides the average PPV for each aneuploidy.

Positive Predictive Values ²	
T21:91%	These PPVs are NOT personalized, but calculated from a published study of 17,885 women. PPV for an individual specimen will vary based on prior risk (ultrasound finding, pregnancy and family history).
T18:93%	
T13:38%	
MX:50%	

Results suggest either vanishing twin, unrecognized multiple gestation, or an increased risk of fetal triploidy

Although these results may indicate a fetus with triploidy, most are cases of an ongoing twin gestation, or a history of a vanishing twin.³ Review of clinical history along with ultrasound and possible diagnostic testing should be considered. Women with a history of a vanishing twin are not good candidates for Panorama, or any other NIPT, as DNA from the demised pregnancy persists in maternal circulation.

No results - Repeat specimen is required for testing

These results typically occur when the fetal fraction is too low to provide sufficient information. While a 2.8% FF is the minimum required, some

samples at higher FF may not produce a result due to other analytic factors affecting the quality of the data. Low fetal fraction has been associated with an increased risk for aneuploidy. The table below can assist in determining the likelihood of success with a redraw.

FETAL FRACTION OBSERVED IN FIRST SPECIMEN					
MATERNAL WEIGHT	FF<= 2.0%	2.0<FF<= 2.4%	2.4<FF<= 2.9%	2.9<FF<= 3.4%	FF> 3.4%
<=165 lbs (75 kg)	57%	66%	73%	82%	87%
166-220 lbs (75-100 kg)	45%	56%	65%	68%	86%
>220 lbs (100 kg)	41%	46%	63%	65%	85%

Source: Internal Natera data. Probabilities based on historical success rates across overall sample size of 1, 874 cases.

No results - DNA pattern cannot be interpreted by this assay. Repeat specimen not indicated.

Fewer than 1% of cases are not able to produce a result and a redraw is not recommended. A small number of individuals have a DNA pattern that cannot be interpreted clearly by this assay. Another form of screening or testing may be more informative for this patient.

Results suggestive of a sex chromosome trisomy (SCT)

Fetal sex chromosome trisomies (XXX, XXY, XYY) will only be reported when the DNA pattern is suggestive of this finding. Risk scores and PPV data are not reported as data is limited. SCTs will be provided whether or not fetal sex is requested.

Follow up

Since the cell-free DNA analyzed by NIPT is placental, it occasionally differs from the DNA of the fetus. Confined placental mosaicism (CPM) is a common source of false positive and false negative results with NIPT. This means that even with high risk results, a fetus may be unaffected. All patients with high risk results should be referred for genetic counseling and offered pre- or post-natal diagnostic testing. Similarly, while a low risk NIPT is reassuring, a residual risk remains. Follow up testing decisions should be made based on review of all clinical history.

LifeLabs Genetics has board-certified genetic counsellors available for healthcare providers or patients that have further questions about NIPT results. They can be reached at **1-844-363-4357** or ask.genetics@lifelabs.com.

Clinician Guide to Results: Microdeletions

Microdeletion Panel: 22q11.2 deletion, 1p36 deletion, Prader-Willi, Angelman, & Cri-du-chat



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Risk score for microdeletions

Risk scores for each microdeletion reflect the positive predictive value (PPV) as established by Panorama's microdeletion validation study.⁴ For each condition, the calculation takes in to account the:

- 1) background incidence of the condition (prior risk)
- 2) adjusted sensitivity of the test (proportion of cases defined by the targeted region)
- 3) false positive rate/sensitivity

Risk scores depend on fetal fraction

Maternally inherited deletions are difficult to detect at fetal fractions less than 7%, and risk scores are adjusted accordingly.

Syndrome	Prior Risk	High Risk	High Risk at lower ff	Low Risk	Low Risk at lower ff
22q11.2 deletion	1/2,000	1/19	1/45	1/13,330	1/3,000
Prader-Willi	1/10,000	1/22	1/22	1/13,800	1/13,800
Angelman*	1/12,000	1/26	Risk unchanged	1/16,600	Risk unchanged
1p36 deletion	1/5,000	1/6	1/15	1/12,400	1/6,300
Cri-du-chat	1/20,000	1/19	1/46	1/57,100	1/27,000

*Angelman syndrome is uniquely caused by a deletion of the maternal copy of chromosome 15. It is not possible to modify the prior risk when FF is <7%, and results are reported as "Risk Unchanged".

Detection of a microdeletion in mother

Panorama identifies microdeletions in the DNA from the mother. If a maternal microdeletion is identified, the fetal risk score will be revised to 1 in 2 (50%), reflecting the autosomal dominant inheritance pattern. In these cases, follow-up diagnostic testing is necessary to determine fetal microdeletion status.

Risk unchanged - Angelman syndrome

This signifies that the data from the sample was not sufficient to generate a modified risk score. This result occurs for Angelman syndrome in ALL cases with a FF of less than 7% because the deletion causing Angelman occurs only on the maternal chromosome and detection requires a FF of at least 7%. In such cases, the risk for Angelman syndrome remains that of the general population: 1/12,000.

Confirmatory testing options for high risk microdeletion results

The optimal diagnostic testing for 22q11.2, 1p36 and Cri-du-chat is microarray analysis, as fluorescence in-situ hybridization (FISH) and other studies may not detect all affected cases. This can be done prenatally by CVS or amniocentesis, or postnatally.

Given the complex etiology of Prader-Willi syndrome and Angelman syndrome, additional testing in the form of uniparental disomy (UPD) analysis and methylation studies are recommended if clinical suspicion for one of these syndromes exists, as microarray analysis alone cannot detect certain cases. The lab performing diagnostic testing should be informed of the need to rule out a microdeletion and both types of UPD (hetero- and iso-disomy).

Microdeletion Condition	Optimal Diagnostic Testing
22q11.2 deletion, 1p36 deletion, Cri-du-chat	*Microarray
Prader-Willi (PWS), Angelman (AS)	**Microarray and uniparental disomy(UPD) testing for both iso-and heterodisomy, or methylation studies

Follow up

Genetic counseling with the option of pre- or post-natal diagnostic testing should be offered for all high risk results. Find a genetics clinic closest to you through the Canadian Association of Genetic Counsellors: <https://www.cagc-accg.ca>

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References: 1. ACOG Practice Advisory of Cell-Free DNA Screening. April 2, 2015. 2. Dar P et al. Am J Obstet Gynecol 2014 Nov;211(5):527
3. Curnow et al. Am J Obstet Gynecol. 2015 Jan;212(1):79. 4. Wapner R et al. Am J Obstet Gynecol 2014; 212(3):332