Clinician's Guide to Results

natera™ | Panorama™ Next-generation NIPT

This guide is designed for clinicians and should be used as a supplement to the Panorama result reports. Panorama is a noninvasive prenatal screening test (NIPT) that provides a fetal risk assessment for common chromosomal aneuploidies and select microdeletion syndromes. Fetal sex is reported when requested, subject to local laws and regulations. Testing can be performed in singleton and twin gestations, as well as singleton pregnancies achieved by egg donation or surrogacy.

Panorama: Final Results Summaries

Fetal Fraction

To produce a Panorama result, each sample must first pass a series of quality metrics. One of the most important metrics is **fetal fraction (FF)**, or the percentage of cell-free DNA in the sample that is derived from the placenta. As per ACMG, ACOG, and SMFM guidelines, FF is a critical component of accurate risk assessment.

Low FF Algorithm

With Panorama, a 2.8% FF is the minimum required for aneuploidy assessment. Some samples with a higher FF will not produce a result due to other analytic factors affecting data quality. **Samples with a low FF cannot be assessed by the standard SNP-based algorithm.** Instead, a proprietary calculation (called the Low FF Algorithm) is automatically performed* to determine whether the FF reflects what is expected based upon the patient's age, weight, and gestational age, or whether the pregnancy is at an increased risk for certain aneuploidies.

Insufficient Fetal DNA

Due to low FF, Panorama could not yield results through the standard SNP-based algorithm. **The Low FF Algorithm determined that the FF could be explained by the patient's age, weight, and gestational age.*** A repeat sample can be submitted. The likelihood of obtaining a result on redraw is stated in a table on the report.

High Risk Due To Fetal DNA Fraction

Due to low FF, Panorama could not yield results through the standard SNP-based algorithm. The Low FF Algorithm determined that the FF is *not* consistent with what is expected based upon the patient's age, weight, and gestational age. **Therefore, this pregnancy is at increased risk for certain aneuploidies associated with low FF**, including trisomy 13, trisomy 18, and triploidy.

The *Risk After Test* of 1/17 (~6%) for these conditions is considered a fetal fraction-based risk (FFBR). Genetic counseling, comprehensive ultrasound, and the option of diagnostic testing should be considered. However, a redraw will be accepted.

*If a clinic chooses to opt out of the high risk due to fetal DNA fraction algorithm, additional risk assessment will not be performed, and the pregnancy could still be at high risk.

Low Risk

These results indicate that the fetus is unlikely to be affected with any of the conditions for which the pregnancy was screened. The *Risk After Test* represents the residual risk for the fetus to be affected. Further testing decisions should be made in the context of clinical and family history.

High Risk

Panorama's SNP-based algorithm determined that the fetus has an increased chance of having the indicated condition. **The *Risk After Test* represents the likelihood that the fetus is affected. Diagnostic testing is recommended to confirm this result.**

Most High Risk results reflect calls made with the highest confidence, and receive a *Risk After Test* consistent with the positive predictive values found in the Panorama Test Specifications table on the report. These values are based on clinical outcome data and Panorama's microdeletion syndrome validation study. Occasionally, reduced confidence calls will produce results with a *Risk After Test* that is lower.

Risk After Test is calculated using the sample's SNP data, FF, the patient's prior risk (based on maternal age and gestational age), and the positive or negative predictive values (PPV/NPV), as determined by Natera's clinical outcome data. This score does not incorporate other possible risk factors, such as family history, previous serum screening results, or ultrasound findings.

Pattern Suggestive Of A Sex Chromosome Trisomy (SCT)

The possibility of a fetal sex chromosome trisomy (XXX, XXY, XYY) will be reported when the DNA pattern is suggestive of this finding. Page two of the report includes the clinical PPVs, sensitivity, and specificity for SCT. Results suggestive of a SCT will be reported even when fetal sex reporting is not requested.

Atypical Finding

Panorama was unable to provide a risk assessment for one or more conditions because an abnormality outside the scope of the test was detected. **Such findings can include (but are not limited to) mosaic aneuploidy, chromosomal copy number variant (e.g. deletion/duplication), and normal variation.**

In some cases, the chromosome involved and the origin of the suspected finding (i.e. maternal vs. fetal/placental) can be discerned and will be mentioned in the *Final Results Summary*. There could also be more specific information about the suspected type of finding (CNV, mosaicism, etc). You can contact a Natera genetic counselor to discuss if this level of information is available.

Since the DNA pattern is not expected to change between samples, repeat cell-free DNA testing is not recommended when an atypical finding is suspected. Genetic counseling and diagnostic testing should be considered.

Panorama: Final Results Summaries (cont'd)

High Risk: Vanishing Twin, Triploidy, or Unrecognized Multiple Gestation

Panorama identified an additional DNA pattern in the sample. **In most cases, this result represents either a vanishing twin or an ongoing twin gestation. If a vanishing twin or ongoing twin pregnancy cannot be confirmed by ultrasound, this result could indicate an increased risk for triploidy.** If there is an ongoing twin pregnancy, please contact Natera for recalculation of the results.

The use of NIPT in pregnancies with a vanishing twin is not advised, as the cfDNA from the demised twin can remain in maternal circulation. At this time, Panorama does not provide a risk assessment for ongoing pregnancies with a known or suspected vanishing twin. Correlation of clinical history, ultrasound, genetic counseling, and the option of diagnostic testing should be considered.

No Result: Uninformative (Suspect Non-Matching) Maternal/Fetal DNA Patterns

Panorama identified an additional DNA pattern in the sample. **Usually, this result occurs because the use of an egg donor/surrogate or history of a maternal bone marrow transplant has not been disclosed to Natera.** Panorama is not recommended for bone marrow transplant recipients. If the clinical history confirms egg donation or surrogacy, please contact Natera for recalculation of the results. If the clinical history is not consistent with the above, a repeat sample can be submitted.

No Result

The *Final Results Summary* could read No Results when quality metrics for the sample were not met, and a risk assessment for one or more conditions could not be performed. This type of result can occur because of **laboratory processing issues or limitations of the testing algorithm.** Many of these issues are thought to be sample-specific and usually resolve with a redraw. The *Final Results Summary* will state if a repeat sample can be submitted. If a **Test Not Performed** result is issued, the reason is usually stated.

Panorama Microdeletion Panel: Uncommon Results

Maternal 22q11.2 Deletion Suspected

Panorama detected a 22q11.2 deletion in the maternal DNA sequence. The *Risk After Test* for this condition in the fetus will be 1/2 (50%) to reflect the risk associated with an autosomal dominant inheritance. **Maternal testing and fetal diagnostic testing are necessary to determine whether the fetus has this microdeletion and to assess risk for future pregnancies.**

Risk Unchanged

In some cases, the SNP data for a microdeletion syndrome is uninformative or insufficient to produce a result. This result can occur due to failed quality metrics such as low fetal fraction or unclear DNA pattern. The result for that microdeletion syndrome will say *Risk Unchanged*, and the *Risk After Test* will reflect the risk for this condition in the general population. A redraw is not recommended.

Limitations of NIPT and Suggested Follow-Up

NIPT is a screening test. Since the cfDNA analyzed by NIPT is placental, it occasionally differs from the DNA of the fetus. Confined placental mosaicism (CPM) is a common source of both false positive and false negative results with any NIPT. Even with High Risk results, a fetus could be unaffected. Low Risk results are reassuring, although a residual risk remains. All patients with abnormal results (such as High Risk result types and Atypical Findings) should be referred for genetic counseling and offered diagnostic testing. Karyotype analysis, chromosomal microarray, or additional studies indicated by the test report should be considered. Decisions about further testing should always be made in the context of the clinical and family history.

Clinician Support

Still have questions? Clinicians can contact a Natera genetic counselor (GC) by phone at 1.650.249.9090 or by email at niptgc@natera.com. You may also reach out to your local Regional Manager (RM) who can put you in touch with a Natera GC, known as a Medical Science Liaison (MSL), to answer clinician questions and to discuss Natera test results.

Your local RM: _____

RM phone number: _____

RM email address: _____

Patient Support

Would your patient like further information? Natera offers complimentary genetic information sessions with a board-certified GC to discuss results with patients by phone. Appointments can be made by:

Calling Natera at 1.877.476.4743

Online at naterasession.com

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