Fetal Aneuploidy Screening

Patient: [redacted] DOB: [redacted] Age: 37 Sex: F **Patient Identifiers:** [redacted] **Visit Number (FIN):** [redacted]	Client: [redacted] Physician: [redacted]	ARUP Test Code: 3004764 Collection Date: 03/09/2023 Received in lab: 03/10/2023 Completion Date: 03/17/2023

Test Information

Method

DNA isolated from the maternal blood, which contains placental DNA, is amplified at specific loci using a targeted PCR assay, and sequenced using a high-throughput sequencer. Sequencing data is analyzed using Natera's proprietary algorithm to determine the fetal copy number for chromosomes 13, 18, 21, X, and Y, thereby identifying whole chromosome abnormalities at these locations, and if ordered, the microdeletion panel will identify microdeletions at the specified loci only. If sample fails to meet the quality threshold, no result will be reported for the specified chromosome(s). The test requires sufficient fetal fraction to produce a result.

Patient Report

Patient's genetic report from Natera continues on following pages.

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Jonathan R. Genzen, MD, PhD, Laboratory Director

Chart continues on following page(s)

Patient Information		Test Information	
Patient Name:	[redacted]	Ordering Physician:	N/A
Date of Birth:		Clinic Information:	ARUP Laboratories
Maternal Age at EDD:	38	Additional Reports:	N/A
Gestational Age:	14 weeks/ 3 days	Report Date:	03/17/2023
Maternal Weight:	139	Samples Collected:	03/09/2023
Patient ID:	[redacted]	Samples Received:	03/11/2023
Collection Kit:			Mother Blood
Accessioning ID:	23068109081		
Case File ID:			

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ABOUT THIS SCREEN: Panorama ™ is a screening test, not diagnostic. It evaluates genetic information in the maternal blood, which is a mixture of maternal and placental DNA, to determine the chance for specific chromosome abnormalities. The test does NOT tell with certainty if a fetus is affected, and only tests for the conditions ordered by the healthcare provider. A low risk result does not guarantee an unaffected fetus.

FINAL RESULTS SUMMARY

Result	*Fetal Sex*	*Fetal Fraction(s)*
HIGH RISK due to fetal DNA fraction	**N/A**	**1.3%**

Fetal fraction is an important quality control metric. There is insufficient fetal DNA in this sample to obtain a reliable result using standard NIPT methods. Therefore, an additional proprietary analysis was performed, incorporating fetal fraction, maternal age, maternal weight, and gestational age. Based upon the results of the additional analysis, this pregnancy is at high risk for triploidy, trisomy 18 or trisomy 13. The risks for trisomy 21 and monosomy X are unchanged.

This is a screening test only. Genetic counseling, comprehensive ultrasound evaluation and the option of diagnostic testing should be considered. Natera will accept a repeat sample. No irreversible decision should be made based upon the results of this screening test alone.

RESULT DETAILS: ANEUPLOIDIES

Condition Tested [1]	*Result*	*Risk Before Test* [2]	*Risk After Test* [3]
Trisomy 21	No Result	1/125	N/A
Monosomy X	No Result	1/568	N/A
Triploidy, Trisomy 18 or Trisomy 13	**High Risk**	1/238	**1/17**

1. Excludes cases with evidence of fetal and/or placental mosaicism. 2. Based on maternal age, gestational age, and/or general population as applicable. References available upon request. 3. Risk after test reflects the results from the fetal fraction based risk (FFBR) algorithm and data from a published study of 1148 women [McKanna et al. Ultrasound Obstet Gynecol. 2018 Jul 16. doi: 10.1002/uog.19176 [Epub ahead of print]].

Testing Methodology: DNA isolated from the maternal blood, which contains placental DNA, is amplified at specific loci using a targeted PCR assay and is sequenced using a high-throughput sequencer. Fetal fraction is determined using a proprietary algorithm incorporating data from single nucleotide polymorphism-based (SNP-based) next-generation sequencing [Pergament E et al. Obstet Gynecol. 2014 Aug;124(2 Pt 1):210-8]. If the estimated fetal fraction is ≥2.8%, sequencing data is analyzed using a proprietary SNP-based algorithm to determine the fetal copy number for chromosomes 13, 18, 21, X and Y [Ryan A et al. Am J Obstet Gynecol. 2014 Nov;211(5):527.e1 527.e17]. If ordered, specific microdeletions will be evaluated using similar methodology [Wapner RJ et al. Am J Obstet Gynecol. 2015 Mar;212(3):332.e1-9]. If a sample fails to meet the quality threshold, or the fetal fraction is insufficient, an additional algorithm is utilized to determine whether there is an increased risk for triploidy, trisomy 18 and trisomy 13 [McKanna et al. The European Human Genetics Conference. Copenhagen, Denmark. May 27-30, 2017]. However, some samples will not produce a result due to failure to meet the necessary quality thresholds.

This test has been validated on women with a singleton, twin or egg donor pregnancy of at least nine weeks gestation. A result will not be available for higher order multiples and multiple gestation pregnancies with an egg donor or surrogate, or bone marrow transplant recipients. Complete test panel is not available for twin gestations and pregnancies achieved with an egg donor or surrogate. For twin pregnancies with a fetal fraction value below the threshold for analysis, a sum of the fetal fractions for both twins will be reported. Findings of unknown significance will not be reported. As this assay is a screening test and not diagnostic, false positives and false negatives can occur. High risk test results need diagnostic confirmation by alternative testing methods. Low risk results do not fully exclude the diagnosis of any of the syndromes nor do they exclude the possibility of other chromosomal abnormalities or birth defects, which are not a part of this test. Potential sources of inaccurate results include, but are not limited to, mosaicism, low fetal fraction, limitations of current diagnostic techniques, or misidentification of samples. This test will not identify all deletions associated with each microdeletion syndrome. This test has been validated on full region deletions only and may be unable to detect smaller deletions. Microdeletion risk score is dependent upon fetal fraction, as deletions on the maternally inherited copy are difficult to identify at lower fetal fractions. Test results should always be interpreted by a clinician in the context of clinical and familial data with the availability of genetic counseling when appropriate.

Reviewed By: Wenbo Xu, M.D., Ph.D., FACMG, Senior Laboratory Director

CLIA Laboratory Director: J. Dianne Keen-Kim, Ph.D., FACMG

IF THE ORDERING PROVIDER HAS QUESTIONS OR WISHES TO DISCUSS THE RESULTS, PLEASE CONTACT US AT 650-249-9090 #3. Ask for the NIPT genetic counselor on call.

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High Risk Due to Fetal Fraction Result

What does this result mean?
This patient's sample has insufficient fetal DNA (low fetal fraction) for analysis using the Panorama SNP-based algorithm. Low fetal fraction has been associated with early gestation age, high maternal weight, sub-optimal sample collection, pregnancy loss, low molecular weight heparin, and certain fetal fraction related chromosomal abnormalities (triploidy, trisomy 18 and trisomy 13). [1-6]

Additional analysis is performed on samples with low fetal fraction to assess the chance for FF-related chromosomal abnormalities. Based on this "low fetal fraction algorithm", which adjusts for maternal age, gestational age, and maternal weight, an increased risk for these conditions has been identified. An increased incidence of pregnancy loss has also been observed with this result. [1]

What are FF-related chromosomal abnormalities?
Pregnancies with triploidy, trisomy 18, or trisomy 13 tend to have smaller than average placentas. [7-9] In general, babies with one of these conditions have serious birth defects and significantly shortened lifespans. It is rare for a baby with triploidy to be liveborn.

The cell-free DNA assessed in NIPT is placental in origin, therefore, it is likely that a pregnancy with a smaller placenta will have a lower fetal fraction. There are other factors known to be associated with lower fetal fraction, including gestational age and maternal weight.

Why is there a "No Result" for trisomy 21 and monosomy X?
Natera's study did not find an increased incidence of trisomy 21 or monosomy X among low fetal fraction cases.1Therefore, these conditions are not considered to be FF-related chromosomal abnormalities. Although some studies have suggested that trisomy 21 and monosomy X might be more common among cases with low FF, most publications are consistent with Natera's findings. [2,7] It is important to note that "no result" is not equivalent to "low risk".

What follow up is recommended?
An ultrasound to confirm viability and gestational age should be performed, if not already done. Once viability and gestational age are confirmed, genetic counseling, comprehensive ultrasound evaluation, and diagnostic testing should be offered in accordance with ACOG and ACMG guidelines. [10-11] Natera will accept a repeat sample.

References

1. McKanna et al. Ultrasound Obstet Gynecol. 2018 Jul 16. doi: 10.1002/uog.19176 [Epub ahead of print]
2. Pergament E, Cuckle H, Zimmermann B, et al. Single-nucleotide polymorphism-based noninvasive prenatal screening in a high-risk and low-risk cohort. Obstetrics and gynecology 2014 Aug;124(2 Pt 1):210-8.
3. Rava RP, Srinivasan A, Sehnert AJ, et al. Circulating fetal cell-free DNA fractions differ in autosomal aneuploidies and monosomy X. Clin chem 2014 Jan;60(1):243-50.
4. Norton ME, Jacobsson B, Swamy GK, et al. Cell-free DNA analysis for noninvasive examination of trisomy. N Engl J Med 2015 Apr;372(17):1589-97.
5. Revello R, Sarno L, Ispas A, et al. Screening for trisomies by cell-free DNA testing of maternal blood: consequences of a failed result. Ultrasound Obstet Gynecol. 2016 Jun;47(6):698-704.
6. Suzumori N, Ebara T, Yamada, T et al. Fetal cell-free DNA fraction in maternal plasma is affected by fetal trisomy. J Hum Genet 2006 Jul;61(7):647-52.
7. Ashoor G, Poon L, Syngelaki A, et al. Fetal fraction in maternal plasma cell-free DNA at 11-13 weeks' gestation: effect of maternal and fetal factors. Fetal Diagn Ther 2012 May;31(4):237-43.
8. P. Wegrzyn, C. Faro, O. Falcon, et al. Placental volume measured by three-dimensional ultrasound at 11 to 13 + 6 weeks of gestation: relation to chromosomal defects. Ultrasound Obstet Gynecol. 2005; 26: 28-32. DOI 10.1002/uog.1923.
9. Sergi C, Schiesser M, Adam S, et al. Analysis of the spectrum of malformations in human fetuses of the second and third trimester of pregnancy with human triploidy. Pathologica 2000 Aug;92(4):257-63.
10. ACOG Practice Bulletin No. 163: Screening for Fetal Aneuploidy. Obstet Gynecol 2016 May;127(5):e123-37.
11. Gregg A et al. Genet Med. 2016 Jul 28. doi: 10.1038/gim.2016.97. Epub 2016 Jul 28.

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Patient Supplement for High Risk Due to Fetal Fraction Result

What does a "High Risk for Triploidy, Trisomy 18, and Trisomy 13" result mean?
The results of the Panorama test show that there is a lower than expected amount of fetal DNA in the blood sample. Although most of the time this finding is associated with a healthy baby and normal pregnancy outcome, this finding may be found with early pregnancy, high maternal weight, sample collection issues, pregnancy loss, and some chromosome abnormalities.

We refer to these chromosome abnormalities as "fetal fraction-related chromosome abnormalities": triploidy, trisomy 18, and trisomy 13. The chance for one of these conditions with this "high risk" result is about 1/17 (5.7%). Most pregnancies with this result do not have one of these conditions, but further evaluation and testing should be considered.

What is triploidy?
Triploidy is caused by an extra set of chromosomes. Usually, humans have 46 chromosomes that come in 23 pairs. Fetuses who have triploidy have three copies of every chromosome instead of two, resulting in a total of 69 chromosomes. Almost all pregnancies with triploidy miscarry. The few babies that are born with triploidy usually do not live past a few days of life. It is rare for a live born baby at full term to have triploidy.1

What is trisomy 18 (Edwards syndrome)?
Trisomy 18, also called Edwards syndrome, is a chromosome condition caused by an extra copy of chromosome 18. Babies with trisomy 18 often have serious birth defects and survivors experience severe intellectual disability. About 1 in 3,000 babies is born with trisomy 18.1

What is trisomy 13 (Patau syndrome)?
Trisomy 13, also called Patau syndrome, is a chromosome condition caused by an extra copy of chromosome 13. Babies with trisomy 13 often have serious birth defects and survivors experience severe intellectual disability. About 1 in 5,000 babies is born with trisomy 13.1

How do these conditions happen?
In most cases, triploidy, trisomy 18, and trisomy 13 happen by chance. There is nothing parents do before or during pregnancy that causes these chromosome conditions. Trisomy 13 and trisomy 18 occur more commonly in pregnancies with older mothers.

What is the next step?
You and your pregnancy healthcare provider should discuss these results. Often your healthcare provider will refer you to a genetic counselor and/or high risk pregnancy specialist who will review the results, and your personal and family history. A detailed ultrasound is often performed to look for any problems, and confirm that the due date assigned is correct. They will also discuss tests that are available that can tell for sure whether or not your baby has one of these conditions.

Two different tests are available during pregnancy to check the baby's chromosomes. One test is chorionic villus sampling (CVS). CVS can be done at 10 to 13 weeks of pregnancy. Another test is amniocentesis (amnio). Amnio can be done as early as 15 weeks of pregnancy. Both of these tests have a small chance of miscarriage.

If you do not want diagnostic testing during pregnancy, chromosome testing can be done after your baby is born, most easily using blood from the umbilical cord at the time of birth.

Where can I learn more about triploidy, trisomy 18, and trisomy 13?
Your healthcare provider can refer you to a genetics professional in your area. A genetics professional can answer any questions you have about your Panorama test results. They can also tell you more about these conditions and about follow-up diagnostic testing.

Additional information on these conditions be found online:

- March of Dimes: **http://www.marchofdimes.com/baby/birthdefects_chromosomal.html**
- The Support Organization for Trisomy 18, 13, and Related Disorders (SOFT): **www.trisomy.org**
- Unique: **http://www.rarechromo.org/information/other/triploidy%20ftnw.pdf**

Where can I find a genetic counselor?
You may find a local genetic counselor through the National Society of Genetic Counselors at **www.nsgc.org** . If you would like to speak with a Natera genetic counselor regarding your high-risk Panorama result, you can schedule a 15-minute information session at **naterasession.com** or by contacting us at 650-249-9090.

References

1. Nussbaum et al. 2007 Thompson and Thompson Genetics in Medicine (7th Ed.) Oxford Saunders, Philadelphia, PA.