GENESYS Diagnostics INC.

prenatal screening report

REPORT RELEASED
Date: 11/23/21 Time: 08:36 PM

PROVIDER INFORMATION
Attn: Jane Doctor, MD
123 Fake Street
Springfield, NY 13531
Phone: (123) 456-7890
Fax: (123) 456-7899

SECOND RECIPIENT

PATIENT INFORMATION
Jane Patient
DOB: 05/01/1981
GA: 10 weeks
Indication: AMA
Medical record/patient ID: 123456789

SAMPLE INFORMATION
Client Sample ID:
Order ID: 742352
Date of Draw: 04/17/18
Date Received: 04/18/18
Pregnancy Type: Singleton

Electronically signed and dated on 11/23/2021 8:36:10 PM:
Lab director's e-signature is required.

ANEUPLOIDY DETECTED

RESULTS SUMMARY:

CHROMOSOME	RESULTS	PPV (%)
Chromosome 21	**POSITIVE: Aneuploidy detected** Results consistent with pregnancy at increased risk for trisomy 21	82.0%
Chromosome 18	**NEGATIVE: No aneuploidy detected** Results consistent with two copies of chromosome 18	
Chromosome 13	**NEGATIVE: No aneuploidy detected** Results consistent with two copies of chromosome 13	
Sex Chromosomes	**POSITIVE: Aneuploidy detected** Results consistent with pregnancy at increased risk for XXY	NA**

CLINICAL COMMENTS: This is a screening test; therefore false positive and false negative results can occur. Results may be reflective of fetal, placental, or maternal conditions. No irreversible clinical decision should be made based on these screening results alone. Clinical correlation is indicated. If definitive diagnosis is desired, chorionic villus sampling or amniocentesis would be necessary. For more clinical information, please refer to the physician information sheet on the following page[s] of the report. Genetic counseling is recommended. The fetal fraction (FF) is estimated to be 8%. FF estimation is one component of this algorithm and is combined with other quality metrics to determine the confidence in the results. The FF estimate is not used in isolation to exclude samples.
Positive predictive value (PPV) is calculated based on stated performance, maternal and gestational age as provided on the Test Requisition Form (TRF). Other factors may impact the patient specific PPV. For more information about PPV please visit us at www.illumina.com/ppv.

PERFORMANCE AND LIMITATIONS

LIMITATIONS OF THE TEST: The Verifi™ Prenatal Test is validated for aneuploidy (both monosomies and trisomies) of all chromosomes, including 21,13, 18, X, and copy number variants (7Mb or greater) in singleton pregnancies, with a gestational age of at least 10 weeks 0 days. This is a screening test that looks only for specific chromosomal abnormalities. A normal result does not eliminate the possibility that the pregnancy is associated with other chromosomal or subchromosomal abnormalities, birth defects, genetic conditions, or other conditions, such as open neural tube defects or autism.

There is a small possibility that the test results might not reflect the chromosomes of the fetus but may reflect chromosomal changes of the placenta (confined placental mosaicism or CPM) or of you (maternal chromosomal abnormalities). Examples are, but are not all inclusive, maternal XXX, sex chromosome status, or benign and malignant maternal neoplasm. Some CPM cases have been associated with a higher chance for pregnancy complications or for uniparental disomy (UPD) depending on the chromosome in question, which may affect the growth and development of the fetus. Some of these rare chromosomal aneuploidies have been found to occur only in mosaic form. Clinical consequences depend on the chromosome(s) involved and cannot be predicted during the pregnancy. Copy number variants (CNVs) are structural changes that have been identified in all human chromosomes and can vary in size. This screening assay detects CNVs that are 7Mb or larger. Depending on the size and location of the CNV, it may correlate with a clinical consequence/effect. This test, like many tests, have limitations, including false negative and false positive results. A negative test result does not guarantee the pregnancy is unaffected.

PERFORMANCE METRICS:†

Chromosome	N	Sensitivity	95% CI	Specificity	95% CI	Accuracy	95% CI
21	500	99.9% (90/90)	96.0-100.0	99.8% (409/410)	98.7 - 100.0	—	—
18	501	97.4% (37/38)	86.2-99.9	99.6% (461/463)	98.5 - 100.0	—	—
13	501	87.5% (14/16)	61.7-98.5	99.9% (485/485)	99.2 - 100.0	—	—
Chromosome	N	Sensitivity	95% CI	Specificity	95% CI	Accuracy	95% CI
Monosomy X	508	95% (19/20)	75.1-99.9	99.0% (483/488)	97.6-99.7	—	—
XX	508	97.6% (243/249)	94.8-99.1	99.2% (257/259)	97.2-99.9	98.4%	96.9-99.3
XY	508	99.1% (227/229)	96.9-99.9	98.9% (276/279)	96.9-99.8	99.0%	97.7-99.7
XXX/XXY/XYY	Other sex aneuploidies will be reported if detected. (Limited data of these more rare aneuploidies preclude performance calculations.)						
Microdeletions, Copy Number Variants, & other autosomal aneuploidies	Microdeletions, Copy Number Variants (CNVs) and other autosomal aneuploidies if requested and detected will be reported. (Limited data of these more rare abnormalities preclude performance calculations.)						

† Data on file at Illumina, Inc. regarding Performance and Method Comparison studies.

TEST METHOD: Nucleic Acid extraction, DNA sequencing, and analysis of sequencing results to determine fetal aneuploidy.

DISCLAIMER: The manner in which this information is used to guide patient care is the responsibility of the health care provider, including advising for the need for genetic counseling or diagnostic testing. Any test should be interpreted in the context of all available clinical findings.

DISCLOSURE: This prenatal test was developed by, and its performance characteristics were determined by Verinata Health, Inc. a wholly owned subsidiary of Illumina, Inc. The VHI laboratory is CAP-accredited and certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing. This prenatal test has not been cleared or approved by the U.S. Food and Drug Administration.

This prenatal test is performed by Verinata Health, Inc., a wholly owned subsidiary of Illumina, Inc.
Illumina, Inc., 200 Lincoln Centre Dr, Foster City, CA 94404 1-855-266-6563
CAP, CLIA, CA Laboratory Director: Sue Beruti, MD, MHA CAP: 7519312 CLIA: 05D2013691 California License #: CDF00340177
State of New York Laboratory Director: Eileen S. de Feo, Ph.D.

Part No. LB-0007, Rev. AC

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General information about positive NIPT results

My patient's NIPT is positive for multiple aneuploidies.
What does this mean? Your patient's NIPT result suggests the presence of aneuploidy of more than one chromosome. The presences of multiple aneuploidies in a pregnancy is very rare, but can occur. However, NIPT is a screening test and false positives can occur. In addition, there may be other underlying biological explanations for a NIPT result suggesting multiple aneuploidies.

Next steps to consider: You should discuss the results and the potential clinical implications with your patient. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine state, "All women with a positive cell-free DNA test result should have further detailed counseling and testing and should have a diagnostic procedure before any irreversible action is taken."[1] Confirmation prior to birth can also help with pregnancy and neonatal management.

Please see below for more information about multiple aneuploidy results.

What is multiple aneuploidy? Multiple aneuploidy refers to the presence of an extra or missing copy of multiple chromosomes.

What are the features of multiple aneuploidy? Most pregnancies with multiple aneuploidies will result in spontaneous miscarriage.[2,3] However, an estimated 0.16% of trisomy 21 cases involve a double aneuploidy with a sex chromosome (XXX, XXY, XYY, or monosomy X).[4] The associated features are dependent upon the exact chromosomes involved.

What is the prevalence of this condition? Unknown, but very rare. For this reason, positive predictive value (PPV) cannot be calculated.

What testing could be considered?

- Several biological explanations may underlie a multiple aneuploidy result on NIPT. These include, but are not limited to:
  - Multiple aneuploidy in the pregnancy
  - Single aneuploidy in the pregnancy
  - Maternal benign or malignant tumor
  - Maternal aneuploidy or other chromosomal change
- Specialized genetic tests such as karyotyping, fluorescence in situ hybridization (FISH), qPCR and microarray are available to confirm the presence of multiple aneuploidies.
- These confirmatory tests are generally performed on cells from chorionic villus sampling (CVS) or amniocentesis during pregnancy, on cord blood or peripheral blood sample after the baby is born, or on products of conception (POC) in case of a miscarriage. Sometimes, maternal chromosome testing may be needed to confirm maternal aneuploidy or chromosomal change.
- NIPT results of multiple aneuploidies have been linked to occult maternal benign and malignant tumors.[5-9]
- Ultrasound evaluation may be useful in aiding with a prenatal diagnosis of multiple aneuploidies, but a normal ultrasound can not exclude this condition.

The information provided in this sheet is based on literature search performed on 11/28/16. This Information Sheet is intended to provide some general overview of the key issues relating to its subject matter. This sheet is not intended to be an exhaustive discussion of the subject covered by the sheet nor should it be used to substitute for the exercise of a Clinical Laboratory or a Healthcare Provider's legal or professional duties relative to interpreting the test results to which this Information Sheet relates. This sheet is also not intended to serve as a recommendation of management. This sheet is not intended to be a substitute for genetic counseling.

References:

1. American College of Obstetricians and Gynecologists. Screening for fetal aneuploidy. Practice Bulletin No. 163. *Obstet Gynecol.* 2016;127:e123-e137.
2. Reddy KS. Double trisomy in spontaneous abortions. *Hum Genet.* 1997;101:339-345.
3. Subramaniyam S, Pulijaal VR, Mathew S. Double and multiple chromosomal aneuploidies in spontaneous abortions: a single institutional experience. *J Hum Reprod Sci.* 2014;7:262-268.
4. Kovaleva NV, Mutton DE. Epidemiology of double aneuploidies involving chromosome 21 and the sex chromosomes. *Am J Med Genet A.* 205;134A:24-32.
5. Bianchi DW, Chudova D, Sehnert AJ, et al. Noninvasive prenatal testing and incidental detection of occult maternal malignancies. *JAMA.* 2015;314:162-169.
6. Osborne CM, Hardisty E, Devers P, et al. Discordant noninvasive prenatal testing results in a patient subsequently diagnosed with metastatic disease. *Prenat Diagn.* 2013;33:609-611.
7. McCullough RM, Almasri EA, Guan X, et al. Non-invasive prenatal chromosomal aneuploidy testing–clinical experience: 100,000 clinical samples. *PLoS One.* 2014;9:e109173.
8. Amant F, Verheecke M, Wlodarska I, et al. Presymptomatic identification of cancers in pregnant women during noninvasive prenatal testing. *JAMA Oncol.* 2015;1:814-819.
9. Dharajiya NG, Namba A, Horiuchi I, et al. Uterine leiomyoma confounding a noninvasive prenatal test result. *Prenat Diagn.* 2015;35:990-993.

Additional Source:

Snyder H, Curnow KJ, Bhatt S, Bianchi DW. Follow-up of multiple aneuploidies and single monosomies detected by noninvasive prenatal testing: implications for management and counseling. *Prenat Diagn.* 2016;36:203-209.

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