Panorama: the next generation of NIPT
Non-invasive prenatal screen
Panorama improves upon first-generation NIPTs

First-generation NIPTs use a “counting methodology” to assess risk

Laboratories that utilize whole-genome sequencing technologies (referred to in this brochure as WGS-1 and WGS-2) and array-NIPT, examine fragments of conserved DNA sequences – the 99% of our DNA that makes us the same. These labs compare counts of fragments from chromosomes of interest, such as chromosome 21, against a selected reference chromosome, such as chromosome 3.

If the ratio of fragments between the chromosome of interest and the reference chromosome is determined by the lab to be out of proportion, then the lab identifies the result as “high risk.”

By looking at conserved DNA sequences and not distinguishing between maternal and fetal DNA, counting methodologies cannot detect triploidy, vanished twin, maternal mosaicism, and complete molar pregnancies.

Failure to identify these conditions can result in false negatives, false positives, and delayed diagnosis of conditions associated with maternal complications.

Panorama’s SNP-based technology offers greater accuracy than first-generation NIPTs1-11

Panorama provides results with fewer false negatives, fewer false positives, and identification of maternal complications.

*Representation of counting methodology for illustrative purposes
Panorama is the only NIPT that can distinguish between maternal and fetal (placental) DNA

Panorama isolates single nucleotide polymorphisms (SNPs) - the 1% of our DNA that makes us different from one another.

Our technology sequences targeted chromosomal regions of interest and plots SNP patterns from maternal and fetal cell-free DNA. The patterns are evaluated by our proprietary algorithm to determine if the allele patterns indicate increased risk of fetal abnormalities.

Panorama’s SNP-based methodology

By distinguishing between maternal and fetal DNA, Panorama can detect triploidy, vanished twin, and complete molar pregnancies. This distinction also minimizes the chance that maternal mosaicism will lead to an incorrect result.

Compared to first-generation NIPTs, Panorama reduces both false negative rates (FNR) and false positive rates (FPR)¹²,¹₆

Array-NIPT is excluded from the FPR chart because data on monosomy X, a leading contributor to false positives for counting methodologies, is not reported in reviewed literature.⁴

*Representation of a SNP plot for illustrative purposes
Panorama’s SNP-based technology results in the highest validated fetal sex accuracy of any NIPT.\textsuperscript{1-4,8,9,17}

Panorama utilizes a specific sex-chromosome algorithm that compares SNPs from X and Y to determine the presence and copy number of Y.\textsuperscript{1,8}

With first generation NIPTs, as many as 1 in 77 cases may report incorrect gender. A wrong call can lead to unnecessary clinical work-up and create anxiety for the patient.

**Fetal sex error rates: summary of validation studies**

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Error Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panorama Natera</td>
<td>0%</td>
</tr>
<tr>
<td>WGS-1 NPT</td>
<td>0.6%</td>
</tr>
<tr>
<td>WGS-2 NPT</td>
<td>1.3%</td>
</tr>
<tr>
<td>Array-NPT</td>
<td>No data available</td>
</tr>
</tbody>
</table>

**Panorama’s SNP-based approach yields the highest commercially available sensitivity for 22q.**

By evaluating unique DNA sequences within the critical region associated with 22q11.2 deletion syndrome, Panorama has a higher detection rate than counting methodologies. First generation NIPTs count conserved DNA fragments for chromosome 22 and can overlook small deletions, like 22q.

**Panorama leads the field in 22q11.2 screening sensitivity**

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panorama Natera</td>
<td>95.7%</td>
</tr>
<tr>
<td>WGS-1 NPT</td>
<td>0-70%</td>
</tr>
<tr>
<td>WGS-2 NPT</td>
<td>No published data</td>
</tr>
<tr>
<td>Array-NPT</td>
<td>No published data</td>
</tr>
</tbody>
</table>
Accurate fetal fraction measurement is essential to accurate results\(^{21}\)

Panorama is the only NIPT that has always measured and reported fetal fraction.

Panorama’s SNP-based method is a gold standard in fetal fraction measurement

<table>
<thead>
<tr>
<th>Method of fetal fraction measurement</th>
<th>Panorama(^{1,2,3})</th>
<th>Array-NIPT(^{1,2,3})</th>
<th>WGS-1 NIPT(^{5,6,7,24})</th>
<th>WGS-2 NIPT(^{9,10,11})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined false negative rate in validation studies (Trisomies 21, 18, 13)</td>
<td>13,392 SNPs</td>
<td>576 SNPs</td>
<td>Distribution of short (&lt;150 bp) cDNA</td>
<td>No data available on methodology or performance</td>
</tr>
<tr>
<td></td>
<td>0.00%</td>
<td>1.33%</td>
<td>1.86%</td>
<td>2.40%</td>
</tr>
</tbody>
</table>

Counting methodologies’ ability to detect abnormalities drops off below 8% fetal fraction, which can produce false negative results\(^{25,26}\)

Deeper sequencing on chromosomal regions of interest enables Panorama to maintain high-quality results at lower fetal fractions

Panorama’s proprietary algorithm incorporates fetal fraction measurement and reflexes samples with lower fetal fraction to a higher depth of read.
Are you offering Panorama to women of all ages?

NIPT is strongly supported by guidelines

The American Congress of Obstetricians and Gynecologists (ACOG), as well as the American College of Medical Genetics and Genomics (ACMG), among other societies, now acknowledges the use of NIPT for all singleton pregnancies, regardless of age or risk.26,30

Panorama is the only NIPT validated in high- and low-risk patients

<table>
<thead>
<tr>
<th>Validation T21, T18, T13, and MX²</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk: Sensitivity: 98.0%</td>
</tr>
<tr>
<td>Specificity: 99.5%</td>
</tr>
<tr>
<td>Low-risk: Sensitivity: 100%</td>
</tr>
<tr>
<td>Specificity: 100%</td>
</tr>
</tbody>
</table>

Professional societies recognize NIPT as a first-line screening option

**ACMG**

“Informing all pregnant women that NIPT is the most sensitive screening option”

ACMG Position Statement, July 2016

**ACOG/SMFM Practice Bulletin #163, May 2016**

“Data on the performance of cell-free DNA testing in the general obstetric population are now available (and)... similar to the levels previously published for the high-risk population.”

**ASHG**

“Different scenarios... are possible, including NIPT as an alternative first-tier option.

ASHG policy, March 2015

**ispd**

“The following protocol is currently considered appropriate; cfDNA screening as a primary test offered to all pregnant women.”

Position statement from the Chromosome Abnormality Screening Committee, June 2015
Panorama helps clinicians triage twin pregnancies effectively\(^2\)-\(^7\)

While choriocity can be reliably detected early in a pregnancy, studies have shown that up to 19% of monochorionic pregnancies are incorrectly classified as dichorionic.\(^6\)

Panorama allows clinicians to align their ultrasound findings with an early and accurate zygosity determination.

Identifying a monozygotic twin pregnancy with Panorama can prompt earlier, targeted ultrasound assessments for choriocity and associated complications. Knowing that a twin pregnancy is dizygotic reduces concerns about TTTS.

References
Patient Information
Patient Name: Jane Doe
Date of Birth: 11/08/1975
Maternal Age at EDD: 37
Gestational Age: 11 weeks/0 days
Maternal Weight: N/A
Patient ID: P94557
Medical Record #: M84555
Collection Kit: 254233-2-N
Accessioning ID: C47695
CaseFile ID: 159466

Test Information
Ordering Physician: Dr. Matthew Goodbirth, M.D. (G123456)
Clinic Information: Natera, Inc.
Additional Reports: N/A
Report Date: 02/01/2013
Samples Collected: 01/31/2013
Samples Received: 02/01/2013
Mother Blood

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: TWINS
Zygosity: Dizygotic
Fetal Sex: Male, Female
Fetal Fraction(s): 8.3%, 8.4%

This is a screening test only. Genetic counseling and diagnostic testing for both fetuses should be offered to further evaluate these findings.

Panorama analyzes DNA from the placenta. In some cases placental DNA can differ from that of the fetus. Therefore, even with high risk results, the fetuses may be unaffected.

RESULT DETAILS: Aneuploidies

<table>
<thead>
<tr>
<th>Condition tested</th>
<th>Result</th>
<th>Risk BeforeTest</th>
<th>Risk AfterTest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>High Risk</td>
<td>1/152</td>
<td>7/10</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>Low Risk</td>
<td>1/111</td>
<td>&lt;1/10,000</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>Low Risk</td>
<td>1/357</td>
<td>&lt;1/10,000</td>
</tr>
</tbody>
</table>

1. Reporting for Monosomy X, Trisomy, and microdeletion syndromes is not available for dizygotic twin pregnancies. Excludes cases with evidence of fetal and/or placental mosaicism. 2. Based on maternal age, gestational age, and/or general population, as applicable. Reference values are subject to refinement. 3. Risk after test for aneuploidy incorporates results from the Panorama algorithm as well as analytical PPV (high risk) and NVP (low risk). Maternal age is utilized in this calculation; however, the "risk after test" may not reflect the actual PPV for the patient, as additional risk factors, including but not limited to results of other screening ultrasound findings, personal/family history, are not included in the risk assessment.

Approved By: [Signature]

Susan Zinser, Ph.D., FACMG Laboratory Director

If the ordering provider has questions or wishes to discuss the results, please contact us at 855-249-6000. Ask for the NPT genetic counselor on call.
**FINAL RESULTS SUMMARY**

Result: **HIGH RISK for Angelman syndrome**

- **Fetal Sex:** Male
- **Fetal Fraction:** 8.3%

This is a screening test only. Genetic counseling and diagnostic testing, either by microarray and UPD testing for both iso- and heterodisomy, or by methylation testing, should be offered to further evaluate these findings.

Panorama analyzes DNA from the placenta. In some cases placental DNA can differ from that of the fetus. Therefore, even with high risk results, the fetus may be unaffected.

**RESULT DETAILS: ANEUPLOIDIES**

<table>
<thead>
<tr>
<th>Condition tested</th>
<th>Result</th>
<th>Risk Before Test</th>
<th>Risk After Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>Low Risk</td>
<td>1/152</td>
<td>&lt;1/1,000</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>Low Risk</td>
<td>1/364</td>
<td>&lt;1/1,000</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>Low Risk</td>
<td>1/1,116</td>
<td>&lt;1/1,000</td>
</tr>
<tr>
<td>Monosomy X</td>
<td>Low Risk</td>
<td>1/255</td>
<td>&lt;1/1,000</td>
</tr>
<tr>
<td>Triploidy</td>
<td>Low Risk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RESULT DETAILS: MICRODELETIONS**

<table>
<thead>
<tr>
<th>Condition tested</th>
<th>Result</th>
<th>Risk Before Test</th>
<th>Risk After Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>22q11.2 deletion syndrome</td>
<td>Low Risk</td>
<td>1/2,000</td>
<td>1/9,000</td>
</tr>
<tr>
<td>1p36 deletion syndrome</td>
<td>Low Risk</td>
<td>1/5,000</td>
<td>1/12,400</td>
</tr>
<tr>
<td>Angelman syndrome</td>
<td>High Risk</td>
<td>1/12,000</td>
<td>1/10</td>
</tr>
<tr>
<td>Cri-du-chat syndrome</td>
<td>Low Risk</td>
<td>1/20,000</td>
<td>1/57,100</td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
<td>Risk Unchanged</td>
<td>1/10,000</td>
<td>1/10,000</td>
</tr>
</tbody>
</table>

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 for aneuploidy incorporates results from the Panorama algorithm and data from a published study of 17,886 women [Das et al. Am J Obstet Gynecol. 2014, Nov27(15):527.e1-27.e17] and are reported as PPV (high risk) and NPV (low risk). Maternal age is utilized in this calculation, however the “risk after test” may not reflect the actual PPV for this patient, as additional risk factors, including but not limited to results of other screening, ultrasound findings, personal/family history, are not included in the risk assessment. Risk after test for microdeletions incorporates results from the Panorama algorithm and data from published studies [Martin et al. Clin Genetics. 2017 Jul 11, Wapner R J et al. Am J Obstet Gynecol. 2015 Mar;212 (3):322.e1-8] and are reported as PPV (high risk) and NPV (low risk). Risk for microdeletions is independent of maternal age. Fetal fraction (FF) is utilized in this calculation. Depending upon FF, in some cases only the paternal allele is evaluated (see page 2). The “risk after test” may not reflect the actual PPV for this patient, as additional risk factors, including but not limited to results of other screening, ultrasound findings, personal/family history, are not included in the risk assessment.
FINAL RESULTS SUMMARY

Result: LOW RISK  
Fetal Sex: Female  
Fetal Fraction: 23.65%

RESULT DETAILS: ANEUPLOIDIES

<table>
<thead>
<tr>
<th>Condition tested</th>
<th>Result</th>
<th>Risk Before Test</th>
<th>Risk After Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>Low Risk</td>
<td>1/125</td>
<td>&lt;1/10,000</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>Low Risk</td>
<td>1/330</td>
<td>&lt;1/10,000</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>Low Risk</td>
<td>1/1029</td>
<td>&lt;1/10,000</td>
</tr>
<tr>
<td>Monosomy X</td>
<td>Low Risk</td>
<td>1/568</td>
<td>&lt;1/10,000</td>
</tr>
<tr>
<td>Triploidy</td>
<td>Low Risk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Excludes cases with evidence of fetal and/or placental mosaicism.  
2. Based on maternal age, gestational age, and/or genetic population, as applicable. References available upon request.  
3. Risk after test for aneuploidy incorporates results from the Panorama algorithm and data from a published study of 17,885 women. [Zheng et al. Am J Obstet Gynecol 2014 Nov;211(S2):S27-A127-e17] and are reported as PPV (high risk) and NVP (low risk). Maternal age is utilized in this calculation, however the “risk after test” may not reflect the actual PPV for this patient, as additional risk factors, including but not limited to, results of other screenings, ultrasound findings, personal/family history, are not included in the risk assessment.

Under collaboration between Mahidol University and Bangkok Cytogenetics Center Limited.

Patient Information
Patient Name:  
Date of Birth:  
Maternal Age at EDD: 39  
Gestational Age: 13 weeks/2 days  
Maternal Weight: 38.6 Kgs  
Patient ID:  
Medical Record #: N/A  
Collection Kit: 5979155-2-N  
Reference ID: N/A  
Accessioning ID:  
Case File ID:  

Test Information
Ordering Physician:  
Hospital/Clinic:  
Additional Reports: N/A  
Report Date: 13 Nov 2018  
Samples Collected: 05 Nov 2018  
Samples Received: 07 Nov 2018  
Mother Blood

Case File ID: 181107_0005

Liquid Box
Bangkok Cytogenetics Center Co., Ltd.
65/18 Soi Vibhavadi-Rangsit 16/6, Vibhavadi-Rangsit Road, Khet Chatuchak, Bangkok 10900 Thailand
Tel: 02-690-0063, 086-306-2084, www.bccgroup-thailand.com, Email: info@bccgroup-thailand.com

Analyzed By: Rachawal
Rachawalan Suriyasaengsri, B.Sc.
Scientist

Approved By: N. Porn
Narat Pornyongvarin, M.D., Ph.D.
Head of Clinical Molecular Pathology Laboratory

IF THE ORDERING PROVIDER HAS QUESTIONS OR WISHES TO DISCUSS THE RESULTS, PLEASE CONTACT US AT 02-690-0063, 086-306-2084 OR SEND US AN INQUIRY TO INFO@BCCGROUP-THAILAND.COM
<table>
<thead>
<tr>
<th>Condition</th>
<th>Test Method</th>
<th>Sample Requirement</th>
<th>Turn Around Time</th>
<th>Minimum Gestation Age</th>
<th>Abnormality Detection</th>
<th>Feasible Location</th>
<th>Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal Sex Determination by Fetal Cell Analysis</td>
<td>Panorama Plus Microdeletions Panel (Thailand / USA)</td>
<td>6-20 ml in heparinized tubes</td>
<td>10-14 working days</td>
<td>9 weeks (recommendation 12 weeks)</td>
<td>1. Anomaly of chromosome 13, 18, 21, X, Y</td>
<td>Thailand, Surat Thani Hospital / USA, Nara, California</td>
<td>Cytoagnostics Bangkok</td>
</tr>
<tr>
<td>Twin Pregnancy</td>
<td>Panorama Plus 22q11.2 Panel (Thailand / USA)</td>
<td></td>
<td></td>
<td></td>
<td>2. Triploidy 18, 21, X, Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Panorama Plus Prenatal Basic Panel (Thailand / USA)</td>
<td></td>
<td></td>
<td></td>
<td>3. 22q11.2 deletion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
References

28. Internal data, Natera.

CAP accredited and CLIA-certified, ISO 13485.

CAUTION: The test restricts these tests/products to sale by or on the order of a physician. Indications, contraindications, warnings and instructions for use can be found in the Test/Product labeling supplied with each test/product. Information for use only in countries with applicable health authority test/product registrations.

CAUTION: The Panorama™ test may be sold only by or on the order of a physician. Not for distribution in the United States.

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