Non-Invasive Prenatal Screening
and
Other Screening

Dr Jay Marlow
Obstetrician and
Maternal Fetal Medicine
Sub-Specialist
Choice

- Nothing
- Combined Screening
- NIPT

COMBINED FIRST TRIMESTER SCREEN
Maternal Risk of T21 increase with age

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Risk for trisomy 21 At Birth</th>
<th>At 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1 in 1527</td>
<td>1 in 898</td>
</tr>
<tr>
<td>25</td>
<td>1 in 1352</td>
<td>1 in 795</td>
</tr>
<tr>
<td>30</td>
<td>1 in 895</td>
<td>1 in 526</td>
</tr>
<tr>
<td>32</td>
<td>1 in 659</td>
<td>1 in 388</td>
</tr>
<tr>
<td>34</td>
<td>1 in 446</td>
<td>1 in 262</td>
</tr>
<tr>
<td>36</td>
<td>1 in 280</td>
<td>1 in 165</td>
</tr>
<tr>
<td>38</td>
<td>1 in 167</td>
<td>1 in 98</td>
</tr>
<tr>
<td>40</td>
<td><strong>1 in 97</strong></td>
<td>1 in 57</td>
</tr>
<tr>
<td>42</td>
<td>1 in 55</td>
<td>1 in 32</td>
</tr>
<tr>
<td>44</td>
<td>1 in 30</td>
<td>1 in 18</td>
</tr>
</tbody>
</table>
Aneuploidy Screening Approach: Observed Detection Rates

Detection Rate (%)

- Age ≥ 35
- Triple
- Quadruple
- Combined
- cffDNA

CFTS

• Maternal bloods
  – From 10 weeks
  – PAPP-A
  – Free HCG

• Nuchal translucency
  – 11-13+6 weeks

• Combined
  – DR of 91-92%
  – FPR 5%

• However NSU
  – DR 72-75%
Nuchal Translucency

• Subcutaneous fluid-filled space located between back of fetal neck and skin

• Measured on USS between 11-13+6 weeks
  • measurement is not valid outside of this time period

• NT increases with gestational age
NT Standard (FMF)

- CRL 45 – 84mm
- Midline- Sagittal plane
- Mid sag face echogenic tip of nose
- Neutral position
  - not extended or flexed
- Away from amnion
- Head and thorax occupy >1/3 of the image
- Widest part of translucency measured
  - “on-to-on technique”
Nuchal Translucency

- Between 11-13+6 weeks >3.5mm considered elevated
  - Diagnostic testing indicated
  - Tertiary anatomy scan at 18-20 weeks
  - Fetal screening echocardiogram indicated ~24 weeks

- Increased NT thickness is associated with:
  - Trisomies 21, 18, 13, triploidy and Turner syndrome
  - Spontaneous fetal loss
  - With normal chromosomes:
    - cardiac defects, diaphragmatic hernia, pulmonary defects, skeletal dysplasias
    - congenital infection
    - metabolic/haem disorders
    - rare single gene disorders

Souka et al. Ultrasound Obstet Gynecol 2001;18:9
<table>
<thead>
<tr>
<th>Nuchal Translucency (mm)</th>
<th>Chromosomal abnormality (%)</th>
<th>Normal Karotype group</th>
<th>Alive and well given original NT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fetal Death (%)</td>
<td>Major Anomaly (%)</td>
</tr>
<tr>
<td>3.5-4.4</td>
<td>21.1</td>
<td>2.7</td>
<td>10</td>
</tr>
<tr>
<td>4.5-5.4</td>
<td>33.3</td>
<td>3.4</td>
<td>18.5</td>
</tr>
<tr>
<td>5.5-6.4</td>
<td>50.5</td>
<td>10.1</td>
<td>24.2</td>
</tr>
<tr>
<td>&gt;6.5</td>
<td>64.5</td>
<td>19</td>
<td>46.2</td>
</tr>
</tbody>
</table>

Chance of a normal birth varies with size of NT measurement.
WHY IS OUR DETECTION RATE SO LOW?
Standard View

Nasal Bone
Case
Nuchal Comparison
Case
Nasal Bone Comparison
Why is our detection rate so low?

- Incorrect maternal data
- Lack of certification/quality control for nuchal
- Erroneous reporting of the nasal bone
- Self reported postnatal diagnosis of T21.
SNP-based NIPT

Non-Invasive Prenatal Testing
What’s in a name?

- NIPTest
- NIPScreen
- Down Syndrome blood test

SCREENING TEST
What is NIPT?

• Screening test to prenatally detect
  – Down syndrome
  – other aneuploidies (extra or missing chromosomes)
    • trisomy 21, 18, 13
    • trisomy of sex chromosomes (XXX, XXY, XYY)
    • Turner syndrome (monosomy X)
    • triploidy (extra copy of all chromosomes)
  – Microdeletions
  – Chorionicity in twins
NIPT

• Measures circulating cell-free DNA (cfDNA) from placenta present in maternal blood

• ~10% of DNA in maternal blood
  – Increases with gestational age

• As early as 9-10 weeks gestation
  – (company specific)

• Dating U/S –
  – viability, accurate GA, exclude multiples

cfDNA comes from apoptotic cells derived from:
  Maternal Circulation
  • Adipocytes
  • White Blood Cells
  • Fetal
    • Placental cells (trophoblasts) in the maternal circulation
The Evolution of NIPT

2011
1st generation: Quantitative or “Counting”

2012
2nd generation: Qualitative or “SNP-based”

2013
Other labs enter domestic NIPT space using 1st generation counting technologies

2014-2017
## NIPT Methodologies

<table>
<thead>
<tr>
<th>Counting</th>
<th>SNP</th>
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<tbody>
<tr>
<td>harmony™</td>
<td>panorama®</td>
</tr>
<tr>
<td>MaterniT21™ Plus</td>
<td>natera prenatal screen</td>
</tr>
<tr>
<td>Counsyl</td>
<td></td>
</tr>
<tr>
<td>informaSeq™</td>
<td></td>
</tr>
<tr>
<td>verifi™ prenatal test</td>
<td></td>
</tr>
<tr>
<td>BambniTest®</td>
<td></td>
</tr>
<tr>
<td>NIFT®</td>
<td></td>
</tr>
<tr>
<td>QNatal® Advanced NIPS</td>
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SNP-based NIPT

Whole chromosome conditions
- Trisomy 21, 18, 13
- Monosomy X
- Sex chromosome trisomies
- Triploidy
- Complete molar pregnancy

Optional
- 22q11.2 deletion syndrome
- Additional microdeletions
- Fetal sex
Counting

Chromosome 21

Chromosome 3
Counting

Chromosome 21

Expected Amount: 20%
Observed Amount: 25%

Chromosome 3

Expected Amount: 80%
Observed Amount: 75%
SNP = Single Nucleotide Polymorphism

- A DNA sequence variation occurring when a single base pair is changed
- Normal genetic changes that occur in every person
- SNP-based NIPT analyzes more than 13,000 SNPs
SNP-based NIPT Technology

Proprietary SNP analysis distinguishes between maternal & fetal DNA
Clinical Advantages of SNP-based NIPT

Uniquely differentiates between maternal and fetal DNA

- Fetal fraction
- Maternal contribution
- Vanishing twins
- Fetal sex accuracy
- Triploidy/complete mole
SNP-based Aneuploidy Screening for Twins
Benefits of NIPT

• Fewer women having diagnostic tests
  – *associated risk of pregnancy loss*

• Early test result *(drawn at ≥ 9-10 weeks at earliest)*

• No risk of miscarriage

• Detects the most common chromosomal aneuploidies

• Higher detection rates and lower false positive rates than CFTS
What can go wrong with NIPT?

- Unusual result
- Not a true result
- Only detects those conditions it tests for
False negative/positive

• Check with invasive testing if you are going to act on the result
Do I still need a nuchal scan?

- Yes.....Early anatomy scan
What if an anomaly occurs later?

• False negative
• Another anomaly
• A non-genetic syndrome
How do I counsel?
Results
**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: P9057
- Medical Record #: M64555
- Collection Kit #: 123223-2-N
- Reference ID: 234223-2-N
- Accessioning ID: CA1695
- Case File ID: 139466

**Test Information**
- Ordering Physician: Dr. Matthew Goodbirth, M.D. (G123456)
- Natera, Inc.
- N/A
- 02/01/2013
- 02/01/2013
- Mother Blood

**FINAL RESULTS SUMMARY**
- **Result:** LOW RISK
- **Fetal Sex:** Male
- **Fetal Fraction:** 8.3%

**Notes by the clinical reviewer, if any, will be shown here.**

**RESULTS DETAILS: ANEUPLOIDIES**

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<th>Risk Before Test</th>
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<td>1/111</td>
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<tr>
<td>Trisomy 13</td>
<td>Low Risk</td>
<td>1/357</td>
<td>&lt;1/10,000</td>
</tr>
<tr>
<td>Monosomy X</td>
<td>Low Risk</td>
<td>1/256</td>
<td>&lt;1/10,000</td>
</tr>
<tr>
<td>Triploidy</td>
<td>Low Risk</td>
<td></td>
<td></td>
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</table>

*1. Positive results with evidence of fetal and maternal samples. 2. Based on maternal age, pathological age, and/or maternal population, as applicable. Reference available upon request. 3. Results are obtained using a combination of genetic analysis of the fetal DNA.*
**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: P99457
- Medical Record #: M8455
- Collection Kit: 123233-2-N
- Reference ID: 254233-2-N
- Accessioning ID: C47695
- Case File 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

**FINAL RESULTS SUMMARY**
- Result: LOW RISK
- Fetal Sex: Male
- Fetal Fraction: 8.3%

**Notes by the clinical reviewer, if any, will be shown here.**

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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. Based on a priori risk and results of analysis of circulating placental DNA.
### Overall Test Specifications for Panorama

The Panorama risk score shown on page 1 reflects the confidence of the algorithm for the result reported for an individual sample. The information in the table below relates to the general performance of the test.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>&gt;99% (97.8-99.9)</td>
<td>&gt;99% (97.9-100)</td>
<td>91%</td>
<td>&gt;99.99%</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>98.2% (90.4-99.9)</td>
<td>&gt;99% (97.9-100)</td>
<td>93%</td>
<td>&gt;99.99%</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>&gt;99% (87.2-100)</td>
<td>&gt;99% (98.9-100)</td>
<td>38%</td>
<td>&gt;99.99%</td>
</tr>
<tr>
<td>Monosomy X</td>
<td>94.7% (74.0-99.9)</td>
<td>&gt;99% (97.7-100)</td>
<td>50%</td>
<td>&gt;99.99%</td>
</tr>
<tr>
<td>Trisomy Y</td>
<td>&gt;99% (66.4-100)</td>
<td>&gt;99% (91.9-100)</td>
<td>5.3%</td>
<td>&gt;99.99%</td>
</tr>
<tr>
<td>XXX, XXY, XYY</td>
<td>N/A-reported when identified</td>
<td>N/A-reported when identified</td>
<td>89%</td>
<td>N/A-reported when identified</td>
</tr>
<tr>
<td>22q11.2 deletion syndrome</td>
<td>95.7% (85.5-99.5)</td>
<td>&gt;99% (96.5-99.9)</td>
<td>20%**</td>
<td>99.97-99.99**</td>
</tr>
<tr>
<td>1p36 deletion syndrome</td>
<td>&gt;99% (2.5-100)</td>
<td>&gt;99% (91.1-100)</td>
<td>7.2%**</td>
<td>99.96-99.99**</td>
</tr>
<tr>
<td>Angelman syndrome</td>
<td>95.5% (77.2-99.9)</td>
<td>&gt;99% (99.1-100)</td>
<td>4%</td>
<td>99.99%</td>
</tr>
<tr>
<td>Cri-du-chat syndrome</td>
<td>&gt;99% (85.9-100)</td>
<td>&gt;99% (99.1-100)</td>
<td>2.2%**</td>
<td>99.99%</td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
<td>93.8% (69.8-99.8)</td>
<td>&gt;99% (91.1-100)</td>
<td>3%</td>
<td>99.99%</td>
</tr>
</tbody>
</table>

Female: >99.9% (99.4-100) Male: >99.9% (99.5-100)
OVERALL TEST SPECIFICATIONS FOR PANORAMA

The Panorama risk score shown on page 1 reflects the confidence of the algorithm for the result reported for an individual sample.

The information in the table below relates to the general performance of the test.

**Sensitivity** is the ability to correctly identify a truly high risk case as high risk. For example, in a group of Trisomy 21 cases, Panorama will correctly identify more than 99% of those cases.

**Specificity** is the ability to correctly identify an unaffected case as low risk.

**Positive Predictive Value** is the likelihood the result says high-risk and the fetus is actually affected. For example, when Panorama shows a high-risk result for Trisomy 21, there is a 91% chance that the fetus is affected by Trisomy 21. In other words, 9% of the time, you may get a high-risk result when the fetus is not affected by Trisomy 21.

**Negative Predictive Value** is the likelihood the result says low-risk and the fetus is truly not affected.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21&lt;sup&gt;1,2,3,4&lt;/sup&gt;</td>
<td>&gt;99% (CI 97.8-99.9)</td>
<td>&gt;99% (CI 99.7-100)</td>
<td>91%</td>
<td>&gt;99.99*</td>
</tr>
<tr>
<td>Trisomy 18&lt;sup&gt;1,2,3,4&lt;/sup&gt;</td>
<td>98.2% (CI 90.4-99.9)</td>
<td>&gt;99% (CI 99.7-100)</td>
<td>93%</td>
<td>&gt;99.99*</td>
</tr>
<tr>
<td>Trisomy 13&lt;sup&gt;1,2,3,4&lt;/sup&gt;</td>
<td>&gt;99% (CI 87.2-100)</td>
<td>&gt;99% (CI 99.8-100)</td>
<td>38%</td>
<td>&gt;99.99*</td>
</tr>
<tr>
<td>Monosomy X&lt;sup&gt;1,2,3,4&lt;/sup&gt;</td>
<td>94.7% (CI 74.0-99.9)</td>
<td>&gt;99% (CI 99.7-100)</td>
<td>50%</td>
<td>&gt;99.99*</td>
</tr>
<tr>
<td>Triploidy&lt;sup&gt;7,8&lt;/sup&gt;</td>
<td>&gt;99% (CI 66.4-100)</td>
<td>&gt;99% (CI 99.5-100)</td>
<td>5.3%</td>
<td>&gt;99.99*</td>
</tr>
<tr>
<td>XXX, XXXY, XXXY&lt;sup&gt;4&lt;/sup&gt;</td>
<td>N/A-Reported when identified</td>
<td>N/A-Reported when identified</td>
<td>89%</td>
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<td>22q11.2 deletion syndrome&lt;sup&gt;7,8,9&lt;/sup&gt;</td>
<td>95.7% (CI 85.5-99.5)</td>
<td>&gt;99% (CI 98.6-99.9)</td>
<td>20%**</td>
<td>99.97-99.99***</td>
</tr>
<tr>
<td>1p36 deletion syndrome&lt;sup&gt;7,8&lt;/sup&gt;</td>
<td>&gt;99% (CI 2.5-100)</td>
<td>&gt;99% (CI 99.1-100)</td>
<td>7-17%***</td>
<td>99.98-99.99***</td>
</tr>
<tr>
<td>Angelman syndrome&lt;sup&gt;7,8&lt;/sup&gt;</td>
<td>95.5% (CI 77.2-99.9)</td>
<td>&gt;99% (CI 99.1-100)</td>
<td>4%</td>
<td>&gt;99.99</td>
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<td>Cri-du-chat syndrome&lt;sup&gt;7,8&lt;/sup&gt;</td>
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<td>&gt;99.99</td>
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<td>Prader-Willi syndrome&lt;sup&gt;7,8&lt;/sup&gt;</td>
<td>93.8% (CI 69.8-99.8)</td>
<td>&gt;99% (CI 99.1-100)</td>
<td>5%</td>
<td>&gt;99.99</td>
</tr>
</tbody>
</table>

Female  | >99.9% (CI 99.4-100) | >99.9% (CI 99.5-100) | >99.9% (CI 99.4-100) |

Male    | >99.9% (CI 99.5-100) | >99.9% (CI 99.4-100) | >99.9% (CI 99.4-100) |

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* Ongoing clinical follow-up is performed to ensure the NPV does not fall below the quoted value but follow up is not obtained for all low risk calls.

** PPV for 22q11.2 deletion syndrome in published studies was 20% when no ultrasound anomalies were seen and was up to 100% when ultrasound anomalies were seen prior to testing.

*** Dependent upon fetal factors, see Panorama Risk score on report for accurate PPV/NPV for a specific patient.

For additional information, please visit: [www.natera.com/panorama-test/test-specs](http://www.natera.com/panorama-test/test-specs)
**Sensitivity** is the ability to correctly identify a truly high risk case as high risk. For example, in a group of Trisomy 21 cases, Panorama will correctly identify more than 99% of those cases.

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**Positive Predictive Value** is the likelihood the result says high-risk and the fetus is actually affected. For example, when Panorama shows a high-risk result for Trisomy 21, there is a 91% chance that the fetus is affected by Trisomy 21. In other words, 9% of the time, you may get a high-risk result when the fetus is not affected by Trisomy 21.

**Negative Predictive Value** is the likelihood the result says low-risk and the fetus is truly not affected.
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- Maternal Weight: N/A
- Patient ID: P99457
- Medical Record #: M84555
- Collection Kit: 254233-2-N
- Accessioning ID: C47695
- Case File ID: 159466

Test Information
- Ordering Physician: Dr. Matthew Goodbirth, M.D. (123456)
- Clinic Information: N/A
- Additional Reports: Report Date: 02/01/2013
- Samples Collected: 01/31/2013
- Samples Received: 02/01/2013

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.

TEST SELECTED: Sex of Fetus

FINAL RESULTS SUMMARY

<table>
<thead>
<tr>
<th>Result</th>
<th>Fetal Sex</th>
<th>Fetal Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH RISK for Trisomy 21</td>
<td>Male</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

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

The Panorama risk score reflects analysis of DNA from the placenta. The placental DNA may not accurately reflect the status of the fetus; therefore, no irreversible decisions should be made based upon results of this screening test alone.

RESULTS DETAILS: ANEUPLOIDIES

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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. Based on a priori risk and results of analysis of circulating placental DNA.

POSITIVE PREDICTIVE VALUES (PPV)

Positive Predictive Value (PPV) is the likelihood that diagnostic testing will confirm a High Risk result. PPV provided is NOT personalized for this patient, but calculated from a published study of 17,885 women. PPV for an individual specimen will vary based on prior risk.

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</tr>
<tr>
<td>Trisomy 13</td>
<td>38%</td>
</tr>
<tr>
<td>Monosomy X</td>
<td>50%</td>
</tr>
</tbody>
</table>
Perinatology.com

NIPT/Cell Free DNA Screening
Predictive Value Calculator

Overview  PPV Calculator  NPV Calculator  Definitions  FAQs  Resources  References

Please select the chromosome condition and maternal age at the time of EDD. Alternatively, you can enter Prevalence directly.

Chromosome condition  Maternal age at EDD or Enter Prevalence Directly

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Use of this site constitutes acceptance of the terms of use.
Please select the chromosome condition and maternal age at the time of EDD. Alternatively you choose to enter Prevalence directly.

**Trisomy 21**

The estimated prevalence of Trisomy 21 at 16 weeks gestation for women who are 37 at EDD is 1 in 186. Where does this number come from? See the FAQs from the menu above for details.

**Sensitivity:**
99.2

**Specificity:**
99.91

The default performance metrics for Trisomy 21 are set at a sensitivity of 99.2 and specificity of 99.91 based on the weighted and pooled data from a meta-analysis by Gil et al (2015). The user may wish to change these inputs to reflect the performance statistics provided by the referral laboratory.

[Calculate] [Clear]
The prevalence of Trisomy 21 at 16 weeks gestation for a woman who is 37 at EDD is 1 in 186.

The probability that the result is a true positive (the fetus is affected). PPV: 86%

Probability that it is a false positive (the fetus is not affected): 14%

PPV (not rounded): 85.62795719896401%
PPV = (sensitivity x prevalence) / ((sensitivity x prevalence) + (1 – specificity)(1 – prevalence))
PPV = (0.992 x 0.005376344066021506) / ((0.992 x 0.005376344066021506) + (1 – 0.9991)(1 – 0.005376344066021506))

Please note: the post-test probability for an individual patient may differ based on other factors that influence her unique prior risk to have an affected pregnancy, such as gestational age of the patient, ultrasound findings and biochemical screening.
The prevalence of Trisomy 21 at 16 weeks gestation for a woman who is 20 at EDD is 1 in 1177.

The probability that result is a true positive (the fetus is affected). PPV: 48%

Probability that it is a false positive (the fetus is not affected). 52%

PPV (not rounded): 48.38080374561029%

\[ PPV = \frac{\text{sensitivity} \times \text{prevalence}}{\text{sensitivity} \times \text{prevalence} + (1 - \text{specificity})(1 - \text{prevalence})} \]

Please note: the post-test probability for an individual patient may differ based on other factors that influence her unique prior risk to have an affected pregnancy, such as gestational age of the patient, ultrasound findings and biochemical screening.
The prevalence of Trisomy 21 at 16 weeks gestation for a woman who is 44 at EDD is 1 in 28.

The probability that result is a true positive (the fetus is affected). PPV: 98%

Probability that it is a false positive (the fetus is not affected): 2%

PPV (not rounded): 97.60397372822981%

PPV = (sensitivity x prevalence) / ((sensitivity x prevalence) + (1 – specificity)(1 – prevalence))
PPV = (0.992 x 0.03571428571428571) / ((0.992 x 0.03571428571428571 + (1 – 0.9991)(1 – 0.03571428571428571))

Please note: the post-test probability for an individual patient may differ based on other factors that influence her unique prior risk to have an affected pregnancy, such as gestational age of the patient, ultrasound findings and biochemical screening.
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: P99457
Medical Record #: M94553
Collection Kit: 254233-2-N
Accessioning ID: C47695
Case File ID: 139466

Test Information
Ordering Physician: Dr. Matthew Goodbirth, M.D. (G123456)
Clinic Information: Natera, Inc.
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.

TEST SELECTED: Sex of Fetus, 22q11.2 Deletion

FINAL RESULTS SUMMARY
Result
HIGH RISK for Trisomy 13

Fetal Sex
Male

Fetal Fraction
8.3%

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

The Panorama risk score reflects analysis of DNA from the placenta. The placental DNA may not accurately reflect the status of the fetus; therefore, no irreversible decisions should be made based upon results of this screening test alone.

RESULTS DETAILS: ANEUPLOIDIES

<table>
<thead>
<tr>
<th>Condition tested</th>
<th>Result</th>
<th>Risk Before Test^2</th>
<th>Panorama Risk Score^3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>Low Risk</td>
<td>1/152</td>
<td>&lt;1/10,000</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>High Risk</td>
<td>1/357</td>
<td>&gt;99/100</td>
</tr>
<tr>
<td>Monosomy X</td>
<td>Low Risk</td>
<td>1/256</td>
<td>&lt;1/10,000</td>
</tr>
<tr>
<td>Triploidy</td>
<td>Low Risk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RESULTS DETAILS: MICRODELETIONS

<table>
<thead>
<tr>
<th>Condition tested</th>
<th>Result</th>
<th>Risk Before Test^2</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>1/13,300</td>
</tr>
</tbody>
</table>

POSITIVE PREDICTIVE VALUES (PPV)

Positive Predictive Value (PPV) is the likelihood that diagnostic testing will confirm a High Risk result. PPV provided is NOT personalized for this patient, but calculated from a published study of 17,883 women. PPV for an individual specimen will vary based on prior risk.

<table>
<thead>
<tr>
<th>Condition tested</th>
<th>PPV</th>
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</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
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</tbody>
</table>
Please select the chromosome condition and maternal age at the time of EDD. Alternatively you choose to enter Prevalence directly.

Trisomy 13 37

The estimated prevalence of Trisomy 13 at 16 weeks gestation for women who are 37 at EDD is 1 in 1575. Where does this number come from? See the FAQs from the menu above for details.

Sensitivity: 91

Specificity: 99.87

The default performance metrics for Trisomy 13 are set at a sensitivity of 91 and specificity of 99.87 based on the weighted and pooled data from a meta-analysis by Gil et al (2015). The user may wish to change these inputs to reflect the performance statistics provided by the referral laboratory.

Calculate Clear
The prevalence of Trisomy 13 at 16 weeks gestation for a woman who is 37 at EDD is 1 in 1575.

The probability that result is a true positive (the fetus is affected). PPV: 31%

Probability that it is a false positive (the fetus is not affected): 69%

PPV (not rounded): 30.732761653474583%
PPV = (sensitivity x prevalence) / ((sensitivity x prevalence) + (1 – specificity)(1 – prevalence))
PPV = (0.91 x 0.0006349206349206349) / ((0.91 x 0.0006349206349206349) + (1 – 0.9877)(1 – 0.0006349206349206349))

Please note: the post-test probability for an individual patient may differ based on other factors that influence her unique prior risk to have an affected pregnancy, such as gestational age of the patient, ultrasound findings and biochemical screening.
Questions???