Non-Invasive Prenatal Testing

Cell-free DNA

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Prenatal Screening

1960s	1980s	1988	1996	1997	2011 – Present	
Maternal Age	**MSAFP**	**Triple Screen**	**Quad Screen**	**FTS NT/Serum**	**NIPT Quantitative**	**NIPT SNP**
27%	36%	60–74%	70–81%	80–95%	66–>99%	92–>99%
All	T21	T21 T18	T21 T18	T21 T18 T13	T21 T18 T13 SCA	T21 T18 T13 SCA Triploidy Microdeletions

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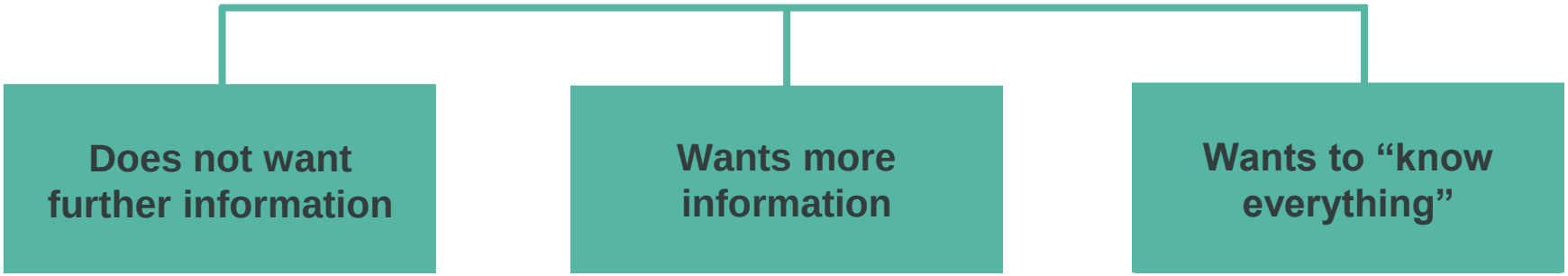
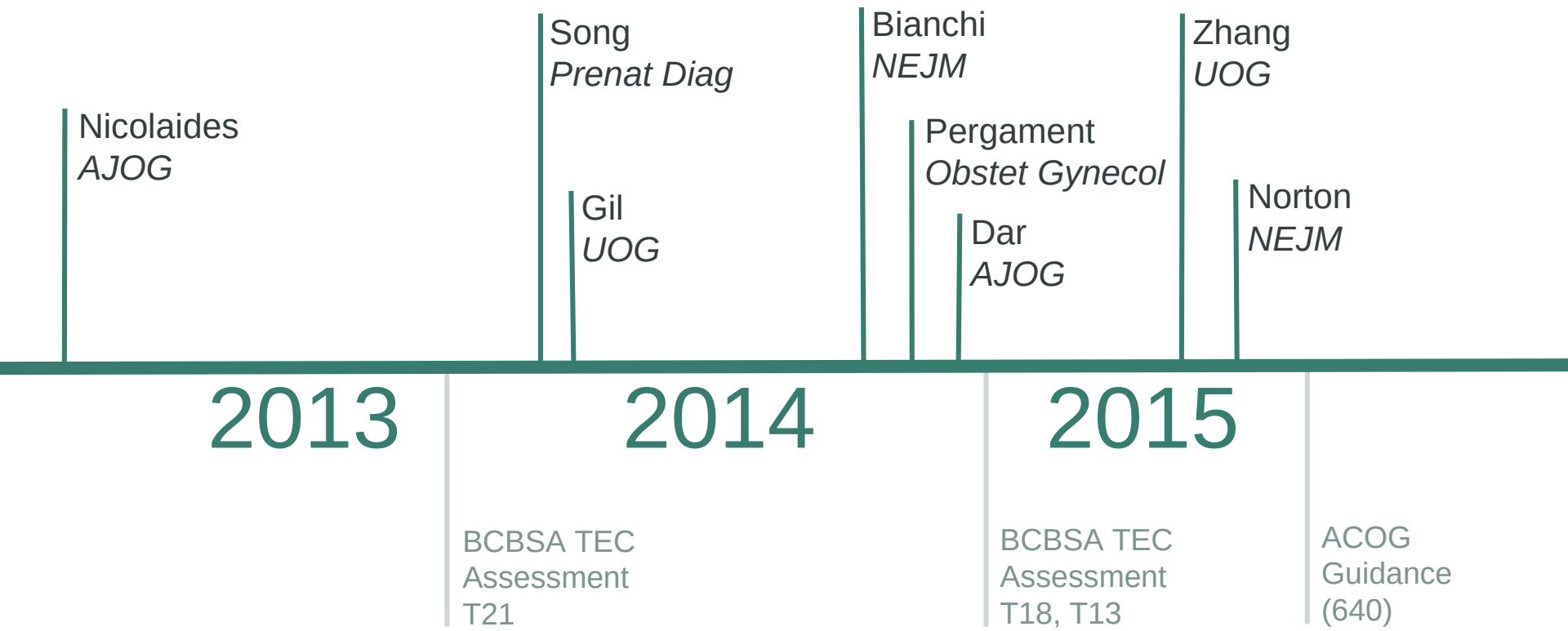
Prenatal Testing Algorithm



NIPT in Average Risk

>90,000 average risk patients evaluated in 8 studies



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Screening for Trisomy 21

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cell-free DNA Analysis for Noninvasive Examination of Trisomy

Mary E. Norton, M.D., Bo Jacobsson, M.D., Ph.D., Geeta K. Swamy, M.D., Louise C. Laurent, M.D., Ph.D., Angela C. Ranzini, M.D., Herb Brar, M.D., Mark W. Tomlinson, M.D., Leonardo Pereira, M.D., M.C.R., Jean L. Spitz, M.P.H. Desiree Hollemon, M.S.N., M.P.H., Howard Cuckle, D.Phil., M.B.A., Thomas J. Musci, M.D., and Ronald J. Wapner, M.D.

	N	Sensitivity	False Positive Rate
NIPT - Avg Risk (<35 years)	11,994	100% (82.4-100)	0.05%
NIPT - All Patients	15,841	100% (90.7-100)	0.05%
Standard Screening	15,841	78.9% (62.7-90.4)	5.4%

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BEST false positive rate = BEST Positive Predictive Values

Positive predictive value= True positives /(True + False positives)

	Total	T21	T18	T13	45X
Number of samples	17,885[a]				
Aneuploidy detected (%)	2.0%				
Aneuploid calls with confirmatory studies	222	154	29	21	18
True positives	184	140	27	8	9
False Positives	38	14	2[a]	13[b]	9
Positive Predictive Values (PPV)	**83%**	**91%**	**93%**	**38%**	**50%**

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[1] Dar P et al. Am J Obstet Gynecol 2014 Nov;211(5):527

Comparing Screening Options

	Maternal Serum Screening[1–6]	NIPT (Panorama®)[7–8]
Gestational age	~11–22 wks	9+ wks
Nuchal Translucency	Sometimes	No
Open Neural Tube Defects	Sometimes	No
T21 Positive Predictive Value	3.4%	91%
False positive rate	5%	<1%

[1]Nicolaides K H et al. Ultrasound Obstet Gynecol. 2005; 25(3)221-6.
[2]Wapner R et al. N Engl J Med. 2003; 349 (15); 1405-13.
[3]Malone FD et al. N Eng J Med. 2005; 353(19): 2001-11.
[4]PerkinElmer Labs / NTD 2013, http://ntdlabs.com/maternal-marker-testing/.
[5]Quest Diagnostics 2014, www.questdiagnostics.com
[6]Norton M et al. NEJM. 2015 Apr 23;372(17):1589-97
[7]Pergament et al. Obstet Gynecol. 2014 Aug;124(2 Pt 1):210-8
[8]Dar P et al. Am J Obstet Gynecol 2014 Nov;211(5):527

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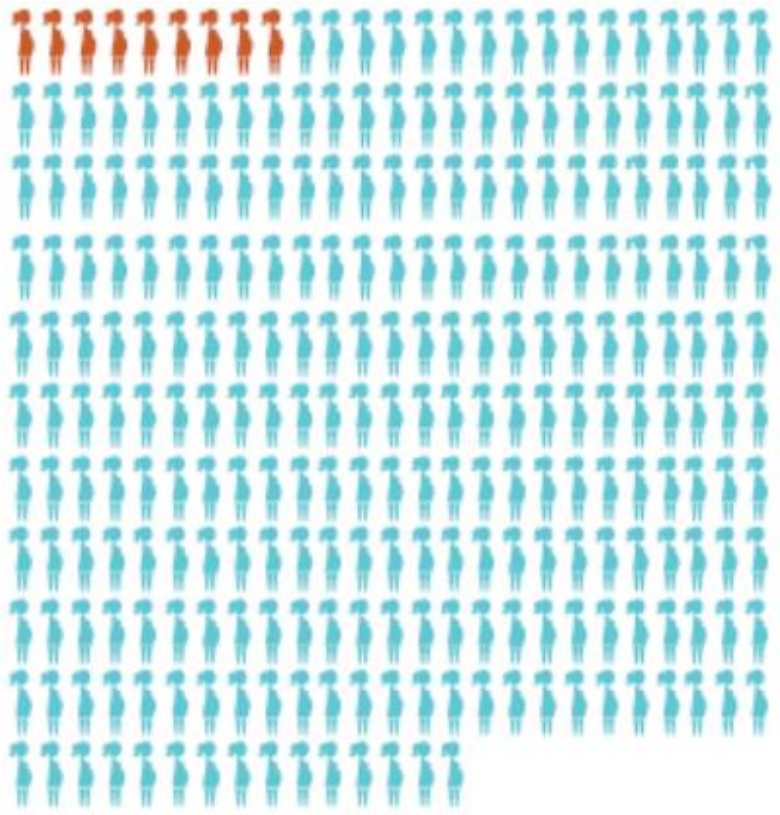
Trisomy 21 Positive Predictive Value

MSS



265 women will undergo invasive testing to discover **9** true positives.[1]

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[1]Norton et al, N Engl J Med 2015.
[2]Dar et al. Am J Obstet Gynecol 2014 Nov;211(5):527

Screening for Trisomy 21

Standard Screening		Cell-free DNA Screening
854	False Positives	9
30	True Positives	38
8	False Negatives	0

Norton M, et al. N Engl J Med. 2015 DOI: 10.1056/NEJMoa1407349

Prenatal Testing Landscape is Rapidly Changing

Professional guidelines

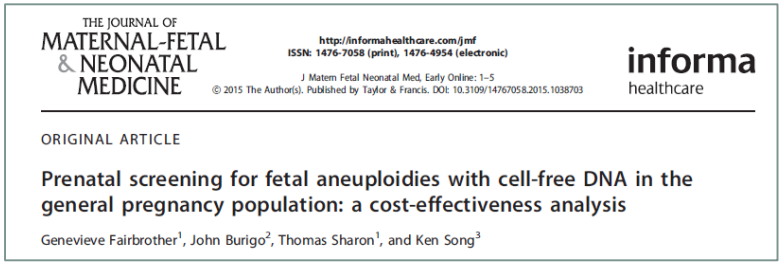
Cost-effectiveness

Insurance coverage

Professional Society Guidelines on NIPT

Organization	Policy	Date
ACMG	"ACMG recommendation that NIPS can be used as a first line screening tool."	Webinar 2015
ACOG	"any patient may choose cell-free DNA analysis as a screening strategy for common aneuploidies regardless of her risk status, the patient choosing this testing should understand the limitations and benefits of this screening paradigm in the context of alternative screening and diagnostic options."	2015
ASHG/ESHG	"Different scenarios are possible, including NIPT as an alternative first tier option"	2015
ISPD	"The following protocol options are currently considered appropriate: 1. cfDNA screening as a primary test offered to all pregnant women."	2015

Cost Effectiveness Data



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informa healthcare

ORIGINAL ARTICLE

Prenatal screening for fetal aneuploidies with cell-free DNA in the general pregnancy population: a cost-effectiveness analysis

Genevieve Fairbrother[1], John Burigo[2], Thomas Sharon[1], and Ken Song[3]

"As NIPT identifies more fetal trisomies than FTS, a NIPT unit cost of $665 allows a cost per trisomy case identified to be equivalent to that of FTS."

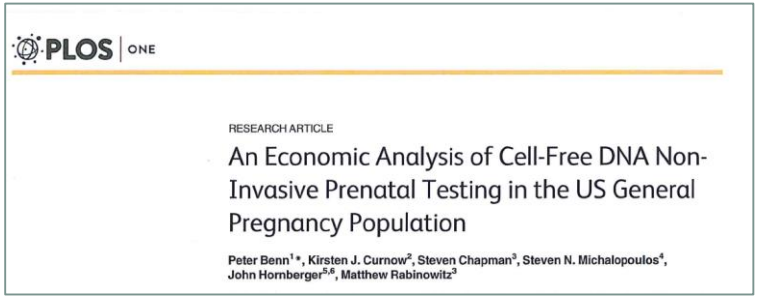
PLOS ONE

RESEARCH ARTICLE

A Cost-Effectiveness Analysis of First Trimester Non-Invasive Prenatal Screening for Fetal Trisomies in the United States

Brandon S. Walker[1], Richard E. Nelson[2], Brian R. Jackson[3], David G. Grenache[3], Edward R. Ashwood[4], Robert L. Schmidt[4]*

"Universal NIPT remained less costly than conventional MSS so long as the cost of NIPT was below $619".



PLOS ONE

RESEARCH ARTICLE

An Economic Analysis of Cell-Free DNA Non-Invasive Prenatal Testing in the US General Pregnancy Population

Peter Benn[1]*, Kirsten J. Curnow[2], Steven Chapman[3], Steven N. Michalopoulos[4], John Hornberger[5,6], Matthew Rabinowitz[3]

"Replacing conventional screening with NIPT would reduce healthcare costs if it can be provided for $744 or less in the general patient population."

Low Risk Insurance Coverage

Cell-free fetal DNA-based prenatal screening for fetal aneuploidy (trisomy 13, 18, and 21) is considered **medically necessary** when all of the following criteria are met:

1. The individual to be tested is carrying a single gestation; and

2. The individual is using this as a screening strategy for fetal aneuploidies **regardless of risk status** and understands the limitations and benefits of this screening paradigm in the context of alternative screening and diagnostic options.

NIPT and the Panorama advantage

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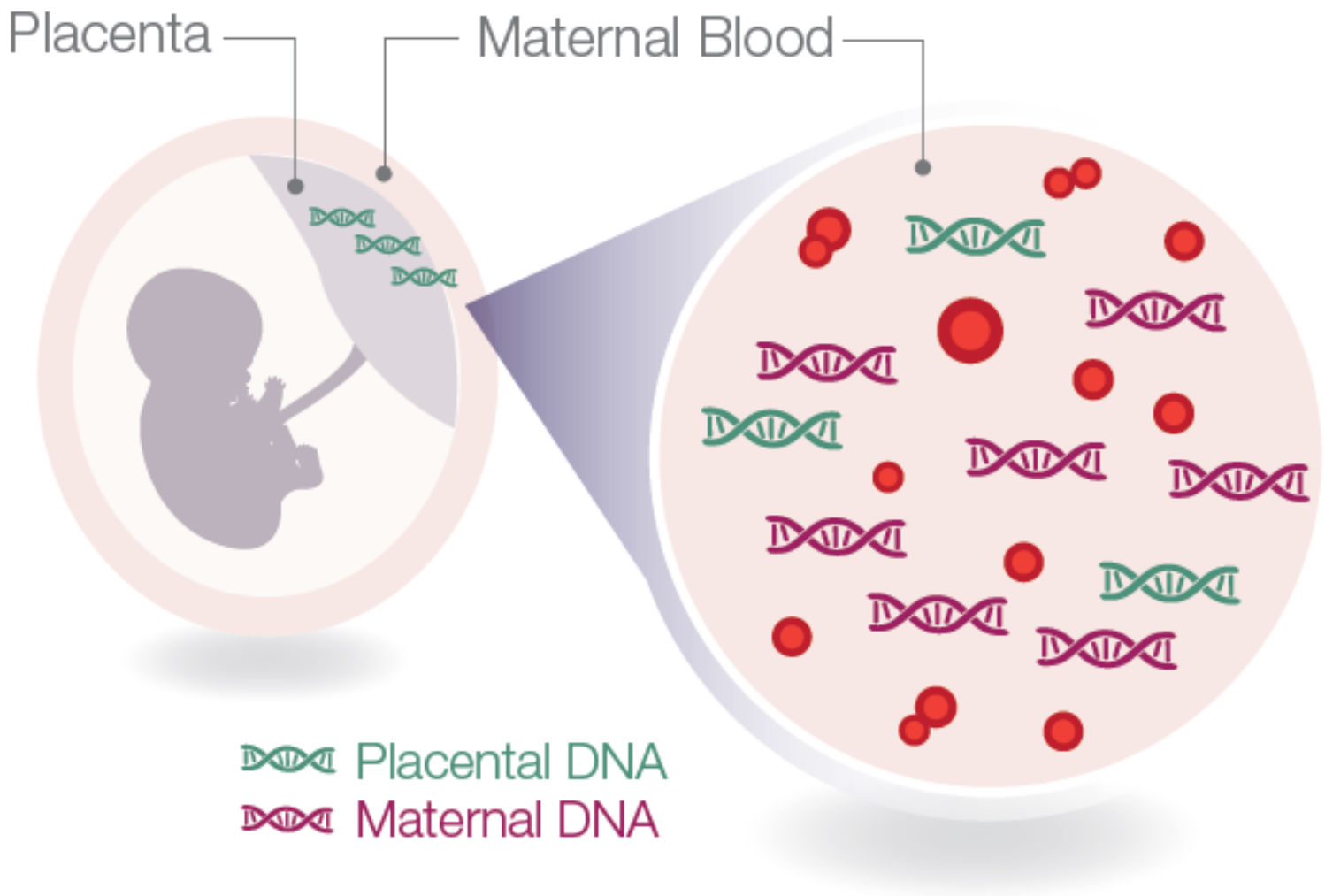
Cell-free DNA



Fetal Fraction (FF) Matters

"…the measurement of fetal cfDNA is a basic quality metric required to ensure reliable interpretation of test results."[1]

$$\frac{\text{Fetal DNA}}{\text{Fetal DNA} + \text{Maternal DNA}}$$

- Average fetal fraction is 10–12%*
- Varies by gestational age, maternal weight, placental and pregnancy factors
- Panorama® cutoff : 2.8%

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[1]Takoudes et al., *Ultrasound Obstet Gynecol* 2015; 45: 112–116
*at time of NIPT

NIPT Methodologies

Counting

harmony™ PRENATAL TEST

MaterniT21® PLUS

Counsyl

informaSeq℠ non-invasive prenatal test

verifi™ prenatal test

BambniTest

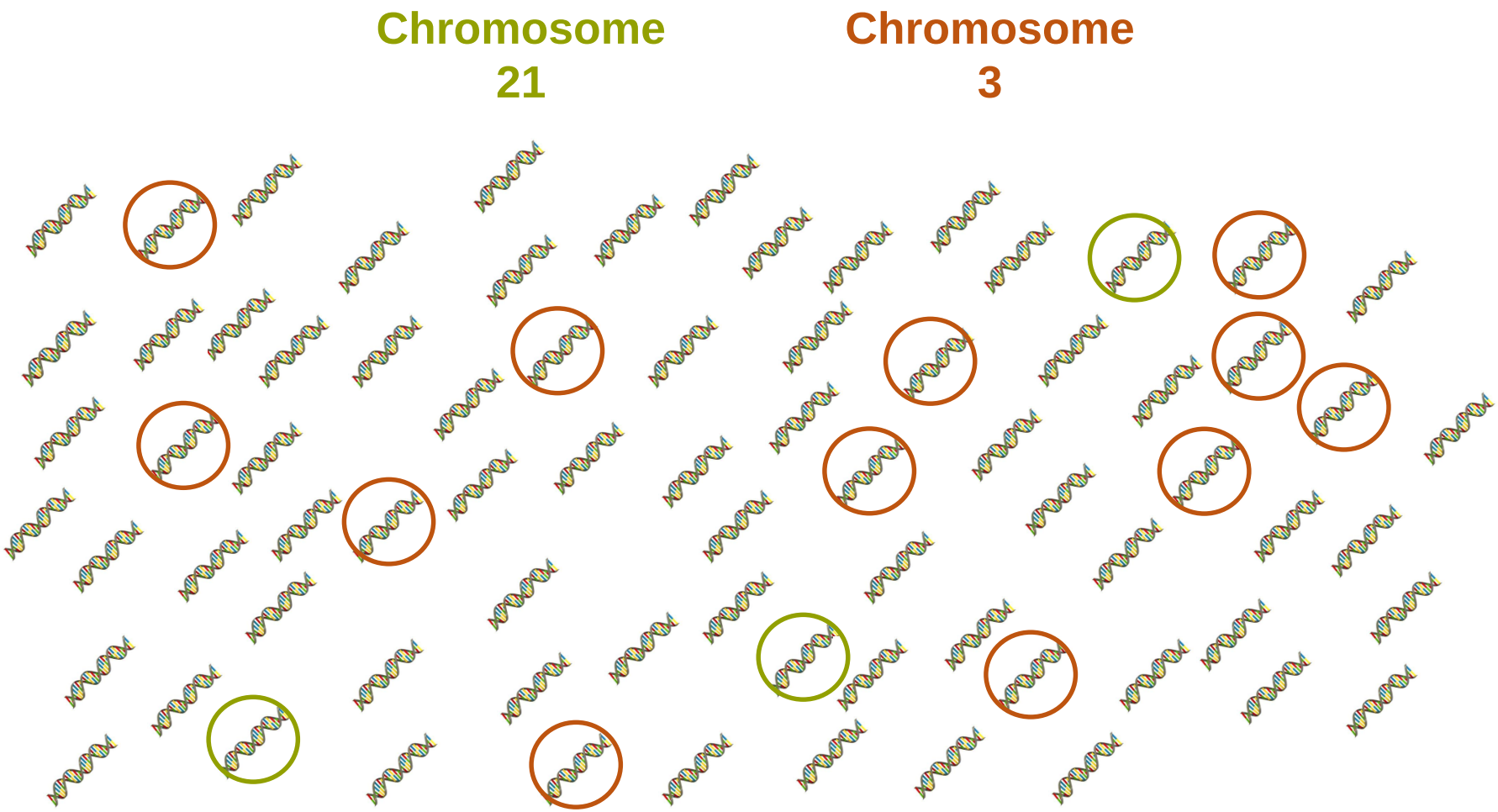
NIFTY® Non-Invasive Fetal TrisomY test

QNatal™ Advanced NIPS

SNP

panorama® natera prenatal screen

Counting



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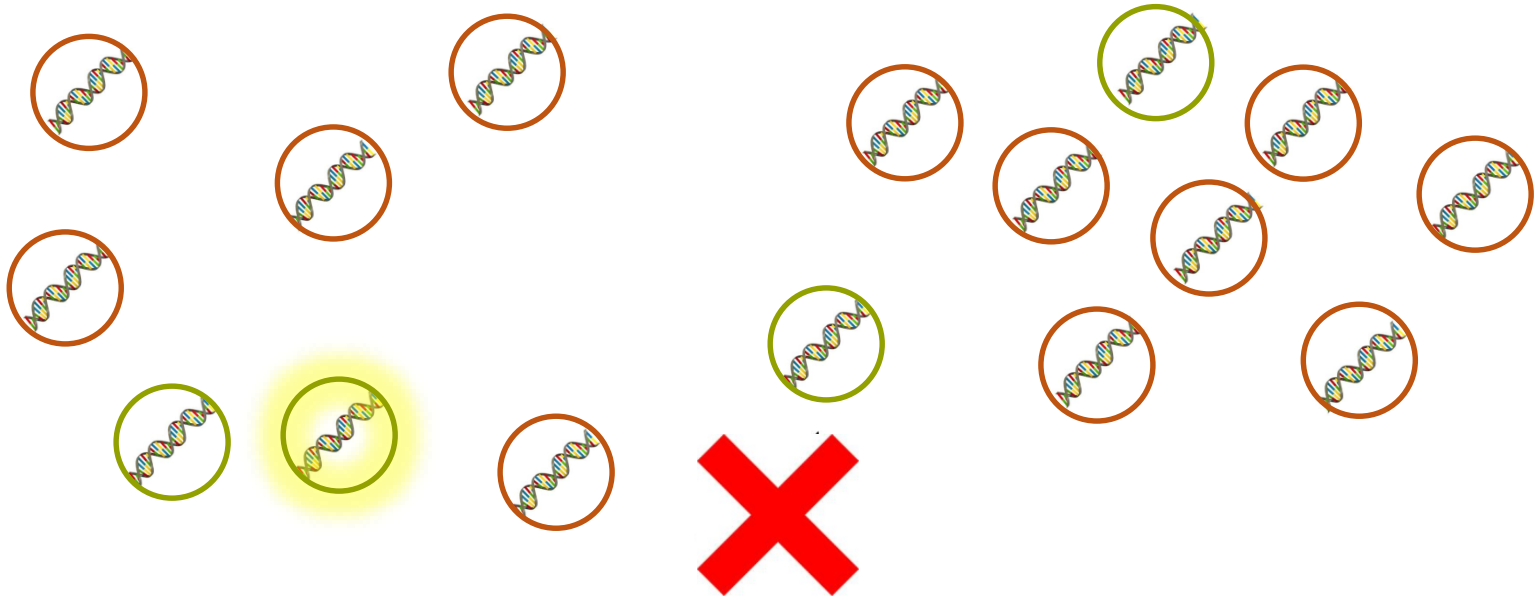
Counting

	Chromosome 21	Chromosome 3
Expected Amount:	20%	80%
Observed Amount:	25%	75%



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SNP = Single Nucleotide Polymorphism

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

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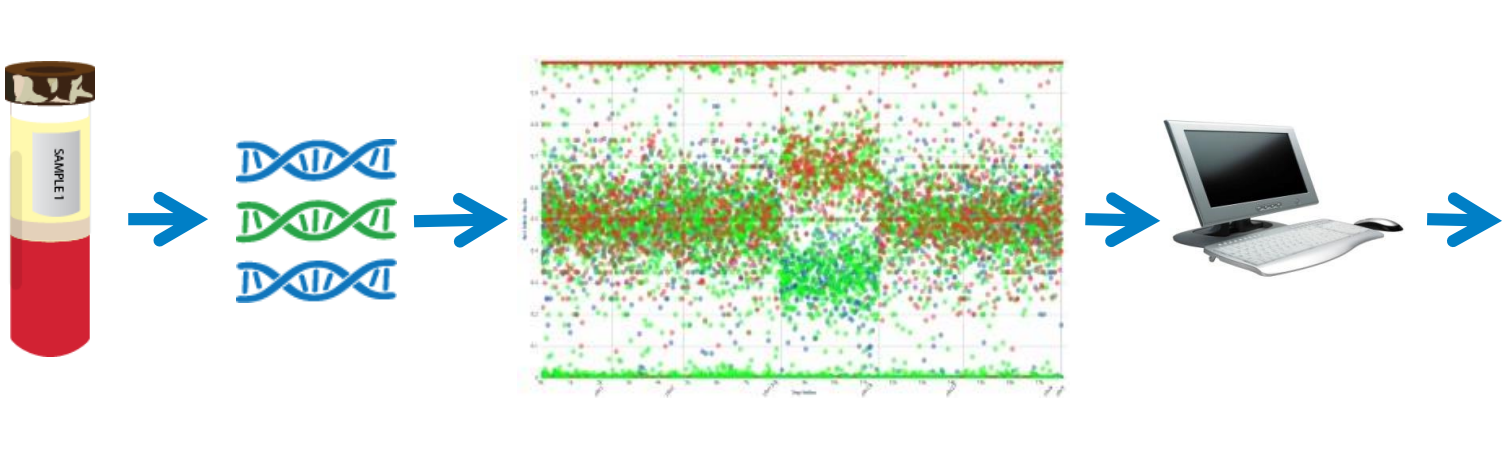
Our Technology

Proprietary SNP analysis distinguishes between maternal & fetal DNA



DNA “fingerprints”

- Panorama® is the **only** NIPT on the market that distinguishes between maternal and fetal DNA.
- Panorama® can identify different DNA “fingerprints” in a maternal blood sample, such as those from a vanishing twin.

Clinical Advantages of SNP

Panorama® uniquely differentiates between maternal and fetal DNA

- Fetal fraction
- Maternal contribution
- Vanishing twins
- Fetal sex accuracy
- Triploidy/complete mole

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NIPT on Non-Pregnant Women

	Counting Lab 1	Counting Lab 2	Counting Lab 3	Counting Lab 4	SNPs Natera
Result	Normal Female	Normal Female	Normal Female	No result	No Result
Fetal Fraction	3.9% 4.3%	Not Measured	Not Measured	Insufficient	0.6% Insufficient

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Takoudes et al., *Ultrasound Obstet Gynecol* 2015; 45: 112–116

Not for Further Reproduction or Use

Case Example: False Negative NIPT

- 35 year-old G_1P_0
- 6.9mm NT at 11+ weeks
- FTS result: high risk for T21 and T18/13
- Follow up by counting NIPT: “No aneuploidy detected”
- Amnio elected after abnormal U/S: 47,XY+21
- Retrospective analysis by the NIPT laboratory:

  Fetal fraction: 1.7%

Allen R., Kezmarsky P., Lescale K., False Negative NIPT and Potential Implications for Genetic Counseling; (Abstract #47). Presented at the 2013 ACMG Annual Clinical Genetics Meeting, 03/22/2013, Phoenix, AZ

Case Example: Low Fetal Fraction

- 36 year-old
- Panorama at 10 weeks: FF<1%
- Redraw Panorama at 12 weeks: FF1.0%
- Sample sent to counting lab: normal female fetus
- Ultrasound at 18 weeks: multiple anomalies
- Amniocentesis: 69,XXX (triploidy)

Clinical Advantages of SNP

Panorama® uniquely differentiates between maternal and fetal DNA

Fetal fraction

Maternal contribution

Vanishing twins

Fetal sex accuracy

Triploidy/complete mole

Case Example: Maternal Contribution

- 38 year-old G_2P_1
- Counting NIPT “positive” for Turner syndrome
- Amniocentesis: 46,XX. Postnatal: 46, XX
- Mother's karyotype: 45,X[2], 46,XX[18]

Clinical Advantages of SNP

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Triploidy/complete mole

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Case Example: Vanishing twin

- 35 year-old G_2P_1
- History of “vanishing twin” at 8 weeks gestation
- Panorama® at 10 weeks: “Results consistent with possible triploid or vanishing twin”
- Counting NIPT at 13 weeks: “Normal male fetus”
- Ultrasound at 17 weeks: female fetus
- Delivery: normal female, 46 XX chromosomes

Su B et al. Discordant NIPT and ultrasound results from vanishing twin pregnancy . *Contemporary Ob/GYN* April 2015.

Clinical Advantages of SNP

Panorama® uniquely differentiates between maternal and fetal DNA

Fetal fraction

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Vanishing twins

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Triploidy/complete mole

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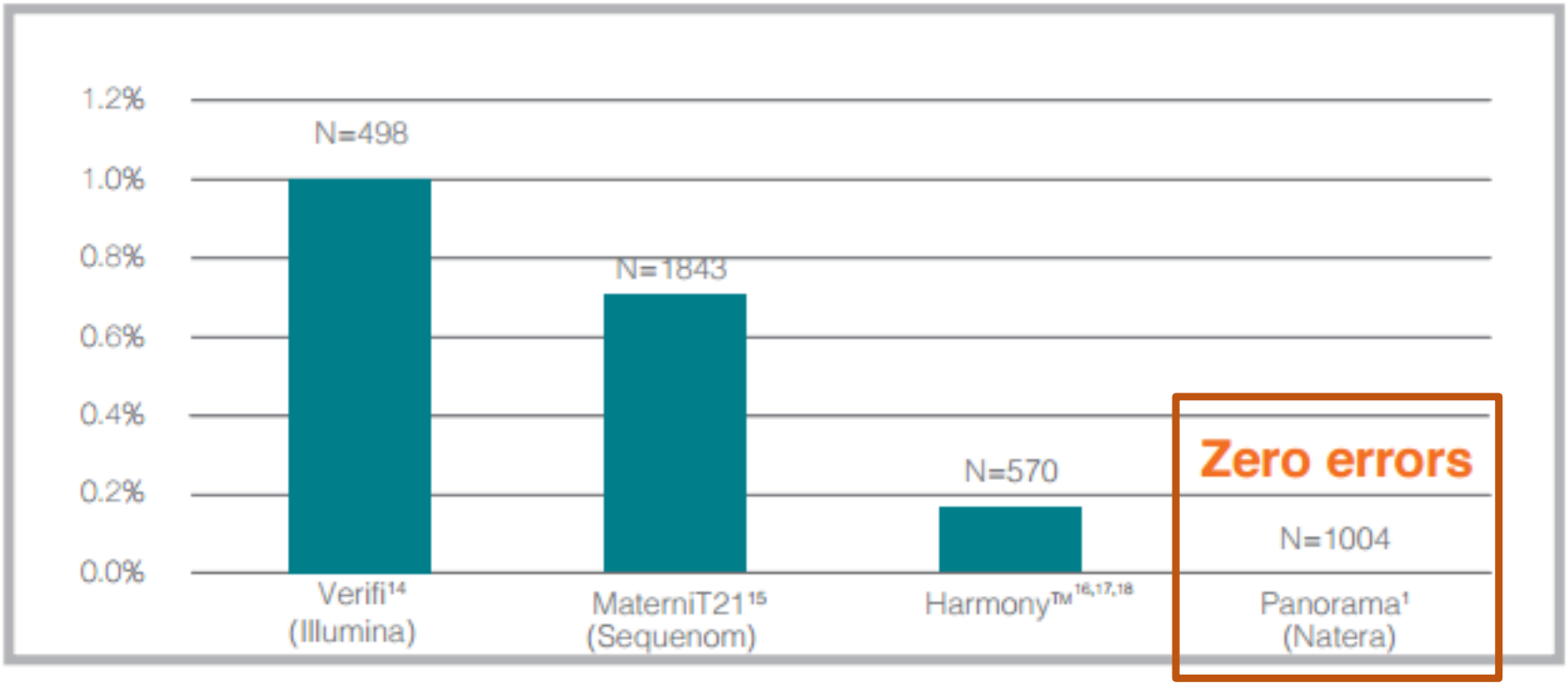
Error Rate in Sex Determination

As many as 1/100 cases can have gender discrepancy when using counting methodologies.



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[1]Mazloom et. al. 2013. Prenat Diagn.
[2]Verifitest.com
[3]Nicolaides et. al. 2013. Fetal Diagn Ther.
[4]Nicolaides et. al. 2013. Prenat Diagn.
[5]Pergament et al. 2014. Obstetrics & Gyn.

Clinical Advantages of SNP

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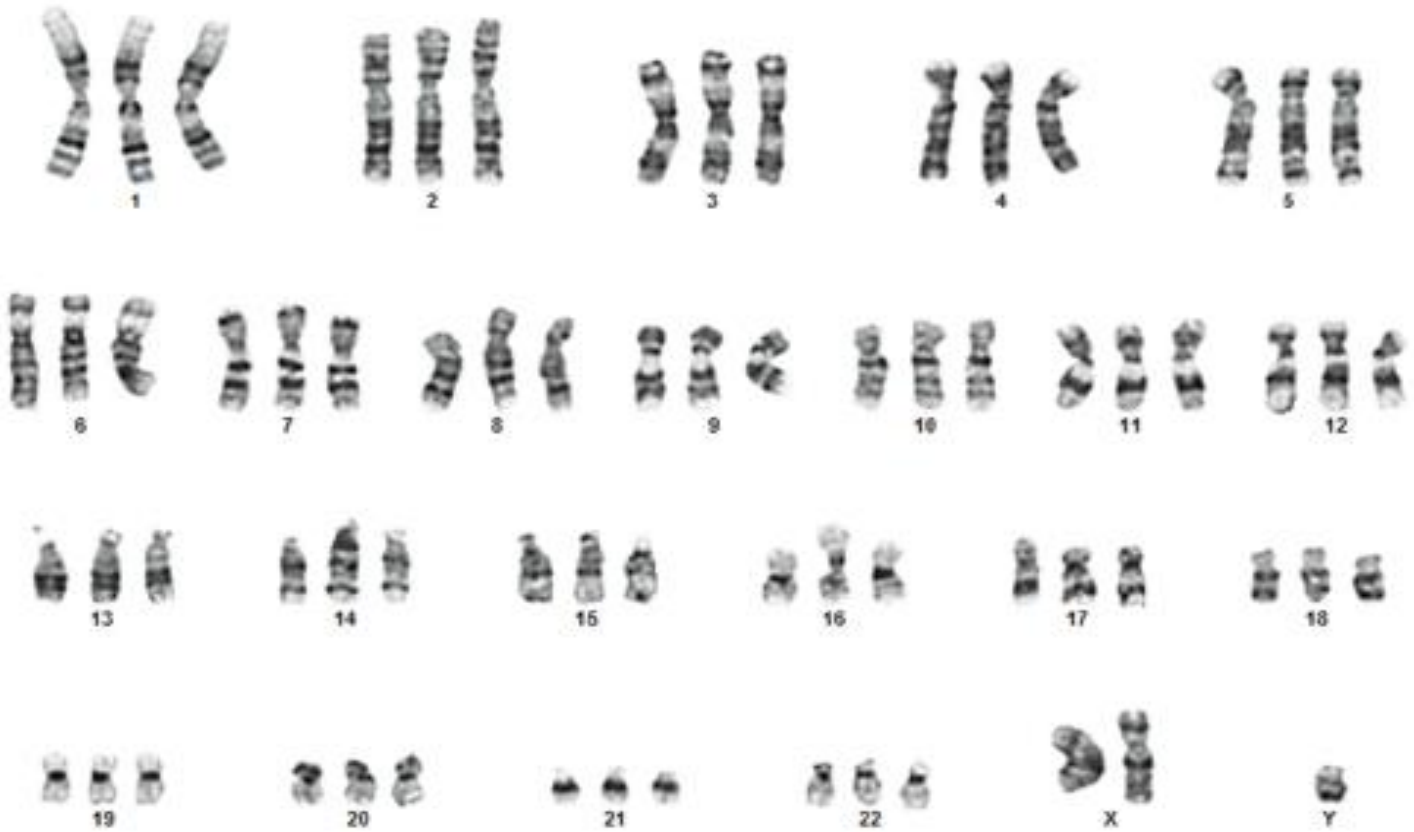
Triploidy



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Only Panorama® Can Detect Triploidy

- 1 in 1000 pregnancies at 10 weeks[1]
- Risk for partial molar pregnancy
- Counting method cannot recognize extra copy of all chromosomes
- Provides risk assessment for couples with prior pregnancy with triploidy

[1]Snijders, et al. Fetal Diagn Ther 1995; 10:357-9.
[2]Berkowitz, RS and Goldstein, DP, Cancer 1995; 76: 2079–2085.
[3]Soper, J. Obstet Gynecol 2006; 108:176–87
[4]Chromosome Abnormalities and Genetic Counseling, Gardner and Sutherland, 2004.

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Case Example: Complete Molar Pregnancy

- 29 yo G_1P_0
- Panorama® at 9 weeks
- No ultrasound performed at time of blood draw
- No significant medical history
- Results show paternal isodisomic uniparental disomy (UPD)

Simon AL et al. Detection of a complete molar pregnancy by single nucleotide polymorphism-based noninvasive prenatal testing. Ultrasound Obstet Gynecol. 2015 Mar 23. doi: 10.1002/uog.14854. [Epub ahead of print]

The Panorama® Advantage

- Superior aneuploidy screening vs. maternal serum screening
- Differentiates between maternal and fetal/placental DNA
- Screening for 22q
- Available for all patients

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panorama™
natera prenatal screen

horizon™
natera carrier screen

spectrum™
natera preimplantation genetics (PGS/PGD)

anora™
natera miscarriage test (POC)

constellation
natera software platform

The tests described have been developed and their performance characteristics determined by the CLIA-certified laboratory performing the test. These tests have not been cleared or approved by the U.S. Food and Drug Administration (FDA). Although FDA does not currently clear or approve laboratory-developed tests in the U.S., certification of the laboratory is required under CLIA to ensure the quality and validity of the tests