SMART

SNP-based Microdeletion and Aneuploidy RegisTry

The largest prospective NIPT study[1,2,3]

PATIENTS	SITES	OUTCOMES
20,000+ studied	21 global centers	~90% of samples with genetic truth

STUDY OBJECTIVE

To measure the performance of single nucleotide polymorphism (SNP)–based non-invasive prenatal testing (NIPT) in a prospective study for trisomies 21, 18 and 13; monosomy X; 22q11.2 deletion; and microdeletion panel in a large cohort of pregnant women clinically receiving NIPT.

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ENROLLMENT FLOW CHART[1]

n = 20,887
Enrolled

- **Pregnancy loss, no additional DNA testing** (*n* = 295)
- **Patient withdrew** (*n* = 94)
- **Lost to follow-up, outcome unknown** (*n* = 1,108)
- **Newborn sample not obtained** (*n* = 608)
- **Newborn sample failed laboratory quality control** (*n* = 285)

n = 18,497
Final cohort for analysis
(cell-free DNA [cfDNA] results and genetic confirmation available)

n = 4,857
High-risk pregnancies

n = 13,640
Low-risk pregnancies

Largest number of low-risk pregnancies with genetic confirmation[1]

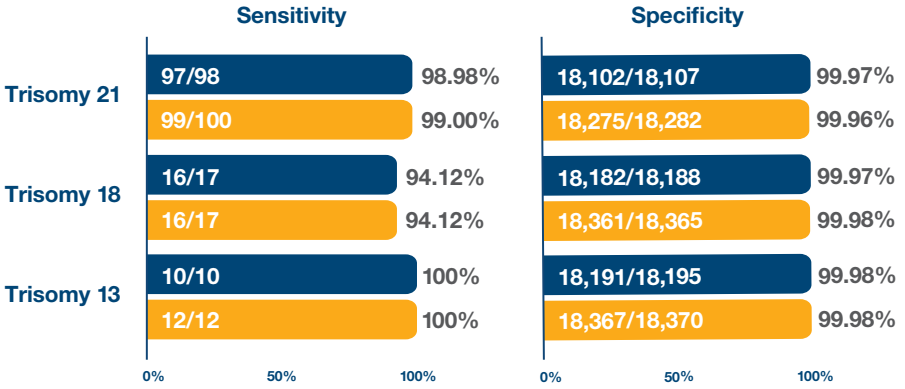
DEMOGRAPHICS & CLINICAL CHARACTERISTICS[1]

Median maternal age	**34.6**	**(30.4-37.5)**	Median fetal fraction	**9.9% ± 4.1%**
Median BMI	**25.0**	**(22.3-29.0)**	US enrollees	**55%**
Median gestational age	**12.6**	**(11.6-13.9)**	Ethnic diversity	**Asian, 8%** **Black, 9%** **Hispanic, 18%** **White, 62%** **Other, 3%**

ANEUPLOIDY DETECTION

The SMART study

- Demonstrated that Panorama's industry-leading sensitivity and specificity were maintained in real-world clinical practice[1]
- Studied the largest number of low-risk pregnancies with confirmatory testing ever[1]
- Validated Panorama AI, the artificial intelligence (AI)-based version of Panorama[1,2,3]



Fewer "no-calls"; more detection

Panorama AI detects more cases because of its lower "no-call" rate[1]

- Two more trisomy 21 cases
- Two more trisomy 13 cases

Panorama (prior version)
Panorama AI

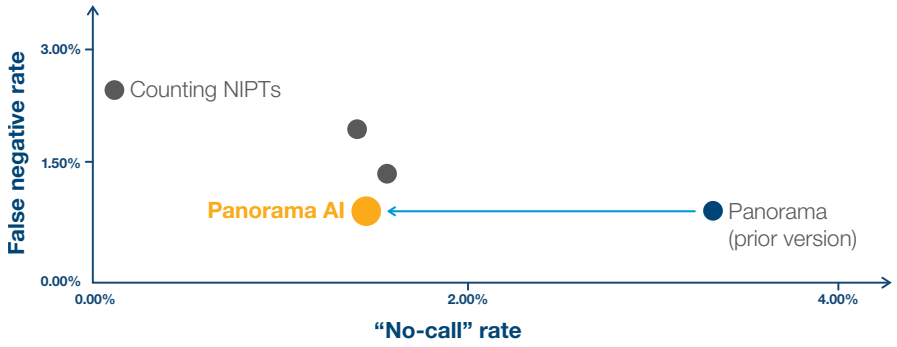
What is Panorama AI?

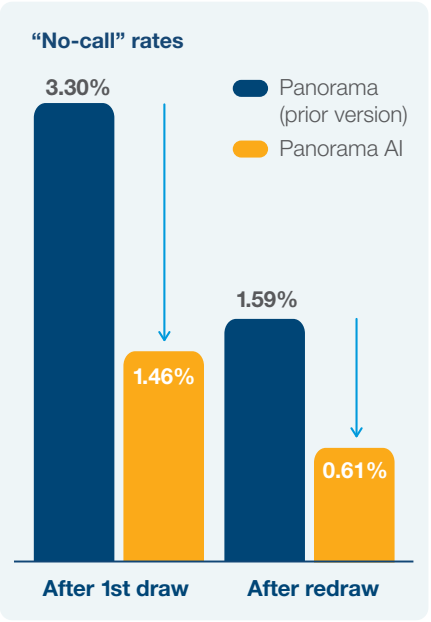
Panorama AI leverages artificial intelligence (AI) to learn from the more than 2 million tests already processed by Natera. The test combines AI with Natera's proprietary SNP-based methodology to give highly accurate results on difficult-to-call cases.

Panorama AI improved "no-call" rates

Historically, a trade-off has existed between false negative rates and "no-call" rates.

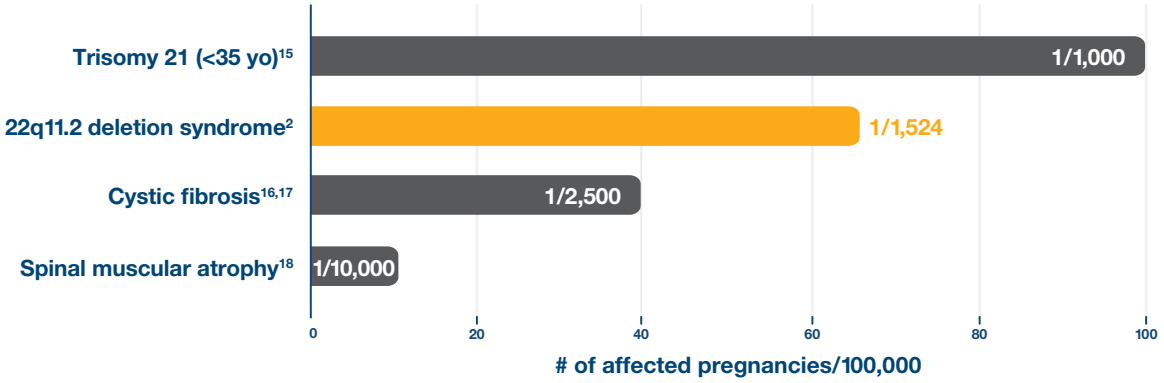
Panorama AI has broken that paradigm, delivering the best of both worlds.[1,4–14]



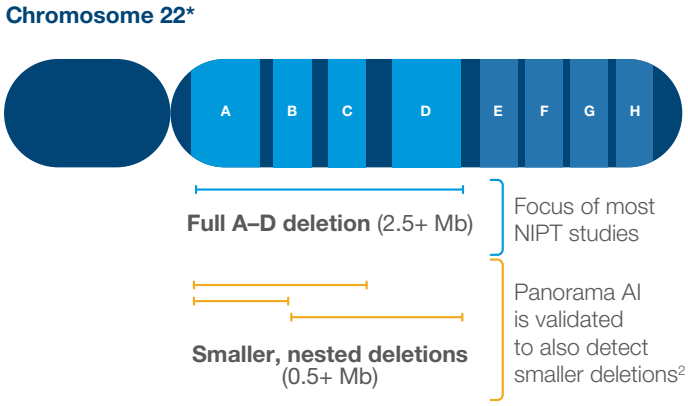


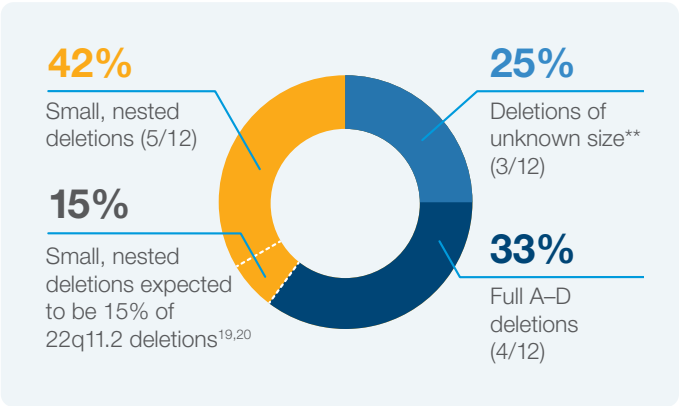
22Q11.2 DELETION DETECTION

22q11.2 deletion syndrome prevalence comparable to commonly screened conditions[2,15–18]



Higher-than-expected prevalence of smaller deletions: Detected by Panorama AI[2,19,20]

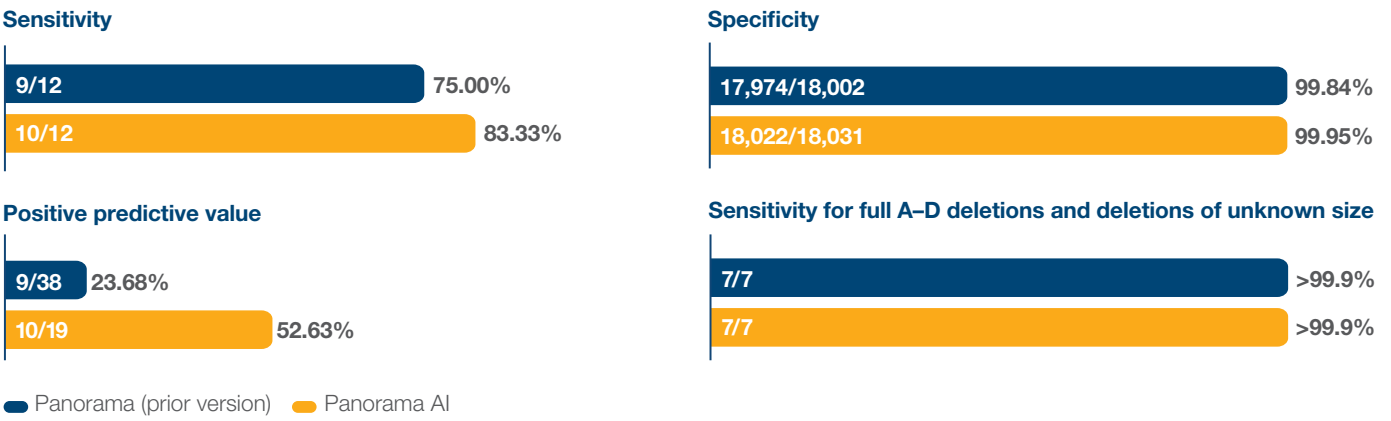




*Not to scale
**FISH or BACS-on-beads used for confirmatory testing; deletion spans A–B region at a minimum

> *"The high prevalence of 22q11.2 deletion syndrome, the limited ability of ultrasound … and the* [highly accurate] *performance of NIPT … provide exciting data to inform discussions around testing … conditions beyond common aneuploidies."*
>
> **MARY NORTON, MD, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO**
> **PRINCIPAL INVESTIGATOR, SMART STUDY**

Improved industry-leading performance: Enabling accurate, early detection[2]



Importance of early, accurate screening[21–24]

Perinatal interventions key to better outcomes
- Delivery at tertiary center
- Calcium-level monitoring
- Delayed live-vaccine administration
- Palatal evaluation for potential feeding and breathing issues

- Children who are not diagnosed prenatally can have an extensive diagnostic odyssey
  - — Average age of diagnosis is almost 5 years old
- Ultrasound findings are nonspecific

Early intervention can reduce the severity of these conditions associated with 22q11.2 deletion syndrome:[21–24]

50%
Hypocalcemia

70-90%
Developmental delay and learning differences

77%
Immune deficiencies

69%
Palatal abnormalities

74%
Congenital heart defects

25%
Schizophrenia in adulthood

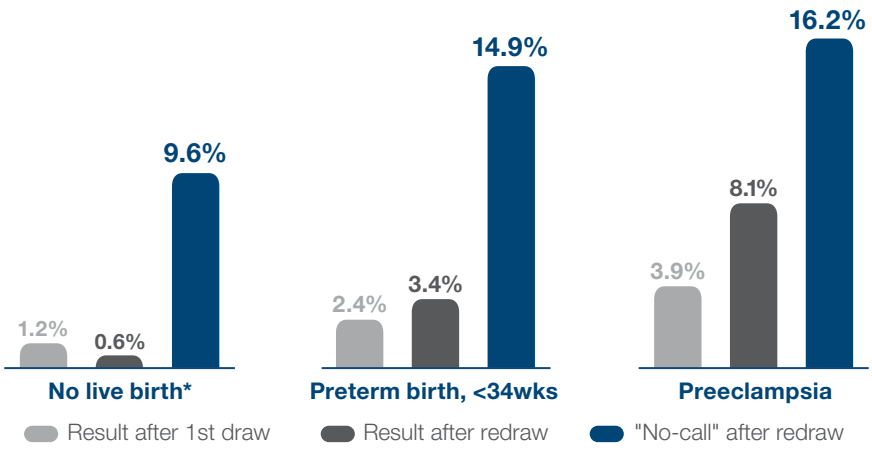
"I believe that the findings of the SMART study provide professional societies with sufficient evidence to consider including screening for 22q11.2 deletions in routine prenatal genetic screening."

PE'ER DAR, MD, ALBERT EINSTEIN COLLEGE OF MEDICINE
PRINCIPAL INVESTIGATOR, SMART STUDY

“No-calls” provide actionable information

SMART showed that, for Panorama, patients with “no-call” results after redraw have significantly higher rates of adverse outcomes — compared to baseline or patients with a call after redraw.[3]

Adverse pregnancy outcome rates for Panorama (prior version)



Based upon data presented by Dr. Mary Norton at SMFM 2021.[3]
*Includes intrauterine fetal demise, stillbirth, miscarriage, and termination.

Clinical utility of “no-calls”

Panorama AI further enriches this increased-risk group, making the “no-call” after redraw group highly actionable.[3,25] Consider the following for this group:

- Increased surveillance for preterm labor and preeclampsia

> *“Patients with failed cfDNA should have follow-up surveillance.”*
>
> **MARY NORTON, MD**[3]

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DEXEUS MUJER (SPAIN)

ALL GENETICS SAMPLES PROCESSED AT THE CHILDREN’S HOSPITAL OF PHILADELPHIA (CHOP) CENTER FOR APPLIED GENOMICS

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