

Invitae PGT-A can accurately detect whole-chromosome aneuploidy, segmental aneuploidy, haploidy, polyploidy, and uniparental isodisomy

OVERVIEW

Invitae's preimplantation genetic testing for aneuploidy (PGT-A) is an NGS-based assay that uses proprietary technology (FAST-SeqS) that allows for robust amplification and deep sequencing (~1 million reads) of over 20,000 regions (Line1 sites) across the genome to call whole-chromosome and segmental aneuploidy. Additionally, Invitae PGT assesses data from over 10,000 single-nucleotide polymorphic (SNP) sites across the genome to call haploidy, all forms of triploidy, other forms of polyploidy, in addition to many instances of uniparental isodisomy (UPiD).

Superior Detection: Invitae PGT can accurately detect a wide-spectrum of abnormalities, including whole-chromosome aneuploidy, segmental aneuploidy (≥ 10 MB), polyploidy, and UPiD.^{1,2,3}

Comprehensive Coverage: Unlike most NGS-based PGT assays (which use whole-genome amplification (WGA)), Invitae PGT's deep sequencing approach captures SNP information, allowing for the detection of haploidy, polyploidy, and UPiD for select chromosomes, abnormalities that are associated with poor reproductive outcomes and are incompletely detected by other NGS-based PGT technologies (Figures 1 and 2).

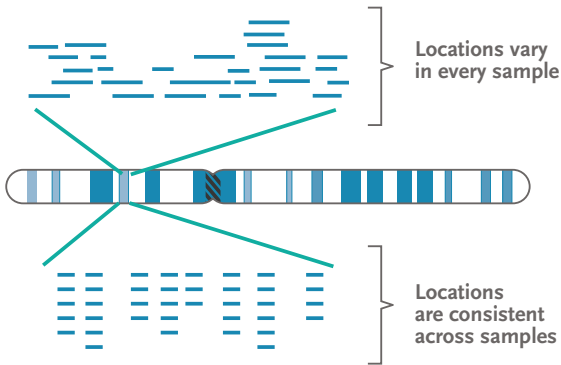
Recent validation studies have confirmed that Invitae's new PGT laboratory, located in San Francisco, California, is able to accurately detect whole-chromosome and segmental aneuploidy, polyploidy, and UPiD. The results of this validation are evidence of this assay's reproducibility and robustness, as similar accuracy was reported from the former lab location in Cambridge, Massachusetts. This paper summarizes these validation experiments and results.

BACKGROUND

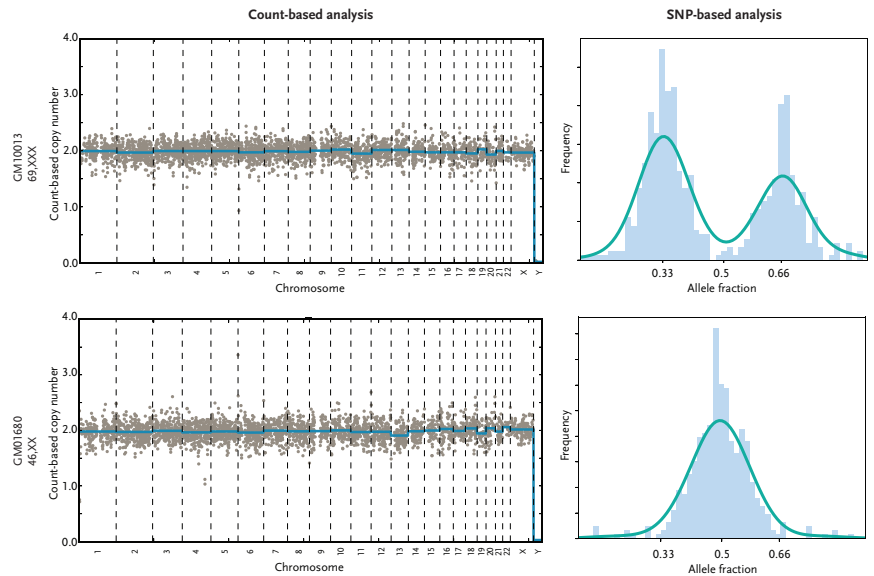
Identifying embryos with the greatest chance of implantation and live birth is vital to improving IVF success rates. To date, all validation studies aimed at assessing Invitae PGT's capabilities have been performed in the Cambridge, Massachusetts, laboratory. Invitae has recently built a new state-of-the-art PGT laboratory in San Francisco, California. Prior to accepting patient samples, a series of validation experiments were performed to confirm Invitae's PGT assay performance in its new laboratory.

METHODS

Samples from whole chromosome aneuploid ($n=6$), segmental aneuploid ($n=121$), triploid ($n=5$), UPiD ($n=3$), and known diploid cell lines ($n=8$, including both euploid and aneuploid samples) were run in replicate, and the resulting data were processed with the validated algorithms in the new San Francisco PGT laboratory. Sample calls were compared to the expected karyotypes to estimate analytical sensitivity and specificity for detection of whole-chromosome aneuploidy, segmental aneuploidy, polyploidy, and UPiD.

Figure 1: PGT-A amplification strategies.


Two different amplification methods are employed by NGS-based PGT assays: WGA (top) and FAST-SeqS amplification (bottom). Both strategies amplify less than 2% of the genome. SNP sequencing cannot be performed by NGS-based PGT platforms using WGA, and it is the SNP analysis that allows for the detection of ploidy.

Figure 2: Result examples using both count-based and SNP-based data.


Count-based assays alone cannot pick up all forms of triploidy. In this example, the 69,XXX result would have been incorrectly diagnosed as 46,XX (euploid) using a count-based analysis. Adding the analysis of SNP data allows for the accurate detection of ploidy and UPiD.

RESULTS

- Sensitivity and specificity for detection of whole-chromosome aneuploidy was 100% (95% confidence interval [CI] 82.4–100% and 77.2–100% for sensitivity and specificity, respectively)
- Sensitivity and specificity for detection of segmental aneuploidy ≥ 10 Mb was 97.7% and 100%, respectively (95% CI 94.1–99.4% and 75.3–100% for sensitivity and specificity, respectively)
- Sensitivity and specificity for detection of triploidy was 100% (95% CI 77.2–100% and 92.0–100% for sensitivity and specificity, respectively)
- Sensitivity and specificity for detection of UPiD was 100% (95% CI 80.6–100% and 92.0–100% for sensitivity and specificity, respectively)

DISCUSSION

Launching an existing assay in a new location requires extensive validation, even if the technology is not changing. As expected, our assay performs similarly in both locations offering a high accuracy for the detection of euploid embryos. Invitae is now accepting patient PGT samples in our San Francisco laboratory. Reporting on haploidy, polyploidy, and UPiD in addition to whole-chromosome and segmental aneuploidy is essential to decreasing miscarriage rates in PGT-derived pregnancies (Figure 3).

Figure 3: Invitae PGT can detect the most frequent causes of miscarriage due to chromosome abnormalities.

Abnormality	Invitae PGT	Other NGS platforms	Frequency in miscarriages ¹⁻⁴
Whole-chromosome aneuploidy	Yes	Yes	77.4–84.8%
Polyploidy (including 69,XXX)	Yes	Some	10.3%
Haploid/molar pregnancies	Yes	No	
Segmental aneuploidy	Yes	Yes	3.4%
Uniparental isodisomy (UPiD)*	Yes	No	<1%
Other	-	-	<1%

*UPiD can be detected for all chromosomes except 17, 19, 20, 21, and 22.

REFERENCES

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