# Clinical Performance of informaSeq Non-Invasive Prenatal Screening

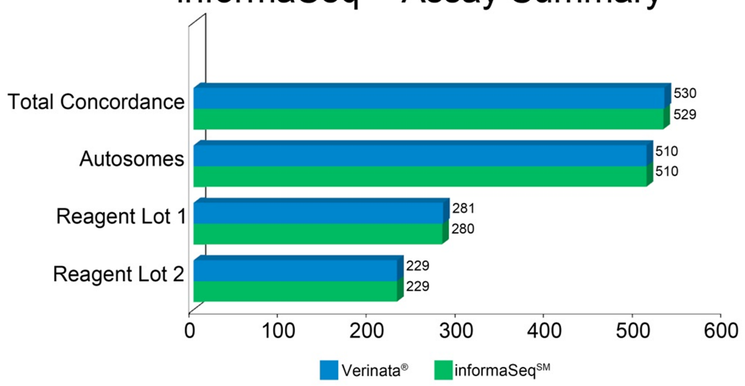
Chevonne D. Eversley, PhD, DABMG, Eddie Williams, MS, CGC, Michelle Burch, MS, CGC, Jordan Dix, MS, CGC, Amy Dexter, MS, CGC, Christine Vaughan, MS, CGC, Emily Walsh, MS, CGC, Mia Salimbene, MS, CGC, Matt Robinson, MS, Angela Leo Kenyon, MS, Stan Letovsky, PhD, Geraldine McDowell, PhD

Integrated Genetics, Laboratory Corporation of America® Holdings

## ABSTRACT

Non-invasive prenatal screening (NIPS) of cell free fetal DNA from maternal plasma is widely utilized in the United States. Integrated Genetics began offering NIPS for trisomy 21, 18 and 13 and sex chromosome aneuploidy in 2014 with a laboratory developed assay utilizing massively parallel sequencing. informaSeq initially was validated by demonstrating concordance to an independent, clinically available NIPS assay. *(Eversley, C., Clinical concordance of informaSeq Non-Invasive Prenatal Test, Abstract 712. 2015 ACMG.)*

informaSeq℠ Assay Summary




More than 90,000 samples were reported in the first year of testing. Clinical outcome data was collected by genetic counselor contact via follow up phone calls at specified post-test intervals or post-delivery. By this approach post-test outcomes were collected for approximately 1,900 patients who screened positive for autosomal aneuploidy. Confirmation of screen negative test outcomes are documented by post-delivery client follow up.

This represents one of the largest cohorts of NIPS outcome data reported to date and the first report of outcome data for a NIPS assay that was validated against an independent NIPS assay. Although NIPS testing is recommended for high risk patient groups, real world utilization of NIPS cuts across all demographics. Approximately 35% of tests ordered did not include clinical indication. While the maternal age was the most frequently utilized indicator for testing, the overall average maternal age at delivery was less than 35. We compare performance of NIPS in this large diverse patient cohort to previously reported metrics.

## METHODS

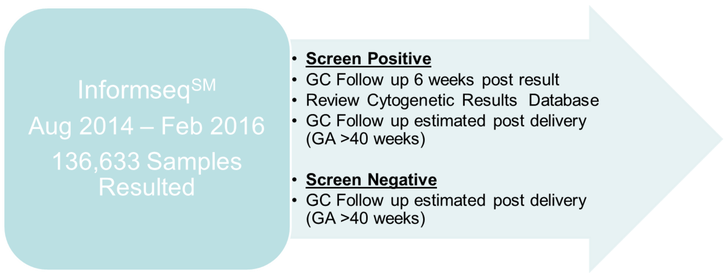



**Figure 1.** Genetic Counseling client follow up.

## CLINICAL DEMOGRAPHICS

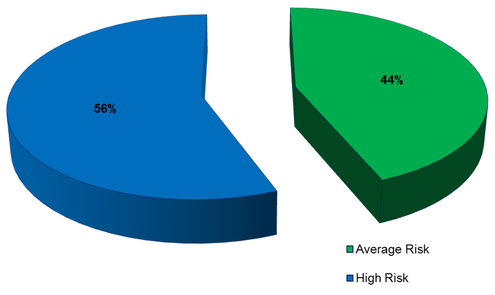
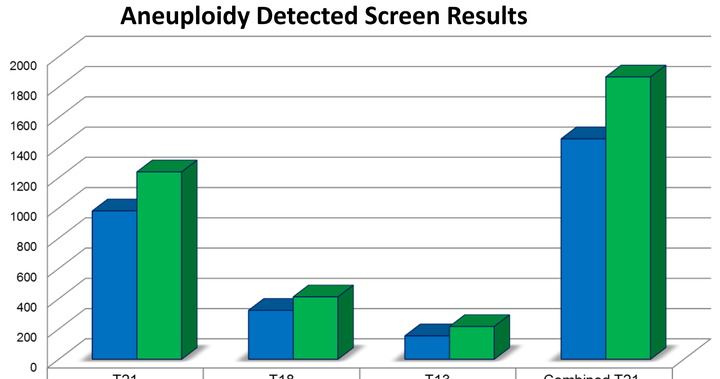



**Figure 2.** Demographics of patient population,

## RESULTS

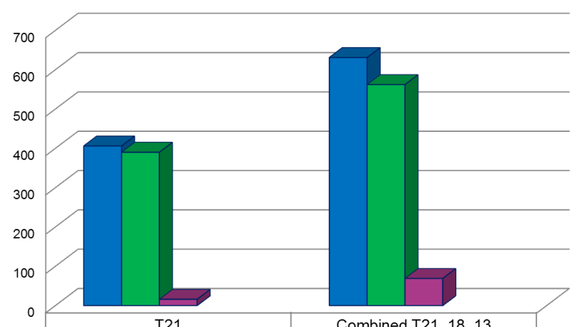
**Aneuploidy Detected Screen Results**




| | T21 | T18 | T13 | Combined T21, 18, 13 |
|---|---|---|---|---|
| High Risk Pts | 980 (0.72%) | 323 (0.24%) | 154 (0.11%) | 1457 (1.06%) |
| All Pts | 1238 (0.91%) | 412 (0.30%) | 216 (0.16%) | 1866 (1.37%) |

**Figure 3.** Total number of all patients and high risk patients that screened positive for each autosomal trisomy. Percentage of total population.

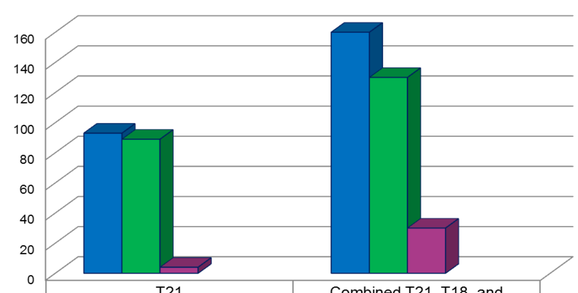
**High Risk Aneuploidy Detected Screen Results**




| | T21 | Combined T21, 18, 13 |
|---|---|---|
| Number of Cases with Follow-up Karyotypes | 406 | 631 |
| Confirmed Positives | 390 | 562 |
| False Positives | 16 | 69 |
| PPV | **96.1%** | **89.1%** |
| NPV | **99.9%** | **99.9%** |

**Figure 4.** Total number of high risk patients that screened positive with diagnostic follow up outcomes. PPV calculated for each autosomal trisomy and all trisomy's combined.

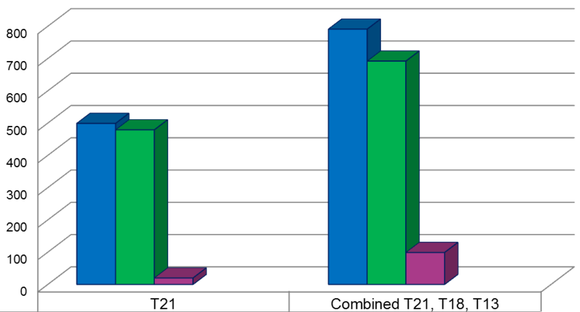
**Average Risk Aneuploidy Detected Screen Results**




| | T21 | Combined T21, T18, and T13 |
|---|---|---|
| Number of Cases with Follow-up Karyotypes | 93 | 160 |
| Confirmed Positives | 89 | 130 |
| False Positives | 4 | 30 |
| PPV | **95.7%** | **81.3%** |
| NPV | **99.9%** | **99.9%** |

**Figure 5.** Total number of average risk patients that screened positive with diagnostic follow up outcomes. PPV calculated for each autosomal trisomy and all trisomy's combined.

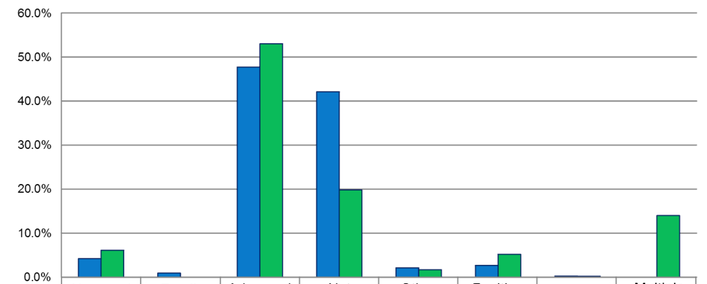
**Aneuploidy Detected Screen Results All Patients**




| | T21 | Combined T21, T18, T13 |
|---|---|---|
| Number of Cases with Follow-up Karyotypes | 499 | 791 |
| Confirmed Positives | 479 | 692 |
| False Positives | 20 | 99 |
| PPV | **96.0%** | **87.5%** |
| NPV | **99.9%** | **99.9%** |

**Figure 6.** Total number of all patients that screened positive with diagnostic follow up outcomes. PPV calculated for each autosomal trisomy and all trisomy's combined.

## Indication for Testing




| | Abnormal Ultrasound | Family history chrom abnormality | Advanced maternal age | Not Provided | Other | Positive Maternal serum screening | Previous Pregnancy with Aneuploidy | Multiple Indications |
|---|---|---|---|---|---|---|---|---|
| No Aneuploidy Detected | 4.2% | 0.9% | 47.7% | 42.1% | 2.1% | 2.7% | 0.2% | 0.0% |
| Aneuploidy Detected | 6.1% | 0.0% | 53.0% | 19.8% | 1.7% | 5.2% | 0.2% | 14.0% |

**Figure 7.** Comparison of clinical indications for testing of patients that screened positive, Aneuploidy Detected and patients that screened negative, No Aneuploidy Detected.

**PPV Comparison**

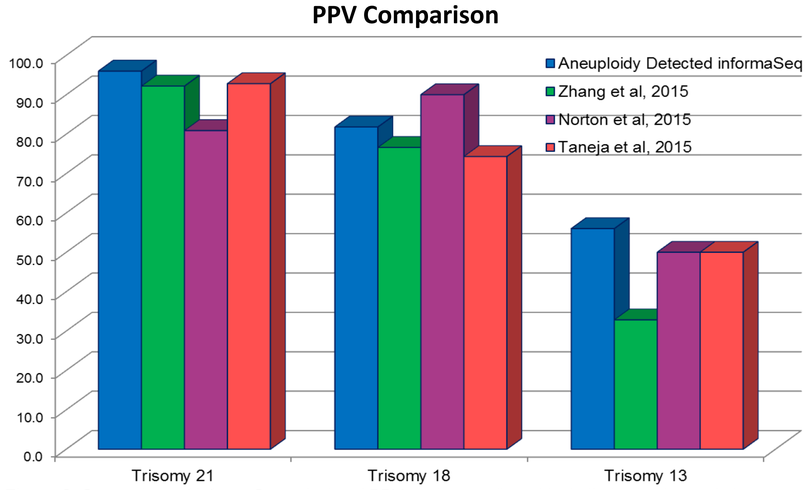



**Figure 8.** Comparison of informaSeq calculated PPV against studies with similarly sized population and the stated PPV published in the literature

| All Patients | Sensitivity | Specificity | Positive Predictive Value |
|---|---|---|---|
| Trisomy 21 | 99.58% | 99.50% | 96.0% |
| Trisomy 18 | 98.74% | 99.13% | |
| Trisomy 13 | >99.9% | 98.91% | |
| Combined | 99.4% | 97.6% | 87.5% |

| High Risk | Sensitivity | Specificity | Positive Predictive Value |
|---|---|---|---|
| Trisomy 21 | 99.74% | 99.60% | 96.1% |
| Trisomy 18 | 99.24% | 99.53% | |
| Trisomy 13 | >99.9% | 99.16% | |
| Combined | 99.6% | 98.3% | 89.1% |

| Average Risk | Sensitivity | Specificity | Positive Predictive Value |
|---|---|---|---|
| Trisomy 21 | 98.89% | 99.90% | 95.7% |
| Trisomy 18 | 96.43% | 99.60% | |
| Trisomy 13 | >99.9% | 99.75% | |
| Combined | 98.48% | 99.26% | 81.3% |

**Table 1.** informaSeq performance in high risk, average risk, and all patients.

## CONCLUSIONS

- informaSeq Non invasive Prenatal Screening results are in line with results reported by other screening laboratories.
- Positive predictive values are not individualized but can be used by clinicians as a guide to assist in counseling patients with a positive result.
- Collection of additional clinical outcome data will continue to further define and improve test performance in high risk and average risk patient groups.

## REFRENCES

1. H. Zhang, Y. Gao, F. Jiang, et al. Non-invasive prenatal testing for trisomies 21, 18, and 13: clinical experience from 146958 pregnancies. Ultrasound Obstet Gynecol 2015 April; 45: 530-538.
2. Norton ME, Jacobsson B, Swamy GK, et al. Cell-free DNA analysis for noninvasive examination of trisomy. N Engl J Med. 2015 Apr 23; 372(17): 1589-97.
3. Taneja PA, Snyder HL, de Feo E, et al. Noninvasive prenatal testing in the general obstetric population:clinical performance and counseling considerations in over 85000 cases. Prenat Diagn. 2015 Dec 30.