A noninvasive prenatal screen with >4% fetal fraction in all samples: Clinical laboratory experience

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All authors were employed by Myriad Genetics, Inc. at the time of this study

INTRODUCTION

- For millions of pregnant patients, noninvasive prenatal screening (NIPS) based on cell-free DNA (cfDNA) detects whether their pregnancies are at elevated risk for fetal chromosomal abnormalities.
- Fetal fraction (FF), the proportion of cfDNA originating from the placenta, can impact the accuracy of NIPS, and many laboratories fail samples with low FF, commonly defined as FF <4%.
- FF has been shown to negatively correlate with body mass index (BMI), pregnancies with trisomy 18 or 13, and early gestational age, resulting in higher test failure rates in these populations.
- A whole-genome sequencing (WGS)-based NIPS that employs FF amplification (FFA) technology for all samples has been shown to increase FF by 3.9-fold for samples with low FF.1

CONCLUSION

- A commercial NIPS using FFA for all samples provides confident results regardless of a patient’s risk factors for low FF. FFA provides ample FF, preventing unnecessary test failures in NIPS.
- This innovative technology identifies pregnancies at risk for chromosome abnormalities regardless of patient BMI.

METHODS

- We retrospectively analyzed results from patients who underwent NIPS with FFA during a two-month period.
- The FFA technology increased FF by preferentially sequencing short cfDNA fragments, known to be enriched for fetal-derived cfDNA. FF was assessed for patients who received a screening result (N=19,433).
- BMI data were available for 12,579 patients.

RESULTS

Figure 1. Fetal Fraction Amplification (FFA) increases FF as compared to standard NIPS.

Table 1. Actual patient cases.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gestational Age</th>
<th>BMI</th>
<th>Other Lab Result (FF)</th>
<th>AMPLIFY Result (FF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>13 weeks</td>
<td>25</td>
<td>Failed due to &quot;Low FF&quot;</td>
<td>Positive T21 (6%) &amp; later confirmed with amnio</td>
</tr>
<tr>
<td>B</td>
<td>10 weeks</td>
<td>25</td>
<td>Failed (2%)</td>
<td>Negative (20%)</td>
</tr>
<tr>
<td>C</td>
<td>10 weeks</td>
<td>39</td>
<td>Failed (3%)</td>
<td>Negative (9%)</td>
</tr>
<tr>
<td>D</td>
<td>11 weeks</td>
<td>&gt;40</td>
<td>Failed (3%)</td>
<td>Negative (12%)</td>
</tr>
<tr>
<td>E</td>
<td>12 weeks</td>
<td>45</td>
<td>Failed (2%)</td>
<td>Negative (9%)</td>
</tr>
</tbody>
</table>

- Median maternal age was 31 years and median gestational age was 12 weeks.
- Fetal fraction increased overall by >2-fold with FFA as compared to standard NIPS without FFA (Fig 1).
- No patients had FF results <4%. Ninety-nine percent of patients had FF >8.1% (Fig 2A).
- In patients with multiple risk factors for low FF, both high BMI and early gestational age draw, FF remained abundant. For example, the average FF was 13.1% among patients with BMI ≥40 with samples drawn at 10 weeks gestation (Fig 2).
- Five samples were identified as having had a previous test failure due to low FF in outside laboratories, including one that had failed to identify Down syndrome (Table 1).


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