Cost-Effectiveness of Exome Sequencing versus Targeted Gene Panels for Prenatal Diagnosis of Fetal Effusions and Non-Immune Hydrops Fetalis

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Background

• Exome sequencing (ES) has a greater diagnostic yield than targeted gene panels for fetal effusions and non-immune hydrops fetalis (NIHF)

• However, cost-effectiveness of ES versus targeted gene panels for fetal effusions and NIHF is not known

Aims

• For prenatally-diagnosed fetal effusions and NIHF that undergo next generation sequencing after non-diagnostic karyotype or microarray, we evaluated the cost-effectiveness of targeted gene panels versus ES

Study Design

• Decision analytic model compared 9 testing strategies:
  - Single test only:
    • ES
    • Targeted gene panel (RASopathy, metabolic, or NIHF)
  - Sequential testing:
    • RASopathy or metabolic panel then NIHF panel or ES
    • NIHF panel followed by ES

• Subgroups of <18, 18-22, and >22 weeks gestation accounted for timing of diagnosis of fetal effusions across gestation and availability of pregnancy termination options up to 24 weeks gestation

• Outcomes evaluated: incremental cost per quality-adjusted life year (QALY), pregnancy termination, stillbirth, neonatal death, and postnatal disease severity

• Model inputs from literature, varied in sensitivity analyses

• Cost-effectiveness threshold $100,000/QALY

Results

Table 1. Number of cases, costs, and effectiveness for nine genetic testing strategies among 1,874 fetal

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cases</th>
<th>Costs ($ million)</th>
<th>Effectiveness (QALYs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targeted gene panel</td>
<td>40,100</td>
<td>39,162</td>
<td>-782</td>
</tr>
<tr>
<td>NIHF panel</td>
<td>39,929</td>
<td>40,007</td>
<td>-288</td>
</tr>
<tr>
<td>ES</td>
<td>39,741</td>
<td>39,929</td>
<td>-753</td>
</tr>
<tr>
<td>ES followed by NIHF panel</td>
<td>39,100</td>
<td>39,384</td>
<td>-1,772</td>
</tr>
<tr>
<td>ES followed by ES</td>
<td>39,684</td>
<td>39,929</td>
<td>-1,772</td>
</tr>
<tr>
<td>ES followed by ES followed by NIHF panel</td>
<td>39,384</td>
<td>39,684</td>
<td>-2,312</td>
</tr>
<tr>
<td>ES followed by ES followed by ES</td>
<td>39,072</td>
<td>39,384</td>
<td>-3,050</td>
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<td>ES followed by ES followed by ES followed by ES</td>
<td>39,741</td>
<td>39,929</td>
<td>-3,788</td>
</tr>
</tbody>
</table>

Figure 1. Decision analysis model.

• ES was the dominant strategy with lowest costs and highest QALYs for all gestational age subgroups (Table 1)

• ES was associated with more pregnancy terminations but fewer stillbirths, neonatal deaths, and affected infants at all gestational ages, even >22 weeks with no option of termination

Conclusion

• For cases of fetal effusions and NIHF that undergo further testing with next generation sequencing after non-diagnostic karyotype or microarray, ES is the dominant strategy at all gestational ages compared to other strategies using targeted gene panels

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Background

- Many phenotypic features of genetic diseases underlying non-immune hydrops fetalis (NIHF) and other fetal effusions such as increased nuchal translucency (NT) are unclear.
- This limits identification of the underlying etiology for fetal effusions and accuracy of prenatal genomic sequencing.

Study Objective

- We aimed to determine the unique fetal phenotypic features associated with single gene disorders in a large cohort of cases with NIHF and other fetal effusions.

Methods

- Secondary analysis of prospective cohort that used exome sequencing in cases with pleural effusion, pericardial effusion, ascites, skin edema, cystic hygroma and/or increased NT >3.5 mm not unexplained by karyotype or microarray.
- Records of prenatal ultrasound and MRI imaging obtained, including gestational age at detection of abnormal fluid, dysmorphic features, structural anomalies, and evolution of features over gestation.
- Phenotypes analyzed by category of genetic disease (e.g., RASopathies, lymphatic disorder).

Results

- Single gene disorder identified in 54 cases (27%).
- Six categories of genetic diseases most prevalent: RASopathies, musculoskeletal disorders, neurodevelopmental disorders, inborn errors of metabolism, lymphatic disorders, and hematologic disorders.
- Examples of patterns observed for phenotypic features within each category (Figure 1):
  - Pleural effusions and skin edema common among RASopathies, musculoskeletal disorders, and lymphatic disorders.
  - Cystic hygroma and increased NT common among neurodevelopmental disorders.
  - Ascites and skin edema seen in all cases of inborn errors of metabolism.

Conclusions

- Phentyping cases with fetal effusions extends beyond the presence of abnormal fluid.
- Understanding the unique fetal features of disease is critical for earlier and more precise fetal diagnosis.

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Evidence-Based Discrimination:
a qualitative study of the implementation of the MFMU VBAC calculator

Nicholas Rubashkin, MD, PhD

Abstract
Background: The implementation of the MFMU VBAC calculator raises important questions about the promise and peril of using race to inform clinical decisions. Some have argued that factoring race into clinical decisions may ameliorate health disparities. Others have expressed concern that race-adjusted clinical algorithms could perpetuate unequal health outcomes. No study has assessed the downstream effects of the VBAC calculator.

Objective: To assess the impact of the VBAC calculator on prenatal and birth care in the US.

Study design: Exploratory and ethnographic.

Sample: 3 cohorts were interviewed: 22 key informants, who were users/non-users of the calculator (scientists, MFMs, OB/Gyns, CNMs, community midwives, doula, lawyers, risk managers, civil society actors), Racial/Ethnic breakdown: 18 White, 5 Black, 2 Asian/South Asian, 17 clinicians (MFMs, OB/Gyns, CNMs), Racial/Ethnic breakdown: 11 White, 2 Black, 3 Hispanic, 1 Asian, 1 pregnant/postpartum woman, Mode of birth: 13 VBACs, 10 planned cesareans, 8 ERCD. Calculator score range: 12-95%, Racial/Ethnic breakdown: 8 White, 2 Asian/South Asian, 1 Native American, 1 Asian, 1 African American, 4 mixed heritage.

Settings: Clinicians worked at 4 institutions. 2 institutions (Northeast and Southwest) required use of the calculator. At 2 other institutions in Northern California, clinicians sporadically used the calculator: 29 pregnant/postpartum women gave birth at these 4 institutions; 2 women planned home births.

Data collection: 22 key informant interviews; 17 clinician interviews; 81 data collection events with pregnant/postpartum women (interviews, observations, recordings of 13 prenatal visits).

Data analysis: The approach was critical and understood race and racism as social processes that structure inequity. Analysis followed modified grounded theory to identify social processes of racism. In presenting results, key informants and providers’ were anonymous, and pregnant/postpartum participants were given pseudonyms to protect their privacy.

Results
• The VBAC Calculator automated the reproduction of racism through three key processes.

Process 1: The statistical outlining of VBAC candidates

Clinicians could adopt the calculator with little reflection as to its potential harms. They used the calculator to automatically segregate VBAC candidates into “high” and “low” probability categories on the basis of race in officially desegregated hospitals.

This quote exemplified how providers hoped the calculator could improve outcomes: “if we counsel people in a way that more women who were going to succeed tried [a VBAC], then we might actually be impacting outcomes,” white MFM

This quote illustrated how trainees automatically adopted the calculator: “I feel like I was indoctrinated into the calculator in medical school. It’s like these are the tools we’re supposed to use. It’s this script that we’ve passed on but at no point were we talking about why these steps are important.” Hispanic MFM

This quote demonstrated how coercion could play a role in risk-stratifying patients: “I can’t tell you the number of times where it was reported that this patient wanted a VBAC...and then you sit down and talk to her about her [low] chance of success...I can’t tell you the number of times patients have changed their mind for an [BCD]...white OB/Gyn.

By contrast, Chloé, a black woman who had a VBAC score of 25%, encountered an OB/Gyn who did a mental calculation, thus hiding the existence of the calculator: “[The OB/Gyn] was like, ‘We’ll schedule your c-section. She didn’t even ask me questions’...I asked her, OK, like...A little like I was pulling her from some of these factors.”

Process 2: Subjective interpretations and mental calculations

Clinicians discussed the probability for a successful VBAC by adding their own subjective interpretation. Subjective interpretations served to encourage or discourage VBAC candidates. Sometimes subjective interpretations also obscured the existence and inner workings of the calculator. When clinicians obfuscated the calculator, they enhanced its automaticity. As clinicians became more familiar with the calculator, they could perform a mental calculation, which also enhanced the calculator’s automaticity. Mental calculations increased the work that VBAC-interested Black and Hispanic women had to do to understand how the calculator factored in race/ethnicity.

This quote illustrated a subjective interpretation. A white MFM said to Justice, a white pregnant participant: “I plugged you into the calculator and it’s predicting a success rate in the 70s...So your risk factors are in your favor.”

This quote illustrated a subjective interpretation. A white OB/Gyn said to Chloé, a Black pregnant participant who was interested in a VBAC, had a calculator score of 12%. Destiny encountered a CNM who told her that her elevated BMI made her too high risk for midwife care. Destiny reacted, “If the midwife had said because you’re African American (can’t take care of me), I would have felt like she was being racist. So it makes sense because of the weight and race together...that makes sense because we [Black people] don’t eat right. [White women] were taught to eat better than we do.”

Process 3: Conflicting risk via a multi-factorial model to predict VBAC

Clinicians and some women confounded the calculator’s variables in order to rationalize the sale of race/ethnicity to the calculator. For instance, some clinicians and women who were uncomfortable with the calculator’s use of race as a variable and instead focused on the contribution of BMI to the probability, even though both variables contributed independently to the probability for a successful VBAC.

Destiny, a Black postpartum participant who was interested in a VBAC, had a calculator score of 12%. Destiny encountered a CNM who told her that her elevated BMI made her too high risk for midwife care. Destiny reacted, “If the midwife had said because you’re African American (can’t take care of me), I would have felt like she was being racist. So it makes sense because of the weight and race together...that makes sense because we [Black people] don’t eat right. [White women] were taught to eat better than we do.”

Conclusion
This study documented how certain uses of the VBAC calculator systematically disadvantaged Black and Hispanic women who were interested in a VBAC.

• Despite increased awareness around racism in US obstetrics, the use of "race" in an epidemiologic model supported the adoption of a discriminatory technology.

• The study of obstetrics continues to contribute to medical and obstetric racism in the US.

References