Assessing the Consistency of Carrier Screening Guidelines

Across Seven Populations and 408,000 Individuals

Presented at ACNM on May 31, 2020
Summer Pierson MS CGC
Provider Engagement & Relationships
Myriad Women’s Health
Prenatal Care Goals: healthy babies & minimized maternal risk

- Early, accurate estimation of gestational age
- Identification of pregnancies at increased risk for maternal or fetal morbidity and mortality
- Ongoing evaluation of maternal and fetal health status

Source: https://www.uptodate.com/contents/prenatal-care-initial-assessment
"Will my baby be healthy?"
--Every patient at every appointment

Recessive and X-linked Conditions are responsible for nearly twice as many pregnancies impacted by shortened lifespan compared to Trisomy 18 and 13 combined.

Reference here
“Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal screening”
## Current carrier-screening guidelines

<table>
<thead>
<tr>
<th>Condition</th>
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<th>ACOG (691)</th>
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“Disorders selected for inclusion should meet several of the following consensus-determined criteria”:

1. ≥ 1-in-100 carrier frequency
2. Well-defined phenotype
3. Detrimental to quality of life
4. Cause cognitive/physical impairment
5. Require surgical or medical intervention
6. Early onset in life
7. Have prenatal diagnosis available.
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What are the consequences of this recommendation?
Open

A data-driven evaluation of the size and content of expanded carrier screening panels

Rotem Ben-Shachar, PhD¹, Ashley Svenson, MS CGC¹, James D. Goldberg, MD¹ and Dale Muzzey, PhD¹
Impact of guidelines on panel constitution & performance
Guidelines impact efficacy of carrier screening
Huge ethnicity dependence in carrier rates:
1-in-100 is woefully underspecified
Impact of guidelines on panel constitution & performance
Interpretation of 1 in 100 has substantial impact on ECS panels.
Panel Selection impacts Clinical Care

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Current Guidelines</th>
<th>Pan-Ethnic</th>
<th>1 in 100 Any ethnicity</th>
<th>176 conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern European</td>
<td>25% 75%</td>
<td>47% 63%</td>
<td>15% 85%</td>
<td>100%</td>
</tr>
<tr>
<td>African/African American</td>
<td>21% 79%</td>
<td>21% 79%</td>
<td>96%</td>
<td>100%</td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>25% 75%</td>
<td>25% 75%</td>
<td>43% 57%</td>
<td>100%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>13% 87%</td>
<td>26% 74%</td>
<td>18% 82%</td>
<td>100%</td>
</tr>
<tr>
<td>East Asian</td>
<td>24% 76%</td>
<td>34% 66%</td>
<td>95%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Creating reproductive options

- Smith-Lemli-Opitz syndrome (SLO syndrome) can cause severe intellectual disabilities and multiple birth defects
- This condition is also associated with a 70-90% peri-mortality rate
- Jennifer and Joe were offered expanded carrier screening and learned they were both carriers for SLO syndrome
- Jennifer and Joe were able to pursue IVF with PGD and have two healthy children

I knew we would both be carriers of something, but I never expected we would both carry the same thing.

- Jennifer, mom to Kinley and Colin
Self-reported ethnicity as proxy for carrier risk

How strong is this correspondence?

Self-reported ethnicity ("SRE") ~ Genetic ancestry ("GA") ~ Carrier status

Need to measure this to find out
Assign dual-component ancestry to patients

60% purple; 40% blue

We derived ancestry from > 95,000 Foresight patients
SRE is a good but imperfect proxy of GA

9% of patients had GA majority inconsistent with SRE
Carrier risk among non-SRE patients with medium amount of genetic ancestry
Carrier risk among non-SRE patients with medium amount of genetic ancestry
Misalignment of ethnicity-specific guidelines

“Our data demonstrate that SRE is an imperfect indicator of GA, which is problematic if the former guides who is offered screening but the latter guides who is a carrier.”

—Kaseniit et al., in prep
SRE is an imperfect tool to assess genetic risk

Missed Opportunity to Have Information

- Tay Sachs disease is a profound disorder of metabolism that causes brain and other nerve cells to die. It is typically fatal in early childhood.
- Tay Sachs is most common in the Ashkenazi Jewish (AJ) population; however it is not exclusive to this population.
- E expressed interest in carrier screening because her partner was of AJ ancestry.
- She was screened for mutations common in the AJ population and was screen negative.
- Her son was diagnosed with TS, further screening found she was a carrier of a mutation more common in Moroccan population.
Ethnic-Specific Guidelines:

**Deficiencies**

Many patients don’t report the ethnicity consistent with their carrier risk and could go undetected.

ESG shortcomings are not overcome by screening all people for all currently recommended conditions (pan-ethnic ESG)

Ethnicity-specific guidelines fail to identify much of the risk captured by ECS panels
Many non-SRE patients are carriers for guideline conditions
77% of carriers detected with ECS would be missed with ESG
Inconsistency of current carrier screening guidelines

<table>
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<tr>
<th>Condition</th>
<th>Rank</th>
<th>Population</th>
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<tbody>
<tr>
<td>1. cystic fibrosis</td>
<td>2</td>
<td>North/South European</td>
</tr>
<tr>
<td>2. spinal muscular atrophy</td>
<td>7</td>
<td>Ashkenazi Jewish</td>
</tr>
<tr>
<td>3. alpha thalassemia</td>
<td>9</td>
<td>African American</td>
</tr>
<tr>
<td>4. Hb beta chain-related hemoglobinopathy</td>
<td>18</td>
<td>South Asian</td>
</tr>
<tr>
<td>5. Gaucher disease</td>
<td>21</td>
<td>Southeast Asian</td>
</tr>
<tr>
<td>6. fragile X syndrome</td>
<td>5</td>
<td>East Asian</td>
</tr>
<tr>
<td>7. GJB2-related DFNB1 nonsyndromic hearing</td>
<td>18</td>
<td>Middle Eastern</td>
</tr>
<tr>
<td>8. dystrophinopathy (including Duchenne/Beck)</td>
<td>21</td>
<td>Hispanic</td>
</tr>
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</table>

**Many conditions outside of current guidelines . . . :**

1. …are more common than conditions in guidelines
2. …have high ethnicity-specific carrier rates
3. …are worthy of panethnic screening
Guideline panel would be >3x larger if every pairing of condition & ethnicity had carrier rate at least as common as CF in East Asians
Our retrospective study of >340k patients showed the ethnicity inequities of current guideline-based screening.
Knowledge Changes Care

- Hereditary fructose intolerance (HFI) is an autosomal recessive condition that, when left untreated, causes vomiting, seizures, liver disease/failure, and hypoglycemic shock
- Couple was identified as at-risk for having a baby with HFI via expanded carrier screening
- Baby was born seemingly healthy, but could not breastfeed, so he was started on formula
- He then started vomiting after every feed and the family rushed him to the ER, where he started going into liver failure
- A geneticist was called and said testing for HFI would take 2 weeks, so they started treating baby as if he had HFI
- His liver enzymes normalized and his diagnosis was confirmed

"I’m so THANKFUL my OB had suggested my husband and I to have that test done."
“Will my baby be healthy?”

Maternal Conditions

Fetal Anatomical Development

Chromosome Abnormalities

Hereditary Conditions

Ethnicity Specific Guidelines

Pan Ethnic Screening

Pan Ethnic Expanded Carrier Screening
Thank You
Section Heading

SUBHEADING
Insert Title Here

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