Carrier Screening in the Era of Expanding Genetic Technology – Achieving Equity

Jim Goldberg, MD
Chief Medical Officer, Myriad Women’s Health
Disclosure

• I am a full-time employee at Myriad Women’s Health
Carrier screening through the years

1970
Tay Sachs for AJ

1988
CF recommended by NIH

1990
Historically limited CF by ACOG

2001
Limited CF by ACOG

2009
Expanded carrier screening available

2008
SMA by ACMG

2011
Panethnic CF by ACOG

2015
ECS joint statement

2013
ACMG position statement

2017
ACOG Opinions #690, 691
Tay Sachs disease carrier screening as a successful model

- AJ predilection – Carrier frequency 1/30
- Inexpensive carrier test available
  - Intermediate levels of hex A described by O’Brien in 1970
- Education of at-risk population and religious leaders led to wide acceptance

Current US guidelines: mostly based on ethnicity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Caucasian</th>
<th>Ashkenazi Jewish</th>
<th>African/AA</th>
<th>Asian</th>
<th>Hispanic</th>
<th>Mediterr.</th>
<th>Southeast Asian</th>
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<tbody>
<tr>
<td>Cystic Fibrosis</td>
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<td>Spinal Muscular Atrophy</td>
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<td>Tay Sachs Disease</td>
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<td>Niemann-Pick Disease Type A</td>
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<td>Sickle Cell Anemia</td>
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<td>Thalassemia</td>
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</table>

ACOG Committee Opinion 691; Gross et al, 2008 (ACMG); Watson et al, 2004 (ACMG); Prior et al, 2008 (ACMG)
Limitation of ethnicity-based screening: ethnicity is not always clear or known

1 out of 7 new marriages is between spouses of **different ethnic backgrounds**

40% of Americans can’t correctly identify the ethnicity of **all four grandparents**

CF and SMA were the first conditions recommended for pan-ethnic screening.

Carrier screening for cystic fibrosis and spinal muscular atrophy should be offered to all women who are pregnant or considering pregnancy.
Why CF and SMA?

Cystic fibrosis
- Most common life-threatening autosomal recessive condition
- First introduced in 2001 (ACOG & ACMG)
  - Non-Hispanic white population
- Pan-ethnic screening recommended in 2011 (ACOG) due to increasing difficulty in assigning single ethnicity to individuals

Spinal Muscular Atrophy
- Second most common life-threatening autosomal recessive condition
- First introduced in 2008 (ACMG)
  - Pan-ethnic screening
- Introduced in 2017 ACOG
- First treatment for SMA became available in 2016
The International Screening Landscape

- Diseases w/carrier freq >1 in 60 and/or disease freq >1 in 15,000 live births. Additional ethnic specific screening

1970s – hemoglobinopathies, Tay Sachs disease
2001 – cystic fibrosis
2017 – spinal muscular atrophy

1970s - hemoglobinopathies
1990s - Tay Sachs disease
2006 - Cystic fibrosis
2012 - Spinal muscular atrophy & fragile X
Expanded Carrier Screening – 2010

• Large panel of disorders
• Inexpensive (relatively)
• Pan-ethnic
ECS identifies carriers across all ethnicities

An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals

Gabriel A. Lazarin, MS¹, Imran S. Haque, PhD¹, Shivani Nazareth, MS¹,
Kevin Iori, BS¹, A. Scott Patterson, MA¹, Jessica L. Jacobson, MD¹,²,
John R. Marshall, MD¹,³, William K. Seltzer, PhD, FACMG¹, Pasquale Patrizio, MD⁴, Eric A. Evans, PhD¹
and Balaji S. Srinivasan, PhD¹,⁵,⁶


Modeled Fetal Risk of Genetic Diseases Identified by Expanded Carrier Screening

Imran S. Haque, PhD; Gabriel A. Lazarin, MS; H. Peter Kang, MD; Eric A. Evans, PhD;
James D. Goldberg, MD; Ronald J. Wapner, MD

JAMA 2016 Aug 16;316(7):734-42
Guideline based screening misses affected pregnancies

Ethnicity-based carrier screenings *miss a significant percentage* of pregnancies affected by serious conditions.

Haque IS, et al. JAMA. 2016;316(7):734-742
Rare diseases are collectively more common than other routinely-screened conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Down Syndrome</td>
<td>1 in 800 births</td>
</tr>
<tr>
<td>Open Neural Tube Defects</td>
<td>1 in 1,000 births</td>
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<tr>
<td>Cystic Fibrosis</td>
<td>1 in 3,400 births</td>
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</tbody>
</table>

US Guidelines: ECS is an “acceptable” screening option

“Ethnic-specific, pan-ethnic, and expanded carrier screening are acceptable strategies for pre-pregnancy and prenatal carrier screening.”
ECS meets the classic and updated Wilson and Junger screening criteria

Box 1. Wilson and Jungner classic screening criteria

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from subclinical stage to recognized disease and the course of the disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients considered) should be economically balanced in relation to possible expenditure on medical care.
10. Case-finding should be a continuing process and not a “once and for all” activity.

Box 2. Synthesis of emerging screening criteria proposed over the past 40 years

- The screening programme should respond to a recognized need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening programme effectiveness.
- The programme should integrate education, testing, clinical services and programme management.
- There should be quality assurance, with mechanisms to minimize potential risks of screening.
- The programme should ensure informed choice, confidentiality and respect for autonomy.
- The programme should promote equity and access to screening for the entire target population.
- Programme evaluation should be planned from the outset.
- The overall benefits of screening should outweigh the harm.
Designing an impactful ECS panel

Systematic design and comparison of expanded carrier screening panels

Kyle A. Beauchamp, PhD1,2, Dale Muzzey, PhD1,2, Kenny K. Wong, MS, CGC1,2, Gregory J. Hogan, PhD1, Kambiz Karimi, PhD1, Sophie J. Candille, PhD1, Nikita Mehta, MS, CGC1,3, Rebecca Mar-Heyming, PhD1, K. Eerik Kaseniit, MEng1, H. Peter Kang, MD1, Eric A. Evans, PhD1, James D. Goldberg, MD1, Gabriel A. Lazarin, MS, CGC1 and Imran S. Haque, PhD1,3
“Disorders selected for inclusion on an expanded panel should meet several of the following consensus-determined criteria:”

1. Have a carrier frequency of ≥1 in 100,
2. Have a well-defined phenotype,
3. Have a detrimental effect on quality of life,
4. Cause cognitive or physical impairment,
5. Require surgical or medical intervention,
6. Prenatal diagnosis is available, or
7. Have an onset early in life.
ACOG Committee Opinion 690: clarification needed

“Disorders selected for inclusion on an expanded panel should meet several of the following consensus-determined criteria:”

1. Have a carrier frequency of $\geq 1$ in 100,
   - in all ethnicities?
   - in at least one ethnicity?
   - what about X-linked conditions?
1 in 100 carrier frequency in any ethnicity maximizes at-risk couple detection

Re-examining ethnicity-based carrier screening

- How closely does patients’ self-reported ethnicity match their genetic ancestry?

- How well are patients served by ethnicity-specific carrier screening guidelines?
Discordance between self-reported ethnicity and genetic ancestry: Ashkenazi Jewish as an example

Ashkenazi Jewish ancestry was observed in various SRE groups

SRE:
- Ashkenazi Jewish
- Other/Mixed Caucasian
- European
- Middle Eastern

SRE: self-reported ethnicity
GA: genetic ancestry
SRE is an imperfect proxy for GA

10% of patients had GA majority inconsistent with SRE

What does this mean for carrier detection?

<table>
<thead>
<tr>
<th>Self-reported ethnicity (SRE)</th>
<th>% of given SRE having &gt; 50% GA</th>
</tr>
</thead>
<tbody>
<tr>
<td>E Asian, 7.3%</td>
<td>93.0 4.7 0.2 0.0 2.0 0.1 0.0</td>
</tr>
<tr>
<td>SE Asian, 2.0%</td>
<td>82.8 *13.0 0.1 0.0 3.9 0.2 0.1</td>
</tr>
<tr>
<td>S Asian, 4.8%</td>
<td>2.8   *96.3 0.2 0.0 0.6 0.1 0.0</td>
</tr>
<tr>
<td>Mid. East, 2.4%</td>
<td>0.1   28.4 *59.2 1.7 10.2 0.1 0.1</td>
</tr>
<tr>
<td>AJ, 10.6%</td>
<td>0.1   0.1 2.7  *80.2 16.8 0.1 0.0</td>
</tr>
<tr>
<td>N. Eur., 23.6%</td>
<td>0.1   0.2 0.5 2.2  *96.9 0.1 0.0</td>
</tr>
<tr>
<td>S. Eur., 3.1%</td>
<td>0.1   0.4 13.5 1.5  *84.0 0.0 0.2</td>
</tr>
<tr>
<td>Afr. Am., 7.6%</td>
<td>0.3   0.4 2.2 0.0 6.3  *90.7 0.1</td>
</tr>
<tr>
<td>Hispanic, 7.3%</td>
<td>0.5   0.1 0.5 0.1  *72.1 1.8 24.4</td>
</tr>
<tr>
<td>Other, 31.2%</td>
<td>1.5   0.9 2.5 3.3 90.8 0.7 0.2</td>
</tr>
</tbody>
</table>

Screening based on SRE misses elevated risk in patients with intermediate GA

SRE: self-reported ancestry
GA: genetic ancestry

Kasenit, ACMG 2019, research.myriadwomenshealth.com
Following ethnicity-based guidelines misses carriers

<table>
<thead>
<tr>
<th>Condition</th>
<th>SRE</th>
<th>non-SRE</th>
<th>low GA</th>
<th>medium/high GA</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha thalassemia (AF/ME/SE/SEA)</td>
<td>47%</td>
<td>64%</td>
<td>3%</td>
<td>50%</td>
</tr>
<tr>
<td>Hb beta chain-related hemoglobinopathy (AF/ME/SE/SEA)</td>
<td>1%</td>
<td>51%</td>
<td>27%</td>
<td>34%</td>
</tr>
<tr>
<td>ABCC8-related hyperinsulinism (AJ)</td>
<td>1%</td>
<td>34%</td>
<td>36%</td>
<td>29%</td>
</tr>
<tr>
<td>Bloom syndrome (AJ)</td>
<td>2%</td>
<td>58%</td>
<td>18%</td>
<td>22%</td>
</tr>
<tr>
<td>Canavan disease (AJ)</td>
<td>3%</td>
<td>77%</td>
<td>3%</td>
<td>17%</td>
</tr>
<tr>
<td>familial dysautonomia (AJ)</td>
<td>2%</td>
<td>39%</td>
<td>31%</td>
<td>28%</td>
</tr>
<tr>
<td>Fanconi anemia type C (AJ)</td>
<td>1%</td>
<td>55%</td>
<td>41%</td>
<td>25%</td>
</tr>
<tr>
<td>Gaucher disease (AJ)</td>
<td>1%</td>
<td>33%</td>
<td>41%</td>
<td>22%</td>
</tr>
<tr>
<td>glycogen storage disease type Ia (AJ)</td>
<td>1%</td>
<td>54%</td>
<td>41%</td>
<td>22%</td>
</tr>
<tr>
<td>hexosaminidase A deficiency (AJ)</td>
<td>2%</td>
<td>69%</td>
<td>12%</td>
<td>18%</td>
</tr>
<tr>
<td>Joubert syndrome 2 (AJ)</td>
<td>1%</td>
<td>35%</td>
<td>34%</td>
<td>24%</td>
</tr>
<tr>
<td>maple syrup urine disease type 1B (AJ)</td>
<td>1%</td>
<td>66%</td>
<td>34%</td>
<td>19%</td>
</tr>
<tr>
<td>mucolipidosis IV (AJ)</td>
<td>3%</td>
<td>41%</td>
<td>36%</td>
<td>23%</td>
</tr>
<tr>
<td>Niemann-Pick disease, SMPD1-associated (AJ)</td>
<td>3%</td>
<td>61%</td>
<td>36%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Proportion of all carriers (%)
Guidelines do not emphasize the right conditions

More frequent than least frequent condition recommended by guidelines
(1 in 161: frequency of CF in Southeast Asian population)
Applied to many more conditions
Ethnicity-specific guidelines result in inequities in care

Proportion of affected pregnancies detected by following ethnicity-specific guidelines

- African American: 79%
- Northern European: 47%
- Hispanic: 26%
- East Asian: 34%

Internal data on ~400,000 patients; Haque IS, et al. JAMA. 2016;316(7):734-742
One simple change to ACOG guidelines vastly reduces inequities

“Disorders selected for inclusion on an expanded panel should meet several of the following consensus-determined criteria:”

✓ Have a carrier frequency of $\geq 1$ in 100 in at least one ethnicity
✓ Have a well-defined phenotype,
✓ Have a detrimental effect on quality of life
✓ Cause cognitive or physical impairment
✓ Require surgical or medical intervention
✓ Prenatal diagnosis is available
✓ Have an onset early in life
Affected pregnancies detected using ECS 1-in-100 carrier frequency in at least one ethnicity

- African American: 79% detected, 96% overall
- Northern European: 47% detected, 85% overall
- Hispanic: 26% detected, 90% overall
- East Asian: 34% detected, 95% overall

Internal data on ~400,000 patients; Haque IS, et al. JAMA. 2016;316(7):734-742
Recommendation: “basic” carrier screen becomes ≥ 1 in 100 carrier frequency in any ethnicity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Carrier frequency</th>
<th>Detects of at-risk couples</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF</td>
<td>1 in 20 (N Eur)</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>1 in 166 (E Asian)</td>
<td></td>
</tr>
<tr>
<td>SMA</td>
<td>1 in 42 (S Eur)</td>
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<tr>
<td></td>
<td>1 in 67 (Af Am)</td>
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</tbody>
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~40 conditions

Carrier frequency ≥ 1 in 100 (in at least one ethnicity)

Detects 89% of at-risk couples*

*Compared to a 176 condition ECS panel

≥ 1 in 100 carrier frequency in any ethnicity

- Approximately 40 conditions
- Detects 98% of carriers
- Detects 89% of at-risk couples
ECS provides essential information about risk for shortened lifespan and intellectual disability.

“Acceptable”

Recommended
Patients use ECS results to make meaningful decisions

Clinical utility of expanded carrier screening: results-guided actionability and outcomes
Katherine A. Johansen Tabor, PhD, Kyle A. Beauchamp, PhD, Gabriel A. Lazarin, MS, Dale Muzzey, PhD, Aishwarya Arjunan, MS, MPH and James D. Goldberg, MD

Preconception
77% Pursued alternative reproductive options

Prenatal
37% Pursued or planned for prenatal diagnosis

Conclusions

• Expanded Carrier Screening detects more at risk couples
• Pan-ethnic screening is more effective and reduces inequities
• A new “Basic” panel should be established
Acknowledgements

- Myriad Women’s Health Clinical Development Team
  - Katie Johansen Taber
  - Aishwarya Arjunan

- All the former employees of “Counsyl”

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