Consistency of carrier screening guidelines across seven populations and 408,000 individuals
Disclosure(s)

I am an employee and stockholder at Myriad Genetics
Purpose of carrier screening

“...the goal of preconception and prenatal carrier screening is to provide couples with information to optimize outcomes based on their personal values and preferences.”

A Joint Statement of the American College of Medical Genetics and Genomics (ACMG), American College of Obstetricians and Gynecologists (ACOG), National Society of Genetic Counselors (NSGC), Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine (SMFM).

-from Expanded Carrier Screening in Reproductive Medicine—Points to Consider
“Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal screening”
Disorders selected for inclusion [in expanded carrier screening] 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
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

- Interpretation of 1-in-100 frequency cutoff has substantial impact on ECS panels
“Disorders selected for inclusion [in expanded carrier screening] 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
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All 208 evaluated conditions met the evidence threshold for supporting a gene-disease association.

203 of 208 (98%) achieved the strongest (“Definitive”) level of gene-disease association.
“Disorders selected for inclusion [in expanded carrier screening] should meet several of the following consensus-determined criteria”:

1. $\geq 1$-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
Evaluation and classification of severity for 176 genes on an expanded carrier screening panel

Aishwarya Arjunan, Holly Bellerose, Raul Torres, Rotem Ben-Shachar, Jodi D. Hoffman, Brad Angle, Robert Nathan Slotnik, Brittany N. Simpson, Andrea M. Lewis, Pilar L. Magoulas, Kelly Bontempo, Jeanine Schulze, Jennifer Tarpinian, Jessica A. Bucher, Richard Dineen, Allison Goetsch, Gabriel Lazarin, Katherine Johansen Taber


Table 2. Mapping of the algorithm's disease traits to ACOG severity criteria.

<table>
<thead>
<tr>
<th>ACOG Severity Criteria</th>
<th>Have a detrimental effect on quality of life</th>
<th>Cause cognitive or physical impairment</th>
<th>Have an onset early in life</th>
<th>Require surgical or medical intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algorithm Disease Traits</td>
<td>Intellectual disability</td>
<td>Intellectual disability</td>
<td>Shortened lifespan: infancy/childhood/adolescence</td>
<td>Availability of treatment</td>
</tr>
<tr>
<td></td>
<td>Impaired mobility</td>
<td>Impaired mobility</td>
<td></td>
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<tr>
<td></td>
<td>Internal physical malformation</td>
<td>Sensory impairment</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Dymorphic features</td>
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<tr>
<td></td>
<td></td>
<td>Mental illness</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunodeficiency/cancer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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START

Consider traits present in ≥25% of affected patients

More than one Tier 1 trait?
- Shortened life span: infancy
- Shortened life span: childhood/adolescence
- Intellectual disability

Yes

PROFOUND

More than one Tier 2 trait?
- Shortened life span: premature adulthood
- Impaired mobility
- Internal physical malformation

Yes

SEVERE

At least one Tier 3 trait?
- Sensory impairment: vision, hearing, touch, other (pain etc.)
- Immunodeficiency/cancer
- Mental illness
- Dymorphic features

Yes

MODERATE

No

MILD

Severity Modifiers:
- Availability of treatment
- Variable expressivity
Evaluation and classification of severity for 176 genes on an expanded carrier screening panel

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Establishing a guidelines consistent panel

- North/South European
- Ashkenazi Jewish
- African American
- South Asian
- Southeast Asian
- East Asian
- Middle Eastern
- Hispanic

- Cystic fibrosis
- Spinal muscular atrophy
- Hb beta chain-related hemoglobinopathy
- Gaucher disease
- Hexosaminidase A deficiency
- Familial dysautonomia
- Caravan disease
- ABCC8-related familial hypertriglyceridemia
- Glycogen storage disease type IIa
- Fanconi anemia, FANC-related
- Usher syndrome
- Niemann-Pick disease, SMARD1-related
- Niemann-Pick disease type C1
- Bloom syndrome
- PCDH19-related disorders
- Fanconi anemia complementation group A
- Glycogen storage disease type Ib
- Niemann-Pick disease type E2

# ACOG criteria

- Disease Association
  - Strong/Definitive
  - Moderate
  - Limited

Condition w/o current guideline

Condition within current guideline

Legend:
- #4
- #3
- #2
- #1
- #0
Establishing a guidelines consistent panel

1. $\geq 1$-in-100 carrier frequency
   40 genes
2. Well-defined phenotype
   173 genes
3. Severity
   a) Detrimental to quality of life
   b) Cause cognitive/physical impairment
   c) Require surgical or medical intervention
   d) Early onset in life
   170 genes
4. Have prenatal diagnosis available
   All genes

COMMITTEE OPINION

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Conclusions

• Using evidence-based analyses, we clarified and operationalized ECS panel design criteria.

• Stringent application of the criteria resulted in the identification of a guidelines-compliant panel consisting of ~40 conditions.

• Additional clarity of guidelines is needed to ensure standardization and equity of care.
Thank you!

Acknowledgements

• Katie Johansen Taber
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• Raul Torres

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Studies

• Research.myriadmomenshealth.com