Should Universal Carrier Screening be Universal?

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Antepartum and Intrapartum Management
June 15, 2017

Disclosures
• Research funding from Natera

Burden of Genetic Disease

• 6000-7000 single gene disorders
  • 20% of infant deaths
• “Everyone carries 5-10 of these”
  • 1/300 pregnancies
• Recessive mutations can pass quietly for many generations
• Carriers usually have no family history

Recessive inheritance

[Genetic diagram showing unaffected carriers and affected individuals]
Why all the focus on Down syndrome?

Availability of Genetic Tests

What is the purpose of prenatal carrier screening?

What is the purpose of newborn screening?
Criteria for carrier screening

- A good test is available
- The disorder is common
- The disorder is severe
- There is an intervention
- Testing is voluntary and patients give informed consent

Carrier Screening - Background

Availability of intervention
- Donor sperm/egg; preimplantation testing; adoption
- Prenatal diagnosis – termination
- Goal: risk assessment, informed decision making

Technology continues to advance
- Increasing complexity and availability of carrier screening tests
- Need to apply these principles – optimal criteria – prior to adding new tests

History of carrier screening

1. Hemoglobinopathies 1970's
2. Tay Sachs disease 1971
3. Canavan disease 1998
4. Cystic fibrosis 2001
5. Familial dysautonomia 2004
6. Spinal muscular atrophy 2008 (ACMG)
7. Spinal muscular atrophy 2017 (ACOG)
8. Expanded Jewish panel 2008 (ACMG)
9. (Fragile X)
10. Expanded Jewish panel 2017 (ACOG)
11. (Expanded carrier screening)
Ethnicity Based Screening

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Screening for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jews</td>
<td>Tay Sachs disease, Canavan disease, cystic fibrosis, familial dysautonomia</td>
</tr>
<tr>
<td>Louisiana Cajun, Fr Canadian</td>
<td>Tay Sachs disease</td>
</tr>
<tr>
<td>Caucasians</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Africans, African Americans</td>
<td>Sickle cell anemia, beta thalassemia</td>
</tr>
<tr>
<td>Southeast Asians</td>
<td>Alpha thalassemia</td>
</tr>
<tr>
<td>Mediterraneans</td>
<td>Beta thalassemia</td>
</tr>
</tbody>
</table>

ACOG 2017 Screening Recommendations

- Screening should be offered to all women before or during pregnancy for:
  - Cystic fibrosis
  - Spinal muscular atrophy
- MCV should be offered to all women who are currently pregnant
- To those at risk for hemoglobinopathies, Hb electrophoresis should be offered (African, Mediterranean, Middle Eastern, SE Asian, West Indian) or if MCV is low

ACOG 2017 Screening Recommendations

- Fragile X screening should be offered to all women with:
  - a family history of FraX related disorders
  - unexplained ovarian insufficiency or failure
- Tay Sachs screening should be offered to those who are:
  - French Canadian
  - Cajun
  - Ashkenazi Jewish

Tay Sachs Disease

- TSD is a lysosomal storage disease caused by hexosaminidase A (hex A) deficiency
- Resultant accumulation of GM2 gangliosides results in progressive neuro-degeneration
- Death in early childhood
- There is no treatment or cure
Even Tay Sachs screening gets complicated, however…

**Enzyme assay vs DNA?**

- Initially screening involved enzyme assay
- Recently, a DNA test was developed
- Both have good sensitivities and specificities, although neither is perfect
  - DNA testing preferable in most cases
  - Enzyme screening is better for non-Ashkenazi Jewish individuals
- In complex cases, a combination of tests may be required

**Spinal Muscular Atrophy**

- Severe hereditary neuromuscular disorder
- Degeneration of motor neurons in spinal cord → proximal muscle weakness and paralysis
- Several types of varying severity
- Most severe type results in death by age 2 from respiratory failure

**Spinal Muscular Atrophy**

- Autosomal recessive
- Second most common fatal AR disorder after cystic fibrosis
- ~1/10,000 live births, 1/40-60 carrier frequency
- Occurs in all ethnic groups
Spinal Muscular Atrophy

- Caused by a deletion in the survival motor neuron gene (SMN)
- 95% of affected patients have a homozygous deletion
- 5% are compound heterozygotes for deletion and a small subtle mutation

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Universal Carrier Screening
Universal (Expanded) Carrier Screening

Utilization of new technologies to identify carriers of multiple genetic conditions simultaneously

Multiplex Panel Screening: Universal Screening

• Multiplex screening now allows testing for many (hundreds) disorders at once
• This is relatively inexpensive ($100-350)
• Should it be offered to everyone?
Gene variants

What criteria are required by laboratories before including variants on panels?

Disease categories

Many of the diseases included in our screen are vital to know about.

**Intellectual disability**
Some result in intellectual disabilities, as with fragile X syndrome and William-Bailey syndrome.
**Limited or no treatment**
Finally, some of the conditions have no treatments available, like spinal muscular atrophy and Canavan disease.

**Early intervention**
Some of the conditions on the Family Prep Screen can be treated early in life, like Wilson disease and PKU.

**Shortened life expectancy**
Others are chronic and require lifelong management, like cystic fibrosis and Marfan syndrome.
Achromatopsia

- Decreased visual acuity, nystagmus
- Increased light sensitivity
- Decreased color discrimination
- Non-progressive
- Does not lead to blindness
- No other organ system affected
- Should this be on panels?

Alpha 1 antitrypsin deficiency

**Causes Chronic Obstructive Pulmonary Disease**
- Smoking influences the onset of COPD
- Non-smokers often have a normal life span
- Extremely rare in children

**Liver disease** – increased risk with age
- Adults – Cirrhosis 15-20% by age 50
- Children – 2% develop liver failure
- Clinical disease is uncommon in carriers
- Smoking increases risk
- Would most consider prenatal diagnosis?

Other mild/minimal/non-disorders

- **Hemochromatosis**
  - Inappropriate absorption of iron
  - Clinical – end organ failure
  - Onset: >40 years
  - 75-90% - asymptomatic
- **MTHFR**
  - Elevated homocysteine
  - Risk for thrombosis, cerebrovascular and cardiovascular disease, stroke
  - Treatment: vitamins
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- Just because we “can”, should we offer this?
- May lead to partner carrier screening.... Anxiety, costs
  - Prenatal diagnosis....
  - “First, do no harm”
**Expanded carrier screening**

- **Need informed consent:**
  - Detection of disorders that are variable or mild
  - Some are adult onset
  - Many are rare with low detection rate
  - Uncertain residual risk

- In a 15 minute office visit, how can one obtain informed consent for all of these disorders?

<table>
<thead>
<tr>
<th>Condition</th>
<th>1/23,453</th>
</tr>
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<tbody>
<tr>
<td>α1AT deficiency</td>
<td>13</td>
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<tr>
<td>CF</td>
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<tr>
<td>DFNB1</td>
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<td>SMA</td>
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<td>Fam Mediterranean Fever</td>
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<td>SLO</td>
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<td>SS/β-thal</td>
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<tr>
<td>Gaucher disease</td>
<td>77</td>
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<tr>
<td>Factor XI def</td>
<td>92</td>
</tr>
<tr>
<td>Achromatopsia</td>
<td>98</td>
</tr>
</tbody>
</table>

Lazarin GA, et.al.. *Genetics in Med* 2012.

**Universal Carrier Screening: Pros and Cons**

- Efficient
- All patients offered same tests
- Detects more conditions
- Does not require ethnicity
- Reduces disparities in screening by racial/ethnic categories

**Conditions may be:**

- Efficient
- All patients offered same tests
- Detects more conditions
- Does not require ethnicity
- Reduces disparities in screening by racial/ethnic categories

- Conditions may be:
  - mild and variable
  - rare, esoteric, hard to explain
  - treatable (PKU)
  - adult onset
  - Some gene variants have uncertain significance
  - Overall process is MORE expensive
Universal Screening

• Different paradigm for universal versus single disorder approach

• Counseling is more generic:
  • “Do you want testing for birth defects?”
  • “Outcomes vary widely but many are serious.”
  • “Not everything is detected by these tests.”

If you offer expanded carrier screening:

• Patients should be told (before testing)
  • Some conditions are not well characterized
  • Some conditions are rare – may not know detection rate, residual risk

• No test can rule out all genetic diseases

• Screening for hemoglobinopathies and Tay Sachs disease may not be as accurate
  • MCV, enzyme testing may be better

Final Thoughts

“…..the foremost purpose of prenatal screening is not to reduce the incidence of genetic disease but to fulfill a couple’s reproductive goals.”

Thank You!