Beyond the bloodspot

Testing and Screening Beyond Newborn Screening:

How do Advances in Prenatal Testing Impact Screening of Newborns?

August 20, 2013

Siobhan Dolan, MD, MPH

Professor of Clinical Obstetrics & Gynecology and Women’s Health
Albert Einstein College of Medicine / Montefiore Medical Center
Bronx, NY
Issues to Consider Across the Preconception / Prenatal / Newborn Continuum

- Expanded Carrier Screening
- Screening and Diagnosis for Aneuploidy
- Screening and Diagnosis for Microdeletion & Microduplication Syndromes
Expanded Carrier Screening

- Expanded panel of carrier conditions, such as is currently offered by Counsyl
  - Over 100 conditions
  - Varying disease prevalence
  - Sensitivity and specificity of the testing for each condition varies widely

- Concerns
  - Residual risk can remain high, even if “screening test” was negative
  - Mutation testing as first line in a condition such as Tay Sachs in a non-Jewish individual would not reveal as much information as enzyme assay
Residual Risk

• Say your patient of Ashkenazi Jewish ancestry is found to be a Tay Sachs carrier

• Offer partner testing for Tay Sachs:
  – Let’s say he is AJ and he is negative for Tay Sachs mutation
    • Residual risk for him to be a carrier = 1/560
  – Should also offer enzyme assay (will miss 11% of AJ carriers if enzyme is not done)
    • Will bring residual risk of him being a carrier down to 1/1451

• Residual risk to the fetus needs to be reported to the couple
  – Mutation testing plus enzyme assay: 1 x 1/1451 x ¼ = 1 / 5804
  – Mutation testing alone: 1 x 1/560 x ¼ = 1/2240

• What would be the best approach for NBS for Tay Sachs?
Expanded Carrier Screening

- If a woman is identified to carry a mutation, next step requires the partner be tested. Often partners cannot be tested if they:
  - Are out of the country for work
  - Are overseas in the military
  - Are incarcerated
  - Are not insured and cannot pay for the testing

- In instances where partners are not available for testing, we often observe:
  - Increased anxiety
  - Significant financial concerns
  - Family is looking for reassurance about the newborn’s health
  - Confusion about what conditions are in prenatal test panels versus newborn screening panels
  - Should a baby be routinely “screened” or should the baby undergo diagnostic testing if prenatal testing reveals increased risk?
  - Say NBS does not cover the condition for which the mother was found to be a carrier?
Screening and Diagnosis for Aneuploidy

• Aneuploidy screening and diagnosis is a major focus of prenatal testing

• This landscape is extremely complicated and ever changing:
  – First trimester screening
  – Quad screening
  – CVS & Amniocentesis
  – Non Invasive Prenatal Testing – is this a really great screening test for a few conditions or a not so great diagnostic test for a lot of conditions?

• Patients often don’t understand precisely what tests they are undertaking and therefore finish the process with the message that “the baby is fine”

• Positive newborn screening results can come as a big surprise
Screening and Diagnosis for Microdeletion / Microduplication Syndromes

• Patients who have a diagnostic test and desire as much information as possible may elect to have chromosomal microarray analysis

• Variants of Uncertain Significance (VOUS)
  – Present significant challenges in the preconception and prenatal period, especially for “information seekers”
  – Despite the uncertain significance, couples need to make decisions, sometimes very quickly
  – Extremely difficult counseling scenarios – time consuming and anxiety provoking
  – Prenatally – some women found this information “toxic knowledge” (Bernhardt 2012: Genetics in Medicine)

• “Sick Child” syndrome
  – One woman who had prenatal CMA said: “I’m a lot more vigilant.” (Bernhardt 2012: Genetics in Medicine)
  – “Watchful waiting” has been described – effect on bonding, parenting, development ??
Screening and Diagnosis for Microdeletion & Microduplication Syndromes

- Our experience with prenatal CMA suggests that there would be challenges with using CMA in NBS:
  - Parental samples are needed to evaluate variants
  - We found benign familial variants to be extremely common (16/22 cases in our center in the first six months)
    - What are the implications for otherwise healthy parents?
    - Do they need medical evaluations?
  - Data sets are needed to allow for prospective risk prediction
    - Data is often based on affected children
  - CMA was most useful in the setting of abnormal ultrasound findings
CMA in Prenatal Diagnosis


- Of 4282 women undergoing amniocentesis who had normal fetal karyotype, findings on CMA were:

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>% clinically significant results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 35 yrs</td>
<td>1.7%</td>
</tr>
<tr>
<td>Elevated risk on screening</td>
<td>1.7%</td>
</tr>
<tr>
<td>Ultrasound anomaly</td>
<td>6.0%</td>
</tr>
</tbody>
</table>
Uncertainty and Risk Prediction

• Represents a tremendous challenge in prenatal testing
• More research is needed in order to be able to interpret results and inform prediction
• Ideally requires pre-test genetic counseling for everyone and significant post-test counseling for those with findings
  – Workforce and availability of genetic counselors may be a limiting factor
  – Educational materials that are culturally competent are needed
• In an otherwise “normal” pregnancy – uncertain information is less welcome and may be considered “toxic knowledge”
• All of these issues would be amplified if CMA were to be scaled up to NBS
Questions for Consideration in Choosing Conditions for Testing Panels

• Prenatally ... What is an improved health outcome?
  – Informed decision making?
  – Fewer affected infants?

• In the newborn period ... What is an improved health outcome?
  – Early intervention?
  – Knowledge alone?

• Should prenatal and newborn screening panels be aligned?
Thank you for your attention!

siobhanmdolan@yahoo.com