

Beyond the bloodspot

Testing and Screening Beyond Newborn Screening:

How do Advances in Prenatal Testing Impact Screening of Newborns?

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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: $1 \times 1/1451 \times 1/4 = 1 / 5804$
 - Mutation testing alone: $1 \times 1/560 \times 1/4 = 1/2240$
- 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

- Wapner et al. N Engl J Med. 2012 Dec 6;367(23):2175-84.
- Of 4282 women undergoing amniocentesis who had normal fetal karyotype, findings on CMA were:

<u>Risk factor</u>	<u>% clinically significant results</u>
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|------------------------------|------|
| • Age > 35 yrs | 1.7% |
| • Elevated risk on screening | 1.7% |
| • Ultrasound anomaly | 6.0% |

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!

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