What’s new in genetics?

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Division of Maternal Fetal Medicine
Objectives

• Review current recommendation for genetic carrier screening and new technology for expanded carrier testing
• Discuss new technology for screening for aneuploidy
• Demonstrate using case examples
Case example

• G2P1001, 39 year old Caucasian, neg family hx, 10 weeks gestation
  – What test would you offer?
    cystic fibrosis
    first trimester screen/quad screen
    CVS/Amnio
  -How would this change if she said she had Ashkenazi Jewish ancestry?
Drowned in next generation sequencing data

HELP!
Universal carrier screening

How does it work?
Who should have it?
What does it look for?
What companies offer it?
How much does it cost?
How do you counsel?
Follow up recommendations
Principles for carrier screening in prenatal setting

• Significant genetic disease
  – Natural history known of the disorders
  – Early on-set
  – Desirable to know

• Accurate test

• Follow up testing available
  – Accurate reproductive options

• Cost effective

Modified from Wilson JMG, Jungner G. (1968) Principles and practice of screening for disease
# The Current Paradigm

<table>
<thead>
<tr>
<th>Disease</th>
<th>ACMG</th>
<th>ACOG</th>
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<tbody>
<tr>
<td>Cystic Fibrosis</td>
<td>⭐⭐</td>
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<tr>
<td>Spinal Muscular Atrophy</td>
<td>⭐</td>
<td>⭐⭐</td>
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<tr>
<td>Tay-Sachs Disease</td>
<td>⭐⭐</td>
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<tr>
<td>Canavan Disease</td>
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<tr>
<td>Familial Dysautonomia</td>
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<td>Bloom Syndrome</td>
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<tr>
<td>Gaucher Disease</td>
<td>⭐</td>
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<tr>
<td>Fanconi Anemia Type C</td>
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<tr>
<td>Mucolipidosis IV</td>
<td>⭐</td>
<td></td>
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<tr>
<td>Niemann Pick Disease Type A</td>
<td>⭐</td>
<td></td>
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<tr>
<td>Sickle Cell Disease</td>
<td>⭐</td>
<td></td>
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<tr>
<td>Beta Thalassemia</td>
<td>⭐⭐</td>
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- 12 tests
- 7 ethnic panels
Ethnicity is a nebulous concept

- 1 in 7 marriages are between spouses of different races/ethnicities
- Multiracial children increased 50 percent since 2000
- 40% of individuals do not know the ancestry of all four grandparents*
- Data from one lab shows that 45% of carriers of “Jewish” diseases report no AJ ancestry

* Source: Condit, 2003. US Census Data 2010
High-throughput technology

DNA Extracted and Amplified

Strands are complementary DNA fragments for the mutation of interest

1000s of strands per chip

Chip Surface
Companies

- Counsyl
- Integrated Genetics
- Natera
- LabCorp Specialty Testing Group
Generic informed consent

- Broad overview of goal of testing
  - Inheritance pattern
  - Negative results are risk-reducing, not risk-eliminating
  - Possible outcomes
- Anxiety in carriers dissipates after counseling, much like any other screening test

Source: Lewis C, Skirton H, Jones R: Can We Make Assumptions About the Psychosocial Impact of Living as a Carrier, Based on Studies Assessing the Effects of Carrier Testing? J Genet Counsel 2011, 20:80–97
How accurate is the testing?

- This is a screening test
- Not all mutations can be detected
- A negative test significantly reduces, but does not eliminate your risk to be a carrier
Case example

• G2P1001, 39 year old Caucasian, neg family hx, 10 weeks gestation

  – What test would you offer?
    Universal carrier testing
    first trimester screen/Quad
    CVS/Amnio

  -What if the carrier screen is abnormal?
Non-invasive prenatal testing

• How does it work?
• Who should have it?
• What does it look for?
• What companies offer it?
• How much does it cost?
• How do you counsel?
• Follow up recommendations
Non-Invasive Prenatal Testing (NIPT)

- Blood draw > 10 weeks gestation
- Currently offered for patients
  - >=35 years of age at EDD
  - Abnormal screening result
  - Abnormal ultrasound
  - Family history
- Turn around time 8-14 days
- Cost
  - List price $795-$2700
  - Patient out of pocket cost dependent on insurance
Suggested Follow up of NIPT

• After **NORMAL** NIPT:
  - Nuchal translucency 11-13 6/7 wks **and**
  - msAFP 15-21 6/7 wks **and**
  - Anatomy ultrasound ~18-22 wks

• **ABNORMAL** NIPT should be confirmed by:
  – CVS 11-13 6/7 wks **or**
  – amniocentesis (>16 weeks) **or**
  – Blood chromosomes at delivery
Cell-free DNA

- As cells turnover, chromosomes fragment releasing DNA into the blood
- Cell-free DNA (cfDNA) are short DNA fragments (50-300 base pairs)
Cell-free DNA in Maternal Blood

- In pregnancy, cfDNA from both the mom and fetus are in maternal blood
- Amount of fetal cfDNA present is a small fraction of the maternal cfDNA
DNA Sequencing

Sequencing tells you which chromosome the ccf fragment comes from.
Companies

- Sequenom
- Verinata Health
- Ariosa Diagnostics
- Natera
Fetal Trisomy Detection

Each bar represents thousands of cfDNA fragments

The overabundance of chromosome 21 cfDNA fragments in trisomy 21, although small, can be measured with DNA sequencing

<table>
<thead>
<tr>
<th>Fetal Fraction</th>
<th>Expected ratio for Trisomy</th>
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<tbody>
<tr>
<td>4%</td>
<td>1.02</td>
</tr>
<tr>
<td>10%</td>
<td>1.05</td>
</tr>
<tr>
<td>20%</td>
<td>1.10</td>
</tr>
<tr>
<td>40%</td>
<td>1.20</td>
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Extra fragments derived from fetal T21

Fetal cfDNA

Maternal cfDNA

Reference chromosome

Chromosome 21 fragments
## Detection and False Positive Rates

<table>
<thead>
<tr>
<th></th>
<th>First trimester screen</th>
<th>Quad screen</th>
<th>NIPT</th>
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<tbody>
<tr>
<td></td>
<td>DR</td>
<td>FPR</td>
<td>DR</td>
</tr>
<tr>
<td>T21</td>
<td>90-95%</td>
<td>2-5%</td>
<td>80-85%</td>
</tr>
<tr>
<td>T18</td>
<td>95%</td>
<td>0.3%</td>
<td>75-80%</td>
</tr>
<tr>
<td>T13</td>
<td>95%</td>
<td>0.3%</td>
<td>-</td>
</tr>
</tbody>
</table>
Cost
Case example

• G2P1001, 39 year old Caucasian, neg family hx, 10 weeks gestation
  – What test would you offer?
    Universal carrier testing
    Non invasive prenatal testing
  - What if the patient had an increased NT?
  - What if the patient had a normal NIPT and an abnormal anatomy scan?
Genetic Counselors

• All of our genetic counselors are board certified and licensed
  – Beth Jiorle
  – Martha Dudek
  – Jill Nichols

• We have clinic at One Hundred Oaks, Clarksville, Columbia, and Franklin

• Appointments: 615-343-5700