Genomics in Women’s Health: Changing the Diagnostic and Therapeutic Paradigm

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Array technologies

- Higher resolution assessment of chromosomal abnormalities
- Numerous well-defined microdeletion/duplication syndromes exist
- Do not need suspicion for specific diagnosis
- New discoveries of previously unknown genomic disorders
The decreasing cost of sequencing…

Genetic Discrimination- the case for a European-level legal response
What is the goal 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

Why Carrier Screening?

• 1/100 babies are born with an inherited disease\(^1\)
• 20-30% of all infant deaths are due to genetic disorders\(^2\)
• 11.1% of pediatric hospital admissions are for children with genetic disorders\(^3\)
• Preconception screening for disease-causing mutations and genetic counseling for carriers can reduce the incidence of these diseases
  • Incidence of Tay Sachs disease was reduced by 90% in AJ due to awareness and screening\(^4\)

\(^1\) Monogenic disorders, World Health Organization
\(^2\) Berry, et al, 1987
\(^3\) Scriver, et al, 1973
\(^4\) Kaback, et al, 2000
Lack of family history is misleading

Rare does not mean trivial:

80% of children born with a genetic disease have no family history of the condition.²

In the US, up to 10% of infant hospitalizations are due to genetic disease.⁴

US, United States.
Ethnic-specific, panethnic, and expanded carrier screening are acceptable screening strategies, with counseling / education guidance and appropriate disease panel selection.

(ACOG Comm Opinion No. 690)
Expanded carrier screening **optimally** addresses the goal of carrier screening

- All individuals, *regardless of race or ethnicity*, are offered screening for the same set of conditions, which can include more than 100 rare genetic diseases.

*Adapted from the ACOG, ACMG Joint Statement on Expanded Carrier Screening*
How does ECS compare with current guideline-driven screening practices in a diverse population?
JAMA study evaluated >340,000 ethnically diverse patients

n = 346,790 ROUTINE EXPANDED CARRIER SCREENING

430,584 PATIENTS SCREENED

83,794 EXCLUDED
- Known carriers
- Positive family history
- Infertility
- Other

≤94 conditions

Looked at only “severe” & “profound” diseases

Largest, most diverse study population reported

*ACOG guidelines for these ethnic categories include testing for hemoglobinopathies. (HbS variants in African or African Americans including beta thalassemia and sickle cell disease, HbA variants including alpha thalassemia in Southeast Asians.) When DNA-based carrier screening for hemoglobinopathies is routinely performed, there is improved detection of at-risk pregnancies. The percentages of pregnancies affected by a non-hemoglobinopathy condition that would be missed by guidelines-based testing are: African or African-American: 82%, Southeast Asian: 81%, Southern European: 74%. Haque IS, et al. JAMA. 2016;316(7):734-742
Affected pregnancy rates across ethnicities

1 in 550 pregnancies in the US are predicted to be affected

Focus on affected pregnancies allows apples-to-apples comparisons

<table>
<thead>
<tr>
<th>Racial/Ethnic Category of Both Parents</th>
<th>Cumulative Risk (95% CI) of All Profound and Severe Conditions³</th>
</tr>
</thead>
<tbody>
<tr>
<td>African or African American</td>
<td>1/275 (1/255-1/297)</td>
</tr>
<tr>
<td>Without hemoglobinopathies</td>
<td>1/1741 (1/1397-1/2168)</td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>1/255 (1/237-1/273)</td>
</tr>
<tr>
<td>East Asian</td>
<td>1/770 (1/640-1/935)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1/1058 (1/922-1/1213)</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>1/516 (1/403-1/670)</td>
</tr>
<tr>
<td>Mixed or other Caucasian</td>
<td>1/649 (1/614-1/686)</td>
</tr>
<tr>
<td>Northern European</td>
<td>1/628 (1/593-1/665)</td>
</tr>
<tr>
<td>South Asian</td>
<td>1/896 (1/729-1/1112)</td>
</tr>
<tr>
<td>Southeast Asian</td>
<td>1/481 (1/375-1/626)</td>
</tr>
<tr>
<td>Without hemoglobinopathies</td>
<td>1/1912 (1/1329-1/2794)</td>
</tr>
<tr>
<td>Southern European</td>
<td>1/583 (1/495-1/688)</td>
</tr>
<tr>
<td>Without hemoglobinopathies</td>
<td>1/631 (1/530-1/754)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1/665 (1/617-1/716)</td>
</tr>
</tbody>
</table>
Guideline-based carrier screenings **miss a considerable percentage** of pregnancies affected by serious conditions.

Current guidelines can miss affected pregnancies.

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAST ASIAN</td>
<td>94%</td>
</tr>
<tr>
<td>HISPANIC</td>
<td>79%</td>
</tr>
<tr>
<td>NORTHERN EUROPEAN</td>
<td>65%</td>
</tr>
<tr>
<td>ASHKENAZI JEWISH</td>
<td>55%</td>
</tr>
</tbody>
</table>
We already screen for conditions that are far less common

1 IN 550 PREGNANCIES will be affected by a severe or profound condition on a sequencing-based expanded panel

1 IN 800 DOWN SYNDROME

1 IN 1000 OPEN NEURAL TUBE DEFECTS

1 IN 3400 CYSTIC FIBROSIS

Key Takeaways

1. ECS identifies **more pregnancies at risk** for severe or profound conditions than guideline-recommended panels, across ethnicities.

2. “...even though current guidelines target a number of diseases prevalent in those of European descent (such as cystic fibrosis), they **do not** identify risk for other conditions that may be **important to diverse populations**.”

Screening Technologies

• Genotyping
  • Used by many companies for routine carrier screening
  • Tests for a limited set of only common mutations
  • Provides limited utility beyond Caucasian and Jewish ethnicities

• Next-Generation Sequencing
  • Comprehensively evaluates the gene
  • Detects all known common and rare disease-causing mutations
  • Delivers higher accuracy across ethnicities
  • Associated with variants of uncertain significance (VUS)
Molecular Approaches to Carrier Screening

- Mutation “panel” – targeted genotyping: molecular techniques with highly reliable detection of known mutations; in some cases very limited detection rates (e.g., 10%)
- Sequencing – higher detection rates, but higher rate of VUS
Systematic design and comparison of expanded carrier screening panels.

Genetics in Medicine, 2017

- Results from 474,644 de-identified carrier screens to highlight strengths and limitations of different ECS methodologies.
- Expected to detect 183 affected per 100,000 US births.
- An algorithm’s sensitivity is impacted by two factors: (i) the methodology used (e.g., full-exon sequencing finds more affected conceptuses than targeted genotyping) and (ii) the detection rate of the screen for diseases with high prevalence and complex molecular genetics (e.g., fragile X syndrome). Need to determine how to handle VUS results with full sequencing screens.
# Technologies for Carrier Screening

<table>
<thead>
<tr>
<th>Test Methodology</th>
<th>Bloom’s syndrome</th>
<th>Canavan disease</th>
<th>Cystic fibrosis</th>
<th>DLD deficiency</th>
<th>Familial dysautonomia</th>
<th>Familial hyperinsulinism</th>
<th>Fanconi anemia group C</th>
<th>Glycogen storage disease 1a</th>
<th>Maple syrup urine disease 1A/1B</th>
<th>Mucolipidosis type IV</th>
<th>Niemann-Pick type A/B</th>
<th>Tay-Sachs disease</th>
<th>Usher syndrome type 1F</th>
<th>Usher syndrome type III</th>
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<tbody>
<tr>
<td>Next-Generation DNA Sequencing</td>
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<td>Multiplex Ligation-Dependent Probe</td>
<td>Alpha-thalassemia</td>
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<td>Amplification (MLPA)</td>
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<tr>
<td>Tri-Nucleotide Repeat PCR &amp;</td>
<td>Fragile X syndrome</td>
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<td>Methylation Analysis</td>
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<td>Enzyme Analysis</td>
<td>Tay-Sachs disease (Hex A)</td>
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<tr>
<td>Hemoglobin Capillary Electrophoresis</td>
<td>Beta-thalassemia</td>
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<td>Genotyping</td>
<td>Gaucher disease</td>
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<td></td>
<td>Nemaline myopathy</td>
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Choice of Laboratory

• Clinical panels found in ACOG and ACMG guidelines – based on ethnic-based assessment

• No one screening technology should be considered to be superior to another; however, certain clinical scenarios may call for the use of a particular technology

• Choice of lab should be based on service, turn-around time, cost and clinical support
Partner testing

• No standard approach
• Mutation panel versus sequencing
Approach to Carrier Screening, Clinical Genetics @ Northwestern and IMG

- Sequencing for all initial patient evaluations, VUS are not reported
- Sequencing for all partner assays, VUS are typically not reported*
Clinically Actionable Results

Comprehensive Set of Known Disease-Causing Mutations

- Rigorous, multi-year process to catalogue and evaluate each gene for all documented disease-causing variants

- Accurate, actionable results that may/may not include variants of unknown significance (VUS)
Our Approach to Carrier Screening

• While no one screening technology should be considered to be superior to another, we utilize NGS technology to evaluate a partner of an identified carrier to maximize our ability to identify a carrier couple.

• We perform an exhaustive, cross-lab assessments of VUS to determine if the variant has a more than likely possibility of pathogenesis
ACOG guidelines emphasize consistency

Carrier Screening in the Age of Genomic Medicine

“Each obstetrician–gynecologist or other health care provider or practice should establish a standard approach that is consistently offered to and discussed with each patient, ideally before pregnancy.”
## cCFNA Performance Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Detection rate (%)*</th>
<th>FPR (%)*</th>
<th>PPV (%)+ 20 yo</th>
<th>PPV (%)+ 40 yo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>930/936 (99.4)</td>
<td>26/32585 (0.16)</td>
<td>33</td>
<td>87</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>280/290 (96.6)</td>
<td>16/32065 (0.05)</td>
<td>13</td>
<td>68</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>70/81 (86.4)</td>
<td>23/24309 (0.09)</td>
<td>9</td>
<td>57</td>
</tr>
</tbody>
</table>

PPV = True Positive/True Positive + False-Positive

*ISPD Position Statement from the Chromosome Abnormality Screening Committee April 2015-Compilation of data from 17 low and high risk studies performed 2011-2015

+ACOG Committee Opinion June 2015
Deletions or duplications missed by karyotype

- G-banded karyotype can miss large (> 7 Mb) and very large (> 10 Mb) deletions or duplications¹
- Prenatal karyotype has a lower resolution than peripheral blood karyotype due to more compact chromatin structure
- Evidence that deletions/duplications greater than 7 Mb can result in abnormal developmental outcomes¹

1. Di Gregorio et al. Large cryptic genomic rearrangements with apparently normal karyotypes detected by array-CGH. *Molecular Cytogenetics* 2014, 7:82
Case study: 7 Mb threshold for deletions or duplications

Represents a sizeable event that would warrant clinical investigation

- Pregnancy with:
  - IUGR
  - Cardiac anomaly
  - Short limbs
  - Agenesis corpus callosum

- Prenatal karyotype performed via CVS indicated a normal female fetus (46,XX)

- Array performed on POC noted de novo translocation:
  - 13.0 Mb duplication at 7p22.3p22.3
  - 12.4 Mb deletion at 11q24.1q25

Di Gregorio et al. Large cryptic genomic rearrangements with apparently normal karyotypes detected by array-CGH. *Molecular Cytogenetics* 2014, 7:82
Consensus Statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies

Microarray analysis is recommended in pregnancies with one or more fetal structural anomalies. Replaces the need for fetal karyotype.

Either karyotyping or microarray in cases with structurally normal fetus

Not restricted to patients > age 35

Recommended for evaluation of fetal demise or stillbirth
Chromosomal Microarray versus Karyotyping for Prenatal Diagnosis

<table>
<thead>
<tr>
<th>Indication for Prenatal Diagnosis</th>
<th>Normal Karyotype</th>
<th>Common Benign</th>
<th>Pathogenic</th>
<th>Uncertain Clinical Significance (N=130)</th>
<th>Total Known Pathogenic and Potential for Clinical Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>no. (%)</td>
<td></td>
<td>Likely to Be Benign</td>
<td>Potential for Clinical Significance</td>
</tr>
<tr>
<td>Any</td>
<td>3822</td>
<td>1234 (32.3)</td>
<td>35 (0.9)</td>
<td>69 (1.8)‡</td>
<td>96 (2.5) [2.1–3.1]</td>
</tr>
<tr>
<td>Advanced maternal age</td>
<td>1966</td>
<td>628 (31.9)</td>
<td>9 (0.5)</td>
<td>37 (1.9)</td>
<td>25 (1.3)</td>
</tr>
<tr>
<td>Positive on Down's syndrome screening</td>
<td>729</td>
<td>247 (33.9)</td>
<td>3 (0.4)</td>
<td>13 (1.8)</td>
<td>9 (1.2)</td>
</tr>
<tr>
<td>Anomaly on ultrasonography</td>
<td>755</td>
<td>247 (32.7)</td>
<td>21 (2.8)</td>
<td>16 (2.1)</td>
<td>45 (6.0) [4.5–7.9]</td>
</tr>
<tr>
<td>Other§</td>
<td>372</td>
<td>112 (30.1)</td>
<td>2 (0.5)</td>
<td>3 (0.8)</td>
<td>5 (1.3) [0.6–3.1]</td>
</tr>
</tbody>
</table>
NICHD microarray study

• 4282 prenatal specimens with traditional karyotype PLUS 1 of 3 array platforms
• ~50% AMA, ~25% abn sono, ~20% +screen
• 100% concordance for common aneuploidies
• 22/22 unbalanced translocations detected
• Sono abnormalities: 6.0% additional array abnormalities detected (normal karyotype)
• AMA or +screen: 1.6% incidence “clinically relevant” CNV detected

Wapner et al, 2013, NEJM
Updated Prospective aCGH results
Signature Genomic Laboratories

<table>
<thead>
<tr>
<th>Indication</th>
<th>Normal (%)</th>
<th>Unclear (%)</th>
<th>Significant (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal ultrasound</td>
<td>2462 (88.5)</td>
<td>135 (4.9)</td>
<td>184 (6.6)</td>
<td>2781</td>
</tr>
<tr>
<td>Abnormal ultrasound: only soft markers(^a)</td>
<td>72 (93.5)</td>
<td>3 (3.9)</td>
<td>2 (2.6)</td>
<td>77</td>
</tr>
<tr>
<td>Abnormal MISH</td>
<td>68 (88.3)</td>
<td>5 (6.5)</td>
<td>4 (5.2)</td>
<td>77</td>
</tr>
<tr>
<td>Family history(^b)</td>
<td>461 (94.7)</td>
<td>11 (2.3)</td>
<td>15 (3.1)</td>
<td>487</td>
</tr>
<tr>
<td>AMA alone</td>
<td>337 (97.4)</td>
<td>8 (2.3)</td>
<td>1 (0.3)</td>
<td>346</td>
</tr>
<tr>
<td>Anxiety alone</td>
<td>94 (98.9)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
<td>95</td>
</tr>
<tr>
<td>Other or not specified</td>
<td>12 (92.3)</td>
<td>0 (0.0)</td>
<td>1 (7.7)</td>
<td>13</td>
</tr>
<tr>
<td>Total (nondemise)</td>
<td>3506 (90.5)</td>
<td>163 (4.2)</td>
<td>207 (5.3)</td>
<td>3876</td>
</tr>
<tr>
<td>Fetal demise</td>
<td>359 (86.1)</td>
<td>34 (8.2)</td>
<td>15 (3.6)</td>
<td>417</td>
</tr>
</tbody>
</table>

*Excludes cases referred with known abnormal karyotype or known parental translocations

Shaffer et al, Prenat Diagn 2012
Use of microarray in prenatal testing

*Insight Medical Genetics*

- From amnio or CVS: same day FISH
- With structural anomalies, normal FISH reflexes to direct array analysis (limited metaphase analysis)
- If structurally normal, patient may elect array (either direct or cultured)
Expanded Indications for PGT (A/M)

• Autosomal dominant and recessive conditions
• X-linked disorders
• Adult-onset disorders
  – Cancer predisposition
  – Cardiovascular disease
• Early-onset Alzheimer’s disease
• HLA genotyping
• Aneuploidy testing by SNP, qPCR, aCGH or NGS
Estimated Number of New Cases in USA for the Four Major Cancers (all ages) by Gender 2017

- **Total Colon & rectum**
  - Male: 900,000
  - Female: 900,000
- **Lung & bronchus**
  - Male: 500,000
  - Female: 500,000
- **Breast**
  - Male: 200,000
  - Female: 200,000
- **Prostate**
  - Male: 100,000
  - Female: 100,000
Steady Increase of PGD cycles for cancer predisposition after first description in 1999
• Familial Adenomatous Polyposis
• Familial Nonpolyposis, Type 1, 2 and 4
• Li Fraumeni Syndrome
• Von Hippel-Lindau Syndrome
• BRCA 1 & 2
• Familial PFB tumor
• Gastric cancer
• Retinoblastoma, RB 1
• Neurofibromatosis 1 & 2
• BCNS, Gorlin Syndrome
• Tuberous Sclerosis, Type 1 & 2
• Ataxia Teleangiectasia
• Fanconi Anemia A, C, D, E, F, J
• Multiple endocrine neoplasm (MEN1 & 2)
• Peutz-Jeghers syndrome
• Exostoses Multiple (EXT 1 & 2)
• Ataxia telangiectasia; AT
• Pleuropulmonary Blastoma
<table>
<thead>
<tr>
<th>Disease</th>
<th># Patient</th>
<th># Cycle</th>
<th># Transfers</th>
<th># Embryo transferred</th>
<th>Pregnancy</th>
<th>Delivery</th>
<th>Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAXIA-TELANGEICTASIA; AT</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>2</td>
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<td>BCNS(GORLIN)</td>
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<td>7</td>
<td>6</td>
<td>10</td>
<td>4</td>
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<tr>
<td>BRAIN TUMOR</td>
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<td>BRCA 1 and 2</td>
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<td>210</td>
<td>150</td>
<td>169</td>
<td>71</td>
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<td>FANCA,C,D,E,F,J</td>
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<td>FAMILIAL ADENOMATOUS POLYPOSIS 1</td>
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<td>HNPCC 1, 2, 4 and 5</td>
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<td>LI-FRAUMENI SYNDROME 1</td>
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<td>MEN1, MEN 2A</td>
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<td>NF1, NF2</td>
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<td>RETINOBLASTOMA; RB1</td>
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<td>VON HIPPEL-LINDAU SYNDROME; VHL</td>
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<td>EXOSTOSIS MULTIPLE EXT1 &amp; EXT2</td>
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<td>22</td>
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<td>PEUTZ-JEGHER SYNDROME</td>
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<td>6</td>
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<td>PLEUROPULMONARY BLASTOMA</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td><strong>349</strong></td>
<td><strong>642</strong></td>
<td><strong>472</strong></td>
<td><strong>696</strong> (1.5)</td>
<td><strong>250</strong> (53%)</td>
<td><strong>227</strong> (90.1%)</td>
<td><strong>263</strong></td>
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</tbody>
</table>
PGT-M

Cardiac Disease
Predisposition
PGT-M for LONG QT SYNDROME TYPE 1

Markers order:
- D11S1984
- D1S1318
- KCNQ1
- D11S4088
- D11S988

191 191
287 187
N N
204 200
124 124

179 191
191 179
S344E N
170 176
130 130

206 195
189 179
N N
174 170
120 120

KCNQ1 A344E

PGD

34 yo

Trophectoderm analysis

1 2 3 4 7 8 9 10

206 179
195 179
195 191
206 179
195 191
195 191
195 191
195 191

197 179
191 179
N N
170 204
120 124
120 124
120 124
120 124

MUTANT MUTANT NORMAL MUTANT NORMAL NORMAL NORMAL NORMAL

NGS 46, XX 46, XY 45, -16, XY 46, XX 46, XX 47, XX, +11, -16, +22

PGT-M for LONG QT SYNDROME TYPE 2

Markers order:
- D75688
- D752426
- KCN2
- D75642
- D752461

154 158
149 144
N G6045
90 88
113 107

156 154
128 136
94 88
107 109

158 156
136 144
N G6045
88 88
109 107

154 156
149 128
N N
90 94
113 107

34 yo

PGD

Trophectoderm analysis

1 2 3 4 12

154 156
149 128
149 149
90 94
113 107

154 156
149 128
149 149
90 94
113 107

NORMAL MUTANT NORMAL NORMAL NORMAL NORMAL

NGS 45, -16, XY 46, XY 46, XX 46, XX 46, XX 46, XX

PGT for LONG QT SYNDROME TYPE 1

EMBRYO #1 46, XX

EMBRYO #10 47, XX, +11, -16, +22

EMBRYO #3 46, XX

EMBRYO #1 45, -16, XY

EMBRYO #3 46, XX
## PGT-M Outcomes for Inherited Cardiac Condition

<table>
<thead>
<tr>
<th>Disease</th>
<th># Patient</th>
<th># Cycle</th>
<th># Transfers</th>
<th># Embryos transferred</th>
<th>Pregnancy</th>
<th>Delivery</th>
<th>Birth</th>
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<tbody>
<tr>
<td>CARDIOMYOPATHY, DILATED - ALL TYPES (TYPE 1A, 1DD, 1E, 1G)</td>
<td>11</td>
<td>23</td>
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<tr>
<td>CARDIOMYOPATHY, FAMILIAL HYPERTROPHIC - ALL TYPES (CMH1, CMH2, CMH4, CMH7, CMH8)</td>
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<tr>
<td>LONG QT SYNDROME - ALL TYPES (LQT1, LQT2, LQT8)</td>
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<td>CARDIOENCEPHALOMYOPATHY</td>
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<td>CARDIOSKELETAL MYOPATHY</td>
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<td>MYOPATHY, MYOFIBRILLAR, 1; MFM1</td>
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<td>HOLT-ORAM SYNDROME; HOS</td>
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<td>NOONAN SYNDROME 1; NS1</td>
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<tr>
<td>ACYL-CoA DEHYDROGENASE, VERY LONG-CHAIN, DEFICIENCY OF; ACADVLD</td>
<td>5</td>
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<td>8</td>
<td>12</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td><strong>44</strong></td>
<td><strong>71</strong></td>
<td><strong>61</strong></td>
<td><strong>85</strong> (1.4)</td>
<td><strong>31</strong> (51%)</td>
<td><strong>29</strong> (93%)</td>
<td><strong>32</strong></td>
</tr>
</tbody>
</table>
Conclusions

• New technologies developed from the Human Genome Project have profoundly altered our approach to conventional prenatal genetic assessment, improving accuracy as well as clinical service.

• The new technologies have allowed us to expand genetic screening and testing from the pediatric and prenatal venues to cancer and adult disease predisposition assessment.
Conclusions

• While in its infancy, germinal and somatic genomic analyses are being used to provide more targeted and effective therapies for cancer and adult diseases, thus ushering in the era of “personalized medicine”
תודה רבה לכם
זה נמרל להיות
בצל אביג!!