Prenatal Genetic Testing
It’s more than Just Chromosomes!

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Disclosure Statement
Anthony R. Gregg, MD

• I have no relevant financial relationships to disclose or conflicts of interest to resolve.
• I will not discuss any unapproved or off-label, experimental or investigational use of a product, drug or device.
Objectives

- NIPS (non-invasive prenatal screening)
- array CGH (chromosome genomic hybridization)
- ECS (expanded carrier screening)

What is the value added for patients?
Some caveats to results interpretation?
Disruptive technologies?
<table>
<thead>
<tr>
<th></th>
<th>DS</th>
<th>Euploid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test +</strong></td>
<td>TP</td>
<td>FP</td>
</tr>
<tr>
<td><strong>Test -</strong></td>
<td>FN</td>
<td>TN</td>
</tr>
</tbody>
</table>

**Sens (DR):** \( \frac{TP}{TP + FN} \)

**Spec:** \( \frac{TN}{TN + FP} \)

Independent of Prevalence

TP = true positive, TN = true negative, FP = false positive, FN = false negative, Sens = sensitivity, DR = detection rate, Spec = Specificity
<table>
<thead>
<tr>
<th>PostTest</th>
<th>DS</th>
<th>Euploid</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Test +</td>
<td>TP</td>
<td>FP</td>
<td>PPV: TP/TP+FP</td>
</tr>
<tr>
<td>Test -</td>
<td>FN</td>
<td>TN</td>
<td>NPV: TN/TN+FN</td>
</tr>
</tbody>
</table>

**PPV:** True Positive Rate

**NPV:** True Negative Rate

**Depends on Prevalence**
Genomic Testing

Analytical Validity

Does the test work in the lab?

Clinical Validity

Does the test work using human samples that are contrived for research purposes?

Marketing

Analytical Validity

Intellectual Property

Venture Capital
# Validation Down Syndrome

<table>
<thead>
<tr>
<th>Company</th>
<th>N</th>
<th>Pop.</th>
<th>DR</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sequenom</strong>&lt;br&gt;MPSS</td>
<td>Eup: 1484 T21: 212</td>
<td>High Risk&lt;br&gt;(prospective)&lt;br&gt;(11-20 wks)</td>
<td>98.6</td>
<td>99.7</td>
</tr>
<tr>
<td></td>
<td>Eup: 410 T21: 39</td>
<td>High Risk&lt;br&gt;(retrospective)&lt;br&gt;(8-36 wks)</td>
<td>100</td>
<td>99.8</td>
</tr>
<tr>
<td><strong>Ariosa</strong>&lt;br&gt;DANSR&lt;br&gt;FORTE</td>
<td>Eup: 123 T21: 36</td>
<td>Selected&lt;br&gt;(retrospective)&lt;br&gt;(&gt; 10)</td>
<td>&gt;99</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td></td>
<td>Eup: 300 T21: 50</td>
<td>High Risk&lt;br&gt;(retrospective)&lt;br&gt;(11-13 wks)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Eup: 2888 T21: 81</td>
<td>Selected&lt;br&gt;(≥10)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><strong>Verinata</strong>&lt;br&gt;MPSS</td>
<td>Eup: 404 T21: 89</td>
<td>High Risk&lt;br&gt;(prospective)&lt;br&gt;(10-23 wks)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><strong>Natera</strong>&lt;br&gt;PS</td>
<td>Eup: 142 T21: 11</td>
<td>Selected&lt;br&gt;(prospective)&lt;br&gt;(≥9 wks)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Eup 192 T21: 25</td>
<td>Selected</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Aneuploidy Screening

Down Syndrome Detection

~ 30%

Age

Decade

1980  1990  2000  2010
Aneuploidy Screening

Down Syndrome Detection

Age

Biochemistry

1980 Decade

~30%

~50%

~69%

~81%

~85-88%

MSAFP

Serum Integrated Quadruple

Triple
Aneuploidy Screening

Down Syndrome Detection

- ~98%
- ~95%
- ~88-94%
- ~85-88%
- ~82-87%
- ~81%
- ~69%
- ~64-70%
- ~50%
- ~30%

- MSAFP
- Nuchal Translucency
- Triple
- Quadruple
- Serum Integrated

- NIPS
- FETAL GENOMICS

ULTRASOUND & BIOCHEMISTRY

Biochemistry

Ultrasound

Stepwise-Sequential
Contingent-Sequential
First Trimester

Age

Decade

1980
1990
2000
2010
Genomic Testing

- Clinical Validity
- Professional Societies
- Analytical Validity
- Marketing

International Society for Prenatal Diagnosis
01’11; 01’12; 05’13; 03’15

National Society of Genetics Counselors
11’12; 01’13

American College of Obstetricians and Gynecologists
12’12; 09’15

American College of Medical Genetics and Genomics
05’13; (2016)
Genomic Testing

Clinical Validity

Analytical Validity

Professional Societies

Marketing

Is the test useful?

Clinical Utility
Clinical Utility of Genetic Testing

- Diagnostic thinking
  - Value of information in understanding the diagnosis, cause, and prognosis
- Therapeutic choice
  - Use of test results in clinical management
- Patient outcomes
  - Quality of life
- Societal impact
  - Cost effectiveness

Subject to Assumptions and Bias

PPV NPV

Grosse and Khoury, CDC
PPV and NPV
Decision Making

Do Nothing
Informed
- Expectations
- Prognosis
- Diagnostic odyssey
- Prevention
- Treatment

Delivery Planning
- Location
- Mode
- Timing

Discontinue
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>T-21</th>
<th>Sens (DR)</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>NIPS</td>
<td>Conv</td>
<td>NIPS</td>
<td>Conv</td>
</tr>
<tr>
<td>Care</td>
<td>~1920</td>
<td>5</td>
<td>100</td>
<td>100</td>
<td>99.7</td>
<td>96.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>47.8-100</td>
<td>99.8-100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Next</td>
<td>15,841</td>
<td>ALL</td>
<td>100</td>
<td>78.9</td>
<td>99.9</td>
<td>94.6</td>
</tr>
<tr>
<td>&lt; 35y</td>
<td>100</td>
<td></td>
<td>100</td>
<td>99.9</td>
<td></td>
<td>76.0</td>
</tr>
<tr>
<td>Low Risk</td>
<td>100</td>
<td></td>
<td>100</td>
<td>99.9</td>
<td></td>
<td>50</td>
</tr>
</tbody>
</table>

Bianchi DW, Parker LR et al. NEJM Feb 27, 2014
Norton ME, Jacobsson B et al. et al. NEJM Apr 29, 2015; 372; 89-97
### Clinical Utility - PPV

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>N</th>
<th>DR</th>
<th>FPR (%)</th>
<th>True Positive</th>
<th>False Positive</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEXT 1</td>
<td>&lt;35</td>
<td>11,994</td>
<td>100%</td>
<td>0.05</td>
<td>19 (1/631)</td>
<td>6</td>
<td>76.0</td>
</tr>
<tr>
<td></td>
<td>≥35</td>
<td>3,847</td>
<td>100%</td>
<td>0.08</td>
<td>19 (1/202)</td>
<td>3</td>
<td>86.4</td>
</tr>
<tr>
<td>BGI 2</td>
<td>&lt;35</td>
<td>40,287</td>
<td>99.0%</td>
<td>0.05</td>
<td>96 (1/420)</td>
<td>22</td>
<td>81.4</td>
</tr>
<tr>
<td></td>
<td>≥35</td>
<td>72,382</td>
<td>99.2%</td>
<td>0.05</td>
<td>624 (1/116)</td>
<td>39</td>
<td>94.1</td>
</tr>
</tbody>
</table>

No significant differences between low risk and high risk for DR and FPR

N= 128,510

2Zhang et al., Ultrasound Obstet Gynecol 2015. 45;530-538
.1%/week increase

21 wks

Mat. Wt. (kg) | # 2nd draw ≥ 4% | # total patients (135 redraws) | % 2nd draw ≥ 4%
---|---|---|---
<90 | 30 | 42 | 71.4
≥90<100 | 14 | 23 | 60.9
≥100<110 | 13 | 22 | 59.1
≥110<120 | 10 | 17 | 58.8
≥120<130 | 2 | 7 | 28.6
≥130<140 | 5 | 13 | 38.5
≥140 | 2 | 11 | 18.2

22,384 patients
1.9% re-draw
56% with >4% on second draw
Mat. Wt.: 103 kg v 73 kg (p<.0001)
GA: 13.9 v 15.8 (P<.0001)

Wang Prenatal Diagnosis 2013, 33, 662–666
## “No Calls”

<table>
<thead>
<tr>
<th></th>
<th>N (1052)</th>
<th>Aneuploid Fetus (n=125)</th>
<th>% Aneuploidy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO CALL</td>
<td>86</td>
<td>20 (16%)</td>
<td>23.3</td>
</tr>
<tr>
<td>RESULTS</td>
<td>966</td>
<td>105 (84%)</td>
<td>10.9</td>
</tr>
</tbody>
</table>

2.5 (1.5-4.3) fold more likely to have a fetus with aneuploidy

Pergament E, Cuckle H, et.al. Obstet and Gynecol August 2014
### Fetal Fraction

<table>
<thead>
<tr>
<th>Aneuploidy (N=20)</th>
<th>Low Fraction (&lt;3.8%)</th>
<th>3.4% (1.5 percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Very Low</td>
</tr>
<tr>
<td>15 (75%)</td>
<td>10 (50%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fraction &lt;3.4% (very low)</th>
<th>N</th>
<th>Aneuploidy</th>
<th>% Aneuploidy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraction &lt;3.4% (very low)</td>
<td>24</td>
<td>10</td>
<td>41.7</td>
</tr>
<tr>
<td>Fraction &gt;3.4%</td>
<td>1009</td>
<td>113</td>
<td>11.2</td>
</tr>
</tbody>
</table>

Pergament E, Cuckle H, et.al. Obstet and Gynecol August 2014
## Next Trial and No Calls

<table>
<thead>
<tr>
<th>Aneuploidy</th>
<th>N (488=3%)</th>
<th>No Calls (N= 488)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>3</td>
<td>ff&lt;4%</td>
<td>192 (1.2%)</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>1</td>
<td>ff unmeasurable</td>
<td>83 (0.5%)</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>2</td>
<td>High assay variance</td>
<td>213 (1.3%)</td>
</tr>
<tr>
<td>Triploidy</td>
<td>4</td>
<td>Maternal Weight (&lt;4%ff))</td>
<td>93.7 (kg)</td>
</tr>
<tr>
<td>Mosaic Trisomy 16</td>
<td>1</td>
<td>Maternal Weight (&gt;4%ff)</td>
<td>65.8 (kg)</td>
</tr>
<tr>
<td>11p deletion</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>13</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of No Calls</td>
<td>1/38 (2.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromosome abn in cohort (N=68)</td>
<td>1/236 (0.4%)</td>
<td></td>
<td>Norton ME, et.al. 2015 NEJM 372;1589-1597 (Ariosa)</td>
</tr>
</tbody>
</table>

*P<.001*
NIPS Take Aways

Summary Points

• Evaluating placental DNA
• Best Screening Test for ALL
• Commonly tested Aneuploidy
• SCREENING test (FP and FN)
• ANY Positive – Offer Dx Testing
• “No Calls” – treat as a positive SCREEN

Add-Ons and Controversies

• Sex chromosomes
• Microdeletion/Duplications
• Calculators

Disruption

• Earlier decision making
• Informed decision making
• Challenges “soft markers”
• Easier to manage “buffet”
Prenatal **diagnosis** of chromosomal abnormalities

- Standard karyotype on metaphase chromosomes
- Rapid FISH for aneuploidy - interphase
- Gene Targeted FISH (metaphase) for specific indications (family history, fetal CHD)

**Genomic resolution**

- G banding [> 4 Mb]
- FISH [40 to 250 Kb per clone]
Limitations of prior approaches

- Microdeletions and duplications are poorly or not detected with Karyotype or Interphase FISH.
- Hundreds of microdeletion and duplication syndromes.
- Often severe phenotype after birth, with no or non-specific prenatal findings, therefore no specific metaphase (targeted) FISH testing.
- Baseline risk 1-2% and heritable
Example: array CGH Trisomy 21

<table>
<thead>
<tr>
<th>Chr</th>
<th>Min. Start</th>
<th>Min. Stop</th>
<th>Max. Start</th>
<th>Max. Stop</th>
<th>RefSeq Genes (max. 50)</th>
<th>Value</th>
<th>Status</th>
<th>Plot</th>
<th>UCSC Similar Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>21:q11.2-q22.3</td>
<td>14,445,069</td>
<td>46,913,767</td>
<td>1</td>
<td>46,944,323</td>
<td>LIPI, RBM11, HSPA13, SAMSN1, NRP1, USP25, C21orf34, CXADR, BTG3, C21orf91, CHODL, PRSS7, NCAM2, MRPL39, JAM2, ATP5J, QABPA, APP, CYYR1, ADAMTS1, ADAMTS5, N6AMT1, ZNF294, RWD2B, USP16, CCTB, C21orf7, BACH1, GRIK1, CLDN17, CLDN8, KRTAP24-1, KRTAP25-1, KRTAP26-1, KRTAP27-1, KRTAP23-1, KRTAP13-2, KRTAP13-1, KRTAP13-3, KRTAP13-4, KRTAP15-1, KRTAP19-1, KRTAP19-2, KRTAP19-3, KRTAP19-4, KRTAP19-5, KRTAP19-6, KRTAP19-7, KRTAP6-3, KRTAP6-2</td>
<td>GAIN</td>
<td>ABNORMAL (POSITIVE FINDING)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
array CGH results

- **Type 1**: Well established microdeletion duplication syndromes
- **Type 2**: Long segments of AOH resulting in increased risk for conditions associated with UPD (imprinting) or recessive conditions
- **Type 3**: Benign or Likely Benign (constant curation)
  - **Type 4**: Unknown clinical significance (incomplete penetrance or variable expression)
  - **Type 5**: Unknown clinical significance (no descriptions within the region)
  - **Type 6**: Complex or uncertain significance (AOH, first cousins), UPD in regions not known to be imprinted
Well established micro deletion/duplication syndromes

- 1p36.3 deletion
- **DiGeorge syndrome**
  - Angelman syndrome / Prader-Willi syndrome
  - Williams syndrome (deletion) / duplication WS region
  - Smith Magenis syndrome / Potocki-Lupski syndrome
  - Miller-Dieker critical region
  - Neurofibromatosis (NF1)
  - MECP2 duplication
## Normal Karyotype

### Clinically Significant CMA

<table>
<thead>
<tr>
<th>Study (N)</th>
<th>AMA (%)</th>
<th>DS Screen (%)</th>
<th>All*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fiorentino</strong> (3,000)</td>
<td>6/1118 (0.5)</td>
<td>0/29(0)</td>
<td>24/3000 (0.8)**</td>
</tr>
<tr>
<td>Shaffer† (2,533)</td>
<td>1/346 (0.3)**</td>
<td>4/77 (5.2)**</td>
<td>140/2533 (5.5)</td>
</tr>
<tr>
<td>Wapner (4,406)</td>
<td>9/1966 (0.5)**</td>
<td>3/729 (0.4)**</td>
<td>35/3822 (0.9)**</td>
</tr>
<tr>
<td></td>
<td>25/1966(1.3)**</td>
<td>9/729 (1.2)**</td>
<td>61/3822(1.6)**</td>
</tr>
</tbody>
</table>

† Uncertain exactly what percent had normal Karyotype
* Includes other categories in study
** Pathogenic  *** potentially pathogenic

Fiorentino et al. Eur J Hum Genet 2013, 21; 725–730
Shaffer et al. Prenat Diag 2012, 32; 986–995
## Abnormal US and Normal Karyotype

### Clinically Significant CMA

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Abn Karyo</th>
<th>Micro Del/Dup (%)</th>
<th>Sono Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiorentino</td>
<td>95</td>
<td>26 (27.4)</td>
<td>6 (6.3)</td>
<td>2 tetrology</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 NT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 hygroma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 SUA</td>
</tr>
<tr>
<td>Shaffer</td>
<td>2534</td>
<td>-</td>
<td>186 (6.5)</td>
<td>14/142 soft markers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>81/1519 isolated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>58/579 multiple anom</td>
</tr>
<tr>
<td>Wapner</td>
<td>755</td>
<td>354 (31.9)</td>
<td>21/755 Path</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24/755 Pot. Path</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Total 6%)</td>
<td></td>
</tr>
</tbody>
</table>

Fiorentino et al. *Eur J Hum Genet* 2013, 21; 725–730  
Shaffer et al. *Prenat Diag* 2012, 32; 986–995  
Comparing two Screening Approaches with array CGH Option

Offer Amnio

Amnio

More diagnoses will be made
Karyotype +/- array CGH
Comparing two Screening Approaches with array CGH Option

- With a low false positive rate the identification of common aneuploidies will be high (high detection rate).
- The number of patients offered an amniocentesis will be relatively low after a +NIPS.
- Will “pick-up” fewer array abnormalities, because of fewer amniocenteses (0.5% FP driver).

39% Uptake

Probability of diagnostic testing after positive MMS and NIPS is available
Comparing two Screening Approaches with array CGH Option

- With a higher false positive rate and high detection the identification of common aneuploidies will be high.
- But the number of patients being offered an amniocentesis will be high (5% FP driver), therefore more array abnormalities diagnosed.
Comparing two Screening Approaches with array CGH Option

NIPS - Offer Screening

Stepwise sequential - Offer Amnio

Approximately 0.5% FP
5% FP

39% Uptake
39-78% Uptake

Amnio - 10X
## Sex Chromosomes and Microdel/dups

<table>
<thead>
<tr>
<th>Whole Chromosome Aneuploidy</th>
<th>Live Birth Frequency</th>
<th>Microdel/ Microdup</th>
<th>Live Birth Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>1/800</td>
<td>22q11.2 (DiGeorge)</td>
<td>1/3,000</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>1/6,000</td>
<td>1p36 del</td>
<td>1/5,000</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>1/7,000-1/33,000</td>
<td>Prader-Willi S.</td>
<td>1/10,000</td>
</tr>
<tr>
<td>45, X</td>
<td>1/2,500</td>
<td>Angelman S.</td>
<td>1/12,000</td>
</tr>
<tr>
<td>47, XXY</td>
<td>1/500</td>
<td>Cri-du-chat</td>
<td>1/20,000</td>
</tr>
<tr>
<td>47,XXX</td>
<td>1/1,000 females</td>
<td></td>
<td></td>
</tr>
<tr>
<td>47, XYY</td>
<td>1/1,000 males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole Chromosome Aneuploidy</td>
<td>Live Birth Frequency</td>
<td>Microdel/ Microdup</td>
<td>Live Birth Frequency</td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------------</td>
<td>--------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>1/800</td>
<td>22q11.2 (DiGeorge)</td>
<td>1/3,000</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>1/6,000</td>
<td>1p36 del</td>
<td>1/5,000</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>1/7,000-1/33,000</td>
<td>Prader-Willi S.</td>
<td>1/10,000</td>
</tr>
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<td>45, X</td>
<td>1/2,500</td>
<td>Angelman S.</td>
<td>1/12,000</td>
</tr>
<tr>
<td>47, XXY</td>
<td>1/500</td>
<td>Cri-du-chat</td>
<td>1/20,000</td>
</tr>
<tr>
<td>47,XXX</td>
<td>1/1,000 females</td>
<td></td>
<td></td>
</tr>
<tr>
<td>47,XYY</td>
<td>1/1,000 males</td>
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</tbody>
</table>
## Treatment

<table>
<thead>
<tr>
<th>Whole Chromosome Aneuploidy</th>
<th>Live Birth Frequency</th>
<th>Microdel/ Microdup</th>
<th>Live Birth Frequency</th>
</tr>
</thead>
<tbody>
<tr>
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<td>22q11.2 (DiGeorge)</td>
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## Diagnostic Odyssey

### Early Childhood Intervention

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</table>
array CGH Take Aways

Summary Points
• Diagnostic test
• CNVs are common
• Greater resolution than Karyotype or interphase FISH
• Brings more actionable results
• Normal result ≠ NO genetic condition
• Follow-up positives with genetics professional

Data
• 6% if US abnormality
• 1-2 % general population

Disruption
• Less likely Used Reflexively Cost VUS
Expanded Carrier Screening in Reproductive Medicine—Points to Consider
A Joint Statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine

Janice G. Edwards, MS, Gerald Feldman, MD, PhD, James Goldberg, MD, Anthony R. Gregg, MD, Mary E. Norton, MD, Nancy C. Rose, MD, Adele Schneider, MD, Katie Stoll, MS, Ronald Wapner, MD, and Michael S. Watson, MD

Facilitator: JGE
American College of Medical Genetics and Genomics: GF, ARG, AS, MSW
Perinatal Quality Foundation: JG, RW
American College of Obstetricians and Gynecologists: NR
Society for Maternal Fetal Medicine: MN
National Society of Genetic Counselors: KS
ECS: What is it? and Why offer it?

- **Identifies** carriers / carrier couples
- **Can inform patients of risks and options**
  - Altered **Preconception decision making**
    - Preimplantation genetic diagnosis
    - Non-carrier donor gametes as additional options.
  - Altered **Prenatal decision making**
    - prenatal management
    - delivery planning and coordination of care
    - pregnancy termination or
    - adoption planning.
- **Education**
  - Early neonatal interventions  
  Edwards JG, et.al. 2015 *Obstet and Gynecol* 653-662
Target Conditions

• The conditions screened for should encompass one or more of the following:
  – Cognitive disability.
  – Available surgical or medical intervention.
  – Impacts quality of life.
  – Conditions for which a prenatal diagnosis may result in:
    • Prenatal interventions that improve outcomes
    • Delivery management that improves care
    • Prenatal education of parents regarding special needs care after birth; this often may be accomplished most effectively before birth (e.g. avoiding the diagnostic odyssey)

Edwards JG, et.al. 2015 Obstet and Gynecol 653-662
Residual Risk

- Population Carrier Frequency
- Detection Rate (DR)

Equation:

\[ \text{Carrier Frequency}_{pop} \times (1 - \text{Detection Rate}) \]
<table>
<thead>
<tr>
<th>Condition</th>
<th>Carrier freq</th>
<th>Condition</th>
<th>Carrier freq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaucher disease</td>
<td>1/15</td>
<td>Fanconi anemia group C</td>
<td>1/89</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1/29</td>
<td>Niemann-Pick disease type A</td>
<td>1/90</td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
<td>1/30</td>
<td>Bloom syndrome</td>
<td>1/100</td>
</tr>
<tr>
<td>Familial dysautonomia</td>
<td>1/32</td>
<td>Mucolipidosis IV</td>
<td>1/127</td>
</tr>
<tr>
<td>Canavan disease</td>
<td>1/40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>DNA DR</th>
<th>Condition</th>
<th>DNA DR</th>
</tr>
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<tbody>
<tr>
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<td>95%</td>
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<td>95%</td>
</tr>
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<td>Canavan disease</td>
<td>98%</td>
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</tr>
</tbody>
</table>

* ACMG Recommended 23 Mutations

ACOG, Committee Opinion No. 442, 2009. Prenatal carrier screening... Eastern European Jewish Descent)
## Pan ethnic: < 1/100 Carrier Frequency

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Carrier Frequency (CF*)</th>
<th>Residual Risk (RR**)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor XI Deficiency</td>
<td>92</td>
<td>133</td>
</tr>
<tr>
<td>Non-Syndromic Hearing Loss</td>
<td>43</td>
<td>163</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>65</td>
<td>189</td>
</tr>
<tr>
<td>MCAD</td>
<td>69</td>
<td>228</td>
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<tr>
<td>Alpha Thalassemia</td>
<td>25</td>
<td>241</td>
</tr>
<tr>
<td>Wilson Disease</td>
<td>90</td>
<td>242</td>
</tr>
<tr>
<td>Smith Lemli Opitz (SLO)</td>
<td>68</td>
<td>249</td>
</tr>
<tr>
<td>Pendred</td>
<td>80</td>
<td>273</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>45</td>
<td>315</td>
</tr>
<tr>
<td>Spinal Muscular Atrophy</td>
<td>60</td>
<td>670</td>
</tr>
<tr>
<td>Malonic/Methylmalonic Aciduria (MMA)</td>
<td>86</td>
<td>774</td>
</tr>
</tbody>
</table>

Carrier frequency is 1/ CF* and residual risk is 1/ RR**
Number of Conditions Screened

Risk

Not Impacted

Conditions Screened

Risk

Not Impacted
Number of Conditions Screened

Risk
- Not Impacted
- Residual Risk

Risk Reduction After Testing

Pretest Risk is Relatively High

Increase Number of Variants

Conditions Screened
Number of Conditions Screened

Pretest Risk is Relatively High

\[ \sum_{i=1}^{N} RR_i \]

Risk Reduction After Testing

Residual Risk

Not Impacted

Conditions Screened
Pretest Risk is Relatively High

Residual Risk

Starting Risk (High v. Low Carrier Freq)

Number of Variants Screened

Risk Reduction After Testing

Risk

Not Impacted

Number of Conditions Screened
Genomic Risk Portfolio

Risk remaining after testing

Cystic Fibrosis after screening

Panel A
Panel B
Panel C

Number of Conditions Screened

Genomic Risk
Not Impacted
ECS Take Aways

Summary Points
• Carrier status
• Some dominant and X linked conditions
• Not the best for ALL Mendelian inherited conditions (Tay Sachs, Hemoglobinopathies)
• Brings more actionable results
• Normal result ≠ NO genetic condition

Data
• Increase work load for results counseling

Disruption
• Replaces ala carte testing
<table>
<thead>
<tr>
<th>Genomic Technology</th>
<th>Value</th>
<th>Results Interpretation</th>
<th>Disruptive?</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIPS</td>
<td>Better Screening Test</td>
<td>Screening Offer Amnio</td>
<td>Yes  $$</td>
</tr>
<tr>
<td>Array CGH</td>
<td>Greater Yield</td>
<td>Can be confusing</td>
<td>No-Reflex $$$</td>
</tr>
<tr>
<td>ECS</td>
<td>More information (AR and AD, XR)</td>
<td>Residual Risk Remains</td>
<td>Yes $$</td>
</tr>
</tbody>
</table>