Debating the Pros and Cons of PGD

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Keck School of Medicine

2018 AAB meeting, Orlando, Florida
PGT-A: Knowledge Gaps and Challenges

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Keck School of Medicine
Disclosures

• ASRM
• No commercial affiliations
Learning Objectives

1) To describe limitations and knowledge gaps in PGT-A
2) To understand the challenges of further PGT-A investigations
3) To counsel patients about the appropriate application of PGT-A
It ain't what you don't know that gets you into trouble. It's what you know for sure that just ain't so.

Mark Twain
Why are we still debating this?

• Numbers are not consistent
• Aneuploidy
  – Unclear rate
• Mosaicism
  – Unclear incidence in blastocysts (and cleavage stage)
  – Unclear effect on accuracy of embryo biopsy
• Unknown damage from embryo biopsy
PGT-A (PGS) 1.0

- Cleavage stage biopsy
- FISH analysis
- Widely utilized
PGS 1.0 meta-analysis

Mastenbroek et al, Human Reprod Update 2011;4:454

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PGS Events</th>
<th>Total Events</th>
<th>PGS Weight</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Control Weight</th>
<th>Risk Difference</th>
<th>Risk Difference, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication Advanced Maternal Age</td>
<td>21</td>
<td>199</td>
<td>36.6%</td>
<td>29</td>
<td>190</td>
<td>38.4%</td>
<td>-0.05 [-0.11, 0.02]</td>
<td></td>
</tr>
<tr>
<td>Staessen 2004</td>
<td>49</td>
<td>206</td>
<td>10.3%</td>
<td>71</td>
<td>202</td>
<td>10.3%</td>
<td>-0.11 [-0.20, -0.03]</td>
<td></td>
</tr>
<tr>
<td>Mastenbroek 2007</td>
<td>3</td>
<td>56</td>
<td>3.9%</td>
<td>10</td>
<td>53</td>
<td>3.9%</td>
<td>-0.14 [-0.26, -0.01]</td>
<td></td>
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<tr>
<td>Hardarson 2008*</td>
<td>16</td>
<td>32</td>
<td>5.8%</td>
<td>16</td>
<td>30</td>
<td>5.8%</td>
<td>-0.03 [-0.28, 0.22]</td>
<td></td>
</tr>
<tr>
<td>Schoolcraft 2008</td>
<td>6</td>
<td>44</td>
<td>8.6%</td>
<td>10</td>
<td>50</td>
<td>8.6%</td>
<td>-0.06 [-0.21, 0.09]</td>
<td></td>
</tr>
<tr>
<td>Debrock 2009</td>
<td>537</td>
<td></td>
<td>100.0%</td>
<td>525</td>
<td></td>
<td>100.0%</td>
<td>-0.08 [-0.13, -0.03]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>95 (18%)</td>
<td>136 (26%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 2.51, df = 4 (P = 0.64); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.38 (P = 0.0007)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Indication Good Prognosis Patient    |             |              |            |               |              |                |                  |
| Staessen 2008*                       | 37          | 120          | 39.7%      | 37            | 120          | 39.7%          | 0.00 [-0.12, 0.12] |
| Jansen 2008*                         | 20          | 55           | 33.3%      | 27            | 46           | 33.3%          | -0.22 [-0.41, -0.03] |
| Meyer 2009*                          | 6           | 23           | 26.9%      | 15            | 24           | 26.9%          | -0.36 [-0.63, -0.10] |
| Subtotal (95% CI)                    | 198         |              | 100.0%     | 190           |              | 100.0%         | -0.17 [-0.39, 0.04] |
| Total events                         | 63 (32%)    | 79 (42%)     |            |               |              |                |                  |
| Heterogeneity: Tau² = 0.03; Chi² = 8.27, df = 2 (P = 0.02); I² = 76% |
| Test for overall effect: Z = 1.56 (P = 0.12) |

| Indication Repeated Implantation Failure |             |              |            |               |              |                |                  |
| Blockeel 2008                         | 15          | 72           | 100.0%     | 26            | 67           | 100.0%         | -0.18 [-0.33, -0.03] |
| Subtotal (95% CI)                     | 72          |              | 100.0%     | 67           |              | 100.0%         | -0.18 [-0.33, -0.03] |
| Total events                          | 15 (21%)    | 26 (39%)     |            |               |              |                |                  |
| Heterogeneity: Not applicable         |             |              |            |               |              |                |                  |
| Test for overall effect: Z = 2.35 (P = 0.02) |
KLINGON PROVERB

Fool Me Once, Shame On You.
Fool Me Twice, Prepare To Die.
Intuitive appeal of PGS

• Additional information
  – Why would you NOT want that???

• Practically
  – Why would I want to transfer an aneuploid embryo?

• Theoretically:
  – Faster time to pregnancy
  – Decreased miscarriage rate
Pressure to perform PGT-A

• Natural appeal of new technology
  – Must be better
• Pressure from consumers
• Pressure from registry
  – Need to optimize outcome of 1st embryo transfer
Gaps in Knowledge

• Biology of the pre-implantation human embryo
  – Rapid division, especially in the trophectoderm
    • Multi-nucleated cells, ?resemble sycytiotrophoblast
    • Predisposed to mosaicism, aneuploidy?

• True incidence of chromosomal abnormalities
  – Aneuploidy, mosaicism
  – Correlation between trophectoderm and inner cell mass

• Embryo biopsy
  – Extent of damage to the embryo
What does screening with PGT-A tell us?

• Information about the genetic make-up of the embryo
  – Improved selection of the 1\textsuperscript{st} embryo transfer
  – Increase in implantation rate of 1\textsuperscript{st} embryo

• No improvement in embryo quality
  – No increase in cumulative pregnancy rate per aspiration
  – Any error/damage must cause decrease in cumulative pregnancy rate
Inherent down-sides of PGT-A

• Blastocyst culture

• Accuracy of testing
  – Error in testing: lab tests are not perfect
  – Inherent error: mosaicism (biopsy not representative) of rest of embryo

• Trauma from embryo biopsy

• Loss of potential live births
  – Discarding or damage to normal embryos
Blastocyst vs Cleavage stage transfer

• Issue is NOT settled
• Increased implantation rate with blastocyst
• No increase when frozen embryos considered
• No stratification by age
  – Difference between 32 yo and 42 yo
  – Is cleavage stage better for older women?

Glujovsky, Cochrane Database 2016:6, CD002118
Incidence of aneuploidy

Franasiak et al, Fertil Steril 2014;101;656
### Incidence of euploidy (based on age and # of embryos)

<table>
<thead>
<tr>
<th></th>
<th>Egg Donor</th>
<th>&lt;35</th>
<th>35-37</th>
<th>38-40</th>
<th>41-42</th>
<th>&gt;42</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 embryos</td>
<td>59</td>
<td>56</td>
<td>47</td>
<td>36</td>
<td>23</td>
<td>14</td>
</tr>
<tr>
<td>4-6 embryos</td>
<td>62</td>
<td>55</td>
<td>48</td>
<td>36</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>7-10 embryos</td>
<td>64</td>
<td>57</td>
<td>49</td>
<td>37</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>&gt;10 embryos</td>
<td>66</td>
<td>58</td>
<td>50</td>
<td>38</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>64</strong></td>
<td><strong>57</strong></td>
<td><strong>49</strong></td>
<td><strong>37</strong></td>
<td><strong>24</strong></td>
<td><strong>16</strong></td>
</tr>
<tr>
<td>Maternal age</td>
<td>Risk of Down’s Syndrome</td>
<td>Risk of all chromosomal abnormalities</td>
<td></td>
<td></td>
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<tr>
<td>33</td>
<td>1/416</td>
<td>1/208</td>
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<tr>
<td>34</td>
<td>1/333</td>
<td>1/151</td>
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<tr>
<td>35</td>
<td>1/250</td>
<td>1/132</td>
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<tr>
<td>36</td>
<td>1/192</td>
<td>1/105</td>
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<td></td>
</tr>
<tr>
<td>37</td>
<td>1/149</td>
<td>1/83</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>1/115</td>
<td>1/65</td>
<td></td>
<td></td>
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<tr>
<td>39</td>
<td>1/89</td>
<td>1/53</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>40</td>
<td>1/69</td>
<td>1/40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>1/53</td>
<td>1/31</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>1/41</td>
<td>1/25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>1/31</td>
<td>1/19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>1/25</td>
<td>1/15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>1/19</td>
<td>1/12</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Hook et al. JAMA 1983.
Accuracy of testing?

Comprehensive chromosome screening is highly predictive of the reproductive potential of human embryos: a prospective, blinded, nonselection study

Richard T. Scott Jr., M.D., a,b Kathleen Ferry, B.S., a Jing Su, M.S., a Xin Tao, M.S., a Katherine Scott, M.S., a and Nathan R. Treff, Ph.D. a,b

NCT 01219517
NCT 01219504
Predictive Value of CCS

• 255 embryos biopsied
  – Average age = 34
    • 113 cleavage, 142 trophectoderm
      – 12 failed to amplify,
      – 11 nonconcurrent copy assignments (?)
  – 232 evaluable microarray results
    • 133 euploid
      – 55 (41.4%) of these resulted in normal children
    • 99 (42.7%) aneuploid
      – 4 (4%) normal children (96% negative predictive value)

Scott et al, Fertil Steril 2012;97:870
<table>
<thead>
<tr>
<th></th>
<th>Implantation</th>
<th>No implantation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Euploid</strong></td>
<td>55</td>
<td>78</td>
<td>133</td>
</tr>
<tr>
<td><strong>Aneuploid</strong></td>
<td>4</td>
<td>95</td>
<td>99</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>59</td>
<td>173</td>
<td>232</td>
</tr>
</tbody>
</table>

41% of the “Euploid” group implanted
4% of the “Aneuploid” group implanted

Error rate: 10/99 (10%) “aneuploid” were actually euploid
4/59 (6.8%) implantations would have been discarded
Trauma from Embryo Biopsy?

Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial

Richard T. Scott Jr., M.D., a,b Kathleen M. Upham, B.S., a Eric J. Forman, M.D., b Tian Zhao, M.S., a and Nathan R. Treff, Ph.D. a,b,c

“Seminal Contribution” NCT 01219504

Scott et al, Fertil Steril 2013;100:624
• All patients < 35 yo
  – Good ovarian reserve
• ET within 3 hours of Bx
  – All 4AA – 4BB
  – Without knowledge of ploidy
• Blastocysts (n=67)
  – No ↓ in implantation rate
  – 54% vs 51%
  • 30/69 aneuploid (42.7%)
• Cleavage stage (n=46)
  – 39% ↓ in implantation rate
  • 19 aneuploid (41.3%)
• Can these results be extrapolated to women > 40?

Scott et al, Fertil Steril 2013;100:624
What does a day 5 embryo look like?

“Buckyball”

- Naturally occurring $C_{60}$
  - 32 faces
    - 20 hexagons
    - 12 pentagons
- Trophectoderm with 64 cells
  - 2 cells/face
- Imagine removing 5 cells
  - Is this really NOT traumatic?
How many embryos do we lose?

• Best-case scenario
• Good prognosis patient
  – Under 35
  – Expected aneuploidy rate?
  – Implantation rate with and without PGT-A?
In incidence of euploidy (based on age and # of embryos)

<table>
<thead>
<tr>
<th>No. of day 5 embryos</th>
<th>Patient Age</th>
<th></th>
<th></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>&lt;35</td>
<td>35-37</td>
<td>38-40</td>
<td>40+</td>
<td></td>
</tr>
<tr>
<td>Euploid Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 embryos</td>
<td>54% 29%</td>
<td>50% 33%</td>
<td>38% 44%</td>
<td>24% 56%</td>
<td></td>
</tr>
<tr>
<td>4-6 embryos</td>
<td>57% 32%</td>
<td>47% 35%</td>
<td>36% 34%</td>
<td>26% 28%</td>
<td></td>
</tr>
<tr>
<td>7-9 embryos</td>
<td>55% 22%</td>
<td>49% 20%</td>
<td>38% 14%</td>
<td>28% 11%</td>
<td></td>
</tr>
<tr>
<td>10+ embryos</td>
<td>52% 17%</td>
<td>46% 12%</td>
<td>35% 8%</td>
<td>28% 5%</td>
<td></td>
</tr>
</tbody>
</table>
Ongoing pregnancy rate per blastocyst transfer

![Bar chart showing ongoing pregnancy rate per blastocyst transfer by maternal age (years) with and without PGS.

Key:
- Dark blue: IVF with PGS
- Light blue: IVF without PGS

- ≤35: 65.0% (IVF with PGS), 49.4% (IVF without PGS)
- 35-37: 64.5% (IVF with PGS), 42.3% (IVF without PGS)
- 38-40: 61.1% (IVF with PGS), 32.9% (IVF without PGS)
- 41-42: 60.2% (IVF with PGS), 20.7% (IVF without PGS)
- ≥42: 53.7% (IVF with PGS), 7.8% (IVF without PGS)

*Internal IGENOMIX data 2016 based on outcomes and 2015 SART data.*
How many embryos do we lose?

• Typical good prognosis patient
  – PGS testing
    • 40% aneuploidy
  – 50% implantation rate before testing
  – 65% implantation rate after testing
100 embryos
100 embryos, 50% implantation rate

50 implant

50 no implant
100 embryos, 50% implantation rate
40% aneuploidy

40 aneuploid

50 no implant

50 implant
100 embryos, 50% implantation rate
40% aneuploidy

50 implant

10 no implant
100 embryos, 50% implantation rate
40% aneuploidy

After PGS, 60 embryos left
New implantation rate:
50/60 = 83.3%
100 embryos, 50% implantation rate
40% aneuploidy

After PGS, 60 embryos left
New implantation rate: 50/60 = 83.3%

Actual implantation rate is: 65% ≈ 40/60
Improvement over 50%
100 embryos, 50% implantation rate
40% aneuploidy

After PGS, 60 embryos left
New implantation rate: 50/60 = 83.3%

Actual implantation rate is: 65% ≈ 40/60
Improvement over 50%
100 embryos, 50% implantation rate
40% aneuploidy

After PGS, 60 embryos left
New implantation rate:
50/60 = 83.3%

Actual implantation rate is:
65% ≈ 40/60
Improvement over 50%

40 implant
10 (20%) lost
10 no implant
General principle

• When we remove from the cohort a sub-group which has a lower incidence of a given characteristic, the average of that characteristic in the remaining group must increase.
• Age
• Height
• Implantation rate
Generalized Efficiency Equation

Embryo implantation (EI) must increase if we are removing lower quality embryos from the population

\[ \text{EI (expected)} = \frac{\text{EI (untested)}}{(\text{percent normal})} \]

\[ \text{Efficiency} = \frac{\text{EI (observed after testing)}}{\text{EI (expected)}} \]

\[ \% \text{ embryos lost} = 1 - \text{Efficiency} \]
Generalized Efficiency Equation

• Previous example:
  – 50% (untested) / (60% normal) = 83.3% (expected)
  – Efficiency = 65% (observed) / 83.3% (expected)
    = 0.80
  – % embryos lost = 1 – 0.80 = 0.20
When is it OK to lose 20% of implantations?

- Specific reason for genetic diagnosis
- Excellent prognosis patient
  - More embryos than she needs
When is it NOT OK to lose 20%?

- Limited number of eggs
  - Fertility preservation patients
  - Patients over 40
What are actual “real life” implantation rates?

- SART CORS registry
- Query the database = “filter” function
# Preliminary Primary Outcome Per Egg Retrieval Cycle

## Patient's Own Eggs

<table>
<thead>
<tr>
<th>Age of Woman</th>
<th>Number of Cycle Starts</th>
<th>Singletons</th>
<th>Twins</th>
<th>Triplets or More</th>
<th>Live Births</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 35</td>
<td>35 - 37</td>
<td>38 - 40</td>
<td>41 - 42</td>
</tr>
<tr>
<td>Number of cycle starts</td>
<td></td>
<td>42728</td>
<td>22675</td>
<td>22101</td>
<td>11899</td>
</tr>
<tr>
<td>Singletons</td>
<td></td>
<td>31.9%</td>
<td>24.7%</td>
<td>16.7%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Twins</td>
<td></td>
<td>8.8%</td>
<td>6.0%</td>
<td>3.3%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Triplets or more</td>
<td></td>
<td>0.2%</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Live Births</td>
<td></td>
<td>40.9%</td>
<td>30.9%</td>
<td>20.1%</td>
<td>9.9%</td>
</tr>
<tr>
<td>(Confidence Range)</td>
<td></td>
<td>(40.4 - 41.4)</td>
<td>(30.3 - 31.5)</td>
<td>(19.6 - 20.6)</td>
<td>(8.4 - 10.4)</td>
</tr>
</tbody>
</table>

- Term
  - 78.2% for < 35
  - 79.4% for 35 - 37
  - 80.2% for 38 - 40
  - 81.1% for 41 - 42

- Pre-term
  - 17.9% for < 35
  - 16.9% for 35 - 37
  - 16.3% for 38 - 40
  - 15.2% for 41 - 42

- Very pre-term
  - 3.9% for < 35
  - 3.7% for 35 - 37
  - 3.5% for 38 - 40
  - 3.7% for 41 - 42
Filters other than Reporting Year cannot be applied to the 'Cumulative Outcome Per Intended Egg Retrieval' and 'Live Birth Per Patient' sections. These sections will be hidden if a filter has been applied.

**Reporting Year**

- **2014**

**Cycle Type**

- All cycle types
- Minimal stimulation
- Natural cycle
- Conventional stimulation
- In vitro maturation

**Diagnosis**

- All Diagnoses

**Additional Filters**

- **eSET**: Include
- **PGD / PGS**: Exclude

---

*Day 5/6 transfer*

*Frozen egg*

*Frozen embryo*

*Gestational carrier*

*ICSI*
### Final Primary Outcome Per Egg Retrieval Cycle

<table>
<thead>
<tr>
<th>Age of woman</th>
<th>&lt; 35</th>
<th>35 - 37</th>
<th>38 - 40</th>
<th>41 - 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cycle starts</td>
<td>10048</td>
<td>2876</td>
<td>1194</td>
<td>316</td>
</tr>
</tbody>
</table>

<p>| | Singletons | Twins | Triplets or more | Live Births |</p>
<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>%</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 35</td>
<td>50.0</td>
<td>0.8</td>
<td>0.0</td>
<td><strong>50.8</strong></td>
</tr>
<tr>
<td>35 - 37</td>
<td>42.7</td>
<td>0.5</td>
<td>0.5</td>
<td><strong>43.1</strong></td>
</tr>
<tr>
<td>38 - 40</td>
<td>31.3</td>
<td>0.1</td>
<td>0.1</td>
<td><strong>31.4</strong></td>
</tr>
<tr>
<td>41 - 42</td>
<td>21.8</td>
<td>0.9</td>
<td>0.9</td>
<td><strong>22.8</strong></td>
</tr>
</tbody>
</table>

(Confidence Range) | (49.8 - 51.8) | (41.3 - 44.9) | (28.6 - 34.0) | (18.2 - 27.4) |

<table>
<thead>
<tr>
<th>Term</th>
<th>&lt; 35</th>
<th>35 - 37</th>
<th>38 - 40</th>
<th>41 - 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term</td>
<td>89.1</td>
<td>88.7</td>
<td>86.7</td>
<td>77.8</td>
</tr>
<tr>
<td>Pre-term</td>
<td>9.1</td>
<td>9.6</td>
<td>10.7</td>
<td>19.4</td>
</tr>
<tr>
<td>Very pre-term</td>
<td>1.8</td>
<td>1.7</td>
<td>2.7</td>
<td>2.8</td>
</tr>
</tbody>
</table>
Filters other than Reporting Year cannot be applied to the 'Cumulative Outcome Per Intended Egg Retrieval' and 'Live Birth Per Patient' sections. These sections will be hidden if a filter has been applied.

### Reporting Year

- **2014**

### Cycle Type

- All cycle types
- Minimal stimulation
- Natural cycle
- Conventional stimulation
- In vitro maturation

### Diagnosis

- All Diagnoses

### Additional Filters

<table>
<thead>
<tr>
<th>Include Only</th>
<th>Exclude</th>
</tr>
</thead>
<tbody>
<tr>
<td>eSET</td>
<td></td>
</tr>
<tr>
<td>PGD / PGS</td>
<td></td>
</tr>
</tbody>
</table>

- Day 5/6 transfer
- Frozen egg
- Frozen embryo
- Gestational carrier
- ICSI

---

[Apply filter] [Reset filter] [Cancel]
# Final Primary Outcome Per Egg Retrieval Cycle

## Patient's Own Eggs

### Cumulative Outcome Per Egg Retrieval Cycle

<table>
<thead>
<tr>
<th>Age of women</th>
<th>&lt; 35</th>
<th>35 - 37</th>
<th>38 - 40</th>
<th>41 - 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cycle starts</td>
<td>2047</td>
<td>1311</td>
<td>1219</td>
<td>418</td>
</tr>
<tr>
<td>Singletons</td>
<td>49.9 %</td>
<td>52.6 %</td>
<td>52.0 %</td>
<td>49.8 %</td>
</tr>
<tr>
<td>Twins</td>
<td>0.8 %</td>
<td>0.5 %</td>
<td>0.3 %</td>
<td>2.2 %</td>
</tr>
<tr>
<td>Triplets or more</td>
<td>0 %</td>
<td>0 %</td>
<td>0 %</td>
<td>0.2 %</td>
</tr>
<tr>
<td>Live Births</td>
<td><strong>50.7 %</strong></td>
<td><strong>53.1 %</strong></td>
<td><strong>52.3 %</strong></td>
<td><strong>52.2 %</strong></td>
</tr>
<tr>
<td>(Confidence Range)</td>
<td>(48.5 - 52.8)</td>
<td>(50.4 - 55.8)</td>
<td>(49.5 - 55.1)</td>
<td>(47.4 - 56.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Term</th>
<th>Pre-term</th>
<th>Very pre-term</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>88.1 %</td>
<td>9.5 %</td>
<td>2.4 %</td>
</tr>
<tr>
<td></td>
<td>90.9 %</td>
<td>7.8 %</td>
<td>1.3 %</td>
</tr>
<tr>
<td></td>
<td>88.6 %</td>
<td>9.7 %</td>
<td>1.7 %</td>
</tr>
<tr>
<td></td>
<td>89.0 %</td>
<td>9.2 %</td>
<td>1.8 %</td>
</tr>
</tbody>
</table>
Generalized Efficiency Equation

• “Real world” example:
  – 50% (untested) / (60% normal) = 83.3% (expected)
  – Efficiency = 50% (observed) / 83.3% (expected)
    = 0.60
  – % embryos lost = 1 – 0.60 = 0.40
Counseling patients about PGT-A

• PGT-A will provide information about the embryo
• PGT-A will likely increase implantation in 1st ET
• PGT-A will add cost
• You will lose 20% - 40% of embryos that might have implanted
• Cumulative pregnancy rate will be decreased
Conclusions – PGT-A

• Useful:
  – Specific diagnosis, e.g. translocation, sex selection
  – Recurrent aneuploidy (RPL) (likely)
  – Age 36-39, with many blastocysts

• Unnecessary:
  – Young good prognosis patients (< 35 yo)

• Not worth it:
  – Limited number of eggs
    • Fertility preservation, women over 40
Incidence of Mosaicism

• Confined placental mosaicism
  – 1-2%

• Incidence in embryos
  – Up to 75% in cleavage stage
  – Up to 20% in blastocysts

• Impact on implantation rates

• Interpretation of PGS results
Challenges in PGT

• Biology of the pre-implantation human embryo
  – Rapid division, especially in the trophectoderm
  – Unique life form

• True incidence of chromosomal content
  – Aneuploidy, mosaicism
  – Significance of trophectoderm aneuploidy

• Embryo biopsy
  – Invasive
The first principle is that you must not fool yourself, and you are the easiest person to fool.

~Richard Feynman
Thank you