PGD: A Celebration of 20 years:

What is Reality and What is Not?

Roma
June 30, 2010

Mark Hughes, M.D., Ph.D.
Professor of Genetics, Internal Medicine, Pathology
Director, Genesis Genetics Institute
Director, State of Michigan Genomic Technology Center
PGD

- Has led to the birth of thousands of healthy children to very desperate, genetically at-risk couples.

- Remains at the very limit of medical diagnostic testing

- The technology continues to improve -
  - but it is not reality to think PGD will ever have a 0% false positive or false negative rate
Reality: We still do not know What is best to biopsy, and when?

- Polar Body
- Blastomere
- Trophoectoderm
## Variation in Biopsy Skill

<table>
<thead>
<tr>
<th>Clinic</th>
<th>Biopsies</th>
<th>+HCG / ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>314</td>
<td>17%</td>
</tr>
<tr>
<td>2</td>
<td>427</td>
<td>26%</td>
</tr>
<tr>
<td>3</td>
<td>181</td>
<td>12%</td>
</tr>
<tr>
<td>4</td>
<td>712</td>
<td>31%</td>
</tr>
</tbody>
</table>
Reality: We all are controversial

• PGD has raised international controversy
  – How is it bioethically different from Prenatal Testing?
  – Who should control the use of these technologies?
  – Should there be government PGD testing standards?

• What is the difference between a Disease and a Trait
  - and who decides?
PGD Disorders (A, B, C)

- ACHONDROPLASIA (FGFR)
- ACTIN-NEMALIN MYOPATHY (ACTA)
- ADRENOLEUKODYSTROPHY (ABCD)
- AGAMMAGLOBULINEMIA-BRUTON (TYKNS)
- ALAGILLE SYNDROME (JAG)
- ALDOLASE A, FRUCTOSE-BISPHOSPHATE
- ALPHA THALASSEMIA (HBA)
- ALPHA-ANTITRYPSIN (AAT)
- ALPORT SYNDROME (COLA)
- ALS: AMYOTROPHIC LATERAL SCLEROSIS
- ALZHEIMER DISEASE (PSEN)
- AMYLOIDOSIS-TRANSTHYRETIN
- ANGIOEDEMA, HEREDITARY (CNH)
- ATAXIA TELANGIECTASIA
PGD Disorders (C-G)

- CONGENITAL DISORDER GLYCOSYLATION, A
- CONGENITAL ERYTHROPOIETIC PORPHYRIA
- COSMAN-SEVERE CYCLIC NEUTROPENIA
- CRIGLER NAJJAR (UGTA)
- CYSTIC FIBROSIS (CFTR)
- CYSTINOSIS

- DARIER DISEASE (ATPA)
- DEAFNESS - GJB CONNEXIN
- DIAMOND BLACKFAN (DBA-RSP)
- DUCHENNE MUSCULAR DYSTROPHY (DMD)
- DYSTROPHIA MYOTONICA- (DMPK)

- ECTODERMAL DYSPLASIA (I EDA)
- EMERY-DREIFUSS MUSCULAR DYSTROPHY
- EPIDERMALYSIS BULLOSA SIMPLEX KRT
PGD Disorders (M-P)

- OCCULOCUTANEOUS ALBINISM II- OCA
- ORNITHINE TRANSCARBAMYLASE DEF (OTC)
- OSTEOGENESIS IMPERFECTA I (COLA)
- OSTEOGENESIS IMPERFECTA II/IV (COLA)
- OSTEOPETROSIS-CLCN & TCIRG

- PACHYONYCHIA CONGENITA (KRT)
- PACHYONYCHIA CONGENITA (KRTA)
- PELIZAEUS-MERZBACHER PMD
- PERIVENTRICULAR HETEROPIA (PH)
- PERSISTENT HYPERINSULINEMIC HYPOGLYCEMIA OF INFANCY (PHHI)
- PHENYLKETONURIA
- POLYCYSTIC KIDNEY DISEASE
- POMPE - GLYCOGEN STOR DZ II
- PROPIONIC ACIDEDEMIA
PGD Disorders (R-Z)

- RETINITIS PIGMENTOSA - RHO
- RETINITIS PIGMENTOSA (ADRP)
- RETINOBLASTOMA (RB)
- RHESUS BLOOD GROUP D (RHD)
- SACRAL AGENESIS (HLXB)
- SANFILIPPO A (MPSIIIA)
- SCIDX (ILRG)
- SEVERE COMB IMMUNODEF (SCID)
- SHWACHMAN-DIAMOND SYNDROME
- SICKLE CELL (HBB)
- SMITH-LEMLI-OPITZ (SLOS)
- SPINOCErellAR ATAXIA
- SPINOMUSCULAR ATROPHY (SMN1)
- SUPRAVALVULAR AORTIC STENOSIS ELN
- SURFACTANT-PULMONARY B (SFTPB)
Two IVF-PGD children without BRCA1 mutation
Fertility Preservation – Oocyte Vitrification

42 babies
4 ongoing pregnancies
PGD for Cancer Susceptibility

- Ataxia Telangiectasia (AT)
- Bloom Syndrome (BS)
- BRCA1 and BRCA2
- Colon Cancer
  - MYH
  - HNPCC
    - MLH1 & 2;
    - MSH6;
    - PMS2
  - FAP (APC)
- Fanconi Anemia (A, C, D, G)
- Li-Fraumeni Syndrome (TP53)
- MEN 1a (MEN1)
- MEN2a (RET)
- Neurofibromatosis
  - NF1 & NF2)
- Retinoblastoma (RB1)
- Severe Comb Imunodeficiency
  - ADA
  - IL7 Receptor
- Von Hippel-Lindau (pVHL)
- Wiskott-Aldrich (WAS)

- PGD Pregnancy (ies)  
- No Pregnancy / Not Performed
The Reality is –

- High Throughput Genotyping is here
- We are still learning what to do with it
Reality:
High Throughput Multiplex Genotyping is here
Reality: we don’t know what to do with it
Not Reality - Designer Babies

- We can order up our babies to design specifications
- GATACCA is here
The Reality is – We still do not know:

- The true degree of embryo mosaicism
  - Important for test reliability
  - But does it even matter to normal human development?

- How important are CNVs?

- How important are InDels?
The Reality is – We still do not know:

• Which InDels are important?
  – 415,436 mapped so far
    • Single base-pair (many)
    • Multi-base pair
      – 3 bp – CFTR: Cystic Fibrosis
      – 4 bp – HexA: Tay Sachs
      – 2-14 bp repeats: Fragile X, Huntington, Myotonic Dystrophy…
    • Transposon mobile elements: Hemophilia, FSHMD, many cancers
Question

• If we could –
  – Sequence the entire genome of an embryo
  – Overnight
  – At a cost effective price
  – For clinical diagnostic decision making

• Does this make any sense as a diagnostic goal?
Reality

• Awareness of mutations will increase PGD
• Homogenization of the human gene pool will decrease risk for recessive conditions
• The cost will continue to decline
• Technology is not the limit anymore
The incidence of aneuploidy after the first meiotic division is nearly 100,000 higher in human than in mouse.
2,136 Embryos tested with array CGH (Genesis-24)

Percentage of Monosomies and Trisomies Seen in All Amped Samples

- Gender XO: 3%
- Gender XXY: 1%
- 1 M: 2%
- 1 T: 2%
- 2 M: 1%
- 2 T: 1%
- 3 M: 1%
- 3 T: 0%
- 4 M: 2%
- 4 T: 1%
- 5 M: 1%
- 5 T: 1%
- 6 M: 2%
- 6 T: 1%
- 7 M: 1%
- 7 T: 1%
- 8 M: 2%
- 8 T: 1%
- 9 M: 4%
- 9 T: 3%
- 10 M: 2%
- 10 T: 1%
- 11 M: 2%
- 11 T: 1%
- 12 M: 2%
- 12 T: 1%
- 13 M: 4%
- 13 T: 3%
- 14 M: 3%
- 14 T: 2%
- 15 M: 3%
- 15 T: 3%
- 16 M: 7%
- 16 T: 3%
- 17 M: 0%
- 17 T: 3%
- 18 M: 2%
- 18 T: 2%
- 19 M: 4%
- 19 T: 3%
- 20 M: 2%
- 20 T: 1%
- 21 M: 4%
- 21 T: 3%
- 22 M: 7%
- 22 T: 3%
Reality

- Long held hypotheses (even dogmas) in biology are sometimes proven incorrect.

- We must avoid forcing data points into a preconceived model.