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Consultant and Professor of Clinical Genetics
Chair British Society for Human Genetics
Genetics lead, National Institute of Health Research
MedicalDirector QuantuMDx Ltd
British Isles Network
of Congenital Anomaly Registers

2009
4,181 congenital anomalies
206 /10,000 births (1 in 49)
National Down Syndrome Cytogenetic Register (NDSCR)

2009  England and Wales

trisomy 21-Down syndrome
1,887 diagnoses of (27 /10,000 births)
62% Down syndrome cases diagnosed prenatally,

163 of trisomy 13 (87% prenatal Dx)
506 of trisomy 18 (91% prenatal Dx)
Overall ESHRE data collection
Report TEN: year of 2007

- 3471/5887 (59%) infertile
- 77% successfully biopsied
- 91% of these diagnosed
- 25% of these transferred
- Clinical pregnancy rate per ET 30%
- Implantation rate 22%
Pre-implantation Genetic Screening

‘240 embryos (36.8%) had normal diploid status’

Staessen et al 2004 Human Reproduction 19;12, 2849–2858
## PGS for advanced maternal age

Moniek Twisk et al Cochrane Library July 2010

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PGS group n/N</th>
<th>Control group n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debrock 2010</td>
<td>6/44</td>
<td>10/50</td>
<td>2.17 [0.65, 5.79]</td>
<td>7.5 %</td>
<td>0.63 [0.21, 1.91]</td>
</tr>
<tr>
<td>Hardarson 2008</td>
<td>3/56</td>
<td>10/53</td>
<td>3.33 [0.87, 12.11]</td>
<td>9.1 %</td>
<td>0.24 [0.06, 0.94]</td>
</tr>
<tr>
<td>Mastenbroek 2007</td>
<td>49/206</td>
<td>71/202</td>
<td>0.73 [0.37, 1.44]</td>
<td>50.9 %</td>
<td>0.58 [0.37, 0.89]</td>
</tr>
<tr>
<td>Schoolcraft 2009</td>
<td>16/32</td>
<td>16/30</td>
<td>1.00 [0.32, 3.27]</td>
<td>7.7 %</td>
<td>0.88 [0.32, 2.37]</td>
</tr>
<tr>
<td>Staessen 2004</td>
<td>21/199</td>
<td>29/190</td>
<td>0.56 [0.26, 1.20]</td>
<td>24.7 %</td>
<td>0.65 [0.36, 1.19]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

537 / 525 = 100.0 %

0.59 [0.44, 0.81]

**Test for overall effect:** $z = 3.35 \ (P = 0.00082)$

- **Favours control group**
- **Favours PGS group**

Testing for trisomy reduces the success rates
Trisomy 3 cell mosaic blastocyst
Deciphering Developmental Disorders
Govt. funded pooled analysis of 12000 families with a multiple malformation

Recruitment started 2011
Lauren and Trudie have Noonan syndrome

- What’s wrong? Diagnosis
- What’s the future? Prognosis
- What’s to be done? Therapy
- Why did it happen? Aetiology
- Will it happen again? Recurrence risk
- Will it be as bad? Clinical Burden
- Are there any tests?
### Functional classification of JDW SNPs

<table>
<thead>
<tr>
<th>SNP Type</th>
<th>Known SNPs</th>
<th>Novel SNPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missense</td>
<td>8967</td>
<td>2421</td>
</tr>
<tr>
<td>Nonsense</td>
<td>44</td>
<td>5</td>
</tr>
<tr>
<td>Synonymous</td>
<td>9121</td>
<td>2261</td>
</tr>
<tr>
<td>UTR</td>
<td>18517</td>
<td>7102</td>
</tr>
<tr>
<td>Intron</td>
<td>922048</td>
<td>381924</td>
</tr>
</tbody>
</table>
DNA genotyping and sequencing on nanowires – “while you wait”

Prof Sir John Burn  MD FRCP FRCPE FRCPCH FRCOG FMedSci
Medical Director

Elaine Warburton  CEO
Sam Whitehouse  COO
Jonathan O’Halloran  Chief Scientist

International Congress of Human Genetics 2011
All authors are stockholders
INEX - Biosensor fabrication
QMDx Sequencing principles

Polymerase

Nanowire

R
QMDx Sequencing principles

- ve - ve - ve - ve

100 Å
Debye Length

Nanowire

Electrical Field
QMDx Sequencing principles

Wash

- ve  - ve  - ve
Wash

- ve  - ve  - ve
- ve

R

Nanowire
Peptide Nucleic Acid Hybridization

**PNA binding**

*to BRCA segment*

**PNA binding**

*to BRCA with mismatch*

**BRCA segment**
DNA Extraction

We are extracting 20-50ng/ul for each chip, from whole blood samples.

Below are results from 3 blanks and 3 blood cassettes. Buffer gives “false positive” at 100ng level

Automated extraction in 4 minutes
In a disposable cassette
Amplification

Heater configuration (heating area) determines cycle ratio without changes to cartridge design.

Ratio: 1 : 2 : 3

Ratio: 1 : 1 : 1
PCR on a disposable cassette
In 6 minutes

Gel using RT-PCR product of a section of the HIV genome x 11 compared to standard technology

Continuous thermal cycling channel

Performed with standard primers used at Tigerberg Hospital, Cape Town.
QuantuMDx technology: The QPoc

Prototype design
Will we diagnose all genetic abnormalities?

- Mosaicism
- Imprinting
- Polygenic traits
- Non-coding RNA
- mitochondria

Starch and iodine show the pattern of missing sweat glands in a girl who carries X linked anhydrotic ectodermal dysplasia.

Girls are a mosaic of cells which have randomly switched off one X chromosome.
The environment can influence expression
Epigenetics
Developmental origins of adult disease

Early development

CVD  Hypertension  Rheumatoid arthritis  Stroke  Obesity  Diabetes mellitus

Adding methyl groups to Cytosine in DNA can change gene function
Non-coding RNAs
“the fingers on the strings”
Mutations in a cis acting elements located in the neighbouring MCM6 gene result in lactase persistence 

2q21.3-2q22.1 (123 SNPs)

Why can some of us drink milk?
Scientists get go-ahead to clone first human embryo

Ministers to tell parents how to do better
Mitochondrial DNA is maternally inherited.

Each human ovum contains about 500,000 mitochondria.

Paternal mitochondria targeted for destruction after fertilisation.
mtDNA mutations segregate unequally between oocytes.
Short stature
Diabetes
Adrenal failure
Myopathy
Ptosis
Cardiac conduction defect with pacemaker
Deafness
Died aged 7

Mother
• 38% mtDNA carries a deletion
• No clinical symptoms

Son: 78% mtDNA carried the deletion

38% 0% 78%
The diagram illustrates a family tree with the following symbols:
- Square: Male
- Circle: Female
- Triangle: Male and Female

The diagram shows:
- I-1 and I-2 as the parents.
- II-1, II-2, II-3, and II-4 as the children of I-1 and I-2.
- III-1, III-2, and III-3 as the children of II-1.

The text at the bottom of the diagram indicates:
- p<sub>H</sub> p<sub>H</sub> SA
HFEA research licence

Paragraph 3(4) of Schedule 2 to the HFE Act 1990:

"a Licence under this paragraph cannot authorise altering the genetic structure of any cell while it forms part of an embryo"

• Problem: what is meant by the term “genetic structure”?
Could we move the parental chromosomes to another oocyte?

Chromosomes from mother and father About to meet

Germinal Vesicle (GV) stage

Metaphase II egg

Pronucleate stage
Germinal Vesicle (GV) stage

Unaffected zygote

Metaphase II egg

Pronucleate stage

Zygote with mutated mtDNA

wild-type mitochondria  mutant mitochondria
Mary Herbert invented an enclosed system to safely handle human oocytes and embryos.

Craven et al. Nature May 2010

Blastocysts:
17% unmanipulated
8.3% PN transfer
Legal and Regulatory issues

- Current legislation: (HF&E Act) makes provision for the therapeutic application of karyoplast transfer subject to the introduction of Regulations

- HFEA expert review panel (March 2011)

Report submitted Department of Health on April, 2011.

“Although optimistic about the potential of these techniques, the panel recommends a cautious approach and advises that this research is carried out, and the results taken into account, before the techniques can be considered safe and effective for clinical use”.
Genetic ART

• PGD is a successful procedure for those who carry a high risk of genetic disorder
• New technologies like nanowire genotyping will widen clinical relevance
• PGS is not recommended with current technology
• PGD for mitochondrial disease is new and yet to be evaluated.