Future of Genetic testing in fertility

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Why do we need genetic testing in fertility at all?

• In vitro fertilization has completely transformed the field of human infertility

• Assisted reproductive technologies (ART) are available throughout the world

• Scientific developments and refinements in clinical and laboratory technologies have led to IVF evolving into a efficient, safe and accessible medical technique
Why do we need genetic testing at all?

- Greater than 50% cleavage and blastocyst stage embryos produced in-vitro are found to be chromosomally abnormal or aneuploid

- Aneuploidy numbers reach as high as 70% in women over 42 years of age

- Prevention of inherited diseases in future generations

Next generation sequencing (NGS) and the rate of partial aneuploidy in preimplantation genetic screening (PGS)

T. Escudero, L. Ribustello, M. Sumarroca, S Munne
Role of Genetic testing in improving implantation outcomes

• Low success of artificial reproductive treatments is observed in embryos that are detected with numerical chromosomal abnormalities

• Aneuploidy clearly has detrimental effects on efficacy of ART

• Up to 70% of chromosomal abnormalities are often observed in cases which result in spontaneous abortions

• Selection of normal (euploid) embryos to transfer during IVF to improve the rates of success for the procedure is necessary
PGD for Gene Defects
Complexity of the human genome

- 3.500 million pairs of bases
- 88 million (2.5%) are different single nucleotide polymorphisms (SNPs) – they make us different from one another
- 3% are coding genes (about 35,000 genes)
- 97% is “junk” DNA with regulatory activity over genes
The Burden Of Genetic Disease

- >6000 single gene disorders
- Combined incidence: 1/300 births (U.S.)
- Everyone carries 14-18 severe recessive mutations that can cause genetic conditions
- Carriers may not have a family history or symptoms of a genetic disease
- Hence, carrier screening is the only way to determine carrier status

Start with Carrier Screening

- Recommended for people who are planning a family or early in pregnancy, even without family history of genetic disease

- 80% children with conditions have no family history of disease

- Includes about 314 conditions categorized based on impact, inheritance, and/or availability of treatment

- About 3.5% of all couples are carriers of genetic disease
PGD for gene disorders

We can do PGD for any monogenic disease provided the mutation is known

**Disease tested:** Acetil Co Oxidase type I deficiency, Adrenoleucodistrophy, Alpha-thalassemia, Alport syndrome, Autosomal Dominant Polycystic Kidney Disease (ADPKD), Autosomal Recesive Polycystic Kidney Disease (ARPKD), Beta-thalassemia, Branchio-Oto-Renal syndrome (BOR), BRCA1 breast cancer predisposition, BRCA2 breast cancer predisposition, Canavan Charcot-Marie-Tooth type IA (CMT1a), Choroideremia, Congenital adrenal hyperplasia (CAH), Congenital neutropenia, Connexin 26 hearing loss, Cystic fibrosis, Duchenne/Becker Muscular Dystrophy (DMD), Ectrodactyly, Ectodermal dysplasia, and Cleft lip/palate syndrome (EEC1), Fabry Disease, Familial adenomatous poliposis coli (FAP), Familial dysautonomia, Familial intrahepatic cholestasis 2, Fanconi anemia, Fragile site mental retardation, Gangliosidosis type 1 (GM1), Gaucher disease, Glomuvenous malformations (GVM), Glycogen-storage disease type I (GSD1), Glycosylation type 1C, Hemoglobin SC disease, Hemophilia A, Hemophilia B, Hereditary nonpolyposis colon cancer (HNPPC), Hereditary pancreatitis, HLA matching Huntington disease, Marfan syndrome, Hypophosphatasia, Incontinential pigmenti, Krabbe disease (Globoid cell leukodystrophy), Long QT syndrome, Marfan syndrome, Meckle gruber, Metachromatic leukodystrophy (MLD), Methylmalonic aciduria cblC type (MMACHC), Myotonic Dystrophy 1, Myotubular myopathy, Neurofibromatosis 1, Neurofibromatosis 2, Niemann-Pick Disease, Noonan syndrome, Oculocutaneous albinism 1 (OCA1), Ornithine carbamoyltransferase deficiency (OTC), Osteogenesis Imperfecta 1, Rapp Hodgkin ectodermal dysplasia, Retinitis pigmentosa, Retinoblastoma, Sickle Cell Anemia, Smith-Lemli-Opitz syndrome (SLOS), Spinal bulbar muscular atrophy (SBMA), Spinal Muscular Atrophy Type 1 (SMA1), Tay Sachs, Tuberous sclerosis 1 (TSC1), Tuberous sclerosis 2 (TSC2), Von Hippel-Lindau Syndrome (vHL), X-linked dominant Charcot–Marie–Tooth (CMTX), etc...... *(see review Gutierrez et al. (2008))
PGD procedures performed

Cases performed: >10,000

Disease genes tested: 778

Top 10 diseases:

Cystic fibrosis
Fragile X
Huntington disease
Sickle cell anemia
Spinal Muscular atrophy

Neurofibromatosis type 1
Beta Thalassemia
Breast cancer (BRCA1, BRCA2)
Myotonic dystrophy
Polycystic Kidney Disease (PKD1)
Faster work-up time for PGD: Karyomapping

Thousands of polymorphisms on each chromosomes
Each chromosome (region) has a unique DNA fingerprint
## Advantages of Karyomapping

<table>
<thead>
<tr>
<th></th>
<th>Karyomapping</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work-up time</td>
<td>2-4 weeks</td>
<td>8-12 weeks</td>
</tr>
<tr>
<td>Embryos correctly diagnosed</td>
<td>99.6%</td>
<td>96.8%</td>
</tr>
<tr>
<td>Clinical error rate</td>
<td>0%</td>
<td>Lab dependent</td>
</tr>
<tr>
<td>Aneuploidy meiotic</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Aneuploidy mitotic</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Parental origin / fingerprint</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Affected by ADO</td>
<td>No</td>
<td>Yes (3.6%)</td>
</tr>
</tbody>
</table>

*Konstantinidis et al (2015) RBO and Reprogenetics data*
What is next: De novo mutations

- De novo mutations occur during gametogenesis and post-zygotically.
- De novo mutations contribute to almost every known genetic disorder.
- Increased paternal age known to contribute towards de novo mutations.


Role of de novo mutations in pregnancy and outcomes

• No evidence exists regarding de novo mutations (SNVs and CNVs) in IVF generated embryos

• Increased load of Copy Number Variations seem to have an increasing role in ASD, Schizophrenia, Bipolar Disorder etc.

• Sequencing based methods capable of detecting both SNV/CNV and aneuploidy simultaneously could be the future of genetic testing
Possible limitations and challenges

• Large number of variants will be detected

• Would require immense automation of variant curation and additional variant curators

• Genetic counselling would be big challenge: What is the new normal?
PGS for aneuploidy
Pre-implantation genetic screening

• Aneuploidy increase is the major cause of reduced fertility with increasing maternal age

• One can use genetic material from embryos to determine ploidy of the embryo

• PGS can test abnormal number of chromosomes and disorders associated with it like Down’s syndrome, Edward’s syndrome, Trisomy 21 and etc.
Waves of technology

- FISH + Micromanipulation (PGS v1)
- CCS + Blastocyst culture (PGS v2)
- Whole genome sequencing + Non invasive biopsy (PGS v3)
Evolution of PGS techniques

PGS data from Reprogenetics US, (*) annualized
Preimplantation Genetics Screening (PGS)

CASE REVIEW
Prospective parents meet with genetic counselor and discuss if additional genetic testing of the couple or other family members is required.

PGD TEST PREPARATION
The PGD lab designs a test unique to each family.

IVF/ICSI
In vitro fertilization is performed and the resulting embryos are incubated.

EMBRYO TRANSFER
An unaffected embryo is transferred. Remaining embryos can be frozen for future use.

PGD
Samples are sent to the PGD laboratory, and testing is performed.

EMBRYO BIOPSY
An embryologist carefully removes one or several cells from each embryo.

6/8/2018
PGS Version 2

Blastocyst biopsy
Comprehensive chromosome screening
Biopsy Techniques- Cleavage stage biopsy

• Cleavage stage biopsy involves obtaining genetic material for PGS by performing biopsy on cleavage stage embryos on day-3 post-fertilization

• However recently it has been replaced by day-5 blastocyst biopsy

• Mosaicism is one of the typical problems that occur during the screening of cleavage stage embryos for chromosominal anomalies
Biopsy Techniques- Blastocyst biopsy

- The most prevalent option nowadays for obtaining genetic material from the embryo

- Trophectoderm biopsy obtains multiple cells for carrying out PGD/PGS. This leads to an overall improved accuracy of the test
Evolution of biopsy techniques:
About 100% of biopsies in US are blastocyst
Blastocyst biopsy: Advantages

**Advantages:**

- More DNA: fewer no results
- Fewer mosaics (21%) than day 3 (33%)
- Reduced impact of embryo biopsy *
- Less embryos to process
- Facilitates single embryo transfer

**Risks:**

- Every center biopsies differently: Some variations are detrimental
- Manipulator dependent

* Scott et al. (2013) Fertil Steril
## Comparison of PGS platforms

<table>
<thead>
<tr>
<th></th>
<th>% embryos</th>
<th>FISH</th>
<th>aCGH</th>
<th>NGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labs Performing Test</td>
<td>100s</td>
<td>180</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Total Independent Data Signals*</td>
<td>11</td>
<td>2,700</td>
<td>700,000</td>
<td></td>
</tr>
<tr>
<td>Resolution in Mb</td>
<td>arm</td>
<td>6Mb</td>
<td>3Mb</td>
<td></td>
</tr>
<tr>
<td>Misdiagnosis aneuploides (a-f)</td>
<td>7%</td>
<td>2%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Unbalanced translocations (g)</td>
<td>2% custom</td>
<td>yes</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Partial aneuploidies</td>
<td>5% no</td>
<td>yes</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Polyploidy</td>
<td>2% yes</td>
<td>no</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Mosaicism (h, i)</td>
<td>20% 20%</td>
<td>4%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Miscarriage rate (j, k)</td>
<td>10-20%</td>
<td>13%</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>

Targeted Next Generation Sequencing
Targeted Next Generation Sequencing (NGS)

Targeted NGS

No WGA. Instead defined pieces of the genome are amplified and sequenced.
Targeted Next generation sequencing (NGS)

- Targeted strategies are generally of lower resolution
- However, they have a couple of key advantages:
  - Guaranteed coverage of specified sequences (genes or polymorphisms)
  - Lower costs and higher throughput
Next Generation Sequencing

Whole genome amplification based
Protocol used for NGS

TE Biopsy

Whole Genome Amp using SurePlex

DNA is fragmented

Normal Chromosome
Thousand of DNA fragments mapped to each chromosome

Addition of barcodes (per embryo) to fragments
Abnormality rates by NGS: Data from >100,000 embryos

Mosaics are MITOTIC and therefore do not increase with age
Mosaics + Aneuploid and Mosaic show constant rates through age

<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>Normal</td>
<td>59%</td>
<td>53%</td>
<td>44%</td>
<td>31%</td>
<td>19%</td>
<td>14%</td>
</tr>
<tr>
<td>Mosaic</td>
<td>16%</td>
<td>18%</td>
<td>17%</td>
<td>13%</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Aneuploid (± mosaic)</td>
<td>18%</td>
<td>20%</td>
<td>28%</td>
<td>38%</td>
<td>41%</td>
<td>33%</td>
</tr>
<tr>
<td>Complex (*)</td>
<td>7%</td>
<td>8%</td>
<td>10%</td>
<td>17%</td>
<td>28%</td>
<td>44%</td>
</tr>
<tr>
<td>Polyploid</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

- Mosaics are MITOTIC and therefore do not increase with age
- Mosaics + Aneuploid and Mosaic show constant rates through age

N = 103,405 embryos. Reprogenetics and Genesis Genetics data to 1/2017
* Complex: >2 full abnormalities
## Validation of NGS

<table>
<thead>
<tr>
<th></th>
<th>Original Analysis method</th>
<th>Reanalysis method</th>
<th>Sample</th>
<th>Confirmed Euploid</th>
<th>Confirmed abnormal</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kung et al. 2015</td>
<td>aCGH</td>
<td>NGS</td>
<td>Same biopsy</td>
<td>44/44</td>
<td>108/108</td>
<td>152/152</td>
</tr>
<tr>
<td>(Reprogenetics)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiorentino et al. 2014</td>
<td>aCGH</td>
<td>NGS</td>
<td>Same biopsy</td>
<td>67/67</td>
<td>141/141</td>
<td>208/208</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wells et al. 2014</td>
<td>aCGH</td>
<td>NGS</td>
<td>Separate biopsy</td>
<td>13/13</td>
<td>28/28</td>
<td>41/41</td>
</tr>
<tr>
<td>(Reprogenetics)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>100% Sensitivity</strong></td>
<td><strong>100% Specificity</strong></td>
<td><strong>0% Error rate</strong></td>
</tr>
</tbody>
</table>
## Criteria for classification of samples

<table>
<thead>
<tr>
<th>Observation</th>
<th>Categorization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero Aneuploid Chro</td>
<td>Normal/Euploid</td>
</tr>
<tr>
<td>1 or 2 Aneuploid Chro</td>
<td>Aneuploid</td>
</tr>
<tr>
<td>1 Aneuploid and 1 Mosaic Chro</td>
<td>Aneuploid</td>
</tr>
<tr>
<td>≥3 Chromosomal Abnormalities</td>
<td>Complex Abnormal</td>
</tr>
<tr>
<td>Up to 20-80% abnormal cells</td>
<td>Mosaic</td>
</tr>
<tr>
<td>80% and greater abnormal cells</td>
<td>Aneuploid</td>
</tr>
<tr>
<td>20% and lesser abnormal cells</td>
<td>Euploid</td>
</tr>
</tbody>
</table>
Comparison between NGS and aCGH: by Type of Abnormality

<table>
<thead>
<tr>
<th>Original (NGS)</th>
<th>Euploid</th>
<th>Aneuploid</th>
<th>Segmental</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euploid</td>
<td>196</td>
<td>0</td>
<td>0</td>
<td>1,2</td>
</tr>
<tr>
<td>Aneuploid</td>
<td>0</td>
<td>222</td>
<td>0</td>
<td>1,2</td>
</tr>
<tr>
<td>Mosaic</td>
<td>16</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Polyploid</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Segmental Translocation</td>
<td>0</td>
<td>0</td>
<td>69</td>
<td>3</td>
</tr>
</tbody>
</table>

NGS advantages

Higher dynamic range than other techniques allows:

- Detection of *triploidy* 69,XYY and 69,XXY
- Detection of *mosaics* (20-80% range of abnormal cells or 1/5)
- **Higher resolution** than other techniques (1.5Mb)
Higher dynamic range,
Less noise than aCGH
Mosacism
Chromosomal mosaicism is the presence of two or more cytogenetically distinct cell lines.

Unlike aneuploidy (meiotic origin), mosaicism caused by mitotic errors occurring after fertilization.

Mosaicism derived from: chromosome non-disjunction, anaphase lagging and endoreduplication.
Higher dynamic range allows NGS to detect mosaics
# Mosaics: a third category

<table>
<thead>
<tr>
<th>aCGH</th>
<th>hr-NGS</th>
<th>impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (61%)</td>
<td>Normal (43%)</td>
<td>100% concordance</td>
</tr>
<tr>
<td>Mosaic (18%)</td>
<td></td>
<td>Improved selection against low implantation, high miscarriage risk embryos</td>
</tr>
<tr>
<td>Abnormal (39%)</td>
<td>Mosaic (3%)</td>
<td>some chance of making a baby</td>
</tr>
<tr>
<td></td>
<td>Abnormal (36%)</td>
<td>100% concordance</td>
</tr>
</tbody>
</table>

21%
PGDIS, COGEN Recommendations

• Report <20% as normal and >80% as abnormal (resolution limit)

• High priority mosaics: those with <40% abnormal cells

• Low priority mosaics: chaotic mosaics or those with >40% abnormal cells

• Low priority mosaics: - with chromosomes X, Y, 13, 18, 21 (live born viability)
  - with chromosomes 14, 15 (risk of UPD)
  - with chromosomes 2, 7, 16 (intrauterine growth retardation)

But there is no evidence that mosaics at blastocyst level have the same impact as mosaics in first trimester.
Next frontier in PGS: Non Invasive
Challenges to conventional PGS

- Requirement of highly skilled personnel for polar body/embryo biopsy
- Biopsy requires purchase and maintenance of a laser
- Time consuming and costly
- Potentially increases the risk to the embryo and might decrease the overall efficacy of PGT
Sources of DNA for NI-PGS: Blastocoeel fluid and spent culture media

• Blastocoeel fluid present in the blastocyst cavity, 120-144 hours post fertilisation

• Media collected after embryo in culture till cleavage or blastocyst stage

• Both sources of extruded DNA and proteins by embryo

• Potential source of biomarkers for embryo viability

• If successful, these would be less intrusive than embryo biopsy

• Aim: To explore blastocoeel fluid and spent media as a potential source of NI-PGT
Initial hypothesis and challenges for NI-PGS assay development

• DNA is likely to be degraded
  • Highly fragmented DNA is difficult to amplify using standard methods
  • Can we successfully amplify DNA from spent culture medium/blastocoel?

• Is the DNA similar to circulating cfDNA found in blood?
  • cfDNA is around ~160bp
  • Source of cell free DNA in blastocoel fluid and spent culture media?
  • Apoptotic cells? → fragmentation of DNA into nucleosome-sized fragments
  • Necrotic cells? → random fragmentation; variable DNA fragment sizes
### Summary of some published results

<table>
<thead>
<tr>
<th>Published study</th>
<th>Year</th>
<th>Journal</th>
<th>Method</th>
<th>Number of samples</th>
<th>Amplification rate</th>
<th>Ploidy concordance rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-invasive preimplantation genetic screening using array comparative genomic</td>
<td>2017</td>
<td>RBMO</td>
<td>Sureplex amplification +aCGH</td>
<td>22 spent media</td>
<td>18/22 = 81.8%</td>
<td>13/18 (72.2%)</td>
</tr>
<tr>
<td>hybridization on spent culture media: a proof-of-concept pilot study</td>
<td></td>
<td></td>
<td></td>
<td>samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>after blastocyst</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>culture compared</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>to PB results; SM</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>collected after</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>assisted</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hatching</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noninvasive chromosome screening of human embryos by genome sequencing of</td>
<td>2016</td>
<td>PNAS</td>
<td>MALBAC + NGS</td>
<td>42 spent media</td>
<td>42/42 = 100%</td>
<td>Euploidy: 21/25 = 84%;</td>
</tr>
<tr>
<td>embryo culture medium for in vitro fertilization</td>
<td></td>
<td></td>
<td></td>
<td>samples</td>
<td></td>
<td>Aneuploidy: 15/17 = 88.2%</td>
</tr>
<tr>
<td>Non-invasive preimplantation genetic screening of human blastocysts</td>
<td>2017</td>
<td>Conference abstract</td>
<td>Sureplex + NGS</td>
<td>25 spent media</td>
<td>25/25 = 100%</td>
<td>overall: 85% (75/20) with respect to TE biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ASRM-Fert Ster</td>
<td></td>
<td>samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monash University</td>
<td>2017</td>
<td>Conference abstract</td>
<td>DOPlify + NGS</td>
<td>178 spent media</td>
<td>94% amplification</td>
<td>for day4 to day5/6 culture: 95%; for day3 to day5/6 culture: 65.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ASRM-Fert Ster</td>
<td></td>
<td>samples</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary of our results

• Spent culture media seems to be a better source for cell-free embryonic DNA as compared to blastocoel fluid

• Preliminary data analysis demonstrates our in-house modified method to be a superior amplification strategy for spent media samples as compared to existing WGA methods (Sureplex, MDA)

• Spent media can be potentially used as a source of DNA for non-invasive PGT, however extensive clinical validation is necessary to determine its efficacy.

• If successful, this can increase patient access to PGT and might be more cost effective compared to the current PGT techniques available.
Beyond the embryo

Endometrial receptivity
Embryo Implantation

Key process for the establishment of a successful pregnancy

• Complex:  - apposition
  - adhesion
  - invasion

• Crucial:  - dialogue between embryo and endometrium
  - implantation-competent blastocyst
  - receptive endometrium

Synchrony between embryo and endometrium
Window of Implantation (WOI)

- LH + 7 (days 19 – 21)
- 12 hours - 2 days
- Displaced WOI in 30% of RIF patients\(^1,2\)

\(^1\) Ruiz-Alonso et al, 2013; Ruiz-Alonso et al, 2014; \(^2\) Sarasa et al, 2017

Identify patient-specific WOI
Personalised embryo transfer
Evaluation of Endometrial Receptivity

Enables identification of a personalised WOI and personalised embryo transfer

- Histologic evaluation\(^1\)
- Evaluation of biochemical markers\(^2\)
- Analysis of gene expression\(^3\)

Identification of transcriptomic signature specific to the WOI

Development of accurate diagnostic tools

\(^1\)Noyes et al, 1950; Noyes et al, 1975
\(^2\)Reviewed in Cavagna et al, 2003
\(^3\)Reviewed in Horcajadas et al, 2006
Scientific data

Studies reporting on accuracy and treatment outcomes

- High accuracy in receptivity status assignment
- Displaced WOI in >25% of RIF patients
- Personal embryo transfer results in improved IVF outcomes
Advantages of ER Testing based on gene expression

Endometrial receptivity testing based on gene expression...

• Provides objective molecular diagnosis test
• Enables personal embryo transfer
• Shows high accuracy and reproducibility
• Provides evidence of a frequently displaced WOI in RIF patients
• Provides an effective strategy to improve clinical outcomes in RIF patients
ACKNOWLEDGEMENTS

Scientists
Katharina Spath, PhD (UK)
Dhruti Babariya, PhD (UK)
Josh Blazek, PhD (US)
Mike Large, PhD (US)
Santiago Munné, PhD (US)
Mark Hughes, MD, PhD (US)
Jacques Cohen, PhD (US)
Tomas Escudero, MSc (US)
Ryan Subaran, PhD (US)
Pere Colls, PhD (US)
Tony Gordon, PhD (UK)
Lia Ribustello, MSc (US)
Katie Bauckman, MSc (US)
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