Institution: King's College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Improved methods for preimplantation genetic diagnosis help couples avoid the risk of bearing children with inherited diseases

1. Summary of the impact

King's College London (KCL) has developed a generic test format which is being used to cheaply and easily detect a large number of single-gene disorders and chromosomal abnormalities in *in vitro* fertilised embryos – a highly significant impact. The test resulted from KCL's research to develop new strategies for preimplantation genetic diagnosis (PGD), which involved developing a small number of DNA probes targeted around a known area of genetic risk to identify mutations as well as methods to detect chromosomal translocations. Because the approach is cheap and easy to apply, it is being used by IVF clinics worldwide as well as by the NHS. The KCL/Guy's and St Thomas' Centre for PGD was licensed in 2008 by the UK Human Fertilisation and Embryo Authority to analyse over 50 genetic conditions affecting single genes and carries out more than half of all the UK's PGD testing. Embryos can now be tested using these techniques for virtually any inherited genetic disease prior to implantation with a 98% success rate, thus reducing the need for later prenatal diagnosis and termination of an affected foetus.

2. Underpinning research

Analysis of inherited genetic disease in embryos before implantation: Since genetic disorders based on a single gene are relatively rare, and in some cases specific to a family, the costs associated with developing a specific test for individual defects are prohibitive. Prior to the development of KCL's innovative new techniques, PGD was only available for a small number of more common genetic conditions.

Adoption of new techniques to enable the accurate analysis of genetic defects in human embryos: Early work in 1998 led by Professor Ogilvie (KCL / Guy's and St Thomas' NHS Foundation Trust, 1990-present) showed that, at that time, genetic analyses performed on single cells isolated from an early stage human embryo were not sufficiently accurate, reproducible or conclusive [1]. Similarly, KCL researchers used mathematical models to assess the accuracy of PGD methods used at the time and found that DNA isolated from a single cell sampled from a human embryo was not a reliable basis for accurate diagnosis of genetic abnormalities [2].

In order to improve preimplantation genetic testing, KCL researchers first had to find a reliable technique for ensuring that sufficient good quality DNA could be extracted from the small amount originally sampled from an early human embryo. Research led by Dr Renwick and colleagues (KCL/Guy's and St Thomas' NHS Foundation Trust, 1998–present) showed that multiple displacement amplification (MDA) could amplify the original amount of DNA around a million-fold, generating a substantial quantity for subsequent genetic mutation analyses [3].

KCL researchers pioneer new, simple and cost-effective methods of single gene and chromosomal genetic analysis: KCL researchers also determined that a small number of DNA probes targeted at specific genetic regions could cheaply and easily detect single gene defects in preimplantation embryos [3]. This novel technique, known as preimplantation genetic haplotyping (PGH), was based on the concept that a small number of DNA probes targeted within or around a known disease risk gene could accurately determine whether or not an embryo harboured an inherited genetic mutation [3]. Meanwhile, Dr Scriven (KCL / Guy's Hospital, 1989-2011) outlined a strategy to diagnose different types of chromosomal translocations – that is, a rearrangement of part of a chromosome onto a different chromosome – in affected embryos as part of PGD [4]. Individuals with balanced chromosomal translocations are themselves usually unaffected but have a high risk of affected pregnancies and therefore require careful PGD. Both these approaches would be quick, cheap and could be performed using basic laboratory equipment.

Detecting genetic disorders to prevent severe inherited disease: In 2006, KCL researchers demonstrated that a generic test based on PGH could detect single gene mutations and would be suitable for use in the NHS environment. Collaborating researchers from the Guy's Hospital Genetics Clinic, KCL Genetics laboratories and KCL Women's Health, Dr Abbs (KCL, 1994-2012), Professor Ogilvie, Dr Renwick and Professor Braude (KCL, 1997–2011), first published proof of this principle using embryos known to be at risk of cystic fibrosis, a common genetic condition caused by a mutation in a single gene, *CFTR* [3]. The most common mutation in the *CFTR* gene, ΔF508, accounts for two-thirds of cases; however, more than 1,500 other known mutations exist. Applying KCL's generic PGH technique identified multiple uncharacterised mutations in the *CFTR* gene of human embryos, and facilitated the implantation of healthy embryos [3]. Thus, the generic PGH technique could accurately distinguish normal (low-risk) and mutated (high-risk) genes in embryos [3,5].

Ongoing KCL research expands the number of inherited genetic diseases available for embryo screening: KCL-pioneered PGD techniques have enabled consistently successful detection of inherited genetic mutations without the need for mapping a family's specific genetic mutation. Using the PGH approach, the number of single-gene conditions detectable by on-demand clinical services has increased to well over 50. At Guy's and St Thomas' Centre for PGD alone, PGH has been used to identify the presence of high-risk genes for multiple inherited diseases in embryos from at-risk couples, including cystic fibrosis [3], Duchenne and Becker muscular dystophy [3,6], trisomy [5], Alport syndrome, Haemophilia A, Huntington's disease, sickle-cell disease and others [6]. Ultimately, KCL research has helped couples avoid the risk of bearing children with inherited diseases or the distress of terminating pregnancies.

3. References to the research

1) **Kuo HC**, **Ogilvie CM**, **Handyside AH**. Chromosomal mosaicism in cleavage-stage human embryos and the accuracy of single-cell genetic analysis. *J Assist Reprod Genet.* 1998;15:276–80.

2) **Lewis CM**, **Pinel T**, **Whittaker JC**, **Handyside AH**. Controlling misdiagnosis errors in preimplantation genetic diagnosis: a comprehensive model encompassing extrinsic and intrinsic sources of error. *Hum Reproduction*. 2001;16:43–50.

3) **Renwick PJ**, Trussler J, Ostad-Saffari E, Fassihi H, Black C, **Braude P**, **Ogilvie CM**, **Abbs S**. Proof of principle and first cases using preimplantation genetic haplotyping – a paradigm shift for embryo diagnosis. *Reprod Biomed Online*. 2006;13:758–67.

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6) **Renwick P**, Trussler J, **Lashwood A**, **Braude P**, **Ogilvie CM**. Preimplantation genetic haplotyping: 127 diagnostic cycles demonstrating a robust, efficient alternative to direct mutation testing on single cells. *Reprod Biomed Online*. 2010;20:470–6.

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4. Details of the impact

Improved accessibility of genetic testing to couples with a history of hereditary genetic disease: The major innovation arising from KCL research is the development of generic tests to identify any genetic defect in disease risk genes and chromosomes in human embryos. KCL techniques can be performed using standard laboratory equipment, and are sufficiently cost-effective for the NHS to use as a universal, affordable PGD service. In the future, it is expected

that the number of genetic conditions for which PGH is available will continue to increase to meet patient demand.

KCL's PGD techniques licensed by the UK's human fertilisation regulating body: Since 2008, Guy's and St Thomas' Centre for PGD has been licensed by the Human Fertilisation and Embryo Authority (HFEA) to analyse over 50 genetic conditions affecting single genes. PGH is recognised as a solid, reliable technique to identify embryos affected by such genetic diseases. The centre has also performed PGD for more than 200 different chromosomal mutations [7] and carries out more than half of all PGD cycles done in the UK [8].

KCL's PGD techniques improve pregnancy success rates: Successful pregnancy rates for couples undergoing preimplantation genetic analysis of embryos using KCL techniques are higher than rates reported for other methods of genetic analysis [9]. 34% of embryos selected using KCL methods of PGD go on to result in successful pregnancies, compared to a national average of 25% [8]. In November 2011, the Guy's and St Thomas' NHS Foundation Trust celebrated the birth of over 300 babies following PGD analysis, an achievement that was widely covered in the press [10].

Adoption of KCL's preimplantation genetic haplotyping technique by *in vitro* fertilisation clinics worldwide: The generic applicability of the KCL-pioneered PGH approach to detect single gene defects in fertilised human embryos has led to the adoption of the technique by human fertilisation clinics worldwide. Clinics in the USA [11], Saudi Arabia [12], Israel [13] and the Czech Republic [14] have all reported success using PGH. Large-scale clinical trials are also under way in Belgium to validate the performance of PGH with a view to ultimately replacing existing labour-intensive and costly PGD techniques [15].

KCL researchers recognised as world-class authorities for *in vitro* genetic testing: The original research performed by KCL scientists has been widely recognised by the wider medical community, and included in publications referred to by clinicians, embryologists and nurses. Both Professor Ogilvie and Dr Scriven were invited to contribute chapters to the second edition of *Preimplantation Genetic Diagnosis*, published by Cambridge University Press [16]. PGH is also referred to in the sixth edition of *Essential Medical Genetics*, published by Wiley-Blackwell, as a landmark advance in the field of medical genetics [17]. KCL researchers also contributed to the Galton Institute's *Guide to Pre-implantation Genetic Diagnosis* [18].

KCL research shapes international genetic-testing guidelines: KCL research has significantly contributed to shaping international clinical guidelines. Consolidated PGD best practice guidelines published in 2011 by the European Society for Human Reproduction and Embryology (ESHRE) not only reference original KCL PGD research (see [1], [2] & [4] above), but KCL researchers Professor Braude and Mrs Lashwood (KCL / Guy's and St Thomas' NHS Foundation Trust, 1991–present) also co-authored the guidelines dedicated to organising a centre for PGD/preimplantation genetic screening [19, 20, 21].

A number of specialist genetics charitable groups have also used KCL research to inform policies and guide patient choices. These include UNIQUE [22], Genetic Alliance UK [23], the Cystic Fibrosis Trust [24] and the Jennifer Trust [25].

5. Sources to corroborate the contribution, impact or benefit

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22) UNIQUE: a rare chromosome disorder support group, contact name available. (www.rarechromo.org)
23) Genetic Alliance UK: a national charity of over 150 patient organisations supporting all those affected by genetic disorders; contact name available. (www.geneticalliance.org.uk)
24) The Cystic Fibrosis Trust: the national charity dealing with all aspects of cystic fibrosis; contact name available. (www.cysticfibrosis.org.uk)
25) The Jennifer Trust: the national charity for all forms of spinal muscular atrophy; contact name available. (www.jtsma.org.uk)