

# New technologies in embryo testing (including embryo biopsy and non-invasive methods for PGD)

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**Strategic delivery:**  Safe, ethical, effective treatment  Consistent outcomes and support  Improving standards through intelligence

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## Details:

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Meeting Scientific and Clinical Advances Advisory Committee (SCAAC)

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Agenda item 5

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Paper number SCAAC (03/02/2020) 005

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Meeting date 03 February 2020

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## Output:

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For information or decision? For information

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Recommendation Members are asked to:

- Consider the use of new technologies in embryo testing such as non-invasive testing of spent culture medium, and the ethical implications of these technologies in fertility treatment.
- Review whether any outputs from the HFEA are required addressing the use of new technologies in embryo testing.
- Advise the Executive if they are aware of any other recent developments.

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Resource implications N/A

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Implementation date N/A

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Communication(s) N/A

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Organisational risk  Low  Medium  High

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Annexes None

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## 1. Introduction

- 1.1. The two main types of embryo testing are preimplantation genetic diagnosis (PGD), also known as preimplantation genetic testing for monogenetic disease (PGT-M), and preimplantation genetic screening (PGS), also known as aneuploidy screening (PGT-A). In PGD, embryos carrying a specific genetic mutation or chromosomal translocation that is prevalent in a patient's family are identified and not transferred. In PGS, embryos carrying a common chromosomal abnormality that cause miscarriage or IVF failure are identified and not transferred; this is principally carried out to improve IVF efficiency. Potential safety concerns regarding biopsy and restrictions to only those embryos suitable for biopsy pose limitations. In addition, embryo mosaicism gives rise to false positives and false negatives in PGS because the inner cell mass (ICM) cells, which give rise to the foetus, are not tested.
- 1.2. At the February 2017 SCAAC meeting, embryo testing techniques were discussed such as karyotyping for PGD and next generation sequencing (NGS) for PGS. Discussions were also had around mosaic embryos and the lack of evidence supporting the use of PGS. The conclusions were that further research is needed on the causes of mosaicism and on non-invasive methods of embryo testing, and that more data is needed in order to determine the benefits of PGS.
- 1.3. At the last horizon scanning meeting at ESHRE 2019, it was highlighted that the HFEA should consider if action is required around the consequences of whole genome sequencing (WGS) of embryo biopsies leading to incidental findings. Scientists and fertility companies are developing more accurate and less invasive techniques for embryo testing, such as WGS, which can simultaneously screen embryos for both genetic and chromosomal abnormalities without the need to develop any disease-specific test. These technologies have the potential to generate additional genetic information and therefore we have to consider the legal and ethical boundaries for testing embryos for genetic conditions and chromosomal abnormalities using these technologies. It was also advised that the HFEA should consider if action is required around the use of embryo testing for polygenic traits where the result is a risk of a trait rather than a diagnosis.
- 1.4. The use of embryo testing for more than one condition or abnormality at a time was discussed at an Authority meeting in 2015 where Authority members were asked to consider if they would allow testing for more than one disease at a time, and how the information generated by the tests would be handled. Some members expressed misgivings about which patients were currently being offered PGS by clinics and how able PGS centres were to interpret complex test results.
- 1.5. There has recently been media interest in claims that DNA measurements can be used to predict which embryos from an IVF procedure are least likely to end up with any of 11 different common diseases such as diabetes, coronary heart disease and testicular cancer but also traits such as intellectual disability and idiopathic short stature. The DNA obtained from biopsied cells is measured at several hundred thousand genetic positions, from which a statistical estimate can be created, called a "polygenic score," of the chance of disease later in life.

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## 2. Recent studies

### Non-invasive genetic testing

- 2.1. A study by Li et al., (2018) tested a less-invasive PGS protocol which utilises spent culture medium combined with blastocoel fluid (ECB) to assess chromosomal aneuploidy. They

compared the chromosomal information obtained from 40 embryos using this method (whole genome amplification) compared to the currently used trophoctodermal biopsy method. DNA concentrations in the ECB were sufficiently high for DNA amplification, NGS and aneuploidy analysis. The new technique however generated information about aneuploidy that was not entirely identical to that obtained from the cell biopsy or the remaining embryo. The conclusion was that the effectiveness of this new approach in selecting the best embryo for transfer needs further long-term evaluation. The same conclusions were reached in a study by Capalbo et al., (2018).

- 2.2.** Hammond et al., (2017) characterized nuclear and mitochondrial DNA (mtDNA) in spent culture media from normally developing blastocysts (n = 227) to determine whether it could be used for non-invasive genetic assessment. The conclusion was that currently DNA from culture media cannot be used for genetic assessment because embryo-associated structures release DNA into the culture medium and the DNA is of mixed origin. The same conclusion was reached by Sanchez-Ribas et al., (2017) and Yang et. Al., (2019).
- 2.3.** A paper by Huang et al., (2019), examined the efficacy of non-invasive preimplantation genetic testing for aneuploidy in the spent culture media of human blastocysts by analysing the cell-free DNA (cfDNA), which reflects ploidy of both the trophoctoderm and inner cell mass. 52 frozen donated blastocysts with trophoctoderm biopsy results were thawed and their spent culture medium analysed by NGS. Results were compared with the sequencing results of the corresponding embryos, and positive predictive value (PPV) and specificity for non-invasive PGS were much higher than trophoctoderm PGS. These results suggest that non-invasive PGS is less prone to errors associated with embryo mosaicism and is more reliable than trophoctoderm PGS.
- 2.4.** Rubio et al., (2019) also studied whether the embryonic cfDNA in the spent media of 115 blastocysts was representative of the chromosomal constitution of the blastocyst. They found that the total concordance rate for ploidy and sex was 78.7%, and sensitivity and specificity were 94.5% and 71.7% respectively. The authors concluded that this was reassuring for considering this non-invasive approach as an alternative to trophoctoderm biopsy for PGS in the future. Yeung et al., (2019) also concluded that cell-free DNA found in spent culture medium could provide ploidy information of an embryo in the same way as trophoctoderm PGS, and a pilot clinical study by Fang et al., (2019) on 45 couples found that non-invasive chromosome screening could identify embryo chromosomal abnormalities in couples either with or without chromosomal rearrangement, with satisfying clinical outcomes.

## Mosaicism

- 2.5.** In a study by Munné et al., (2017), the pregnancy outcome potential of mosaic embryos, detected by PGS with NGS was investigated. 41% of mosaic embryos produced an ongoing implantation, and complex mosaic blastocysts had a lower ongoing implantation rate (OIR) than other mosaics. The results suggested that embryos with >40% abnormal cells and those with multiple mosaic abnormalities (chaotic mosaics) are likely to have lower OIRs and should be given low transfer priority. The same conclusion was reached by Fragouli et al., (2017), and a study by Lledo et al., (2017) suggested that the transfer of some mosaic embryos achieve full term pregnancies, but additional studies are needed to clarify how embryo mosaicism affects the outcomes of the IVF cycle

## Polygenic disorders

- 2.6.** In a paper by Treff et al., (2019) a method of testing aneuploidy, structural rearrangements and monogenic disorders using a single platform was studied in 48 rebiopsies of discarded embryos. They also claimed to be able to predict the risk of polygenic disorders for the first time, and performance was established for two common diseases, hypothyroidism and type 1 diabetes. The conclusion was that the availability of expanded testing to evaluate the risk of polygenic disorders in a preimplantation embryo has the potential to lower the prevalence of common genetic diseases in humans.
- 2.7.** In a study by Karavani et al., (2019), the researchers used data from genetic studies to simulate the effects on IQ and height in the offspring of various pairings of couples. They used polygenic scores, which are calculated using genetic data on many of an individual's genes to predict their chances of inheriting a certain trait and combined these with preimplantation genetic testing to maximise the polygenic score for the target traits in their offspring. They found that selecting embryos based on their genetic predisposition for height or IQ resulted in an increase of only 2.5 centimetres in height or 2.5 IQ points above average for a sample of five embryos. This suggests that there are factors involved in the inheritance of complex traits other than genes.

## Adult onset conditions

- 2.8.** The Ethics Committee of the American Society for Reproductive Medicine (2018) released a committee opinion on the use of preimplantation genetic testing for testing monogenic defects for adult-onset conditions. The consultation was that this procedure is ethically permissible as a matter of reproductive liberty for a range of conditions including when the condition is serious and no safe, effective interventions are available.

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## 3. Conclusions

- 3.1.** There is growing interest in the use of non-invasive preimplantation genetic testing, specifically the process of analysing cell-free and mtDNA in the spent culture media of human blastocysts. Studies have come to different conclusions regarding the specificity and efficacy of these methods, showing a need for increased research in this area and larger studies. Studies analysing cfDNA have showed more promise than others, because of greater specificity and the potential for less mosaicism.
- 3.2.** WGS could offer the potential to prioritise embryo transfer not only on testing for specific genes, but also on the overall genetic constitution of the embryo. However there are currently no guidelines on how to use this information, and on the ethical consequences of generating this additional genetic information. There is therefore a need for future research on the impact of this.
- 3.3.** There is a need for further research around the use of embryo testing for polygenic disorders and consideration of the ethical implications of embryo testing for polygenic traits where the result is a risk or a trait rather than a diagnosis.

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## 4. Recommendations

- 4.1.** Members are asked to

- Consider the use of new technologies in embryo testing such as non-invasive testing of spent culture medium, and the ethical implications of these technologies in fertility treatment.
- Review whether any outputs from the HFEA are required addressing the use of new technologies in embryo testing, for instance increased access to genetic counselling for patients. Currently our Code of Practice says that where PGS is carried out using technologies that give rise to additional genetic information, the centre should ensure that people seeking treatment are offered access to genetic counselling and, where appropriate, infertility counselling before and after treatment has occurred.
- Advise the Executive if they are aware of any other recent developments.

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## 5. References

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