Twelve years of assessing the quality of Preimplantation Genetic testing for monogenic disorders

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Introduction

GenQA (previously UK NEQAS for Molecular Genetics), has provided external quality assessment (EQA) of preimplantation genetic testing for monogenic disorders (PGT-M) since 2008.

Couples can use this procedure as an alternative to invasive prenatal diagnosis or therapeutic termination of pregnancy if they are at risk of passing on a genetic condition to their offspring.

Reliable and accurate testing protocols are typically based on PCR with primers specific for the genetic pathogenic variant plus the addition of linked markers, typically STR markers or SNPs. This direct test plus linkage approach allows testing for the presence or absence of the pathogenic variant(s) as well as contamination and/or amplification issues.

To date, PGT-M for eight disorders including recessive, dominant and X-linked diseases (incorporating triplet repeat disorders) have been provided and has identified common and novel issues.

Material & methods

The EQA format follows a mock PGT case and is provided as two stages to mimic end-to-end testing.

Stage 1: Feasibility testing

❖ Sample type

DNA for a "mock" couple wishing to undergo PGT and an "affected" family member.

❖ Submission requirements

Proforma with genotyping results, providing details of proposed testing strategy including:

- Limitations and risk of misdiagnosis
- Whether strategy deemed sufficient to proceed to stage 2*.

Stage 2: Embryo testing

❖ Sample type

Cells to mimic embryos.

Laboratories chose either#:

- Single cells (blastomere testing) or
- A set of six cells (trophectoderm testing)

❖ Submission requirements

Fully interpretative reports stating genetic suitability for transfer

Proforma detailing haplotyping results.

*Laboratories that were unable to perform PGT following stage 1 were withdrawn.

#From 2008-2013, laboratories provided with single cells only. Since 2014, choice of testing made available.

Assessment

Submissions were assessed anonymously against peer-ratified marking criteria.

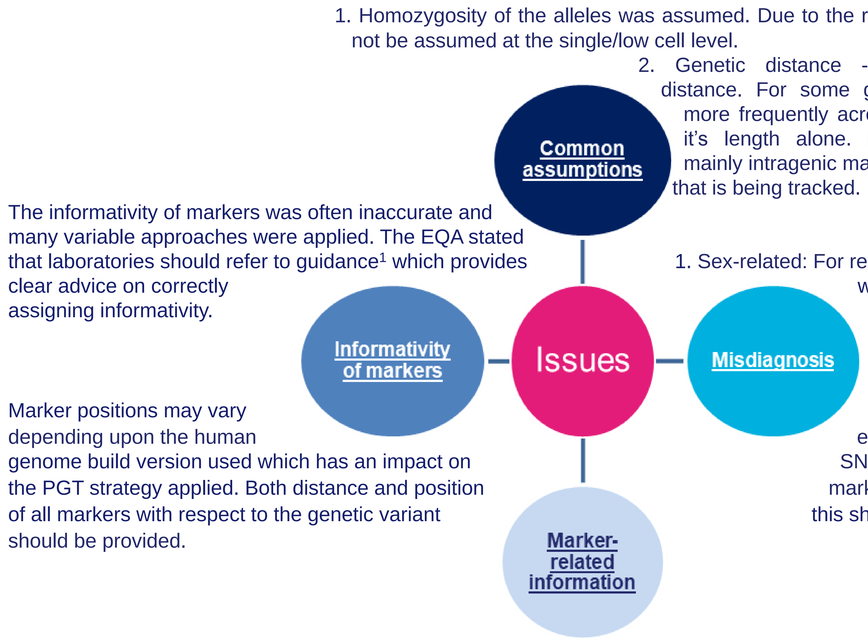
Samples were validated for STR analysis (2008 to 2015) and both STR and SNP analysis since 2016, for the disease specified for that EQA run prior to distribution.

Results

Participation: There has been a 5-fold increase between 2008 and 2021, from 12 to 68 participating laboratories.

Methods: STR linkage analysis remains the most used method (59% laboratories in 2020), despite the widespread adoption of SNP-based automated platforms from 2013 onwards.

Material tested: Trophectoderm samples were most frequently used for embryo testing; ≥77% laboratories in 2018-2020.



Performance: Issues remain as evidenced in the 2021 EQA with two laboratories (3%) reporting incorrect results for embryo testing and four laboratories (6%) reporting interpretation errors.

Conclusion

GenQA provides a service that measures the clinical accuracy of PGT results and helps to ensure a high standard of care. Sharing of EQA findings and regular laboratory participation in EQAs leads to better laboratory testing by identifying areas for enhancement This educational aspect of EQA promotes improvements to PGT laboratory services.

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References [1]ESHRE PGT Consortium Steering Committee, ESHRE PGT Consortium good practice recommendations for the organization of PGT. Hum Reprod Open May 29;2020(3)

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