# Parental Quality Control (PQC) with PGT-Complete

Taking PGT-A beyond aneuploidy screening to provide a new standard of care with PGT-Complete

## Highlights

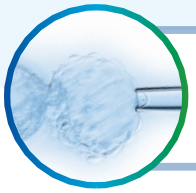
- Our innovative PGTai® 2.0 technology is improved with simultaneous analysis of parental inheritance during PGT-A for embryo biopsies in PGT-Complete
- This sophisticated analysis leverages information from parental and embryonic genomes to provide more confidence that the embryo biopsy has the expected (maternal & paternal) genetic contribution
- This cutting-edge analysis is powered by our artificial intelligence (AI) and allows us to accurately identify inheritance patterns
- This test is now available as part of our PGT-Complete, a 4-in-1 genetic test that provides a new standard of care in PGT

## PGT-Complete

*Four-in-one genetic test to advance the standard of care*

- Includes PGT-A and all the benefits of our innovative and proprietary AI to help improve the chances of IVF success
- Parental QC helps reduce parental anxiety of potential mix-ups and provides reassurance that the intended gametes were used
- Origin of aneuploidy information supports the clinic and patients to guide future gamete donor decisions
- Genetic PN check provides the capability to identify and rescue true 2PN embryos and might enable additional embryo transfers[1]

1. JBRA Assist Reprod. 2020 Apr-Jun; 24(2): 143–146. Blastocysts Derived From 0PN Oocytes: Genetic And Clinical Results



**A four-in-one genetic test**

for the most complete clinical insights

***NEW: REASSURANCE THAT AN EMBRYO BIOPSY INHERITED THE EXPECTED PARENTAL GENOMES***

For a full review of our PGTai® 2.0 technology please see our **white paper**

## Introduction

Over the past 20+ years, technological advancements in the fields of single-cell genomics and IVF embryo handling have made it possible to accurately assess the chromosomal copy number (PGT-A/SR) and/or disease status (PGT-M) of human embryos prior to transfer into the prospective mother or surrogate.[2,3,4,5]

In 2019, CooperSurgical® Fertility Solutions exhibited its leadership in the PGT-A market with the launch of PGTai® 2.0, the first technology to leverage both genome-wide copy number variations (CNV) **AND** single nucleotide polymorphism (SNP) assessment to fully evaluate the copy number of an embryo. Furthermore, if combined with information from the parental genomes used to create the embryo, the PGTai® 2.0 technology further leverages SNPs to accurately identify the parental origin of meiotically derived aneuploidies in the embryo.

**Through continued assay and bioinformatics innovation, along with enhanced sequencing capabilities, our new PGT-Complete offering now assesses parental genome inheritance patterns in a trophectoderm biopsy. This added analysis is called Parental Quality Control (PQC). This additional analysis helps provide confidence in the genetic relatedness of the embryo biopsy with its intended biological parents/gamete sources.**

The following pages describe the validation and performance of the Parental QC analysis and its importance in quality control for pre-biopsy embryo culture and downstream PGT-A.


2. De Rycke M, Berckmoes V. Preimplantation Genetic Testing for Monogenic Disorders. Genes (Basel). 2020 Jul 31; 11(8):871. doi: 10.3390/genes11080871. PMID: 32752000; PMCID: PMC7463885.

3. Natesan SA, Bladon AJ, Coskun S, Qubbaj W, Prates R, Munne S, Coonen E, Dreesen JC, Stevens SJ, Paulussen AD, Stock-Myer SE, Wilton LJ, Jaroudi S, Wells D, Brown AP, Handyside AH. Genome-wide karyomapping accurately identifies the inheritance of single-gene defects in human preimplantation embryos in vitro. Genet Med. 2014 Nov;16(11):838-45. doi: 10.1038/gim.2014.45. Epub 2014 May 8. PMID: 24810687; PMCID: PMC4225458.

4.Handyside AH, Harton GL, Mariani B, Thornhill AR, Affara N, Shaw MA, Griffin DK. Karyomapping: a universal method for genome wide analysis of genetic disease based on mapping crossovers between parental haplotypes. J Med Genet. 2010 Oct;47(10):651-8. doi: 10.1136/jmg.2009.069971. Epub 2009 Oct 25. PMID: 19858130.

5. Gould RL, Griffin DK. Karyomapping and how is it improving preimplantation genetics? Expert Rev Mol Diagn. 2017 Jun;17(6):611-621. doi: 10.1080/14737159.2017.1325736. Epub 2017 May 15. PMID: 28459185.

## Maternal and paternal inheritance assessment with PQC

ParentalQC was developed using 189 Trios (maternal DNA + paternal DNA + embryo biopsy) from 42 families with expected inheritance patterns. These were determined by PGT-M analysis that utilized genome-wide SNP analysis (Karyomapping). As part of the Trio selection, both families with and without known consanguinity were included in the development process to ensure the algorithm's robustness in various circumstances.

Parental genomic DNA (gDNA) obtained from buccal swabs and DNA from embryo biopsies were processed through our PGT-A workflow and analyzed for CNV by the PGTai®2.0 algorithm. Embryo biopsies, regardless of ploidy status, were analyzed alongside the confirmed correct parents to establish reference ranges for expected inheritance. To generate data for the potential unexpected inheritance patterns, sequencing data from each embryo biopsy was subjected to the Trio analysis under three different conditions:

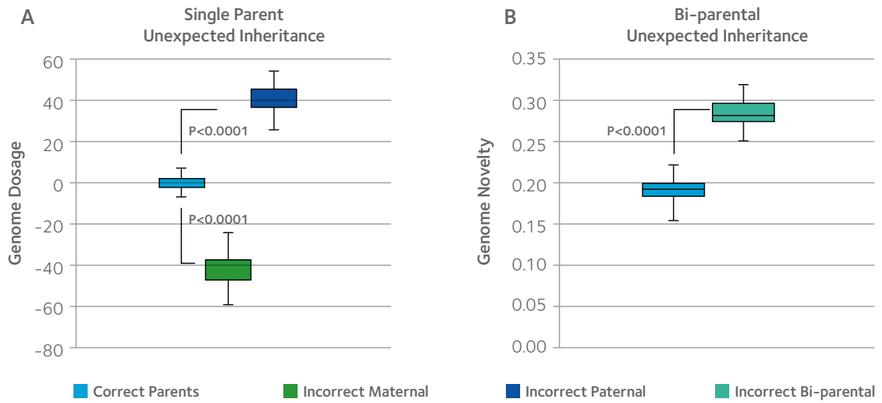
1. correct maternal + incorrect paternal,
2. incorrect maternal + correct paternal,
3. incorrect maternal + incorrect paternal.

Each embryo biopsy was tested against at least 3 different incorrect parental samples for each scenario described to ensure robustness in the resulting PGT-Complete test.

Two novel outputs of the Trio analysis are leveraged in the automated classification model for expected vs. unexpected inheritance observation in embryo biopsies (Figure 1). The genome dosage, an internal metric describing the quantity of genomic material for any given member in the trio, was significantly different from reference when only one incorrect parental sample is included in the analysis, (Figure 1A). Furthermore, genome novelty, an internal metric describing new genomic material, was significantly different from reference when compared against Trios where both parents were incorrect during analysis (Figure 1B).

### Figure 1A & 1B: Classification model for Single Parent (1A) vs. Bi-parental (1B)

Summary: Our novel and comprehensive validation pathway ensures robustness of the analysis for overall greater confidence in reporting.




In total, 189 correct Trios, 887 Trios with unrelated maternal sample, 899 Trios with unrelated paternal sample, and 837 Trios with both parental samples unrelated were analyzed to assess the performance of the PGT-Complete parental QC algorithm (Table 1).

**Total accuracy for Parental QC of 99.85% (2808/2812)**

- **Sensitivity of 99.96% (95CI: 99.79 - 100)**
- **Specificity of 98.43% (95CI: 95.48 - 99.67)**

### Table 1: Parental QC Performance Assessment Table

Summary: Parental QC was validated by more than 2,800 samples to yield a calculated accuracy rate of 99.85%. This high accuracy rate demonstrates the technical robustness and reporting confidence Parental QC provides.

| | | Known Relatedness[6] | | | |
|---|---|---|---|---|---|
| | | Related Parents | Unrelated Maternal | Unrelated Paternal | Unrelated Parents |
| PQC Result | Related Parents | 188 | 0 | 3[8] | 0 |
| | Unrelated Maternal | 1[7] | 887 | 0 | 0 |
| | Unrelated Paternal | 0 | 0 | 896 | 0 |
| | Unrelated Parents | 0 | 0 | 0 | 837 |

6. Relatedness refers to association with the embryo
7. False positive result caused by maternally-derived tetraploidy (92,XXXY)
8. False negative results caused by an embryo with >7 aneuploidies analyzed with 3 different unrelated paternal specimens.

## Additional Causes for Genetic Unrelatedness

**Parental QC provides additional confidence in the PGT-A result for any given embryo as well as assurance in the relatedness of the biopsy with its respective parental contributions.** While findings of unexpected inheritance are anticipated to be rare, there are several potential contributors to consider (Table 2). Based on internal data, the most common cause of an unexpected relatedness finding will be significant maternal cell contamination (MCC) in the trophectoderm biopsy. It is important to note that Parental QC in PGT-Complete does not provide a specific reason on why the unexpected finding was observed. In all cases of unexpected relatedness, a team of internal subject matter experts will review the findings prior to release to the clinic. Communication regarding potential or recommended next steps will be handled on a case-by-case basis.

### Table 2: Origins of Unexpected Relatedness Findings

Summary: Potential causes of unexpected inheritance can vary and one common cause is thought to be maternal cell contamination.

| Finding | Potential Cause(s) |
|---|---|
| **Unexpected Maternal Inheritance** | • Genome-wide paternally-derived UPD (lethal/molar pregnancy)<br>• Mosaic genome-wide paternally-derived UPD<br>• Unlabeled Egg donor/incorrect maternal BSK<br>• Unintended maternal gamete used in embryo creation |
| **Unexpected Paternal Inheritance** | • Maternal Cell Contamination within biopsy sample<br>• Maternally-derived haploidy<br>• Genome-wide maternally derived UPD<br>• Mosaic genome-wide maternally-derived UPD<br>• Unlabeled Sperm donor/incorrect paternal BSK<br>• Unintended paternal gamete used in embryo creation |
| **Unexpected Bi-parental Inheritance** | • Exogenous contamination within biopsy sample<br>• Unlabeled Egg & Sperm donor<br>• Incorrect biopsy labelling or accidental biopsy of an embryo unrelated to the couple<br>• Incorrect gametes used in embryo creation |

# The CooperSurgical® Difference

*Reassure, Empower, Safeguard*

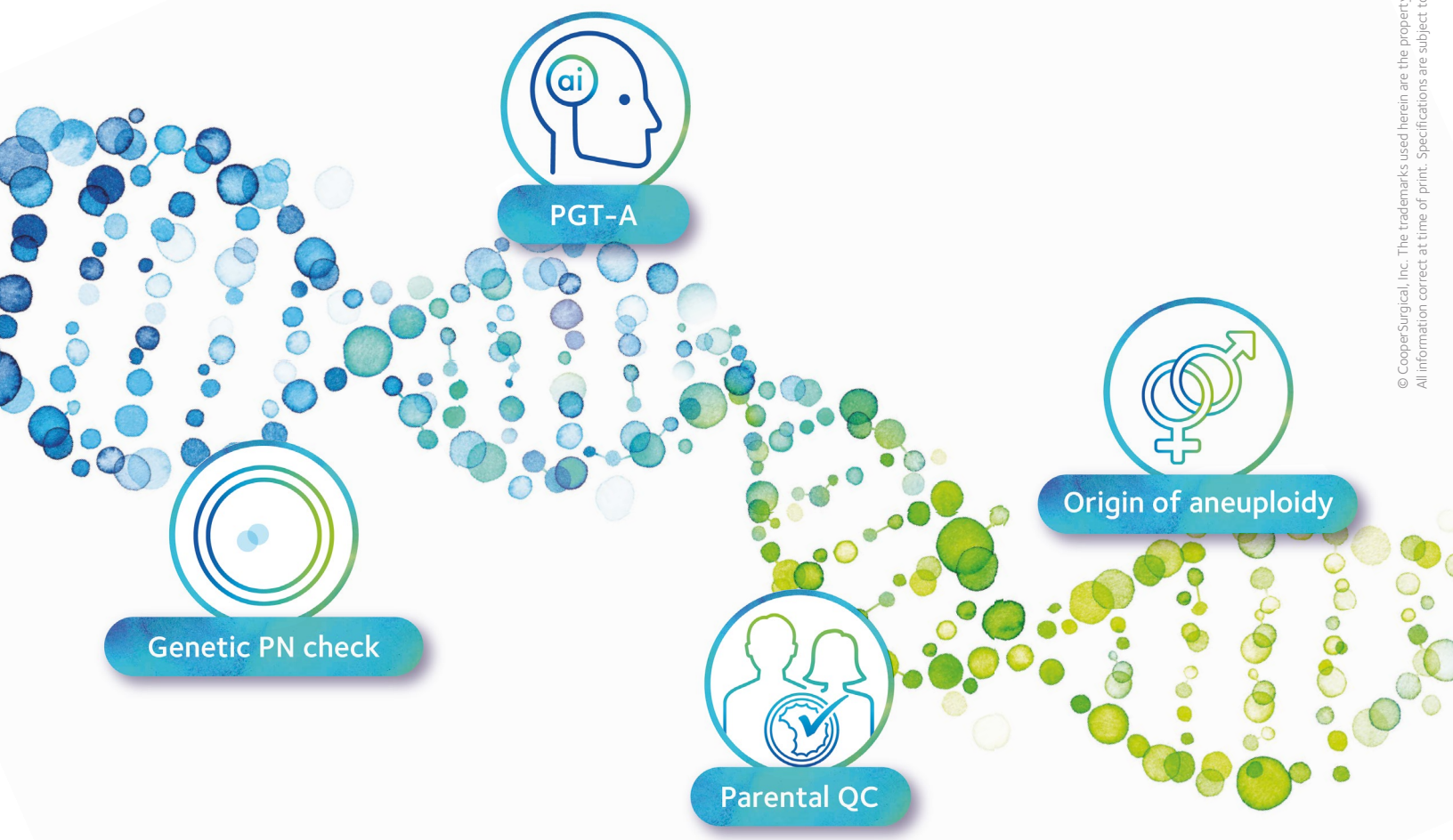
At CooperSurgical we understand the need for the utmost traceability and transparency for all stages of the patient journey and therefore we also offer our RI Witness™ solution.

Parental QC and RI Witness complement each other perfectly to provide a market-leading solution for clinics to help prevent mix-ups, and to provide a powerful tool to externally demonstrate the robustness of their protocols, as well as significantly reduce parental anxiety of mix-ups with a simple genetic confirmation.

- RI Witness is a market-leading electronic witnessing system used to help prevent mixups in the IVF laboratory and ensure adherence to set SOPs supporting the overall IVF laboratory management
- Parental QC (which is part of our innovative PGT-Complete test) is designed to provide patients reassurance that the intended egg and sperm were used, and to help reduce parental anxiety of potential mix-ups
- Both Parental QC and RI Witness can be used by the clinic to demonstrate to their customers the extra steps they take to help safeguard patients' samples and offer full transparency and an audit trail

At CooperSurgical Fertility Solutions, we are very proactive in ensuring the best overall service to our clients and hence their patients through innovation and this is reflected in our most comprehensive PGT-A platform yet.

PGT-Complete, *setting the new standard of care in PGT.*



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