PGTai℠ 2.0 – The next generation of PGTai

Primary (CNV) and secondary (SNP) assessment of aneuploidy for all samples

Highlights

The revolutionary PGTai 2.0 analysis is the first PGT-A platform that combines best-in-class CNV (copy number variation) analysis with global SNP (single nucleotide polymorphism) analysis, powered by artificial intelligence (AI) technology.

- The PGTai 2.0 platform delivers:
  - » Enhanced confidence of embryo chromosomal compliment, through secondary assessment of ploidy status
  - » Detection of all forms of ploidy embryos, including but not limited to:
    - Female triploidy (69XXX)
    - Haploidy supports pro-nuclei scoring (2PN)
  - » The power to establish the source of maternal and paternal aneuploidy (PGTai 2.0 Plus; when parental samples available)
- PGTai 2.0 development
  - » CNV baseline built from 1000 euploid embryos resulting in a sustained pregnancy and/or healthy live birth outcomes
  - » SNPs validated utilizing embryos also run on SNP arrays

Introduction

The theory of PGT-A has been discussed for more than 20 years with the understanding that if the genomic content of the embryo can be accurately determined, this information can be used to prioritize embryo transfer and reduce the chances of an adverse outcome.

Over these years, the understanding of human genomics and genomic testing technology – including PGT-A – has increased tremendously, massively increasing our ability to reliably test an embryos genomic content.

The first complete human genome sequence was released in 2001,[1] demonstrating that the human genome is approximately 3 billion base-pairs in length. Since then many thousands of human genomes have been sequenced, revealing that every person has an estimated 5 million SNVs (single base-pair differences) distributed throughout their genome, many of which are now know to be SNPs (single nucleotide polymorphisms). These differences are changes in the genetic code, which have accumulated over time and are in the majority of cases benign or without phenotype correlation.

The development of NGS (next-generation sequencing) has powered rapid advancements in human genetic research and diagnostics, both in terms of CNV and SNP detection and utilization. NGS is now the number one technology used in PGT-A ploidy detection, with the most advanced platforms able to robustly detect CNVs as small as 5 Mb in screening tests. It has been confirmed that over 99.8% of an individual's unique SNP variants are inherited into the next generation in a mendelian fashion[2] and is an established method of assessing unique parental allelic contributions.

Due to the highly predictable nature of inheritance of SNPs into future generations, it is possible to build models of inheritance and test samples against these models. Any deviation away from the expected can be scored and, increasingly within global genomics testing, this type of information can be used to provide a secondary method to assess individual chromosome and genome wide aneuploidy. As well as being able to provide secondary confirmation of aneuploidy, the ability to measure and track SNPs is very powerful for two additional reasons. Firstly, it allows the determination of the gametic origin of the aneuploidy, i.e., maternally- or paternally- derived. This information can be used to advise best next steps for IVF treatment. Secondly, SNPs provide the information necessary to verify the true ploidy of the samples (haploid, diploid, triploid) which when present in female form (X, XX, XXX) may be indistinguishable by copy number analysis alone.

The PGTai 2.0 analysis has incorporated this ability to score genome-wide SNP content as an additional secondary assessment of the genomic content of an embryo (Figure 1). This world-first advancement in our PGT-A ensures CooperSurgical Fertility and Genomic Solution continues to lead the field in genomic testing of embryos (Figure 2).

The PGTai platform

As the ability to accurately detect mosaicism in embryos has improved, knowledge of the significance of mosaicism on embryo transfer outcomes has increased.[3-5] Embryos have a reduced potential when mosaicism has been detected, relative to euploid embryos.

Segmental changes (partial chromosome gains and losses) have also been difficult to resolve with standard PGT-A technologies. Here, the additional information provided by SNP data is particularly pertinent to these analyses. Segmental changes are at particular risk to result in either a failure to implant or in live births where the child can have severe developmental delays.[6,7] For this reason it is imperative to use the most robust and accurate technology possible.

CooperSurgical Fertility and Genomic Solutions has revolutionized PGT-A data analysis with the PGTai platform. This revolution is set to continue with PGTai 2.0.

The PGTai 2.0 platform

The PGTai 2.0 technology platform builds upon the experience and knowledge gained since launching PGTai in November 2018. Utilizing the same approach as the first release of the PGTai platform (where 1000 known outcome embryo biopsies were used to build the CNV baseline), but increasing the amount of sequencing to 4 million paired-end sequencing reads, PGTai 2.0 technology enables double assessment of the copy number status of the embryo.

The SNP detection of aneuploidy and maternal and paternal inheritance patterns has been extensively validated by ensuring concordance against our gold standard PGT-M SNP array technology (Illumina). PGTai 2.0 provides a vastly larger dataset for baseline than other available PGT-A software in use today and utilizes the power of machine learning from large and known outcome data to deliver the best-in-class analysis and result for PGT-A cases.

The extra sequencing power used in PGTai 2.0 has enabled the detection of additional clinically relevant information, most noticeably all forms of triploidy (inclusive of female triploidy). It is also better able to accurately call mosaic chromosomes, as well as both full segmental and mosaic segmental changes due to the increased ability to differentiate true signal from noise using the two methods of assessment.

It is very important to understand that the data used to generate the PGTai analysis platform came from multiple centers, and multiple CooperGenomics laboratories. Thus, we have captured and modeled all aspects of the

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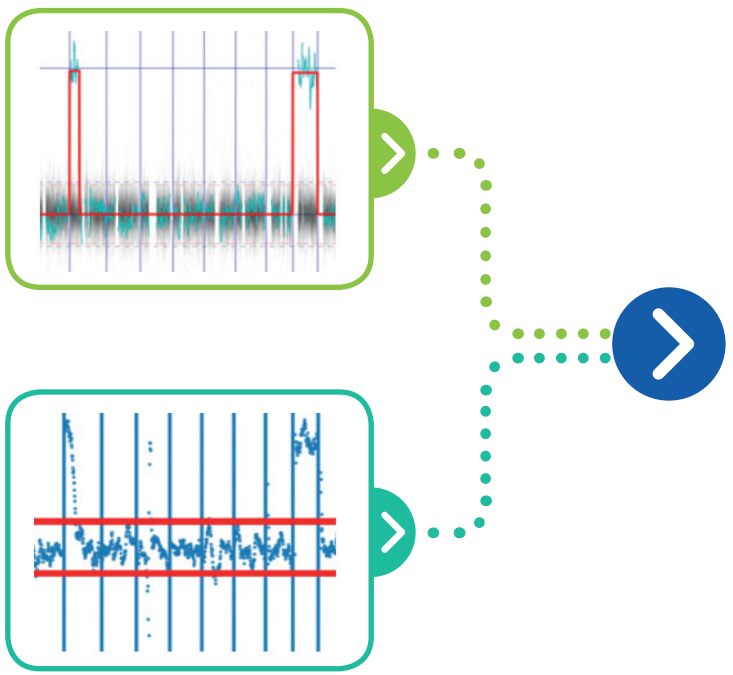
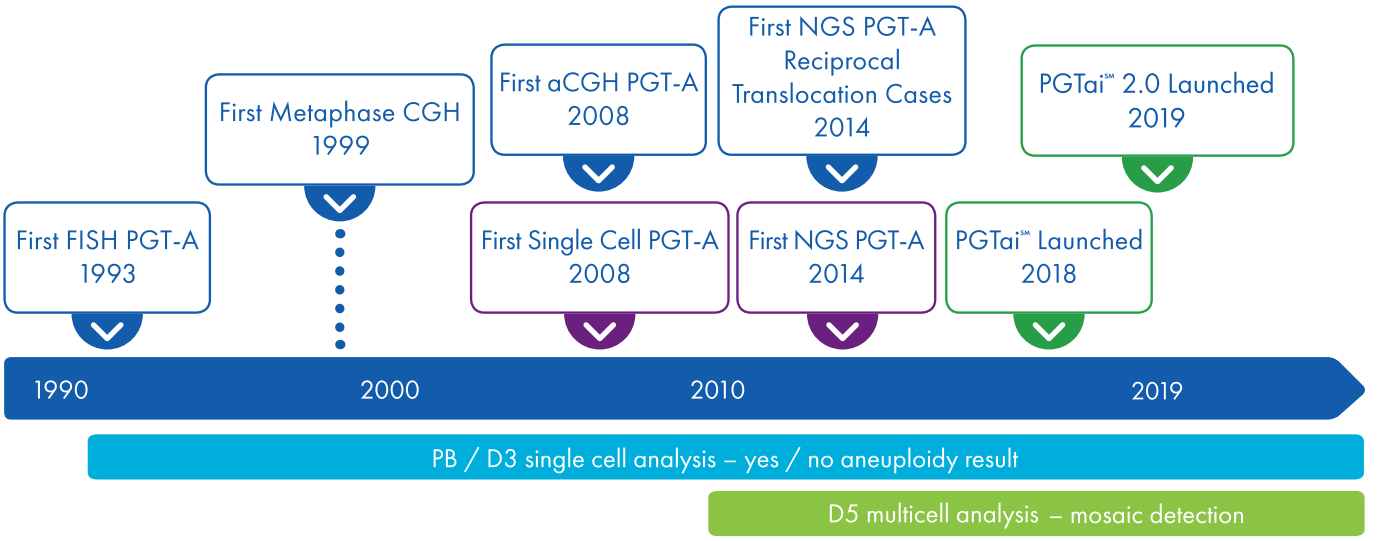
Figure 1. The PGTai 2.0 platform – Primary and secondary method to assess aneuploidy



Primary and secondary assessment of aneuploidy

- Removal of artifacts
- 5Mbp resolution
- Best-in-class mosaic calling

Figure 2. The history of PGT-A



noise that can affect PGT-A data outcomes including; biopsy differences, embryo quality and run-to-run variables. Other analysis software packages often use single laboratory data and controls and do not account for the variabilities that can affect calling; this can lead to significant and unpredictable results for any given clinic.

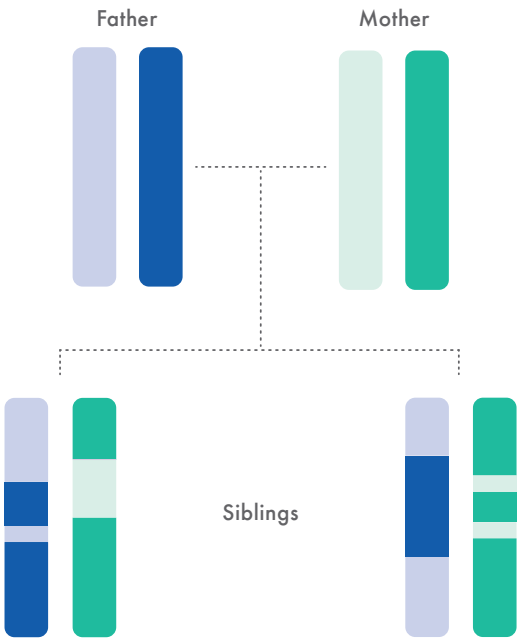
Maternal and paternal inheritance detection with PGTai 2.0 Plus

As referenced above, each individual has approximately 5 million SNPs within their genome, and these benign (non-disease causing) variants are passed onto the next generation in exactly the same way as any other genetic information.

By using parental DNA references, PGTai 2.0 Plus provides the opportunity to:

- Establish that the embryo has inherited both maternal and paternal chromosomes for each chromosome (meiotic changes only)
- In the event of an aneuploid chromosome or chromosome segment, determine the origin of the aneuploidy as maternally- or paternally-derived

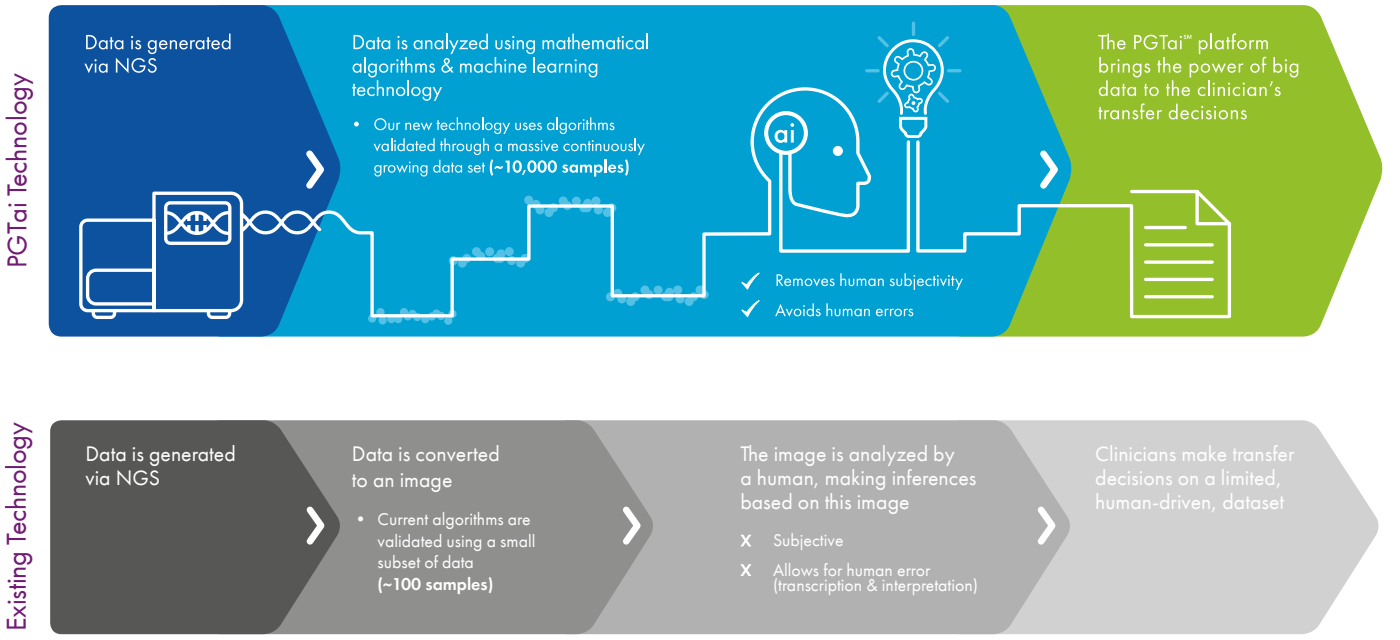
Figure 3. Inheritance tracking



The CooperSurgical PGT-A solution

The PGTai 2.0 analysis platform is both another leap forward in the accuracy of PGT-A analysis, and also an easy solution for those wishing to investigate inheritance of meiotic aneuploidy. This provides IVF centers with the highest level of confidence in the prioritization of embryos available for transfer.

At CooperSurgical Fertility and Genomic Solutions, we are very proactive in ensuring the best overall service to our clients. We have developed an entire sample pathway from sample receipt through to report delivery, minimizing the human interaction that is required therefore minimizing any potential for errors in reporting.



References

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