Preimplantation Genetic Testing

PGT-A, PGT-M & PGT-SR
Pioneers in PGT

CooperGenomics is the global leader in PGT

Through constant dedication to innovation CooperGenomics remains at the forefront of PGT. Our expertise allows us to accept even the most complex of PGT-M/SR cases and with the launch of the revolutionary PGTai™ technology platform, and the additional benefits included in the PGTai 2.0 technology upgrades, we provide the most robust PGT-A test in the market.

We can trace our legacy back to the birth of preimplantation genetic testing. Our pioneering scientists include Mark Hughes PhD and Santi Munné PhD, the founders of PGT-M and PGT-A/PGT-SR respectively.

References
1978
Louise Brown, the first IVF baby is born

1985
The PCR technique is developed, marking a key milestone in the field of genetics

1992
A research group including Dr. Mark Hughes is the first to use PGT-M clinically. A healthy baby girl is born to parents who are both cystic fibrosis carriers

1993
Dr. Santi Munné is the first to present reports on the use of FISH for PGT-A, assessing abnormalities on chromosomes X, Y, 13, 18 and 21

1998
Dr. Santi Munné publishes successful results from the first clinical uses of FISH for PGT-SR

2001
PGT for HLA typing for stem-cell transplantation to an affected sibling is used for the first time

2001
PGT for HLA typing for stem-cell transplantation to an affected sibling is used for the first time

2009
Karyomapping technology is developed

2010
PCR-based method for PGT-SR is developed

2013
Legacy CooperGenomics companies are the first to launch PGT-A by NGS for clinical use

2013
Legacy CooperGenomics companies are the first to launch PGT-SR by NGS for clinical use

2018
CooperGenomics launches the PGTai platform, a first-of-its-kind platform that uses artificial intelligence to improve PGT-A analysis & reporting

2019
CooperGenomics launches the PGTai 2.0 platform, the first PGT-A analysis with secondary confirmation of aneuploidy
Turning innovation into ART

Our focus on innovation drives ground-breaking solutions such as the PGTai technology platform, which harnesses the power of artificial intelligence and machine learning to improve PGT-A calling.

We believe knowledge sharing is key to nurturing innovation

Global Centers of Excellence
Our industry-leading ART development program includes our worldwide Centers of Excellence as well as collaborations with our external partners’ training facilities. We offer a wide range of courses and workshops for embryologists, clinicians, lab managers, and R&D scientists at every level of experience.

ART Scientific
Our publication, ART Scientific, written in cooperation with leading KOLs around the world, shares insights on focus topics.

External partnerships to drive innovation
We see collaboration with clinics and universities as an essential part of our development.
Preimplantation genetic testing involves the biopsy of a developing embryo and genetic testing of the biopsied cell(s). Preimplantation genetic testing can be categorized as preimplantation genetic testing for aneuploidies (PGT-A), monogenic/single gene defects (PGT-M), or chromosomal structural rearrangements (PGT-SR).

<table>
<thead>
<tr>
<th>PGT Type</th>
<th>Patient Population</th>
<th>Goal</th>
<th>Genetic Test Type</th>
<th>Requires Personalized Test Preparation</th>
<th>Also Known As</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGT-A</td>
<td>All IVF patients</td>
<td>Increase chances of achieving a successful pregnancy</td>
<td>Screens for chromosome abnormalities</td>
<td>No</td>
<td>PGS: Preimplantation Genetic Screening, CCS: Comprehensive Chromosome Screening</td>
</tr>
<tr>
<td>PGT-M</td>
<td>Patients at high-risk of having a child with a specific genetic disorder</td>
<td>Reduce risk of passing on an inherited condition</td>
<td>Screens for a specific single gene disorder</td>
<td>Yes</td>
<td>PGD: Preimplantation Genetic Diagnosis</td>
</tr>
<tr>
<td>PGT-SR</td>
<td>Patients with a chromosome rearrangement</td>
<td>Increase chances of achieving a successful pregnancy with a normal/balanced chromosome constitution</td>
<td>Screens for specific unbalanced chromosome rearrangements</td>
<td>No, pending case review and approval</td>
<td>PGD: Preimplantation Genetic Diagnosis</td>
</tr>
</tbody>
</table>
Benefits of PGT-A

PGT-A has been shown to increase implantation rates, reduce miscarriage rates, and increase live birth rates. PGT-A also enables more confident single embryo transfer, reducing the risk of complications associated with twin or triplet pregnancies.

**PGT-A increases live birth rates**¹

### Per embryo transfer

<table>
<thead>
<tr>
<th>Maternal age</th>
<th>PGT</th>
<th>Untested</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>53%</td>
<td>37%</td>
</tr>
<tr>
<td>35-37</td>
<td>52%</td>
<td>28%</td>
</tr>
<tr>
<td>38-40</td>
<td>50%</td>
<td>12%</td>
</tr>
<tr>
<td>41-42</td>
<td>47%</td>
<td>7%</td>
</tr>
<tr>
<td>&gt;42</td>
<td>42%</td>
<td>3%</td>
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</tbody>
</table>

### Per retrieval

<table>
<thead>
<tr>
<th>Maternal age</th>
<th>PGT</th>
<th>Untested</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>44%</td>
<td>33%</td>
</tr>
<tr>
<td>35-37</td>
<td>38%</td>
<td>21%</td>
</tr>
<tr>
<td>38-40</td>
<td>28%</td>
<td>10%</td>
</tr>
<tr>
<td>41-42</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>&gt;42</td>
<td>7%</td>
<td></td>
</tr>
</tbody>
</table>

**PGT-A reduces miscarriage rates**¹

<table>
<thead>
<tr>
<th>Maternal age</th>
<th>PGT</th>
<th>Untested</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>54%</td>
<td>17%</td>
</tr>
<tr>
<td>35-37</td>
<td>28%</td>
<td>7%</td>
</tr>
<tr>
<td>38-40</td>
<td>37%</td>
<td>10%</td>
</tr>
<tr>
<td>41-42</td>
<td>44%</td>
<td>3%</td>
</tr>
<tr>
<td>&gt;42</td>
<td>17%</td>
<td></td>
</tr>
</tbody>
</table>

¹ Final SART data from 2014-2016 and preliminary SART data for 2017. Data provided by, and published with permission from, Dr David McCulloh.
Aneuploidy and age correlation

PGT-A provides information about the chromosomal health of an embryo, helping to select the embryo most likely to lead to a successful pregnancy.

- Correct number of chromosomes
- Highest likelihood of successful pregnancy

Euploid embryos

- Incorrect number of chromosomes
- May result in failed implantation, miscarriage or live birth of a child with a genetic disorder

Aneuploid embryos

- Two or more populations of cells with different genotypes
- Are more likely to miscarry and less likely to implant than euploid embryos but can sometimes result in a live birth

Mosaic embryos

All patients are at risk of producing chromosomally abnormal embryos¹

The risk of producing aneuploid embryos significantly increases as a woman ages, whereas mosaicism has been shown to be independent of maternal age. However, the mosaicism rate decreases slightly with age due to the increased likelihood that an embryo with a mosaic abnormality will also have a meiotic aneuploidy. This results in the embryo being classified as aneuploid rather than mosaic.

¹ CooperGenomics internal data: PGTai technology platform, Nov 2, 2018 through May 31, 2019
Data is analyzed using mathematical algorithms & machine learning technology

The PGTai SM technology platform

CooperGenomics PGT-A analysis is completed via the revolutionary PGTai technology platform. This ground-breaking algorithm harnesses the power of big data, machine learning and artificial intelligence to maximize both sensitivity and specificity during PGT-A.

The most innovative and robust test in the market

The PGTai platform is the only analytical method:

- Built on >1,000 live birth and sustained pregnancy outcomes
- Validated using sequencing data from >10,000 embryo biopsies, analyzed and reviewed one by one for accuracy

Traditional PGT-A

PGT-A platforms that rely on humans to analyze and make subjective inferences based on NGS data have limited clinical utility and can potentially result in transcription and/or interpretation errors.

Vs

PGTai technology

The PGTai platform analyzes data using artificial intelligence trained on a massive reference set. Removing the limitation of human subjectivity, the technology allows clinicians to make transfer decisions supported by big data and machine learning.

Data is generated via NGS

Allowing detection of: aneuploidy, polyploidy, unbalanced translocations, segmental aneuploidy & mosaicism

Data is analyzed using mathematical algorithms & machine learning technology
More euploids
In the first 7 months of reporting results through the PGTai platform, we reported an extra 1300+ euploid embryos.

Increased rate of euploid embryo reporting
- 7.7% relative increase in euploid embryo reporting
- 21.2% relative decrease in mosaic embryo reporting
- 4.2% relative decrease in aneuploid embryo reporting

Greater chance at a euploid embryo transfer
Since launch, we have observed an increase in the percentage of patients across all age groups with at least one reported euploid embryo.

More euploids, more confidence, more transfers

Removes human subjectivity
Avoids human errors

The PGTai platform brings the power of big data to the clinician’s transfer decisions
PGTai 2.0: The next generation of the PGTai platform

The PGTai 2.0 platform provides the most robust embryo assessment in the market. Built on the basics of the PGTai platform, the technology has been upgraded to generate increased data through paired-end sequencing and deeper analysis through single nucleotide polymorphism (SNP) pattern detection. Now using on average >10x more data than before, the next-generation platform delivers added accuracy and offers even greater confidence for embryo transfers.

Clinical benefits of the PGTai 2.0 platform

- **Double aneuploidy assessment**
- **Detect all forms of ploidy**
- **Parent of origin assessment***
- **2PN validation**

*Optional, included in PGTai 2.0 Plus test. DNA samples are required from both partners for parent of origin testing.

Paired-end reads

Paired-end sequencing increases the amount and quality of data generated from each biopsy sample. Reading each DNA fragment from both ends not only provides double coverage and enhances coverage of hard-to-sequence regions, it improves read alignment and availability by more than 15%, allowing highly sensitive analyses to be performed.
Double aneuploidy assessment
SNP patterns can provide secondary aneuploidy assessment. By independently counting both NGS copy number and global SNP coverage – a world first in PGT-A – the PGTai 2.0 platform reduces noise and artifacts to provide added assurance in PGT-A analysis and reporting.

Detect all forms of ploidy
Triploidy affects approximately 1–3% of IVF embryos and can result in partial molar pregnancies and miscarriage. The PGTai 2.0 platform can detect all forms of ploidy, including previously undetected forms of triploidy such as female triploidy caused by meiosis II errors. This enhanced accuracy can help patients avoid the physical and emotional burden of a miscarriage.

Optional parent of origin aneuploidy assessment
Not all whole chromosome aneuploidy is maternally derived; approximately 10% is of paternal origin.¹ Mitotic segmental aneuploidy is most often of paternal origin (70%).¹ The PGTai 2.0 Plus test option provides a direct assessment of gametic contribution to embryo aneuploidy, enabling more confident donor gamete decisions and giving patients piece of mind.

2PN validation
With expanded detection of haploidy and polyploidy via the PGTai 2.0 platform, the embryology lab can streamline their workflow and elect to deprioritize PN checks.

SNP (‘snip’)
A common form of genetic variation involving the change of a single nucleotide in a specific stretch of DNA. Each person has approximately 4 to 5 million SNPs throughout their genome. Most have no effect on health or development, but can act as biological markers providing information about the inheritance of the stretch of DNA.

Confident embryo transfer

PGT-A aims to improve IVF outcomes by identifying the embryos that are most likely to achieve a successful pregnancy. Euploid embryos have the highest potential and, therefore, are prioritized first for transfer.

More transfer opportunities

Compared to prior (subjective) methodology, the PGTai platform identifies more embryos as euploid, and fewer as mosaic or aneuploid. Furthermore, reporting via the platform significantly increases the percentage of patients with at least one euploid embryo identified (71.5 vs 67.7%, p<0.0001), providing patients of all age ranges with a greater chance of a euploid transfer.¹

Mosaic reporting

In accordance with society guidelines and current research, CooperGenomics reports mosaicism based on the percent aneuploidy and the number of chromosomes impacted. Samples with low-level mosaicism (20–40% abnormal cells) involving a single chromosome may be prioritized when no euploid embryos are available. High-level mosaics (>40–80% abnormal cells) and complex mosaics (mosaicism in ≥3 chromosomes) are given lower priority.

Possible PGT-A results

<table>
<thead>
<tr>
<th>Number of chromosomes per cell</th>
<th>Euploid</th>
<th>Low-level mosaic</th>
<th>High-level mosaic</th>
<th>Aneuploid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>High</td>
<td>Mixed (some normal &amp; some abnormal)</td>
<td>Lower</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Likelihood of producing a successful pregnancy</td>
<td>High</td>
<td>Low</td>
<td>Lower</td>
<td>Very low</td>
</tr>
<tr>
<td>Transfer priority</td>
<td>High</td>
<td>Intermediate</td>
<td>Low</td>
<td>Not prioritized</td>
</tr>
</tbody>
</table>

Appropriate counseling by a physician and/or genetic counselor is recommended for all PGT-A cases. Prenatal diagnosis by amniocentesis should be offered for all pregnancies resulting from mosaic embryo transfer.

¹ CooperGenomics internal data: prior (subjective) methodology, Jan 1, 2018 through Nov 1, 2018 vs PGTai technology platform, Nov 2, 2018 through May 31, 2019
The PGT-A process

PGT-A can be seamlessly added to IVF to help increase the chances of cycle success. Genetic counselors are available to inform, support, and guide families throughout the process.

**IVF**
*In vitro* fertilization is performed and the resulting embryos are incubated. ICSI is not required for PGT-A.

**Embryo biopsy**
An embryologist carefully removes a small cell sample from each embryo.

**PGT-A**
Samples are sent to the PGT laboratory, testing is performed, and results are released to the IVF center.

**Vitrification**
Embryos are frozen while awaiting PGT results.

**Embryo transfer**
Embryos are prioritized based on PGT-A results. Additional embryos may remain frozen for future use.
PGT-M for monogenic/single gene defects

PGT-M, or preimplantation genetic testing for monogenic/single gene defects, is a genetic test performed before pregnancy to significantly reduce the risk of having a child with a specific genetic disease. PGT-M involves screening embryos created through IVF for a particular condition and then transferring only unaffected embryos.

Candidates for PGT-M may have a genetic condition themselves or may have learned of their risk status through an affected family member, child, or pregnancy, or as a result of carrier screening. PGT-M can be performed for almost any single gene disorder with an identified mutation and availability of appropriate family members.

Our detailed case review process plus individualized test design enables us to select the technology most appropriate for each family. The latest PGT-M technique, Karyomapping, investigates >300,000 data points across the genome to increase the accuracy of embryo diagnosis.

Karyomapping enables:
- Faster test preparation in 4–8 weeks
- Testing of multiple conditions at once
- Addition of PGT-A without the need for an additional sample
- HLA matching

PGT-M can be performed for >6,000 single gene disorders, including:
- Breast/Ovarian Cancer (BRCA1/2)
- Cystic Fibrosis
- Fragile X Syndrome
- Spinal Muscular Atrophy
- Huntington’s Disease
- Sickle-Cell Disease

1. Internal CooperGenomics data inclusive of autosomal recessive and X-linked disease
2. Internal CooperGenomics data
Karyomapping technology

Karyomapping technology analyzes the SNP pattern surrounding the gene in question, comparing the pattern associated with the mutation compared to that associated with the normal copy of the gene. Each PGT-M test design is unique and specific to the family, so DNA samples from both partners, and often additional family members, are required in order to design a test. Then, linkage analysis is used to determine the ‘genetic fingerprint’ of the mutation and diagnose each tested embryo as affected or unaffected.

Example: PGT-M by karyomapping for an autosomal recessive condition

When PGT-M is performed for an autosomal recessive condition, unaffected and carrier embryos may be available for transfer (i.e. embryos 1, 2 and 3).
PGT-SR, or preimplantation genetic testing for chromosomal structural rearrangements, is a genetic test available for carriers of balanced reciprocal translocations, Robertsonian translocations, inversions, and other complex chromosome rearrangements.

Though carriers of balanced chromosome rearrangements are typically healthy, they are at increased risk for producing embryos with the incorrect amount of chromosomal material, resulting in reduced viability or potential for children with physical and/or intellectual disability. PGT-SR can help identify embryos with the correct amount of chromosomal material that are most likely to lead to a successful pregnancy and healthy live birth.

If one parent is a carrier of a reciprocal translocation, approximately 75% of resulting embryos will be unavailable for transfer.\(^2\)

The majority of PGT-SR cases are performed via NGS and:

- Parental samples are not required
- Are automatically paired with PGT-A at no additional charge\(^3\)

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2. Internal CooperGenomics data
3. Exclusions apply
The PGT-M/SR process

**Case review**
The ordering provider submits a test requisition form along with genetic testing reports for case review and approval.

**Genetic consultation**
Registered patients speak with a genetic counselor. PGT-M consultations will include the requirement of any additional family member testing.

**Test preparation** (PGT-M only)
The PGT lab collects DNA samples from the couple and appropriate family members and designs a test unique to each family.

**Embryo biopsy**
An embryologist carefully removes a small cell sample from each embryo.

**IVF**
*In vitro* fertilization is performed and the resulting embryos are incubated.

**Embryo transfer**
Embryos are prioritized based on PGT results. Additional embryos may remain frozen for future use.

**Vitrification**
Embryos are frozen while awaiting PGT results.

**PGT-M/SR**
Biopsied samples are sent to the PGT laboratory, testing is performed, and results are released to the IVF center.
Patient coordination
Dealing with fertility struggles or genetic risks during the family planning process can be overwhelming. All PGT patients are paired with an experienced patient coordinator whose goal is to make the logistics of genetic testing as simple and seamless as possible, being sensitive to each family’s unique circumstances.

Genetic counseling
We are committed to offering personal, in-depth genetic counseling to responsibly guide patients through the preimplantation genetic testing process. Our team of board-certified, licensed genetic counselors are specially trained in PGT and are available to patients before, during and after testing.

Logistics

Requesting kits
We provide embryo biopsy kits for PGT sample collection. In addition, we supply shipping boxes, styrofoam coolers, and if desired, ice packs for your return shipments. Please email courier@coopergenomics.com to request kits (72 hour notice is requested).

Sending samples
Sending PGT samples is easier than ever with our concierge courier services. Simply e-mail courier@coopergenomics.com prior to biopsy to request package pick-up, and our dedicated logistics team handles the rest. We partner with private medical couriers and monitor package status to ensure safe, reliable and expedient sending of patient samples.
PGT-A
✓ >150,000 cases performed
✓ Data analysis via PGTai 2.0 platform
  (two independent methods for assessment of aneuploidy)
✓ Detects all forms of ploidy
  (including female triploidy)
✓ Reliably detects mosaicism
✓ Parent of origin testing available
✓ Comprehensive genetic counseling
✓ Concierge courier services provided

PGT-M/SR
✓ >8,000 cases performed
✓ Single gene disorders & chromosome rearrangements
✓ Karyomapping and/or NGS technology
✓ Option to add PGT-A to any PGT-M/SR case
✓ Parent of origin testing available
✓ Able to test for multiple conditions with a single sample
✓ HLA matching available
✓ Comprehensive genetic counseling
✓ Concierge courier services provided
A solution as unique as your business

At CooperSurgical, we partner with you to drive clinical efficiency

When you partner with CooperSurgical you become part of a truly global network of clinical experts ready to support you with highly specialized solutions, both for individual clinics and across large organizations. By providing you with optimal products, services and training our aim is to offer you the best possible support to drive the efficiency of your clinic – and achieve the best results.

*Day-to-day delivery may vary according to geographical location*