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WHITE PAPER

# Improving fertility outcomes through IVF innovation

AUTHOR
Erica Kantor, Head of Women's Health

On the journey to parenthood, infertility is one of the most distressing challenges prospective parents can face. While there are more options available for fertility treatments today, including In Vitro Fertilisation (IVF), success rates remain frustratingly low. At 25-30% success per IVF cycle, many women must undergo multiple painful and expensive treatment cycles – and there is no pregnancy guarantee. Recent advances in technology – including genetic testing, imaging techniques, and artificial intelligence (AI) – are now emerging, offering a ray of hope. However, in order to be successful, new solutions must be designed to address the needs of all stakeholders, including the prospective parents, and the busy embryologist.

**Erica Kantor**
Head of Women's Health

As Head of Women's Health at Sagentia Medical, Erica's mission is to help companies design breakthrough solutions that will change the future of healthcare. She is particularly passionate about improving patient outcomes through holistic, user-centric design across the full spectrum of women's health and the fertility journey.

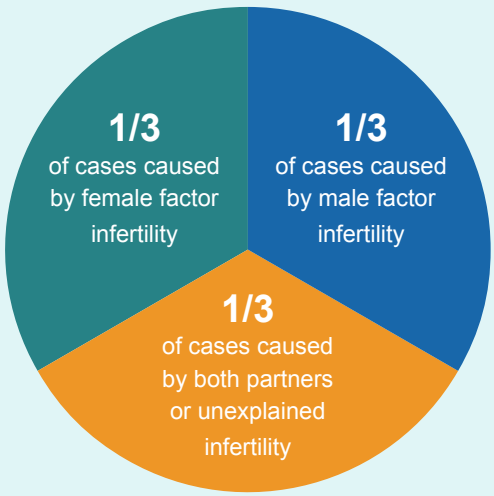
# Introduction: The causes of infertility

Infertility affects around 48.5 million couples worldwide[1]. Infertility is defined by the World Health Organization as a disease of the reproductive system characterised by the failure to achieve a clinical pregnancy after twelve months or more of regular unprotected sexual intercourse[2]. The rising age of first-time mothers is just one component of the complex picture driving these trends.

Myriad factors may affect our ability to reproduce. Some medical issues have the potential to be addressed through surgical intervention, such as blockages in the fallopian tubes, or scarring within the uterus. Others, such as polycystic ovary syndrome (PCOS), may require treatment using assisted reproduction technology (ART). Unfortunately, establishing the root cause of infertility is not always easy. One third of cases can be caused by male factor infertility, one third by female factor infertility, and one third by issues with both partners or by unexplained infertility[3]. Environmental, lifestyle, and social factors can also be at play, and can be harder to mitigate.

### Female Infertility Causes

- Pelvic inflammatory disease
- Primary ovary insufficiency
- Thyroid problems
- Endometriosis
- PCOS
- Fibroids
- STIs
- Age
- Obesity
- Being underweight




### Male Infertility Causes

- Low sperm motility
- Low sperm count
- Abnormal sperm
- Varicoceles
- STIs
- Age
- Obesity
- Cystic fibrosis
- Thyroid problems
- Premature ejaculation

*Figure 1: Causes of infertility*

Infertility is still a taboo subject, so it can be surprising, embarrassing, and isolating to discover that you may struggle to conceive naturally. Thankfully, there are a number of established and emerging solutions to support prospective parents on their journey from conception to parenthood.

# Assisted Reproductive Technology (ART)

ART techniques, such as Intrauterine Insemination (IUI) and IVF, are being increasingly explored by individuals and couples who can't conceive naturally, including same-sex couples, single women, and cancer patients looking to preserve their fertility.

## Intrauterine Insemination

Among the options available to prospective parents is IUI, also known as artificial insemination, where sperm – from the biological father or a donor – is inserted directly into a woman's womb. IUI was originally developed in animal husbandry and is one of the oldest ART techniques still in use. The first successful human pregnancy using IUI was reported in London in 1793 by surgeon John Hunter, although some historians believe earlier successful attempts went unreported[4].

## In Vitro Fertilisation

IVF, a more recent development, has come a long way since the birth of Louise Brown, the first child born as a result of IVF treatment in 1978, and is now widely considered to be the gold standard in assisted reproduction. The global IVF market is currently worth an estimated USD 24.62 billion, and is expected to rise to USD 50.32 billion by 2027[5].

IVF typically involves hormone treatment to stimulate production of multiple eggs in a prospective mother, which are then removed from her ovaries and fertilised with sperm in a laboratory. Issues with the motility or number of the father's sperm may necessitate Intracytoplasmic Sperm Injection (ICSI) – where a single sperm is injected into the egg by an embryologist. In either case, if fertilisation is successful, embryologists will allow multiple embryos to develop, typically for a period between two and six days, and select the most promising to be transferred to the mother's womb.

## In Vitro Maturation

A new approach is emerging, offering a possible alternative to IVF for people who struggle with hormone treatment. IVF typically requires the follicles to be matured within a woman's ovaries through daily hormone injections using thick needles containing viscous liquids that are painful to administer. For In Vitro Maturation (IVM), little to no hormone treatment is required. The follicles are removed from the woman's ovaries and matured in the lab, prior to fertilisation using ICSI. This process is ideal for women with PCOS, who are particularly prone to ovarian hyperstimulation syndrome (OHSS) with conventional IVF treatment.

While IVM is simpler and cheaper than IVF, it is still considered experimental in many countries, and only beneficial to certain patient groups. However, as success rates start to approach those achieved with IVF, we may see IVM become the standard of care in the future.

# The key considerations for prospective parents

## Cost

Cost is one of the biggest considerations for people seeking fertility treatment, and can vary widely from country to country, and clinic to clinic. Influencing factors include the type of treatment required (IUI vs IVF), and whether there is a need for additional processes and services, such as medication, genetic testing, or embryo vitrification.

Another factor affecting cost is whether individuals have insurance coverage, which can depend on where they live, their employee benefits, and whether they meet their insurance policy's eligibility criteria. To address this challenge, fertility services are now being offered as a corporate benefit by some companies, including those offered by Progyny – the first corporate "family benefits" company to launch on the stock market.

Finally, multiple cycles of treatment may be required, with each cycle potentially adding to the burden of cost.

## Success rates

Prospective parents will often choose their fertility clinic based on reported success rates. However, the way in which success rates are reported can vary, making this data difficult to interpret and compare. Data may be provided per oocyte retrieval, per cycle of IVF, or per embryo transfer. Confounding the data further, success may be measured against implantation rates, pregnancy rates, or live birth rates. Further standardisation in outcome reporting is required to ensure consistency and transparency.

Of course, for the prospective parent, the key questions are: "What is my chance of getting pregnant?", and "How quickly could I expect to get pregnant?" These are not simple things to predict, particularly when some of the most influential factors for success are specific to the individual.

## Access

There are broad, global inequalities in the access to fertility treatment. Even in countries where IVF is available through universal healthcare, like the NHS in the UK, prospective parents may face long waiting lists – ranging from a few months to several years. There may also be limitations on the number of IVF cycles covered by insurance (i.e. a maximum of 3 cycles for women under 40, or 1 cycle for women aged 40 to 42 in the UK).

Private options offer greater flexibility in this regard, but the cost of treatment – averaging USD 12,000 in the US, before medications, which typically run to another USD 3,000 to 5,000 – may be prohibitively expensive.

Insurance policies can also be restrictive. Some require individuals to prove that they have been trying to conceive for a set length of time, or that they have a clinical infertility diagnosis. This can preclude single people and same-sex couples from accessing the same level of treatment or financial support available to others.

As a result of these limitations, some individuals are resorting to "IVF tourism", travelling to other countries where they may find more affordable, successful, or accessible fertility treatment.

For prospective parents, it can be difficult to find the data necessary to make informed decisions about their health and fertility treatment options, particularly when it comes to cost, success rates, and access.

# The IVF journey

The IVF journey (pictured on the next page) presents a unique set of challenges for prospective parents. Time devoted to blood tests, ultrasound scans and daily injections of hormones required to stimulate follicle growth can impact their ability to work. The egg retrieval procedure can be extremely painful, and the wait while the embryos are developed in the lab can be nerve-wracking. This rollercoaster of anxiety, anticipation, hope, and possible disappointment is a significant emotional burden.

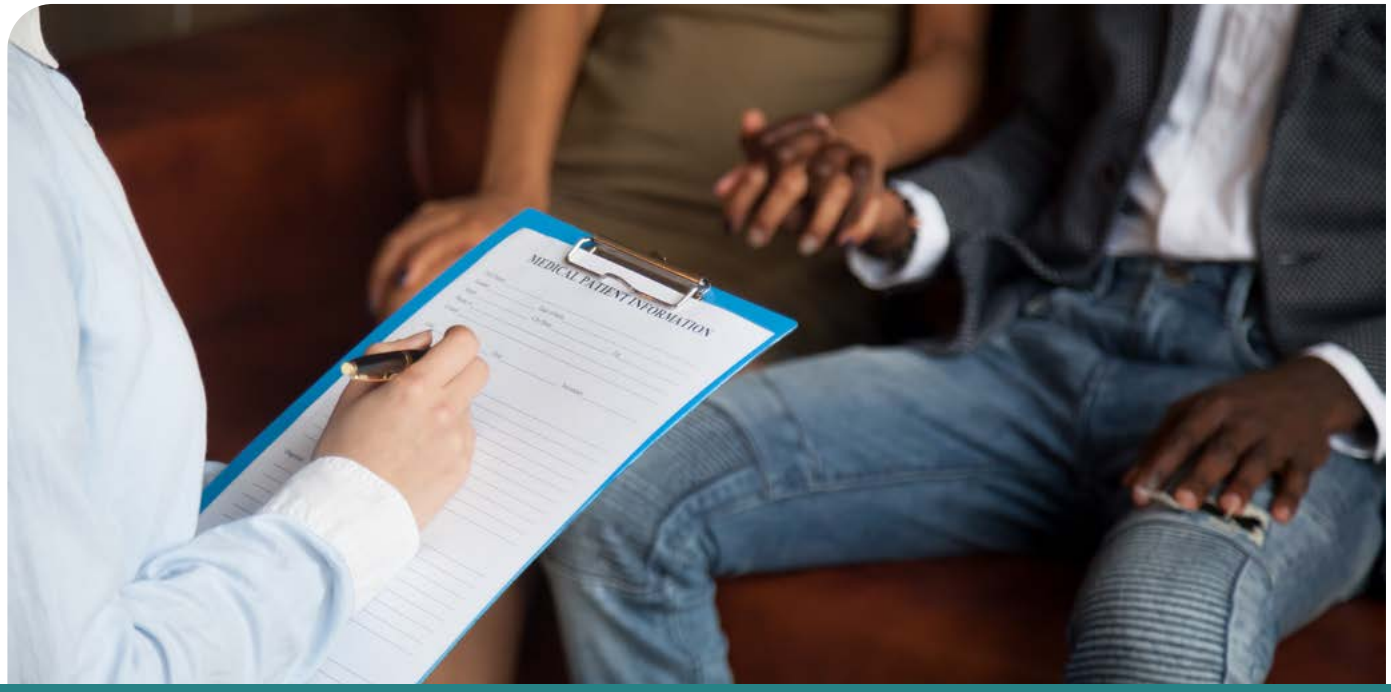
There is growing awareness of the importance of supporting the mental health of prospective parents throughout their ART journey. Studies have shown that IVF is associated with increased anxiety, depression, and stress in potential mothers[6], particularly after a failed round of treatment[7]. New solutions are emerging, offering advice and resources to support wellbeing during this challenging process.

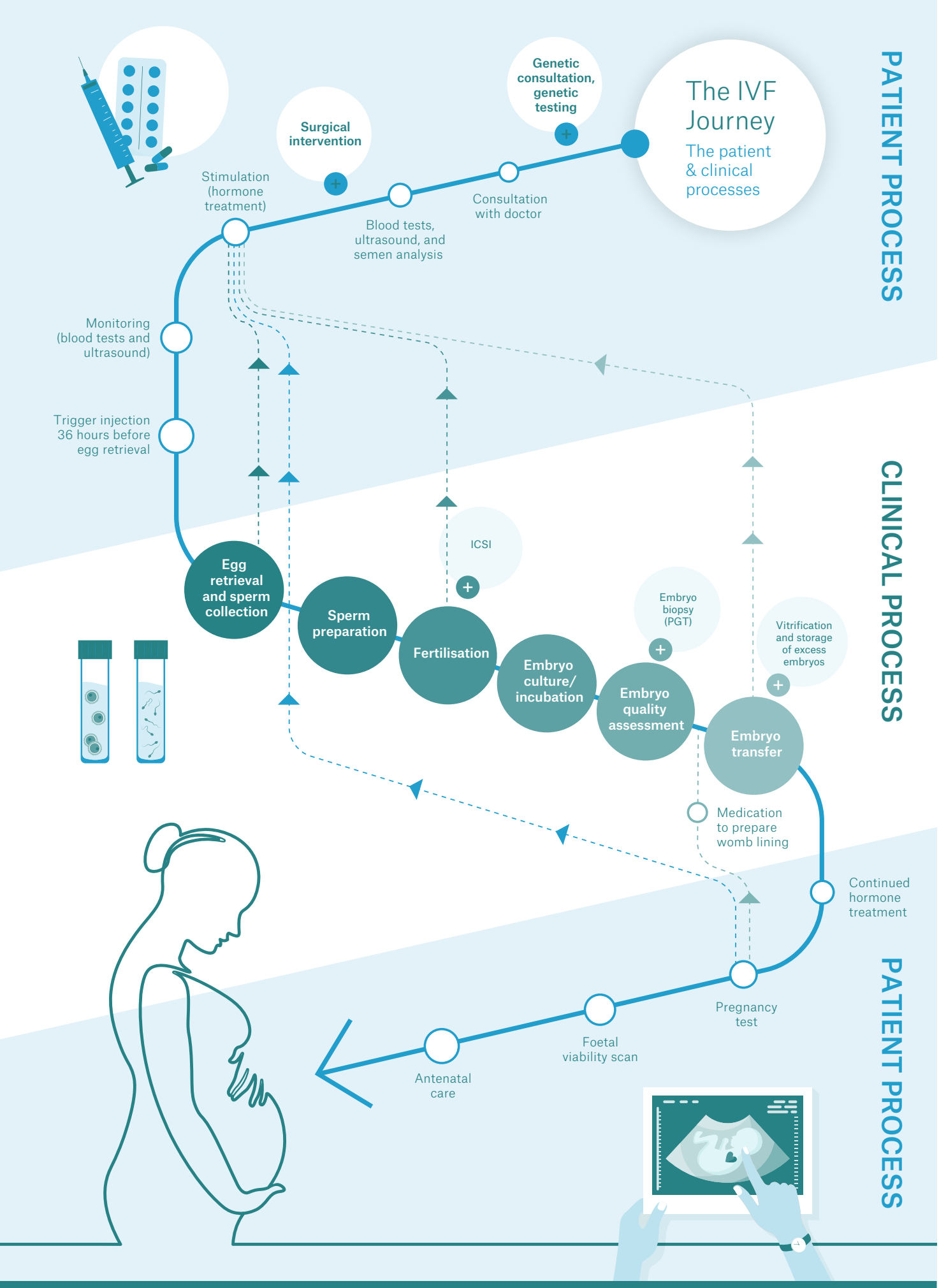
## The waiting game

Many women report that the journey through the laboratory process, into embryo transfer and beyond, can be a frustrating and often anticlimactic waiting game which may end in disappointment after the results of the first pregnancy test, typically conducted two weeks after the embryo has been transferred. Women may also end up having to repeat parts of the process if their first cycle of treatment is unsuccessful. IVF has a success rate of just 25 to 30% per cycle according to the UK's National Institute for Health and Care Excellence[8], around three times the technique's initial success rate back in the 1970s and 80s. The cumulative effect of three full cycles of IVF can increase the chances of a successful pregnancy to between 45 and 53%[9], yet this is still disappointingly low.

## Developments in IVF

Advances in technology – including developments in embryo selection, automation of clinical processes, and improved analysis of available data – are starting to make IVF more effective. These tools may also offer greater choice, improved precision, and reduced uncertainty, the latter of which is often a key cause of stress for those undertaking the IVF journey. One such example is the Univfy PreIVF Report, an AI-powered platform, which generates personalised reports on the probability of an individual or couple having a baby with IVF in the first three cycles at a specific treatment facility, as well as individual factors that may impact their chances of success. Future developments – as we shall go on to explore in greater detail – promise to drastically improve the picture by standardising the IVF process, offering new tools to clinicians, and improving the chances of a successful pregnancy.




The IVF Journey
The patient & clinical processes
PATIENT PROCESS
CLINICAL PROCESS
PATIENT PROCESS
Genetic consultation, genetic testing
Surgical intervention
Stimulation (hormone treatment)
Blood tests, ultrasound, and semen analysis
Consultation with doctor
Monitoring (blood tests and ultrasound)
Trigger injection 36 hours before egg retrieval
Egg retrieval and sperm collection
Sperm preparation
ICSI
Fertilisation
Embryo culture/ incubation
Embryo biopsy (PGT)
Embryo quality assessment
Vitrification and storage of excess embryos
Embryo transfer
Medication to prepare womb lining
Continued hormone treatment
Pregnancy test
Foetal viability scan
Antenatal care

# The most exciting areas for IVF innovation

IVF presents several pain points along the patient treatment pathway, as well as bottlenecks for clinicians, which innovative technologies are helping to address. Many of these are designed to support the embryologist and optimise the clinical lab process. There is huge variation in the types of instruments used – and services provided – by labs, and innovations in this area could help to standardise the IVF process, leading to more predictable and desirable outcomes for prospective parents.

## Selecting the best embryo

One of the biggest challenges facing embryologists when beginning the process of culturing an embryo is how to monitor its development as closely as possible without affecting its quality. Whatever test or analysis is to be carried out – whether it's genetic testing of an embryo, or visual inspection to track its development – there is always a risk associated with traditional manual handling techniques, where embryos are physically removed from an incubator to be examined. One interesting innovation in this space is the use of time-lapse imaging to capture longitudinal 3D data about the maturation process, providing continuous information on the shape and morphology of the embryo, how many cells are present, and how quickly the embryo is dividing. **Vitrolife** has been notably active in this area, their EmbryoViewer graphically depicting pixel-to-pixel changes from one time-lapse image to the next.

## Genetic testing

Some couples may undergo genetic counselling before starting IVF, meeting with a specialist to review family history, ethnicity, personal health, and pregnancy history. This information enables the counsellor to determine if any genetic testing would be beneficial in providing data to guide reproductive planning.

Additionally, pre-implantation genetic testing (PGT) may be performed as part of the IVF process, to screen for possible chromosomal abnormalities to help select the best embryo for implantation. There are challenges with existing PGT, including a risk during the embryo biopsy process that the embryo may be damaged, leading to reduced viability. Research is currently being conducted to explore the possibility of non-invasive PGT, which would analyse the cell-free DNA in spent culture media.

Examples of commercially available genetic testing technologies include **Illumina's** PGT platform, which determines the chromosomal status of an embryo by screening all 23 chromosome pairs prior to transfer in an IVF cycle, through analysis of cells obtained during a biopsy of an embryo. **Celmatix's** Fertilome test assesses a number of genetic markers associated with conditions that affect fertility, including recurrent pregnancy loss, primary ovarian insufficiency, endometriosis, and polycystic ovary syndrome, and the company offers a range of other AI-powered reproductive health services.

## Combatting data overload

An additional challenge presented by the abundance of new data, however useful, is how best to process it. Embryologists are extremely busy and adding an additional process – in having to sift through this extra information – is less than ideal. Automation, both in terms of information gathering and processing, is increasingly needed to avoid data overload. AI shows enormous potential in this respect.

Smart software is gradually being integrated into systems to help clinicians make appropriate decisions, with G**enea Biomedx's** Geri just one example of how this technology can be applied, in this case in an incubator with an integrated embryo monitoring system. Vitrolife has developed AI-powered tools, including KIDScore, which uses mathematical algorithms to support ranking of embryos monitored by time-lapse imaging. Vitrolife's Guided Annotation technology makes use of deep learning to automatically estimate cell division events, PN number, and blastocyst morphology. Its latest development, iDAScore, takes the entire history of an embryo's development into account to rank them according to implantation potential.

While we're not quite at the point where AI is able to replace the expertise of highly skilled embryologists, research has demonstrated the future potential for AI systems to classify and select embryos based on imaging data[10].

## Cryopreservation

Many women are also choosing to have their eggs – and, increasingly, embryos – frozen using various cryopreservation techniques, most notably vitrification. This may happen as part of the IVF process, when several good quality embryos may be created. It is typically best practice to freeze the remaining embryos in this instance, as transfer of multiple embryos increases the risk of multiple births, a scenario which may carry attendant health risks. Freezing (cryopreservation) also enables a woman to avoid having to repeat the egg collection and fertilisation stages of treatment, if multiple cycles are required. Genea Biomedx's product, Gavi, is an instrument which fully automates the often time-consuming process of manual vitrification.

Egg or embryo freezing may also be employed as a standalone procedure – particularly to provide options for future conception, prior to undergoing treatment for cancer, for example. This market is expected to grow by 25% annually over the next two years[11].

## Tracking samples in the lab

Technological advances promise to help remove human error from lab processes, where increasing demands on time mean that mistakes can happen, around once every 1,000 witness steps according to one estimate[12]. Human error is particularly problematic given the sensitive context of IVF treatment. Relatively simple techniques – including bar and QR codes, and RFID microchips – can help to ensure samples are labelled accurately and can be tracked throughout their clinical journey. More advanced systems, including **CooperSurgical's** RI Witness, can further reduce the burden on embryologists by automating processes to ensure sample safety, efficient workflow management, and auditing for quality control.

That's not to say that technology is 100% reliable, of course. In March 2018, more than 4,000 eggs and embryos were destroyed as the result of a freezer tank failure at the University Hospitals Fertility Center in Beachwood, Ohio. Innovations in this area, including remote monitoring of cryo-systems, inbuilt redundancy measures, and better environmental controls, are required to help prevent these kinds of disastrous outcomes in the future.

# The future of IVF

## Key considerations when designing disruptive IVF solutions

While there are many exciting areas for disruption in the IVF clinical process, the challenge comes in developing a solution that will be readily adopted by clinicians. The key considerations include:

### 1. Ease of use and implementation

When introducing new solutions into the IVF lab, the needs and pain points of the embryologist must be fully understood. Often, embryologists will have optimised their process over many years, down to the minute details of the environmental conditions in the lab. There must be sufficient incentive to change. At the very least, new solutions must not add to the embryologist's workload, and should look to provide incremental improvements to current practice, streamlining and reducing steps to ensure adoption.

### 2. Clinical efficacy and standardisation

Standardisation, between countries, clinics, and operators, is a key challenge in IVF. Advanced technologies could help to establish best practice by reducing this variability, particularly for critical steps like embryo selection, which remains a subjective assessment. However, as with any successful innovation, the clinical efficacy must first be established. This is especially important in a market like IVF, where prospective parents may rush to embrace any novel intervention, regardless of the level of evidence available.

### 3. Cost

New solutions must show clear commercial value, both for the clinic and the patient. The innovations we have considered, while potentially more expensive than traditional techniques, could reduce the overall cost of treatment by increasing success rates and reducing the number of cycles ultimately required to get to pregnancy. Automation and improvements in the overall efficiency of the IVF process, including reducing the workload placed on embryologist and allowing them to perform multiple procedures at once, are another way cost could be reduced.

## The Radical Possibilities for IVF in the Future

In the long term, what are the radical possibilities for assisted reproduction?

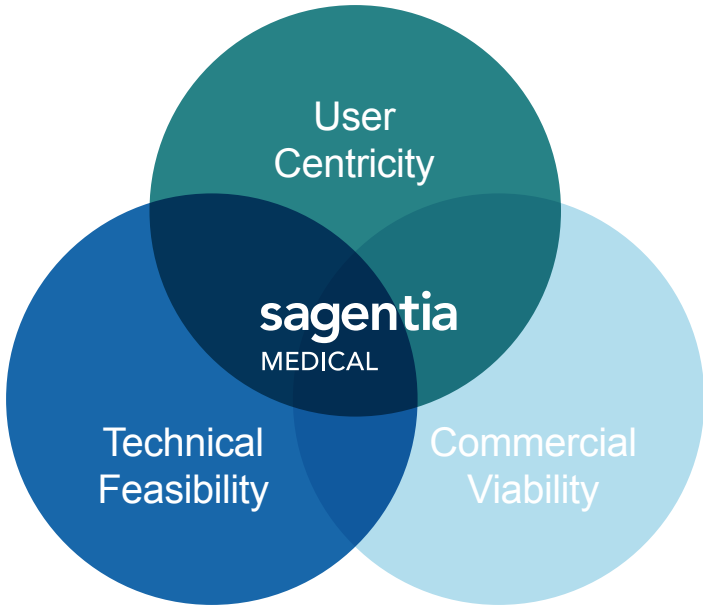
Could PGT eliminate diseases like cancer? We can already screen embryos for cancer-related mutations, such as the BRCA1 or BRCA2 mutation. If IVF and genetic testing became affordable enough, and readily accessible, could it become common practice for the general population?

Could eggs and sperm be produced from stem cells? Stem cells is an ongoing area of research relating to fertility and reproduction, and success has been shown in producing sperm and eggs from mouse pluripotent stem cells that have led to healthy, fertile mouse pups. Could this research be extrapolated to humans, allowing infertile couples to have biological children?

Finally, could the IVF lab become fully automated and AI-enabled? Through technologies like machine learning, automation, and microfluidics, there is the possibility of creating a seamless, repeatable, perfectly optimised process. Will there ever be a point where we replace the embryologist completely?

# Conclusions

IVF is an extremely promising technology which has the potential, through technology advancements that support both prospective parents and clinicians, to offer greater rates of success in the future. In the short term, however, there is a need for incremental innovation, leveraging and optimising current lab processes to reduce costs and increase access to IVF globally. A practical, user-centric approach is required to ensure a full understanding of the needs of all stakeholders involved, and to develop new solutions that are commercially viable, technically feasible, and improve patient outcomes.




# How Sagentia Medical can help

The ART market is unlike any other in medicine for a variety of reasons, including the “parent over patient” mentality, and the deep-seated drive prospective parents have to succeed, pushing the commercial impetus in this market. IVF labs that can offer improved success rates hold a unique advantage over their competitors.

Our expertise in cutting edge technology – including microfluidics, point-of-care diagnostics, bioinformatics, sensors, and image analysis – combined with our experience in medical grade software, multidisciplinary device development, user experience (UX, UI), and human factors is brought to bear on any project we undertake. Our scientific grounding in the chemistry and biology that drive developments in IVF make us ideally placed to help you bring breakthrough innovations to market. Whether it’s helping a busy embryologist to work more efficiently, or bringing insight and empathy to the patient journey, get in touch to find out how we can support your next development.

**To receive the next papers in our women’s health series, email info@sagentiamedical.com**

## References


1 A unique view on male infertility around the globe (nih.gov)
2 Infertility definitions and terminology (who.int)
3 How common is infertility? | NICHD - Eunice Kennedy Shriver National Institute of Child Health and Human Development (nih.gov)
4 Intrauterine Insemination | The Embryo Project Encyclopedia (asu.edu)
5 Assisted Reproductive Technology Market Size USD 50.32 Bn by 2027 | CAGR of 9.3% (emergenresearch.com)
6 The psychological concomitants of in vitro fertilization: Journal of Psychosomatic Obstetrics & Gynecology: Vol 6, No 3 (tandfonline.com)
7 The psychological well-being of infertile women after a failed IVF attempt: the effects of coping - PubMed (nih.gov)
8 The importance of 3 full cycles of IVF | Blog | News | NICE
9 The importance of 3 full cycles of IVF | Blog | News | NICE
10 Artificial intelligence-enabled system for embryo classification and selection based on image analysis - Fertility and Sterility (fertstert.org)
11 The Fertility Boom | Global Wellness Trends (globalwellnesssummit.com)
12 Human error and systems failure caused IVF mix up (nih.gov)

## About Sagentia Medical

Sagentia Medical is a specialist independent advisory and leading-edge product development services focused on science and technology initiatives in healthcare. Working across diagnostics, surgical devices, and medical devices, Sagentia Medical works with start-up disruptors through to world leading brands in MedTech to extract maximum value from R&D and innovation investments.

sagentia.com/medical

For further information visit us at:
sagentia.com/medical or
email info@sagentiamedical.com


**Sagentia Ltd**
Harston Mill
Harston
Cambridge
CB22 7GG
UK

**Sagentia Ltd**
First Floor
17 Waterloo Place
London
SW1Y 4AR
UK

**Sagentia Inc**
1150 18th Street
Suite 475
Washington
D.C. 20036
USA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