

Automation in Intracytoplasmic Sperm Injection: Technologies, Outcomes, and Future Directions

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Abstract

Since its introduction in 1992, intracytoplasmic sperm injection (ICSI) has gained significance in assisted reproduction. In certain instances of male infertility, fertilization is made possible by the microsurgical insertion of a single sperm cell straight into the cytoplasm of an oocyte. These days, the majority of in vitro fertilizations worldwide use ICSI, which is carried out manually by qualified embryologists. However, automation is encouraged to increase overall uniformity and efficiency because manual ICSI is labor-intensive and subject to inconsistency depending on the skill of the embryologist. The state of the art in ICSI automation is outlined in this article, which includes computer vision-guided control mechanisms, robotic micromanipulation systems, and artificial intelligence (AI) for sperm selection. We discuss the technical advancements that allow robots to perform key ICSI steps with high precision, such as automated sperm detection, sperm capture, oocyte detection, oocyte fixing, and injection using microneedles and piezo-electric actuators. Emerging AI algorithms that evaluate and select optimal sperm in real time and machine learning imaging systems for oocyte and embryo assessment are also examined. We present current outcomes from studies of automated ICSI, including the first healthy births achieved with a robotic ICSI platform, and compare technical and clinical results to conventional manual ICSI. Finally, we explore future directions and challenges, like integrating multiple lab procedures into an autonomous workflow, safety concerns, regulatory, and ethical considerations. Automation in ICSI has begun to show potential promise in improving reproductive technology, which leads to a new era of innovation in embryology labs.

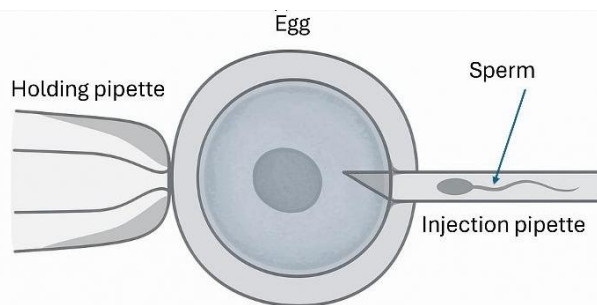
Keywords

Intracytoplasmic sperm injection; in vitro fertilization; assisted reproductive technology; automation; robotics; artificial intelligence; computer vision

Introduction

The development of intracytoplasmic sperm injection (ICSI) in the early 1990s revolutionized treatment for male-factor infertility. In 1992, Palermo and colleagues achieved the first successful human pregnancies via ICSI [1]. Since then, ICSI has been rapidly adopted worldwide and is now used in roughly 70% of all in vitro fertilization (IVF) cycles in 2013 [2]. This broad utilization exceeds the proportion of infertility cases strictly attributable to male-factor issues, reflecting an expansion of ICSI beyond its original indication [3] [4]. Large studies in the United States have found that ICSI offers no significant

Figure 1: Intra-Cytoplasmic Sperm Injection (ICSI).



improvement in outcomes for couples without male-factor infertility compared to conventional IVF [4]. Nevertheless, the technique's popularity has grown, contributing to an estimated millions of births globally conceived via ICSI [5].

Manual ICSI is a technically demanding microsurgical procedure. It is typically performed on an inverted microscope equipped with micromanipulators and involves immobilizing a single sperm and injecting it through the oolemma into the oocyte's cytoplasm using a fine glass pipette [1] (check Figure 1). The outcome of ICSI is highly operator-dependent, subtle differences in technique can impact fertilization and embryo development [6] [7]. For example, the site of sperm deposition and method of oolemma penetration may influence oocyte survival and fertilization rates [7] [8]. Greater cytoplasmic aspiration has been associated with poorer blastocyst development, although the assessed chromosomal endpoints did not differ [9]. To minimize such risks, embryologists align the oocyte's internal structures prior to injection (often by rotating the oocyte so that the first polar body is at the 6 or 12 o'clock position) in order to avoid the meiotic spindle [10]. The ICSI procedure's success thus relies on a high degree of microsurgical skill and experience. Operator expertise has been correlated with fertilization rates and blastocyst development, seasoned practitioners achieve

consistently higher success, whereas trainees show greater variability [6] [11]. In one analysis, embryos implanted from ICSI performed by very experienced embryologists had significantly higher sustained implantation rates than those from less experienced operators [6]. ICSI is also labor-intensive, requiring an individual embryologist to inject oocytes one by one. A typical ICSI cycle may involve tens of oocytes, and prolonged exposure of eggs outside the incubator during the injection process can be detrimental [12] [13]. Pujol et al. associated a longer retrieval-to-ICSI interval with lower biochemical and clinical pregnancy [13]. Furthermore, the delicate nature of ICSI raises some safety considerations. For instance, historical comparisons of assisted reproduction

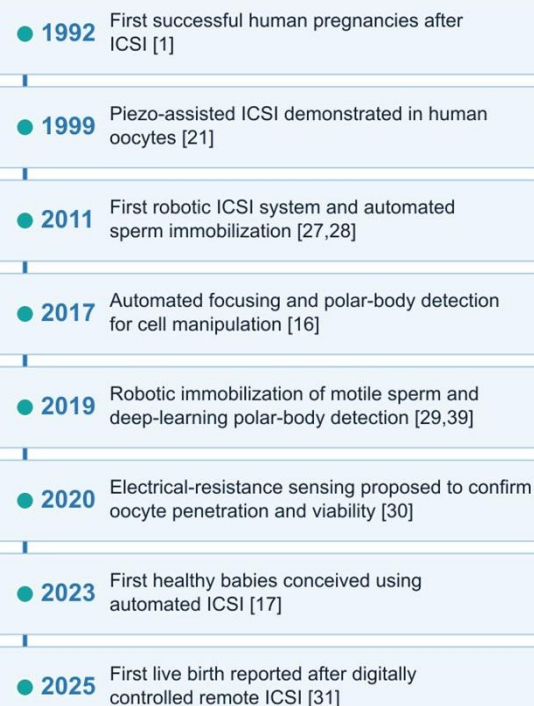


Figure 2: Major milestones in ICSI automation. Dates reflect publication or reported clinical achievement and reference numbers correspond to the manuscript bibliography.

with spontaneous conception raise safety questions, although the available evidence does not distinguish the contribution of ICSI from that of IVF [14]. Given the high technical demands, inter-operator variability, and throughput limitations of manual ICSI, there has been great interest in automating the ICSI process. Automation offers the potential to standardize technique, reduce human error, and ease the workload in IVF laboratories [15] [16]. In recent years, researchers have begun applying advanced technologies, including precision robotics, microfluidic devices, artificial intelligence (AI),

and computer vision, to replicate the actions of an embryologist during ICSI. Initial milestones have already been achieved, such as the first reported births from robot-assisted ICSI in 2023 [17].

Global experts have begun to establish best-practice guidelines and performance indicators for IVF laboratory operations (e.g. the Vienna consensus for ART labs) [18], and automation will need to meet or exceed these quality benchmarks. With continued innovation, ICSI automation may augment human embryologists and help make IVF more consistent, accessible, and efficient for the growing number of patients worldwide seeking assisted reproduction [19].

This review provides an overview of the current state of automation in ICSI. We first summarize the conventional manual ICSI procedure and its limitations. We then examine the emerging technologies enabling ICSI automation: robotic micromanipulation systems, AI-driven sperm selection methods, and computer vision coupled with intelligent control software (e.g. the ROS2 robotics framework). We compare the technical performance and early clinical outcomes of automated ICSI to those of manual practice. Finally, we discuss future directions, including the integration of additional laboratory steps into automated platforms, and consider the remaining technical, regulatory, and ethical challenges on the path toward fully automated IVF. Figure 2 summarizes the major milestones in the development of ICSI automation.

Manual ICSI Overview

In the standard ICSI procedure, a single spermatozoon is injected directly into the cytoplasm of a mature oocyte using micromanipulation under a microscope [1]. The oocyte is held in place by a holding pipette, while an injection pipette (approximately 5-6 μm inner diameter) is used to penetrate the zona pellucida and oolemma and deposit the sperm. Before injection, sperm are typically immobilized (by tail scoring) to facilitate capture in the needle. The embryologist then advances the injection pipette into the oocyte, usually entering at the 3 o'clock position to avoid the meiotic spindle apparatus located near the polar body [10]. Gentle suction is applied to aspirate a small amount of ooplasm along with the sperm, followed by expulsion of the sperm into the oocyte. Fertilization rates of around 70% can be attained by skilled operators by minimizing cytoplasmic leakage through precision pipette extraction.

Subtle differences in technique affect success rates since ICSI demands a high level of skill. Nagy et al. discovered that both the sperm implantation site and the oolemma rupture technique (abrupt vs. slow penetration) have an impact on fertilization and embryo development [7]. Palermo et al. found a correlation between post-ICSI oocyte survival and certain oolemma features, such as pliability, indicating varying vulnerability to injection-induced

damage [8]. As a result, improper pipette placement or excessive force during insertion may result in aberrant oocyte activation or permanent damage [9]. As a result, before injecting, embryologists meticulously position the oocyte and frequently employ instruments like polarized light microscopy to verify the spindle site [10]. Research indicates that the embryo has a lower chance of developing normally if the spindle is not aligned with the injection angle [10].

ICSI is a technically challenging technique, thus who does it has a significant impact on success rates. Tiegs and Scott discovered that while less experienced personnel had greater rates of complete fertilization failure, experienced embryologists had much higher rates of fertilization and blastocyst formation [6]. In a busy IVF center, maintaining consistency in results between staff members can be challenging. Additionally, manual ICSI is difficult to scale. Only one egg can be injected at a time by an embryologist, and each oocyte takes several minutes. It can easily take more than an hour to process a batch of fifteen to twenty eggs. The eggs are left out of the incubator and exposed to room conditions during this time, which may result in cellular stress. Longer intervals between egg retrieval and sperm injection reduced fertilization and pregnancy rates, as demonstrated by Pujol et al.'s findings [13]. For embryologists, doing this by hand for hours is also physically taxing. During lengthy lab sessions, this weariness can readily result in minor errors in accuracy [11] [12]. ICSI carries slightly higher risks than standard IVF, including a modest rise of new chromosomal problems or birth abnormalities, despite the fact that procedure is normally safe [14]. This could occur as a result of ICSI physically invading the egg and avoiding natural sperm selection. Even though these risks are small, they are a major reason why researchers want to improve and standardize the technique.

Over the years, incremental improvements have been made to the manual ICSI process to enhance success and reduce oocyte trauma. One major innovation was the use of piezo-electric actuators to facilitate oocyte membrane penetration. Initially demonstrated in animals such as mice [20] and later applied in humans [21] [22], piezo-ICSI involves mounting the injection pipette to a device that delivers rapid mechanical pulses. These piezo pulses drive the pipette through the zona and oolemma with minimal deformation of the oocyte, reducing the sheer force required by the operator. Yanagida et al. reported in 1999 that a piezo microinjector could improve fertilization and embryo development in humans, especially in cases of hardened zona pellucida [21]. Zander-Fox et al. showed that piezo-ICSI increases fertilization rates compared with standard ICSI, especially for patients over 38 years old [23] [24]. In a clinical comparison, Takeuchi et al. reported improved fertilization and cleavage with piezo-assisted zona penetration followed by conventional oolemma puncture [22]. Piezo actuation has become routine

for ICSI in certain animal species (e.g. mouse ICSI) where it dramatically increases survival of oocytes that are otherwise highly sensitive to mechanical stress [20]. Specialized pipette designs are among the other technological advancements. For instance, Fernandez et al. developed a modified holding pipette that prevents the cell from losing important material during the injection by keeping the oocyte constant without drawing in excess

procedure, reducing down on cellular stress and egg handling times.

Automation Technologies

Robotics and Micromanipulation Systems

At the heart of ICSI automation is robotic technol-

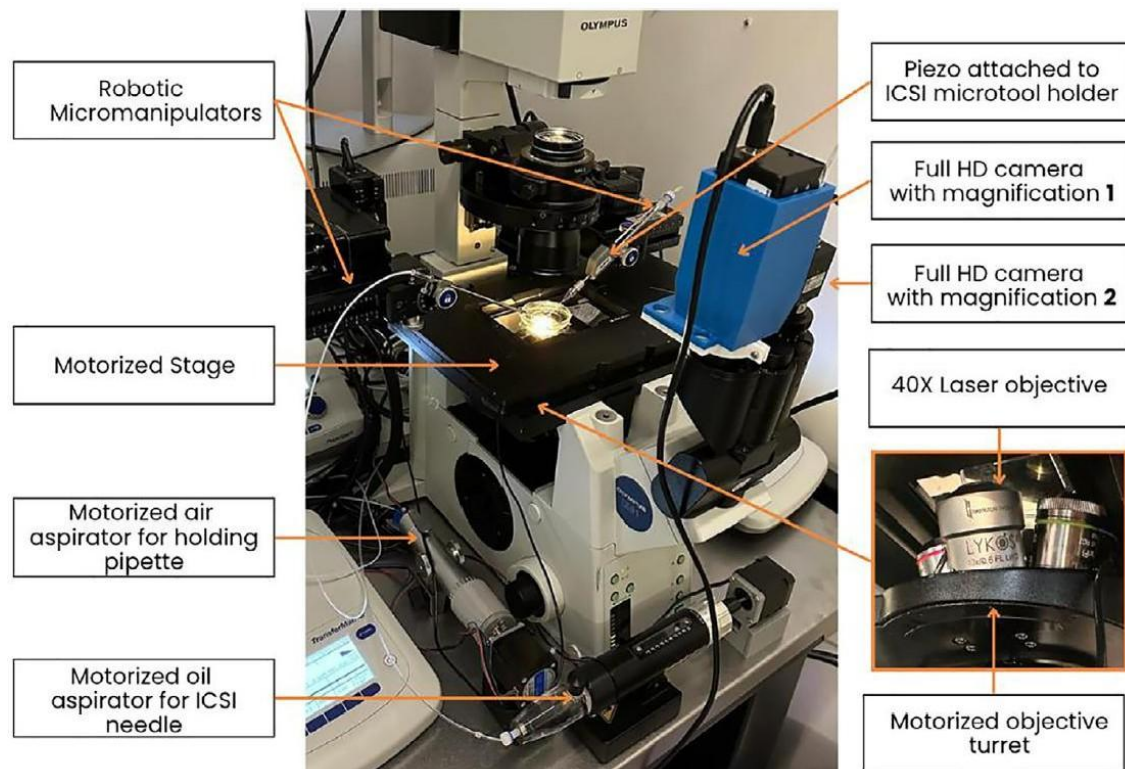


Figure 3: The remote controlled and motorized intracytoplasmic sperm injection experimental set-up. Reproduced from Mendizabal-Ruiz et al. [31] under CC BY-NC-ND license.

cytoplasm [25]. Additionally, researchers have experimented with incorporating haptic feedback into micromanipulators. This helps the embryologist avoid applying excessive force on the egg by allowing them to feel the resistance against the pipette [26]. When combined, these technological advancements have greatly increased the dependability of manual ICSI. Nevertheless, the process is still very complicated and entirely depends on the embryologist's expertise. In order to avoid human mistake and improve consistency, academics are currently investigating automation. No matter who operates the equipment, consistent, high fertilization rates might be achieved by automating the exact movements and choices of sperm injection. Additionally, it might expedite the

ogy, which aims to precisely and consistently reproduce the delicate actions of an embryologist. Early work in this area began over a decade ago. In 2011, Lu et al. reported a robotic ICSI system that used computer-controlled actuators and visual tracking to guide sperm injection [27]. Leung and colleagues separately developed an automated sperm-immobilization apparatus that visually tracked a motile sperm and controlled a micropipette to immobilize it, achieving an 88.2% immobilization success rate in 1000 trials [28]. Building on these advances, Zhang et al. demonstrated a clinical-oriented robotic platform that achieved 96.0% sperm-head tracking success and 94.5% immobilization success in 400 sperm, distinguishing tracking performance from

the immobilization outcome [29]. Together, these studies established that key ICSI subtasks can be automated reproducibly.

Modern robotic ICSI workstations typically consist of high-precision mechanical micromanipulators (sometimes piezo-actuated) mounted on an inverted microscope, all under computer control. These systems can execute the same steps as a human operator: capture a sperm cell, position the injection needle, puncture the oocyte, and inject the sperm. Electrical resistance measurement has also been proposed for confirming oolemma penetration and oocyte viability during manual or robotic ICSI [30]. Costa-Borges et al. reported normal fertilization in 13 of 14 robot-injected donor oocytes and the birth of two healthy babies after transfer of robot-derived euploid blastocysts [17]. This marked the first instance of live human births from robot-performed sperm injections. Not long after, a case report described the first baby born from a remotely-operated ICSI procedure, in which an operator in one location commanded a robot in an IVF lab elsewhere to carry out the sperm injection. Most of the ICSI micromanipulation steps in that system were automated, with the remainder executed by the robot under remote human guidance [31]. Their system is a fully automated, remotely controlled ICSI system built entirely from commercially available parts. It uses an inverted microscope with a heated stage, a laser for non-contact cutting, a piezo actuator, a motorized XY stage, a motorized objective turret, oil/air microinjectors, and high-resolution cameras. All of this lets the whole ICSI process be watched and controlled digitally (Figure 3).

These milestone achievements underscore the potential of robotics to reproduce the delicate maneuvers of ICSI. Notably, the robotic system by Costa-Borges et al. employs a piezo-electric drill on the injection pipette that is triggered automatically by the control software to penetrate the oocyte membrane, rather than relying on the tactile judgment of an embryologist [17]. This ensures a consistent application of minimal necessary force. The same system automates critical steps such as precise pipette positioning and depth control, under the oversight of computer vision and AI algorithms. In addition to sperm injection itself, robotics is being introduced to other lab tasks surrounding ICSI. For example, robotic systems have been developed to automate the preparation of embryo culture dishes and handling of micro-droplets for IVF, tasks traditionally done by hand. Lattin et al. (2024) describe an automated robotic platform for preparing embryo culture dishes with consistent medium droplets and oil overlay, improving standardization in the IVF lab [32]. There are also efforts to robotically automate oocyte han-

dling before and after ICSI. For instance, moving oocytes from one dish to another or loading them into a microfluidic device. Ultimately, fully automated IVF workstations may integrate multiple functions: sperm sorting, ICSI, embryo culture, and cryopreservation. Palermo and colleagues have patented a design for a microfluidic-based “ICSI device” that combines all steps of sperm injection into a single closed system. Their design includes reservoirs and channels for holding oocytes, loading sperm, and culturing embryos. This basically combines several different pieces of lab equipment into a single disposable microfluidic chip [33]. If developed on a bigger scale, this system might minimize lab expenses while reducing the dangers of contamination, human error, and manual labor. But to make this work, precise robots, dependable microfluidics, and stringent environmental controls must be combined.

Robotic ICSI uses sophisticated control software to use sensor data to coordinate motors and actuators in real time. For this type of lab and medical robotics, the Robot Operating System 2 (ROS2) is frequently utilized [34]. In addition to allowing real-time operation and feedback loops, ROS2 provides a flexible, modular architecture that makes it simple to connect various devices, such as micromanipulators, cameras, and piezo actuators. In contrast to previous ROS versions, ROS2 was created to satisfy the real-time, safety, and reliability needs of critical systems. It utilizes a data distribution service (DDS) that can be configured for deterministic, low-latency communication between components. In optimized setups, sub-millisecond timing of actions is achievable, though this depends on the specific DDS implementation, transport, and system tuning rather than being a default guarantee. In the context of ICSI automation, a ROS2-based control system can simultaneously manage the motion of the injection pipette, the holding pipette, the microscope stage, and any auxiliary devices (e.g., a piezo driver or laser), all while receiving continuous updates from imaging systems. Park et al. (2020) demonstrated ROS2’s capability for multi-agent real-time coordination, which is directly applicable to controlling multiple robotic axes in an ICSI procedure [35]. While Mendizabal-Ruiz et al. [31] described a digitally controlled remote ICSI system using proprietary software interfaces without explicitly naming the underlying framework, such tele-operated platforms typically rely on ROS-like middleware design patterns to ensure low-latency command translation [31]. The reliability of such control is critical, for example, to instantly halt the injection if an unexpected resistance is detected, or to execute a series of piezo pulses with exact timing and amplitude. As robotic ICSI systems evolve,

their control software will increasingly incorporate sophisticated decision-making algorithms (such as AI-driven adjustments based on live imaging), but ROS2 provides the backbone to integrate these higher-level functions with the low-level motor control in a safe and real-time manner [35].

In conclusion, robotic micromanipulation systems have advanced from early 2000s proof-of-concept devices to current clinically tested prototypes. As demonstrated by comparable fertilization and blastocyst rates to manual ICSI in early studies, they are able to automate the mechanical parts of ICSI with high precision. In a very small number of cases thus far, robotic ICSI has produced healthy babies [17] [31]. As of right now, these systems still need human supervision or a hybrid configuration in which an engineer may remotely supervise certain components while other processes operate automatically [31]. However, clinics are heading toward complete autonomy as the technology establishes itself. Robotics and intelligent software can take over the repetitious, physically taxing aspects of ICSI, freeing up embryologists to concentrate solely on supervision and important choices. We are getting closer to a completely automated lab process as this type of automation spreads to other areas of the IVF facility. Strict IVF safety standards must be upheld as this technology is implemented, and each automated stage must treat eggs and sperm with the same care as a skilled embryologist. Early results are encouraging in this regard, and ongoing refinements (such as better force feedback, more sensitive vision systems, and improved microfabricated devices for handling gametes) will further enhance robotic ICSI performance.

AI-Assisted Sperm Selection

Selecting a viable, high-quality sperm is a prerequisite for successful ICSI. In conventional practice, an embryologist subjectively chooses a sperm cell by assessing its morphology (e.g. head shape, absence of vacuoles) and motility under magnification. This process is inherently variable and depends on the operator's judgment and experience. In recent years, artificial intelligence has been introduced to assist and standardize sperm selection for ICSI [15] [16]. AI-driven sperm selection tools typically use computer vision and machine learning algorithms to evaluate sperm images or videos in real time and identify which sperm cell is most likely to lead to successful fertilization and development.

One example of such a tool is the Sperm Selection Diagnosticscope (SiD) software developed by Mendizabal-Ruiz et al. [36]. SiD employs a form of artificial vision and machine learning to analyze the motility

patterns of individual sperm in real-time during an ICSI procedure. In a study of 383 sperm videos, this AI computed quantitative motility parameters such as straight-line velocity and head movement periodicity and generated a "score" for each sperm based on features that correlated with successful fertilization and blastocyst formation. The authors found that sperm selected by embryologists which went on to fertilize oocytes and form blastocysts had significantly higher AI-derived scores (indicating more linear and less erratic movement) than those that failed [36]. This suggests that AI can detect subtle differences in sperm behavior that are predictive of fertilization success. The retrospective analysis illustrates the potential of quantitative motility features to support sperm assessment, while prospective studies are needed to determine their value for selection and clinical outcomes.

Artificial intelligence has shown promise for assisting sperm assessment and selection. In a systematic review of 34 studies published between 2010 and 2023, Cherouveim et al. identified applications involving sperm morphology, motility, and DNA integrity. The authors concluded that AI could improve the objectivity and reproducibility of sperm assessment but emphasized that model performance depends strongly on the size and quality of the training dataset [15].

Automated sperm selection goes past basic digital imaging. Other new methods are also being integrated with automation. Microfluidic sperm sorting devices, for instance, offer a way to select sperm based on physical and fluid-dynamic properties (such as motility and the ability to navigate microchannels) without manual pipetting. These chips can be seen as a form of "passive" automation for sperm selection. Recent clinical data show that microfluidic sperm selection can improve ICSI outcomes in certain scenarios. The chip-selected sperm also yielded more high-quality embryos, suggesting that this method enriched for physiologically competent sperm [37]. Automated systems can incorporate such microfluidic modules to handle sperm selection upstream of the ICSI robot. For example, an integrated platform might use a microfluidic device to isolate the best sperm, then an AI microscope to pick the top sperm from those, and finally a robot to inject it, thereby combining physical and AI-based selection mechanisms. Such patents indicate that future automated ICSI workstations will likely include a sperm selection subsystem where sperm are processed and evaluated by AI prior to injection.

The introduction of AI into sperm selection aims to

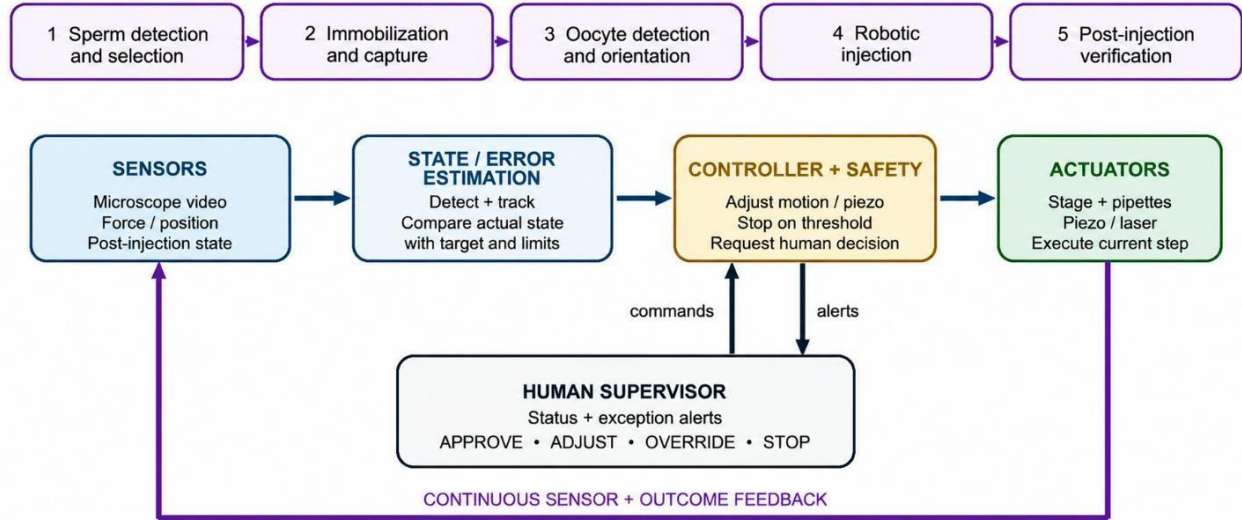


Figure 4: Human-supervised closed-loop control for automated ICSI. Sensor measurements are converted into a state/error estimate, the controller updates robotic motion and actuation, and the measured result is fed back continuously. The operator receives status and exceptions and may approve, adjust, override, or stop the procedure.

make the process more objective and data-driven. By continuously learning from large datasets of sperm features and ICSI outcomes, AI systems could potentially identify sperm characteristics (or combinations of characteristics) that humans are not readily aware of. AI is able to identify minute irregularities in sperm head movement or small form defects associated with DNA damage that humans could overlook. By ensuring that the injected sperm has the highest possible chance of producing a viable embryo, using these methods could easily increase ICSI success or embryo quality. AI eliminates the uncertainty and subjective bias that typically lead to inconsistent outcomes by standardizing selection across various employees and labs, even if it only establishes a baseline. Of course, before being widely used, these AI tools still require rigorous validation. While they can score or rank sperm, the ultimate proof of efficacy is improved clinical outcomes (fertilization, embryo development, live birth rates) in controlled studies. Thus far, limited data (mostly retrospective analyses) suggest equal or improved outcomes with AI-assisted selection [36], but more prospective trials are needed.

Overall, AI-assisted sperm selection is a rapidly evolving component of ICSI automation. It complements mechanical robotics by tackling the decision-making aspect of which gametes to use. In an automated ICSI scenario, one could envision a sperm being automatically isolated on a microfluidic platform, then an AI scans it and others to pick the top candidate, and finally a robot injects the chosen

sperm into the oocyte. Each of these steps, isolation, evaluation, and injection can be integrated for seamless operation. As of now, many clinics are starting to adopt AI systems in a decision-support role (with the embryologist still making the final call), but fully automated selection is on the horizon. If these technologies continue to advance, the days of an embryologist peering into a microscope to subjectively choose a sperm may give way to an era in which smart machines present the “best” sperm for injection based on measurable criteria and big data insights. Figure 4 summarizes the integrated, closed-loop workflow from sperm selection through post-injection verification.

Computer Vision and Robotic Control

Automating ICSI would not be possible without sophisticated computer vision to replicate the eyes of the embryologist, and advanced control software to coordinate movements based on visual feedback. High-resolution imaging and real-time image analysis (often facilitated by AI algorithms) enable a robot to “see” and react during the delicate steps of ICSI. One of the fundamental tasks is identifying and locating the oocyte and key structures (like the polar body) in the dish. Traditional ICSI relies on the embryologist’s visual assessment to orient the oocyte correctly. In an automated system, computer vision algorithms take on this role. Researchers have developed methods to automatically detect oocytes and their orientation using image processing techniques. Chen et al. (2016) described an algorithm that could

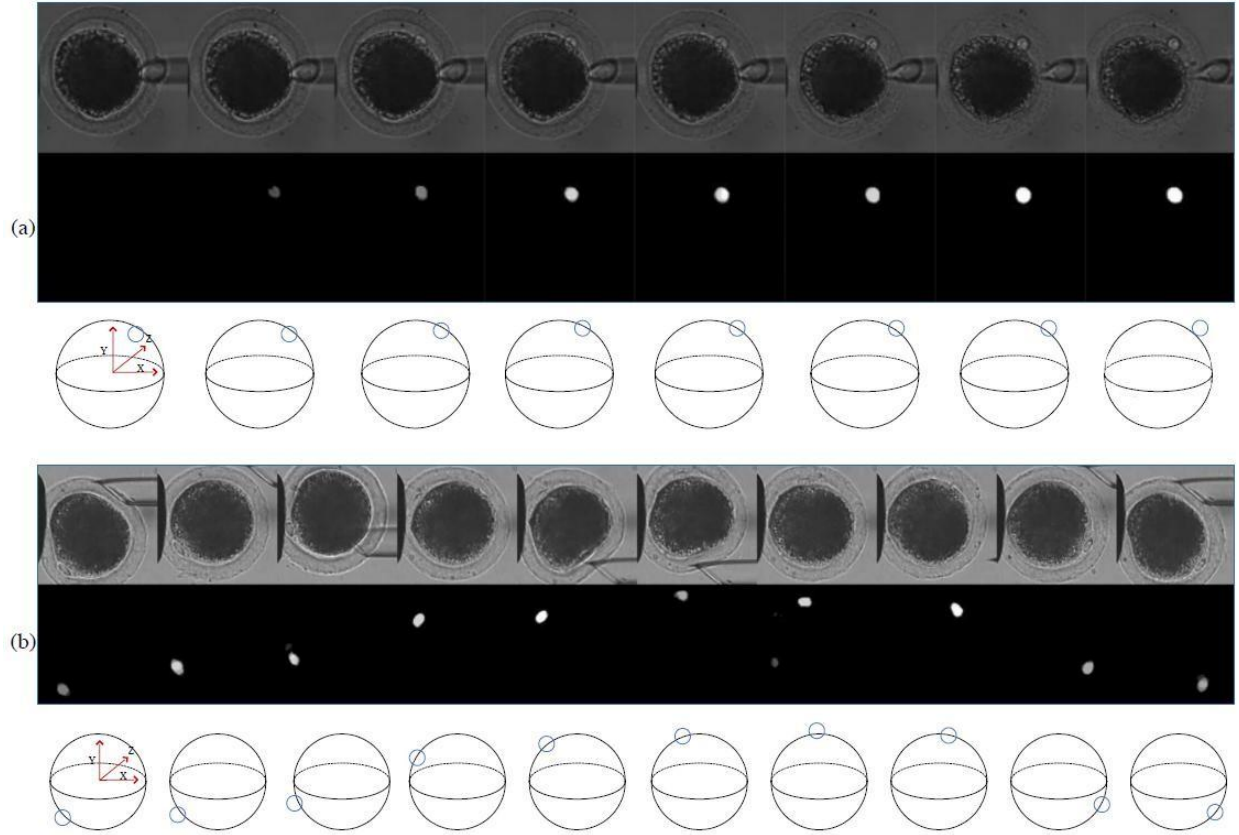


Figure 5: Polar body detection results of two oocytes. (a) Different visibilities. (b) Different rotations. Reproduced from Wang et al. [39] under CC BY license.

recognize the outline of an oocyte and the presence of the polar body in microscope images using contour detection and machine learning classification (support vector machines) [38]. In a subsequent improvement, Wang et al. (2019) implemented a deep learning approach for polar body detection that was robust even under varying light or slight oocyte shape differences (Figure 5) [39]. These algorithms allow the robotic control system to ascertain where the polar body is located so that the injection pipette can be directed to the opposite side, avoiding damage to the spindle. Similarly, computer vision can track the position and angle of the injection needle in relation to the oocyte. Wang et al. (2017) demonstrated an autofocus and image-detection system that keeps both the oocyte and injection pipette in sharp focus and can detect the pipette tip's position relative to the oocyte's membrane [16]. This ensures that the robot advances the needle the correct distance into the oocyte before releasing the sperm.

Another critical aspect for future closed-loop control is monitoring oolemma behavior. Yagi et al. retro-

spectively analyzed recordings from 93 oocytes, including 38 with rupture and 55 without rupture, and investigated rupture prediction using image features and a support-vector machine [40]. This was a rupture-prediction study; it did not demonstrate real-time automatic termination of piezo pulses. Prospective integration would require validation of decision thresholds, latency, and effects on oocyte survival.

To handle such real-time decisions, the control software, often built on frameworks like ROS2 must integrate visual data with actuator control. The robot's control algorithm continuously processes the live video feed: when the oocyte is in view, it calculates the target coordinates for injection based on the oocyte's geometry; as the pipette moves, it adjusts course if the pipette drifts from the target or if the oocyte moves; when the pipette tip contacts the oolemma, it triggers the piezo driver and watches for the membrane break; once detected, it halts further movement and commands sperm release. All of these actions happen on the order of milliseconds to seconds. ROS2's real-time messaging and multi-threaded handling allow parallel processing of these

tasks (one thread for image analysis, one for motion control, etc.) without compromising synchronization [35]. In essence, computer vision provides the feedback loop that turns open-loop robotic motion into a closed-loop controlled process, much like an embryologist constantly adjusts their hand movement by watching through the eyepiece. There have also been efforts to achieve full 3D visualization of oocytes and microneedles to guide robots more accurately. Tang et al. (2021) reviewed approaches for achieving automated rotation and orientation of biological cells in micro-manipulation [41]. Techniques such as microvortex flows and optical traps can reorient oocytes or embryos, and 3D machine vision can be employed to identify an oocyte's spatial orientation from multiple angles [41]. While not yet routine for ICSI, these methods could eventually allow a robot to automatically rotate an oocyte to the desired orientation (for example, turning the oocyte until the polar body is detected at the top) without human intervention, before performing the injection. This would be especially useful in a fully enclosed microfluidic system where manual rotation via a holding pipette might be challenging.

Another sensor modality that can complement vision is force sensing, measuring the resistance on the injection pipette. Some automated systems incorporate tiny force sensors or measure pressure changes to detect when the pipette has penetrated the zona and oolemma. Johnson et al. (2018) introduced a flexure-guided piezo drill that reduced lateral vibration and deformation during zona penetration in mouse oocytes [42]. In a robotic context, such force feedback can be used in parallel with vision: the vision system guides the pipette to the oocyte, and the force sensor confirms penetration and can prevent overshooting beyond the far side of the oocyte. Ensuring the robot exerts only the minimal necessary force is important for oocyte viability.

Recent studies have also explored lightweight computer vision approaches for sperm detection in Micro-TESE procedures. One such system, SD-CLIP (Sperm Detection using Classical Image Processing), was designed for low-sperm environments associated with non-obstructive azoospermia (NOA) [43]. Unlike computationally intensive deep-learning pipelines, SD-CLIP utilizes morphology-based image processing and principal component analysis to identify sperm heads and tails in unstained DIC microscopy images. The method achieved substantially reduced computational time and lower false positive rates compared with previous MB-LBP-based approaches, while maintaining practical real-

time clinical applicability for real-time sperm retrieval support [43]. The authors also suggested that such lightweight systems could be integrated into future automated sperm extraction and robotic ART platforms [43]. Beyond standalone detection systems, researchers have also begun integrating AI-based analysis directly into microscope visualization workflows. Augmented reality (AR) systems combined with AI-based computer vision are also emerging as promising tools for assisted reproductive procedures. Mohamed et al. proposed an AI-assisted AR microscope system for Micro-TESE that integrates YOLOv5-based sperm detection, DeepSORT tracking, and real-time visual overlays within the microscope eyepiece [44]. Figure 6 illustrates the overall concept of the AR-assisted microscope system and its real-time visualization workflow. The system provides immediate visual guidance to embryologists by highlighting detected sperm and displaying motility-related information during microscopic examinations. In comparison to previous hand-crafted methods, operator testing showed a sperm-detection rate of 66.9% with AR versus 30.8% without AR, approximately 2.17-fold, or a 36.1-percentage-point difference [44]. This type of setup demonstrates how merging AI with augmented reality might speed up the sperm hunting process in the lab by reducing the embryologist's physical and eye strain.

To put it briefly, the fundamental building blocks of automated ICSI are computer vision and intelligent software. They take care of both the sensory input and the real decision-making, enabling the robot to monitor visual changes and instantaneously modify its actions. Thus far, researchers have effectively automated the focusing and alignment of injection instruments [16], as well as the detection of oocytes and polar bodies [38], [39]. These days, systems can identify sperm in intricate Micro-TESE environments using lightweight models [43], detect membrane penetration in real time [40], and employ augmented reality powered by AI to assist with sperm retrieval [44]. Together, these advances improve consistency in individual automation tasks, although clinical equivalence to experienced embryologists remains to be established. The vision program will undoubtedly incorporate more sophisticated AI features in the future. Rather than merely monitoring the polar body, sophisticated algorithms might assess oocyte maturity or identify vacuoles associated with subpar egg quality, instantly changing the injection parameters.

The system can respond to dynamic lab settings by

integrating computer vision with control architectures such as ROS2. When a sperm or oocyte moves within the pipette, the robot recognizes the change and instantly adjusts its course. Even though automated ICSI systems currently use simple image processing, precision will continue to be driven by technological advancements. For instance, spectral imaging could assess cell health during handling, and increasing frame rates and resolutions will enhance the detection of the "zonal crack" at the precise instant of puncture. A gentle, reliable, and highly repeatable process is ensured by controlling these inputs within a real-time control loop. A smooth, delicate, and repeatable injection process will be produced by feeding all of these data streams into the control loop that ROS2 or comparable architectures oversee.

Technical and Clinical Outcomes

The ability of any automation in ICSI to match or surpass the results attained by proficient human practitioners is the ultimate test. Fertilization rate

formation rate), embryo quality, live birth rate, and offspring health are important outcome indicators. Multiple healthy blastocysts and euploid embryos were obtained, indicating that the viability of the oocytes and embryos was not significantly compromised by the automated injection. In the 2023 study, normal fertilization occurred in 13 of 14 robot-injected and 16 of 18 manually injected donor oocytes, and two singleton births followed transfer of robot-derived euploid blastocysts [17]. These findings provide early clinical feasibility evidence and support larger comparative studies. Mendizabal-Ruiz et al. similarly reported a successful live birth from their digitally controlled, remote ICSI system, a case that underscores the potential for tele-operated or fully automated fertilization in settings where experienced embryologists may not be physically present [31].

From a technical standpoint, these initial uses of automated ICSI have highlighted both achievements and areas for improvement. On the positive side, the

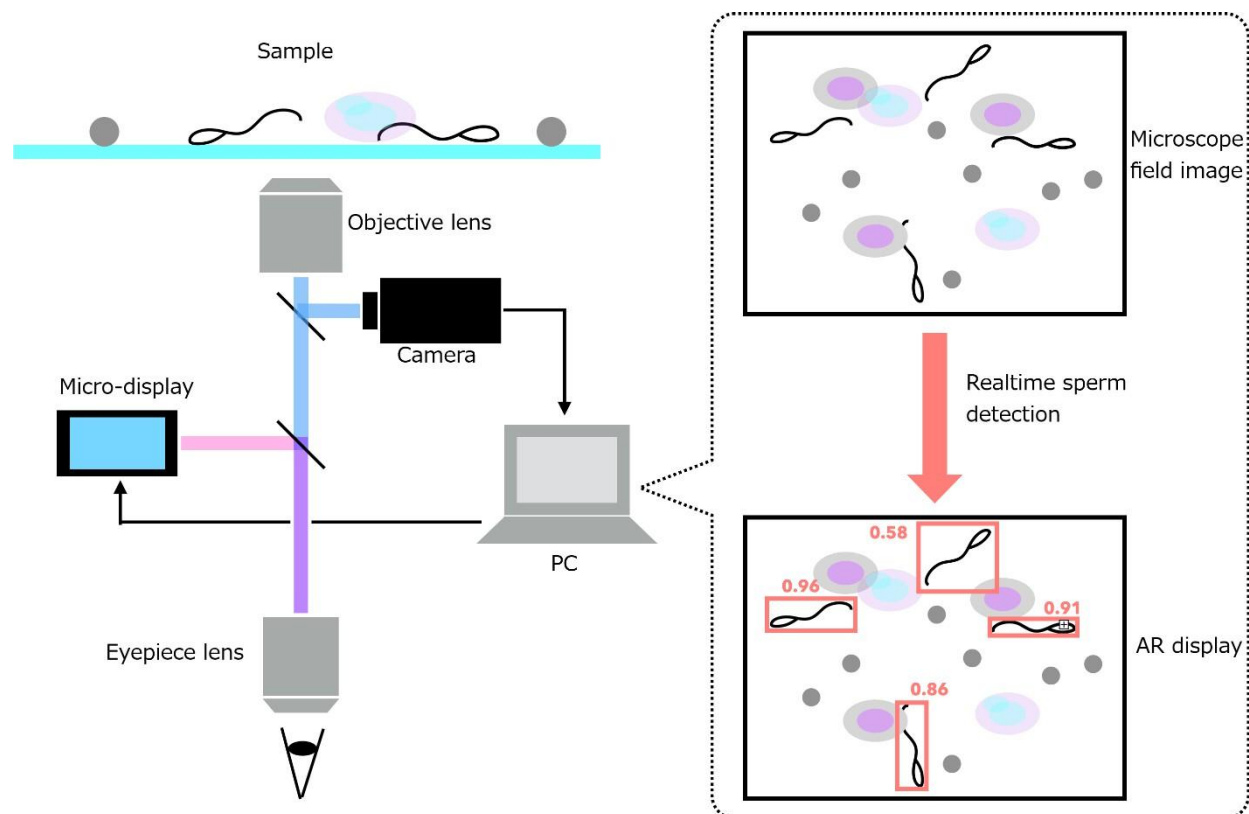


Figure 6: Conceptual overview of the AI-assisted augmented reality microscope system for real-time sperm detection and tracking during Micro-TESE procedures. Adapted from Mohamed et al. [44] under CC BY license.

(percentage of injected oocytes that fertilize normally), embryo development rate (e.g., blastocyst

consistency of the robotic movements can reduce some forms of oocyte trauma. The ICSIA system, for

example, applies very standardized piezo pulse patterns for membrane penetration, which may avoid excessive oolemma stretching or cytoplasmic turbulence that can occur with variable manual force [17]. Additionally, a robot does not fatigue or lose focus and each injection is performed with the same steady hand. This could be particularly beneficial in cases with high oocyte yield (e.g., some polycystic ovary syndrome patients) where an embryologist might be injecting dozens of eggs in one session. It's conceivable that automation could maintain a high performance even after many injections, whereas a human might be more prone to errors or slower operation as time goes on.

On the other hand, current automated systems still have some technical limitations that the clinical results reflect. One limitation is sperm selection and loading, which in reported cases was still done manually. This means the overall success still partly depended on the human factor of choosing a good sperm. If that selection was suboptimal, the outcomes (failed fertilization or poor embryo development) would not necessarily be the robot's fault. Going forward, the incorporation of AI-based sperm selection could further improve outcomes by systematically picking sperm with higher developmental potential (e.g., those with high motility and low DNA fragmentation). Another challenge observed is that the robotic system needs to accommodate variability in oocyte properties (size, zona thickness, etc.). Humans intuitively adjust injection dynamics for a very large oocyte or a very thick zona (for instance, by applying more piezo pulses). A robot might initially use a one-size-fits-all approach. If an oocyte requires slightly more force and the robot's preset is too gentle, it could fail to penetrate on the first try, requiring multiple attempts which might stress the oocyte. Conversely, if it's too aggressive for a given oocyte, it might cause an avoidable fracture in the zona. Fine-tuning adaptive control, perhaps using force feedback or computer vision cues will be needed to handle such variability. For instance, one group is investigating algorithms to predict if an oocyte is at risk of rupture from injection and modulate the approach accordingly [40].

In terms of embryo development and clinical pregnancy rates, it will require larger studies to determine if automated ICSI can match the gold standard set by expert embryologists. The two live births achieved via the automated system resulted in healthy infants with normal birth weights [17], suggesting the technique does not disrupt early development. However, randomized controlled trials are

necessary to demonstrate therapeutic efficacy. Future studies should utilize a split-oocyte model, dividing a patient's oocytes between robotic and manual injection to directly compare embryo progression and outcomes. Given the ethical and practical hurdles, we may first see more observational data accumulate from cases where automation is used out of necessity or in validation studies.

Aside from fertilization metrics, other technical outcomes of interest include procedure time and throughput. One goal of automation is to increase efficiency. In the remote ICSI case report, the authors noted that roughly 50% of the steps (e.g., fine positioning, injection actuation) were done autonomously, which did help standardize the procedure [31]. The total time per injection was reported to be similar to that of an experienced operator, though not necessarily faster [31]. With further optimization, robots could potentially perform injections faster or in parallel (imagine a multi-pipette system injecting multiple oocytes at once, if engineered). Even modest time savings per oocyte can translate into oocytes spending less time in suboptimal conditions, potentially improving outcomes for sensitive oocytes (like those from older patients). Another technical outcome is error rate, e.g., how often the robot misses or drops an oocyte, or fails to inject properly. In manual ICSI, it's not uncommon for an oocyte to lyse if mishandled or for the spindle to be accidentally aspirated, etc. We would want an automated system to have an error rate no worse (and ideally better) than the human benchmark. So far, reported automated cases did not mention any catastrophic errors, but the numbers are small. Developing robust error-detection (like recognizing if the sperm was not actually deposited and trying again) is an ongoing area of work.

One interesting outcome to consider is whether automation could enable improvements in environments or conditions that are challenging for humans. For example, microgravity in space makes manual ICSI nearly impossible due to lack of sedimentation and difficult handling, but a robotic system could potentially operate in a closed chamber in space with minor modifications. Chaplia et al. discuss that as humans contemplate reproduction beyond Earth, automated systems will be crucial to perform delicate ART procedures in non-terrestrial environments [45]. While purely theoretical at this stage, it suggests that automated ICSI might have unique advantages in specialized scenarios (extreme environments, remote locations with tele-medicine, etc.) that extend beyond simply replacing an embryologist in a standard clinic.

In animal reproduction and research, automated microinjection has already shown impactful outcomes. Robotic microinjection systems have been used to inject large batches of zebrafish embryos for research, achieving very high survival and hatching rates [46] [47]. Wang et al. developed a fully automated system for zebrafish embryo microinjection (not sperm injection, but transgene injection) that could process embryos in assembly-line fashion with a success rate around 99% [46]. While fish embryos are quite different from human oocytes, these successes in other models underscore how automation can drastically improve throughput without sacrificing viability. Similarly, a force-sensing multi-cell injection robot was able to inject dozens of fish embryos with consistent quality, something extremely tedious for a human to do one by one [48]. The outcomes (in terms of embryo survival to hatching) were on par with manual experts, but with much higher speed [48]. These analogues in research suggest that automated ICSI could maintain high performance over large numbers of oocytes, which might be beneficial in animals like livestock where dozens of oocytes are routinely handled, or in humans if IVF ever moves toward mild stimulation with many small cohorts across multiple sessions.

In human clinical use, an automated ICSI system will ultimately be judged by live birth rates and neonatal health outcomes. The initial case reports are reassuring, but long-term follow-up of more babies will be needed. It is worth noting that even manual ICSI has some ongoing debates regarding subtle risks (as mentioned, slightly higher *de novo* genetic abnormalities or epigenetic concerns have been raised [14]). Developers must ensure that automation does not introduce extra mechanical stress or alter handling times in ways that impact imprinting. To date, no such complications have emerged. Furthermore, standard IVF safety protocols, such as preimplantation genetic testing and detailed prenatal screening, are well-equipped to catch any early genetic or developmental abnormalities.

Overall, small clinical trials confirm that automated ICSI matches the success rates and feasibility of traditional manual methods. High fertilization rates, high blastocyst development, and successful pregnancies have all been achieved with robotic systems. While these results are preliminary, they provide a proof of principle that automation need not compromise effectiveness. As larger datasets are gathered, we will learn whether automation can consistently match the fertilization and live birth per egg retrieval statistics that are common with manual ICSI in

good-prognosis patients. There is reason for optimism that it can, given the precise control and lack of fatigue in robots. Moreover, automation could shine in scenarios where manual performance might drop. For example, during very lengthy procedures or with very difficult samples (extremely low motile sperm count where AI might help identify the single viable sperm, etc.). The ultimate measure of success will be widespread clinical adoption, which will only occur if outcomes under automation are at least as good as those by top embryologists. The coming years will likely see iterative improvements to address the current limitations (like fully automating sperm loading, refining vision algorithms, etc.), leading to even more reliable performance. With those advancements, it would be normal to see automatic ICSI results match or even outperform manual results in certain areas. For example, by almost completely preventing oocyte lysis or continuously increasing fertilization even under unfavorable circumstances. Until then, the collaborative model (human oversight with robotic assistance) might serve as a link that produces positive results while fostering confidence in the technology.

Future Directions and Challenges

There are a number of significant future prospects and challenges as automation in ICSI and IVF continues to progress. The complete automation of the fertilization process will be one of the main priorities. Current robotic ICSI systems handle the mechanical injection well, but still rely on humans for upstream and downstream steps such as sperm processing, oocyte handling, and embryo culture. In the future, these could be integrated into a single seamless automated workflow. For example, an oocyte could be picked up from a retrieval dish by a robotic arm, loaded into a microfluidic ICSI chip, automatically injected with a sperm, then moved into an onboard culture chamber, all without human touch. Achieving this will require uniting multiple modules: sperm selection, injection, and embryo culture. Some progress is already evident. Patents have been filed for comprehensive IVF platforms that incorporate sperm preparation and ICSI in one system [33] [49]. Millan et al. have invented a robotic system for sperm preparation that uses AI to automate steps like mixing, centrifugation, and aspiration of the semen sample [50]. The same group also patented an automated vitrification device for oocytes/embryos, where a robot can carry out the delicate series of transfers into cryoprotectant solutions and onto a cryo-device with minimal manual input [51]. In the coming years, we can expect these pieces like auto-

mated sperm prep, automated ICSI, automated embryo handling to be connected, leading to the first truly “closed” IVF systems. Such closed systems would enhance reproducibility and potentially reduce the risk of human error (for instance, eliminating the chance of sample misidentification or mishandling between steps). They could also improve lab safety by minimizing exposure of gametes to the external environment.

Even with the encouraging trajectory, there are still many obstacles to overcome before completely automated IVF is commonplace. Ensuring the dependability and safety of automated systems is a major challenge. Because every egg and embryo is valuable, reproductive medicine has an extremely low tolerance for error. Robotic systems require powerful error detection and recovery mechanisms in order to be failsafe. For example, instead of injecting air or harming the oocyte, a robotic ICSI system should identify the problem and either retry or notify a human if it is unable to pick up a sperm or an oocyte slips from the holding pipette. It is crucial to have redundancies in emergency stop mechanisms and vital senses (vision and force). Furthermore, a thorough validation process will be required. Before a completely autonomous system can be extensively used, regulatory organizations would probably demand that it show that it is not inferior to human operators in a broad variety of scenarios. Multicenter trials or at the very least thorough observational studies under regulatory supervision may be involved in this. Another challenge is earning patients' and practitioners' trust. Patients with infertility frequently develop a rapport with the embryologists who handle their gametes; at first, the thought of a machine conducting the work may cause unease or anxiety. Evidence of safety and education will be beneficial. For instance, sharing success stories of infants born using automated ICSI or displaying videos demonstrating how accurate and gentle the robotic movements are. Clinicians may also be reluctant to give up control. Incorporating user-friendly interfaces that enable embryologists to supervise and take appropriate action is one method to address this. A future model is actually highlighted by the remote ICSI example: an expert embryologist could oversee several IVF labs remotely, intervening via tele-operation only when the automated system encounters an unusual situation. This would increase the expert's reach while maintaining a layer of human oversight [31].

Adapting to various clinical situations presents another difficulty. Patients undergoing IVF differ greatly. Older individuals may have more delicate

oocytes; some may have very few sperm, necessitating careful handling of tiny volumes; others may have non-standard oocytes (e.g., gigantic oocytes in specific situations, or oocytes with hard zona in post-ovarian tissue transplant instances). To tackle these edge circumstances, automated systems must be adaptable. AI-driven modifications may be necessary for this. An oocyte's quality or zona thickness, for example, may be evaluated in real time by AI image analysis, which might then modify injection parameters (more piezo pulses for a thick zona, or extra gentle handling for a delicate oocyte). Modular designs and various pipette kinds or modes that the operator can choose from (such as a “fragile oocyte” mode with more cautious settings, etc.) may also be involved. It is difficult to ensure that automation can handle the entire range of instances that expert embryologists handle.

Another thing to think about is the financial element. Automation may lower prices over time due to labor savings and increased efficiency, but the initial cost of such equipment is significant. IVF clinics must be persuaded of the ROI. High-volume labs or research facilities that can support it may be the first to embrace automated ICSI. Smaller clinics may be able to use the technology as it develops and possibly becomes more affordable (for instance, by producing microfluidic chips in large quantities or making precision robots more widely available). A larger patient population will be able to obtain reproductive treatments if automation successfully lowers lab labor and raises per-cycle success rates.

There are significant concerns regarding openness and accountability when AI is used in gamete and embryo selection. To adequately counsel patients, clinicians need to know exactly how an algorithm selects a certain sperm or evaluates an embryo. In order to retain oversight, regulatory frameworks will probably need a “human in the loop” for crucial clinical judgments in the early stages. A number of these ethical issues in ART were brought to light by Zammit (2023), including algorithmic bias, data privacy concerns with cloud-based platforms, and the significance of maintaining the dignity of human reproduction in the face of increasing automation [52]. Open communication and doable actions are needed to resolve these problems. For instance, employing localized, secure servers helps safeguard patient privacy, while training models on a variety of medical data can lessen bias. In the end, automation seeks to assist fertility teams rather than take their place. The empathy and nuanced decision-making of healthcare providers are irreplaceable, even as automated systems take over repetitive lab tasks.

Future developments could involve integrating time-lapse embryo imaging directly into the automated ICSI workflow. Advanced prognostic AI could evaluate unfertilized oocytes to predict their developmental potential. Armed with these real-time analytics, an automated system could assist in triage decisions, such as prioritizing specific oocytes or identifying cases where the prognosis is too poor to warrant injection. Although adjusting clinical strategies based on automated predictions raises significant ethical questions and remains speculative, it represents a clear technical direction as predictive accuracy improves. Another future direction is combining gene editing or other advanced manipulations with ICSI in a streamlined automated process (for research or clinical applications under proper regulation). If CRISPR or other tools are to be used on gametes or zygotes, an automated system might precisely inject the gene-editing reagents immediately after sperm injection, thereby minimizing additional handling, something much harder to coordinate manually.

In the nearer term, one concrete direction is refining the integration of automated ICSI with preimplantation genetic testing (PGT) workflows. Automated systems could potentially biopsy embryos or coordinate with biopsy robots. Also, as cryopreservation is often performed (either freezing sperm, eggs, or embryos), having a robotic system that can seamlessly move an embryo from culture to a vitrification device (as in the patent by Millan et al. [50]) could ensure that embryos are frozen with minimal stress and operator variability.

Finally, training and workforce implications should be acknowledged. Embryologists will probably shift away from tedious benchwork and toward system oversight, quality control, and handling complicated situations as labs become more automated. Training programs will need to change as a result, teaching students how to handle automated technology and interpret AI diagnostics in addition to conventional embryology methods. By automating high-volume repetitive procedures, these tools provide a solution to industry personnel shortages and exhaustion rather than replacing embryologists [12]. During a transitional phase when manual and automated workflows will unavoidably overlap, it frees up embryologists to make complex clinical decisions and oversee patient care. During this time, maintaining skills in both will be important. Professional guidelines may emerge on how to validate an automated system before clinical use and how to maintain it (for example, calibration schedules, proficiency testing using dummy oocytes, etc.).

A 2026 proof-of-concept study evaluated sequential automated sperm preparation, oocyte handling, and ICSI in 11 cases [53]. In the automated arm, 45 of 70 injected oocytes fertilized (64.3%), 19 of 45 zygotes formed usable blastocysts (42.2%), and embryo transfers resulted in five live births [53]. Although the corresponding descriptive outcomes were higher with manual procedures, the sample was too small for statistical comparison, and some automated steps required direct operator intervention or digital control. These findings demonstrate feasibility rather than superiority and highlight the need for independent replication, larger comparative studies, and transparent reporting of which steps are autonomous, digitally controlled, or manually performed.

In conclusion, the future of ICSI and ART laboratory automation is promising but will require careful navigation of challenges. The next milestones will likely be incremental: an increase in fully automated ICSI cases reported in the literature, development of combined sperm selection-injection devices, and perhaps the first head-to-head clinical trial of automation vs. manual. Each success will pave the way for broader acceptance. If challenges of safety, acceptance, and cost are met, we may witness in the coming decades an IVF lab that looks quite different from today's, perhaps more akin to a high-tech incubation box that runs largely on its own, supervised by clinicians from a control station. Such a lab might function in settings as diverse as a hospital with few specialists in a developing nation. The main ethical objective remains the same despite all of this: assisting patients in having safe, healthy infants. Autonomy is not the objective in and of itself; it is merely a means to that end. Fertility treatments can be made more accurate, reliable, and accessible by carefully combining robotics and digital technologies with human clinical knowledge.

Conclusion

Automated ICSI has rapidly progressed from a theoretical idea to practical clinical application. These days, sophisticated sperm injection activities can be performed by robotic devices and AI models with an accuracy comparable to that of a human embryologist. Normal fertilization rates and healthy live births have already been attained in early clinical applications, demonstrating the effectiveness of the strategy in practice [17]. Despite being relatively new, the technology is advancing quickly. IVF labs are gradually moving toward automated, highly standardized operations thanks to ongoing advancements in micromanipulation, computer vision, and real-time control software.

Instead of replacing human expertise, automation seeks to improve reproductive medicine. In actuality, automated ICSI can serve as a lab utility to lower procedural variance, boost throughput, and alleviate personnel shortages. Embryologists will continue to play crucial roles in direct patient interaction, complex case management, and system oversight. Clinical confidence will inevitably spur wider usage as more evidence demonstrates these systems' reliability and safety. By reducing reliance on highly skilled manual skills and standardizing clinic results, this change could greatly increase access to fertility care.

There are still significant obstacles to overcome, most notably making sure automated platforms can handle the great diversity of clinical samples while upholding strict quality control. To maintain the safety and moral integrity of robotic embryo creation, ethical and regulatory standards must keep up with these technological developments [52]. In this process, interdisciplinary cooperation between engineers, reproductive biologists, physicians, and ethicists will be essential.

In the end, automated ICSI signifies a significant change in assisted reproduction. The first successful live births from robotic injections, AI-guided sperm selection, and real-time computer vision are examples of achievements that point to a future in which human judgment and machine prediction collaborate to improve fertility treatment. A large portion of the IVF lab will probably be automated or semi-automated over the course of the next ten years, resulting in an intelligent system that directly supports the embryologist. This combination can help more patients start families, increase success rates, and reduce procedural risks. ICSI started out as a daring manual method that revolutionized the treatment of infertility [1], but it is now entering a phase when automation and remote connectivity [31] may make IVF much more dependable and accessible. The ethical soundness and efficacy of this technological advancement will be guaranteed by a sustained emphasis on clinical evidence and patient safety.

List of abbreviations

ART	Assisted reproductive technology
AI	Artificial intelligence
ICSI	Intracytoplasmic sperm injection
IVF	In vitro fertilization
ROS2	Robot operating system 2

ROI	Return on Investment
DNA	Deoxyribonucleic Acid.
PGT	Preimplantation genetic testing
NOA	Non-obstructive azoospermia
AR	Augmented reality
DDS	Data distribution service

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No new datasets were generated or analyzed in this review. All information discussed is available in the cited publications.

Consent for Publication

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Conflicts of Interest

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AI Declaration

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