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Artificial Intelligence in Andrology: From Semen Analysis to Image Diagnostics

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Artificial intelligence (AI) in medicine has gained a lot of momentum in the last decades and has been applied to various fields of medicine. Advances in computer science, medical informatics, robotics, and the need for personalized medicine have facilitated the role of AI in modern healthcare. Similarly, as in other fields, AI applications, such as machine learning, artificial neural networks, and deep learning, have shown great potential in andrology and reproductive medicine. AI-based tools are poised to become valuable assets with abilities to support and aid in diagnosing and treating male infertility, and in improving the accuracy of patient care. These automated, AI-based predictions may offer consistency and efficiency in terms of time and cost in infertility research and clinical management. In andrology and reproductive medicine, AI has been used for objective sperm, oocyte, and embryo selection, prediction of surgical outcomes, cost-effective assessment, development of robotic surgery, and clinical decision-making systems. In the future, better integration and implementation of AI into medicine will undoubtedly lead to pioneering evidence-based breakthroughs and the reshaping of andrology and reproductive medicine.

Keywords: Artificial intelligence; Andrology; Deep learning; Diagnostic imaging; Machine learning; Neural networks, computer

INTRODUCTION

1. Definition of artificial intelligence

Artificial intelligence (AI) pertains to the development of computer systems and robots that can perform tasks usually requiring human intelligence or maneuverability [1]. Artificial intelligence is generally defined by the ISO/IEC TR 24028:2020 as the "capability of an engineered system to acquire, process and apply knowledge and skills." The term AI was originally coined by John McCarthy in 1955 at the Dartmouth Summer Research Project on Artificial Intelligence [2]. AI is applied in medicine with the use of algorithms that are developed from data analysis to help in improving healthcare-related outcomes and experiences. Advances in computer science, medical informatics, robotics, and the need for personalized medicine have paved the way for AI to play an integral role in modern healthcare [3]. AI applications are being developed to support physicians in inpatient, outpatient, and surgical settings and to help deliver patient-centered precision medicine. AI has already been applied throughout many medical fields, with up to 12,517 articles published since the 2000s on the health care of patients, and only a few,

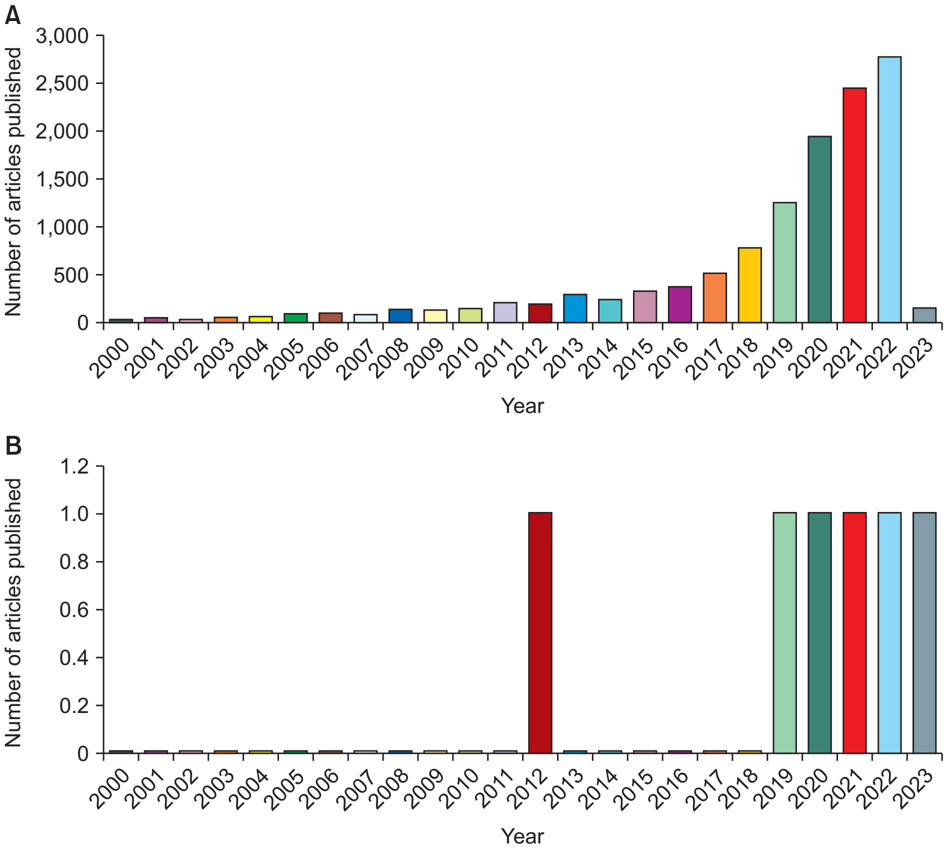


Fig. 1. Number of articles on artificial intelligence and health care (A), and on artificial intelligence and andrology (B) published since the 2000s (source: Scopus; accessed on January 2023).

recently, in the field of andrology (Fig. 1).

AI, in which machines or computerized devices acquire the ability to learn and display intelligence, continues to develop rapidly. AI applications, such as machine learning (ML), artificial neural networks (ANN), and deep learning (DL), show great potential in reproductive medicine. Its advances are fueled by the growing amount of data available in this field. The analysis of big data using the various branches of AI, such as ML, ANN, DL, robotics, natural language processing, etc., yields valuable and practical applications in the different aspects of reproduction, including sperm classification, oocyte, and embryo selection, prediction of outcomes, robotic surgery, clinical decision systems, cost-effectiveness, and sperm selection [4,5]. Many recent reviews have highlighted the uses and implementations of AI in reproductive medicine and fertility treatment [4,6-8]. In andrology, AI is applied in automation for evaluating sperm motility and morphology. AI can also serve as a support system in making medical decisions via supervised machine learning (sML) algorithms, which are ML-based prediction models.

AI-based prediction models and automated semen analysis are set to become valuable tools that could support and aid in diagnosing and treating male infertility and improve the accuracy of patient care. These automated, AI-based predictions could offer consistency and efficiency in terms of time and cost in infertility research and clinical management [9].

ARTIFICIAL INTELLIGENCE: MACHINE LEARNING, NEURAL NETWORK AND DEEP LEARNING

1. Machine learning

ML is one of the subfields of AI, which detects the underlying links between inputs and outputs to create an automated algorithm [10]. To develop ML, large datasets are critical for training the algorithm to find complicated patterns and associations faster than traditional statistical models that usually focus only on a small number of variables, with better or, at least, comparable accuracy [11,12]. Differences between data analysis and statistical analysis are shown in Table 1 [13].

The principle in ML modeling consists of three pro-

Table 1. Differences between Big Data (Data Science) and Statistics [13]

Domain	Data science	Statistics
Definition	Process of screening, meticulous inspection, presentation, and displaying of simple reports of big data sets to non-technical people	Science-based on the collection and mathematical interpretation of quantitative data
Process	The problems are tackled by a modeling process. The latter focuses on the predictive accuracy of the model. The data scientist compares the predictive accuracy of different machine learning methods and selects the most accurate model	Statisticians begin with a simple model and the data is tested to find out if it is consistent with the assumption of that model. The analysis is completed when the statistician is sure that all assumptions have been tested and none of them are violated
Quantifying uncertainty	Rarely applied in machine learning	Extensively applied
Data Size and Nature	A huge database usually cannot be stored on one PC and retrieved from a data warehouse	Usually, small dataset
	It is considered an information asset with high volume, velocity, and variety, that needs to be transformed into value [1,2]	Could be retrospective (historical) or prospective
Data Collection	The precision of data collection and source is not a primary concern	The precision of data collection and its quality is a major concern
Nature of the studied problems	Related to making predictions and optimizing the search of large databases	Draws a conclusion about what causes what, based on the quantification of uncertainty
Human resources	Usually, engineers	Usually, mathematicians
Tools	Learning Example instance	-

cesses: data set preparation, model selection with data fit, and model evaluation or validation [12]. In ML, there are four commonly used learning methods: supervised, unsupervised, semi-supervised, and reinforcement learning [10,12]. Each technique can be used to solve different tasks. For example, supervised ML is mainly used for pattern recognition, while unsupervised ML is more beneficial for clustering [12].

In recent years, AI and ML have been extensively studied to assist physicians in diagnostic and therapeutic approaches [14-16].

The distinguished feature of ML algorithms has also led to its applications in andrology, both for male infertility [14,15,17]. There are several instances of ML application in andrology. Supervised ML is used to develop a scoring calculator to identify patients with Klinefelter syndrome among azoospermic patients [18]. A random forest model has also been designed to predict improvement in post-varicocelectomy sperm analysis with superior performance compared to traditional logistic regression [9]. Other than that, several studies have also shown the benefit of ML for automated sperm classification, sperm selection, fertility prediction, and prediction of *in vitro* fertilization (IVF) outcomes [5,19,20].

2. Neural network and deep learning

Neural networks are a subtype of AI mainly inspired by the work of the human brain, which mimics a set of algorithms comprised of four key components: inputs, weights, bias or threshold, and output. The neural network will use a training dataset, then it recognizes the patterns in these data sets and formulates algorithms that can be used to predict the output of a testing data set. The basic operation is given a weight for each input and set a threshold to decide whether the output is true or false. For instance, training data sets of thousands or millions of hand-written data sets are fed into the neural network to recognize hand-written digits. The neural network will recognize the pattern and develop several algorithms that can be used if a small series of hand-written digits are fed. The neural network will precisely identify these digits. Hence, the basic structure of a neural network is an input (data to be analyzed), hidden layers (series of nodes/algorithms which process the input and produce an output of true or false to the next layer), and the output (the final output whether to accept or reject the question).

In contrast, DL is an extensive neural network with multiple hidden layers, hence the name "deep." It refers to the depth of layers in a neural network that, if they consist of more than 3 layers inclusive of inputs and outputs, can be considered a DL algorithm [21]. Consequently, DL or deep neural networks deal with complex and sophisticated problems compared to standard neural networks, for instance, image and voice recognition. Deep neural networks are feed-forward flowing in one direction from input to output. DL automates much of the process's feature extraction, eliminates some of the manual human intervention required, and enables the use of large data sets, earning the title of "scalable machine learning" [22].

3. Decision tree and random forest

The mechanisms by which a ML algorithm works could generally be divided into three different classes, namely supervised, unsupervised, and reinforcement learning [10]. In supervised learning, the input contains the data and the desired result, and the algorithm will detect the relationship, so it can predict the outcome if raw data is provided. A real example of supervised learning is when smartphones are trained to know fingerprints, so they can later identify the correct fingerprint and reject others. However, in unsupervised learning, only the input data is provided. Thus, the algorithm works on its own to discover information such as a pattern/structure in a set of uncategorized data (clustering) or relationships between variables in larger databases (association).

A decision tree is a supervised learning algorithm that diagrammatically solves a question based on specific attributes [23]. Its shape is an inverted tree with the top/starting position being the root (root node), and the branches are the outcome of a decision (leaf nodes). A decision goes through several levels if a particular characteristic is present until a final answer is reached. A random forest algorithm is a collection of decision trees. Instead of using a single decision tree to answer a question, multiple trees are randomly selected. The final question is answered based on the most selected answers by individual trees to yield more accurate results [23].

4. Radiomics

Radiomics is a medical approach that aims to extract a large number of quantitative features from medical images using data characterization algorithms. It can be done manually, semi-automatically, or fully automatically using AI. The main tasks performed by radiomics software are quantification tasks, including region segmentation or performing automated measurements. The overall imaging and evaluation by radiomics not only present the characteristics of the lesion (e.g., tumor), such as volume, shape, surface area, density, intensity-based features, texture, localization, and elongation but also indicates its surrounding microenvironment. This makes it possible to guide the targeted agents before a procedure or to be aligned with a biopsy to maximize the clinical implications [24].

Radiomics can be used for many imaging modalities, including radiography, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) studies. Radiomics is based on improvements in quantitative image software analysis, applying automated, or semi-automated high-throughput extraction of substantial amounts of quantitative features of medical images. After stratification processes, the obtained digital dataset can be linked to additional genomic or proteomics data, and histopathologic markers obtained by other novel radiographic techniques. Compared to traditional imaging, radiomics provides quantitative information on meaningful biological characteristics and the application of DL, which sheds light on the complete automation imaging diagnosis [25].

Radiomics can increase diagnostic accuracy, prognosis assessment, and treatment response prediction, especially in combination with clinical, biochemical, and genetic data. Various imaging studies in different fields have been published, highlighting the potential of radiomics to enhance clinical decision-making. This technique has been used in a variety of fields in the health care system such as in brain tumor/pathology [26,27], colorectal carcinoma [28-31], coronary heart disease [32,33], and diabetes [34].

Still, it could potentially be applied in the field of male infertility, e.g., characterization of the testicular parenchyma with objective and reliable quantitative parameters using testicular ultrasound. The technique allows the evaluation of testicular spermatogenesis and hypothalamic-pituitary axis effects during image segmentation, image preprocessing, and texture features extraction image analysis. Image analyses were performed using Biolab [35].

One of the most critical problems in male infertility is assessing the normal or pathological status of the different portions of the seminal tract (mainly epididymides, prostate, and seminal vesicles) for their possible implications on semen quality (motility, leukocytospermia, sperm DNA fragmentation [SDF], reactive oxygen species, etc.). In the present era, where non-invasive diagnostic procedures are almost mandatory; radiomics might provide precious information otherwise unachievable. However, the field faces several significant challenges, mainly due to various technical factors influencing the extracted radiomics characteristics [36].

MRI plays a role in predicting testicular sperm extraction (TESE) in men with non-obstructive azoospermia (NOA). Karakus and Ozyurt [37] found choline and creatine peaks to be the most important metabolites obtained by spectroscopic examination of five NOA patients with mTESE sperm retrieval. The testicular normalized apparent diffusion coefficient (ADC), obtained using a conventional monoexponential model, is a parameter that reflects the diffusion movement of water. The latter mainly correlates with tissue cell density and extracellular space [38]. The restriction in water diffusion in the testis arises from the seminiferous tubules, compact connective tissue, and interstitial tissue that contain Leydig cells, blood, and lymphatic vessels. Tsili et al. [39] found that the ADC is an additional diagnostic tool that was most useful for identifying NOA patients who have foci of spermatogenesis in a study of 20 NOA patients. Patients with a Johnsen score (JS) ≥8 have a significantly higher mean ADC compared to patients with a lower JS.

ARTIFICIAL INTELLIGENCE IN ANDROLOGY RESEARCH AND LABORATORY

1. Computer-assisted semen analysis systems

Clinical decision-making can be influenced by the subjectivity of the evaluation of microscopic sperm parameters (concentration, motility, and morphology) as well as by human error and intra-operator variability. All of this factors can affect the accuracy of the results. In the past 25 years, the classic semen analysis was flanked by computer-assisted semen analysis (CASA) to provide reliable and less subjective results [40]. CASA systems are automated instruments that use cameras and software to analyze the microscopic findings and give sperm parameter results [41]. CASA systems may be used to evaluate sperm kinematic parameters and hyperactivation, as described in the 2021 WHO lab manual for examining and processing human semen (WHO, 2021). Furthermore, the use of the CASA system is more objective and reproducible than the assessment of motility performed by the operator. Additionally, it is superior for assessing sperm kinematic parameters, which are predictors of IVF together with sperm count, compared to manual methods [42].

Some uncertainties that are still not clarified have unfortunately prevented its routine use. A systematic review showed a high correlation of sperm concentration and motility between manual and CASA-based semen analysis, but only for samples with average sperm concentrations (15–60 million/mL), with residual variability depending on the tool used [41]. Unfortunately, sperm morphology remains challenging to assess with CASA due to the high number of different types of abnormalities and the various classification systems [41]. In the future, artificial intelligence optical microscopic (AIOM) technologies could be helpful in also overcoming this problem, helping the CASA systems to "learn" how to classify sperm morphology correctly. Nowadays, DL networks can have over 100 layers and billions of nodes, far away from the first VGG-16 algorithm technologies. However, further studies are needed.

2. Artificial intelligence in semen analysis

Semen analysis is considered a fundamental and essential diagnostic test for male infertility. However, most sperm parameters are calculated manually, which is a time-consuming process, especially in the context of a busy lab. Nonetheless, it requires a lengthy training process, is highly subjective, and is prone to intra-observer variability and human error [41]. Obstacles, such as those mentioned above, could be overcome using AI.

An automated model of AI was developed using microscopic optical technology for sperm concentration, motility, and seminal pH assessment, and the results were compared with manual assessment. A high degree of correlation in concentration, progressive motility, and progressively motile sperm concentration was observed between the automated AI model and the manual analysis [43,44]. However, some other studies have found a poor correlation between AI analysis by other similar devices and manual semen analysis [45]. Further limitations of studies focusing on AI in the context of assisted reproduction and the prediction of sperm motility include having small datasets and an unclear evaluation procedure [46].

3. Artificial intelligence and sperm DNA fragmentation

Among the available methods of SDF measurement, Comet assay and sperm chromatin dispersion test do not use flow cytometry in their protocol [47]. Hence, the evaluation of SDF with these techniques depends on a manual measurement under the microscope, which is highly subjective [48]. AI could potentially improve these techniques by making them more objective.

Several studies have used AI to quantify the amount of DNA damage or alternative markers, particularly in cancer cases [49-51].

A disadvantage of the Comet assay is that it lacks standard protocols or a cut-off line [52]. The high accuracy of this method was demonstrated and later applied to a DL-based system for SDF evaluation. A convolutional neural network (CNN) was used to predict the single-cell DNA fragmentation index in semen. This method allows for selecting sperm with the highest DNA integrity [53].

4. Artificial intelligence in capacitation scores and sperm hyperactivation

AI can be used to detect sperm capacitation as a complementary test for sperm function. For example, CASA, through specific gating methods, can detect kinematic properties of sperm motility, including sperm hyperactivation. To improve the CASA system, AI was used to classify sperm motility patterns occurring during capacitation by creating a training set of different motility tracks based on mice sperm models and loading them into the CASA machine. The CASA then created support vector machine equations that accurately detect motility patterns specific for capacitation [54]. AI was also used to predict fertilization during IVF in normozoospermic men by combining sperm parameters, such as membrane potential, motility of hyperactivated spermatozoa, and intratesticular sperm pH [20]. However, more research is needed to investigate the ability of AI to predict male fertility potential and the success of IVF/intra-cytoplasmic sperm injection (ICSI) by incorporating sperm capacitation with other semen parameters in different patient groups [20].

5. Artificial intelligence and sperm selection for assisted reproductive techniques

Although assisted reproductive techniques (ART) use single spermatozoa to fertilize oocytes, there is still no universally accepted system for selecting the functionally best male gametes [55]. An ideal method for sperm selection to be used for ART should be non-invasive and cost-effective, should allow the identification of high-quality sperm, and obtain a high and reproducible success rate in terms of pregnancy and birth rates [56]. Similarly, ML can improve the information available to physicians for better decision-making in selecting the best spermatozoon. The ability of ML algorithms to process large amounts of data offers the potential to correlate sperm quality metrics, such as morphology, DNA integrity, protein expression, or chromosomal aneuploidy at the level of an individual sperm [5].

Several steps must be undertaken to realize a clinical ML algorithm for sperm selection [20,57]. The solution to this problem is offered by the development of advanced imaging methods. A high-speed off-axis holographic system [58] or automatic magnification switching method [59] can be useful for obtaining high-resolution images of moving spermatozoa [5].

ANN are mathematical models based on human neural networks [60]. A multilayer perceptron (MLP) network (a type of ANN with an architecture of several layers of neurons, i.e., perceptrons) was used to predict sperm concentration and motility from questionnaire-based lifestyle and environmental factors. These predictions could help diagnose seminal disorders early or when selecting potential donor candidates [61]. Lifestyle and environmental factors input could also be used to predict semen quality by applying other AI techniques such as support vector machine (SVM) and particle swarm optimization on fertility parameters [62] or fuzzy radial basis functional neural network [63].

A newer approach to predicting fertility in men is to use the sperm whale algorithm optimization method along with ANN (MLP network) to tackle optimization issues via its adaptable search mechanisms that can yield more than 99.96% accuracy in predicting men's fertility status [64]. Another ANN-based study used data from eleven survey questions to generate an initial assessment and prediction tool of semen profile and sperm concentration for evaluating male infertility or potential sperm donors [65]. The back propagation neural network model (a type of ANN) was used with various categories of semen parameters as inputs to predict parameters, such as total protein, fructose, zinc content, and glucosidase activity in seminal plasma. These biochemical marker predictions could potentially assist in diagnosing male infertility in ART centers [66].

The use of ML is rapidly extending into numerous biomedical applications. The ability of ML to process and analyze large amounts of data, particularly image data, will greatly assist in sperm selection. Embryologists, using properly trained ML algorithms, could improve and standardize sperm selection, thereby improving the ART success rate [5].

6. Big data in andrology

Big data refers to a large data set in terms of volume, speed, and variety whose computation requires specific technologies and methods to derive predictive values. Therefore, processing these data requires sophisticated computational methods to manage a large amount of data, establish links between the various phenomena, and predict future outcomes. Big data can be used for numerous purposes, including in andrology.

AI has the potential to classify sperm motility [54] and morphology [67] as well as predict biochemical markers, e.g., zinc [66], leptin [68], and/or chromosomal abnormalities [69]. It also considers the role of environmental and/or lifestyle factors that can affect sperm quality [61]. AI methods can take into account all this amount of data and predict their effect on fertility [70]. These predictive models can therefore help screen infertile patients and early identification of men with subfertility who could benefit from an intervention to prevent their fertility from decreasing over time [15].

7. Artificial intelligence for medical records and data meaning

Healthcare services are constantly growing, expanding relentlessly with innovative modalities. This created a need for comparable data management systems to cope with such a complex realm. Many researchers have advocated the implementation of AI and ML using many of the stored electronic medical record (EMR) data, which encompass all patients' details spanning from administrative functionalities to precise medically related whereabouts. AI offers the benefit of processing and analyzing tremendously larger data and enables a higher precision in classifying disease states [71]. One of the challenges faced with AI is the sensitivity of the handled material with privacy concerns. Hence, simultaneous data security is mandatory [72]. Structured health-related data, being the set of information recorded based on a fixed template, is considered the most commonly used data structure for AI use, unlike unstructured data with text and images, which is regarded as unpredictable, and hence may offer limitations towards ML [71]. Such unstructured data sets are typically used by natural language processing (NLP) when extracting and processing meaningful information from unstructured data sets and transforming them into structured, analyzable data [73]. It is believed that AI-integrated hospitals, also known as smart hospitals, are more efficient and cost-reducing when it comes to patient experience and operational activity [74].

8. Artificial intelligence in animal andrological studies

Considering the employment of AI in animal andrological studies, CASA has enabled significant potential in sperm evaluation of animal models, namely pigs and bulls. CASA has been claimed to contribute to a more objective and standardized assessment of spermatozoa and, in turn, of the overall male fertility status [75]. An automated, quantitative method aided by SVM in terms of supervised ML was the first AI model developed to assess and classify five motility patterns of mouse spermatozoa, captured and evaluated by CASA. This appeared effective even in a large and heterogeneous population, such as spermatozoa featuring severe motility defects due to mutations [76]. AI further plays an essential role as a clinical diagnostic tool aiming to predict sperm parameters and reproductive outcomes. ANNs have been trained to accurately estimate the impact of varicocele on rat fertility as well as post-thaw motility before freezing in bulls [77]. Recently, a computerized staging system of spermatogenesis in mice enabled the evaluation of the quality of the spermatogenic process and the detection of developmental defects facilitating a less laborious assessment [78].

ARTIFICIAL INTELLIGENCE IN CLINICAL ANDROLOGY

1. Diagnostic trees for andrological evaluation and management

Decision trees and random forests are powerful algorithms useful in classification and forecasting. A decision tree includes various nodes, consisting of several tests to predict the class label, and is computed to obtain the probability [61]. Andrologists and other physicians prefer decision trees as a white box model. This is easier to interpret and understand than different algorithms, such as neural networks. Furthermore, people can improve the performance of this model by combining it with other decision-making techniques [4].

Current CASA systems [54] can analyze motility percentage, kinetic parameters, and subpopulations of human spermatozoa with an overall accuracy of 89.92% and predict chromosomal abnormalities. Data including height, total testicular volume, follicle-stimulating hormone, luteinizing hormone, total testosterone, and ejaculate volume were combined to predict chromosomal abnormalities more than 95% accurately. In addition, environmental factors and lifestyle data can also support predictions of sperm quality by specific neural networks [61].

In 2014, Sahoo and Kumar [62] used five AI techniques and eight feature selection methods to increase accuracy in predicting male fertility rates. In particular, selecting features contributes to improved performance, data visualization, size reduction, and effective noise removal.

AI systems can predict fertility potential and successful sperm retrieval leading to a paradigm shift in the treatment of infertile males [28]. AI algorithms may soon be fully used in computing sperm retrieval for ART optimization .

A combination of SVM equations (a type of supervised ML) and a multiclass decision tree was used to develop the human CASA nova model that classifies sperm motility patterns reflecting those of washed human spermatozoa [54]. AI technology is also involved in the smartphone-based home assessment of sperm parameters. Using a combination of AI image recognition algorithm and cloud computing technology, sperm motility-related parameters (such as motility and concentration of motile spermatozoa) were accurately measured by a smartphone-based home sperm motility measurement system composed of a microscope and microfluidic modules adaptable to different smartphone models [79]. This form of motility analysis could potentially be used in assessing sperm quality, detecting infertility, and monitoring its treatment [79]. Another study showed how the analysis of sperm motility parameters could be automated using DL, CNN, and multimodal data analysis to examine sperm recordings and predict motility variables such as progressive, nonprogressive, and immotile spermatozoa [19].

Sperm morphology imaging can be used to identify spermatozoa with normal shapes. The SVM approach was used to help with sperm morphology analysis by classifying sperm images using one-dimensional waveforms and gray-level characteristics to achieve 88.9% accuracy from 10 training samples and test samples of 160 spermatozoa (80 normal and 80 abnormal) [80]. Principal component analysis was used to perform feature extraction for sperm image recognition and the k-nearest neighbor classification algorithm (a simple but effective, lazy-learning ML algorithm), which provided a healthy diagnostic accuracy of 95.7% from 10 training samples and 160 test samples (80 normal+80 abnormal) [81]. The SVM approach has also been used in automating the analysis of sperm morphology classification and in selecting spermatozoa for use in IVF techniques [82]. Human spermatozoa could also be classified using DL methods. For example, CNN could classify spermatozoa into WHO categories based on head shape using freely available sperm head datasets to achieve a 94% true positivity rate [83].

2. Natural language processing

NLP is part of AI. It is the knowledge that focuses on building a machine or computer's ability to understand human language rather than equations or programs [73,84]. NLP was developed in the 1950s at the confluence of linguistics and AI [85]. Its application in medicine is crucial in analyzing large-scale data, such as physicians' narrative writings in the EMR [86].

This technology enables machines to extract classifications, such as International Classification of Diseases (ICD) diagnosis codes, from unstructured data, hence enabling physicians to write more naturally rather than having to input specific formatted text or numbers for data analysis [84]. As with other AI, NLP is a self-learning tool that will increase the utility of its predictions along with the growing number of datasets. This, therefore, enables NLP to become more “natural” and representative of the patient population [84]. NLP enables raw data extraction to structured data, which ML models will then analyze. Furthermore, NPL using CNN, recurrent neural network (RNN), or as the superior algorithm, bidirectional RNN processing algorithm was shown to help optimize data extraction processes for reduced disease-coding errors in different specialties in medicine [86].

In reproductive medicine, NLP has been studied and used for research purposes, sperm classification, oocyte selection, embryo selection, clinical decision-making systems, cost-effective assessment, surgery outcome prediction, and robotic surgery development [4]. For example, Osadchiy et al. [87] used NLP in social media to study patients' perceptions of hypogonadism and its treatments. With more research to come, the application of AI, particularly NLP, will help physicians and patients with obtaining a better diagnosis and treatment of andrological cases.

ARTIFICIAL INTELLIGENCE IN THE SURGICAL MANAGEMENT OF ANDROLOGICAL DISEASES

1. Augmented reality

Augmented reality (AR) assisted surgery is based on the overlay of medical images on the surgical field during a surgical procedure, particularly in minimally invasive surgery [88]. AR has several applications, including surgical planning, guidance, and navigation. It also has a role in education and surgical training [89].

Few studies have evaluated the use of AR during surgery for andrological diseases. Interestingly, Porpiglia et al. [90] published a prospective study including patients with localized prostate cancer who underwent AR-robotic assisted radical prostatectomy (AR-RARP). The authors concluded that AR-enabled the surgeon to tailor the surgical procedure to the specific anatomy and assist in locating the cancer. However, further research is mandatory to confirm these findings. Another recent study described using AR to guide the surgeon to the stenosis area during endoscopic surgery for urethral or ureteral strictures [91]. Potential perspectives of AR could be its implementation in microsurgical testicular sperm extraction (micro-TESE) to guide navigation and improve the detection of functional seminiferous tubules.

2. Robotic fertility surgery

Robotic fertility surgery for male infertility has several potential practical benefits, including reduced tremor, three-dimensional visualization, and decreased need for skilled surgical assistance [92]. The first robotic male infertility microsurgery was studied in an animal model in 2004 [93]. Since then, a number of small retrospective studies have described the use of robotic-assisted reversal of vasectomy with clinical outcomes similar to that of the traditional microsurgical approach. However, these studies have reported a reduction in operative time [92,94,95].

Several robotic-assisted varicocelectomy studies were also reported with the advantage of excellent visualization and potential reduction of physiological hand tremors. Still, these studies are limited by their retrospective nature, single-institution experience, and lack of comparison groups [95]. The studies of robotic-assisted micro-denervation of the spermatic cord were similar to robotic-assisted varicocelectomy and had the advantage of excellent visualization but did not show better results than the conventional microsurgical approach [95]. One robotic-assisted micro-TESE report shows the safety and effectiveness of this procedure but the patient characteristics, operative time, and sperm retrieval rates were not reported [96]. Additional studies are needed to assess the robotic micro-TESE and determine its added value [95]. Although robotic fertility surgery procedures are evolving, no substantial clinical evidence suggests improved outcomes [96,97]. Parekattil and Gudeloglu performed robotic TESE procedures without any complications. They stressed the safety and the feasibility of the approach in surgical sperm retrieval and described the technique as being marginally easier in terms of tissue handling and dissection compared to micro-TESE [98]. However, sperm retrieval rate and immediate and long-term complications were not reported. In the future, more rigorous studies are needed to compare robotic fertility surgery with conventional microsurgery and evaluate outcomes and cost-effectiveness.

3. Microsurgical surgery

While it has not been a century since the emergence of microsurgery, its rapid progress has made it usable in numerous surgeries. In the urological field, microsurgical techniques have been used in many procedures since the mid-1970s, paving the way for improvement in the development of further procedures. It is believed that in the 1980s, the Vasovasostomy Working Group, chaired by Belker et al. [99], reported the results of more than 1,400 microsurgical vasectomy reversals, sparking interest in urological microsurgery. In andrology, microsurgical techniques have been applied to various surgical problems, including treating male infertility. Vasectomy reversal, vasoepididymostomy for obstructive azoospermia, testicular autotransplantation for high undescended testis, penile revascularization, varicocele treatment, and microdissection TESE are some of these procedures. The application of microsurgery in urology is likely to become widespread with the increasing use of the DaVinci surgical robot, especially for vasectomy reversal and orchialgia treatment [100,101].

Krenz et al. [18] evaluated the potential of using sML algorithms to differentiate between azoospermic patients with or without Klinefelter syndrome (47, XXY karyotype) to improve the diagnosis rate and treatment. A prior study employed logistic regression to identify possible predictors and develop an ML neural network to detect chromosomal abnormalities in azoospermic patients [69]. A retrospective cohort study showed that an ML model could be used to accurately predict (area under the curve=0.8) the presence/absence of sperm by TESE in patients with non-obstructive azoospermia [102].

As we move further ahead into the future, new procedures are likely to emerge with greater technological advances. With the development of the growing urological microsurgery cohort and technological advancements, the future of microsurgery is set to expand further.

ARTIFICIAL INTELLIGENCE IN ANDROLOGICAL RADIOLOGY

1. Ultrasound testis, epididymis, prostate, and seminal vesicle

AI in andrological ultrasonography has been mainly applied in prostate cancer studies using transrectal prostate ultrasound. Prostate cancer' diagnosis, treatment, and monitoring require accurate prostate volumes and boundaries segmentation. In this respect, ultrasonography is inexpensive, does not emit radiation, and allows for real-time monitoring. However, it has a low signal-to-noise ratio and speckle noise that complicates the automatic segmentation of ultrasound images [103].

To improve the diagnostic power of prostate ultrasonography, some studies have used AI to achieve automatic segmentation of transrectal ultrasound images to facilitate the diagnosis of cancer, image-guided surgical planning, and even therapy planning [4,104-108].

In contrast, very few studies, to date, have evaluated the application of AI on testicular ultrasonography. A study investigated the use of an SVM classification system on testicular contrast-enhanced ultrasound images to classify 10 benign and 10 malignant lesions, demonstrating that this method allows for the correct identification of the disease in 100% of cases. Despite the low number of cases, this study suggests that AI may play a role in testis-sparing surgery [109], a therapeutic approach that is increasingly used [110]. Another study, using a radiomics approach, evaluated the usefulness of 44 textural features derived from the echogenicity of testicular images. Of these, 13 correlated with semen parameters resulting in predictive sperm concentration, total count, progressive and total motility, and morphology. Furthermore, many of these features also had a predictive value on gonadotropin levels but not testosterone levels. The authors of this pilot study suggested the possibility of predicting the gonadal function of patients using a subjective evaluation (testicular echogenicity) and turning it into an objective evaluation based on numerical values [35]. In contrast, no studies to date have evaluated the use of AI in ultrasound imaging of inflammation of the epididymis and seminal vesicles.

2. Artificial intelligence, computed tomography, and magnetic resonance imaging

Applications of AI in brain MRI scans for Alzheimer's, Parkinson's, and attention deficit hyperactivity disorder (ADHD) are established and help predict the diagnosis and stage of disease [111]. In urology, AI is combined with MRI to create algorithms that can assist the radiologist with lesion detection and classification to improve diagnostic performance and avoid unnecessary biopsies.

In CT image reconstruction, AI may offer the possibility of a further dose reduction through improved image quality [112]. Similar to MRI, the methods used in CT image reconstruction are ML and DL [112]. The current international literature offers very limited data on the application of AI in andrological radiology, but the horizon perspectives of such applications are very promising. Some examples of AI applications in CT image reconstruction include abdominal and pelvic imaging. More incidental findings are identified with the rapid growth in medical imaging, especially CT. AI may assist in the characterization of these lesions as benign or malignant, prioritizing in this way the treatment and the follow-up evaluation of these lesions [113]. Nevertheless, further computational advances are still needed to use AI algorithms in CT image reconstruction in clinical practice.

Some studies have found a better detection rate by AI. In terms of predicting clinically significant cancer, Winkel et al. [114] compared the results of 4 supervised ML models (namely gradient boosting machines, neural networks, random forest, and SVM) with that of Prostate Imaging Reporting and Data System, version 2.1 (PI-RADS v2.1) assessment scores as determined by expert radiologists. The PI-RADS v2.1 is used to standardize the multi-parametric MRI reporting of the prostate. They found that the assessment by ML models outperformed that of the established PI-RADS v2.1 . Others, such as Sanford et al. [115], reported similar results in detection rates of malignant lesions between AI and qualitative evaluation by an expert radiologist. They created a CNN model of DL and compared it with previous radiology advice with moderate agreement. As ML continues to develop, and as more information is fed into the databases, AI continues to improve. Thus, it is hoped that we may eventually transition to AI-assisted precision medicine in the future.

3. Shear wave elastography

Shear wave elastography (SWE) is a medical imaging modality that uses ultrasound or MRI tracking technology to display elastic images in real-time. The technique allows the non-invasive assessment of tissue mechanical properties. In particular, it can give indications of the stiffness of the tissue by using various colors [116]. Ultrasound-based SWE is widely used in the diagnosis of breast and thyroid cancers, lymph node diseases, and other surface organ diseases. It is a valuable addition to the uses of conventional ultrasound [117].

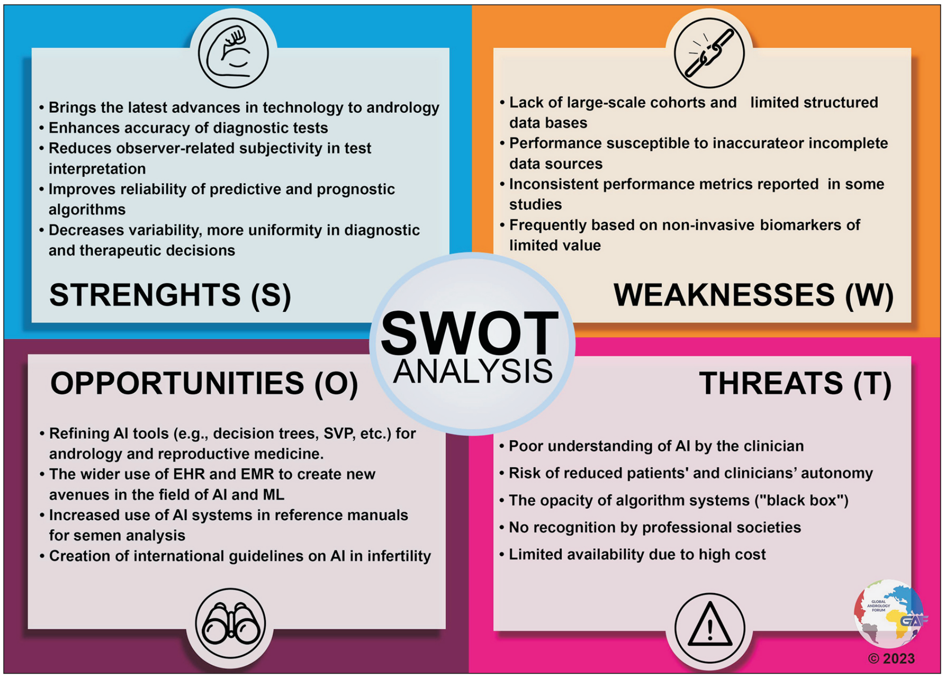
Ultrasound-based SWE was also used to detect and quantify testicular stiffness in cases of varicocele [118], undescended testes [119], and testicular microlithiasis [120]. More recently, the technique was used to study the relationship between testicular stiffness and male infertility with satisfactory preliminary results [121,122]. In 2022, Cui et al. [30] conducted a cross-sectional study on 1,116 consecutive patients undergoing IVF/ICSI treatment. They concluded that ultrasound-based SWE was an effective supplement to differentiate between obstructive and non-obstructive azoospermia and also between severe oligozoospermia and non-obstructive azoospermia from other groups. More studies are needed to evaluate further and perfect this new AI-based modality.

LIMITATIONS AND CHALLENGES OF ARTIFICIAL INTELLIGENCE IN ANDROLOGY

AI has been established in many areas of technology and industry, but its use in medicine is still early [67,123]. The currently available models are limited and, therefore, have to be developed for each specific application, in this instance, andrology. Although the utilization of AI in andrology is promising, it faces several challenges to overcome. Data Science does not focus on overcoming uncertainty. Also, data sources are often inaccurate or incomplete. Second, there are no standardized protocols to run the limited number of AI models that are currently available. In addition, the approval of AI for medical applications is not standardized across governing bodies [124]. Third, AI may limit the autonomy of patient care. Currently, most clinicians value a combination of patient-centric and evidence-based decision-making. Nevertheless, a recent survey of German healthcare providers demonstrates a willingness to adopt AI technology in medical care [125]. Fourth, the cost of developing and validating an AI model in andrology is a significant challenge due to the lack of widely available funding [126]. This is particularly true given the relatively small size of the andrology specialty compared to other areas of medicine. Finally, ethical concerns are raised regarding the applicability of AI models to all patients, especially when significant individual variations are likely [127]. Generally, an ethical dilemma that can arise with the introduction of novel and expensive tools is the allocation of payment for and beneficiaries of this technology, given the disparity of insurance and financial resources across the medical landscape in many countries [126].

SWOT ANALYSIS ON THE USE OF ARTIFICIAL INTELLIGENCE IN ANDROLOGY

The strengths and weaknesses of AI in andrology are summarized through a SWOT analysis (SWOT stands for strengths [S], weaknesses [W], opportunities [O],



STRENGHTS (S)

- Brings the latest advances in technology to andrology
- Enhances accuracy of diagnostic tests
- Reduces observer-related subjectivity in test interpretation
- Improves reliability of predictive and prognostic algorithms
- Decreases variability, more uniformity in diagnostic and therapeutic decisions

WEAKNESSES (W)

- Lack of large-scale cohorts and limited structured data bases
- Performance susceptible to inaccurateor incomplete data sources
- Inconsistent performance metrics reported in some studies
- Frequently based on non-invasive biomarkers of limited value

SWOT ANALYSIS

OPPORTUNITIES (O)

- Refining AI tools (e.g., decision trees, SVP, etc.) for andrology and reproductive medicine.
- The wider use of EHR and EMR to create new avenues in the field of AI and ML
- Increased use of AI systems in reference manuals for semen analysis
- Creation of international guidelines on AI in infertility

THREATS (T)

- Poor understanding of AI by the clinician
- Risk of reduced patients' and clinicians' autonomy
- The opacity of algorithm systems ("black box")
- No recognition by professional societies
- Limited availability due to high cost

Fig. 2. Strengths, Weaknesses, Opportunities, and Threats (SWOT) analysis.

and threats [T]) (Fig. 2). The "strengths" (S) and "weaknesses" (W) are related to the internal environment. At the same time, the "opportunities" (O) and "threats" (T) are all external factors that can respectively enhance or hinder the development of AI in andrology [85].

CONCLUDING REMARKS AND FUTURE DIRECTIONS OF ARTIFICIAL INTELLIGENCE IN ANDROLOGY

1. Summary and conclusions

AI applications can be utilized in several important fields [4,14,15,19,35,43,54,69,109,128,129]. A summary of AI applications in andrology is provided in Table 2 [9,43,44,57,61,63,79,82,130-141].

2. Significant big data analytics

AI can create high-quality evidence by collecting data in a variety of ways. It can create an interconnected network of patient data from around the world. Additionally, AI has the potential to change the way medicine is practiced through the combination of medical data from EMRs, medical images, lab tests, genetic information, and medical records. This will be reflected in many benefits for the healthcare sector. These include:

- Stronger evidence for guidelines to be used by the scientific bodies and societies;
- More data and information for national and international healthcare centers;
- Better evidence for high-quality research;
- Health services could leverage AI for adequate use of electronic health record data. It can predict data heterogeneity across hospitals and practices, verify outliers, perform clinical tests on data, unify patient representation, improve future models that predict diagnostic tests, and analyses, and create transparency with a benchmark for the analysis of the services provided.

3. The diagnostic decision system

AI can help clinicians make better clinical decisions based on patient clinical data using dynamic programming, reinforcement learning techniques, and massive amounts of data to build models. The models can be continuously optimized by comparing the diagnoses of expert healthcare professionals and ultimately be applied to AI-assisted diagnosis. Through this field of AI, many advantages can be achieved. These include:

- Achieve better and more specific diagnoses;
- Support the training of personnel working in health services;
- Reduce the cost of health care;
- Compensate for international shortages of medical personnel;

Table 2. Summary of various artificial intelligence (AI) technologies in andrology[a]

AI technologies in andrology	Purpose	Company name	Article type: Research/ Method/ Review	Supporting papers
a) Currently used in clinical care				
Smartphone sperm analysis	Sperm motility	Yo test	Research	
Chromatographic immunoassay technology	Sperm analysis	SpermCheck	Research	
Chromatographic immunoassay technology	Sperm analysis	Fertell	Research	
Centrifugal motion to determine sperm cell count	Sperm analysis	Trak Male Fertility Testing System	Research	
Smartphone sperm analysis	Concentration and motility	Men's Loupe	Research	
Colorimetric dye technology	Motility	Swim Count Sperm Quality	Review	
Colorimetric dye technology	Motility	FertilitySCORE	Review	
Smartphone sperm analysis	Concentration and motility	SEEM® (Recruit Lifestyle Co., Ltd.)	Research	
Smartphone sperm analysis	Sperm count	ExSeed Home Sperm test	N/A	N/A
Artificial intelligence optical microscopic (AIOM) technology	Sperm concentration, motility and seminal pH	LensHooke™ X1 PRO (X1 PRO)	Research	
Computer assisted sperm analysis	Sperm analysis	Microptic SCA	Research	
b) Undergoing clinical trials				
Evaluating Piezo-ICSI. - The EPI Study	Microinjection (ICSI) is performed using the Piezo-ICSI technique.			NCT04669652
Convolutional Neural Network in Ovarian Follicle Identification	Mask Region-based Convolutional Neural Network in Ultrasound Follicle Identification			NCT04545918
Evaluating iDA Selection Ability. The VISA Study	iDAScore®			NCT04969822
Use of Artificial Intelligence for Clinical Assessment of Assisted Reproductive Techniques and IVF Outcomes (AI in ART)	AI to analyze 3-D ultrasound			NCT04255615

Table 2. Continued 1

AI technologies in andrology	Purpose	Company name	Article type: Research/ Method/ Review	Supporting papers
c) Currently in the research and development phase				
Artificial neural network	Sperm morphology		Research (abstract)	
Image recognition algorithm	Sperm motility		Research	
	Chromosomal abnormalities in azoospermic males, semen analyses, sperm identification		Review	
In the medical field, three main categories of AI methods are used: (1) machine learning, (2) natural language processing, and (3) robotic surgery. Integrated AI component with image analysis Various algorithms of machine learning: - Decision tree - Random forest - Supports vector machines (SVM) - Naïve Bayes classifier - Neural network and deep learning: - Neural networks and deep learning - Unsupervised learning	Select and predict which spermatozoon has the best quality to implement the treatment success rate	Current applications of AI in reproductive medicine are limited and largely semi-automatic. Further studies are needed on diagnostic aspects and for personalized treatment, a competent remote medical system, and automated reproduction assisted by AI	Review	
Neural networks	To predict the effects of environmental pollution and lifestyle habits on human sperm concentration and motility		Research	
Decision Tree (DT), Multilayer perceptron (MLP), Navie Bayes (Kernel), support vector machine (SVM) plus Particle swarm optimization (PSO), and SVM	Influence of lifestyles and environmental pollution on sperm parameters and fertility rate		Research	
VGG16, a deep convolutional neural network	Sperm morphology		Research	
The following three models of supervised machine learning models were evaluated: logistic regression, random forest, and support vector machine	Predict the benefit that patients with varicocele will have from varicocele repair.		Research	
Report sixteen approaches to AI and ML	All of the following parameters were taken into account: sperm morphology, sperm identification, identification of follicles empty or containing oocytes, prediction of embryo cell stages, prediction of blastocyst formation, assessment of human blastocyst quality, prediction of live birth from blastocysts, improvement of embryo selection, and development of optimal controlled ovarian hyperstimulation protocols.		Conference review	
Automated, artificial intelligence optical microscopic (AIOM)-based technology, LensHooke™ X1 PRO (X1 PRO)	Sperm concentration, motility, and seminal pH		Research	
			Research	

Table 2. Continued 2

AI technologies in andrology	Purpose	Company name	Article type: Research/ Method/ Review	Supporting papers
d) Futuristic potential for AI technologies				
	Patient data from all over the world can be interconnected through data mining. They include health records, medical data from electronic medical images, medical records, laboratory tests, and genetic information		Review	
	Increased accuracy using a larger, heterogeneous, multicenter cohort			
	Cloud computing and data archiving techniques to optimize big data processing could, in the near future, be used to speed up the process by adopting concepts such as intermediate data caching.		Research	
	Increase accuracy (currently only 70%) Consensus on how to compare the performance of various AI models for optimal methods. Reduce heterogeneity between different AI platforms limiting their ability to cross-sync and link with electronic health records. Consensus on how to compare the performance of various AI models for optimal methods. Reduce heterogeneity between different AI platforms limiting their ability to cross-sync and link with electronic health records. Need for "gold standard" for comparison		Review	

[a] Artificial intelligence (AI) technologies in andrology: a) currently used in clinical care, b) undergoing clinical trials, c) currently in the research and development phase, and d) futuristic potential for AI technologies.

ADHD: attention deficit hyperactivity disorder, AI: artificial intelligence, AIOM: artificial intelligence optical microscopic, ANN: artificial neural networks, AR: augmented reality, AR-RARP: augmented reality-robotic assisted radical prostatectomy, ART: assisted reproductive technique, CASA: computer-assisted semen analysis, CNN: convolutional neural networks, CT: computed tomography, DL: deep learning, EMR: electronic medical record, GBM: gradient boosting machines, ICD: international classification of diseases, ICSI: intra-cytoplasmic sperm injection, IVF: *in vitro* fertilization, KNN: k-nearest neighbor, micro-TESE: microsurgical testicular sperm extraction, ML: machine learning, MLP: multilayer perceptron, MRI: magnetic resonance imaging, NLP: natural language processing, NN: neural networks, PET: positron emission tomography, PI-RADS v2.1: Prostate Imaging Reporting and Data System, version 2.1, PSO: particle swarm optimization, RCTs: randomized controlled trials, RF: random forest, SCD: sperm chromatin dispersion, SDF: sperm DNA fragmentation, sML: supervised machine learning, SVM: support vector machine, SWE: shear wave elastography, SWOT: strengths, weaknesses, opportunities, threats, TEST: testicular sperm extraction, WHO: World Health Organization.

- Bridging the gap in health services between urban and rural areas and also between developing and developed countries.

4. Medical expert system and predictive medicine

AI-assisted diagnosis is one of AI's most important uses of AI that can help doctors solve complex medical problems. In this way, AI is an auxiliary tool for clinical practice. Indeed, it can identify meaningful relationships in raw data, can support outcome prediction in many medical situations, and enable clinicians to proactively manage disease onset.

5. Future applications of AI in reproductive medicine

The efficiency of ART can be effectively improved by integrating new technologies for non-subjective selection of spermatozoa and embryos, oocyte denudation by the mechanical removal of cumulus cells, oocyte placement, fertilization, oocyte culture embryo, and monitoring the development of the embryo in an automated device. Therefore, further use and development of AI will bring more benefits to infertile couples.

AI will bring major innovation in reproductive medicine and healthcare through improved treatment options for infertile patients, better procedure planning, and ultimately higher ART success rates, thereby reducing the costs of treatment, and enabling predicting which patient with azoospermia requires further genetic testing, thus limiting the delay to early diagnosis. Other cutting-edge developments include the 3D printing of viable testicular spermatozoa to develop male gametes for use in ART and the use of AI in robotic andrology surgeries to improve patient outcomes.

Many automated methods of semen analysis have started to be used and have the potential for future development such as AI optical microscopic-based technology, an advanced CASA with the web-based program to have a better estimation of sperm kinematic parameters and hyperactivation would play an important role in future objective evaluation of spermatozoa. In addition, automatic semen analysis based on ML can become a valuable tool in male infertility investigation and research.

Furthermore, AI will play a role in the testicular evaluation of different diseases. AI will be able to improve the accuracy of sperm retrieval prediction in patients with non-obstructive azoospermia by using leptin and ANN. AI can enable testicular biopsy evaluation using computer-assisted testicular histology, using ultrasound texture as a mirror of the hypothalamic-pituitary-gonadal axis function in terms of reproductive aspects, and can use relevant perfusion patterns from contrast-enhanced ultrasound data to classify a testicular lesion as benign or malignant.

Conflict of Interest

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