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Predictive modeling in reproductive medicine: Where will the future of artificial intelligence research take us?

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Artificial intelligence (AI) systems have been proposed for reproductive medicine since 1997. Although AI is the main driver of emergent technologies in reproduction, such as robotics, Big Data, and internet of things, it will continue to be the engine for technological innovation for the foreseeable future. What does the future of AI research look like? (Fertil Steril® 2020;114:934–40. ©2020 by American Society for Reproductive Medicine.)

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In the early 1990s, the web was built using static information, with no way for users to change the data. In assisted reproductive technology (ART), clinics gathered data using paper-based methodologies; communicated with patients either by phone, letter, or in person; and communicated with society through newspapers and television. In the late 1990s, Web 2.0 involved a switch into a more interactive and dynamic experience through server-side processing forms, databases, and social media. Web 2.0 was less about the information and more about the interaction. Fertility clinics started to implement electronic medical records and converted to communicating with society using social media (LinkedIn, Instagram, Facebook, Twitter, TikTok, and more). The complexity of the data captured increased exponentially with the more use of digitization found in electronic witnessing, digital and continuous quality control, genetic testing, and time-lapse systems. We suddenly found ourselves in the era of Big Data, struggling to find effective and consistent decision-making algorithms with traditional statistics often based on subjective observations. Artificial intelligence (AI) seemed perfectly suited to resolve the challenges brought on by Big Data. The increased number of publications in the past couple of

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years demonstrates the promising capabilities of AI to bring more consistency and efficacy to ART.

THE ERA OF AI IN ART HAS ONLY JUST BEGUN

Web 3.0 is the next generation of internet technology that relies on the use of AI to process data and create a personalized user experience, leveraging peer-to-peer technologies, blockchain software, virtual reality, internet of things (IoT), and more. Web 3.0 would be device agnostic, and the information would be democratized, open, and decentralized. Users would then have complete ownership of their data, without the need for the data to be processed by network or cellular providers. Many parts of fertility treatment can be undertaken virtually. From virtual consultations to at-home testing and to pretreatment diagnostics, and fertility assessments can be made digital and patient centric.

Given the large amount of information and metadata that are being generated and made publicly available, it is believed that Web 3.0 technologies (machine learning [ML], AI, IoT, natural language processing) will allow computer agents to automatically link any kind of data of any system to build inferences from that information. This information retrieval accessibility would represent an important advantage for the development of better personalized healthcare technologies, including matching patients to treatment plans and predicting fertility success rates.

IMPLEMENTATION OF AI SYSTEMS AT THE POINT OF CARE

There are significant challenges to implementing an AI system in a meaningful way into a clinical in vitro fertilization (IVF) laboratory workflow. Implementation of an AI at the actual point of care in a routine, easy, and automated fashion is nearly impossible for most IVF laboratories that still use paper charts and do not capture and store even a single digital image of their patients' embryos, much less videos. In addition, data management solutions to augment patient demographics, clinical and laboratory key performance indicators (KPIs), and other relevant data streams (ultrasound images and preimplantation genetic testing results, competency assessments) into a single dashboard are lacking.

Aside from the current lack of prospective data, there is another glaring flaw in all studies that seek to use embryo images and video (analyzed by AI and statistical models) to predict pregnancy outcome. The most common type of images used are blastocyst images taken before biopsy and cryopreservation, thawing, and transfer. The culture conditions of the laboratory, technical competency of the operator (1, 2) (clinical and laboratory), embryo quality, and/or expansion postthaw are not analyzed in models that use clinical pregnancy as an end point, despite being dependent on them.

Another problem is that seemingly similar parameters can vary between clinics. For example, if one clinic captures blastocyst images at 110 hours, another clinic might capture them just before freezing—a time that may vary based on embryo development speed and current workload in the laboratory. We need to set a standard for the exact time the images are captured or create an AI that is invariant to such differences. Perhaps one that has learned from data originating from many clinics.

Looking to the future, AI for reproduction will go beyond simply repackaging previously established pregnancy predictors in new machine-learning algorithms. Through prospective design, Big Data, standardized outcome measures, and external validation, integration of clinical and laboratory KPIs, plus patient demographics, novel variables, and hidden relationships that allow for superior predictive capabilities will be identified.

In the near future AI will access multiple sources of data to reveal patterns in diagnosis, treatment, and results. Using Big Data, AI systems will be able to predict individual patient risk and suggest treatment options. It will be able to assess the real chance of achieving a pregnancy and a healthy baby for each patient. It will also be more suitable at anticipating complications during pregnancy, perhaps identifying patients at high risk better than currently feasible. Artificial intelligence will also reduce "time to pregnancy" and improve efficiency, which is the time it takes to perform certain tasks or reduce embryo waste. The most powerful use of AI is to enhance human capabilities, minimize variability, improve precision, and speed, and not to replace them. The impact of AI will be most visible through the use of natural language processing and ML. There will be patient-oriented AI, clinician-oriented AI, and administrative- and operational-oriented AI. Using these systems, patient engagement in their care will be enhanced and streamlined.

In a prospective, real-world setting, how much better is AI at embryo selection than traditional approaches is a fundamental question. Also, is the improvement worth the investment that will inevitably stem from licensing or purchasing AI software and changing and revalidating existing clinical workflows?

To solve the concern of introducing bias into the process at the AI training stage (e.g., training AI on a dataset that is not representative of the data it will be used on prospectively) we need to assemble realistic datasets that reflect the diversity seen in real-life clinical settings. For example, a broader set of embryos need to be included, not only those selected for transfer. The AI models need to be trained on such datasets, and validated extensively on independent datasets that are equally representative. The implementation of AI in IVF will depend on the speed of digitalization, standardization, and optimization of IVF using extensive and well-characterized data. Once established, we anticipate that AI programs would self-improve through continuous learning, continuous revalidation, and inclusion of novel data. When deciding to implement an AI system within a clinical setting, it is important not to neglect the learning capabilities of some models. A process of tuning should be allowed for these systems, followed by rigorous and regularly applied quality assurance.

The good news is that there is increasing confidence in AI-driven approaches and devices. Recently, the US Food and Drug Administration has expedited the approval of medical devices and therapies (39 as of July 2019) that use partially and/or fully independent AI-based systems (3).

Once adopted, it is hoped that the advantages of AI will include lower error rates and able to perform laborintensive, tedious, and repetitive tasks more efficiently, without emotional factors or physical constraints. The potential drawback of AI is the machine replacing human decision-making and the absence of the human connection and empathy. However, we envision that AI will not replace humans but make them more productive. In addition, the privacy and security of patient data, which is associated with increased use of digital technologies, are a concern and need to be addressed appropriately. This is particularly important in an era where there is increased use of cloud-based data storage.

EXPLAINABLE AI

One of the most pressing current goals for embryology AI is to have the computer select the best embryo based on images alone, without relying on subjective annotations. One of the frequent criticisms of AI is that it tends to be seen as a black-box (i.e., it is difficult or perhaps impossible to explain how AI renders a decision). Ideally it would be desirable if AI could provide reliable probabilities for achieving a pregnancy, thus equipping physicians with a dependable tool for making decisions as to the optimal number of embryos to transfer. It would be important if one could provide an explanation of how the computer reached its conclusions. This would also be critically essential to convince embryologists and patients to trust AI predictions. Generally, this is known as explainable AI, and some ML models are known for being difficult to explain. This is exacerbated in modern deep learning, which includes millions of parameters that are fine-tuned during training. Some classic AI methods based on expert systems and decision trees are more explainable, but they tend to be much less accurate than deep learning. The ability to explain of deep learning models is an active area of research and some methods are emerging as useful guides, such as class activation mapping (e.g., highlighting relevant parameters or parts of an image). We also argue that instead of just asking the AI to predict pregnancy chances, it may be an idea to ask other questions at the same time (i.e., to train multiple AI models on different end points) or combine AI results with further analyses. For example, if an embryo is deemed low quality (e.g., aneuploid) by an AI model, it may have genetic defects. This may serve as an explanation for a low pregnancy chance. It is also important that AI and users of AI speak the same language. Embryologists may feel more confident in a prediction that is based on traditional annotations, although there have been several projects that have successfully used AI aimed at automating annotations. Combining all these models may result in a more explainable AI. In the future, more parameters, such as medical history and treatment protocols will be included in the AI prediction models. Then, explainable AI may suggest adjustments to treatment protocols, with the goal of increasing the chance of pregnancy in succeeding cycles (Fig. 1).

MACHINE LEARNING

For the successful implementation of AI in the field of IVF, the combination of computer science, clinical, and biological knowledge is required. That implies computer scientists with reproductive scientists joining forces on the academic or business level. The complexity of AI implementation is extensive and represents a challenge for groups seeking to develop AI models that will be useful in the clinical setting. Embryologists and computer scientists need to learn to "speak the same language," combine their understanding of IVF and embryo biology with a grasp of computer science techniques, as well as their strengths and limitations. A similar problem existed when the first computers came on the market. At that time it was necessary to be familiar with computer programming languages to be able to use computers. With the development of graphic user interfaces, the applicability of computers became widespread.

Similarly, we are predicting the development of the programs that will help us apply AI with more limited knowledge of computer programming. In the ML field, the two most popular deep learning frameworks (Hajirasouliha and Elemento [4]) are Tensorflow (Abadi et al. [5] with optional Keras add-on [Chollet {6}]) and PyTorch (Paszke [7]). These frameworks interface with specialized hardware to automate much of the mathematics (calculus) needed for training models and making predictions, but they still require advanced knowledge in Python programming and ML to use (4). There is ongoing research on automated ML tools, which do not require any programming (8). Start-ups and large technology companies (e.g., Amazon, Google, Microsoft, IBM) compete to provide the best automated ML solutions through their respective cloud services. They allow for businesses without strong ML expertise to create predictive models. These are often divided into three categories based on data type, as follows: tabulated data, computer vision for images, and natural language processing. Automated ML tools have the potential to revolutionize the field by democratizing access, but do not address some of the key pitfalls, such as the need to input clean, well-labeled data with limited bias and sufficient quantity, and the tendency of ML methods to overfit the data. Predictive models often incorporate domain knowledge into the algorithms, and

FIGURE 1

Application of the immersive realities (augmented, virtual, and mixed reality) using time lapse microscopy embryo images.

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combining images with tabulated or textual content may not be supported by automated ML. More research is needed before these can be achieved with the same results as ML experts using Python and other languages (9).

AI FOR QUALITY CONTROL AND ASSURANCE IN THE IVF LABORATORY

Manual procedures currently predominate in the IVF laboratory. Automation and AI systems promise to lessen the burden of the more subjective, menial, or mundane aspects of the embryology laboratory. These systems may decrease technician variability, and may even address environmental stressors, which can impair gamete function and embryo development.

The advent of the sensor and IoT presents IVF laboratories with the opportunity to better monitor and operate their facilities (10). The IoT devices are usually low-cost, low-power electronics connected wirelessly to gather data or act on events in real-time. These environmental sensors, actuators, networks, software, and more can be deployed for real-time monitoring of room temperature, humidity, volatile organic compounds, door open count, and so forth. A more advanced, experimental form of IoT is a concept called smart dust. Smart dust are nodes of multiple microelectromechanical systems, no more than a few millimeters wide, that can detect changes in light, position, acceleration, stress, pressure, humidity, sound, and vibration. These disposable sensors transmit information wirelessly with autonomous power to a central computer or a cloud where data are compiled, analyzed through algorithms, and—if required—can instruct other devices to respond.

The IoT devices are frequently connected to cloud-based applications to collect, store, retrieve, and analyze data (11). At present, laboratory instrumentation also collects quality control data, which can be connected to the same cloud infrastructure. These data lend support to standardization of quality control parameters and may soon offer the opportunity to be integrated with electronic health records and relate measured parameters to clinical outcomes.

Staff competency is another crucial component of the IVF laboratory quality management systems. It impacts clinical outcomes and informs the KPIs used to continuously monitor and assess culture conditions. Contemporary quality control and assurance in the IVF laboratory is automated (collection, storage, retrieval, and analysis) and strives to elevate quality control and assurance beyond the cursory monthly review. Automated data collection can monitor the performance of individual embryologists and AI can predict trends, such as deterioration of implementation, perhaps earlier than is currently possible. Automated monitoring may also help assess early embryo developmental stage markers, and AI models may predict necessary changes in the embryo culture environment for optimal results. The link between quality control and patient outcome has been demonstrated (12). We anticipate that AI systems will automate these quality assurance processes, provide systemic, early detection of adverse outcomes, and identify clinically relevant shifts in pregnancy rates. Two abstracts presented at the American Society for Reproductive Medicine in 2019 were the first to hint at the use of AI to monitor embryologists performing intracytoplasmic sperm injection in a clinical setting. The extremely low coefficient of variation between the manual and AI-based quality assurance assessment methods demonstrate the high accuracy of the automated AI system (13, 14).

AI AND ROBOTICS FOR EMBRYO CULTURE SYSTEMS

As the IVF laboratory intersects with advanced microscopy, robotics, microfluidics, computer science, automation, AI, and digitalization of manual processes are pushing the boundaries of embryo culture systems. Robotic and microfluidic platforms can perform visual tracking of a single sperm, immobilization of sperm, aspiration of sperm with picoliter volume, and insertion of that sperm into an oocyte. Fertilization of mouse embryos and continuous culture on a single platform, as well as automated vitrification systems, hint at the promise of fully integrated robotic and automated workflows in the human IVF laboratory (15–22).

Artificial intelligence analyses of embryo development patterns in response to different culture media or to conditions like temperature or pH (collected from IoT and mobile applications), taken together with patient demographic data may further optimize the culture conditions for embryo culture. In the future embryo culture media may include therapeutic strategies, treating each embryo with their own media formulations composed of optimized energy sources, antioxidants, or growth factors (23, 24).

BIG DATA DEFICIENCY AND SYNTHETIC DATA

Generative adversarial networks (GANs) are commonly known by their ability to generate “deep-fakes” (i.e., authentic-looking digital content). Videos, faces, even the first-ever portrait auctioned at Christie’s (British auction house) was generated by an algorithm. Two neural networks “work against” each other, they are both fed with training data but given a separate problem to solve. The first network is termed the generator and is responsible for generating outputs through imitations of training examples. The second network is the discriminator tasked with deciding whether the fabricated outputs are real by comparing them with training data. The process repeats until the discriminator is not able to tell whether the output is real or fabricated. Generative adversarial networks can provide low-cost, diverse medical image data (e.g., change in the size and location of a tumor in millions of combinations, which could be hard to achieve organically). The use of synthetic data instead of real patient data at least partially overcomes privacy and data sharing concerns.

A drawback when using synthetic data in reproductive medicine would be the generation of unlabeled data with unverifiable outcomes. For example, the generation of a synthetic blastocyst’s image based on features extracted from 10 embryos (e.g., morphokinetic sequence, trophectoderm, inner cell mass, textures) will not have a known or verifiable outcome (for ploidy, implantation, live birth), making the predictions of the algorithm unverifiable and potentially leading to training bias, in the case of predictions based on images and videos. In addition, it is unclear whether such algorithms can generate the entire spectrum of images seen in the clinical setting, including edge cases.

A quick survey of PubMed reveals no results for "Generative Adversarial Networks + IVF" but yields dozens of results for medical applications such as cancer diagnosis, spinal imaging, medical images, electronic health records, radiation reduction, and artifact correction. A group from the National Institutes of Health Clinical Center used GAN to modify contrast images into noncontrast ones to perform computerized tomography segmentation tasks with superior performance. At the 2018 Institute for Electronics Engineering international conference, researchers demonstrated that AI trained using GAN-generated synthetic data for tissue recognition can reach equal accuracy levels (98.83%) to humans.

MINING SOCIAL MEDIA FOR HEALTH DATA

In the quest for annotated Big Data, we must look at different avenues of data collection. Integrated diverse datasets, including self-reporting, lifestyle, and exposures, clinical-grade data and data collected from wearable devices, self-administered surveys, electronic health records, and personal health records will become paramount to future AI studies. Artificial intelligence used to gather and interpret opinions is a hot topic referred to as sentiment analysis. Social media provides huge datasets of people's opinions, complete with demographic information and detailed data regarding specific users for AI-driven data mining (25). Statistical analysis of Big Data can help clinical researchers discover medical knowledge, such as adverse drug events (26), disease comorbidities, and effectively signal an outbreak of disease epidemics in early stages (27).

A medical natural language processing tool—MetaMap (28)—was developed to mine data from the literature and electronic health records, but it has also been successfully applied to mine social media for mentions of medical concepts. Public social media posts have been mined to better understand public opinions on controversial health topics (e-cigarettes, vaccines, Affordable Care Act, diabetes), for pharmacovigilance (especially for new drugs), drug repurposing, and understanding drug effects in the context of other factors, such as concurrent use of other drugs, diet, and lifestyle, as well as to predict postpartum depression and to monitor prescription medical abuse.

Natural language processing could be applied to reproductive problems (e.g., to explore embryo resilience or correction of mosaicism by data mining). A group on Facebook called My Perfect Mosaic Embryo, which has >2,600 members who post images of their mosaic embryos, the exact preimplantation genetic testing diagnosis, and miscarriage or success of embryo transfers, is an example.

MOBILE APPLICATIONS

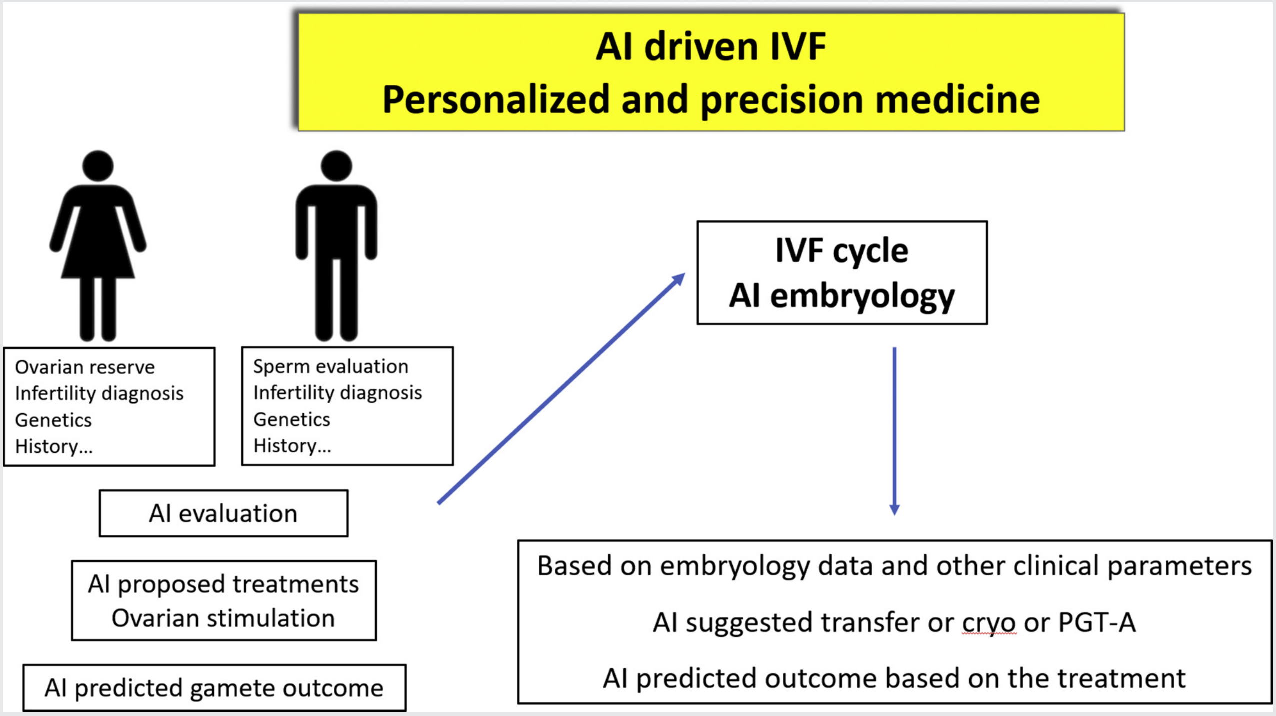
It has been estimated that ≤500 million smartphone owners use a health care application. This is of great importance to the field of reproduction. Artificial intelligence models that can interact with patient apps and or "wearables" like ovulation tracking devices. Patients are using apps to crowdsource tips on improving fertility and preventing pregnancy, to chart cycles by last menstrual period date, to time intercourse, to track and chart medical information (cervical fluid, basal body temperature, and fertility medications), to seek support, and to share experiences. Providers are using apps for reference and communication tools, for electronic health records, diagnostic point-of-care, clinical trials research, and patient health management (29). In 2019, Apple announced the undertaking of three new major medical research studies in partnership with academic institutions. Along with a comprehensive heart/movement and hearing study, Apple announced a major fertility initiative to perform screening and risk assessment of conditions like polycystic ovary syndrome, infertility, osteoporosis, pregnancy, and menopausal transition.

AUGMENTED REALITY, VIRTUAL REALITY, AND MIXED REALITY IN IVF

In recent years, advances in augmented, virtual, and mixed reality (AR/VR/MR) have paved the way for real-world applications with the biomedical field. On one end of the MR continuum (30), there is AR, where virtual objects are overlaid onto the real world. At the other end there is VR, where the full world is entirely digital. Whether handheld and always in our pockets, like smartphones, or head-worn, like Oculus Quest and Microsoft HoloLens 2, these devices have only two goals—extend the boundaries of how we perceive, process, and interact with data by bringing them into our reality as tangible and malleable objects in our hands and redefine the way we collaborate by bringing us into the same room regardless of geographic distance or time.

To understand the benefits of such technology in IVF one can consider the following scenario: assessing and selecting human embryos alone, with collaborators, and reviewing results with patients. Recent technological advances in image capturing methods have resulted in an explosion of data. To select the appropriate embryo, an embryologist has to review many time lapse microscopy images before making the final call. With the advent of AI in IVF, novel methods for automated and robust assessment have emerged, cutting down review time significantly, often minimizing the review to mere tens of images. Capabilities and limitations of AI are bound to its training dataset, often leaving gaps that the embryologist is called to fill in. The AR/VR/MR offers a new approach to review data, transforming thousands of two-dimensional images into a single four-dimensional dataset per embryo, a three-dimensional object over time overlaid into the embryologist's reality. The embryologist can view and manipulate blastocysts and leverage new input methods, such as hand and eye-tracking or voice recognition, to further control and filter the dataset (Fig. 2). Leveraging AI, it can overlay annotations or segmentations on the four-dimensional dataset and allow slices or selections to be viewed across time. With regard to collaboration, whether in the same physical location or not, embryologists can share the same view and collaborate on the same embryo, brainstorm, and co-assess it by changing

FIGURE 2



The future of in vitro fertilization (IVF): personalized and precision evidence-based medicine. AI = artificial intelligence; PGT-A = preimplantation genetic testing for aneuploidy.

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its representation at a moment's notice, making it easier to convey ideas or justify selection criteria. Finally, with its cross-platform nature, an embryo that has been reviewed in a more sophisticated MR device can be presented and placed as a tangible object in the patient's reality, allowing the practitioner to consult with the patient on the next appropriate treatment steps. The AR/VR/MR shows promise in advancing the field of embryology in clinical, research, and educational aspects.

MULTICENTER COLLABORATIONS AND DATA SHARING

The future in technology, the direction it takes, and the speed of its implementation, often depends on collaboration. Artificial intelligence is no exception.

At present, most IVF AI research has happened in academic laboratories and in a handful of small companies. This has resulted in fragmentation of the IVF AI landscape and limited application beyond where the research was performed. In the future, large IVF groups or clusters of individual clinics may form collaborative efforts (possibly including AI developers) to gather the wealth of data required to achieve sufficient sample size and diversity. This is needed for AI to be broadly applicable and eventually assess and implement AI at the point of care. Collaboration should allow for the development of robust AI systems that could be easily implemented universally, rather than developing tailor-made clinic AI models that sacrifice efficiency and the benefits large datasets accessibility.

As discussed previously, there are obstacles to data sharing, including; interclinic competition, absence of patient consent for sharing, and data privacy. The improved participation of patients in research, together with the advent of secure technologies for data-sharing, such as blockchain hubs (31), may facilitate these collaborations. These issues will need to be addressed for AI to thrive and positively impact patient care.

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