Patents

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Intellectual property and assisted reproductive technology

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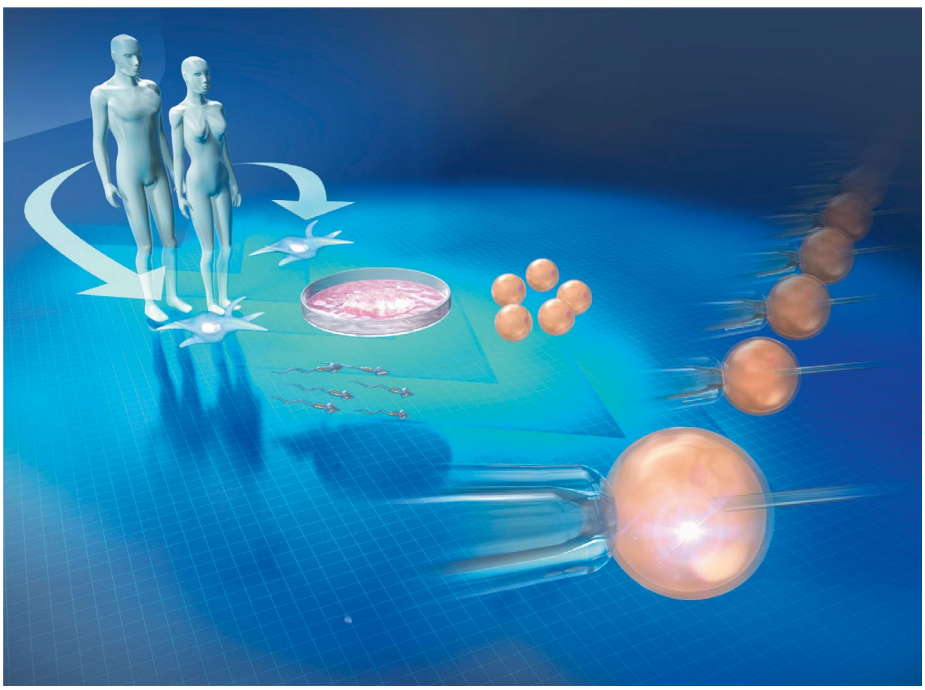
Over the past fifty years, intellectual property has not played a major role in the spread of assisted reproductive technology, but with in vitro gametogenesis — a technique likely to dominate the future of reproduction — it might.



Stanford bioethicist Henry Greely predicts that a large proportion of human pregnancies — perhaps even 90% in the United States — will one day result from in vitro gametogenesis (IVG), the production of eggs and sperm from undifferentiated human cells[1]. Whether or not this prediction proves accurate, it is likely that IVG will fundamentally change how humans reproduce. IVG could offer the possibility of reproduction to those experiencing infertility, allow parents to choose from hundreds of genetically characterized embryos, enable relatively safe germline genetic modification, and open the door for same-sex parents to have genetically related offspring. Some assisted reproduction experts, like Jacques Cohen of the ART Institute of Washington, predict that IVG will replace virtually all conventional in vitro fertilization (IVF) procedures for those experiencing problems with fertility (J. Cohen, personal communication). Greely suspects that eventually most prospective parents — even those without fertility problems — will opt for IVG to reduce the risk of bearing offspring with genetic defects or to select for desirable traits.

It is not surprising, then, that researchers who are putting together the pieces of IVG have started to stake out intellectual property (IP) claims. Nor is it surprising that biotech companies, eyeing potential profits, are starting to pop up after convincing investors to pump tens of millions of dollars into this new endeavor "to eliminate infertility"[2,3].

But history tells us something interesting about financial windfalls from assisted reproductive technology (ART): so far, they have not really materialized. The precursor to IVG, today's IVF technology, was largely developed in the 1970s with little attention to patents or commercial gain. Even as academic researchers and collaborating physicians transformed IVF with new techniques like intracytoplasmic sperm injection, few sought to patent these developments. Once success was achieved, the technologies spread quickly to clinics around the world. Companies did, and still do, sell proprietary reagents for enhanced IVF protocols. And there are, of course, for-profit fertility clinics. But these are service industries based on shared technologies. The core of IVF and related ARTs have propagated to clinics around the world mostly unfettered by IP claims.

If IVG supplants conventional IVF, however, a new array of methods, reagents and devices will replace current ones, and this rebuilding will take place in an environment where biotech entrepreneurs and established pharmaceutical companies are exploring new business opportunities. A range of outcomes could ensue, from a single player with a powerful patent portfolio used to monopolize the market to a virtually patent-free environment, as exists with ART today. Each has its pros and cons. The presence of one or a few companies controlling the market through patents, for example, could make it easier to regulate and ensure safe and ethical use of this risk-burdened technology, but that could come at the expense of robust competition, widespread innovation and equitable access, creating a social divide between reproductive haves and have-nots. IP concerns demand our consideration before IVG makes its way to the clinic.

Early IVF: innovation without IP

The early development of ARTs was generally led by academic scientists whose principal focus appears to have been on meeting patient needs, advancing science for its own sake,

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achieving recognition and publishing work in academic journals, but not on obtaining IP protection for their discoveries.

Gianpiero Palermo, who pioneered intracytoplasmic sperm injection, now used in an estimated 60% of IVF procedures[4], says that when he developed it at Vrije Universiteit Brussel in the early 1990s, "I was a little naive and didn't know that things could be patented" (G. Palermo, personal communication). According to Alan Trounson, who developed key ARTs including cryopreservation and vitrification techniques, "We were rewarded by being recognized as scientists. That seemed reward enough for most of the people" (A. Trounson, personal communication). Even fertility drugs — now a multibillion-dollar market — were developed with this scientific ideal in mind. The first method to purify human gonadotropins, an essential element used in the first IVF procedure, for example, was published in a scientific journal in 1954 specifically to prevent companies from patenting and monopolizing its use[5]. "We believed in a different kind of medical ethic. We wanted our discovery to belong to the whole world," says co-developer Bruno Lunenfeld[6]. ART researchers shared IVF techniques freely through publications and personal visits. Teams in the United States, for example, learned about the value of sperm pre-incubation and controlled ovulation from colleagues in Australia[7], where the second IVF baby was born.

Moreover, because ART treatments were generally considered to be in-office medical procedures rather than drugs or medical devices, they have not been heavily regulated at a national level, whether in the United States, Europe or Japan[8]. Rather, such procedures are generally overseen, if at all, by local medical licensure boards, which have fewer requirements than national drug and device regulations. Because of this lightweight regulatory environment, collaborating clinicians have been able to introduce and test new ARTs without costly clinical trials. The deep pockets of industry were not necessary to launch and develop this field, as they often are with drugs requiring large-scale clinical trials before marketing approval is conferred.

The open sharing of IVF techniques and information and the lack of blocking IP rights led to a rapid dissemination and adoption of the technology around the world. Five years after the first IVF birth, in England, IVF had been achieved in over a dozen countries. Today there are more than 3 million IVF procedures per year in 80 countries, resulting in hundreds of thousands of births[4].

The shifting ART landscape

Today the environment is different. First, regulators in several countries have asserted jurisdiction over new ARTs. Various strategies used to invigorate egg cells that have emerged since the turn of the century, for example, have been subject to regulatory scrutiny and have not yet been permitted to enter the market[9,10,11]. Though investigator-led clinical studies are still possible, regulatory hurdles discourage academic researchers from pursuing clinical translation of these technologies.

Academic research culture has also changed as academic institutions have increasingly focused on the patenting and commercialization of university-developed technology[12]. Scientists often actively pursue commercial opportunities related to their discoveries, and, if they do not, university technology licensing offices encourage them to do so.

Furthermore, with the growth of ART, IVF-related patents have proliferated. This started slowly in the 1980s, led by companies such as Serono and Ferring Pharmaceuticals, which patented recombinant follicle-stimulating hormones and other gonadotropins, which are used to improve IVF success rates[13]. The pace picked up at the turn of the century, in the wake of the first isolation of human embryonic stem cells. The number of patents related to ART jumped to hundreds per year and has remained at that level[14]. These patents cover a broad range of techniques relating to new embryo culture, oocyte and follicle monitoring, embryo assay and genetic analysis.

During this time, the price of IVF has steadily increased[15]. An IVF cycle in the US now costs in the range of $25,000, with a substantial portion of that cost attributable to fertility drugs. Given that failures are frequent and more cycles are often needed, the average patient today spends $50,000 on IVF, according to data from FertilityIQ[16]. Various groups lobby for insurance coverage of IVF, but it is still limited[17]. In Europe, coverage is more common, though in many cases ethical or financial restrictions limit the availability of procedures[18].

There are various strategies for finding cheaper IVF. Some patients, especially in the United States, purchase fertility drugs overseas to take advantage of lower prices[19]. And it is possible to forego some of the pricier options that have become or are becoming standard. For example, patients can skip the latest genetic examinations and embryo assays and limit themselves to relatively inexpensive drugs like Clomid (clomiphene). To broaden access to IVF in Africa, the Low Cost IVF Foundation offers a stripped-down treatment for around $300 (ref. 20).

These tiered versions enable most people in developed and even in some developing countries to access some form of IVF. However, the emergence of various new IVF approaches shows the increased appetite among industry and researchers for a piece of the ever-expanding ART market.

The road to the clinic for IVG

The goal of IVG is to take cells from a person's blood or skin, reprogram them to an embryonic-like pluripotent state (in which they are known as induced pluripotent stem cells, or iPS cells), and then coax the iPS cells to become eggs or sperm that can be used in IVF procedures. The allure of IVG is that there is no limit to the number of pluripotent cells, and thus the number of potential eggs and sperm, that can be made.

The proof-of-principle has been achieved in mice. Over a decade ago, researchers took mouse iPS cells and converted them to primordial germ cell-like cells (PGCLCs). The PGCLCs, which simulate a critical stage in natural gamete development, became sperm and, after having been introduced back into mouse testes, produced offspring[21,22]. Introduced into mouse ovaries, the PGCLCs likewise turned into fertilizable eggs and produced offspring[23]. Another breakthrough was reproducing the signaling environment of the reproductive organs in vitro so that the entire process could be reproduced outside the body. Using disassociated gonadal cells, Japanese scientists achieved this milestone in mice in 2016 (ref. 24).

Clues from mouse experiments have led to progress toward human IVG. Human PGCLCs have been created[25,26] and turned into rudimentary oocytes when cultured with mouse ovarian cells[25] and rudimentary sperm when cultured with mouse testicular cells[27]. But, in the quest for human IVG, researchers are still navigating fundamental differences between human and mouse reproductive systems. They must also surmount ethical and regulatory considerations that limit or prevent access to human tissue and forbid the use of in vitro gametes to create embryos (as is the case in Japan currently)[28]. As of this writing, no one has created embryos from human gametes developed in vitro.

However, there have been other advances toward human IVG. Researchers have derived ovarian follicles from pluripotent mouse cells[29], which can be used instead of

disassociated cells from ovarian tissue to culture oocytes. Recently scientists have claimed success in creating structures similar to ovarian follicles from human cells. Such methods could accelerate research on later-stage human gamete development and lay the groundwork for clinical IVG[30].

Researchers are also working on ways to accelerate the time required for a single IVG procedure. Initial IVG methods aimed to recapitulate the natural developmental pathway of gametes, but this takes several months. A potential shortcut being explored by several groups is the introduction of transcription factors to catapult pluripotent cells past the natural developmental stages to functional gametes[31]. This could make gametes within days, a speed that would have clear benefits in the clinic. And an altogether different method, which uses cloning techniques to create gametes from skin cells, has recently proven successful in mice[32].

Scientists will also need to demonstrate that IVG is safe. The IVG process could result in subtle but important genetic and epigenetic discrepancies[33,34]. Furthermore, gametes produced from somatic cells using IVG will inherit the mutations of those cells. Since somatic cells mutate at a much higher rate than germ cells, the IVG-derived gametes could accelerate the accumulation of genetic disease[35]. Given the need to thoroughly characterize the genetics of the gametes, most scientists do not anticipate clinical use of IVG for at least a decade.

IVG will also face regulatory hurdles on the way to the clinic. Many jurisdictions already limit IVF, and those restrictions would likely be applied to IVG. The United Kingdom, for example, limits the use of another new ART, mitochondrial replacement therapy, to disease avoidance and has not yet allowed its use as a treatment for infertility[10]. The same restriction applied to IVG would greatly limit its use. And while part of IVG's appeal is that it allows the production of dozens or hundreds of embryos that could be screened for disease or other traits, Italy and Germany already restrict the number of embryos that can be created to those that will be transplanted, and scholars like Greely predict that, in the wake of the recent US Supreme Court decision in *Dobbs v. Jackson Women's Health Organization*, the United States might do so as well[36].

The emerging IVG industry

Until recently, IVG research took place primarily in academic laboratories, with the biggest breakthroughs coming from Japanese universities. But over the past few years, venture capital funding started flowing to a handful of companies aiming to bring IVG to the clinic, with the largest investments in the United States. For example, Conception Biosciences, a 2017 spinoff from a University of California, Berkeley–affiliated incubator, has raised $20 million in funding from prominent high-tech investors and entrepreneurs[37]. The company says it has hired 27 scientists[38], and its CEO has predicted a viable IVG egg in 2023 (ref. 39).

Similarly, Gameto, based in New York, has raised $40 million from leading tech venture capitalists and entrepreneurs[40]. Gameto was founded by Martin Varavsky, the founder and chairman of Prelude Infertility, currently the largest IVF provider in the United States.

Three other companies — Ivy Natal, Dioseve and Houjou — have seen more modest investments. San Francisco-based Ivy Natal, founded in 2020, has received early-stage funding of $250,000 from IndieBio[41]. Dioseve, founded in Tokyo in June 2021, has received $2.6 million in start-up funding from ANRI, a venture fund focused mainly on Japanese consumer goods. Kyoto-based Houjou was established as a nonprofit organization. Any earnings will be used for research and development or maintaining licenses, according to CEO Masakazu Kobayashi. Its founders, Mitinori Saitou at Kyoto University and Katsuhiko Hayashi at Kyushu University, received the majority of their funding either from the government or from the philanthropic fund, Open Philanthropy. Open Philanthropy, which made grants of $4 million to Saitou[42] and $2.5 million to Hayashi, has also provided $1.66 million to Kotaro Sasaki, a former member of Saitou's laboratory now at the University of Pennsylvania[43,44], $2.5 million to Sue Hammoud at the University of Michigan[45], and $4 million to Shoukhrat Mitalipov at the Oregon Health Sciences University for his cloning-based IVG research. The fund states that IVG "could eventually enable people with fertility challenges to have children and could eventually help reduce the incidence of a wide variety of high-burden disorders (such as heart disease, chronic pain, depression and Alzheimer's disease)"[42].

These companies all claim to be developing unique methods in pursuit of IVG, but few details are available to the public. While Conception aims to recapitulate the natural process of gamete formation in vitro, Gameto, Dioseve and Ivy Natal are aiming for direct induction methods that quickly push pluripotent cells to gametes. The scientists leading Houjou have published key findings related to both strategies.

Owning IVG: early IP strategies

We have identified a dozen IVG-related patents and patent applications across jurisdictions, all of which list scientists connected with the companies mentioned above as inventors (Table 1). A 2011 patent filed by Saitou and Hayashi covers a method using specific cytokines to reproduce the first stages of gamete production, up to PGCLC stage. Saitou's subsequent patents and patent applications cover the use of transcription factors to force direct induction of PGCLCs, modifications for using the PGCLC derivation method from mice in humans, a method for making spermatogonial stem cells using reconstituted testes in mice, and an improved method for maintaining and amplifying PGCLCs and then producing oocytes from them. Hayashi's subsequent patents and applications claim a method to derive mature oocytes from primordial germ cells, a method of deriving follicles from primordial germ cells, and a method of direct induction of immature oocytes from pluripotent cells using four types of genes.

The patent situation promises to get much more complicated as other companies get involved. In September 2019, Dioseve filed a Japanese patent application for a method using four genes to induce immature oocytes to become mature; the patent refers specifically to the short culture period in this direct induction method. In November 2021, Conception filed an international patent application with 154 claims; the array of biochemicals included in the claims overlaps with previous claims by Saitou and Hayashi. In July 2022, three scientists with ties to Gameto published two preprints describing methods of using transcription factors to produce human ovarian follicles and human oogonia in vitro[30,46]. The articles name three provisional US patent applications on which the three scientists are inventors. Gameto reportedly will share any IP rights with Harvard Medical School[37], where those three inventors have positions.

Since the IVG process begins with iPS cells, earlier patents related to iPS cell technology could also come into play, though it is likely that those patents will have expired before the commercialization of IVG.

Potential limits on the ability to patent IVG technology

Despite the emergence of patents claiming IVG techniques, not all aspects of IVG are eligible for patent protection, and different rules apply in different countries.

Table 1 | Key patent families relating to IVG methods for creating gametes from somatic cells

Publication no.	Description	Applicant or assignee	Inventors	Status	Priority date
Granted					
WO2012/020687	Method of producing PGCLCs from PSCs, using cytokines to recapitulate natural development states	Kyoto University	Mitinori Saitou, Katsuhiko Hayashi	Granted: JP, EP, US	8/13/2010
WO2014/133194	Method of producing PGCLCs from epiblasts, using three transcription factors (direct induction for part of maturation process)	Kyoto University	Mitinori Saitou, Fumio Nakaki	Granted: US, JP	3/1/2013
WO2017/002888	Method of producing human PGCLCs from PSCs at a high efficiency and high reproducibility	Kyoto University	Mitinori Saitou, Kotaro Sasaki, Shihori Yokobayashi	Granted: US, JP	6/29/2015
WO2017/047799	Method for differentiating PGCLCs into functional mature oocytes using dissociated cells (IVG produces functional mouse oocytes, but still requires tissue for culture)	Tokyo University of Agriculture, National Agriculture and Food Research Organization, Kyushu University	Yayoi Obata, Yuji Hirao, Katsuhiko Hayashi	Granted: JP	9/17/2015
WO2018/225802	Method for producing sperm stem cells from PSCs, enabling long-term culture and sperm production	Kyoto University	Mitinori Saitou, Yukiko Ishikura	Granted: JP	6/7/2017
Pending					
WO2019/107576	Method for long-term maintenance and amplification of PGCLCs and conversion to oocytes	Kyoto University	Mitinori Saitou, Hiroshi Ohta, Hidetaka Miyauchi	Pending	11/30/2017
WO2019/244581	Method of producing ovarian follicles from PGCLCs in vitro (making possible in vitro oocyte maturation without live tissue)	Kyushu University	Go Nagamatsu, Yohei Nishimura, So Shimamoto, Katsuhiko Hayashi	Pending	6/21/2018
WO2021/049613	Direct induction method for rapidly producing oocytes from PGCLCs or PSCs, skipping intermediate states	Nobuhiko Hamazaki, Dioseve	Nobuhiko Hamazaki, Katsuhiko Hayashi	Pending	9/12/2019
WO2022/094628	Methods of generating ovarian follicular cells from PSCs	Conception Biosciences, Inc.	Rhishikesh Bargaje, Karmen Bianka Seres, Pablo Hurtado-Gonzalez, Alyssa Miller	Pending	11/2/2020
US provisional application no. 63/326,607	Methods and compositions for producing oogonia-like cells		Pranam Chatterjee[a], Christian Kramme[a], Merrick Pierson Smela, George M. Church[a]	Provisional	
US provisional application no. 63/326,640	Methods and compositions for producing granulosa-like cells		Pranam Chatterjee[a], Christian Kramme[a], Merrick Pierson Smela, George M. Church[a]	Provisional	
US provisional application no. 63/326,656	Methods and compositions for producing PGCLCs		Pranam Chatterjee[a], Christian Kramme[a], Merrick Pierson Smela, George M. Church[a]	Provisional	

JP, Japan; EP, Europe; US, United States; PGCLCs, primordial germ cell-like cells; PSCs, pluripotent stem cells. Sources: Lens.org, bioRxiv.org [a]Affiliated with Gameto, Inc.

Ordre public and morality exclusions. The World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs) allows member countries to exclude inventions from patentability if they offend morality or public order. In the past, this exception has been invoked in various contexts by the European Patent Office (EPO), which, for example, has refused to allow patent claims involving stem cells obtained through the destruction of human embryos. IVG will allow various ethically fraught practices such as amplified embryo production and widespread genetics-based embryo selection. It is conceivable that such a patentability exception could be applied to patents seeking to claim these IVG techniques.

Natural phenomena. In the US, while patent-eligible subject matter is defined as "any new and useful process, machine, manufacture, or composition of matter," there is a judicial exception for natural phenomena and products of nature. Debate over the patent eligibility of some ART technologies has already emerged. For example, early embryo viability assessment (EEVA), which claims to indicate which embryos are the 'best' based on time-lapse photos during in vitro development, has raised concerns that companies are patenting natural phenomena[47]. Given that many of the IVG patents claim to be recapitulating natural gamete development, such patents could be challenged on these grounds. But even patents covering these processes are not allowed, it is possible that courts could uphold patents on the accelerated form of IVG, using transcription factors.

Prohibitions on patenting human organisms. In the United States, section 33(a) of the Leahy-Smith America Invents Act (AIA) provides that "no patent may issue on a claim directed to or encompassing a human organism." The legislative history of the AIA clarifies that stem cells are patent eligible but patent claims directed to or encompassing human embryos and fetuses are prohibited[48]. Similarly, a 1998 European Union directive bans patenting "the entire human body in all its developmental phases" as well as processes for cloning human beings, processes for modifying the germ-line genetic identity of human beings, and the use of human embryos for industrial or commercial purposes[49]. Accordingly, patent claims directed to the gamete cells produced using IVG techniques could be barred by these provisions. However, while this might apply to gametes or cell types created in the IVG process, they would not necessarily invalidate patents claiming the methods used to produce them.

Medical procedures. Both the United States and Europe effectively prohibit the patenting of medical procedures such as surgical techniques and dialysis[50]. While, to our knowledge, challenges to patents claiming ART techniques have not yet been brought, the possibility exists that at least some aspects of in-clinic ART procedures would be covered by these exclusions.

A possible future for IVG patenting

A quarter century ago, Michael Heller and Rebecca Eisenberg hypothesized the possible emergence of an "anticommons" or "thicket" in biomedical research as growing numbers of parties obtained patents covering overlapping aspects of new technologies and imposed increasing, sometimes insurmountable, transactional costs on those seeking to deploy such technologies[51]. Many have concluded that a patent thicket in various biomedical technologies has failed to materialize[52,53], but the situation may be changing as biomedical innovations move from the classic model of 'one drug, one patent' to a landscape populated with greater numbers of patents held by different parties[54]. For example, the biologic drug Humira (adalimumab) is allegedly covered by a thicket of over 100 patents[55,56]. Similar patent thicket concerns have been raised with respect to CRISPR gene-editing technology[57]. If the issuance of seemingly overlapping patent rights described above continues apace, then IVG providers may be faced with the daunting prospect of obtaining licenses from multiple parties to perform these procedures, a feat that may prove difficult for small or nonprofit providers and clinics.

Another issue that may emerge with respect to IVG is the breadth of early patents in the field. It is not unusual for an emerging field to be dominated by broad 'blocking' patents obtained by pioneering researchers or their institutions. This is how the field of CRISPR-based gene editing appears to be evolving, with key patents held by institutions that were early leaders in developing the technology[58]. IVG, however, may present a different model.

As discussed above, new companies that have not been active in the ART market are seeking broad patent coverage on potential aspects of IVG treatment. Given the early stage of clinical development of this technology, it is unlikely that these companies have successfully implemented these procedures in human subjects. Yet patent claims can be drawn broadly to clinical applications long before they are feasible even in the laboratory, a practice known as 'gun jumping'. This is possible because, despite requirements that inventions be "reduced to practice" in order to be patentable, applicants can speculate about possible approaches and techniques that have not been perfected, not to mention 'prophetic' experiments that are conceived but never actually carried out[59]. In the case of IVG, for example, patent claims drawn to human applications could be based on work done in mice, despite the long road from mouse models to humans in actual practice.

The result is that numerous patents, especially in the US, claim inventions that the patentee has not actually reduced to practice and that may never be suitable for use in the clinic. Nevertheless, such patents remain available to their owners as tools for extracting licensing fees or blocking new entrants to the market. For example, the now-defunct blood analysis company Theranos obtained hundreds of patents covering microfluidic testing of blood and other samples even though it never developed a working product. When the company ceased operations, a creditor acquired the patents and began to assert them against the developers of emerging COVID-19 diagnostic tests[60]. Though the litigation was eventually withdrawn, the Theranos patents remain on the books and continue to pose a threat to diagnostic companies. In a nascent field like IVG, small players such as clinics and medical practices may lack the expertise and resources to challenge the validity of asserted patents, whether or not they are valid.

The strategy of early and broad patent claiming is not new, yet it can become problematic. Even when academic work appears to give a researcher a clear claim to an invention, the patent situation can be complicated. Kyoto University's Shinya Yamanaka, for example, won universal recognition, including a Nobel Prize, for his invention of a four-factor recipe to create iPS cells. But a different patent — which preceded both Yamanaka's patent and his published results — predicted a method to produce such pluripotent cells[61]. Another patent, claiming a method that used only three factors to create iPS cells, was filed shortly after Yamanaka's[62]. Dozens more patents, many issued to entities that were not leaders in the development of the technology, have raised questions about how patents might affect the development of iPS cell technology[63,64]. For IVG as well, foundational academic research does not ensure control over all critical patents.

It is also possible for those who have made early patent filings to use continuations to claim improvements to the technology subsequently made or proposed by others. This practice was seen, for example, in the case of Rambus, a memory chip designer that was found to have adapted the claims of pending patent applications to fit technologies being discussed at meetings of a standards organization of which it was a member[65]. A similar scenario is possible for IVG, which will likely be continually modified even after its initial clinical use.

All of these trends seen in other technology areas could easily arise in the emerging area of IVG patenting.

Implications of the expanding IVG patent landscape

As shown in the preceding sections, the patent landscape of IVG will likely differ substantially from that of its predecessor IVF. IVF was largely unencumbered by patents, at least in its formative stages, whereas companies have begun to use patents to stake out important aspects of IVG technology and could come to dominate the clinical administration of IVG treatment. The implications and eventual consequences of this shift to a more corporate and patent-intensive ART landscape remain to be seen, but at this early stage a few observations can be made.

Incentives versus access. On one hand, by giving their holders exclusive rights to exploit new technologies for a period of years, patents create financial incentives to develop

those technologies. In some cases, when the cost of R&D is high, it is only the promise of market exclusivity that induces innovators to make the expenditures necessary to bring new products to market. This incentive rationale is rooted in the US Constitution, which authorizes Congress to secure to inventors the exclusive rights to their discoveries in order to "promote the progress of science and useful arts." Conversely, because patents allow a single entity to monopolize the market for particular patented products or processes, patents can limit competition in those markets. This reduction in competition, at least during the term of a patent, enables the patent owner to charge higher prices and potentially limit the supply of patented products. For example, patented drugs are often unaffordable to patients who lack adequate insurance coverage or live in low-income countries. When patents expire and generic manufacturers are permitted to enter the market, prices for the drugs often drop, thereby increasing access.

This fundamental tension between incentives and access has motivated patent policy discussions for decades[66,67]. Recently, it has been at the forefront of debates over prescription drug pricing[68], genetic diagnostics[69], CRISPR–Cas9 gene editing[70] and COVID-19 vaccines[71]. While the case for strong patent incentives is often made in the area of prescription drugs, in which the cost of bringing a new drug to market is estimated to range from hundreds of millions to billions of dollars, this argument is less compelling when discoveries are likely to have been made whether or not patents are awarded. For example, Contreras[69] observes that the *BRCA1* and *BRCA2* genes, which were the subject of controversial patents held by the company Myriad Genetics, would almost certainly have been discovered about the same time by competing academic researchers absent Myriad's efforts. Likewise, research shows that patents have played a negligible role in groundbreaking research relating to the human microbiome[72].

Whether significant financial incentives will be required to advance IVG technology remains an open question. As noted above, IVF was developed during the 1970s without much private funding and has matured into a worldwide industry that remains largely patent free. Technologically, IVG is far more complex than IVF. Also, as discussed above, it appears that IVG may be subject to greater regulatory scrutiny than IVF. These two factors could drive up the cost of IVG innovation, suggesting that patent incentives might be helpful to advance the technology to commercialization. This being said, it is unlikely that IVG, even if regulated, will require the amount of capital necessary to bring a new small-molecule drug, biologic or gene therapy to market. Thus, the lengthy period of patent protection for a technology such as IVG could unjustifiably increase costs and limit access to this potentially transformative technology.

It seems likely that IVG patents held by different parties will, to some extent, overlap or complement each other. The extent to which they might pose obstacles to widespread use may depend on the ambitions of the patent holders. The majority of IVG research to date has taken place in academia, where researchers have been funded by public grants or philanthropy. Saitou has indicated that he hopes IVG technology will be widely and freely used, and says he has no intention of using patents to restrict reasonable access by others (M. Saitou, personal communication). His company aims to use IVG for species conservation and creating a sustainable food supply, in addition to fertility. By contrast, the IVG companies funded by venture capital firms will likely seek to profit from the potentially lucrative ART market.

Access-expanding measures by universities and research funders. Even in a patent-intensive industry, measures exist to ensure broad public access to a technology's benefits. For example, many important scientific discoveries are made at research universities. In the field of IVG, foundational methods have been developed by researchers at Kyoto University and others. To the extent that universities with clear public missions hold patents and other rights to IVG technologies, they may make those rights available broadly at modest charges, as the University of Michigan did with its patents on the *CFTR* gene in relation to cystic fibrosis and as Stanford and Columbia did with respect to PCR and recombinant DNA technology, respectively[69]. In addition, when universities license their patents and technologies to the private sector, they may impose restrictions on how those technologies will be used and made available in practice. For example, universities that license their patents to private IVG providers or product vendors could impose contractual constraints as to pricing and access. Such approaches have recently been proposed in the context of CRISPR–Cas9 and COVID-19 vaccine technology[70,73,74].

Likewise, governmental funding entities such as the US National Institutes of Health (NIH) could impose such requirements on the recipients of grant funding and other research support. Much biomedical research in the United States and other countries is derived from government-funded work (particularly research at universities), so such constraints could be far-reaching. For example, the NIH once required that companies that were parties to cooperative R&D agreements with the government fairly price any resulting products[69]. Similar proposals have recently been made in the context of COVID-19 vaccines and treatments[75].

International patent considerations. Patent protection is national in scope, meaning that a separate patent must be obtained in each jurisdiction where exclusive rights are sought. In the case of pharmaceutical products, only a few countries have domestic manufacturing capabilities, and securing patents in these countries is typically sufficient to control global supply of the products. ART technologies, on the other hand, are administered locally in clinics and hospitals around the world using reagents and other materials that may be sourced locally. Accordingly, IVF treatments are currently offered in approximately 80 different countries[4].

If the same holds true for IVG, then its worldwide deployment might not be dependent on the acquisition of patented drugs or reagents from high-income countries. Moreover, as discussed above, patents on IVG technology may not be available in some countries as a result of moral and subject matter limitations of the patent law. As a result, IVG treatments may emerge in any country with a suitable healthcare infrastructure. If they wish to control the global administration of IVG procedures, patent holders will be required to expend considerable sums to secure protection around the world, as the performance of IVG procedures in countries where patents have not been obtained cannot be restricted. Early patent coverage for IVG technologies appears to be limited to major economies (Table 1).

The result of this limited coverage could have unexpected effects. For example, medical tourism could arise in countries where IVG procedures can be performed at a lower cost than in countries where patents exist. Or such considerations may encourage patent holders to moderate their charges, so as not to drive customers out of their markets entirely.

Conclusions

IVG technology and the companies that hope to sell it still face many challenges, both regulatory and scientific. Yet these hurdles have not

stopped companies from seeking patents on a range of potential IVG approaches. Even with inherent limitations on patent-eligible subject matter, it is possible that large swaths of the IVG technology landscape will be claimed by patents. IVG could set a new standard of reproductive health, with social implications far beyond its predecessor, IVF. But unlike IVF, the administration of IVG may shift from thousands of independent clinics around the world to a handful of corporate providers or their licensees. The implications of this shift are difficult to predict at this early stage. Yet while much has been written about the need to move slowly to ensure that IVG risks are minimized, we must also ensure that its fruits are broadly distributed without exacerbating existing global reproductive disparities.

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Competing interests

D.C. works at Institute for the Advanced Studies of Human Biology, which carries out some of the research referred to in the article. His employer, Kyoto University, holds some of the patents discussed.