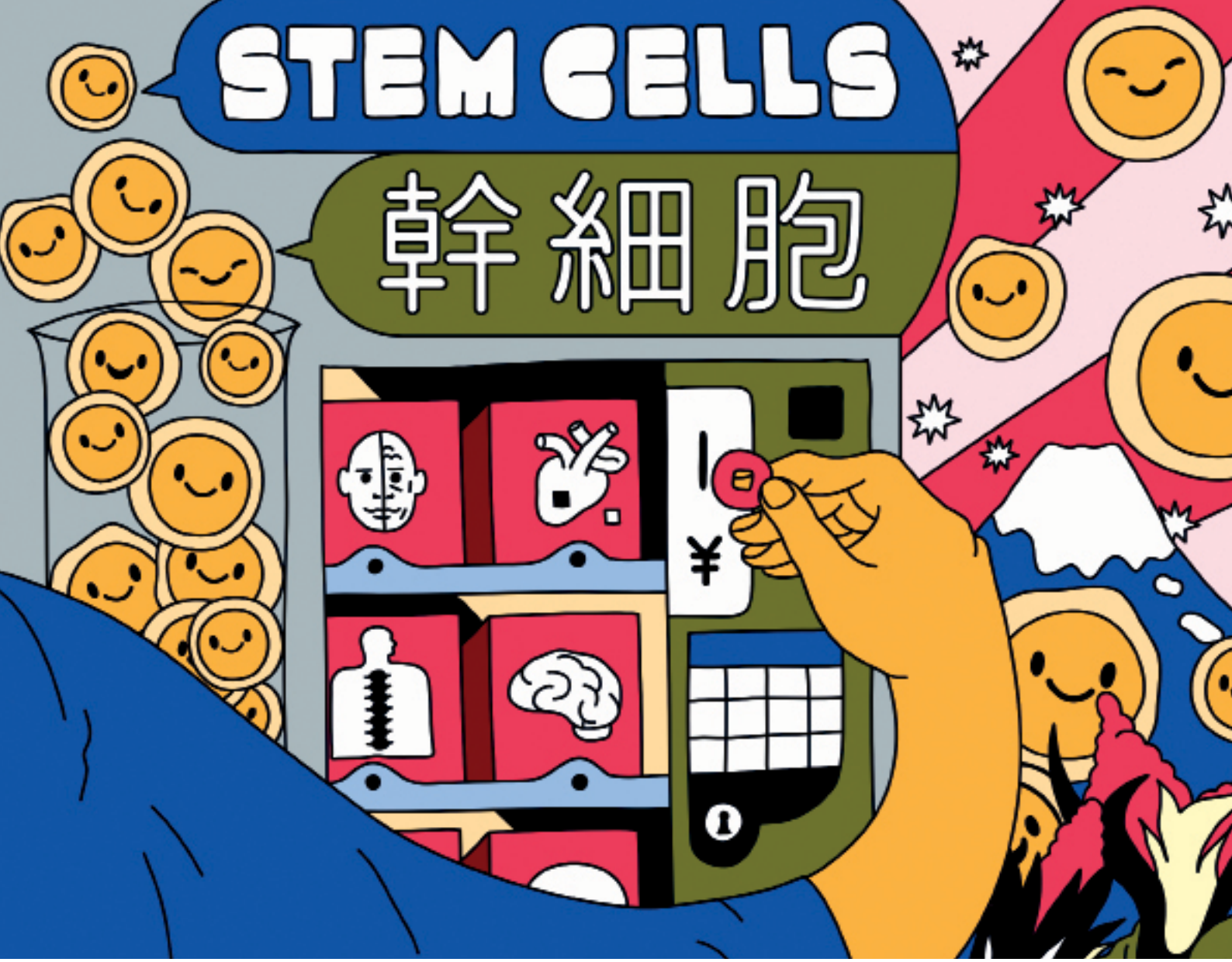

STEM CELLS 2 GO

Japan has turned regenerative medicine into a regulatory free-for-all. Patients across the world could pay the price.

BY DAVID CYRANOSKI

Tucked away in Tokyo's trendiest fashion district — two floors above a pricey French patisserie, and alongside nail salons and jewellers — the clinicians at Helene Clinic are infusing people with stem cells to treat cardiovascular disease. Smartly dressed female concierges with large bows on their collars shuttle Chinese medical tourists past an aquarium and into the clinic's examination rooms.

In a typical treatment at Helene, clinicians take skin biopsies from behind the ear and extract stem cells from the fat tissue within. Then they multiply the cells, infuse them intravenously and, they claim, let them home in on the damage — in this case, arteries stiffened by atherosclerosis.

Two posters on the wall outline promising results backed by major pharmaceutical companies and published in top scientific journals. They lend an air of legitimacy, but neither presents data on treatments offered at the clinic. When pressed for details by a visitor (who did not identify himself as a journalist), a concierge said that she could not offer evidence that Helene's services are effective at treating the condition, mainly because results vary by patient. She eventually explained that the treatment is more for prevention. "It's for anti-ageing," she said.

When *Nature* later contacted the company with a list of questions, a representative declined to provide evidence that the treatment works or

ILLUSTRATION BY FABIO BUONOCORE

information on the number of people treated or their outcomes, saying that the company would be announcing the results in future conference presentations. He affirmed that Helene Clinic conducts all the necessary reviews and approvals for the procedures it performs as required by law, and that patients have not developed side effects.

Clinics such as this, which sell unproven cell-based therapies, aren't new and aren't unique to Japan. They've become common globally, from Mexico to Ukraine, India and Australia, and regulators are struggling to keep up. In the United States, authorities have grappled with a surge of clinics selling therapies that are unsupported by evidence and, in some instances, have harmed people. In Japan, however, the proliferation of stem-cell clinics is different: it is sanctioned and promoted at the top echelons of government, thanks to a pair of regulatory acts designed to stimulate business and position Japan as a world leader in regenerative medicine.

Five years after Japan adopted these regulations, more than 3,700 treatments, including many based on stem cells, are on offer at hundreds of clinics across the country, and a wave of foreign companies has set up shop there. "Japan has become a focal point for the development of innovative therapies," says Gil Van Bokkelen, chief executive of the biotechnology company Athersys in Cleveland, Ohio, which is pursuing clinical trials of a stem-cell based treatment for stroke and respiratory disease in Japan.

Many companies, however, are taking advantage of the regulatory paths to avoid rigorous testing of their therapies and get them on the market fast. Scientists say that people who use them are probably not getting effective treatments. Most of the therapies approved for serious illnesses are supported by scant evidence, and there have been at least four reports of adverse events, including one death. Even government researchers and academic scientists who support the regulations say that changes are necessary.

Clinics maintain that they are operating within the law. And government officials argue that Japan's system is safer than those in other countries because it keeps tabs on the treatments being offered. But the policies might be giving people false hope about how effective these therapies are.

Meanwhile, Japan's bold experiment in deregulation is beginning to influence others. Taiwan and India, for example, have started to follow the country's lead, and regulators elsewhere are feeling pressure from companies, patients and other advocates to speed up the approval process. "If we're left with very different global regulatory standards, it's going to be a really big problem," says Peter Marks, director of the Center for Biologics Evaluation and Research at the US Food and Drug Administration (FDA).

One of the harshest critics, cardiologist Yoshiki Yui at Kyoto University in Japan, says that the acts made quick gains in terms of business development, but were short-sighted. "They've given no thought to what happens when things go wrong," says Yui.

SAFETY, NOT EFFICACY

Shortly after taking office in December 2012, Japanese Prime Minister Shinzo Abe promised to invest ¥110 billion (US$1 billion) over the next decade into regenerative medicine. The bullish attitude came just months after Shinya Yamanaka at Kyoto University won the Nobel Prize in Physiology or Medicine for his work on induced pluripotent stem cells. Abe boasted that Japan is the world leader in regenerative-medicine research, but lamented the slow pace of clinical application. He soon announced two measures that he hoped would change that (see 'Deregulation in two acts').

One of these, the Act on the Safety of Regenerative Medicine (ASRM), adopted in November 2014, allows hospitals and clinics to market cellular therapies without going through the usual kinds of trials to prove that a medicine is effective. To start offering such treatments, hospitals need to show that they have a cell-processing facility that is certified by the Ministry of Health, Labour and Welfare and then pass their proposal by an independent review committee, which must also be certified by the ministry.

Before the legislative change, rogue clinics were springing up and taking advantage of medical tourism. The act was meant to make sure that all clinics are registered so there would be no surprises, says Masayo

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Takahashi, an ophthalmologist and prominent member of the Japanese Society for Regenerative Medicine who has been on government regenerative-medicine advisory panels. "The strategy is to include everyone, then get gradually stricter" about what deserves to be listed, she says.

But the ASRM's registry can be misleading, say critics. Doug Sipp, who researches regulatory policy at RIKEN in Kobe, says that it has brought "more transparency to the industry". It has forced rogue clinics to meet some basic standards. There is a real risk, however, that patients will view the registry, "as a kind of validation", he says.

For example, Avenue Cell Clinic, a sleek operation in Tokyo that looks more like a spa than a medical centre, features the fact that its treatments are listed on the ASRM registry prominently on its website. At least ten patients have had fat-derived stem cells injected into their blood to cure or slow the progression of the neurodegenerative disorder amyotrophic lateral sclerosis (ALS).

An Avenue Cell Clinic customer service representative said on the phone to someone calling for information (who did not identify himself as a journalist) that the symptoms of 50–70% of patients improved after the therapy, which costs ¥1.5 million per dose. Those who benefit are advised to continue infusions every two or three months. "Some people can afford that," the representative said. The clinic has about 1,000 patients per year for other indications.

Five scientists working on regenerative medicine for ALS who were contacted for this story said that there was no convincing evidence that this kind of stem-cell treatment would help people with the disease, and there are several reasons to think that it wouldn't work. Robert Baloh, who studies ALS at the Cedars-Sinai Regenerative Medicine Institute in Los Angeles, California, put it bluntly: "Quackery and false treatments have been marketed directly to patients for hundreds of years, and this is no different." A representative from Avenue Cell Clinic refused a formal request for an interview from *Nature*, but stated in an e-mail that the clinic is acting in accordance with the ASRM. When pushed for a response to the verdict from ALS scientists, the representative said that they were too busy treating patients to respond.

In addition to the questions about evidence and efficacy, there are also concerns about the qualifications and independence of the committees that approve such treatments for inclusion in the registry. The health ministry requires that these committees comprise five to eight people, and include specialists in cell biology, regenerative medicine, clinical research and cell culture. It also requires input from lawyers, bioethicists and biostatisticians. But rules about conflicts of interest on the committee have been lax.

Helene Clinic, for example, had an in-house committee that approved some of its therapies, including a treatment for atherosclerosis. A representative for the company says that this therapy was never given to patients and Helene now uses an independent, third-party committee. The in-house committee was disbanded in March, according to the

DEREGULATION IN TWO ACTS

Two laws introduced in Japan in 2014 offer a fast track to the market for stem-cell-based treaments and other types of regenerative medicine. The Act on the Safety of Regenerative Medicine (ASRM) allows companies to register a therapy under one of three risk categories.

Classification	Requirements	Number of therapies registered (by June 2019)
Class III (low risk)	Treatments using cells from a patient and performing a function similar to the one they originally served, such as immune cells activated to fight cancer.	3,373
Class II (moderate risk)	Treatments using cells from a patient, but performing a different function, such as stem cells derived from fat used to treat atherosclerosis or amyotrophic lateral sclerosis.	337
Class I (high risk)	Treatments using cells from a riskier source such as embryonic stem cells, gene edited cells or cells from another person.	0

The Pharmaceutical and Medical Devices Act allows for conditional approval of treatments that have gone through some clinical testing. It gives companies the opportunity to market a treatment nationally and to receive insurance payments, but companies must collect extra data on efficacy over a seven-year period. Only three treatments have received this approval.

Treatment	Purpose
HeartSheet	Cells from skeletal muscle are used to seed a sheet of tissue designed to help heal damaged heart muscle.
Stemirac	Uses stem cells derived from bone marrow to try to treat spinal-cord injury.
CLBS12	Uses blood-forming stem cells to treat critical limb ischaemia.

health ministry. The ALS treatment and several other therapies offered by Avenue Cell Clinic were approved by a committee that includes a staff physician. The clinic did not respond to questions about this.

The ministry instituted policies in April to prevent such conflicts. But even with fully independent committees, clinics can shop around for the answer they want. Yoji Sato, who heads the cellular therapeutics unit of Japan's National Institute of Health Sciences in Kawasaki and who sits on two committees himself, says that "committee surfing" is a big problem.

The government is considering extra fixes, such as requiring training to make the committee system better. "Maybe there is a conflict of interest in the committees, maybe the treatments are not effective, but that's our limit right now," Sato says.

He nevertheless argues that the system is superior to what exists in the United States, where regulators are continually chasing rogue clinics. Sato cites the case of two people who lost their sight after receiving an unproven and unapproved stem-cell treatment in Florida. It took the FDA four years and a tortuous legal battle to stop the company from offering the treatment. In Japan, for those lacking committee approval, "the police can go and arrest people", Sato says.

CONDITIONAL APPROVAL

The other important policy that Abe's government implemented in 2014 is known as the Pharmaceutical and Medical Devices Act. Under it, a company can earn 'conditional approval' to sell a treatment nationwide — not just at a single clinic or hospital — and have the costs covered by the insurance system. Unlike with the ASRM, the firm needs to present data that suggest efficacy from a small clinical trial. It can then sell the treatment for up to seven years, as it ostensibly collects better efficacy data. So far, only three treatments have earned conditional approval: one for spinal-cord injury, one for heart disease and one for critical limb ischaemia, a painful condition characterized by reduced blood flow to the extremities.

But the pared-down clinical trials necessary for conditional approval have stoked concern in the scientific community. A 2016 report from the International Society for Stem Cell Research said that giving marketing approval on the basis of small-scale trials could slow down rigorous evaluations of the treatments and "erode confidence in the scientific standards of the field"[1].

Anecdotally, some people have reported issues. One man with a chronic heart condition, who asked not to be named to protect his privacy, tried an experimental treatment that involves creating a thin sheet of tissue using transplanted muscle cells extracted from a patient's thigh and placing it onto the damaged heart during open-chest surgery. A version of the treatment, called HeartSheet, was conditionally approved for treating a condition known as ischaemic cardiomyopathy in 2015. The man, who had a different type of cardiomyopathy, met one of the technology's co-creators, Yoshiki Sawa, a surgeon at Osaka University in Japan. Sawa told the man that he would be a good candidate for the experimental treatment. The man, who was under the impression he was receiving HeartSheet, was worried because few people with his diagnosis had received the treatment, and he had never had heart surgery before. But he gave it a chance.

The man says that he never felt his condition improve. Nine months later, he suddenly started feeling a shortness of breath he had never experienced before. Diagnosed with cardiac failure, he was hospitalized for a month. A month after being released, he was hospitalized again. A little more than a year after trying the procedure, he was told he needed a heart transplant. "I was told things were getting worse," he says.

Without more information, it is impossible to say whether the experimental treatment contributed to the man's cardiac failure. It is just one case, and other explanations are possible. But the uncertainty illustrates part of the problem. The clinical trial that led to HeartSheet's conditional approval included only seven people. Terumo Corporation, which markets the treatment, is still collecting data on its effectiveness for ischaemic cardiomyopathy; it says the patient did not receive HeartSheet as part of his treatment.

Central to the debate over Japan's policy is the value of randomized, placebo-controlled trials. These are conventionally considered to be the gold standard for clinical research, but Japan's government followed a position floated by the Japanese Society for Regenerative Medicine in 2012, which specifies that trial designs to prove efficacy should not always require control groups receiving a placebo or conventional therapies.

In clinical trials leading to the approval of HeartSheet, Sawa stated that the natural progression expected for such patients was steady degeneration. Five of the seven people who received HeartSheet didn't get worse, and so the treatment looked like it was helping. But a study of some 3,500 individuals in Japan shows that most people with a similar severity of heart disease to the people in Sawa's trial get better or are stable without drastic intervention[2]. Sawa did not respond to a request for comment.

Japan's health ministry has stuck by its stance on placebo-controlled clinical trials for regenerative medicine. Following the criticism of a treatment for spinal-cord injury called STR01 that went on sale in May, Shinji Miyamoto, a health-ministry representative, argued that double-blinded experiments with the therapy were "structurally impossible" and said that a sham procedure or placebo "would raise ethical issues"[3].

Bioethicists have long debated the potential harms caused by sham treatments in clinical trials and whether they are fair to participants. Some are certainly too invasive, says Jonathan Kimmelman, a bioethicist at McGill University in Montreal, Canada, who has advised the Japanese government on clinical-trial policy. But doctors researching stem-cell therapies for spinal-cord injury say that a placebo-controlled trial for this condition would be relatively easy.

Osamu Honmou, a neurosurgeon at Sapporo Medical University in Japan who offers STR01, had previously advocated for double-blinded, placebo-controlled trials to prove the treatment's efficacy in people who have had a stroke. According to a 2016 publication[4], he expected to be in the middle of carrying out just such a trial by now. But he did not respond to *Nature*'s request for clarification as to what makes such trials appropriate for treating the damage caused by stroke, but not for spinal injuries. A health-ministry representative says that a sham procedure would

be unethical in the latter case because patients need treatment within a certain window of time, after which therapy might prove less effective. Such arguments, however, assume that the procedure is effective.

Several prominent scientists in Japan have told *Nature* that STR01, also known as Stemirac, shouldn't have been approved for spinal-cord injury. "Abe's cabinet needs one or two successful examples of success in science urgently," says one cardiologist, who did not want to be named. "Abe's cabinet is being too aggressive." The administration did not respond to requests for comment.

GLOBAL AMBITIONS

Despite holes in the system, Japan is trying to get its regenerative-medicine policies adopted elsewhere, in part to secure markets for its treatments. According to a five-year plan released this March by the health ministry's drug-regulating division, the government funds outreach programmes aimed at "disseminating Japan's model for regulating regenerative-medicine products, and fostering trust towards Japanese regulatory agencies and get Japan's regulatory model introduced in other countries".

The efforts seem to be making an impact, says Sato. Taiwan has drafted a conditional-approval law for regenerative medicines based on Japan's legislation, and South Korea approved a system similar to Japan's in August. India mentioned Japan's system in deliberations leading to its first regenerative-medicine conditional approval in 2015. And this year, mainland China announced a draft policy that would give hospitals free rein to use stem cells as "medical practice". "Several other countries have responded in kind, prioritizing a skewed vision of economic competitiveness over patient welfare," says Sipp.

Some hope to see a similar system in the United Kingdom, and say that the timing — with the country's exit from the European Union looming — is right. In a February 2018 interview with the BBC, Ajan Reginald, co-founder and chief executive of Celixir, a company in Stratford-upon-Avon, UK, that makes a cellular therapy called Heartcel for heart disease, said that Brexit could offer the United Kingdom a chance to introduce its own accelerated regulatory pathway.

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"There is a lot of enthusiasm amongst certain people in the UK to adopt the Japanese model," says Patricia Murray, a stem-cell biologist at the University of Liverpool, UK. The kind of deregulation done in Japan, she says, "will enable companies to sell their bogus therapies direct to consumers".

And the rapid pace of development has presented a challenge for regulators elsewhere. The FDA has been under increasing pressure from businesses and patient groups — including the California Institute for Regenerative Medicine and conservative thinktank The Heartland Institute — to take an approach more like Japan's[5].

Marks says it's a problem because people point to Japan and say, "'You guys at the FDA, you're just not approving stuff.'" Marks was responding to questions at a medical journalism conference in Baltimore, Maryland, in May and he affirmed that his group wants to see new treatments made available. "We just want to see that they're safe and effective."

Lee Buckler, the chief executive of regenerative-medicine company RepliCel in Vancouver, Canada, which licensed its skin-rejuvenation product to the Tokyo-based cosmetics company Shiseido in 2016, sees this pressure as a plus. He says people who desire fast access to medicines see what's happening in Japan and "press for similar access in their country".

Pride over Japan's achievements in stem-cell biology and regenerative medicine have played a large part in the efforts to grow the industry. But Yamanaka, who has been one of the most prominent faces of those achievements, has remained relatively quiet on matters of deregulation.

In contrast to the quickly moving currents elsewhere in the country, Yamanaka's institute, which is dedicated to bringing stem-cell treatments to the clinic, seems unwilling to rush through a clinical trial. "Double-blinding control should be considered whenever possible," Yamanaka told *Nature*. And although he understands that this can be difficult for some cell therapies, even in those cases, "scientists should do their best to make clinical trials as objective and scientific as possible".

In the absence of objective and scientific measures, it becomes difficult to know what and who to trust, say some stem-cell researchers. "There is a problem," says Takahashi. "The law was made for men of good nature, but there are many that are not good." Still, she takes the long view: "In 10 years, cell therapy will be very good. So we can tolerate criticism now." ■ SEE EDITORIAL P.463

KYODO NEWS/GETTY

Japanese Prime Minister Shinzo Abe (front) with stem-cell biologist Shinya Yamanaka (left) and then RIKEN president Ryoji Noyori at a lab visit in 2013.

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1. Daley, G. Q. *et al. Stem Cell Rep.* **6**, 787–797 (2016).
2. Tsuji, K. *et al. Eur. J. Heart Fail.* **19**, 1258–1269 (2017).
3. Miyamoto, S. *Nature* **569**, 40 (2019).
4. Honmou, O. *Jpn J. Neurosurg.* **25**, 979–984 (2016).
5. Sipp, D. & Sleeboom-Faulkner, M. *Science* **365**, 644–646 (2019).

CORRECTION

The News Feature ‘Stem cells 2 go’ (*Nature* **573**, 482–485; 2019) stated that an anonymous patient received a treatment called HeartSheet, developed by Yoshiki Sawa. The patient was told he was receiving a sheet of muscle cells from his thigh, which matches the description of HeartSheet, and was under the impression that Sawa was administering HeartSheet. Terumo, the company that produces HeartSheet, says the experimental treatment the patient received was not HeartSheet. Sawa has not returned *Nature*’s numerous requests for information or comment.