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Debunking rapid-onset
gender dysphoria

Plus
The end of Roe

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HIS IS THE GENDER ISSUE, OUR FIRST.

Frankly, it is a topic that this magazine and others in its space gave too little thought to for too many decades. Not only has gender long been a differentiator in the way people experience technology, but technology also increasingly mediates the way we understand and experience gender. When we started planning for this issue months ago, it felt both overdue and like an important lens through which to view the limitless possibilities of the future. Now, as we're wrapping it up, it feels urgent in a wholly new way.

As we were putting it together, the US Supreme Court overturned *Roe v. Wade*, stripping away the constitutional right to abortion. This revanchist decision took us backwards in time. Rather than representing progress or possibility, it is a calamitous setback for human rights and public health. Melissa Gira Grant opens the issue on page 24 with a deft portrait of the threats posed by an analog court in the digital world. On page 19, Susie Cagle shows what extending legal “personhood” all the way back to conception could mean for fertility treatments.

Those treatments could look very different in the future. On page 28, Jessica Hamzelou looks at the race to make human sex cells in the lab. If successful, it could mean the end of infertility itself, and open up all sorts of new routes to parenthood. “If a cisgender woman could create her own sperm cells, she could use them to fertilize the egg of a partner,” Hamzelou writes. “Likewise, a cisgender man could produce his own eggs to be fertilized by the sperm of his partner.”

Meanwhile, a difficult political attack is playing out over the rights and realities of trans people. Ben Kessen looks at the history of how a flawed study on rapid-onset gender dysphoria, or ROGD, went viral online and was repeatedly enlisted as a bloody shirt to wave for anti-trans legislation. It was, Kessen writes on page 84, a “vivid example of how questionable science can be weaponized to achieve political goals.”

Because although science and technology have long pushed the boundaries of sex and gender, too often they have acted as constraints. Margaret

O’Mara’s excellent piece on the history of women’s progress (or lack thereof) in Silicon Valley, on page 42, explores this tension and the sorry truth that “tech remains mostly a straight, white man’s world.” Consequentially, O’Mara notes, “one striking thing about today’s activists, organizers, and whistleblowers is that nearly all of them are female, gender-nonconforming, or queer.” I’ll leave you to read her conclusion on your own.

In 2018, we began publishing themed issues of this magazine every other month. The idea is that each issue could dive into a topic and explore it from all sorts of perspectives. Themed issues also helped give an organizing principle to a publication that exists outside the buzz and whine of the daily news cycle.

You may have noticed a change in recent issues. Themes no longer run cover to cover. We’ve begun to give the opening pages of the magazine some recurring elements and departments that often have nothing to do with a particular theme. Some of these are meant to highlight the best of our online journalism. Some will serve to highlight the work of new writers, artists, inventors, and innovators. Others, we hope, will offer a little bit of eye candy. You’ll continue to see these sections evolve in the coming issues. But we will also continue to weigh in on themes that we see as foundational to tech, science, and humanity.

I hope this issue inspires and provokes. I also hope you are enjoying the changes we are bringing to this magazine. As always, I’d love to know what you think: mat.honan@technologyreview.com.



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"The way we make babies could be about to change. Maybe."



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DISCOVERING A BETTER FUTURE FOR SAUDI ARABIA AND FOR THE WORLD

We all know how difficult the past two years have been for many people and nations across the globe. Yet from adversity springs opportunity.

As governments and policy-makers around the world came to recognise the necessity of global cooperation when faced by a threat such as Covid-19, a new age of possibility was born.

That's why Saudi Arabia is prioritising Research, Development and Innovation (RDI) as a central part of its transformation, committing to investing tens of billions of dollars over the coming decade to address the issues affecting us all.

We will make it easier for public and private bodies to work together, by ensuring cooperation with major research centres, institutions and international companies.

A new RDI Authority will provide leadership, direction, secure funding and develop talent to drive innovation and advance technological development.

Our ambitions and financial resources will be aimed squarely at what we think are the four most pressing areas of global concern. These are: Health and Wellness, Sustainable Environment and Supply of Essential Needs, Energy and Industrial Leadership, and Economies of the Future.

Human health is not merely a medical concern. It is also, as the pandemic demonstrated starkly, about how livelihoods and wellbeing across the whole world can be affected by events in one part of it. We are putting finance and the best human capital to work on these problems, seeking to prevent and control disease with our genome mapping project, in conjunction with those of other nations.

Environmental sustainability also has profound implications. As we see the world's breadbaskets become less reliable, not least since

the war in Ukraine has caused a severe shortage of wheat, and drinking water grows ever scarcer, the Kingdom aims to address both challenges.

Having developed advanced, environmentally friendly desalination technology, we are demonstrating how this innovation provides not only clean water for drinking but how it can revolutionize agriculture in previously barren areas, with great possibilities for food security in the Middle East and Africa.

Saudi Arabia has prospered over the past century, in large part thanks to our oil reserves. Now, as the world embraces renewable energy, we intend to lead the pack with an effective energy transition. The Kingdom is preparing to diversify from its current energy strategy, innovating and changing, while continuing our role in international energy security.

We will work together with nations and institutions around the world to build stable economies of the future, exploring the potential of space and the deep sea as new frontiers for innovation and discovery. We will also reimagine the future of urban living. Human-centric, zero carbon, 'Cognitive Cities' are crucial to improving the quality of life for citizens in the Kingdom and internationally.

This initiative will supercharge our sustainable innovation capacity. By 2040, we expect that Saudi Arabia's spend on innovation will reach 2.5% of GDP. RDI in the Kingdom will create hundreds of thousands of new jobs. We will be opening our doors to top research talent from Saudi and countries around the world.

Our commitment to this mission addresses what lies ahead, its uncertainties, and its bright hopes too. This is the first chapter in a new story we are writing with the world to build a better future for humanity.

His Excellency Munir Eledsouki - President of King Abdul Aziz City for Science and Technology (KACST).

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The Download



Scientists hacked a locust's brain to sniff out human cancer

The cyborg insects could one day be used in a breath test to screen for disease—or inspire a new type of device.

By Jessica Hamzelou

Cyborg locust brains can help spot the telltale signs of human cancer in the lab, a new study has shown. The team behind the work hopes it could one day lead to an insect-based breath test for use in cancer screening, or inspire an artificial version that works in much the same way.

Other animals have been taught to spot signs that humans are sick. For example, dogs can be trained to detect when their owners' blood-sugar levels start to drop, or if they develop cancer, tuberculosis, or

even covid. In all cases, the animals are thought to be sensing chemicals that people emit through body odor or breath. The mix of chemicals can vary depending on a person's metabolism, which is thought to change when we get sick.

But dogs are expensive to train and look after. And making a device that mimics a dog's nose has proved extremely difficult to do, says Debajit Saha, one of the scientists behind the latest work, which has not yet been peer-reviewed.

"These changes are almost in parts per trillion," says Saha, a neural engineer at Michigan State University. This makes them hard to pick up even with state-of-the-art technologies, he adds. But animals have evolved to interpret such subtle changes in scents. So he and his colleagues decided to "hijack" an animal brain instead.

The researchers chose to work with locusts because these insects have been well studied in recent years. In a preliminary setup, they surgically exposed the brain of a living locust. Saha and his colleagues then inserted electrodes into lobes of the brain that receive signals from the insects' antennae, which the locusts use to sense odors.

The team also grew three different types of human oral-cancer cells, as well as human mouth cells that were cancer-free. They used a device to capture gas emitted by each of the cell types, and delivered each of these to the locusts' antennae. The locusts' brains responded to each of the cell types differently. The patterns of electrical activity recorded were so distinct that when the team puffed the gas from one cell type onto the antennae, they could correctly identify whether the cells were cancerous from the recording alone.

It is the first time a living insect brain has been tested as a tool to detect cancer, says Saha, who hopes to be able to use the brain and antennae in a portable device, which could then be tested on real people.

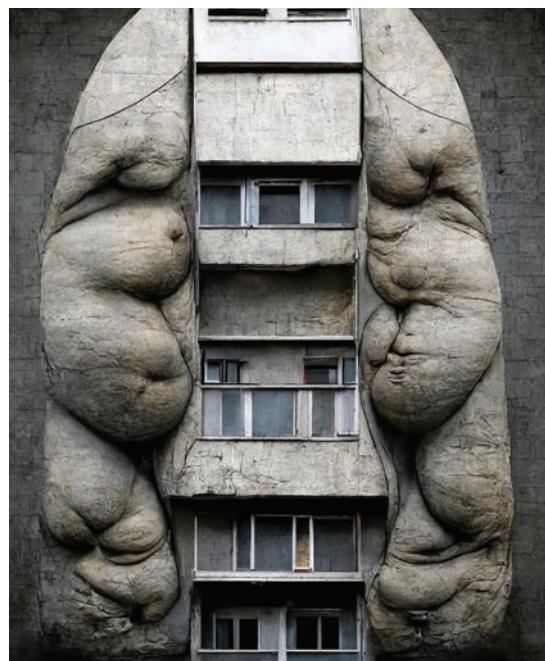
Natalie Plank, who is developing nano-material-based health sensors at Victoria University of Wellington in New Zealand, thinks the work is "super cool." "The potential of just being able to breathe on something and then know if you're at risk for cancer ... is really powerful," she says. Visit www.technologyreview.com to read the full story. ■

Sketching in algorithms

Increasingly, AI is being used at all stages of the creative process.

Image-generation models like DALL-E (a portmanteau of *Wall-E* and Dalí) and Midjourney have come a long way in just a few years. Both create images from text captions for a wide range of concepts expressible in natural language. Both are sending creatives happily down a rabbit hole.

Some fear that AI might replace writers, architects, and other creative workers. But designer Andrew Kudless—founder of Matsys, a design studio exploring the emergent relationships between architecture, engineering, biology, and computation—doesn't see these tools replacing anything but, rather, adding a new way for designers to explore history, culture, and their own imaginations. Explaining his experience with Midjourney, he says, “I see these images as a type of collaborative ‘sketching’ with the AI model as the images bounce back and forth between the neural network of the AI and the imagination and desires of the human. Although rife with assumptions, biases, and misunderstandings, what conversation between any two humans isn’t?” ■



A bold new vision for the future of AI

One of the godfathers of deep learning pulls together old ideas to sketch out a fresh path for artificial intelligence.

By Melissa Heikkilä and Will Douglas Heaven

Around a year and a half ago, Yann LeCun realized he had it wrong.

LeCun, who is chief scientist at Meta's AI lab and one of the most influential AI researchers in the world, had been trying to give machines a basic grasp of how the world works—a kind of common sense—by training neural networks to predict what was going to happen next in video clips of everyday events. But guessing future frames of a video, pixel by pixel, was just too complex. He hit a wall. After spending months figuring out what was missing, he has a bold new vision for the next generation of AI. In a draft document, LeCun sketched out an approach that he thinks will one day give machines the common sense they need to navigate the world.

For LeCun, the proposal could be the first step on a path to building machines with the ability to reason and plan like humans—what many call artificial general intelligence, or AGI.

But his vision may raise more questions than it answers. The centerpiece of the new approach is a neural network that can learn to view the world at different levels of detail. Ditching the need for pixel-perfect predictions, this network would focus only on those features in a scene that are relevant for the task at hand. LeCun proposes pairing this core network with another, called the configurator, which acts as the system's controller.

LeCun thinks that animal brains run a kind of simulation of the world, which he calls a world model. Learned in infancy, it's the way animals (including humans) make good guesses about what's going on around them. Infants pick up the basics by observing the world, says LeCun. Seeing a dropped ball fall a handful of times is enough to give a child a sense of how gravity works.

In many ways this kind of common sense amounts to the ability to predict what's going to happen next. But teaching it to machines is hard. Today's neural networks need to be shown thousands of examples before they start to spot such patterns.

That's why LeCun is now trying to train a neural network that can focus only on what's relevant. He says he has built an early version of this world model that can do basic object recognition and is training it to make predictions. But how exactly the configurator should work remains a mystery, he says. He envisions it deciding what level of detail the world model should focus on to make predictions possible, adjusting the model as required.

"I'm putting this out there," he says, "because I think ultimately this is the way to go." Visit www.technologyreview.com to read the full story. ■

Chicago's Array of Things

How an urban sensing project used edge computing and AI to answer big questions about city life.

By Christian Elliott

At a table in the Berghoff German restaurant in downtown Chicago in 2012, Charlie Catlett feverishly drew software architecture on a napkin. A senior computer scientist at Argonne National Laboratory at the time, Catlett had been working with scientists from the US Environmental Protection Agency to understand the

effects of air pollution on residents' health. But he felt limited by the agency's data. There were only a dozen air quality sensors in the entire city. Catlett dreamed of something bigger: a vast network of low-cost sensors that could measure everything from the urban heat island to noise pollution.

The timing was right—Chicago was about to put up 300,000 new streetlights, perfect locations for Catlett's "fitness tracker for the city." Over the next 10 years, with \$12 million in National Science Foundation funding, Catlett's Array of Things initiative brought together scientists, residents, and government departments to transform the field of precision urban sensing. The team devised an intentionally conspicuous package that looks like four large white mixing bowls stacked upside down. Inside are cameras

and a microphone, along with sensors for humidity, vibration, magnetic fields, temperature, air pollution, and barometric pressure.

Each node in the Array of Things was equipped with an Nvidia graphics processing unit (or GPU) to perform computations on images out in the field and sent only processed data along to the network—a form of edge computing. As an added privacy safeguard, the nodes are designed to be installed temporarily. "I would rather not see edge computing blanketed across the city, where everywhere you walk there's a camera that's analyzing what you're doing," Catlett says. "That to me is more dystopian than I'd like to see. But I do think that these edge devices have a place for diagnosis. You drop that capability in for a purpose, and then you pull it out." ▶



Between 2016 and 2019, the team attached 140 AoT nodes to Chicago streetlights. In a participatory process, the team at Argonne and local universities worked with everyday Chicagoans and city departments to decide where to place the sensors.

Dozens of studies have since used the sensor data. The nodes have been used to assess the safety of at-grade rail crossings, monitor pedestrian crosswalk usage, and detect flooding along the Chicago River. Kathleen Cagney, a collaborator on the project who directs the Institute for Social Research at the University of Michigan, used environmental data from the sensors for a study on public health, finding higher asthma rates in places where sensors detected more air pollution.

Catlett's team has since taken on lower-tech projects. Last year, for example, he and his colleagues partnered with Microsoft Research to install 115 low-cost solar-powered air quality sensors on bus shelters across the city. The resulting data showed pollution hot spots near industrial corridors on Chicago's South and West Sides in unprecedentedly high resolution. Environmental and community groups are now pressuring the city to make policy changes. The team plans to expand to thousands of air quality nodes in coming years.

The Array of Things is also expanding beyond Chicago through a project called SAGE. Unlike other urban sensing systems, which tend to be proprietary, SAGE allows anyone to write software for its nodes, which contain high-resolution hyperspectral cameras, lidar, and audio recorders.

Catlett says the team is now entering its deployment phase. By the end of the year, it plans to install 50 of the \$10,000 nodes in Chicago, replacing the earlier-generation Array of Things nodes. Several dozen have already been deployed across Southern California to detect wildfires and on towers nationwide to analyze weather and climate change. The National Science Foundation wants 80, one for each of their National Ecological Observatory Network towers. Oregon wants 100 to help detect earthquakes. The Australian science agency CSIRO put in an order. The library of open-source applications, which is available on GitHub, is growing constantly and includes programs for identifying birds by their songs and classifying funnel clouds from images.

The “fitness tracker for the city” has gone global—just in time to study our changing world. ■

We can do better than “male,” “female,” and “other”

Providing more-expansive gender options is not a difficult coding problem.

By Everett Franchuk

For transgender and nonbinary people like me, a society organized into only “male” and “female” makes us feel excluded. And it’s something that happens frequently, especially online.

Take Gmail. There are three gender options when you register. If you choose “other,” you can write in any gender identity. But first you must choose how you’d like Google to refer to you—as “male,” “female,” or “other.”

Why something as dehumanizing as “other”? Even a choice of the three most popular—“he,” “she,” and “they”—would be reasonable. From a coding perspective, it would be quite simple to update the dropdown language.

It should not be difficult for companies to improve gender inclusivity on existing forms. Providing additional options often requires just changing or adding a few lines of code. Here’s what it would look like to add a third gender category in PHP, which is used to program many web forms:

```
<select name="Gender">
<option value="">Select...</option>
<option value="M">Male</option>
<option value="F">Female</option>
<option value="N">Non Binary</option>
</select>
```

Of course, not all software is easy to update. That’s why it’s important for developers to create an inclusive program during the design stage, so that gender-diverse users can feel welcome at launch.

Though a minority, trans people are still a large demographic for software. According to estimates, there are over 1.4 million transgender adults in the US—around twice the population of Alaska. How is it that we accept one of the least populated states as the second option in an alphabetized menu of dozens of options, but find it inconvenient to add a few more genders?

“Female” and “male” should be at the top of the list; 99.5% of the population shouldn’t have to scroll excessively to find their gender. As a trans person, I’m simply asking that developers include options for everyone who uses their software. As a developer, I know that’s not too big an ask. ■

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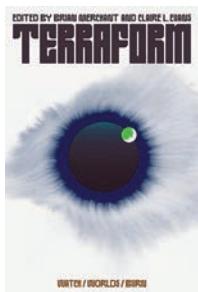
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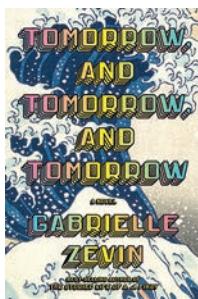
Book reviews



Terraform

Edited by Brian Merchant and Claire L. Evans
MCD x FSG Originals, 2022

A science fiction anthology with the epigraph “The splinter in your eye is the best magnifying glass” pulls no punches. The quote is by Theodor Adorno; the stories conjure enough near-future scenarios—automated labor systems, megafires, someone who sleeps so you don’t have to—to keep you company in the bunker when the apocalypse finally does hit.



Tomorrow, and Tomorrow, and Tomorrow

By Gabrielle Zevin
Knopf, 2022

Sam and Sadie meet playing Super Mario as kids, an experience that bonds them for life. They go on to spend the bulk of their time living or working in virtual worlds as game designers, and Zevin does an exceptional job making that pursuit interesting on the page, even if you haven’t touched a joystick since Space Invaders. Above all, this is a book about creativity and collaboration, love and loss, as immersive as any MMOG.



Geopedia

By Marcia Bjornerud
Princeton University Press, 2022

Earth has a deep backstory: 4.5 billion years’ worth of plot twists, tumult, and change. The words we use to describe the planet’s geology have stories behind them, too. In this compact illustrated volume, geologist Marcia Bjornerud presents a curated list of some of the more delightful entries in the geological lexicon. The result is a unique way to delve into Earth’s rich history—and future. ■



Cutting through the cosmic dust



Star formation is a violent business. This picture of a portion of the Carina Nebula, one of the first images released by the James Webb Space Telescope, makes that stunningly clear. “Offscreen,” above the top of this image, are hot, young stars blowing stellar winds and shedding intense ultraviolet light. This radiation has carved a ragged bubble inside the nebula, which is filled with dust and gas—the building blocks of future stars and planets.

Aspirations are high for JWST science. The telescope has six times the light-collecting area of the Hubble Space Telescope,

making it sensitive to much fainter objects. Its instruments are also geared to see infrared light. That capability allows the telescope to hunt for molecules of interest in the atmospheres of exoplanets and cut through dust to see new planetary systems being born. JWST will also be able to see deep into the universe’s history, all the way back to the first stars and galaxies. The light from these early objects has become redder as it has made its way to our solar system, the waves stretching as the universe itself has expanded. ■

Saudi Arabia plans to spend \$1 billion a year researching treatments to slow aging

The oil kingdom fears that its population is aging at an accelerated rate and hopes to test drugs to reverse the problem. First up might be the diabetes drug metformin.

By Antonio Regalado

The Saudi royal family has started a not-for-profit organization called the Hevolution Foundation that plans to spend up to \$1 billion a year of its oil wealth supporting basic research on the biology of aging and finding ways to extend the number of years people live in good health, a concept known as “health span.”

The sum, if the Saudis can spend it, could make the Gulf state the largest single sponsor of researchers attempting to understand the underlying causes of aging—and how it might be slowed down with drugs.

The fund is managed by Mehmood Khan, a former Mayo Clinic endocrinologist and the onetime chief scientist at PepsiCo, who was recruited to the CEO job in 2020. “Our primary goal is to extend the period of healthy life span,” Khan said in an interview. “There is not a bigger medical problem on the planet than this one.”

The idea, popular among some longevity scientists, is that if you can slow the body’s aging process, you can delay the onset of multiple diseases and extend the healthy years people are able to enjoy. Khan says the fund is going to give grants for basic scientific research on what causes aging, just as others have done, but it also plans to go a step further by supporting drug studies, including trials of “treatments that are patent-expired or never got commercialized.”

“We need to translate that biology to progress toward human clinical research. Ultimately, it won’t make a difference until something appears in the market that actually benefits patients,” Khan says.

Khan says the fund is authorized to spend up to \$1 billion per year indefinitely, and will be able to take financial stakes in biotech companies. By comparison, the division of the US National Institute on Aging that supports basic research on the biology of aging spends about \$325 million a year.

Hevolution hasn’t announced what projects it will back, but people familiar with the group say it looked at funding a \$100 million X Prize for age-reversal technology and has reached a preliminary agreement to fund a test of the diabetes drug metformin in several thousand elderly people.

That trial, known as “TAME” (for “targeting aging with metformin”), has been touted as the first major test of any drug to postpone aging in humans, but the study has languished for years without anyone willing to pay for it. Nir Barzilai, a researcher at the Albert Einstein College of Medicine in New York who conceived of the TAME trial, told an audience in London this April that Hevolution had agreed to fund one-third of its cost.

That agreement, if it’s finalized, would be an endorsement of what’s called the “geroscience hypothesis”—the still-unproven idea that some drugs, by altering basic aging processes inside cells, may be able to delay the onset of many diseases, including cancer and Alzheimer’s.

The term “geroscience” was popularized by Felipe Sierra, the former head of the division of aging biology at the US National Institutes of Health, who was

recently hired to be Hevolution’s chief scientific officer. Reached by email, Sierra declined to comment, but he has previously called geroscience the observation “that aging is by far, and I mean by far, the major risk factor for all chronic diseases.”

Aging fast

The Saudi government may be partially motivated by the belief that diseases of aging pose a specific threat to that country’s future. There is evidence that people living in the Gulf States “are aging faster biologically than they are chronologically,” according to materials prepared by Hevolution and viewed by MIT Technology Review.

Basically, the country is being beset by diseases of affluence brought on by rich diets and too little exercise. Even though Saudi Arabia has a relatively young population, with a median age of around 31, it is experiencing increasing rates of obesity and diabetes. In a 2019 study in the Saudi Medical Journal, Saudi public health officials said the country’s prosperity had led to an “urgent need to establish prevention and control programs.”

Hevolution was chartered by royal order in December 2018, and its chairman is Saudi crown prince and de facto ruler Mohammed bin Salman. Also on the board are Evgeny Lebedev, a Russian-British businessman; the American billionaire Ron Burkle; and Andrew Liveris, the former CEO of Dow Chemical, according to the Hevolution promotional materials viewed by MIT Technology Review.

The timing of the royal decree suggests the project may exist partly to burnish the reputation of Saudi Arabia and bin Salman, which had nosedived in October 2018 owing to the assassination of a Washington Post journalist by a hit squad that the US says acted on orders from the prince. The murder of the journalist, Jamal Khashoggi, caused Joe Biden, at the time a candidate for president, to call Saudi Arabia a “pariah” state with “very little social redeeming value in the present government.”

The actions of the Saudi autocrat mean US research organizations will



have to weigh whether they should take Hevolution's money, which is likely to be offered via a US nonprofit arm that Khan's team is establishing.

One group that decided accepting Saudi money would not be a problem is the American Federation for Aging Research, a nonprofit representing geroscience researchers, including Barzilai, that has been trying for the past several years to raise \$55 million to carry out the TAME trial.

"The board looked and found there are many institutions around the US that take money from the Saudis, and that we could too. That was the bottom line," says Stephanie Lederman, who is the federation's executive director. "This is an opportunity for thousands of people to benefit—initially the scientists, and then the population of the world. It could be a lot of people living healthier longer."

Diabetes drug

Eight years ago, Barzilai won attention for his efforts to persuade the US Food

The timing of the royal decree suggests the project may exist partly to burnish the reputation of Saudi Arabia and bin Salman.

and Drug Administration to permit the first-of-a-kind study. Since aging itself is not easily measured, or even considered a disease by regulators, the target of the TAME trial is instead to see if taking metformin can delay the onset of a range of age-related diseases.

The investigators say they hope to enroll 3,500 people over 65 at 16 US centers and then, after five or six years, determine whether they have less heart disease, dementia, and cancer than people who haven't taken the drug.

Metformin is an old drug, but it drew interest because a large study of British medical records showed that diabetics taking it were living longer than expected—even longer than healthy people.

Other drugs cited as possible general-purpose anti-aging compounds include rapamycin, an immune suppressor shown

to extend the life span of laboratory mice that has also been tested in pet dogs. So far, however, no drug has been proved to delay aging in humans, and some early experiments haven't fared well. In 2019, human tests of a version of rapamycin flopped after the drug failed to boost elderly people's resistance to respiratory infections.

No one knows if metformin will work either. One long-term study of diabetics, published this year, found the drug didn't result in any protection against heart problems. But even if metformin doesn't delay aging, the trial could carve a path for other geroscience drugs to enter human studies. Lederman says she expects the trial to finally get underway if the Saudi money comes through. "It's mind-boggling to me that it's been so hard to fund," she says. Visit www.technologyreview.com to read the full story. ■



Doctors using AI catch breast cancer more often than either does alone

A new study shows that artificial intelligence can also handle more than half of scans automatically, dramatically reducing radiologists' workloads.

By Hana Kirov

Radiologists assisted by an AI screen for breast cancer more successfully than they do when they work alone, according to new research. That same AI also produces more-accurate results in the hands of a radiologist than it does when operating solo.

The large-scale study, published in July in *The Lancet Digital Health*, is the first to directly compare an AI's solo performance in breast cancer screening with its performance when used to assist a human expert. The hope is that such AI systems could save lives by detecting cancers doctors miss, free up radiologists to see more patients, and ease the burden in places where there is a dire lack of specialists.

The software being tested comes from Vara, a startup based in Germany that also led the study. The company's AI is already used in over a fourth of Germany's breast cancer screening centers. With help from radiologists at the Essen University Hospital in Germany and the Memorial Sloan Kettering Cancer Center in New York, the Vara team tested two approaches. In the first, the AI works alone to analyze mammograms. In the other, the AI automatically distinguishes between scans it thinks look normal and those that raise a concern. It refers the latter to a radiologist, who reviews them before seeing the AI's assessment. Then the AI issues a warning if it detected cancer when the doctor did not. In the study, the AI examined old scans and compared its assessments with those of the radiologist who reviewed them originally.

To train the neural network, Vara fed the AI data from over 367,000 mammograms—including radiologists' notes, original assessments, and information on whether the patient ultimately had cancer—to learn how to place these scans into one of three buckets: "confident normal," "not confident" (in which no prediction is given), and "confident cancer." The conclusions from both approaches were then compared with the decisions real radiologists originally made on 82,851 mammograms sourced from screening centers that didn't contribute scans used to train the AI.

The second approach—doctor and AI working together—was 2.6% better at detecting breast cancer than a doctor working

alone, and raised fewer false alarms. It accomplished this while automatically setting aside scans it classified as "confident normal," which amounted to 63% of all mammograms. This intense streamlining could slash radiologists' workloads.

After breast cancer screenings, patients with a normal scan are sent on their way, while an abnormal or unclear scan triggers follow-up testing. But radiologists examining mammograms miss one in eight cancers. Fatigue, overwork, and even the time of day all affect how well radiologists can identify tumors as they view thousands of scans. Signs that are visually subtle are also generally less likely to set off alarms, and dense breast tissue—found mostly in younger patients—makes signs of cancer harder to see.

AI generally excels at image classification. So why did Vara's AI on its own underperform a lone doctor? Part of the problem is that a mammogram alone can't determine whether someone has cancer—that requires removing and testing the abnormal-looking tissue. Instead, the AI examines mammograms for hints. When the AI was unsure, the study defaulted to the original radiologist's reading. That means it couldn't test how using AI affects radiologists' decisions—and whether any such changes may create new risks. Thilo Töllner, a radiologist who has used the program for two years, admits he spends less time scrutinizing scans Vara labels normal than those it deems suspicious. "You get quicker with the normals because you get confident with the system," he says.

Curtis Langlotz, director of Stanford's Center for Artificial Intelligence in Medicine and Imaging, is impressed, but he says the next step would be to confirm how well the AI performs over a long period of time in actual clinics with real patients.

So far, attempts to fully replace radiologists with AI have failed. A 2021 review found that in 34 of 36 studies, the AI did worse than a single radiologist at screening for breast cancer from mammograms. All 36 were less accurate than the consensus of two radiologists, which some countries require.

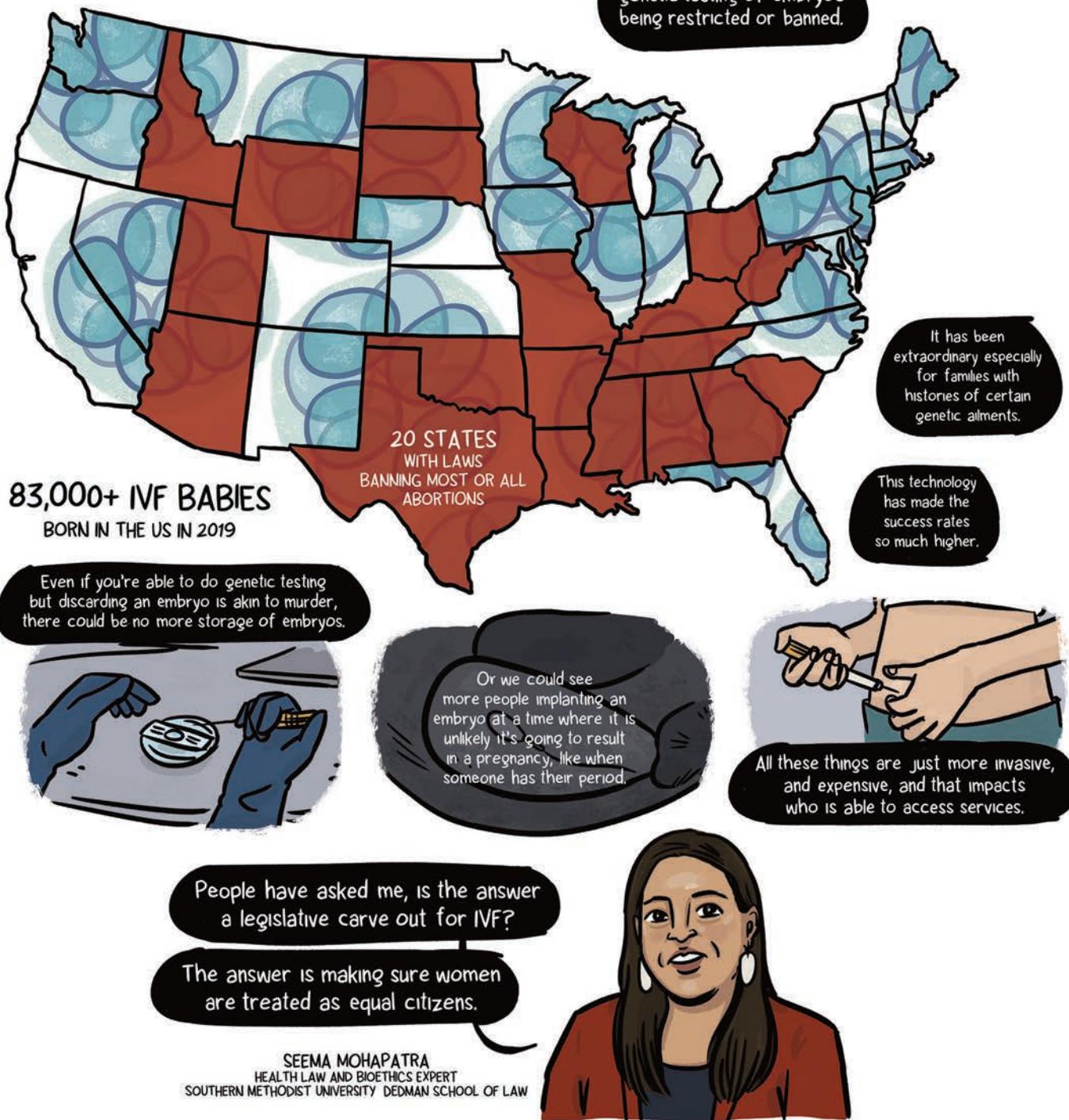
"We often say that AI will not replace radiologists," Langlotz says. "This study doesn't change that, but in the proposed AI-driven process nearly three-quarters of the screening studies didn't need to be reviewed by a radiologist, while improving accuracy overall." That, he says, is "groundbreaking."

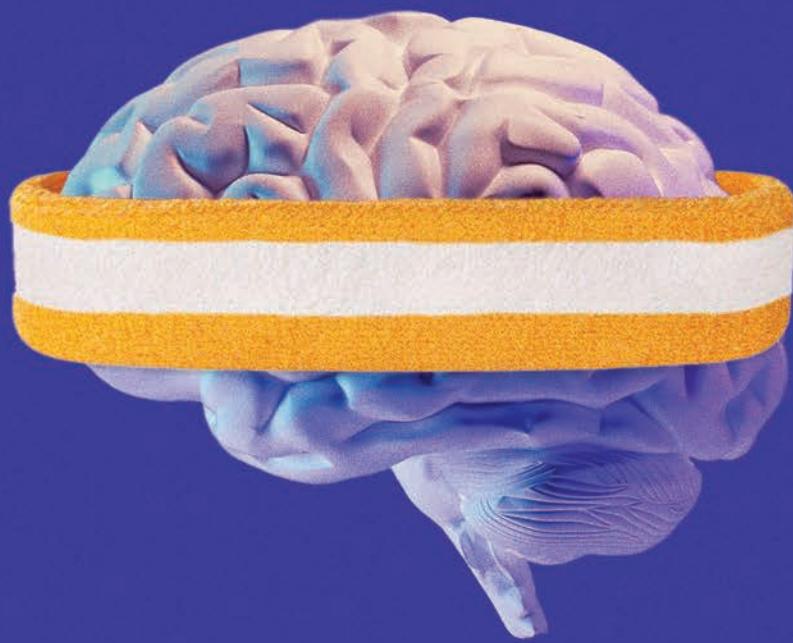
Langlotz adds that this approach could ease the shortage of radiologists, especially in countries such as Malawi, where there is one radiologist per 8.8 million people, or India, a country of 1.4 billion served by one radiologist for every 100,000 people. Even the US, which proportionally has 10 times as many radiologists as India, is projected to be short 17,000 radiologists by 2033.

Töllner is optimistic that more radiologists using AI will mean earlier breast cancer detection, which could improve survival rates. He also hopes Vara will help quash the high number of false positives—patients recalled for further testing who are actually fine. *To read the full story, visit www.technologyreview.com.* ■

How laws banning abortion might threaten fertility treatments

By Susie Cagle





How do strong muscles keep your brain healthy?

By Bonnie Tsui
Illustration by Selman Design

We've often thought about muscle as a thing that exists separately from intellect—and perhaps that is even oppositional to it, one taking resources from the other. The truth is, our brains and muscles are in constant conversation with each other, sending electrochemical signals back and forth. In a very tangible way, our lifelong brain health depends on keeping our muscles moving.

Skeletal muscle is the type of muscle that allows you to move your body around; it is one of the biggest organs in the human body. It is also an endocrine tissue, which means it releases signaling molecules that travel to other parts of your body to tell them to do things. The protein molecules that transmit messages from the skeletal muscle to other tissues—including the brain—are called myokines.

Myokines are released into the bloodstream when your muscles contract, create new cells, or perform other metabolic activities. When they arrive at the brain, they regulate physiological and metabolic responses there, too. As a result, myokines have the ability to affect cognition, mood, and emotional behavior. Exercise further stimulates what scientists call muscle-brain "cross talk," and these myokine messengers help determine specific beneficial responses in the brain. These can include the formation of new neurons and increased synaptic plasticity, both of which boost learning and memory.

In these ways, strong muscles are essential to healthy brain function.

In young muscle, a small amount of exercise triggers molecular processes that tell the muscle to grow. Muscle fibers sustain damage through strain and stress, and then repair themselves by fusing together and increasing in size and mass. Muscles get stronger by surviving each series of little breakdowns, allowing for regeneration,

rejuvenation, regrowth. As we age, the signal sent by exercise becomes much weaker. Though it's more difficult for older people to gain and maintain muscle mass, it's still possible to do so, and that maintenance is critical to supporting the brain.

Even moderate exercise can increase metabolism in brain regions important for learning and memory in older adults. And the brain itself has been found to respond to exercise in strikingly physical ways. The hippocampus, a brain structure that plays a major role in learning and memory, shrinks in late adulthood; this can result in an increased risk for dementia. Exercise training has been shown to increase the size of the hippocampus, even late in life, protecting against age-related loss and improving spatial memory.

Further, there is substantial evidence that certain myokines have sex-differentiated neuroprotective properties. For example, the myokine irisin is influenced by estrogen levels, and postmenopausal women are more susceptible to neurological diseases, which suggests that irisin may also have an important role in protecting neurons against age-related decline.

Studies have shown that even in people with existing brain disease or damage, increased physical activity and motor skills are associated with better cognitive function. People with sarcopenia, or age-related muscle atrophy, are more likely to suffer cognitive decline. Mounting evidence shows that the loss of skeletal muscle mass and function leaves the brain more vulnerable to dysfunction and disease; as a counter to that, exercise improves memory, processing speed, and executive function, especially in older adults. (Exercise also boosts these cognitive abilities in children.)

There's a robust molecular language being spoken between your muscles and your brain. Exercise helps keep us fluent in that language, even into old age. ■

Emoji tend to codify stereotypical gender roles. Paul D. Hunt is working to change that.

By Tanya Basu
Portrait by Josh Robenstone

Designing more inclusive emoji

Last year the Unicode Consortium—the group responsible for the selection and design of emoji—released a new series that reflected the multiplicity of gender identities. That's thanks to Paul D. Hunt, who since 2016 has been a key advocate for making emoji more inclusive, less sexist, and a better reflection of the human experience.

Fighting to dismantle the gender stereotypes we see in emoji may seem unimportant. But consider that since their invention in 1999 by Shigetaka Kurita, emoji have expanded from 176 simple, pixelated icons to (as of September 2021) 3,633 increasingly detailed images. Every day, more and more people around the world have access to mobile phones and to emoji that add expressiveness to their text-based communications.

The fight for gender inclusivity in emoji is personal for Hunt, who is nonbinary and transgender. Hunt is also a trained typographer and designer rooted in linguistics and art. There may be no better person on the planet to think about what it means to produce and consume emoji that reflect the multiplicity of gender identities.

Hunt's interest in "language and alphabets and design and culture" was rooted in their small-town childhood in a Mormon community embedded within the Navajo Nation in Arizona. They went to college intending to study for an international business degree but switched to design. Hunt was active in an online community of typographers, Typophile, while interning at a type foundry in Buffalo, New York, and

spent time drawing letters and designing fonts before earning a master's in typeface design at the University of Reading in the UK and becoming a leading typeface designer at Adobe, specializing in fonts that don't use the Latin alphabet.

But it is their participation in the emoji subcommittee of the Unicode Consortium that has garnered Hunt the most acclaim. And their thinking on gender and emoji had a surprising source: *RuPaul's Drag Race*.

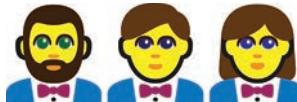
At first, Hunt rolled their eyes at the flamboyance of the *Drag Race* contestants. "I used to think RuPaul was too camp, and I didn't really understand this whole drag queen phenomenon," they say. But Hunt's husband was a fan, so Hunt began watching the show and was increasingly drawn into it, moved by the contestants' refusal to fall into conventional gender roles and stereotypes. This led to an epiphany: gender was a performance. Every day we make choices "to skew our appearance one way or another, whether that's masculine or feminine," they explain, "and it made me ask what it means to be masculine or feminine."

Emoji tended to codify gender with traditional signs of masculinity (beard, mustache, short hair) and femininity (painted nails, longer hair, skirts). Hunt found this limiting, even disturbing: Why was a nurse a woman and a police officer a man? Why were "frivolous" activities like getting your nails painted or dancing depicted as feminine, while "serious" activities

like construction were always depicted as masculine? Why were these images so staunchly gendered anyway?

Hunt decided to do something about this. They were already part of the Emoji Subcommittee, a group of designers and industry experts within the nonprofit Unicode Consortium, which works with hardware and software companies to make emoji readable and universal across all devices. So in 2016, Hunt submitted a proposal to push for gender-inclusive emoji, which they defined as "a humanized appearance that employs visual cues that are common to all genders by excluding





New designs feature typically masculine, gender-inclusive, and feminine features, respectively.

stereotypes that are either explicitly masculine or feminine.”

It was revolutionary. To many, emoji were cutesy, simplistic additions to text, not humanistic and certainly not political. Hunt acknowledges as much, diplomatically saying there was a bit of skepticism from those running the committee. Some designers pointed to Google, which had tried to skirt gender and race with its yellow blobs in Gchat. On some level this worked, but Hunt found the accommodation a bit odd: Why couldn’t emoji express more of the nuances of human experience without resorting to abstraction?

PAUL D. HUNT

Hunt’s proposal found an audience in Jennifer Daniel, who now leads the Unicode Emoji Subcommittee and has been instrumental in redefining the linguistics of emoji by ushering in an era that celebrates inclusivity and creative use of the symbols as a means of expression.

Daniel told me that when she joined the subcommittee, in 2018, “none of them [the gender-inclusive emoji Hunt had proposed] were properly supported.” She pushed for implementation of Hunt’s proposal, releasing guidelines for the creation of a gender-neutral class of emoji as well.

For Hunt, emoji are powerful means of expression precisely because words sometimes fail us. They recall meeting their future husband, an Australian, while living in San Francisco: “When you get to know someone, you build a common story together and develop your own little language.” That language for Hunt and their spouse included the heart emoji with sprinkles, which became a “logo” for the budding relationship. “That emoji meant a lot to me,” they say. “It still does.” ■

Tanya Basu is a senior reporter for MIT Technology Review.



“This is it,” said SCOTUSblog media editor Katie Barlow on TikTok,

“The Con
does not
a right to

We discovered *Dobbs* on the
same device that could convict us.

posting live from outside the court. “It’s loading. Give me a minute.”

stitution confer abortion.”

By Melissa Gira Grant



I learned on a liveblog that I had lost the right to have an abortion.

When the United States Supreme Court reversed *Roe v. Wade* on the morning of June 24, 2022, I was one of the nearly 16,000 people reading SCOTUSblog, a news site launched 20 years ago, which has no official relationship with the Supreme Court, which has never been granted press credentials to the court, and which won a Peabody Award in 2013, the first blog to do so. On opinion days, its writers offer rapid-fire analysis and field reader questions on the liveblog, a space where legal-news obsessives follow updates alongside first-time readers who just want the news and sometime a place to vent. When landmark opinions are anticipated—and *Dobbs v. Jackson Women's Health Organization* was one—the liveblog readers often get word before those watching cable news networks.

"This is it," said SCOTUSblog media editor Katie Barlow on TikTok, posting live from outside the court. Barlow was one of the few correspondents on camera the moment the opinion was released. "It's loading. Give me a minute." She was silent for a few seconds, glancing down at her phone, nodding, before looking up again and succinctly announcing the crux of it: "The Constitution does not confer a right to abortion." A reader on TikTok commented that it was hard to watch live as Barlow silently read the opinion, "to see the reality of the decision wash over you," adding: "Thank you for your work." It was a fitting way to enter the official post-*Roe* age: on platforms that can feel so personal to their publics, even as history unfolds. And even more so because the Supreme Court is so notoriously opaque, while also wielding such immediate power over the most intimate parts of our lives. When opinions are read from the bench, most of us don't get to watch the justices as they dictate the boundaries of our liberty. We are left to imagine them.

Though the SCOTUSblog team reported from outside on the day of the decision, they had more freedom than those with credentials, who would typically—but for covid-19—be inside. Before

the pandemic, reporters who gained entry to the press room at the Supreme Court would not be permitted to bring phones or other personal devices to their seats in the press gallery, many of them with an obstructed view of the bench. All that gear would have to remain back in the press room, where significant real estate is still occupied by typewriters and broadcast booths. Those who wanted to remain online would have to stay behind in the press room too, and listen in via an audio feed. (Not until the covid-19 pandemic did the court even post an audio-only livestream for the public.) A few minutes after 10 a.m., when opinions are released, print copies would be made available there. News organizations dispatch interns to grab these documents and run them from the court to the cameras set up just outside. It is a startling anachronism, especially now that anyone can just go on CourtListener.com, search for a legal opinion, screencap it, and tweet it out with commentary (and a link back to the full document, so readers can reference it themselves) in minutes or seconds. The press room, in other words, may as well exist in a pre-*Roe* world.

On January 22, 1973, a New York Times reporter called the Austin law office of Sarah

On the day
of the ruling,
the National
Network of
Abortion Funds
reported
\$3 million
in new donations
across its
97 member funds,
from
33,000
**new
donors.**

Weddington, who had argued for Roe's side in the case. The reporter wanted to know if she had a comment on *Roe v. Wade*. But Weddington wasn't there. "Is there some particular reason she should have a comment about it today?" her secretary asked. Yes, he told her: the decision had been announced minutes before. Weddington was in Washington, DC, where an NBC reporter for *The Today Show* called her office to ask for comment. But Weddington had her own question: What had the court said?

There was one other way she could have heard the news. Earlier that morning, an issue of Time magazine appeared on newsstands, announcing that "abortion on demand" had been legalized by the Supreme Court. Through a combination of shoe-leather reporting and advantageous scheduling, David Beckwith, a new reporter, had scooped the court's own announcement by a few hours. "No one had any mal intent," he told Jane Mayer at the New Yorker this year. "They just had the bad judgment to trust me." Even though other outlets didn't pick up the story, Justice Harry Blackmun, who authored the majority opinion, was incensed. He'd been ready to release the opinion earlier but believed it was held back so that it would not upstage the second inauguration of President Richard Nixon.

The Time scoop is hardly what most people remember about that day, though it acquired a new resonance when the draft opinion overturning *Roe* was leaked in May. They would sooner recall the news delivered in a familiar broadcast voice, like that of Walter Cronkite on CBS, over pastel renderings of the justices' faces—all men, like the experts solicited to

The weeks after *Dobbs* have only made it more plain that the war on abortion is also a war on information.



provide commentary. NBC correspondent Betty Rollin gave the “pro-abortionist” reaction from a clinic and the “against” view from the Roman Catholic Church in New York, after the network cut into the coverage to announce the death of former president Lyndon Johnson. *Roe* would play second in most headlines.

Throughout the day, Weddington and her staff “pumped reporters for information,” she later wrote in her 2013 book *A Question of Choice*. She found a lawyer friend who could go to the Supreme Court to pick up a copy of the opinion and read her “the significant portions,” but Weddington had to give interviews before she could read it herself. They worked the phones to get the news to those who had been part of the effort; they could not reach the woman known as Jane Roe to tell her personally. The next morning, Weddington woke up early to get all the major newspapers and read about her own case. She received a telegram from the Supreme Court. “Judgment Roe against Wade today affirmed in part and reversed in part,” it read. “Opinions airmailed.” Paper copies arrived a few days later.

On June 24, 2022, there were no telegrams announcing the decision in *Dobbs*—they barely exist anymore. The Center for Reproductive Rights tweeted out the opinion at 10:11 a.m. The phone might still be how you learned of the decision made by six justices, but now the phone could also give an instant voice to millions whose rights were rolled back with their ruling. Accounts on Twitter like @AbortionStories, run by the group We Testify, aggregated personal narratives by people who have had abortions. Overall, according to one report

from a Tufts University research initiative, there were 1.8 million negative Twitter mentions of the decision. Those whose rights were stripped did not wait for the news media, with its professional legal commentators opining on what they called “a very dark day in America,” to put a face on their future.

The phone where we received the news was the same device that could let us help someone we have never met before travel to a state where abortion is still legal. On the day of the ruling, the National Network of Abortion Funds reported \$3 million in new donations across its 97 member funds, from 33,000 new donors, even though its website briefly crashed that morning. The phone was how we learned where we can still get an abortion, through services like INeedAnA.com, and through Plan C, which shares information on self-managed abortions with pills—one mifepristone and four misoprostol—that can still be ordered online.

If anything, though, the weeks after *Dobbs* have only made it more plain that the war on abortion is also a war on information. Because the phone, groups like Digital Defense Fund have advised, brings with it security threats: exposing our browser histories, our private messages, our location data, to platforms and law enforcement alike. This is what could make abortion riskier after *Roe*. The otherwise safe procedure itself is no more dangerous. But without *Roe*, the tools people use to quickly share information and resources—the ways we keep each other safe—have themselves been made dangerous. ■

The race to make human sex cells in the lab

Scientists might soon be able to create eggs and sperm from skin and blood cells.

Will the sex of the parents become irrelevant to baby-making? Or are artificial sex cells destined to stay in the lab?

By
Jessica Hamzelou

Illustrations by
Amrita Marino

The way we make babies could be about to change. Maybe.

An embryo forms when sperm meets egg. But what if we could start with other cells—if a blood sample or skin biopsy could be transformed into “artificial” sperm and eggs? What if those were all you needed to make a baby?

That’s the promise of a radical approach to reproduction. Scientists have already created artificial eggs and sperm from mouse cells and used them to create mouse pups. Artificial human sex cells are next.

The advances could herald the end of infertility—there’s no need to worry about a lack of healthy eggs or sperm if you can create new ones in the lab. It would open up alternative routes to parenthood as well. Same-sex couples could have genetically related children. If a cisgender woman could create her own sperm cells, she could use them to fertilize the egg of a partner. Likewise, a cisgender man could produce his own eggs to be fertilized by the sperm of his partner. And why stop there? The technology would allow four parents to make equal genetic contributions to a baby, for example. Or a single person could produce both the sperm and the egg that create an embryo.

That’s the vision, at least, after a decade of tantalizing results in the lab. We know, more or less, how to do it. The problem is actually getting there and—maybe even harder—untangling the knot of ethical issues that will come up along the way.

Human sex cells are proving far trickier to generate than mouse sperm and eggs. So tricky, in fact, that some researchers who have spent years trying to create them are starting to give up. The work is fiddly and requires an expert knowledge of how cells differentiate into sperm and eggs and how human embryos develop—the precise mechanisms of which are still poorly understood.

The big question is whether we’ll ever be able to turn promising lab results into acceptable and safe changes in how we reproduce. In many ways, it’s still a deep mystery how sperm and eggs form. And without that knowledge, lab-made egg and sperm cells could carry risks of devastating diseases that might not become evident until the resulting babies are born, or even later in their lives.

Optimists might argue that the same concerns were originally raised about in vitro fertilization; these days, around 73,000 babies are born each year as a result of assisted reproduction technologies like IVF in the US alone. If we can find a way to do it safely, the use of artificial sex cells could transform reproduction even more radically, and potentially redefine what it means to be a biological parent.

But that is a big “if.”



Recipes for sperm and eggs

Over the last decade or so, Mitinori Saitou, a developmental biologist at Kyoto University, has led and participated in the most groundbreaking research in the field of in vitro gametogenesis, as the creation of artificial egg and sperm cells in the lab is formally known. Much of the work relies on a Nobel Prize-winning technique developed in 2006 that allows scientists to turn adult cells into stem cells, which can form pretty much any specialized cell in the body: heart cell, liver cell, brain cell—you name it. The trick is working out how to encourage the stem cells to form egg or sperm cells.

In mice, placing stem cells in a petri dish alongside cells taken from mouse embryos seems to work—the cells first turn into primitive, precursor cells, which then eventually develop into egg cells. These eggs can even be fertilized with sperm to generate embryos.

Back in 2012, Saitou, Katsuhiko Hayashi, and their colleagues were the first to use this approach to create primitive mouse egg cells in the laboratory; in 2016 the team generated mature egg cells. Some of the stem cells the team used were taken from mouse embryos, but others were created using cells from the animals' tails.

These eggs were matured and fertilized with sperm, and the resulting embryos were transplanted back into female mice, which gave birth to apparently healthy babies. The feat was a remarkable breakthrough by any standard, and news channels around the world were quick to state that human reproduction was about to change forever.

Saitou and Hayashi, as well as other teams, have had similar successes with mouse sperm.

The race is now on to do the same with human cells. Researchers have managed to generate immature sex cells and are working on ways to push the cells further along, to a state where they can be used to create an embryo. Today, Saitou focuses on eggs. His team has pushed human cells to the oogonia stage—the stage before they become eggs—after culturing cells in the lab for four months.

Meanwhile, in 2015, Kotaro Sasaki, a former mentee of Saitou based at the University of Pennsylvania, turned men's blood cells into stem cells and generated the primordial cells that lead to sperm. "It's kind of a recipe to make an early-stage [sex] cell," says Sasaki. Since then, the team has been trying to encourage these primitive cells to mature into sperm in the lab. Most recently, the team managed to get what are known as spermatogonia—the immediate precursor of sperm cells. "We are one step closer now to making sperm in a dish," says Sasaki.

But a critical final step is so far proving exceptionally elusive in the case of both eggs and sperm cells. Mature eggs and sperm have half as many chromosomes as other

body cells. This is vital—it allows the two cells to fuse and form an embryo with a full set of chromosomes. Precursor cells must go through a special type of cell division called meiosis in order to halve their chromosomes. No one has managed to replicate this with human cells in the lab—yet.

Sasaki thinks he's close. In unpublished work, he says he has managed to push the immature sperm cells one step further along the path to maturity, and that these cells have started to undergo meiosis. Once meiosis is completed, the sperm could be used to fertilize an egg, even if they are not fully matured.

But there are other hurdles—some so challenging that many scientists have given up. For one thing, nudging the stem cells in the right direction requires, it seems, a unique touch and expertise. Not just anyone will be able to make egg and sperm cells in the lab, says Saitou.

Top chef

Saitou and Hayashi, now at Kyushu University, lead world-renowned teams of extraordinary skill. Their achievements might not have been possible without the contributions of Hiroshi Ohta, for example. Ohta is an expert in anesthetizing newborn mice using ice, performing intricate surgery on them, and injecting cells into the animals' miniature gonads. The entire procedure must be completed within five minutes or the animals die. Only a few people have such skills, which take months

Scientists already know how to turn adult cells into stem cells, and—in mice—how to coax those into eggs and sperm. The race is now on to do the same with human cells.

to develop. "I think our group was kind of lucky," says Saitou. "It was a get-together of many talented scientists."

The work is hampered by the lack of in-depth knowledge about how the primitive forms of egg and sperm cells develop naturally in the embryo—a process that is far from fully worked out in humans. Some of the embryo's cells begin to differentiate into these primitive sex cells at around 14 days. But in some countries, it is illegal for researchers to even grow human embryos beyond 14 days. "They would send me to jail if I went beyond day 14," says Azim Surani, who is working with precursors to artificial sex cells at the University of Cambridge in the UK.

The problem, from a research point of view, is that the 14-day rule "comes in just as the embryos start to get

How it works



— 1

Cells are harvested from a skin biopsy or a blood sample.



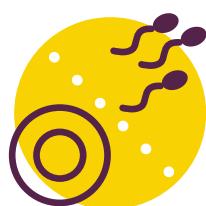
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Harvested cells are turned into stem cells.



— 3

Stem cells are grown in an embryo-like environment.



— 4

Precursor sex cells form, and eventually they mature into sperm or egg cells.



— 5

The lab-grown cells are used to create an embryo in an IVF lab.



— 6

If the embryo is healthy, it can be transferred into a uterus, hopefully resulting in pregnancy.

interesting,” says Surani. Without being able to easily study the critical process of how primitive cells begin forming egg and sperm cells, scientists are limited in their ability to mimic it in the lab.

Even if scientists were able to study embryos more freely, some mysteries would remain. Once the cells that make eggs and sperm are created, they are held in a kind of suspended animation until puberty or ovulation. What happens to them in the years in between? And how important is this phase for the health of mature eggs and sperm? “The honest answer is we don’t know,” says Surani.

The stem cells in the lab must also be generated and cared for under precise conditions. To survive, they must be bathed in a cocktail of nutrients that must be replaced every day. “It’s very time consuming and labor intensive ... and it takes a lot of money,” says Bjorn Heindryckx at Ghent University in Belgium, one of the scientists who have given up on creating human eggs this way in the lab. “The outcome was too limited for the effort and the money that we spent on it,” he says.

Part of the challenge is that for the precursor stem cells to develop into fully matured egg or sperm cells, they must be placed in an environment mimicking that of newly developing ovaries or testes. Researchers studying mice use tissue taken from mouse embryos to induce the stem cells to differentiate into sex cells. But similarly using human tissue from discarded embryos is ethically and legally problematic. So scientists are working on ways to create the right environment without using tissue from embryos.

The upshot is that it will likely take a highly skilled team years of dedicated research. “It’s not impossible, but it would not be easy to do,” says Surani.

That hasn’t discouraged a handful of biotech companies from taking an interest in artificial sex cells.

Conception, a company employing a team of around 30 scientists in Berkeley, California, aims to “turn stem cells into human eggs” to enable older or infertile women, as well as male couples, to have genetically related children. “I’m gay, and it’s something I was very personally interested in,” says Matt Krisiloff, the company’s CEO.

Krisiloff says his team has made “quite a bit” of progress, and that he’s “very excited” about his results. But he won’t say what they are. The company has not published its research, although Krisiloff says that he does plan to at some point. Krisiloff envisions that in the near future—he won’t say when—the company will be able to create egg cells from people’s blood cells. He expects to eventually partner with an IVF clinic, which would fertilize the eggs to produce embryos.

When I told Heindryckx about the company, his response was: “Oy, you’re kidding.”

Dangerous mutations

While everyone contacted by MIT Technology Review was confident that eventually we'll be able to create artificial human egg and sperm cells in the lab, there is less certainty over whether we'll ever be able to safely use them for reproduction.

One worry is that our cells accumulate DNA damage as we get older—it's thought to be one of the reasons many cancers are more likely to affect us later in life. And body cells are thought to have more mutations than germ cells that form eggs and sperm. A skin cell taken from a 50-year-old is going to have many more mutations than a typical egg or sperm cell from a 30-year-old. We don't know if or how these might affect an embryo, or a baby.

Saitou reckons that if the technology were ever to become a clinical reality, you'd likely have to store your cells ahead of time—ideally at birth.

Scientists also worry that the technique would influence how DNA works in babies born from artificial sex cells. Certain molecules can attach themselves to our DNA and change the way our genes are expressed—essentially changing the way they make proteins. These so-called epigenetic changes can switch genes on or off, or just turn them up or down. Epigenetic changes are made to our DNA throughout life and are thought to be influenced by what we eat, how much we exercise, whether or not we smoke, and other lifestyle factors.

But they might also be triggered when cells are grown in a dish. This is thought to occur in IVF, even if embryos are only left in culture for a few days. These epigenetic changes probably explain why babies conceived via IVF tend to have different birth weights from those conceived spontaneously—and this can vary depending on the brand of nutrient-rich liquid the cells are bathed in.

If a few days in a dish can influence the way genes are expressed, what about weeks or months? The most advanced human sex cells generated so far have been cultured in the lab for four months. "It's very long, and not natural," says Heindryckx.

And while scientists have been able to generate mouse pups from stem cells, a closer look at the study results suggests that the vast majority of the embryos created that way were far from healthy.

Thousands of eggs need to be created in order to generate a few that are healthy enough to be successfully fertilized. Then almost all the embryos created with artificial eggs die—and they die in strange ways. The embryos look misshapen and appear to have many abnormalities, says Saitou.

"The focus is always...on the one born mouse," he says. "But if you have one live-born mouse, you have 999 dead embryos." The success rate hasn't improved in the last 10 years, either, says Saitou.

"I don't think there's a fundamental biological reason why it wouldn't work," says Heidi Mertes, a medical ethicist at Ghent University who has scrutinized the ethical implications of deriving sex cells from body cells. "But I wouldn't want to be the first patient to try this, let's put it that way."

Going rogue

All that might not stop someone from trying it. We all saw what happened when He Jiankui used CRISPR genome-editing technology to alter the DNA of two embryos, resulting in the birth of gene-edited twin baby girls known as Lulu and Nana, as well as a third baby. He ostensibly set out to lower the twins' risk of contracting HIV—but may have exposed them to other health risks that may only make themselves apparent later in the girls' lives. He was widely condemned and was eventually sentenced to prison in China.

The truth is that there will always be someone willing to bend the rules to be the first to achieve some scientific feat—even if it is an ethically dubious one. And when it comes to reproductive medicine, a dangerous mix of huge sums of money and limited regulation enables new, experimental treatments to be speedily tested on willing, and often desperate, would-be parents. "There are always mavericks," says Surani.

Academic researchers must get approval from an ethics committee before they undertake any significant research involving people. And any individual who carries out an

Human artificial gametes are set to become a scientific reality in the coming years. Just how soon depends on who you ask.

experimental treatment at a hospital will need approval from that hospital's ethics committee, too. But people who work outside these institutions may not be held to the same ethical standards.

Last year, the International Society for Stem Cell Research—an international group of researchers working in the field—published updated guidelines for research and treatments. The guidelines explicitly forbid the use of eggs or sperm generated from stem cells to enable people to have babies. The procedure is designated "not allowed; currently unsafe." But the ISSCR guidelines are just that—they are not laws.

Reproductive medicine is poorly regulated in the US as it is, and a person who uses artificial sex cells to help



someone get pregnant might argue that it's not breaking any laws. When I asked a representative of the American Society for Reproductive Medicine how the use of artificial gametes might be controlled in the US, his response was: "By asking that question, you have put yourself ahead of pretty much every policymaker in the US."

"It's a little unclear, honestly," says Krisiloff, who has been in conversations with consultants about how to run FDA-approved clinical trials with artificial eggs. "I think that this might be the type of thing where ... they might get a cease-and-desist letter after the fact," he says. "But there may not be a totally clear legal framework to say it's illegal to do so in the first place."

It's easy to draw comparisons with IVF; that technology was also hyped as offering an end to infertility and decried by others as unnatural. IVF appears to be safe for babies so far. Millions of healthy babies have been born as a result of the technology.

But some argue that we still don't really know if IVF has long-term effects. The first person born using the technique, Louise Brown, is now 44—we don't know if there are health risks that will only become apparent in later life. "No one has really considered these long-term effects," says Saitou.

"And these would probably be more profound if you start with artificial gametes."

Mertes, the medical ethicist at Ghent, asks if we should even be trying, given the safety risks. Having genetically related children is not the only path to parenthood—there are other options for people who are unable to conceive with their own sperm and eggs. "We shouldn't keep reinforcing the idea that genetic parenthood is something that justifies a lot of risks," she says.

But the topic is sensitive, and Mertes has been subject to backlash for airing her thoughts. Why shouldn't everyone have the same parenthood options as cisgender, heterosexual, fertile men and women?

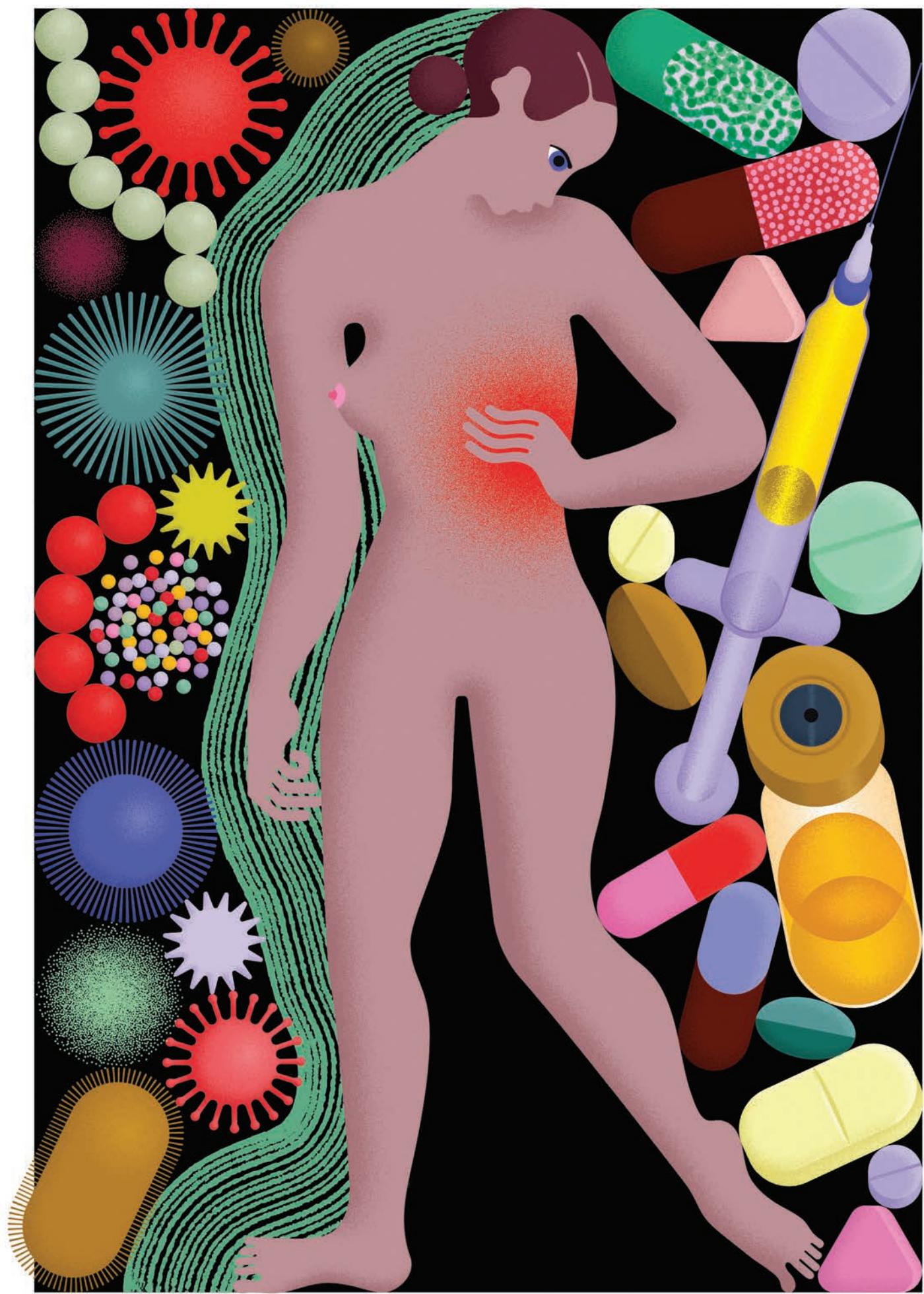
"I don't know if it should be done, and we don't know if it's safe," says Sasaki. "But it's possible, so from an ethical and legal perspective, you need to discuss it intensely."

Now is the time for these discussions. Human artificial gametes are set to become a scientific reality in the coming years. Just how soon depends on who you ask. "To be very honest, I don't like to guess," says Saitou. "With some unexpected roadblocks, suddenly the progress stops, but with some unexpected breakthroughs, it suddenly speeds up."

Saitou is acutely aware of the implications of his work. In Japan, he says, the general public regards the technology with awe, but some fellow scientists aren't as convinced. Some have argued that perhaps the genes of people with infertility should not be passed to the next generation. The process is too artificial, they argue; the resulting embryos—and babies—may struggle to survive.

The argument reminds Saitou of a legendary manga comic book by Osamu Tezuka, called *Hi No Tori*, or Phoenix, which is set in the future. "There's a story about how all mammals are created ... in some artificial ways," he says. In the story, the animals are kept alive in what are essentially test tubes. As soon as the animals leave this protective environment, they die: "They are just so unfit and artificial."

Saitou wonders if embryos—or potentially babies—generated from artificial sex cells may suffer a similar fate, given the low odds of success seen in mice. "This time may come," he says. "It's a comic, but ... [as science progresses], I somehow see that our society is gradually approaching what [Tezuka] depicted." ■



A

D I V I D E D

Biological sex influences how our immune system responds to diseases and vaccines, but its effects have long been overlooked.

D E F E N S E

By Sandeep Ravindran

Illustration by Julia Schwarz • Photographs by Rosem Morton

S

abra Klein is deeply aware that sex matters. During her PhD research at Johns Hopkins University, Klein learned how sex hormones can influence the brain and behavior. “I naively thought: Everybody knows hormones can affect lots of physiological processes—our metabolism, our heart, our bone density. It must be affecting the immune system,” she says.

But when she graduated in 1998, she struggled to convince others that sex differences in the immune system were a worthy topic for her postdoctoral research. “I wasn’t able to find a microbiologist or an immunologist who was going to let me study sex differences,” she says.

She ultimately found a postdoctoral position in the lab of one of her thesis committee members. And in the years since, as she has established a lab of her own at the university’s Bloomberg School of Public Health, she has painstakingly made the case that sex—defined by biological attributes such as our sex chromosomes, sex hormones, and reproductive tissues—really does influence immune responses.

Through research in animal models and humans, Klein and others have shown how and why male and female immune systems respond differently to the flu virus, HIV, and certain cancer therapies, and why most women receive greater protection from vaccines but are also more likely to get severe asthma and autoimmune disorders (something that had been known but not attributed specifically to immune differences). “Work from her laboratory has been instrumental in advancing our understanding of vaccine responses and immune function on males and females,” says immunologist Dawn Newcomb of the Vanderbilt University Medical Center in Nashville, Tennessee. (When referring to people in this article, “male” is used as a shorthand for people with XY chromosomes, a penis, and testicles, and who go through a testosterone-dominated puberty, and “female” is used as a shorthand for people with XX chromosomes and a vulva, and who go through an estrogen-dominated puberty.)

Through her research, as well as the unglamorous labor of arranging symposia and meetings, Klein has helped spearhead a shift in immunology, a field that long thought sex differences didn’t matter. Historically, most trials enrolled only males, resulting in uncounted—and likely uncountable—consequences for public health and medicine. The practice has, for example, caused women to be denied a potentially lifesaving HIV therapy and left them likely to endure worse side effects from drugs and vaccines when given the same dose as men.

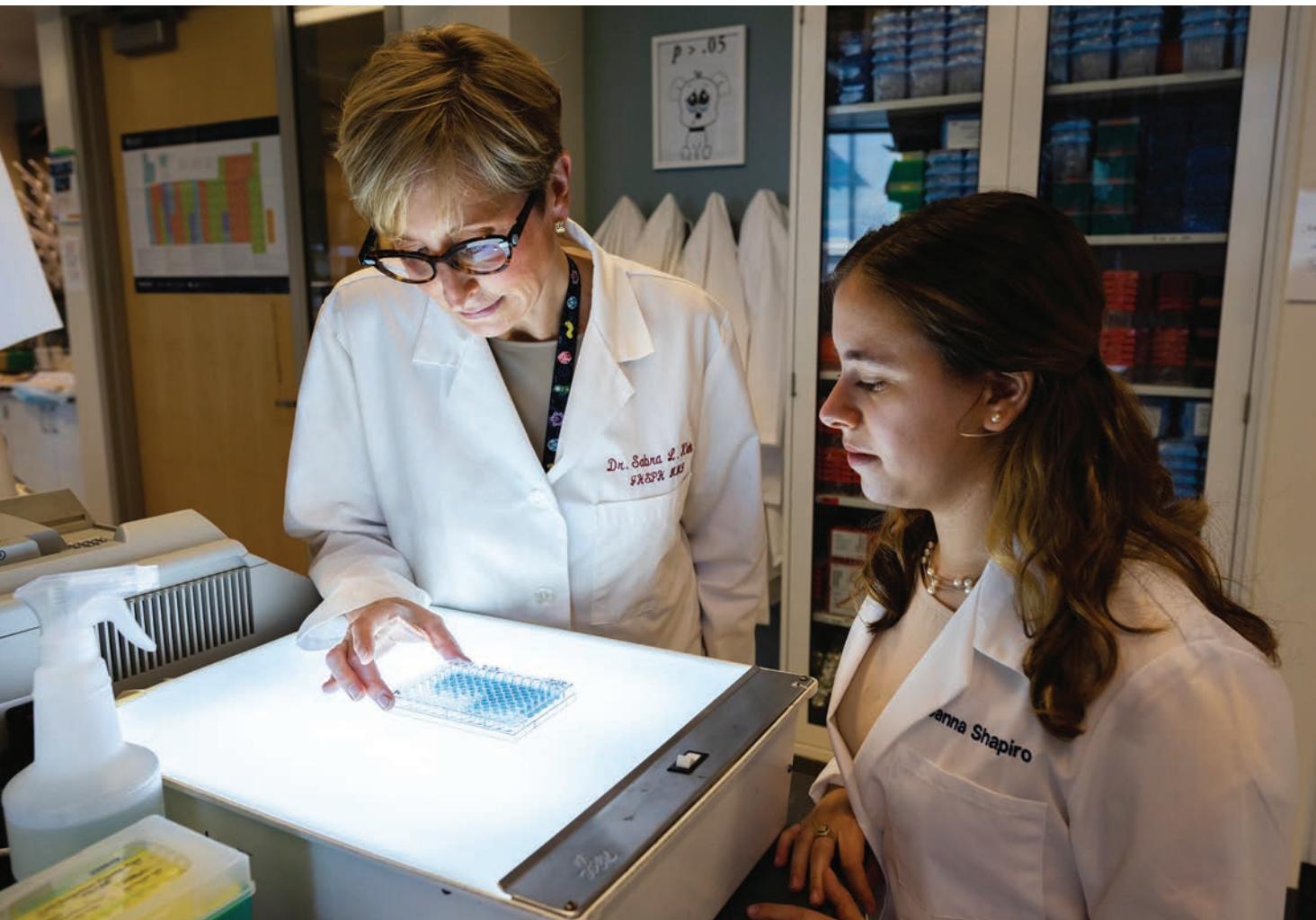
Thanks in part to the efforts of Klein and others, along with changes at journals and government funding agencies, the proportion of immunology studies that include both sexes increased from 16% in 2009 to 46% in 2019. Klein “did a great job organizing conferences and also putting pressure on journals’ editors to … request that data be presented stratified by sex or gender,” says Christine Stabell Benn, a professor of global health based at the University of Southern Denmark, in Copenhagen.

In addition to making existing treatments safer and more effective, investigating the mechanisms underlying sex differences in immunology could pave the way for new therapies; trials for multiple sclerosis and asthma are already showing some promising results. “If you’ve got this situation where there’s two groups that have a difference, that’s like a gold mine for discovery,” says Eileen Scully, an immunologist and infectious disease researcher at the Johns Hopkins University School of Medicine.

But humans are not just defined by our biology. Making the most of these immunological discoveries will require scientists to take into account the sociocultural and environmental factors that affect health, and their intricate interactions with biological sex. Scully says, “I think this is part of the broader push toward precision medicine—the idea that we have the right treatment for the right person.”

Men and women don’t experience infectious or autoimmune diseases in the same way. Women are nine times more likely to get lupus than men, and they have been hospitalized at higher rates for some flu strains. Meanwhile, men are significantly more likely to get tuberculosis and to die of covid-19 than women.

“If you’ve got this situation where there’s two groups that have a difference, that’s like a gold mine for discovery.”



Sabra Klein (left) and Janna Shapiro in Klein's laboratory at Johns Hopkins University in Baltimore, Maryland.

In the 1990s, scientists often attributed such differences to gender rather than sex—to norms, roles, relationships, behaviors, and other sociocultural factors as opposed to biological differences in the immune system.

For example, even though three times as many women have multiple sclerosis as men, immunologists in the 1990s ignored the idea that this difference could have a biological basis, says Rhonda Voskuhl, a neuroimmunologist at the University of California, Los Angeles. “People would say, ‘Oh, the women just complain more—they’re kind of hysterical,’” Voskuhl says. “You had to convince people that it wasn’t just all subjective or environmental, that it was basic biology. So it was an uphill battle.”

Despite a historical practice of “bikini medicine”—the notion that there are no major differences between the sexes outside the parts that fit under a bikini—we now know that whether you’re looking at your metabolism, heart, or immune system, both biological sex differences and sociocultural gender differences exist. And they both play a role in susceptibility to diseases. For instance, men’s greater propensity to tuberculosis—they are almost twice as likely to get it as women—may be attributed partly to differences in their immune responses and partly to the fact that men are more likely to smoke and to work in mining or construction jobs that expose them to toxic substances, which can impair the lungs’ immune defenses.

How to tease apart the effects of sex and gender? That's where animal models come in. "Gender is a social construct that we associate with humans, so animals do not have a gender," says Chyren Hunter, associate director for basic and translational research at the US National Institutes of Health Office of Research on Women's Health. Seeing the same effect in both animal models and humans is a good starting point for finding out whether an immune response is modulated by sex.

But you can't find sex differences if you're only studying one sex. Klein remembers a meeting where a researcher on nematodes, a type of parasitic worm, mentioned that his experiments were done only in male mice, because female mice didn't get infected. She recalls being flabbergasted that he never thought to study why the nematodes couldn't infect the females. "Oh my God, you might have a cure for these nematodes that wreak havoc!" she recalls thinking.

In 1992, the US Food and Drug Administration approved a medication called Ambien to help people sleep. It later became clear that the active ingredient in the drug, zolpidem, could cause some serious complications, including "sleep driving"—like sleepwalking, but potentially far more dangerous. By 2013, laboratory studies and driving simulations had shown that eight hours after taking zolpidem, women were more likely than men to have enough of the drug left in their blood to impair driving and increase their risk of traffic accidents. That year, the FDA set the drug's dosage for women at half the level for men. Studies in both animals and humans showed that females take longer to metabolize the drug and are more susceptible to its effects.

Ignoring such differences prior to a drug's approval can increase the risk of harmful, and potentially even life-threatening, effects. That is assuming those differences are studied in the first place; historically, the vast majority of clinical trials enrolled primarily men. Women often bore the worst of the side effects. Between 1997 and 2001, eight out of 10 drugs that the FDA pulled from the market were found after approval to pose greater health risks in women. "The drugs that came on the market were really for men," says Rosemary Morgan, one of Klein's colleagues at Hopkins.

Preclinical animal studies, which are often precursors to clinical trials, have a similarly bad track record. As recently as five years ago, more than 75% of rodent drug studies were conducted only on males.

It can take more effort—and money—to study animals of both sexes. Many scientists avoid female animals because they don't want to account for their reproductive cycles, even though studies have shown that female mice, rats, and hamsters are no more variable—and in some cases are less variable—than their male counterparts in traits ranging from gene expression to hormone levels. Other researchers use

only females, because males are more likely to fight when you put them together in a cage. (Klein says researchers can get around this by obtaining male animals before puberty and letting them grow up together for a few weeks.)

In the mid-1990s, Voskuhl made good use of both male and female mice to investigate why females were so much more susceptible to autoimmune diseases such as lupus and multiple sclerosis. There was a well-studied mouse model of multiple sclerosis, but up until that point most researchers had focused on how the disease progressed in female mice, because the males didn't get as sick. Voskuhl zeroed in on that difference. Among other things, she transferred immune cells from mice of one sex to mice of the other and found that immune cells derived from females were more likely to induce the disease than immune cells from males.

The finding helped make it clear that biological sex also affects susceptibility to multiple sclerosis (other factors, like gender, may also play some role; women are, for example, generally more likely to seek health care). "It showed that there were very basic biological differences," Voskuhl says. That's important, because showing that sex is a factor is a necessary precursor to investigating the immune mechanisms at work.

By the mid-1990s, the clinical trial situation was also improving. In 1993, the US Congress passed a law requiring that women be included in all clinical research funded by the NIH. As for animal studies, in 2016 the NIH instituted its "Sex as a Biological Variable" policy, mandating that grant applications consider sex in the design, analysis, and reporting of research in vertebrate animals and humans. Similar policies had already been enacted in Canada and Europe, but the NIH is the world's largest public funder of biomedical research.

But these changes were just a start—especially in immunology, which in a 2011 review had ranked last out of 10 biological disciplines for reporting the sex of human or animal subjects in published papers.

In 2010, for example, Klein reanalyzed publicly available data on a long-standing, highly effective vaccine for yellow fever. The researchers who generated the data hadn't analyzed it by sex. When Klein did, she found a previously undetected difference in the immune response to the vaccine, with females experiencing a stronger response and potentially better protection. "That really stands out as a great contribution to the field and really showed the value of analyzing data stratified by sex," Benn says. "The overall kind of blurry result was actually covering some very significant differences in responses between males and females."

Around that same time, Klein had set her sights on an enduring mystery—why women tended to have better

The same heightened immune responses that help keep babies alive also increase the risk of autoimmune diseases.

protection from flu vaccines and more severe responses to the flu. Klein found that female mice infected with flu typically have more inflammation and tissue damage in their lungs than males, and more severe outcomes overall, as a result of their stronger immune response. “Pick an immune response, and our female mice mount significantly higher immune responses than males,” she says.

Klein’s work suggests that these biological sex differences affect how we respond to viruses. Women are known to report more adverse events after vaccines, and this has long been thought to be due to gender rather than sex—for example, maybe men are reluctant to report such events, or women are more likely to report perceptions of pain. But by the late 2000s, Klein and others showed that in addition to any such differences, females need far less vaccine to mount the same antibody response as males.

These findings were “really groundbreaking,” Benn says. “That seems quite clear from the research that Sabra has done, and others, that we need perhaps to have sex-differential vaccination programs.”

Giving women a lower dose of the flu vaccine, which could be equally effective while reducing side effects, could potentially reduce vaccine hesitancy. Klein has advocated for such a policy in numerous lectures, interviews, and scientific articles, as well as in a 2009 New York Times op-ed titled “Do Women Need Such Big Flu Shots?” So far, however, the idea has gained little traction.

Benn suggests multiple reasons why it hasn’t caught on, including the fact that it can seem counterintuitive to treat the sexes differently in order to ensure similar outcomes. “Researchers can come to an agreement about such things long before policymakers start moving there,” she

says. “And you can also see that administratively, it might be a bit more complicated.”

But Klein points out that it wouldn’t be that different from giving people over 65 a higher dose of the flu vaccine than younger adults, something we already do.

Women aren’t the only ones who might benefit from vaccine policies that account for sex differences. Janna Shapiro, who recently completed her PhD with Klein and Morgan, found that older males who received flu or covid vaccines showed a much more drastic decline in vaccine-induced immunity over time than older females. Not only is the third dose of the covid vaccine particularly important for older males, but Shapiro suggests that they might greatly benefit from a midseason flu booster shot, even though there’s currently no such shot available to them.

A stronger female immune response shows up in many different species, from sea urchins and fruit flies to birds and rodents to macaques and humans. “If we were to kind of take a Darwinian perspective, there must be some type of evolutionary reason why these differences have evolved,” Klein says.

One hypothesis suggests that a stronger immune response in female mammals could help transfer more antibodies to their babies in utero and through their milk, thus protecting offspring from infections. The same heightened immune responses that help keep babies alive also increase the risk of autoimmune diseases when females are older, but the trade-off may be worth it from an evolutionary standpoint.

Within our genomes, the sex differences in the immune system often play out on the X chromosome, which hosts a large number of genes involved in immune signaling and response. “Having two Xs really differs in terms of immune issues from an X and a Y,” says Marcia Stefanick, director of the Stanford Women’s Health and Sex Differences in Medicine Center in California. Two X chromosomes can mean twice as many copies of some of these immune genes. In principle, only one copy should be active, but in practice, the result is higher gene expression and a stronger immune response.

The X chromosome gene called *TLR7*, or toll-like receptor 7, has been implicated in a number of immunological sex differences. *TLR7* plays an important role in recognizing pathogens and activating the immune system, and it may contribute to higher female prevalence of autoimmune diseases, particularly lupus. “If we eliminate *TLR7*, we eliminate that female-biased immunity and protection following vaccination,” says Klein.

TLR7 may also play a role in explaining why women tend to have a stronger immune response to HIV than men. Researchers didn’t know about this immunological sex difference in the 1990s, when decisions on who was eligible for HIV therapy were sometimes based on how much

virus you had—your “viral load,” says Scully. But it is the immune response and not the viral load that is the dominant predictor of the progression of HIV to AIDS. That meant many women who should have received treatment did not.

“That was a major hole in the eligibility of women for therapy,” says Scully. “That’s just an example of how a biomarker—in this case HIV viral load—did not perform in the same way in males and females, and it had a clinically significant impact on treatment recommendation.”

Sex chromosomes also interact with sex hormones such as testosterone, progesterone, and estrogen, and these hormones can themselves directly influence immunity. Just about every immune cell type in your body has receptors that sex hormones can bind to and then regulate gene expression.

Klein has found that estrogen protects female mice against the flu by dampening inflammatory responses and increasing antibody responses to vaccination. These mechanisms may apply to humans as well. “We’ve published studies showing both in younger- and older-aged women that the higher your estrogen level, the better your antibody response to the flu vaccine,” says Klein.

Whether a disease changes after puberty or menopause or during pregnancy can offer clues about the involvement of sex hormones. “Pregnancy is known to be very good for MS patients. It makes them go into remission,” says Voskuhl. She traced this effect to estriol, an estrogen uniquely produced during pregnancy; it has anti-inflammatory and neuroprotective properties. Voskuhl has been testing estriol in clinical trials as a potential treatment against multiple sclerosis, and she says so far results have been promising.

Asthma is another disease where sex hormones seemed likely to play a role, given that its prevalence changes dramatically after puberty. Asthma is more prevalent in boys than girls during childhood, but after puberty it becomes more common and more severe in women than men.

Newcomb has found that in mice, removing androgens—hormones such as testosterone that are dominant in males—increased asthma-associated airway inflammation, whereas removing estrogen signaling decreased asthma. “That told us that estrogens increased and androgens decreased airway inflammation,” she says.

Androgens such as testosterone may be too blunt a tool to serve as a therapy for asthma, but researchers are currently testing the effects of a related hormone, DHEA, that doesn’t have systemic effects. If all goes well, it could be useful not just in preventing asthma, but also in some autoimmune diseases such as lupus and multiple sclerosis.

While there’s plenty left to investigate about the role of sex hormones and sex chromosomes, it’s also becoming increasingly clear that other types of sex differences also play a role—through genes outside the sex chromosomes, for example, and through microbial activity in our digestive

systems. The 10 trillion to 100 trillion microbes that reside in our gut and their associated genomes, known as the gut microbiome, also differ between males and females. They are known to influence our immune system and may play a role in greater female susceptibility to autoimmune diseases.

Research into these other mechanisms underlying immunological sex differences is still in its infancy, but the future seems bright. “It’s really a frontier that’s ripe for therapeutics,” says Voskuhl.

For research on sex differences to fulfill its promise for human health, scientists will also have to pay attention to how sex interacts with gender.

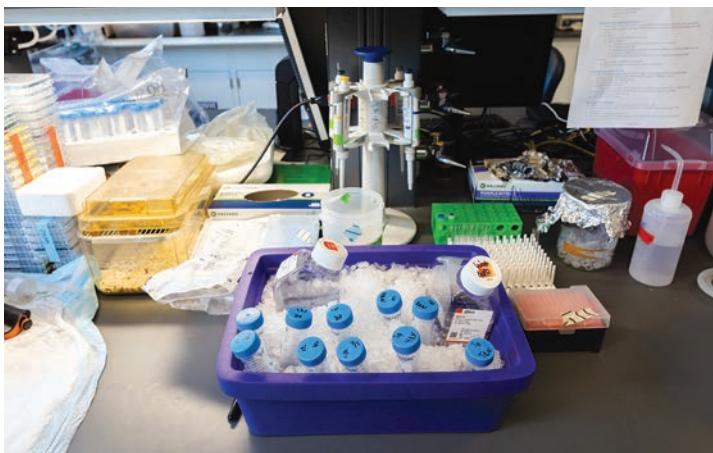
The covid-19 pandemic put this need into sharp relief. Early reports out of China in 2020 had suggested that men were more likely to die of covid-19 than women, and initial hypotheses focused on gender differences. “Early on, people were saying it was because of smoking behavior, differences in access to care, all that kind of thing,” says Shapiro.

But as the pandemic spread worldwide, men consistently fared worse in terms of mortality (at least if the effects of race are excluded—a 2021 study found that in some regions Black women died at more than three times the rates of white men and Asian men). “To me that says there’s gotta be something fundamental,” says Klein.

Klein was quick to start looking for mechanisms behind sex differences in covid-19 infection. She found in a hamster model of the disease that males get sicker, have more damage to their lungs, and experience more pneumonia-like symptoms, similar to what was reported in humans.

But interpreting how humans respond to infectious diseases is complicated by sociocultural factors such as race and gender. “Certainly there are behavioral factors: acceptance

“There is drastic underrepresentation of gender and sexual minorities in clinical research.”



Researchers in Klein's lab use viruses, immune cells (on ice at bottom), and other tools to study sex differences in the immune system.

of masks, vaccine uptake, workplace exposure, all these things that feed into your risk of acquiring disease," says Scully. Women are more often in positions where they're exposed to covid infection, whether as nurses, teachers, or caretakers of sick family members.

Researchers are also hoping to better account for the entire gender spectrum, including people who are non-binary or transgender. "For many reasons, some of which are historical underrepresentation, or maybe not feeling welcome in medical research, there is drastic underrepresentation of gender and sexual minorities in clinical research," Shapiro says. She and other researchers have been incorporating surveys of gender-related behavior

and attitudes into studies to generate gender scores. These assessments could allow scientists to study the influence of gender on health and disease, separate from the effects of biological sex and even self-reported gender identity.

In a rare immunological trial involving transgender people, Scully has started looking at the effects of hormone therapy and gender identity in a cohort of transgender women. "Transgender women in particular are a population at very high risk for HIV acquisition," she says, "so there's a real interest in trying to understand what the best treatment options are for them." Hormone therapy could change an individual's immune response, but social factors could lead to increased stress and thus also potentially affect immune response. Scully's goal is to understand these effects and take them into account when studying potential HIV treatments or cures.

There are still groups of people whose immune systems have barely been studied, such as those who are intersex. They can have variations in sex chromosomes, reproductive anatomy, genes, and hormones that do not fit typical notions of male or female bodies.

Not only will a better accounting of sex and gender diversity help increase our knowledge of health and disease for more people, but it might provide fascinating insights into how sex chromosomes, sex hormones, genes, and gender interact to influence the immune system and susceptibility to disease. "We need to look at how men and women and gender minorities are impacted differentially so we can have better health care, better medicine, better vaccines," says Morgan.

For her part, Klein is hoping to expand the field of sex differences even further. Fresh from putting together the first major symposium on sex differences in the immune response for the American Association of Immunologists in May 2022, she's organizing a major international gathering of scientists in April 2023, at the first Gordon Research Conference on sex differences in immunology. "I want to learn from people working in cancer, I want to learn from people working in autoimmune diseases, I want to learn from people who are studying immune responses in the brain," says Klein. "I'm trying to bring us together under this theme of understanding the biology of sex differences, so that we might find some uniform truth or subtle differences across fields."

The conference will certainly look and feel different from those during Klein's early days in immunology, when she often felt alone in talking about sex differences. After two decades of work to push these ideas into the mainstream, she says, things have changed: "I think as a field immunology is taking this seriously." ■



Circa 1955: An office worker sorts punch cards near the IBM 705 III mainframe computer, owned by the US Army.



WHY CAN'T TECH FIX ITS GENDER PROBLEM?

By
Margaret O'Mara

The things that perpetuate it are some of the same things responsible for Silicon Valley's remarkable ability to churn out one generation of successful tech companies after another.

A full decade has passed since Ellen Pao filed a sexual discrimination suit against her employer, the legendary Silicon Valley venture capital firm Kleiner Perkins. Two years later came the toxicity and misogyny of Gamergate, followed by #MeToo scandals and further revelations of powerful tech-business men behaving very badly. All catalyzed an overdue public reckoning over the industry's endemic sexism, racism, and lack of representation at the top. And to what effect?

Many slickly designed diversity reports and ten thousand Grace Hopper coffee mugs later, the most striking change has been in the size and wealth of the technology sector itself. Even as the market overall turned bearish in 2022, the combined market capitalization of the five largest tech companies approached \$8 trillion. Despite the sector's great wealth and loudly self-proclaimed corporate commitments to the rights of women, LGBTQ+ people, and racial minorities, tech remains mostly a straight, white man's world. The proportion of women in technical roles at large companies is higher than it used to be but remains a painfully low 25%. Coding schools for people of marginalized genders are expanding, and the number of female majors in some top computer science programs has increased. Yet overall, representation remains low and attrition high, especially for women of color.

Much of the burden for changing the system has been placed on women themselves: they're exhorted to learn to code, major in STEM, and become more self-assertive. In her 2013 bestseller *Lean In*, Sheryl Sandberg of Meta urged women to push harder and demand more—by acting the way men did.

Self-confidence and male-style swagger have not been enough to overcome structural hurdles, especially for tech workers who are also parents. Even the mass adoption of remote work in the covid-19 era failed to make tech workplaces more hospitable. A recent survey by Deloitte found that a majority of women in the industry felt more pessimistic about their career prospects than they did before the pandemic. Nearly six in 10 expected to change jobs as a result of inadequate life-work balance. More than 20% considered leaving tech altogether.

At Amazon, Apple, Google, and Microsoft, the CEO baton has passed from one man to another. Sandberg announced in June that she was stepping down, Elizabeth Holmes awaits criminal sentencing for fraud as CEO of Theranos, and the #girlboss moment has given way to swaggering performances of tech-mogul masculinity such as Jeff Bezos, in spacesuit and cowboy hat, soaring skyward in a phallic rocket.

After the US Supreme Court decision overturning *Roe v. Wade*, large tech companies were among the first to announce



that they would cover the costs for employees who needed to travel to another state to end a pregnancy. But they refrained from taking positions on the ruling itself. Meta discouraged employees from talking about it on company message boards, even limiting the visibility of social media posts by Sandberg lamenting the decision. Support for abortion rights and the women advocating for it only went so far.

Much of tech's gender problem is a corporate America problem. Women, especially women of color, remain grossly underrepresented in top executive ranks across sectors. But tech is an industry that promised to think different, change the world, and make money without being evil. It also has a long history of employing many technical women.

Software programming once was an almost entirely female profession. As recently as 1980, women held 70% of the programming jobs in Silicon Valley. That ratio has completely flipped. Female technicians once outnumbered male workers on the Valley's hardware assembly lines by more than two to one. Those jobs are now nearly all overseas. In 1986, 36% of those receiving bachelor's degrees in computer science were women. The proportion of women never reached that level again.

Many things contributed to the shift: the educational pipeline, the tech-geek stereotypes, the industry's long-standing and enthusiastic reliance on hiring by employee referral, the tiresomely persistent fiction of tech as a gender-blind "meritocracy." None explain it entirely.

What really lies at the core of tech's gender problem is money.

The technology industry has generated significant, and sometimes enormous, personal fortunes. Most of this money has gone to men. Tech executives have become the richest people in human history. Only two women currently appear on the list of tech's 20 richest people: one is a widow of a male tech billionaire, the other an ex-wife of one.

Venture capital investment has been and remains the tech ecosystem's least diverse domain. White and Asian men make up 78% of those responsible for investing decisions and manage 93% of venture dollars overall. While there are now more female-led investment funds than there were a few years ago, the majority of venture capital firms still have zero women as general partners or fund managers.

Of the few women in these roles, nearly all are white. The US venture capital industry invested a record-breaking \$329 billion across more than 17,000 deals in 2021. Only 2% of this bonanza went to startups founded solely by women—the lowest level since 2016. Less than 0.004% of the venture capital

invested in the first half of 2021 went to startups with Black female founders.

The lack of investor and founder diversity has far-reaching consequences. It does not only determine who gets rich. It also shapes the kinds of problems technology companies set out to solve, the products they develop, and the markets they serve.

The patterns seen today in venture capital firms have been more than seven decades in the making. That is one reason they are so difficult to unwind. But there's another, thornier problem. The things that have worked against venture diversity—and tech diversity in general—have also been secrets of the American technology industry's success since the very start.

Beginnings: "A future without boundaries"

There was never really a golden age for women in tech. If a job was female-dominated, it often paid less and was valued less, and its occupants were considered easily replaceable. When women did the same jobs as men, they were regarded as a curiosity, a blip in a male-dominated corporate world.

In 1935, IBM chief executive Thomas Watson Sr. made a great show of hiring 35 newly minted college graduates as his company's first class of "Systems Service Women," tasked with giving technical support to new customers. Men held these jobs too, but only the women spent their first week of employment being feted like debutantes, welcomed with bouquets of flowers and a formal dinner dance hosted by Watson.

The women who programmed wartime computer projects in the 1940s were first called "operators," their jobs seemingly little different from those held by the thousands of fast-thinking women who sat before the nation's telephone switchboards. With the arrival in the early 1950s of program compilers—a technology and term invented by a woman—the workers became "coders," a word reflecting a persistent misunderstanding of programming as something mechanistic, practically stenographic.

Around the same time, IBM executives placed mainframes in the lobby of the company's New York City headquarters and hired female programmers to work in view of passersby. That way, one supervisor explained to a female recruit, the machines "will look simple and men will buy them."

Meanwhile, corporations aggressively recruited technical men, promising good paychecks and likely promotion. In the late 1950s and early 1960s, the gender-segregated classified employment pages brimmed with ads enticing male engineers through promises like "Your own enthusiasm and professional growth are the only limits to a future without boundaries."



A female operator at the control desk
of the world's fastest calculator,
the IBM Selective Sequence
Electronic Calculator, in IBM's New
York offices in 1948.

Early computing history abounds with these stories, reflecting the endemic sexism of American corporate culture before equal-opportunity laws and other victories of modern feminism. Notably, the women who rose to senior technical positions during this period often worked for military agencies or at NASA, where clearly codified standards for promotion better protected women from managerial whims.

Growth: “The Olympics of capitalism”

While technical women stayed mainly within large organizations, male engineers gradually began to leave academia and corporate life to start their own companies. This entrepreneurial model reached its apex in Northern California’s Santa Clara Valley.

Stanford University-trained engineers had been starting companies in local garages and disused farm buildings since



the 1930s, but it wasn’t until the 1950s that the Valley became a tech powerhouse. Cold War spending transformed Stanford, filled the Valley with defense contractors, and fueled growth of a new cluster of silicon-semiconductor startups. The firms gave Silicon Valley its name, built many of its first great fortunes, and left an indelible imprint on its corporate culture.

Life in early Silicon Valley chip firms was like *Mad Men* with fewer suits, more all-nighters, and the occasional screaming match over circuit-board design. Secretaries were usually the only women in sight. Employees were expected to show up before 8 a.m., work as late as they could bear, and then go out for beers. The countercultural 1960s never really happened in the semiconductor industry; this was engineering, not an encounter group. Management rewarded rational minds and thick skins. “I hired you,” National Semiconductor executive Don Valentine once told a new recruit, “because you were the only one I couldn’t intimidate.”

Women were the mainstay of Fairchild Semiconductor’s busy production line in 1964.

Making all this intensity possible were stay-at-home wives—the most hidden of tech’s hidden figures, whose care of children and home allowed for their husbands’ total work immersion. The rare female executive had to keep pace, acting as if similarly unbothered by personal demands, sneaking phone calls to her children on the side.

By the 1970s, the success of these firms had minted hundreds of millionaires, most men in their early 30s. High-tech entrepreneurship, one Valley investor declared, was “the Olympics of capitalism.”

Not competing in this Olympics, but still contributing to the industry’s success, were the thousands of women who worked in the Valley’s microchip fabrication plants and other manufacturing facilities from the 1960s to the early 1980s. Some were working-class Asian- and Mexican-Americans whose mothers and grandmothers had worked in the orchards and fruit canneries of the prewar Valley. Others were recent migrants from the East and Midwest, white and often college educated, needing income and interested in technical work.

With few other technical jobs available to them in the Valley, women would work for less. The preponderance of women on the lines helped keep the region’s factory wages among the lowest in the country. Women continue to dominate high-tech assembly lines, though now most of the factories are located thousands of miles away. In 1970, one early American-owned Mexican production line employed 600 workers, nearly 90% of whom were female. Half a century later the pattern continued: in 2019, women made up 90% of the workforce in one enormous iPhone assembly plant in India. Female production workers make up 80% of the entire tech workforce of Vietnam.

Venture: “The Boys Club”

Chipmaking’s fiercely competitive and unusually demanding managerial culture proved to be highly influential, filtering down through the millionaires of the first semiconductor generation as they deployed their wealth and managerial experience in other companies. But venture capital was where semiconductor culture cast its longest shadow.

The Valley’s original venture capitalists were a tight-knit bunch, mostly young men managing older, much richer men’s money. At first there were so few of them that they’d book a table at a San Francisco restaurant, summoning founders to pitch everyone at once. So many opportunities were flowing it didn’t much matter if a deal went to someone else. Charter members like Silicon Valley venture capitalist Reid Dennis called it “The Group.” Other observers, like journalist John W. Wilson, called it “The Boys Club.”

The venture business was expanding by the early 1970s, even though down markets made it a terrible time to raise



Georges Doriot, “the Father of Venture Capital,” declared, “An average idea in the hands of an able man is worth much more than an outstanding idea in the possession of a person with only average ability.”

Master intimidator Don Valentine founded Sequoia Capital, making early-stage investments in Atari and Apple, and later in Cisco, Google, Instagram, Airbnb, and many others.



Gene Kleiner left Fairchild Semiconductor to cofound Kleiner Perkins, whose long list of hits included Genentech, Sun Microsystems, AOL, Netscape, Google, and Amazon.



As John Doerr once put it, the most successful founders “all seem to be white, male nerds who’ve dropped out of Harvard or Stanford, and they absolutely have no social life.”



money. But the firms founded and led by semiconductor veterans during this period became industry-defining ones. Gene Kleiner left Fairchild Semiconductor to cofound Kleiner Perkins, whose long list of hits included Genentech, Sun Microsystems, AOL, Google, and Amazon. Master intimidator Don Valentine founded Sequoia Capital, making early-stage investments in Atari and Apple, and later in Cisco, Google, Instagram, Airbnb, and many others.

Generations: “Pattern recognition”

Silicon Valley venture capitalists left their mark not only by choosing whom to invest in, but by advising and shaping the business sensibility of those they funded. They were more than bankers. They were mentors, professors, and father figures to young, inexperienced men who often knew a lot about technology and nothing about how to start and grow a business.

“This model of one generation succeeding and then turning around to offer the next generation of entrepreneurs financial support and managerial expertise,” Silicon Valley historian Leslie Berlin writes, “is one of the most important and under-recognized secrets to Silicon Valley’s ongoing success.” Tech leaders agree with Berlin’s assessment. Apple cofounder Steve Jobs—who learned most of what he knew about business from the men of the semiconductor industry—likened it to passing a baton in a relay race.

Venture capitalists often believed that the person was as important as the product, if not more so. “An average idea in the hands of an able man,” declared Georges Doriot, the Harvard Business School professor known as “the Father of Venture Capital,” “is worth much more than an outstanding idea in the possession of a person with only average ability.”

One surefire way to find “able men” was to fund or recruit people you had successfully worked with before. This is another critical dimension of the Silicon Valley model: tightly knit networks that often work together in multiple startups. The most famous of these groups acquired nicknames. The men who left the Valley’s first silicon chipmaker, Shockley Semiconductor, to start Fairchild Semiconductor were called “the Traitorous Eight.” Four decades later, a group of men, many of whom had met writing for Stanford’s conservative student newspaper (including Peter Thiel, who cofounded it), became a core part of the founding team of PayPal. With the company’s acquisition, they became “the PayPal Mafia,” using their wealth to found new venture-backed companies and become investors in many others.

Venture capital firms became the connective tissue joining clusters of fortunate coworkers into an even larger network. One of the first firms to invest in PayPal was Sequoia Capital.





The men who left the Valley's first silicon chipmaker, Shockley Semiconductor, to start Fairchild Semiconductor in 1957 were called "the Traitorous Eight."

When it came to people an investor didn't already know, reliance on personal attributes and a healthy dose of gut feeling led venture partners to bet on founders who seemed to share a lot of the same qualities as those who had succeeded before—in short, people like those already in their networks. “Pattern recognition” was how Kleiner Perkins partner John Doerr once put it. The most successful founders “all seem to be white, male nerds who've dropped out of Harvard or Stanford, and they absolutely have no social life”; when they showed up in his office, he said, he knew it was time to invest.

The remark was an unintended gaffe—don't say the quiet part out loud!—but it was true. Doerr had risen up the ranks at Intel and took what he had learned in chipmaking to build one of the most successful venture careers in tech history. He funded and mentored Marc Andreessen of Netscape, Sergey Brin and Larry Page of Google, and Jeff Bezos of Amazon—all men.

Doerr and venture capitalists before and after him were eager to absorb new ideas, but their experiences had persuaded them that tech was a meritocracy and allowed them ignore the exclusion perpetuated by Silicon Valley's tight-knit networks.

Money: “The Golden Geeks”

Hardware companies dominated both Silicon Valley and Boston through the 1970s. Software was rarely a stand-alone product but was bundled into a computer purchase or given away free. This helps explain why many women continued to hold programming jobs even as the field professionalized, rose in prestige, and came to be regarded by many corporations as an environment best suited for “antisocial, mathematically inclined males.”

When desktop computers first arrived on the market, some employers embraced programming as a job perfect for working mothers, who could plug in a modem and code from home between school pickups and household chores. That moment was short-lived, for the personal computer business also created the immensely profitable desktop software industry. Programming was no longer just for introverts and elementary school moms. It minted billionaires.

The colossus at the industry's center was Microsoft, led by the most famous software geek of all, Bill Gates. By the late 1990s, the company's products ran on over 90% of the personal computers on the planet. Gates was the world's richest man and Valley venture capitalists were early-stage investors in his company. On Microsoft's campus outside Seattle, armies of software engineers worked seven days a week. The workforce was so overwhelmingly male that one observer called it “the frat house from another planet.” Microsoft's stock awards turned roughly 10,000 employees, mostly men and many under 30, into millionaires. Money ruled the 1980s, the 1990s,

and beyond. “Striking It Rich,” read a 1982 Time headline hovering over a depiction of Apple’s Jobs on the magazine’s cover. Gates followed in 1984, twirling a floppy disk. In 1996, Time handed the crown to Netscape cofounder Andreessen. “The Golden Geeks,” the magazine crowed, picturing the 24-year-old multimillionaire hamming it up while sitting barefoot on a gilded throne.

Power: “I’m CEO ... bitch”

After 2000, Silicon Valley was the undisputed high-tech capital, no longer just a place in California but shorthand for the industry itself. Founders of this new generation had a new set of mentors to learn from and admire. Jobs’s triumphant 1997 return to Apple after being forced out over a decade earlier had made him a business legend. His untimely death in 2011 further enshrined his legacy as the founder to emulate.



Andreessen was now a successful venture capitalist dispensing managerial wisdom over coffee and pancakes, just as an older generation had done for him decades before. “He became a sounding board about management and how to build a strong technology company,” recalled Mark Zuckerberg of the regular meetups he had with Andreessen in the early days of Facebook. “He has strong views on that, and they helped shape mine.”

The new generation of founders tended to be younger and brasher. Men who had spent their boyhoods staring into computer screens now had power, money, and swagger. A few months into Facebook’s existence, Zuckerberg realized he needed business cards. He ordered up two versions. One simply said “CEO.” The other: “I’m CEO ... bitch!”

The workplace cultures of today’s large technology companies are as all-consuming as those of any early chipmaker. And the perks that firms showered on their white-collar employees

pre-pandemic said a lot about the kinds of workers tech companies most valued. In 2017, Apple moved into an extraordinary new \$5 billion headquarters with a two-story yoga room and seven cafes. Although it was designed to hold 12,000 employees, it did not have a child-care center.

Tech’s reckoning?

Today, the baton is passing to crypto enthusiasts and Web3 evangelists. While the cast of characters is slightly more diverse than it once was, the potential superstars of the next generation—Coinbase’s Brian Anderson and FTX’s Sam Bankman-Fried, to name two—remain mostly white and male.

Tech’s gender reckoning has been among a number of things fueling a new wave of employee activism. For the first time, Silicon Valley’s white-collar employees are speaking out publicly against their employers and, in some instances, successfully pressuring them for changes to corporate practices.

One striking thing about today’s activists, organizers, and whistleblowers is that nearly all of them are female, gender-nonconforming, or queer. Several are nonwhite. Outside and less beholden to tech’s charmed circles, they have been able to see tech’s problems more clearly. Women were six of the seven organizers of the 20,000-strong Google walkout in 2018, which protested the \$90 million severance package awarded to top executive Andy Rubin after credible claims of sexual harassment. Computer scientist Timnit Gebru was recruited to Google because of her groundbreaking work on algorithmic bias and then was fired, reportedly because of the company’s discomfort with her findings. She has since become a powerful critic of Silicon Valley business and research practices. Data scientist Frances Haugen worked at Google, Yelp, and Pinterest before she came to Facebook, where alarm at the company’s business practices prompted her to copy thousands of pages of internal documents and leak them to reporters. (Haugen admitted that she was able to blow the whistle at Facebook because her tech career had made her wealthy enough to leave her job.)

Within companies, employee activism grows by the day. It is not only changing the culture but also—quite remarkably, given Silicon Valley’s history—fueling cross-class support for employee unionization. Women and gender-diverse employees are on the front lines of these movements as well.

The tech industry loves to talk about how it is changing the world. Yet retrograde, gendered patterns and habits have long fueled tech’s extraordinary moneymaking machine. Breaking out of them might ultimately be the most innovative move of all. ■

Historian Margaret O’Mara is the author of *The Code: Silicon Valley and the Remaking of America*.



Computer scientist Timnit Gebru was fired from Google, reportedly because of the company's discomfort with her research findings. She has since become a powerful critic of Silicon Valley business and research practices.



E X T R A X

L I V I N G

W I T H A N

Sex chromosome variations are the most common chromosomal conditions, but most people don't even know they have them.

By **Bonnie Rochman**



hen Ollie's mother, Katie, was nine weeks pregnant, her obstetrician-gynecologist's office in Boulder, Colorado, offered her a special \$100 price on a new prenatal blood test that she was told could detect major chromosomal hiccups such as Down syndrome and trisomy 18. She and her husband agreed—who can say no to a deal?—with one caveat. “Remember,” Ollie’s mother told the nurse, “we don’t want to know the sex.”

But they ended up finding out anyway when they received an unexpected phone call from their ob-gyn. “He said, ‘Unfortunately, I need to call and say you’re having a boy and he has XXY,’” Katie says.

Katie and her husband, Simon, had never heard of XXY, and their obstetrician wasn’t much help either. Also known as Klinefelter syndrome, XXY is a genetic condition that can cause infertility and other health issues; it occurs when a child, typically assigned male at birth, is born with an extra X chromosome in addition to the typical X and Y.

Sex chromosome variations, in which people have a surplus or missing X or Y, are the most common chromosomal conditions, occurring in as many as one in 400 births. Yet the majority of people affected don’t even know they have them. That’s because these conditions can fly under the radar; they’re not life threatening or necessarily even life limiting and don’t often have telltale characteristics that raise red flags. Still, the diagnosis can cause distress.

As more expectant parents opt for noninvasive prenatal testing in hopes of ruling out serious conditions, many of them are surprised to discover instead that their fetus has a far less severe—but far less well-known—condition. Because so many sex chromosome variations have historically gone undiagnosed, many ob-gyns are not familiar with these conditions, leaving families to navigate the unexpected news on their own. Many wind up seeking information from advocacy organizations, genetic counselors, even Instagram as they figure out their next steps.

The information landscape has shifted dramatically since the advent of noninvasive prenatal screening (NIPS) a decade ago. The increasingly popular first-trimester blood tests that debuted in 2011 to detect Down syndrome have, over time, added a broader spectrum of conditions to their panel, including sex chromosome aneuploidies—the medical name for an atypical number of chromosomes.

In 2020, the American College of Obstetricians and Gynecologists endorsed NIPS at any age, effectively making the blood test a routine part of pregnancy care. Parents typically use these tests to rule out Down syndrome or more severe conditions, only to find out in many cases about something they didn’t even realize their baby was being screened for. “The scariest part is here is this diagnosis based on a test that we didn’t really understand,” says Simon. Adds Katie: “We were assuming the test would detect only very serious things.”

To add to the complexity, NIPS is not as reliable for sex chromosome aneuploidies as it is for Down syndrome, underscoring the importance of confirming a positive screening result during pregnancy via amniocentesis or chorionic villus sampling (which examines placental tissue), or with a blood sample after the baby is born. Yet data suggests that “some women have elected to terminate pregnancies solely on the basis of [noninvasive prenatal screening] results, potentially aborting unaffected fetuses,” according to a 2016 article in *Prenatal Diagnosis*.

About 40% of men with XXY are diagnosed over the course of their lifetimes, usually when they experience fertility problems as adults, says Nicole Tartaglia, a global expert on sex chromosome variations. People with XXY may have learning difficulties and challenges with social interaction, along with physical traits such as small testes, a less muscular body, and less facial and body hair. But most people with Klinefelter syndrome grow up to live productive, healthy lives.

Meanwhile, only 10% of people with XXX or XYY are aware of their condition. But these numbers are growing as genetic testing becomes more widespread. “Judging by the number of phone calls we are getting, the proportion of those who are going undiagnosed is getting smaller,” she says.

When families learn that their fetus has a sex chromosome variation, one of the first places they turn is AXYS, the Association for X and Y Chromosome Variations, an advocacy and support organization that has seen its calls from confused families skyrocket as NIPS has become more popular. “People come to us very scared,” says Carol Meerschaert, the organization’s executive director. “They don’t know about

these conditions, and their doctors don't know about them either, but they are much more common than Down syndrome."

XXY occurs in about one of every 650 male births; XXX affects one in 1,000 female births, and XYY one in 1,000 males. "I like to say that you have met someone with one of these conditions," she says. "You just didn't know it, and they may not know it!"

The availability of genetic counseling and information about X and Y variations isn't keeping pace with the growing number of families learning about such variations in their unborn children. This void is what prompted Lilian Cohen, a pediatric geneticist, to help launch a center dedicated to X and Y variations at Weill Cornell Medicine in New York City. "Noninvasive prenatal testing is one of the reasons why in one week I had four patients, three of whom were diagnosed prenatally," she says. "Couples are not getting the counseling they need."

Depending upon what condition the screening tests are analyzing for, the accuracy of results can range significantly. "These X and Y variations are found accidentally through this technology," says Cohen, who believes that access to genetic counseling is an essential part of testing. "My bias as a geneticist is that this knowledge is powerful."

If people don't go for genetic counseling after a positive screening result—few do, Cohen says—they may overestimate the severity of the condition and decide to end the pregnancy. "They may never even make it to our office," she says. "I only see the tip of the iceberg."

When families do come see her, she explains how different X and Y variations are from Down syndrome, which can be accompanied by heart conditions, intellectual disability, and complex congenital problems. "As much as I love my patients with Down syndrome," Cohen says, "that is a different kind of decision-making."

It's a perplexing time in history to have a sex chromosome variation. We



live in a world where there is confusion and mystery around the intersection of sex and gender. In fact, it's not uncommon for people with these variations to be labeled as intersex, a term that encompasses unique variations of sex or reproductive anatomy, including genitalia, hormones, internal organs, and/or chromosomes. While some people consider sex chromosome aneuploidies like Klinefelter to be under the intersex umbrella and do identify with intersex movements, some do not. "Parents are worried that people will think their son isn't as much of a man because they have an extra chromosome, so people don't talk about it," says Meerschaert. "This isn't simple."

Numerous companies and labs offer noninvasive prenatal screening, which analyzes tiny fragments of placental DNA that float in the gestating parent's circulation to determine if there are chromosomal abnormalities. The global market, valued at more than \$3 billion in 2021, is expected to more than double by 2028 as companies—including giants such as Illumina, Roche, and LabCorp—compete with one another to validate their tests for additional conditions.

Natera, one of the leading players, offers one of the more comprehensive screening tests. The company was fourth to market in early 2013; shortly after, a paper in Prenatal Diagnosis demonstrated its test's ability to detect sex chromosome trisomies. Natera had previously included these trisomies as incidental findings, but after the paper's publication, it added them as a routine part of every patient's results. "The requisition form clearly states what is being screened for," says Sheetal Parmar, a genetic counselor who is Natera's vice president of medical affairs.

Yet it's a rare patient who reads all the fine print. "It's always a challenge for people to fully understand all the things they're being screened for," says Parmar. "But having the information about a sex chromosome aneuploidy gives families time to prepare."



PEOPLE WITH XXY
MAY HAVE LEARNING DIFFICULTIES AND
CHALLENGES WITH SOCIAL INTERACTION,
ALONG WITH PHYSICAL ISSUES,
BUT MOST GROW UP TO LIVE
PRODUCTIVE, HEALTHY LIVES.

On one hand, Katie is grateful for her son's diagnosis "because it forces us to be aware and have a big safety net around Ollie if he ever needs it." On the other hand, it can be a source of frustration. Is Ollie's tendency to get teary when a task feels frustrating a consequence of XXY or just his nature? Katie wonders. (Challenges regulating emotions can characterize XXY.) "I will question how much of this should we worry about versus 'This is who he is,'" she says. "My mama heart is always wondering, 'Is this the thing? Do we need to freak out?'"

It can be challenging to lump all sex chromosome aneuploidies into one bucket. Symptoms can vary widely from condition to condition—girls with an extra X chromosome tend to be taller than their peers, for example, while those with just one X tend to be short—and there is plenty of variability even within the same condition.

While Ollie hasn't needed any behavioral intervention, Robby, an eight-year-old boy with XXY who lives

in Seattle, has had a different experience. His mother, Claire, also learned about her son's extra chromosome through NIPS; she cried in a parking garage after her doctor called with the results. "I was in a prenatal yoga class where everyone was going around saying, *I'm this far along and I'm having a boy or a girl*," she says. "I remember feeling jealous that things were so simple."

Robby was late to toilet train, and at preschool he'd knock over other kids' toys, running around and making messes at cleanup time. On one particularly tough day, Claire asked the teacher: "Is his behavior outside the norm?" The teacher said yes.

Robby's prenatal diagnosis prompted Claire to seek early intervention. For starters, she called the eXtraordinarY Kids Clinic at Children's Hospital Colorado, where she'd turned for guidance during her pregnancy. The clinic was recruiting participants for a study about emotional regulation in preschoolers with XXY, and Robby was the first child to enroll. A neuropsychiatric evaluation assigned him superior scores for language and spatial reasoning, but in terms of processing speed and adaptive skills—tasks like washing hands independently or eating with a fork—he was below average.

After being diagnosed with autism, anxiety, and ADHD, Robby has met with a battery of therapists, including an occupational therapist for managing anger and honing fine and gross motor skills. "It's hugely affected our family," says Claire, who has three children younger than Robby. "I didn't think his challenges would be this significant."

Robby's parents have told him about his extra X by using a Lego analogy: "Everybody has a book of Lego instructions that talk about their bodies. Your Lego book has an extra page, which is why you feel things so deeply and you're so tall." But they do have concerns about his friends' parents looking up the condition and pigeonholing him. "It's his story to tell," Claire says. "If he wants to be the Ryan Bregante of boys, that's fine. But we want him to decide."

Ryan Bregante, a 36-year-old photographer and internet personality, is one of the most outspoken men within the XXY community. Growing up in San



Diego, he was bullied and struggled with reading, writing, and spelling, but he didn't know much about his condition until 2017, when he attended an AXYS conference. "I met 20 guys with XXY," he says. When he left, he spent three months surfing PubMed and scouring research papers to learn more about his genetics. He was dismayed by much of what he found: doom and gloom. "It was all 'You're stupid, you're not going to amount to anything,'" he says. "When I Wikipediaed it, there was nothing but 'rapists' and 'psychopaths.'" Though the stigma of those outdated stereotypes persists, Bregante works to dispel it.

In September 2017, Bregante made his first YouTube video, which was followed quickly by a website, Living with XXY, and an Instagram account where he solicits experiences from others with XXY and shares his own day-to-day. "What is positive about your life with XXY?" he asks.

"I want to show that we can live happy, successful lives," he says. "Most men I know with XXY aren't open about it, and neither are their families. I tell families, 'If your son were deaf, would you act like this?' The hardest thing about this diagnosis is we are walking around in plain sight. Keeping the diagnosis to yourself is perpetuating the shame."

Parents of boys with XXY are used to deflecting questions about whether their sons are more feminine than boys without an extra X. That's a driving force behind why most of the parents interviewed for this article didn't want to be identified by their full names. It's a conundrum: they realize that not being open about their child's diagnosis may perpetuate stigma, but they're not willing to risk compromising their child's privacy.

In 2011, the year that NIPS emerged onto the scene, a review in *Genetics in Medicine* of published studies found that as many as 85% of parents decided to terminate a pregnancy after they received an XXY diagnosis.

It's unclear what effect the overturning of *Roe v. Wade* may have on terminations of pregnancies affected by sex chromosome variations. It is plausible that the rate of abortions will decrease, but testing is not likely to become any less common. Families want to do prenatal testing in order

to be better prepared for potential outcomes, and in some cases decide whether they want to terminate based on the results or pursue treatment.

Tartaglia, who runs the eXtraordinarY Kids' Clinic, supports a somewhat unorthodox approach: giving boys with XXY testosterone shots early in infancy, when all babies undergo a "mini puberty"—a few months when hormones spike and set the stage for the development of reproductive organs.

Testosterone supplementation in baby boys with XXY is thought to support neurodevelopment. The theory is that a deficit could lead to low muscle tone or problems with speech.

Ollie's parents say they didn't seriously consider ending Katie's pregnancy, but they needed to be reassured that Ollie could thrive. "Is the mountain this kid will have to climb every day so unbelievably hard that every day is a battle?" Simon asked the doctor, who said no, though he added that Ollie might grapple with learning disabilities and infertility.

To try to mitigate some of those outcomes, Ollie was enrolled in a study in which he got testosterone infusions starting at eight weeks old. In a full-day assessment at the eXtraordinarY Kids' Clinic when he was two, he could drink from a cup, put on a jacket, thumb through a book—achievements that showed he was developing on schedule.

Five years later, at age seven, he's continuing to meet and surpass milestones. He is in an advanced reading group at school and hasn't needed any interventional services related to XXY. "He's continued to thrive as a little boy," says Katie.

In her practice, Tartaglia encounters some families that work hard to put a positive spin on their child's diagnosis. "They say, 'It's okay. We can fix it,'" she says. Tartaglia gently redirects them: "Yes, we can help, but we can't get rid of that extra chromosome."

"Everyone has strengths and weaknesses," says Tartaglia. "We need to celebrate and embrace the idea that there is diversity in the way we all think, speak, act, and feel." ■



ANI LIU'S ART
EXPLORES THE
WAYS REPRODUCTIVE
LABOR IS

HIDDEN,
ROMANTICIZED,
TECHNOLOGIZED—
AND UNDervalued.

BY:

ALEXANDRA LANGE

PHOTOGRAPHS:

CELESTE SLOMAN

NATURAL - CHILD-BIRTH

Untitled (feeding through space and time)
uses 328 feet of plastic tubing filled with
synthetic milk.

MESSY

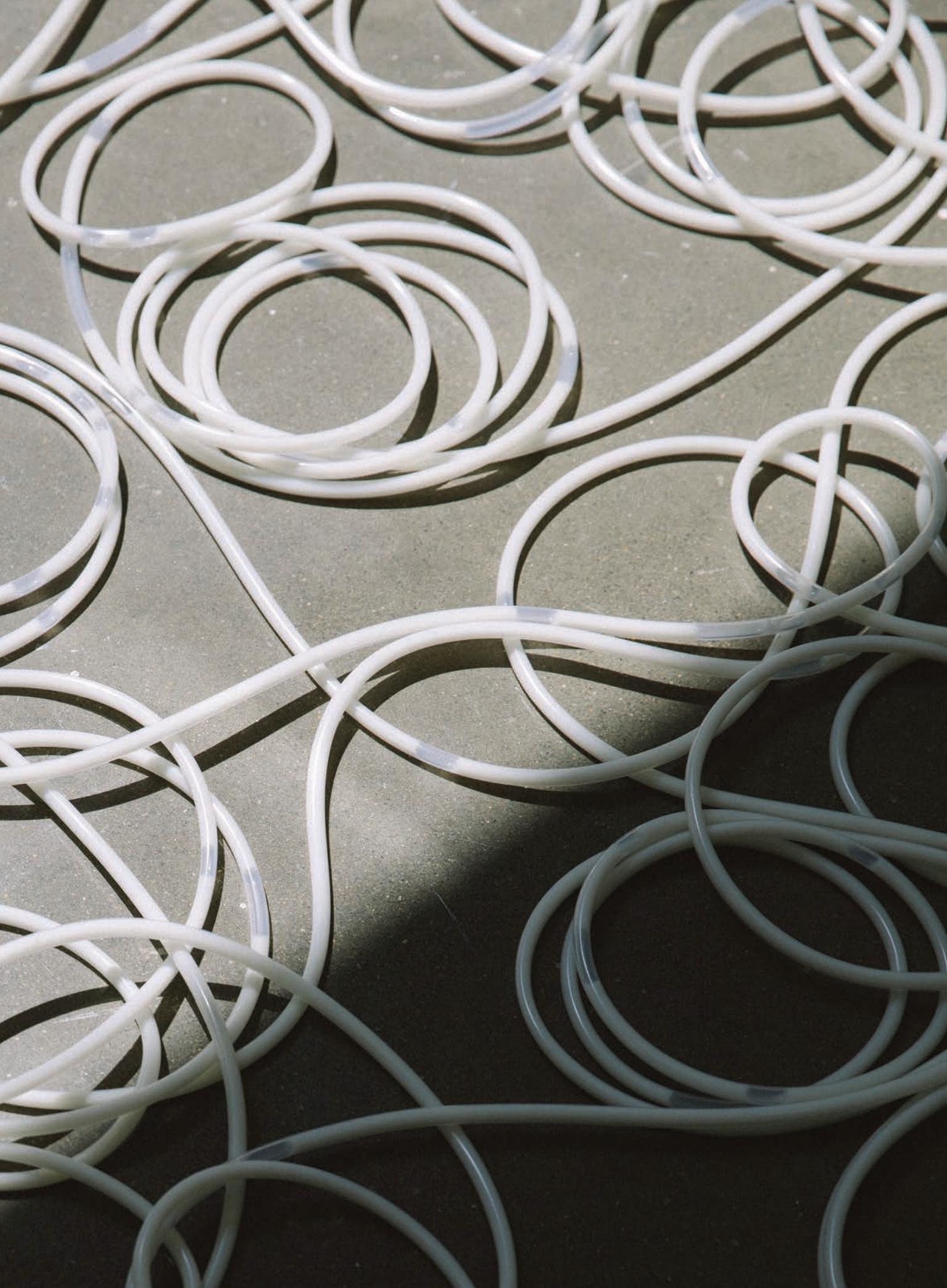
coils of plastic tubing sprawl across the gallery's concrete floor. The liquid inside—opaque, white with a yellowish tinge—pulses once, twice, and the eye tracks its progress thanks to the air bubbles cycling through the loops. Could that be ... milk? Follow the tubing back to an unassuming rectangular box. If it is milk, a panicked brain might ask, where is the mother?

At this moment the mother, artist Ani Liu, is standing by the door of the pocket-size Cuchifritos Gallery + Project Space in Lower Manhattan, wrapped in a tie-dyed T-shirt dress for tonight's opening of her solo exhibition, "Ecologies of Care." But she has also sat, pumping milk, in the broom closet next to her classroom at the University of Pennsylvania; in her basement studio in Queens; on trains and in cars. The volume of milk circulating through *Untitled (pumping)* and *Untitled (feeding through space and time)* represents a month of such sessions, or 5.85 gallons—some of the invisible labor of motherhood. It also represents modern breastfeeding technology—specifically, the Spectra pump that allowed Liu the alleged freedom to return to the workplace just weeks after having her first child. After headlines about a national formula shortage earlier this year, the liquid seems even more precious.

The milk in this exhibit is not real. After much experimenting, Liu ended up filling the pump with "magician's milk," a proprietary formula, purchased from a magic shop, that requires no refrigeration and comes with the warning "Not a food product. Do not drink!" Nevertheless, it looks convincing. When installing the piece, Liu originally considered having the milky coils take over the whole gallery floor, even more aggressively immersing visitors in the visual and aural landscape of newborn care.

Liu, who holds graduate degrees from the Harvard Graduate School of Design and the MIT Media Lab, resumed teaching just five days after she gave birth in 2021. She had just signed a new contract as an associate professor of practice at Penn, and the university offers maternity leave only







to employees of more than a year. Though she was initially allowed to teach over Zoom from her home in Queens, she ended up pumping more than nursing. “I developed this really intense relationship with my pump, where just hearing the sound of it made me let down, rather than my baby’s cry. It was just such a weird Donna Haraway cyborg moment,” she says, referring to the feminist science and technology scholar who wrote, of the cyborg, that it “does not dream of community on the model of the organic family.”

It was also a moment that led Liu to new research. Her discoveries emerge in the works on display in the Cuchifritos Gallery, which include a series of three-dimensional meditations on technology, motherhood, and childhood in our algorithm-enabled world.

Pumping is also on display as part of the second edition of the exhibition “Designing Motherhood,” now at the MassArt Art Museum in Boston. Michelle Millar Fisher, part of the curatorial team, wrote that the work “cuts right to the heart of the ways in which reproductive labor is hidden, romanticized, socially taboo, and undervalued.”

Liu’s work has additional urgency and resonance after the overturning of *Roe v. Wade*. Who controls, who supports, and who performs reproductive labor are not just bedroom or broom closet questions (and never should have been); they are playing out on the streets, in state houses, and in the Supreme Court.

Millar Fisher has drawn parallels between Liu’s pumping installation and the work of the artist Hiromi Marissa Ozaki, known as Sputniko!, whose 2010 *Menstruation Machine* simulates the experience of menstruation; the video part of the piece shows a fictional day in the life of a young man who builds a device to experience life as a person with a uterus.

Liu has long been fascinated by this sort of simulated experience. In 2019, after watching YouTube videos of men sampling simulated labor pains in order to understand their wives’ experience, and finding them wanting on multiple levels, she decided to create her own apparatuses, including



OPPOSITE :

In *Untitled (milk fat globules)*, a milk molecule, photographed under a microscope, is layered, color-corrected, and printed on an aluminum panel shaped after a popular brand of scallop-edged nursing pads.

ABOVE :

The volume of synthetic milk circulating through *Untitled (pumping)* represents a month’s worth of milk pumped in the workplace.

**ABOVE :**

Described by Liu as “a response to Donald Trump’s statement ‘Grab them by the pussy’ during the 2016 presidential campaign,” *Mind Controlled Spermatozoa* allows women to control the directional movement of sperm using their thoughts.

OPPOSITE :

Untitled (Consumerist Pregnancy Reports): A set of ritual devices and consumable products made to simulate the biological experience of pregnancy.

a garment called *Untitled (woman pains)*, fitted with a belly and electrodes, that would allow any non-pregnant person to experience the weight and discomforts of pregnancy. Another in the series, *Untitled (small inconveniences)*, simulates incontinence. Made in collaboration with fabricator Randi Shandroski, the garments look like lingerie and simulate one result of sex, but these are not experiences generally considered sexy.

Her pieces demonstrate a mischievous humor, embedded in the everyday indignities of modern life. Consumer culture might seem to celebrate pregnancy, but the products pushed to pregnant people focus on all the things that are “wrong” with the pregnant body: mood swings, stretch marks, incontinence. In response, Liu created *Consumerist Pregnancy*, which includes a series of creams, masks, and medications, designed in high millennial style (monochrome packaging, sans serif fonts) but honestly labeled “Fatigue,” “Shortness of Breath,” “Swelling.” If you saw them on a pharmacy shelf you would be initially attracted, but once you read the description, even as a person who has been pregnant, it would be hard not to say *No, thank you*.

The Surrogacy features a 3D-printed model of a multichambered pig’s uterus which, upon approach, reveals human fetuses in each chamber, a commentary on the ethics of assisted reproduction and the exploitation of human surrogates. Hung on the wall of the gallery is a spreadsheet that, upon inspection, reveals itself to be a minute-by-minute accounting of all the touchpoints of the first month of Liu’s daughter’s life (she’s now two): every feeding, every pee, every poop. One inspiration for the spreadsheet was *Post-Partum Document*, a 1973–’79 work by conceptual artist Mary Kelly, in which Kelly displayed the liners from her son’s cloth diapers as monochromes in white frames.

Liu’s work stands out not just for its topicality, or the precision with which it zeroes in on the frustrations of 21st-century motherhood, but for its range. She is the kind of artist of whom you might say that she “works at the intersection of art and technology.” But that should really be “technologies,”



Untitled (small inconveniences): A garment designed to simulate incontinence as one of the symptoms of pregnancy.

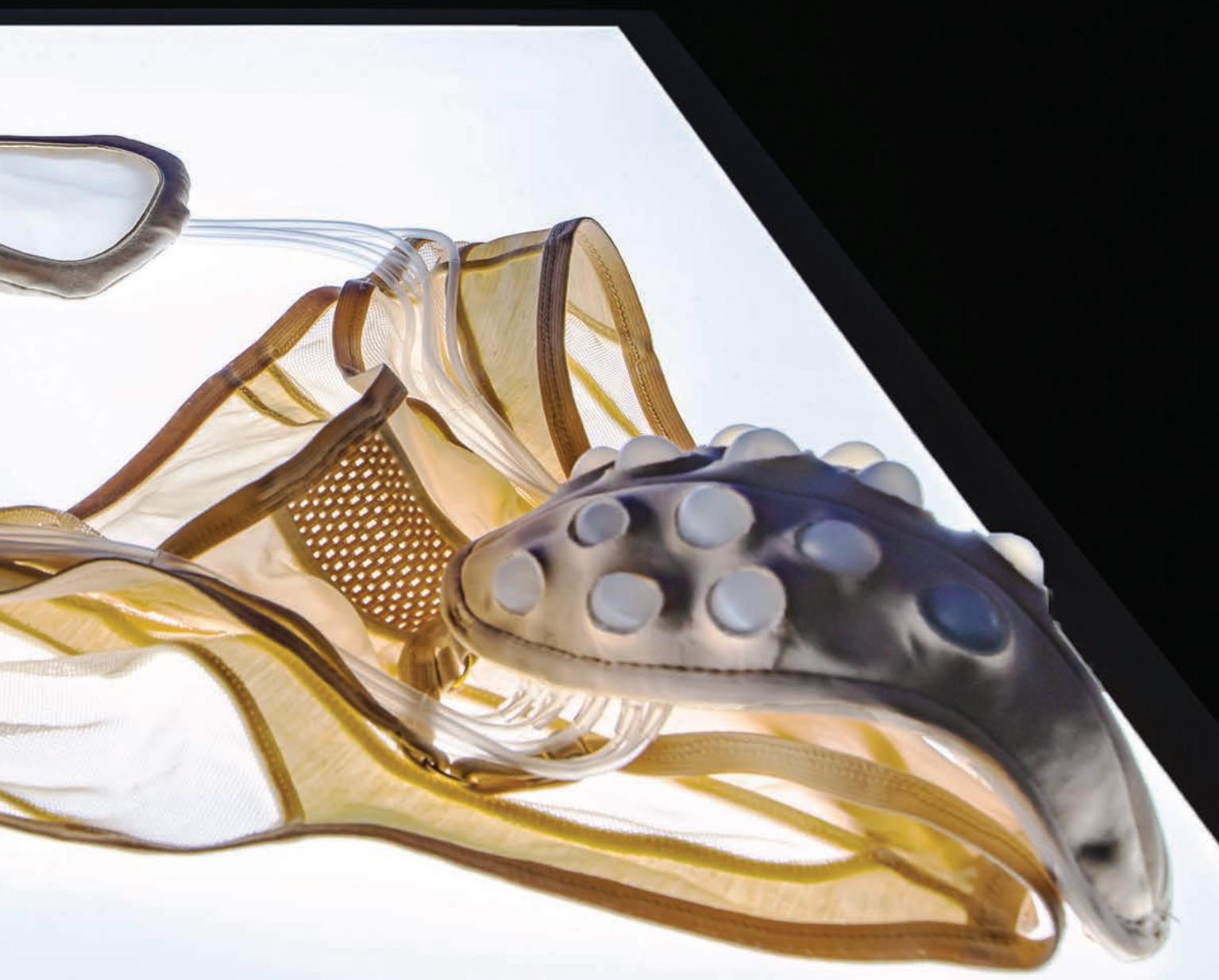
plural. Different pieces have required her to delve into the intricacies of pumps, circuitry, machine learning, microscopy, and 3D printing, developing enough understanding of each field to identify the necessary expertise of her collaborators. When she was at the Media Lab she joined a bio-hacking club, which she found to be the ideal educational experience. No matter the question, she says, “someone would sit down with a beer and explain it.”

Even her thesis project at the Media Lab, *Mind Controlled Spermatozoa* (2016–2017), recently wiggled back into the news as six Supreme Court justices, five male and one female, declared jurisdiction over child-bearing bodies.

For that project Liu researched galvanotaxis, the directed movement of an organism or cell in response to an electric field or current. In the accompanying video, she dons an EEG machine, which measures electrical activity in the brain. She then applies those signals to a magnified sample of her now-husband’s sperm and is actually able to direct the movement of spermatozoa to the left and right with her thoughts. (The science is real, if dramatized for the video.) As she writes, “I seek to challenge this status quo by engineering a system by which I (a woman) can control something inherently and symbolical male: spermatozoa (sperm).” The subtitle of the piece is “Women of STEAM Grab Back.”

A week after the leak of the draft Supreme Court decision overturning *Roe v. Wade*, Liu put the piece up on her Instagram with a new caption. “In the few times I’ve shown this work, men have often expressed to me how violating and unnatural it is to control sperm—sperm that is not even theirs, or in their body,” she wrote. “[T]hink of the plight of female bodies, that are constantly under threat of being controlled, regulated, censored.” Liu’s work attempts to shed light on the constant policing of cisgender women’s bodies, using the very machines and marketing techniques that typically oppress. ■







What are you on?

Psychedelic drugs may be getting closer to market as studies begin to show their promise for improving women's health outcomes.

By
Taylor Majewski

Illustration by
Kate Dehler



Nikhita Singhal's breath still catches when she talks about how her life changed. A psychiatry resident at the University of Toronto, Singhal says it was using psychedelic drugs—ayahuasca, ketamine, and MDMA—that finally addressed the eating disorder she'd had since she was seven years old.

"It was really emotionally and psychologically painful," she says, recounting a particular ayahuasca trip she took with her parents. "I felt like I could see myself and I was in the middle of this storm of chaos where I felt comfortable and safe being sick because it was so entrenched for 20 years. I couldn't ever imagine shifting my mindset, but now I'm in a place I would have never thought possible."

Singhal's experiences in and out of treatment centers growing up prompted her to go into psychiatry as a profession. Now, she imagines a not-too-distant future where she's able to offer psychedelic therapy herself. "It's mind-blowing to see the huge leaps that [patients] can make in a [psychedelic] session that might have taken years and years in traditional psychotherapy," she says. "They come out utterly changed."

Psychedelics are having a moment. After decades of prohibition and vilification, they are increasingly being employed as therapeutics. Drugs like ketamine, MDMA, and psilocybin mushrooms are being studied in clinical trials to treat depression, substance abuse, and a range of other maladies. And as these long-taboo drugs stage a comeback in the scientific community, it's possible they could be especially promising for women.

Not just Singhal but several other women interviewed for this story described how they had successfully experimented with psychedelics—not for recreational purposes, but to heal. One woman recounted how psychedelic-assisted therapy addressed her postpartum depression. Another described how microdosing psilocybin alleviated symptoms of premenstrual dysphoric disorder (PMDD) and an ayahuasca trip eliminated her condition altogether. Online, women on Reddit and in Facebook groups share how they've used psilocybin, LSD, ketamine, and MDMA to address PMS, menopause, low sexual desire, postpartum depression, and PTSD from sexual trauma. Jennifer Gural, a psychotherapist in California, spoke of how psychedelics helped her, and how she's seen them help her female patients: "It shifted the focus of my life. It really helped me to tackle how my brain works and how I was thinking... It was such a profoundly life-changing experience. I have done ayahuasca and I've done psilocybin. I don't know if I'll ever do it again, but I'm open to that if it's needed—which I think is how we should use psychedelics."

After Ayelet Waldman's book *A Really Good Day: How Microdosing Made a Mega Difference in My Mood, My Marriage, and My Life* came out in 2017, chronicling her monthlong experiment with microdosing LSD to treat severe "mood storms," thousands of women from all over the world reached out to her. "I think it speaks to a desperation in women's health," she says. "And part of the reason for that is we all know that nobody bothers to study women, and nobody listens to women, especially when we report our specific mental-health issues."

"I think it speaks to a desperation in women's health. And part of the reason for that is we all know that nobody bothers to study women, and nobody listens to women, especially when we report our specific mental-health issues."

Much of modern medicine is built on research performed exclusively on cisgender men: clinical research was not required to include women until the 1990s, when Congress passed the National Institutes of Health Revitalization Act. This means the science that informs medicine—including the prevention, diagnosis, and treatment of disease—routinely fails to consider the crucial impact of sex and gender. As a result, women's pain and symptoms have been, and continue to be, consistently dismissed by doctors. In the case of more than 700 diseases, women receive diagnoses significantly later than men, sometimes waiting up to 10 years for the correct diagnosis. They're also at greater risk for adverse side effects from medication; a recent study found that 86 medications approved by the US Food and Drug Administration were more likely to cause such problems in women than men.

The rising tide of women self-treating with psychedelics may be a result of frustrations with our existing health-care system, and it does pose risks such as dangerous interactions between psychedelics and prescription drugs, or—worse—psychedelics that are adulterated with other substances, like fentanyl. But more official research around these drugs has begun to emerge over the past few years.

Women are more likely to have PTSD than men, and transgender and gender-diverse individuals are at a much higher risk of developing PTSD than the general population. Women also experience depression more often, with one in seven women suffering from postpartum depression alone. Studies suggesting good results from just a few doses of MDMA or psilocybin combined with therapy have led the

FDA to designate those drugs as breakthrough therapies (a priority status given to promising drugs proposed to fill an unmet need) for PTSD and treatment-resistant depression, respectively.

Gender is also a factor in eating disorders such as anorexia nervosa, which is three times as prevalent among women as men. The Multidisciplinary Association for Psychedelic Studies (MAPS) is currently conducting a study on MDMA-assisted therapy to treat anorexia, bulimia, and binge-eating disorders; the treatment works by reducing activity in the amygdala, the part of the brain that processes fear and threat. The Centre for Psychedelic Research at Imperial College London is also leading a clinical trial on psilocybin-assisted psychotherapy as a treatment for anorexia.

Is this the beginning of a brighter future for women's health, one where common mental disorders, symptoms of chronic pain, and intense mood swings are managed with mind-altering trips? Psychiatrists are optimistic, but they are rightly concerned about the potential for abuse in psychedelic-assisted therapy.

Enter the pharmaceutical companies

The search for psychedelic drugs that specifically address women's health conditions has already begun. Felicity Pharma, a biotech company focused on "mood disorders in women," developed a proprietary drug that uses a psychedelic to treat PMDD and postpartum depression. Olivia Mannix, the CEO and founder of Felicity, says the drug is currently ready for proof-of-concept pilot studies, but her long-term vision is to shake up the stagnant antidepressant market.

The problems with conventional anti-depressants such as selective serotonin reuptake inhibitors (SSRIs) are well-known. “SSRIs will only take you so far,” says Julie Holland, a psychiatrist, author, and medical advisor to MAPS. “There’s some emotional numbing, there’s some physical numbing; it’s harder to cry, it’s harder to climax. I think psychedelics for a lot of women are really more of a thorough solution to their problems instead of a Band-Aid.”

People who study the brain know that SSRIs may gradually increase neuroplasticity, which is the brain’s ability to form new connections between neurons. Neuroplasticity can be impaired among depressed people. A 2021 study conducted at Yale suggests that psilocybin has the ability to prompt neuroplasticity, disconnecting some of the hardwired, repetitive thought patterns often involved in conditions like depression and eating disorders, and research shows that psychedelics like psilocybin may also be as effective as SSRIs for treating depression, if not more so.

“Whenever you’re talking about any kind of rigid, compulsive behavior that you

do over and over again, [as in] anorexia or obsessive-compulsive disorder, you really need to be quote-unquote ‘rewired.’” Holland says. “The psychedelics are going to do a much better job at that than SSRIs, because they can often really get more to the root cause of what’s going on and unpack what’s driving the behavior as opposed to just sort of slapping a plaster over it.”

In Holland’s psychiatric practice, many of her female patients are taking antidepressants, and she often sees low libido as an unfortunate side effect of these drugs. These days, she’s particularly interested in the potential of “rare” psychedelics that can reliably enhance sexual experiences—like 2C-B, which was sold in Europe in the 1990s as a party drug and aphrodisiac.

Eastrra Health, another startup working on psychedelic medicine specifically for women, has filed two patents for treatments that use 2C-B to alleviate female sexual dysfunction and PMS symptoms. Jeremy Weate, Eastrra’s CEO, told me his working hypothesis is that 2C-B can flatten the rise and fall of estrogen levels

experienced during the menstrual cycle. Research and development have been slow, however, because the company has struggled to secure significant funding.

But funding is flowing into psychedelic-assisted therapy, especially around one drug in particular: ketamine. Over the past few years, ketamine-assisted therapy (which is legal in the US) has surged in popularity as an effective—albeit expensive—alternative treatment for depression and anxiety. (Typically, ketamine treatments in the US range from \$600 to \$1,200 per session, and the standard course of treatment is six sessions.)

“We started our company knowing that women over 40 are prescribed anti-depressants at more than three to four times the rate of men, which has led to one in every five women taking an anti-depressant to get through the day,” says Juan Pablo Cappello, cofounder and CEO of the ketamine therapy platform Nue Life, which is FDA approved and raised \$23 million in April.

Through platforms like Nue Life, or in one of the hundreds of ketamine therapy

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clinics across the US, patients can take a controlled amount of a psychoactive substance under the careful guidance of a trained clinician to induce an altered state of consciousness (a trip). Having received tons of airtime in recent years for its supposed ability to treat PTSD, anxiety, and substance abuse, ketamine is now being studied as an effective way to alleviate symptoms of postpartum depression as well.

A recent study in the *Journal of Affective Disorders* suggests that in patients at high risk of postpartum depression, a single dose of ketamine administered before anesthesia during cesarean sections could be effective in preventing it. Another ketamine therapy startup, Field Trip, is also about to start in-person, phase I clinical trials for FT-104, a psychedelic molecule that's similar to psilocybin but has a much shorter trip time. (Nikhita Singhal's father, Sanjay Singhal, an entrepreneur who started audiobooks.com, is an advisor to Field Trip.) "FT-104 has all the characteristics that make psilocybin so interesting and attractive from a therapeutic perspective—safety and efficacy—but with a very short duration of action," Field Trip cofounder and executive chairman Ronan Levy told me. According to Levy, Field Trip's existing preclinical studies signal that FT-104 will leave the body after 12 hours, meaning breastfeeding can hypothetically resume within 24 hours—something that will need to eventually be validated in human trials and undergo scientific peer review.

Kelsey Ramsden, the former CEO of Vancouver-based psychedelics company Mindcure (which was researching MDMA-assisted psychotherapy to help women with a lack of sexual desire until it shut down earlier this year for lack of funds), also says the postpartum depression market is appealing for psychedelic development because there's currently only one drug for the condition (Zulresso). Ramsden is a believer in part because psychedelics worked to alleviate her own symptoms after she had her first child. "The change in my lived experience resulted in recurring

"I have done ayahuasca and I've done psilocybin. I don't know if I'll ever do it again, but I'm open to that if it's needed—which I think is how we should use psychedelics."

depressive cycles, and it wasn't necessarily a hormonal thing that was the ongoing problem," she says. "It was just the change in my experience as the result of becoming a mother in a society that expected me to be a certain way." She says she tried SSRIs and traditional therapy at first, but she finally arrived on stable footing after trying psychedelic-assisted psychotherapy.

Ramsden believes that the entire psychedelic industry is still in its earliest days. But she can envision a culture where it is normal for women to openly take psychedelic drugs. When something health-related *works* for women, she believes, the good news spreads like wildfire.

Allison Feduccia, who has a PhD in neuropharmacology, believes that the best evidence we have of how psychedelics affect women is still mostly anecdotal. For example, there are accounts suggesting that peyote boosts milk production, an idea supported by preliminary research from the 1970s. For years, folks have reported the ways psychedelics have altered their menstrual cycle, linking them to heavier periods, a period that arrives early, or—alternatively—a more regular cycle. Research has shown that estrogen intensifies the brain's dopamine reward pathway, so it's also possible that a woman's reaction to a particular drug is more pleasurable depending on the phase of her menstrual cycle.

Feduccia posits that psychedelics might be particularly helpful for the "rites of passage" that most women go through. "Psychedelics could bring better perspective when you get your first period, have your first child, and then go through menopause," she says. "I just hope that women can benefit [from psychedelics]

without having to drop \$20,000 for a guided approach."

That guided approach is not only expensive but fraught with ethical concerns. Multiple high-profile cases of abuse in psychedelic therapy have made headlines in recent years. Richard Yensen, an unlicensed therapist who was a sub-investigator for MAPS, was accused of sexually assaulting a PTSD patient during a MAPS clinical trial on MDMA. Allegations of sexual abuse were also made against Aharon Grossbard and his wife, Françoise Bourzat, leaders of a prominent group in the Bay Area that has been practicing psychedelic-assisted therapy for over 30 years.

"I've been hearing stories about psychedelic therapists molesting their patients or shamans molesting their clients for decades," Holland says. She notes that while it shouldn't be women's responsibility to fix this issue, her peers in the field who are also women—researchers, doctors, and founders—are informally discussing potential solutions. The ideas include setting up a governing body to report transgressions to and establishing clearer guidelines for consent *before* a person enters into an altered state of consciousness.

"So many people in the psychedelic community are so worried about the progress being jeopardized by these reports," Holland says. "The truth is, [the space] is too big to fail. It can withstand some scrutiny now, because if not now, when? If we're building the foundation of something that's going to last, we better make sure the foundation doesn't have any cracks." ■

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Meta banned filters that “encourage plastic surgery,” but a massive demand for beauty augmentation on social media is complicating matters.

By
Tate Ryan-Mosley

The fight for “Instagram face”

In October 2021, Facebook announced a massive pivot, changing its name to Meta and going all in on augmented and virtual reality through a futuristic vision of the internet called the metaverse. In fact, the strategy had been taking shape gradually for years, with help from a seemingly frivolous product feature on Instagram. Face filters that add puppy ears to your hairline or make your lips appear bigger sit on a sophisticated technical infrastructure for AR and VR that the company, which owns Instagram as well as WhatsApp, has built to support such effects. Thousands of creators have contributed filters free of charge, and the millions of people around the world who use the feature each day have provided Meta with troves of data.

The little research that exists about digital beauty culture has found that visual platforms like Instagram, which rely on AI recommendation algorithms, are narrowing beauty standards at a stunningly rapid pace. Through filters, they’re also helping

users achieve those ideals—though only in the digital world. There is evidence that excessive use of these filters online has harmful effects on mental health, especially for young girls. “Instagram face” is a recognized aesthetic template: ethnically ambiguous and featuring the flawless skin, big eyes, full lips, small nose, and perfectly contoured curves made accessible in large part by filters.

But behind every filter is a person dragging lines and shifting shapes on a computer screen to achieve the desired look. Beauty may be subjective, and yet society continues to promote stringent, unattainable ideals that—for women and girls—are disproportionately white, slender, and feminine.

Instagram publishes very little data about filters, especially beauty filters. In September of 2020, Meta announced that over 600 million people had tried at least one of its AR features. The metaverse is a concept much bigger than Meta and other companies investing in AR and VR

products. Snap and TikTok capture huge numbers of filter users, though Snap is also investing in place-based AR. Meta’s product suite includes the Oculus headset and Ray-Ban smart glasses, but it’s focused on what made Facebook popular—the face.

Beauty filters, especially those that dramatically alter the shape of a face and its features, are particularly popular—and contested. Instagram banned these so-called deformation effects from October 2019 until August 2020 because of concerns about the impact they have on mental health. The policy has since been updated to outlaw only filters that encourage plastic surgery. The policy states that “content must not promote the use or depict the sale of a potentially dangerous cosmetic procedure, as per the Facebook Community Standards. This includes effects that depict such procedures through surgery lines.” According to a statement to MIT Technology Review in April 2021, this policy is enforced by “a combination of human and automated systems to review effects as they are submitted for publishing.” Creators told me, however, that deformation filters often get flagged inconsistently, and it’s not clear what exactly encourages the use of cosmetic surgery.

“It became sensational”

Though many people use beauty filters merely for fun and entertainment, those puppy ears are actually a big technical feat. First they require face detection, in which an algorithm interprets the various shades of pixels picked up by a camera to identify a face and its features. A digital mask of some standard face is then applied to the image of the real face and adjusts to its shape, aligning the mask’s virtual jawline and nose to the person’s. On that mask, graphics developed by coders create the effects seen on the screen. Computer vision technology of just the past few years has allowed this to happen in real time and in motion.

Spark AR is Instagram’s software developer kit, or SDK, and it allows creators of augmented-reality effects to more easily

make and share the face filters that cover the Instagram feed. It is in this deep rabbit hole of filter demonstration videos on YouTube that I first came across Florencia Solari, a creative AR technologist and a well-known creator of filters on Instagram. She showed me how to make a face filter that promised to plump and lift my cheeks and fill out my lips for that Kardashiansque, surgically enhanced face shape.

"I have this inflate tool that I am going to apply with symmetry," Solari said, "because any modifications that I do to this face, I want to be symmetrical." I tried to keep up by dragging the outline of my digital mannequin's cheekbone up and out with my cursor. Next, I right-clicked on the map of her bottom lip and selected "Increase" several times, playing God. Soon, with Solari as my guide, I had a filter that, while sloppy and simple, I could upload to Instagram and unleash to the world.

Solari is part of a new class of AR and VR creators who have made a career by mastering this technology. She started

coding when she was around nine years old and was drawn to the creativity of virtual-world development. Making her own filters on Instagram was a hobby at first. But in 2020, Solari left a full-time job as an AR developer at Ulta Beauty to pursue online AR full time as an independent consultant. She's recently worked with Meta and several other big brands (which she says she can't disclose) to create branded AR web experiences, including filters.

Solari's very first filter, called "vedette++," went viral back in September 2019. "I tried to make an interpretation of what the superstar of the future would be," Solari says. The filter applies an iridescent, slightly green shine to the skin, which is smoothed all over and inflated under each eye to the point that it looks as if half a clementine has been shoved inside each cheek. Lips double in size, and face shape is adjusted so that a distinct jawline tapers into a small chin. "It was kind of a mix of an alien, but with a face that looked like it was full of Botox," says Solari. "It really became, like, sensational."

Though Meta doesn't make its filter data public, it does provide creators with some metrics, and I asked Solari and others to share the data with me. The numbers are stunning; vedette++ was viewed 130 million times and used over 1.2 million times in 3.5 months. Solari says the filter was one of the first ever to go viral. It helped that vedette++ was used by model and influencer Bella Hadid. "Influencers have a huge impact on how this spreads ... You will get an influencer or a celebrity to use them, and then it will go more viral organically," she says. According to Solari's statistics from Meta, vedette++'s impressions spiked exponentially in the days after Hadid used the filter.

Deformed virality

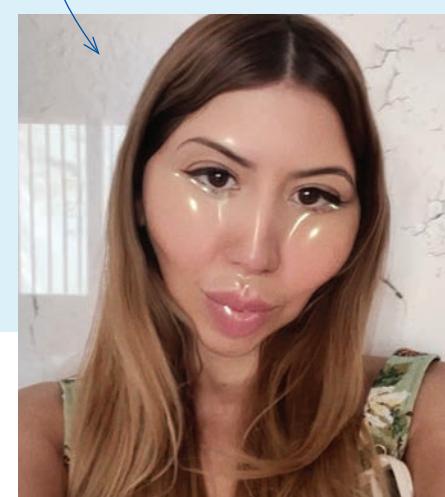
Creators say that deformation effects and influencer shares are the keys to virality where filters are concerned. Several creators said the demand for deformation beauty filters is so consistent that they can essentially gamify virality by making a



Solari in BEAUTY

by Denis Rossiev

3.5B	Impressions	129.6M
1.6B	Opens	17.7M
27M	Shares	1.2M



Solari in VEDETTE++

by Solari

certain kind of effect that fits the “Instagram face” aesthetic.

“This is something we don’t speak about—that deformation can make your filter go viral. If you don’t use deformation, your filter won’t succeed as much as the other ones, even if the others are more technically complicated,” says Lucie Bouchet, a popular filter creator. Bouchet notes that there are exceptions to this pattern, and filters that are especially fun, trendy, or unique also see massive success.

Bouchet has stopped using deformation effects in many of her filters and now builds in a feature that enables the deformation effects only if users choose.

But the statistics are hard to ignore. Bouchet’s most popular deformation filter, called “Golden Hair,” amassed almost 300 million impressions, while a similar one without deformation effects garnered a measly 7.2 million. Around 70% of the people using her filters are between 13 and 24.

“Society is like this”

Bouchet’s concerns about the harmful effects of deformation filters, especially on girls, are shared by many creators who make them. I spoke with researcher Claire Pescott in the spring of 2021, when I first wrote about the effects of beauty filters on social media. Pescott studies the behavior of preteens on social media and has observed gender differences in filter use. She found that boys use filters primarily for fun and experimentation, and girls use them to enhance their appearance.

Though Meta declined to speak with me on the record for this story, the company has taken some steps to address recent criticism surrounding the negative impact that Instagram can have on the mental health of users, particularly teenage girls. When whistleblower Frances Haugen came forward with internal company documents, some showed that its leaders had known about these problems for years. According to reporting by the Wall Street Journal, a March 2020 slide presentation by Facebook researchers read, “Thirty-two percent of teen girls said that when they felt bad about

“Thirty-two percent of teen girls said that when they felt bad about their bodies, Instagram made them feel worse.”

their bodies, Instagram made them feel worse.” Another slide said, “We make body image issues worse for one in three teen girls,” and acknowledged that “comparisons on Instagram can change how young women view and describe themselves.”

Filters on platforms like Meta, TikTok, and Snapchat are not the only technology working to narrow beauty standards. Photo-editing tools have also exploded over the past 10 years with the rise of social media, and the results can have similar effects on aesthetics and mental health online. Recommendation algorithms and social preferences for certain looks can also create harm on visual platforms.

But Solari thinks technology itself is not to blame in the first place. “It is not the filters that are making this [problem], but society is like this,” she says. “These are the values that society has and sees as beautiful. And that’s why it goes viral.” Creators observe a consistent and shockingly high demand for deformation beauty filters that fit a particular aesthetic.

Authenticity and freedom

In December 2019, Instagram banned vedette++ as part of its clampdown on deformation effects. Solari says she wasn’t trying to encourage plastic surgery and believes that most people using her filter wanted to “perform with a face that just looked kind of out of this world.”

She responded to the deformation ban with a scathing Medium post that was widely shared among filter creator communities. It reads: “This isn’t about plastic surgery. This is about FREEDOM. It’s

about preserving the most valuable and unique thing we own: Who we are. Our individuality... The internet was our free space. It was a mask, yes, indeed. A mask that served us to be able to BE TRUE to ourselves. Express ourselves beyond our bodies, beyond our physical realities, explore the trans-human and the fantasy.”

It’s this fantasy—this opportunity for escapism and expression—that many creators point to when they defend filters, saying that AR and VR offer the ability to test out certain personas and play. Pescott, the researcher, told me that trying on different identities and demonstrating them socially is an essential and healthy part of adolescence. For many people, filters offer a new way to do that.

Solari has thought a lot about the tension between censorship and safety since vedette++’s viral success and subsequent ban. “I don’t believe in censorship of that kind of content, because I believe that people should be able to choose what they want to adopt or not,” she says. But Solari also believes that strict beauty standards do make it hard for people to accept themselves fully. “If we actually want to address this,” she says, “we have to look for a way to help people to really build the strength to say ‘I like myself as I am. I want to show myself as I am.’”

“I find beauty in authenticity, in freedom, and in what I find to be the perfect balance between order and chaos,” she says. ■

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The Milky Way as seen from the South Rim of the Grand Canyon.

Lit streets,

LEDs are billed as a more environmentally friendly approach to outdoor lighting. But there is no simple panacea for light pollution.

Late one evening in June of 2016, John Barentine stood alone at Mather Point, an iconic and rarely empty overlook at Grand Canyon National Park. The moon slid away, leaving the darkness of a crisp, clear sky. The stars that make up our galaxy seemed to align overhead. The inky chasm of the ancient canyon spread out below, and he marveled at a feeling of being unmoored in time and space.

An astronomer who worked for the International Dark-Sky Association (IDA), Barentine had a special reason to revel in the scene. With his help, the park had recently been given provisional status as an International Dark Sky Park, a designation given to public land that exhibits “exceptional” starry nights. Few publicly

By Shel Evergreen

accessible places on Earth experience this kind of pristine darkness. Indeed, the view is quite different 200 miles away in Tucson. There, photons from the city’s lights scatter in the sky, forming an obscuring dome of light called sky glow—a feature now common to major cities.

Scientists have known for years that such light pollution is growing and can harm both humans and wildlife. In people, increased exposure to light at night disrupts sleep cycles and has been linked to cancer and cardiovascular disease, according to a 2016 report by the American Medical Association. Meanwhile, the ecological impacts of light pollution span the globe. It can affect the reproduction patterns of male crickets, causing them to chirp during the

dark skies

daytime instead of at night, when they typically call mates. Baby sea turtles, which have evolved to evade predators by rushing to the ocean upon hatching, can be disoriented by lights near the shore. Owls lose their stealthy advantage over prey. Even trees can struggle, holding onto leaves longer and budding earlier than they should because the brightness of their surroundings gives them incorrect information on the time of year.

Astronomers, policymakers, and lighting professionals are all working to find ways to reduce light pollution. Many of them advocate installing light-emitting diodes, or LEDs, in outdoor fixtures such as city streetlights. Watt for watt, LED streetlights are now comparable in efficiency to traditional sodium vapor streetlights—and are in some cases more efficient. But the crucial difference is that they are better at directing light to a targeted area, which means less light and energy are needed overall to achieve the desired illumination.

Several major cities across the globe, including Paris, New York, and Shanghai, have already adopted LEDs widely to save energy and money. But a growing body of research suggests that switching to LEDs is not the straightforward panacea some might expect. In many cases, LED installations have worsened light pollution. Steering a path toward reducing the problem requires more than just buying some energy-efficient fixtures. Cities must develop dark-sky-friendly policies, and lighting professionals need to design and manufacture products that enable those policies to succeed. And they must start doing so now, say many light pollution experts, including Karolina Zielinska-Dabkowska, an assistant professor of architecture at Gdańsk University of Technology in Poland. LEDs already make up more than half of global lighting sales, according to the International Energy Agency. The high initial investment and durability of modern LEDs mean cities need to get the transition right the first time or potentially face decades of consequences.



Paris, the "City of Light," viewed from the International Space Station.

Zielinska-Dabkowska may understand the potential and drawbacks of using LEDs better than anyone. In the 2000s, she worked for various lighting companies on high-profile projects, including the Tribute in Light memorial in New York City. The striking installation shoots two beams of light into the sky to echo the two World Trade Center towers lost on 9/11. Soon after it was completed in 2002, the tribute turned out to be trapping migrating birds in its hypnotizing beams.

The piece is now switched off at times to allow birds to disperse, but light pollution ultimately became an issue Zielinska-Dabkowska could not ignore, and she wrapped research on solutions into her work. "I wanted to make a change," she says.

There are four main elements of light pollution, Zielinska-Dabkowska says. The most recognizable is sky glow, which can affect migrating birds hundreds of miles away. Another is light trespass, the photons that cross boundary lines. They can creep in through windows and can affect sleep and circadian rhythms. Glare, meanwhile, is a change in contrast—the sort that happens when you walk from a highly lit area into a darker one, forcing your eyes to adjust. Lastly, and most significant, she says, is over-illumination—lighting things up much more than necessary.

LEDs have the potential to combat all four of these problems. The bulbs can, for example, be installed in "smart" housings that can be remotely tuned and programmed. "You can control LEDs," Zielinska-Dabkowska says. "You can dim them down to 0%."

The city of Tucson implemented smart lighting controls in its streetlights in 2016, replacing 18,000 sodium lights with shielded LEDs to help prevent light from escaping upward. A 2018 study on which Barentine was lead author found that Tucson's sky glow decreased by 7% after the transition. The "color temperature" of those lights—a measure the industry uses to describe the warmth or coolness of their tone—is a moderate 3,000 K. But that color temperature now exceeds the IDA guidelines for outdoor lighting, which were released last year; researchers agree a warmer temperature of 2,200 K is a better cutoff. Bluer, cooler-toned lights with higher Kelvin ratings have shown the clearest evidence of disruption to the circadian rhythms of people and animals, which causes a cascade of health and environmental impacts.

The switch to LEDs has been habitually lauded as an environmental win, but experts say they are often used to extremes. One problem, says Pete Strasser, a Tucson resident and technical director at the IDA, is the excessive use of bright white LED lighting in cities such as Los Angeles, which has boasted about its ability to make streets brighter. "We hear that people feel a lot safer with the white light," Ed Ebrahimian, then director of LA's street lighting, said in a 2014 Department of Energy video on LED streetlights. Light pollution experts say this feeling of safety seems to stem from fact that one can see a greater range of colors under white light, which gives the sensation that one can see better.

Tracking the global extent of light pollution is challenging. Researchers have mainly relied on low-resolution satellite sensors

and a radiometer suite aboard the Suomi National Polar-orbiting Partnership satellite, says Alejandro Sánchez de Miguel, an astrophysics postdoc at the Complutense University of Madrid. The instrument provides higher-resolution images, but its infrared sensors exclude wavelengths found in many LEDs. "The more blue light a light has, the less light the satellites see," says Sánchez de Miguel. "We are color-blind, and we are thinking that everything is red." Last year, he and his colleagues found that previous studies had probably lowballed global light emissions. Their study estimated that artificial light had grown by at least 49% around the planet between 1992 and 2017, and as much as 400% in some regions.

The adoption of cool white LEDs—alongside factors like increasing population and electrification—is likely responsible for some of this growth. The attraction is understandable. They are cheaper and more efficient than warm LEDs, Zielinska-Dabkowska explains.

But flipping the switch on light pollution involves more than changing colors. Even LEDs that look warm in tone still have a spike of blue that signals daylight in our brains, Zielinska-Dabkowska says. And different species display diverse responses to light, according to a study published in 2021 in the journal Integrative & Comparative Biology. For example, photoreceptors are more red-sensitive in freshwater species of the teleost fish than in marine species—a distinction that illustrates the complexity of responses to light even among similar animals. The study cautioned that efforts to deal with light pollution are "accumulating faster than our basic knowledge of sensory

Artificial light grew by an estimated 49% globally between 1992 and 2017—and as much as 400% in some regions.

systems." Picking a single hue, even a warmer one, and blasting it into the night will likely have significant repercussions, says Valentina Alaasam, a PhD candidate at the University of Nevada, Reno, and lead author of the study. "Everything that affects species interactions winds up affecting evolution and species distribution," she says. "Animals that can cope better with the city and with lights are moving into cities, and animals that can't cope are moving out." She says it's a problem that has gotten really big, really fast.

Barentine says the color can't be taken in isolation from other aspects like shielding, brightness, distribution, and timing. For example, he says, dark-sky-friendly lighting might have cooler-toned light at a lower intensity, ultimately still resulting in less blue light emission.



A global view of Earth assembled from data acquired by the Suomi National Polar-orbiting Partnership (NPP) satellite.

For light pollution researchers, the key hurdle to overcome is no longer technology but communication. “The biggest obstacle that we have to making more progress in this realm is a lack of awareness and education on the part of people that are in municipal government,” says Barentine, who now works on dark-sky policies as an independent consultant.

Career civil servants like city administrators or engineers, he says, are most often the people who make day-to-day decisions or recommendations in municipal governments, rather than elected officials. “My perception is that a lot of their information comes from the lighting industry, for better or worse,” Barentine says. Until recently, those companies were at odds with light pollution researchers, Barentine says. “There was just tremendous skepticism within the lighting manufacturing industry,” he says, adding that he thinks there was an intrinsic belief that the issue was simple: light is good and darkness is bad.

Barentine says he makes sure to communicate to the lighting industry that his work is about “dark sky,” not “dark ground.” The IDA has worked with industry since the 1980s, he says: “Our message, in so many words, was ‘If you follow our principles that reduce light pollution, you won’t sell any less lighting than you sell now; you’ll be selling different lighting.’”

Still, the advent of white LEDs that promised perfect illumination and the boom that followed led to a misalignment of goals, whether real or perceived. Lighting professionals and researchers continued to speak about light in fundamentally different ways.

To illustrate and quantify the communication gap, Catherine Pérez Vega, a doctoral candidate at the Leibniz Institute of Freshwater Ecology and Inland Fisheries in Berlin who works with Zielińska-Dabkowska, led a systematic review of more than 200 studies of artificial light at night. The results, published in the journal Sustainability earlier this year, found a disconnect between researchers and professionals such as lighting architects, urban lighting designers, and electrical illumination engineers. In some cases, the two groups were essentially speaking different languages. For example, those studying artificial light use a metric called “irradiance” to talk about brightness, while those in the lighting industry go with a different measure, called “illuminance.” In a list of 19 physical measurements of light, only one term has the same level of usage—and it is rarely used by either group.

“I think [the review] has stimulated a conversation in this field that is a long time in coming,” Barentine says. “We are beginning to realize that even though we have similar goals—and I think we do—we often talk past one another.”

Arizona, with its dozens of observatories and arid desert skies, is a major hub for astronomy research. As a result, Tucson has been relatively successful in its dark-sky endeavors. But the priorities are different in other cities. Pittsburgh, for example, also



has observatories nearby, but to some people, light pollution can seem an insignificant concern compared with other issues the city is tackling, such as air pollution, food deserts, and road maintenance. Even so, Diane Turnshek, a physics lecturer and assistant professor at Carnegie Mellon University (CMU), thinks it shouldn’t be hard to address.

Turnshek spent many nights under the stars while studying astronomy at the University of Arizona in the 1970s. Decades later, she briefly returned to join the Mars Desert Research Station, a NASA laboratory for learning how to live in a harsh, isolated, Mars-like environment.

Inspired once again by the desert’s starry skies, Turnshek became a vocal dark-sky advocate when she returned to Pittsburgh. But she struggled to be heard. Lighting professionals, in her experience, have “zero” idea light pollution is even a research field. “We’re not even talking in the same units,” she says, pointing to Pérez Vega’s study. “There’s no overlap.”

Earlier this year, Pittsburgh was slated to begin work on a streetlight upgrade. But Turnshek says the process has been opaque. An earlier description of the project said the city intended to add 15,000 new LEDs, something that Turnshek worried would lead to over-illumination.

The latest city estimate is that 3,000 to 15,000 new LED lights will be needed, says Angie Martinez, a senior manager in

Pittsburgh's Department of Mobility and Infrastructure. But the first task for the winning consultant will be a citywide street-light inventory that addresses the current state of individual streetlights, as well as their overall distribution. "The challenge of taking on a project of this magnitude is that it just gets really complex," Martinez says. "We can't just assume that every single light in the city of Pittsburgh is in the most optimal location." It's possible, she says, that there may end up being fewer total streetlights.

Specifications in the current proposal provide a starting point for planning, including a color temperature cutoff of 3,000 K in line with Pittsburgh's dark-sky ordinance, which passed last fall. However, Martinez says that is the maximum, and as they look for consultants, they'll be taking into account which ones show dark-sky expertise. The city is also considering—budget and infrastructure permitting—a "network lighting management system," a kind of "smart" lighting that would allow them to control lighting levels and know when there is an outage.

Martinez says there will be citywide engagement and updates on the status as critical milestones are reached. "We're in the evaluation period right now," she says, adding that the next milestone is authorization of a new contract. She acknowledges there is some "passionate interest in street lighting," and that she too is anxious to see the project come to fruition: "Just because things seem to go quiet doesn't mean work is not being done."

While they aren't meeting with light pollution experts right now, Martinez says the ones they met with during the last pro-

Light pollution experts generally say there is no substantial evidence that more light amounts to greater safety.

posal round—Stephen Quick and Diane Turnshek of CMU—were "instrumental" in adopting the dark-sky ordinance.

In recent months, Zielinska-Dabkowska says, her "baby" has been the first Responsible Outdoor Light at Night Conference, an international gathering of more than 300 lighting professionals and light pollution researchers held virtually in May. Barentine was among the speakers. "It's a sign that all of this is really coming along, both as a research subject but also something that attracts the interest of practitioners in outdoor lighting," he says of the conference.

There is more work to be done, though. The IDA recently released a report summarizing the current state of light pollution research. The 18-page report includes a list of knowledge

gaps to be addressed in several areas, including the overall effectiveness of government policies on light pollution. Another is how much light pollution comes from sources other than city streetlights, which a 2020 study found accounted for only 13% of Tucson's light pollution. It is not clear what makes up the rest, but Barentine suspects the next biggest source in the US and Europe is commercial lighting, such as flashy outdoor LED signs and parking lot lighting.

Working with companies to reduce light emissions can be challenging, says Clayton Trevillyan, Tucson's chief building officer. "If there is a source of light inside the building, technically it's not regulated by the outdoor lighting code, even if it is emitting light outside," Trevillyan says. In some cases, he says, in order to get around the city's restrictions, businesses have suspended illuminated signs inside buildings but aimed them outside.

For cities trying to implement a lighting ordinance, Trevillyan says, the biggest roadblocks they'll face are "irrelevant" arguments, specifically claims that reducing the brightness of outdoor lighting will cut down on advertising revenue and make the city more vulnerable to crime. The key to successfully enforcing the dark-sky rules, he says, is to educate the public and refuse to give in to people seeking exceptions or exploiting loopholes.

Light pollution experts generally say there is no substantial evidence that more light amounts to greater safety. In Tucson, for example, Barentine says, neither traffic accidents nor crime appeared to increase after the city started dimming its streetlights at night and restricting outdoor lighting in 2017. Last year, researchers at the University of Pennsylvania analyzed crime rates alongside 300,000 streetlight outages over an eight-year period. They concluded there is "little evidence" of any impact on crime rates on the affected streets—in fact, perpetrators seemed to seek out better-lit adjacent streets. Barentine says there is some evidence that "strategically placed lighting" can help decrease traffic collisions. "Beyond that, things get murky pretty quickly," he says.

Still, the perception of security is a factor that cities need to take seriously, Barentine says. For example, a study published in the journal *Remote Sensing* earlier this year found that people in various neighborhoods of Dalian, China, felt safer in consistent levels of warm light, something easily achieved with controlled LED lighting.

Many light pollution experts say LEDs simply need to be used to their full potential to avoid over-illuminating the skies. Responsible lighting doesn't seem to disadvantage anyone, but there's a mysticism about the night to overcome, Barentine says: "At the end of the day, there's a real, entrenched, human fear of the dark." ■

Research suggesting a transgender contagion arrived at just the right moment to be taken up by social media and a new wave of anti-trans political effort.

By
Ben Kessen

A rapid-onset gender theory

When Jay told his mom he was bisexual at 14, she was supportive. But when he came out as transgender a few years later, she pushed back. She felt blindsided by the news. YouTube videos and online forums soon convinced her that she was right to feel that way. To her, it was clear that Jay was simply mistaken. A trans “contagion” called “rapid-onset gender dysphoria,” spread through social media, had caught hold of him and convinced him he was not female, she said. The Internet had “turned” him trans.

Widely introduced four years ago in a PLOS One paper by Lisa Littman, a physician and researcher, the concept of ROGD hypothesizes a “potential new subcategory” of gender dysphoria—the feeling of distress that one’s gender and assigned sex do not match. Young people with ROGD, the theory claims, feel symptoms of gender dysphoria and identify as trans as a result of peer influence, especially online. They hide

behind a false diagnosis of gender dysphoria, the thinking goes, instead of confronting whatever issues are truly challenging them.

Littman polled parents and reported that they “describe a process of immersion in social media … immediately preceding their child becoming gender dysphoric.” Once a teen identifies as trans, Littman argued, they can unduly—and perhaps unwittingly— influence peers to do the same. This can partially explain the rising numbers of trans youth, she said, adding that the dynamic particularly affects those assigned female at birth.

The paper, which was based on parent surveys recruited from explicitly anti-trans or trans-skeptical websites and forums, almost immediately drew criticism. Shortly after its publication in August 2018, PLOS One, a peer-reviewed open-access journal covering science and medicine, issued a comment that questioned Littman’s methodology. Brown University, her then-employer, retracted its press release about the study. In early September, the World Professional

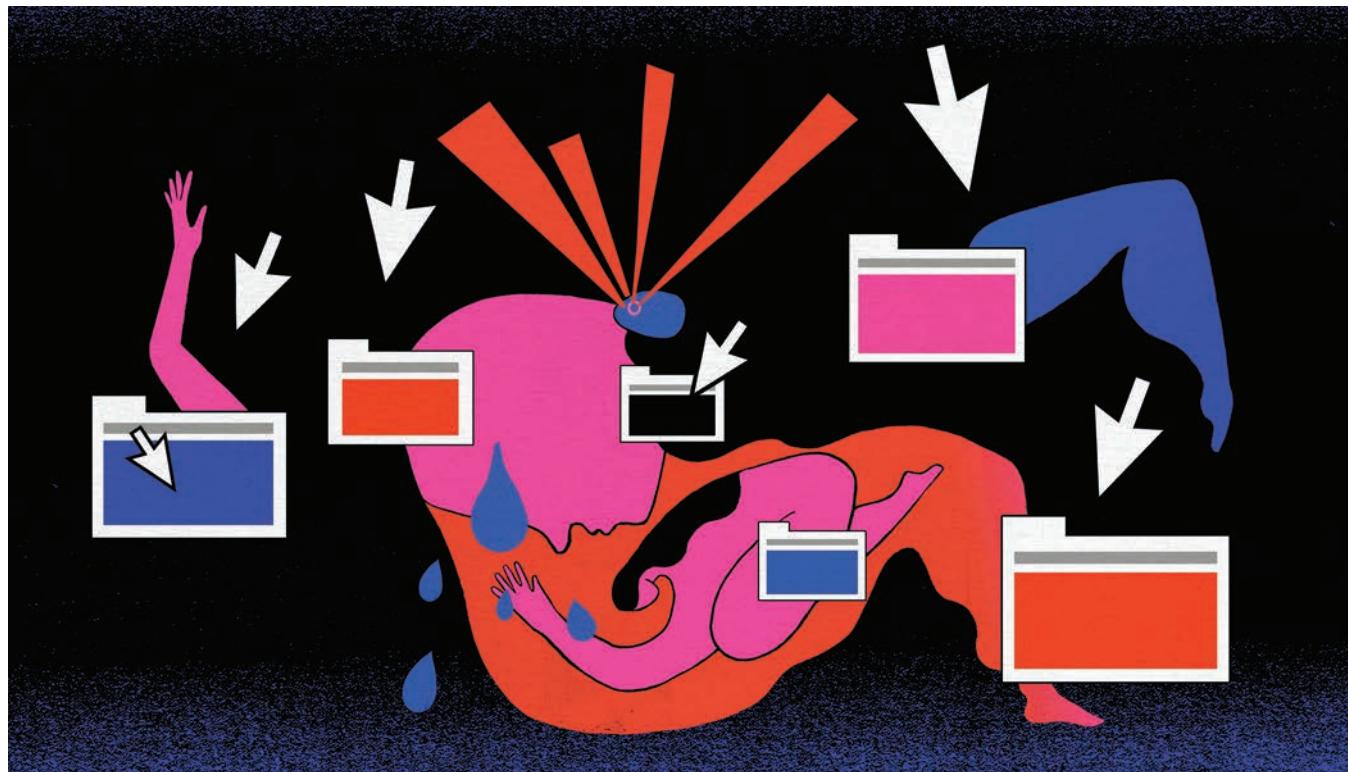
Association for Transgender Health put out a statement saying ROGD “constitutes nothing more than an acronym” and urged restraint in using the term. Six months after that, PLOS One reissued the study with a large correction emphasizing that Littman’s paper was simply a “descriptive, exploratory” one and had not been clinically validated. In 2021, the Journal of Pediatrics published a comprehensive study that found no evidence for ROGD’s existence. More than 60 psychology organizations, including the American Psychological Association, called for elimination of the term.

The scientific community, in short, agreed there was no such thing as ROGD. But did it matter?

The paper was a turning point. While theories and rumors about something like ROGD had quietly percolated online before the paper was published, Littman’s descriptive study gave legitimacy to the concept. Soon after, it took on a life of its own. People describing themselves as “parents of ROGD kids” formed online support groups. Abigail Shrier’s anti-trans tome *Irreversible Damage: The Transgender Craze Seducing Our Daughters* sold more than 100,000 copies and has been promoted on extremely popular conservative podcasts. YouTube videos peddling the theory have scored hundreds of thousands of views. Justifications for anti-trans bills, like a memo on Florida’s attempt to stop Medicaid funding for adult transition-related health care, routinely cite the study in their footnotes.

Five years later, Jay’s mom still doesn’t believe that he’s trans.

Littman believes her study has been misinterpreted, but the concept of ROGD continues to provide scientific fuel to anti-trans rhetoric and legislation, including a current wave of state laws targeting trans youth. Understanding the theory’s ascent from fringe forums to scientific journals to the halls of Congress helps clarify some of the moral panic and pernicious logic employed to restrict the autonomy and rights of trans people today. It also serves as a vivid example of how questionable science can be weaponized to achieve political goals.



A number of studies on trans youth have taken on “misinformational afterlives,” says TJ Billard, an assistant professor of communications at Northwestern University and executive director of the Center for Applied Transgender Studies. Among them are four papers published between 2008 and 2013 that have together been used to claim that most children “grow out” of gender dysphoria and opt not to transition. All have been shown to have numerous shortcomings. In some, nearly 40% of young people surveyed did not meet the criteria for the official gender dysphoria diagnosis in the Diagnostic and Statistical Manual of Mental Disorders edition used at the time. In two, researchers classified some subjects as having detransitioned—or reversed their transition—purely on the basis of whether a parent or third party said it happened. A 2018 study found that three of the papers labeled those who had stopped responding to researchers as detransitioners; and in one, a subject who identified as nonbinary was classified as detransitioning.

“There’s a wealth of bad science that is out there, and this science doesn’t stay in journals,” Billard says. Parents unfamiliar with trans issues, who don’t understand gender-affirming health care and don’t have the expertise to read the studies themselves, often fall under its sway.

Think of it this way: Your teen, who you think you know better than anyone else does, “suddenly” identifies in a way you never expected. You’re confused. You might ask some friends for advice, but you mostly feel alone in dealing with this revelation. Late one night, you take to Google. Maybe you read the Wikipedia page for “gender dysphoria in children,” some news articles, a report from the CDC.

You’re inundated with words you’ve never heard, concepts that challenge a gender binary you’ve never questioned. You panic.

What often happens next, Billard says, is “you stumble upon a blog post or a news article or a YouTube video that says: ‘This

is only bullshit, and somebody is just trying to corrupt your child.’”

You learn about ROGD and read about a “social contagion” infecting lonely children online. You discover that there are thousands of parents whose kids have it too, and there’s even a whole book about it. So you go back to your child, who you know better than they know themselves, right? Because they’re only a kid. And you say, *Actually, no, you’re not trans. Honey, you’ve been duped.*

The problem: Overwhelming evidence shows that your child almost certainly hasn’t been duped. Although some people do reconsider or reverse their transition, once a person starts identifying as trans, it’s quite unlikely they’ll change their mind. No matter how strongly you believe that the internet, social contagion, and positive representations of transgender people turned your child trans, chances are your child disagrees.

Littman began her research after noticing that in her small town in Rhode Island, a few teens in the same friend group started

identifying as trans. She had not previously studied gender dysphoria or trans health care, but she thought it was peculiar and merited some exploration. She did not approach the work with “a chip on my shoulder,” she says.

At that time, one thing most researchers studying trans youth agreed on is that there was a dearth of unbiased studies on the subject. Scientists had been researching trans youth for decades, but studies often had small sample sizes, unreliable methodology, or little longitudinal follow-up. By 2016, researchers had begun to take note of a rise in youth identifying as trans, but there was (and still is) no easy explanation for why, although there were many theories—some based on existing research and some just on hunches.

When Littman took up the question, she decided to survey parents, who she felt would be easier to reach than trans youths themselves. In her Methods section, she writes that “to maximize the chances of finding cases meeting eligibility criteria”—meaning youths who suddenly became gender dysphoric, according to their parents—she turned to three websites: 4thwavenow.com, a “community of people who question the medicalization of gender-atypical youth”; transgender-trend.com, which says it’s concerned about “the unprecedented number of teenage girls suddenly self-identifying as ‘trans’”; and youthtranscriticalprofessionals.org, a now-private website that was “concerned about the current trend to quickly diagnose and affirm young people as transgender.”

The results were in line with what one might expect given those sources: 76.5% of parents surveyed “believed their child was incorrect in their belief of being transgender.” More than 85% said their child had increased their internet use and/or had trans friends before identifying as trans. The youths themselves had no say in the study, and there’s no telling if they had simply kept their parents in the dark for months or years before coming out. (Littman acknowledges that “parent-child conflict may also explain some of the findings.”)

The ROGD paper was not funded by anti-trans zealots. But it arrived at exactly the time people with bad intentions were looking for science to buoy their opinions.

Arjee Restar, now an assistant professor of epidemiology at the University of Washington, didn’t mince words in her 2020 methodological critique of the paper. Restar noted that Littman chose to describe the “social and peer contagion” hypothesis in the consent document she shared with parents, opening the door for biases in who chose to respond to the survey and how they did so. She also highlighted that Littman asked parents to offer “diagnoses” of their child’s gender dysphoria, which they were unqualified to do without professional training. It’s even possible that Littman’s data could contain multiple responses from the same parent, Restar wrote. Littman told MIT Technology Review that “targeted recruitment [to studies] is a really common practice.” She also called attention to the corrected ROGD paper, which notes that a pro-gender-affirming parents’ Facebook group with 8,000 members posted the study’s recruitment information on its page—although Littman’s study was not designed to be able to discern whether any of them responded.

But politics is blind to nuances in methodology. And the paper was quickly seized by those who were already pushing back against increasing acceptance of trans people. In 2014, a few years before Littman published her ROGD paper, Time magazine had put Laverne Cox, the trans actress from *Orange Is the New Black*, on its cover and declared a “transgender tipping point.” By 2016, bills across the country that aimed to bar trans people from bathrooms that fit their gender identity failed, and one that succeeded, in North Carolina, cost its Republican governor, Pat McCrory, his job.

Yet by 2018 a renewed backlash was well underway—one that zeroed in on trans youth. The debate about trans youth

competing in sports went national, as did a heavily publicized Texas custody battle between a mother who supported her trans child and a father who didn’t. Groups working to further marginalize trans people, like the Alliance Defending Freedom and the Family Research Council, began “printing off bills and introducing them to state legislators,” says Gillian Branstetter, a communications strategist at the American Civil Liberties Union.

The ROGD paper was not funded by anti-trans zealots. But it arrived at exactly the time people with bad intentions were looking for science to buoy their opinions. The paper “laundered what had previously been the rantings of online conspiracy theorists and gave it the resemblance of serious scientific study,” Branstetter says. She believes that if Littman’s paper had not been published, a similar argument would have been made by someone else. Despite its limitations, it has become a crucial weapon in the fight against trans people, largely through online dissemination. “It is astonishing that such a blatantly bad-faith effort has been taken so seriously,” Branstetter says.

Littman plainly rejects that characterization, saying her goal was simply to “find out what’s going on.” “This was a very good-faith attempt,” she says. “As a person I am liberal; I’m pro-LGBT. I saw a phenomenon with my own eyes and I investigated, found that it was different than what was in the scientific literature.”

One reason for the success of Littman’s paper is that it validates the idea that trans kids are new. But Jules Gill-Peterson, an associate professor of history at Johns Hopkins and author of *Histories of the Transgender Child*, says that is “empirically untrue.” Trans children have only recently started to be

discussed in mainstream media, so people assume they weren't around before, she says, but "there have been children transitioning for as long as there has been transition-related medical technology," and children were socially transitioning—living as a different gender without any medical or legal interventions—long before that.

Many trans people are young children when they first observe a dissonance between how they are identified and how they identify. The process of transitioning is never simple, but the explanation of their identity might be.

Others have slower and more complicated journeys, where identity is murky and gender is anything but straightforward. This compounds confusion among cisgender people who have only been exposed to the simple trans narratives of "being stuck in the wrong body." Perhaps they can comprehend being "born a man" and wanting to "be a woman" but not the limitless options in between.

When we first talked in 2019, Jay was using different pronouns. He knew he wasn't cis; he knew he was trans. But he was working through the specifics and asking himself questions. Growing up, Jay—like a lot of queer and trans kids—had trouble making friends. Online, he had room to explore his identity while living in a home where he wasn't embraced.

His mom thinks of that online space differently. She "thinks because the trans community is accepting of me, which other communities haven't always been, that I'm gonna stick with them," Jay says.

If Jay goes on testosterone, as he hopes to, he'll be kicked out of the house. After countless arguments during the five years he's identified as trans, he says, his mom "still believes I've been brainwashed by trans activists on the Internet." When he presented evidence that debunked ROGD, he says, she claimed it was engineered by trans activists. "She doesn't listen or care, because she doesn't trust anything I say about this," he says. (To protect Jay's safety, MIT Technology Review did not reach out to his mother and used only his first name for this story.)

Many people who are citing Littman's work probably haven't even read the study or seen the correction, Billard says: "People are citing a Reddit post in which somebody invoked the idea of Littman and her research." Littman agrees with this characterization. "It boggles my mind how people are comfortable holding forth on topics that they haven't actually read papers [about]," she says.

Littman thinks her ROGD paper is often misappropriated to speak to the trans experience at large. "It does not apply to all cases of gender dysphoria," she says. "This doesn't imply that nobody benefits from transition. People will take it to assume that."

But Littman stands by the core claims made by her paper and thinks more research needs to be done (which she herself continued with a 2021 survey on young people who reversed their transition).

When Littman's paper appeared in 2018, there was science that supported youth transition, but little longitudinal research and few studies with large cohorts. Researchers are still filling in the gaps.

There are researchers and clinicians treating patients who agree with Littman and say ROGD is a real and growing phenomenon that they've witnessed firsthand.

But a July 2022 study found that five years after socially transitioning, 94% of youth surveyed still identified as transgender and 3.5% identified as nonbinary.

And research has shown that family acceptance and appropriate medical intervention can have lasting benefits. In February 2022, for example, researchers reported that trans and nonbinary youths who went on puberty blockers or hormones had 60% lower odds of depression and 73% lower odds of suicidality, compared with those who did not.

Lawmakers in more than 25 states have introduced anti-trans bills during 2022 legislative sessions. Politicians writing such legislation have plenty of questionable studies, partisan doctors, and associations that lobby against transgender rights to draw on. Littman's ROGD study is often a

go-to. The Coalition for the Advancement & Application of Psychological Science wrote in 2021 that many of the "over 100 bills under consideration in legislative bodies across the country that seek to limit the rights of transgender adolescents" are "predicated on the unsupported claims advanced by ROGD."

Littman says she is "personally opposed to legislative bans on medical interventions for gender-dysphoric youth." She does believe, however, that "the majority of young people with gender dysphoria will often grow up to be lesbian, gay, or bisexual adults who are not transgender." Overall, she says, the conclusions of her research "are not justifications for banning, or for not covering" trans health care altogether. Rather, they show the need for caution.

Still, a June 2022 report commissioned by Florida's Republican governor, Ron DeSantis, as part of his effort to stop Medicaid funding for transition-related adult health care cites her work multiple times. In 2019, US Representative Doug Collins of Georgia read part of her study into the Congressional Record when voicing his opposition to the Equality Act, which would broadly prohibit discrimination on the basis of sex, sexual orientation, and gender identity.

Even as the voices saying he's been brainwashed get louder, Jay, who is now 21, has only become more confident in his identity.

He can't wait until he can get out of the house, live on his own, and finally start hormones. He's on a waitlist for an assessment to get the process started. Not being able to be himself, he says, can feel miserable and isolating. Thinking of the future is what keeps him hopeful.

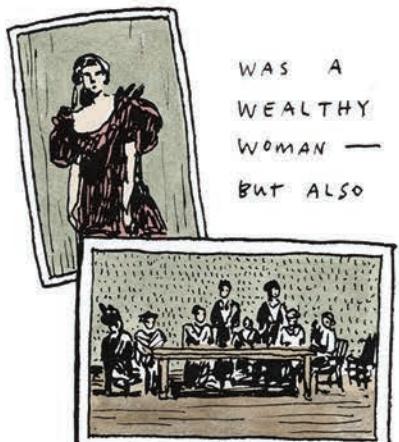
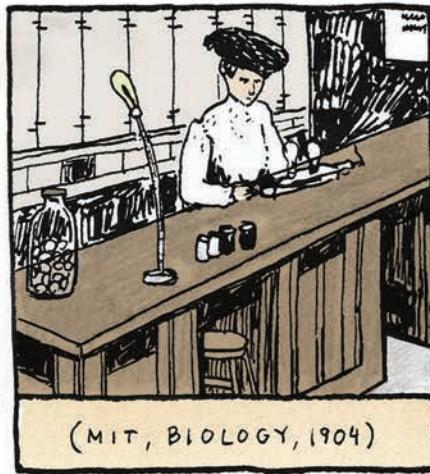
But Jay speaks of a dark alternative timeline where he is never able to medically transition and live the life he wants. In that scenario, which he makes clear is only hypothetical, he dies by suicide.

He thinks he knows what his mom would say after he died:

"The trans activists on the internet killed my daughter." ■

SECRET SMUGGLER

Illustration by Lauren Simkin Berke



A PASSIONATE ACTIVIST
FOR WOMEN'S RIGHTS.

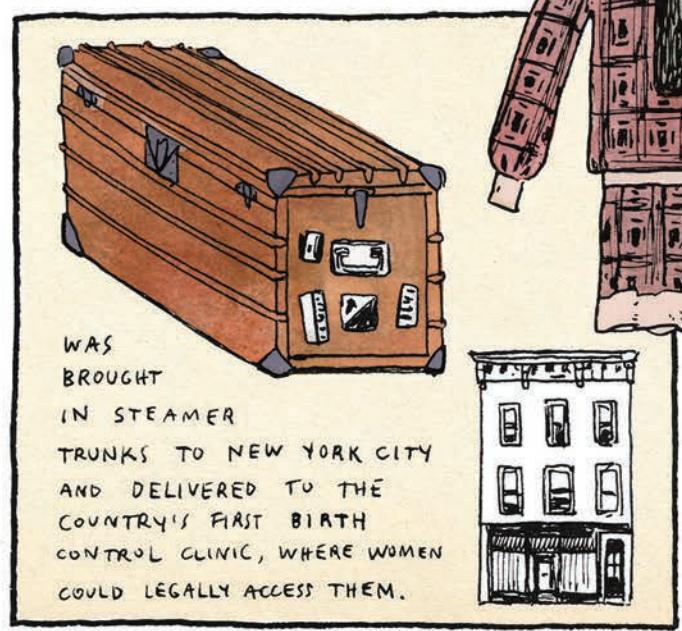


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THE 1920S, SHE MADE SUMMER TRIPS...

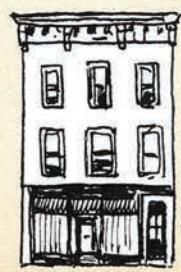
TO EUROPE TO PROCURE HUNDREDS OF
DIAPHRAGMS (ILLEGAL THEN IN THE US) AND THEN
HAD THE CONTRACEPTIVE DEVICES



SEWN INTO THE LININGS
OF FANCY CLOTHES
SHE'D PURCHASED IN PARIS.
THE PRECIOUS CARGO...



WAS
BROUGHT
IN STEAMER
TRUNKS TO NEW YORK CITY
AND DELIVERED TO THE
COUNTRY'S FIRST BIRTH
CONTROL CLINIC, WHERE WOMEN
COULD LEGALLY ACCESS THEM.



DECades
LATER
McCORMICK
WOULD
PROVIDE
ALMOST EVERY SINGLE DOLLAR
NECESSARY TO DEVELOP THE
ORAL CONTRACEPTIVE.



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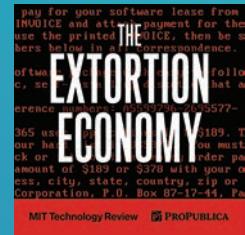
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