



EQUILIBRIUM

The Future of Science

EQUILIBRIUM

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Logo Design

Jessica Li
Casey Rheault

Layout Design

Casey Rheault

Contact us

misciwriters.magazine@umich.edu

Website

www.misciwriters.com/equilibrium

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Letter from the Editors

Jennifer Baker and Christina Del Greco

Hi there,

Thanks for picking up a copy of *EquilibriUM* edition 2! We're so excited to finally share what we've been working on.

The brainchild of former editor-in-chief Sarah Kearns, *EquilibriUM* started as a special project to commemorate the 5th anniversary of our organization, Michigan Science Writers. The first edition of any project always faces challenges. Ours was attempting to distribute a tangible product in December 2020, when all non-essential activities were pushed into the virtual realm due to COVID-19. I (Jenn) remember stopping by Sarah's house on a snowy night, the eerily quiet kind, to pick up magazines for distribution. For the first time during the project, Sarah and I chatted—in person—in the quiet darkness. It wasn't clear then how wide-reaching our words, stacked in boxes lining the porch, would be. However, I knew that this project had awakened something in me that would stick.

And I (Christina) remember seeing the printed first edition one day sitting in an office and thinking to myself, *I sure hope I can get involved with that the next time they do it*. Fast forward to August 2022—Jenn and I were setting up for an uncomfortably warm recruitment event under a tent on the Rackham lawn, stacking copies of the first edition of *EquilibriUM* to give away to incoming students. The magazine had been on my mind since I first got involved with MiSciWriters, but previous leadership teams seemed (rightfully) daunted by the task of restarting it. Once Jenn and I—two humans notorious for over-involving ourselves in this organization—joined the leadership board, it felt like the time was right. Individually, we were nervous about taking on such a big task alone. But since we were both excited about this magazine, we thought, *well, what's one more project*, and decided to take it on together, starting with learning where that sneaky “s” goes in the correct plural form of our position: editors-in-chief.

The following months that ensued were full of imagining—what could this project be, if it wasn't an anniversary project? How could we expand our team of authors, editors, and illustrators into as many scientific disciplines as possible? And how could we learn from our prior experiences to make the second edition into something that could become a third, and a fourth? You'll see from these pages that we have kept all the best things about the first edition—most importantly,

integrating science, technology, engineering, art, math, and medicine (STEAMM) for a rich reader experience that engages the creative and analytic alike. We've also brought our own ideas, like the cohesive style curated by our graphic designer, and a tendency to lean literary, as exemplified by the addition of poetry and speculative fiction to this edition.

Perhaps most prominent in this encore edition is the addition of a theme, "The Future of Science." As scientists early in our careers, our team has so many ideas for what the coming years of innovation might look like. We see much work to be done with respect to gender equity in medical device engineering (Rodríguez-Calero) and the social contract between scientists and the public (Shannon). We see the next iteration of immunotherapy as integral to equitable access to cancer treatment (Jungles) and artificial intelligence as a game-changer for patients and physicians alike, if it can be mastered (Han). We see the potential for technology to enhance our lives—beautify, even—and the inherent risks that come with this type of innovation (Giffin). And we see how the human urge for exploration of a world beyond what we can observe directly will remain intact, whether it's focused on the forces holding the universe together (Amarasinghe) or the molecular structures within our cells (Roberts).

Despite the wide range of topics our authors chose to write about in this edition, all of their pieces encompass the balance between disciplines—between science and art—that inspired the title of this magazine. The word "equilibrium" comes from the Latin *aequus* for "equal" and *libra* for "balance," and Sarah named this project *EquilibriUM* to remind readers to seek balance between science and art throughout everyday life. This idea of equilibrium only becomes more relevant when thinking about what our world might look like in the future.

You can probably tell from this letter that, while this magazine is about science, it is also about people. It is impossible to think about the future of science without also thinking about the humans who do the science, direct and fund the science, and are impacted by science—simply put, everyone. To create the best possible future, scientists must seek balance between striving for progress and accounting for what their work means for society at large. Finding this equilibrium will not be easy, but it is essential for keeping our goals for science aligned with our goals for society.

For us, this experience has solidified our own vision of the future of science—an expansion in the understanding that interdisciplinary engagement with and communication between scientists and the public

is critical. This future, as with the re-launch of this magazine and the visions described on these pages, is not without its challenges. But we think this future is worth the work, and, after reading this, we hope you agree.

-Christina and Jenn

* * *

Jenn (right) is a grad student in microbiology and immunology at UM and editor-in-chief of the MiSciWriters blog. Her research seeks to understand how bacteria in the lung and gut affect—and are affected by—acute lung injury. When she's not in the lab, you can find her doing Zumba or taking care of her indoor jungle of plants.

Christina (left) is a grad student in genetics and genomics at UM and logistics coordinator for MiSciWriters. She studies rare disease caused by genetic mutations that prevent cells from performing protein synthesis. Christina is keenly interested in the intersection between biomedical science and policy, especially how improved science communication can bring scientists and policymakers together more effectively.

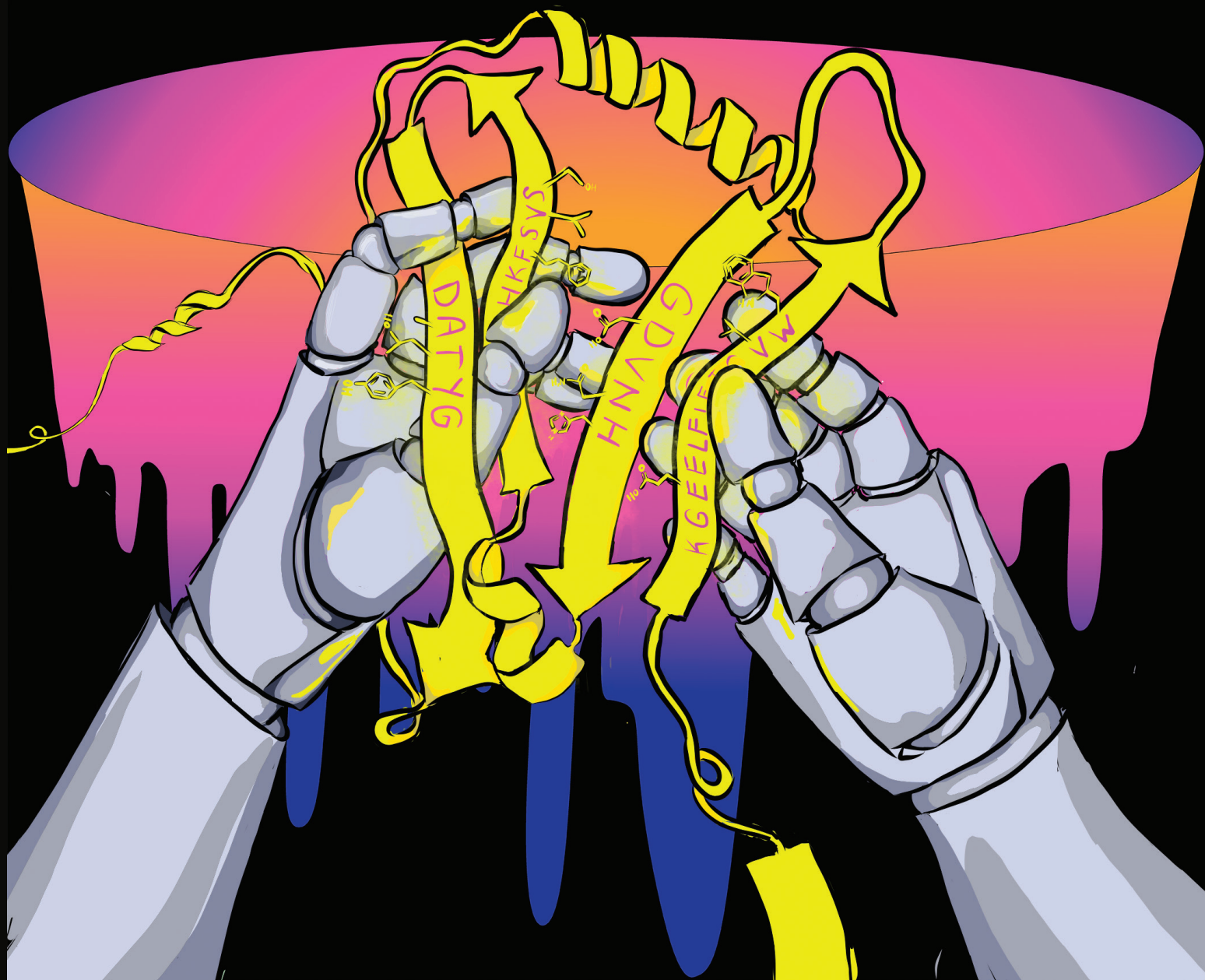


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Protein Folding In The Hands Of AI

Jacquelyn Roberts

“Structure implies function” is a phrase often repeated by biochemists to describe how molecular machines work in the body. For a protein, structure is formed as its string of amino acids twists and folds into a globular final form. If amino acids are beads on a string, then the folded protein is the final necklace or finished work. This “final form” lends clues to the protein’s role in the cell. Often, like a lock and key, proteins and their chemical partners fit together perfectly. But for a long time, we had absolutely no idea how or why proteins reproducibly twist and fold in the same way every time to adopt a consistent final form.

Christian Anfinsen first postulated that the amino acid sequence determines the final form of a protein in 1973 and received a Nobel Prize for his work.¹ However, the daunting task of predicting the structure of a protein from only the order of its amino acids remained a challenge for nearly 50 years. At the time, the rules governing protein folding weren’t understood completely, and the computational power required to make such predictions seemed out of reach. So, scientists took to experimentally determining the structure of their protein of interest. To do this, they painstakingly crystallize their protein of interest and bombard it with x-rays, or irradiate a flash-frozen sample with electrons. A successful experiment generates 2D images that are used to create a 3D model, into which the amino acid chain can be fit by hand. These *de novo*, or “from scratch,” renderings of proteins take months to complete and are dependent on the quality of the data collected.

In 2021, artificial intelligence (AI) brought us AlphaFold,² a program developed by Google’s DeepMind that takes the amino acid sequence of a protein and predicts what its 3D structure might look like. AlphaFold does this by using all of the previous structures that scientists have experimentally derived and uploaded to the global Protein Data Bank (PDB). In the two years since its release, AlphaFold has predicted the structures of over 200 million proteins,³ changing the way biol-

ogists and chemists plan studies and analyze results. Armed with DNA sequences which can be translated into amino acid sequences, any scientist can predict what their protein of interest might look like in seconds. Experimentally verifying this prediction can take months or even years, but now scientists have a starting point they could have only dreamed of decades ago when *de novo* protein design was the norm.

This artwork anthropomorphizes AI, lending human qualities to the incredibly computational task of predicting the shape of a protein. Human-like robot hands are entwined in the beta sheets of yellow fluorescent protein (YFP) as if one could knit with a string of amino acids, connoting both the artistry and analysis involved in determining a protein’s structure *de novo*. The protein itself, YFP, is derived from bioluminescent jellyfish and is routinely used by scientists to track the movement of other proteins through the cell, attaching YFP to other cellular proteins like travelers attach colored tags to their luggage so it stands out among a sea of black suitcases. This technique is only useful, however, if YFP is attached to the protein at an innocuous site—if the YFP is attached to the protein being tracked at a location that interferes with its function, the experiment is rendered useless, and thus, in another sense, knowing the structure of the protein is essential to knowing its function. In the background is a graphical depiction of the energy landscape of protein folding. In its final form, the protein will be in a deep valley, signifying a stable conformation. Above the scene is a search bar containing the amino acid sequence of YFP, the only information needed for AlphaFold to predict its structure.

* * *

Jacquelyn is a biological chemistry grad student at UM, where she determines the architecture of molecular structures used by bacteria to cause disease. She has always been drawn to both science and illustration, and nearly enrolled in a medical illustration program before obtaining a degree in biochemistry.

Science and Society: Building the Trust of Our Benefactors

Austin Shannon

In a democracy, government money is public money and should ideally be accountable to the interests of the public as negotiated through the political process. However, if the stewards of that money (i.e., elected officials or citizens) know little about what they are paying for, then how do they know that public interests are being upheld?

Investment in the United States scientific enterprise after World War II (WWII) largely followed the logic of the “linear model.” The idea was that well-funded basic research inevitably creates societal benefit through unpredictable advancements that become technologies through market incentives. For example, Alexander Fleming’s discovery that mold could inhibit the growth of bacteria was largely happenstance, but it incentivized another team to extract and purify the compound involved. That compound was then used in hospitals to help people overcome bacterial infection. This was the development of penicillin, the world’s first pharmaceutical antibiotic. In retrospect, penicillin appears to have experienced a seamless transition from discovery to new technology, but the truth is that its development took nearly two decades and was driven by external circumstances, like the need for mass production of the drug during WWII.¹

While the linear model persisted, scientists were entrusted to chart the course of scientific inquiry, holding each other accountable through the self-correcting norms of modern science. This is the “social contract” view of science and society, where the government funds basic research and grants substantial autonomy to scientists for the promise of societal benefit and economic growth. According to scholars like political scientist David Guston, author of *Between Science and Politics: Assuring the Integrity and Productivity of Research*, the social contract ended in the 1980s following decades of intermittent controversies involving scientists. Congressional hearings in the ‘80s regarding fraud in the scientific community and worries about slowing innovation in the U.S. precipitated the creation of the Office of Research Integrity (ORI) and the Office of Technology Transfer (OTT), respectively.² The social contract for science ultimately failed to grapple with the human fallibility of scientists and scientific institutions, relying too much on norms to maintain accountability. It also failed to conceptualize a productive and accountable relationship between

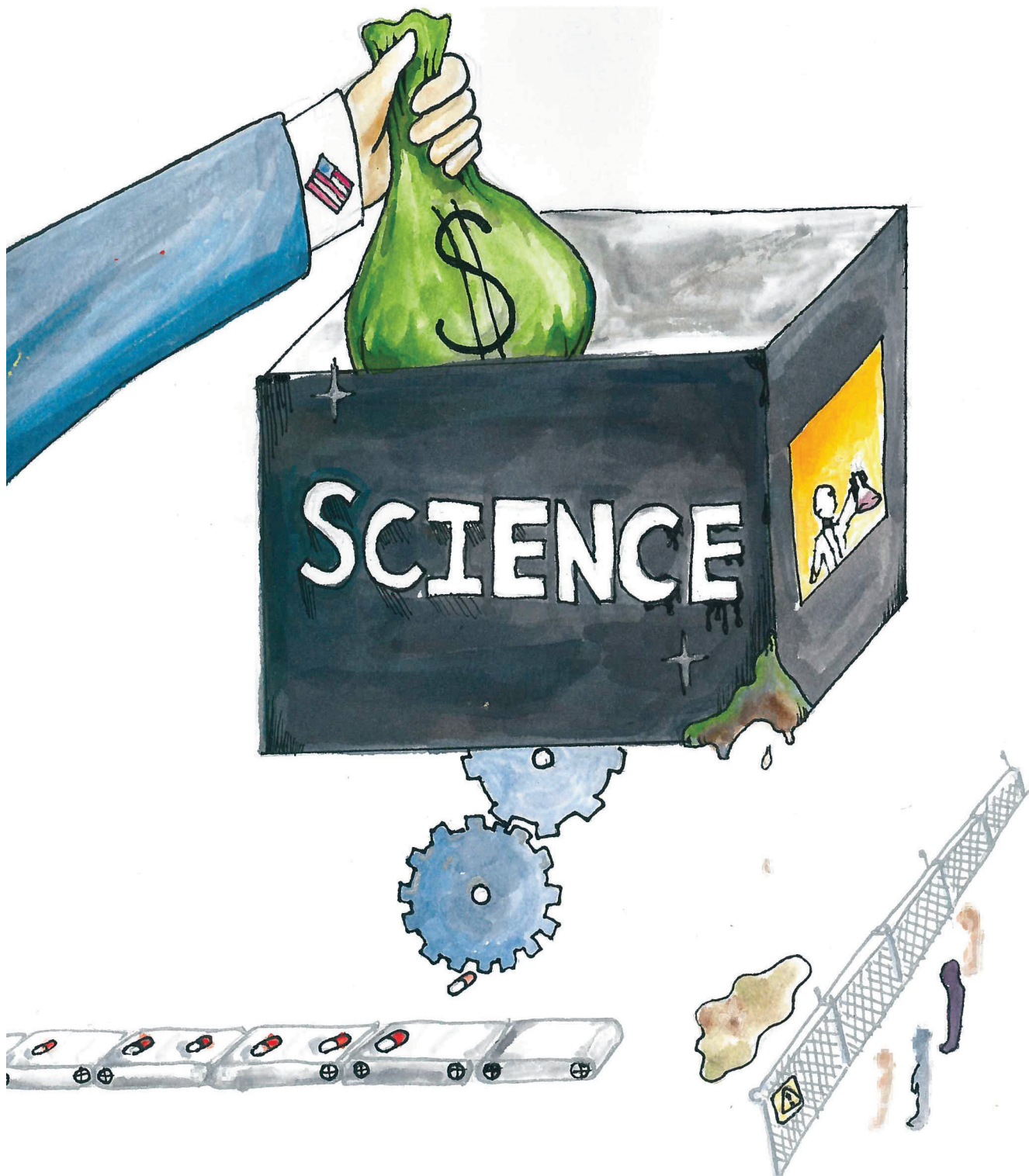
government and scientists that prioritized the public interest.

The relationship between science and society today involves far more checks and balances, trending each decade towards more openness and oversight into the process of knowledge creation. However, the current paradigm still largely excludes the primary benefactors of basic research: average citizens. Informed largely by the work of Guston, this article describes some ways the social contract fell apart and how laws and scientific institutions changed in response to those breakdowns. I then discuss how the SARS-CoV-2 pandemic complicated the relationship between science and society, and how this relationship may develop in the future.

Not Living Up To Expectations

The social contract for science was built on the belief that scientific institutions, guided by the norms and incentives of modern science, were self-correcting in cases of scientific misconduct. In the decades following WWII, controversies involving scientists occasionally bubbled to the surface of the public consciousness. These cases instigated congressional hearings that sometimes resulted in the creation of new institutions, offices, or laws to hold scientists more accountable, signaling a shift in the government’s attitude towards scientists and their work.

From the early 1930s until the early 1970s, researchers at the Tuskegee Institute conducted a highly unethical study monitoring the course of untreated syphilis in black men and how it affected their bodies over time. Despite penicillin becoming available and prescribed for syphilis by the 1940s, the nearly 400 study participants with syphilis were left untreated so their condition could be documented.³ In 1974, shortly after the horrors of Tuskegee went public, Congress passed the National Research Act,⁴ which formally created what is known today as Institutional Review Boards (IRBs).⁵ IRBs are committees formed of at least five individuals with different backgrounds, including at least one researcher and one member whose primary concerns are not scientific. They enforce ethical principles of biomedical research at all research institutions involved with human subjects.⁶ Recognition that scientists may shirk ethical principles in the pursuit of data, along with more widely-accepted and inclusive concepts of



human dignity and its inviolability, led directly to the creation of these important institutional mechanisms for accountability in research.

In addition to ethical violations, a number of public scandals put into contention the view of scientists as impartial and objective. A high profile fraud scandal in the late 1980s reinforced the idea that scientific institutions were not exceptional, and that they, like any other institution, required formal, rather than

normative, checks and balances. The case in question involved accusations of data fabrication in a paper published by Thereza Imanishi-Kari and co-authored by Nobel laureate David Baltimore. The controversy sparked nearly a decade of investigations by universities and a number of governmental institutions such as the National Institutes of Health (NIH) and the U.S. Secret Service.⁷ Accusations of research misconduct like this were a topic of congressional attention in the

1980s, as Congress increasingly perceived oversight by universities, the NIH, and other research institutions as inadequate. During this time, two different offices were created to deal with research misconduct (the Office of Scientific Integrity at the NIH and The Office of Scientific Integrity Review within the Office of the Assistant Secretary for Health), which were subsequently merged into the Office of Research Integrity (ORI) in 1992.⁸ The perception of automatic accountability as the norm in scientific institutions eroded, leading to the creation of new instruments of government oversight like the ORI.

IRBs and the ORI are examples of what Guston coined as “collaborative assurance.”⁹ Collaborative assurance is a more formal process of oversight and incentivization involving the work of boundary organizations that operate at the interface between science and politics. Boundary organizations, such as the Intergovernmental Panel on Climate Change and the U.S. National Bioethics Advisory Commission, are interdisciplinary organizations that involve scientists and non-scientists in the work of negotiating societal, political, ethical, and legal dimensions of an issue while preserving the autonomy of scientists.^{9,10} This increased oversight of the research process is analogous to the government’s attempt to increase the output and application of research in the 1970s and ‘80s, culminating in the creation of the Office of Technology Transfer (OTT) and the passage of the Bayh-Dole Act.⁹ The former assists scientists in translating their research into new technologies and the latter incentivizes commercialization by giving researchers the ability to patent findings made with public money. Unfortunately, while the ethos of collaborative assurance stabilizes the relationship between scientists and the government, public distrust of institutions is on the rise.

Modern Distrust of Scientific Institutions

Public trust in institutions has degraded over recent decades.¹¹ Trusting that scientific institutions know what they are doing and that they are not ideologically motivated is foundational to their continued existence. In 2020 and 2021, the SARS-CoV-2 pandemic put the messiness of science-in-the-making on full display through the globalized information soup of the internet, causing many to infer a corrupting allegiance of scientists to political ideology or commercial interests. Some of what could be considered normal deliberation between experts who disagree was intensified by the political need to act decisively during an emergency, and these disagreements were amplified by media of all forms. Rather than communicating largely settled science or exciting breakthroughs that may only be relevant after

years of validation and refinement, experts were asked to comment on the research as it was being generated so that people and their governments could act on it *now*. While you would be hard-pressed to find more than a handful of scientific “facts” that enjoy a 100% consensus amongst experts, this emergency provided very little time for even a rough consensus on many issues before the public needed answers. The scientific community did incredible, important work during this time that saved countless lives, but not everyone ended up with more trust in scientific institutions in the end.

The most reputable scientific journals in the world publish papers only after an extensive review by other researchers in that field, which is a process called peer review. In this case, the review process was overwhelmed with papers about COVID-19 and the virus that causes it, SARS-CoV-2. Doctors and public health officials had little time to wait for new research and news organizations were reporting on unreviewed preprints of papers while scrambling for experts to comment. Faced with a firehose of arcane experimental results and differing expert interpretations of data on masks, social distancing, vaccines, and treatments, individuals and news organizations decided who to trust and who to distrust. This was the public’s first large-scale exposure to the iterative and complicated work of science-in-the-making, but with few institutional guardrails and extremely high stakes.

Importantly, the decision of how to act depends entirely on one’s values, so people understandably internalized only the research results and interpretations that confirmed their priors. Many claimed that objective science was on their side well before the issue was settled, using that to legitimize their position, silence debate, and in some cases, to enforce their values. While some saw the power and promise of science on display with the swift development and implementation of effective vaccines and treatments, others saw government overreach, corporate greed, and scientific arrogance. Some of this, of course, is attributable to the circumstances of the current political climate rather than the actions of scientists themselves, but it is important to recognize that our institutions bear the costs no matter what, and that this moment has likely changed the relationship between science and society moving forward. Perhaps it could help to lean further into the ethos of collaborative assurance that marks the modern scientific enterprise of the U.S.

A New Chapter for Science and Society

In a world where scientific advancements look riskier and riskier (think AI and human gene editing with

CRISPR), the public desire to fund basic research will dwindle unless the benefits of science become more visible, funding priorities shift towards mitigating the risks of these technologies rather than advancing them, or the public is given a more important role in decision-making. So how might the next chapter of this necessary but sometimes fraught relationship between science and society look?

First of all, turning the incisive eye of the scientific method inward on scientific institutions is a promising way to understand and improve scientific institutions in the future. The field of metascience—the science of science—is a mixture of sociology and data analytics focused on understanding the scientific enterprise. Data on funding and publishing can help us understand how researchers choose their research questions and draw trendlines between what research is funded and what industries are innovating. Information about the role of institutions, mentorship, personal background, and various metrics of success in a scientist’s career (e.g., publication history, awards, grants, and tenure) can help us increase and diversify our scientific workforce while identifying important barriers and perverse incentives in science. Furthermore, metascience helps us understand why the linear model of basic research leading directly to new technologies is an oversimplification, and how incentives may be better aligned to improve faltering U.S. innovation.¹²

Operation Warp-Speed was a governmental investment in the rapid development of COVID-19 vaccines that included pre-ordering millions of doses and expediting clinical trials by allowing phases 2 and 3 to overlap.¹³ Warp-Speed demonstrated that government-defined goals, incentives, and regulatory frameworks can help us accomplish specific goals far faster than they otherwise would. With the success of this initiative, it seems reasonable that the U.S. government will focus more on industrial policy in the future. Industrial policy is an attempt to shape the economy to achieve a specified goal. This usually means combatting market failures like, in the case of Warp-Speed, a company’s hesitancy to invest in the expensive process of vaccine development without a guarantee that the vaccine will succeed in the market. It could also mean bolstering certain technologies in the market through research investment, tax incentives, or subsidies. Success is not guaranteed, however. We need only look to the embarrassing 2009 propping up of solar energy start-up Solyndra (bankrupted in 2011) to see how improper vetting of government loan or grant recipients can go wrong.¹⁴ Either way, there are other important projects that could benefit from an industrial policy approach (e.g., renewable energy, lab-grown meat) and

pressure from big issues like climate change will further encourage these interventions.

As industrial policy and metascience bolster the relationship between government, science, and industry, we may also see an attempt to improve public trust and support through the democratization of science. For instance, recognition of broader concepts of expertise (e.g., indigenous knowledge, lived experience) along with increased public engagement with either the scientific process itself or with tech policy assessment will likely become an essential legitimizing force for scientific institutions. Boundary organizations that can build trust between scientists, government officials, and the public through meaningful engagement and mutual respect may help us overcome some of the epistemological dangers of emergency situations like the recent pandemic. Citizen panels, consensus conferences, and advisory committees will become increasingly important as advances in biotechnology, geoengineering, and AI lurch from questions of “can we?” to “should we?”

Public Support Is Essential to a Thriving Scientific Enterprise

We will likely see the role of boundary organizations expand to meet the societal and governmental demands on science, creating new institutions that prioritize societal values and explicit public buy-in for basic research oriented towards specific societal goals. This may be realized through new federal funding efforts in metascience and industrial policy, along with increasingly substantive public engagement from scientific institutions. It is not enough to simply trust that the norms of science will prioritize public interests, continually improve and inform our lives, as well as safeguard our future while remaining shrewdly under-budget. Scientific institutions have so much to offer society, but our discoveries will either fall upon deaf ears or simply remain undiscovered without the trust and support of non-scientists.

* * *

Austin is a grad student in microbiology and immunology, where he studies how the bacteria that causes cholera releases proteins into its environment. He recently completed the Science Technology and Public Policy certificate through the Gerald R. Ford School of Public Policy, where he found inspiration for this article.

Illustrated by Jacquelyn Roberts

Could artificial intelligence replace doctors in the future? A case study with ChatGPT

Peijin Han

Imagine you had the misfortune of waking up one day with a crippling headache. You have been experiencing neck pains and headaches for a couple of years, but doctors always told you this was a neck strain and prescribed a muscle relaxer. However, today is your third day of suffering from this headache, which doesn't seem to be alleviated by anything you have at home. In the past, you would have navigated the outside world to go to a clinic. But today, instead of dragging yourself out of bed and enduring onerous wait times, you opt to receive medical attention from the comfort of your home.

You open an online medical service app and type, "I have a headache," and then proceed to answer questions about whether you had nausea or vomiting, saw lights before the headache started, have a history of sinusitis, or took any medications. Based on your answers, the app provides a list of possible diagnoses: migraine (92% probability), neck strains (5% probability), tension headache (2.5% probability), or sinusitis headache (0.5% probability). Based on the highest probability diagnosis, the app recommends that you stay at home, rest in a dark room, stay hydrated, and take the medication it prescribes, all the while sending the recorded conversation and prescription to the pharmacy on file. An on-call physician supervises all of these activities: they will verify the prescription and sign the note while watching for any abnormalities. You take the medication and the headache magically stops. You wish you had consulted the app sooner to find out the true culprit!

This scenario might sound like something out of a science fiction novel, but believe it or not, it is a reality made possible by ChatGPT! ChatGPT, one of the emerging artificial intelligence (AI) technologies built on large language models, was first released by OpenAI¹ in 2022 and is attracting lots of attention this year. ChatGPT is able to complete many language tasks like question answering, text generation, and summarization using large language models, which belong to the generative pre-trained transformer (GPT) family. Unlike Siri or Alexa, ChatGPT better engages people in conversations because it can analyze and respond to a wide range of topics and subjects. You can ask ChatGPT anything, from general questions like, "How can I grow a plant?" to difficult academic questions like, "Can you help me with this math proof?"

Although ChatGPT doesn't always have a perfect answer, it still responds to the questions with ease and wit. Shockingly, although with the minimum passing scores, it passed the United States Medical Licensing Examination without prior training,² suggesting that there is untapped potential for the use of ChatGPT in medicine. But before delving into how ChatGPT might revolutionize healthcare, it is first useful to understand the inner workings of ChatGPT.

How does ChatGPT work?

To some extent, the way ChatGPT learns is similar to how humans do. When asked a question, we need to first understand and interpret the voice we hear or the text we read—in other words, "decode" information. Next, we decide on the best response using the knowledge that comes from what we've read, heard, or previously experienced. Finally, we organize our thoughts and speak or write our responses for other people to understand.

ChatGPT works similarly by attempting to analyze the input question and then spitting out strings of words that it predicts will best answer the question based on accumulated knowledge or, for ChatGPT, the data it was trained on. First, ChatGPT "decodes" text data by categorizing it into words, numbers, and punctuation. These elements are converted to numbers by a deep learning neural network, which is essentially a series of complex mathematical models inspired by signaling in the human brain. These complicated equations consist of billions of parameters, and they are updated through thousands of training iterations. The resulting neural network generates probability scores to predict what text should come next based on its prior knowledge: the data it was trained on. Like children who read a lot and are generally good at writing, the more training data ChatGPT sees, the more patterns it learns from the human language, and the more plausible texts it can generate. In fact, ChatGPT has been training on a massive corpus of data—basically, anything you can find on the open internet. This training corpus is on the scale of billions of language elements, which enables ChatGPT to accumulate prodigious amounts of knowledge. In this way, ChatGPT can acquire information about medicine using its pattern recognition process from open-access medical journals, websites from public health organizations like the



Center for Disease Control, and other entities like WebMD and Medscape.

A ChatGPT Case Study

To test the strengths and weaknesses of ChatGPT in a medical setting, I asked ChatGPT a question from a popular question bank for United States Medical Licensing Examination preparation:

A 24-year-old woman is evaluated for a lump in her neck. She discovered the lump a week ago while showering. The patient feels well and has no associated pain, fever, night sweats, or weight changes. Her medical history is unremarkable, although she has had irregular menses for a year since insertion of an intrauterine device. The patient does not use tobacco, alcohol, or illicit drugs. Her mother died during surgery for thyroid cancer. Blood pressure is 133/80 mm Hg and pulse is 78/min. On examination, there is a palpable 2-cm nodule in the right thyroid lobe. The remainder of the examination, including chest, abdomen, extremities, and skin, is normal. Serum thyroid stimulating hormone (TSH) and calcium levels are normal

and calcitonin is elevated. Ultrasound-guided aspiration biopsy reveals malignant cells. Which test is the best next step in the evaluation of this patient?

Here is the response from ChatGPT:

Based on the clinical presentation and findings, the patient may have thyroid cancer, and the best next step in evaluation would be to perform imaging studies to determine the extent and stage of the disease. Among the imaging modalities, the most appropriate test for initial evaluation of thyroid cancer is a neck ultrasound, which can provide information on the size and location of the thyroid nodule, as well as the presence of any suspicious cervical lymph nodes.

Other imaging tests that may be useful in the evaluation of thyroid cancer include computer tomography (CT) scan of the neck and chest, magnetic resonance imaging (MRI) of the neck, and radioactive iodine (RAI) scan. However, the initial imaging study of choice is a neck ultrasound, which is non-invasive, readily available, and has high sensitivity and specificity for detecting thyroid nodules and cervical lymph nodes.

In summary, the best next step in the evaluation of a 24-year-old woman with a palpable thyroid nodule and elevated calcitonin levels is to perform a neck ultrasound to determine the extent and stage of thyroid cancer.

In the scenario posed in the test bank question, the patient has all of the symptoms that would lead an experienced doctor to suspect the patient likely has an inherited form of medullary thyroid cancer and may have a form of multiple endocrine neoplasia type 2 if other certain types of tumors are present.³ The standard next decision would be to screen for one of those other types of tumors, specifically pheochromocytoma, a non-cancerous tumor on the adrenal glands which makes and secretes hormones like norepinephrine and epinephrine. This condition can lead to life-threatening high blood pressure during thyroid tumor removal surgery since the norepinephrine and epinephrine typically made by the adrenal glands will be dysregulated because of the adrenal tumor.

However, ChatGPT answers something regarding how to diagnose a thyroid nodule with a “neck ultrasound” in the first paragraph and explains why it is preferred in the second paragraph. We can see that ChatGPT makes three mistakes here. First, *it doesn’t know the diagnosis of thyroid cancer is confirmed for the patient*. The answer it gave is essentially “how to determine whether this thyroid nodule is cancer.” However, the question stated that malignant cells have already been identified. Second, *it doesn’t link the patient’s symptom to the underlying cause*—it fails to recognize this is an inherited form of medullary thyroid cancer, maybe because it ignores the supporting evidence, specifically increased calcitonin and family history of thyroid malignancy. Third, *it misses other features that are associated with this underlying cause*—it doesn’t link medullary thyroid cancer to multiple endocrine neoplasia type 2 and ignores the fact that pheochromocytoma is associated with this condition. Instead, it regurgitates sentences that will likely come next for “something related to thyroid nodules,” which is more common based on the billions of data points it sees. These three errors all point to a fundamental difficulty when applying AI to complex problems: it is challenging to teach ChatGPT the correct answers because it relies on *guessing* instead of *understanding*.

ChatGPT: the secretary instead of the boss

Although there is still much room for improvement in making diagnoses and treatment plans, ChatGPT can be a great “secretary” for physicians. For one, ChatGPT can help with administration and paperwork, such as generating notes and sending messages, on which physicians spend an average of 15.5 hours per week.⁴



In fact, many high-tech companies have been working on AI documentation tools,⁵ which generate clinical notes within seconds from conversations with patients conducted in person or via telehealth. ChatGPT can also help with patient-provider communication, like explaining complicated diseases or procedures, sending orders and prescriptions, and generating patient handouts and instructions.

In addition to reducing the administrative burden of practicing medicine, ChatGPT’s impact on the clinical workflow could be more complex and far-reaching. Healthcare providers are almost always working in a high-stress and fast-paced environment, where they are prone to mistakes because of burnout, not being up-to-date with the current medical guidelines, and missing information due to a lack of time to examine patients thoroughly. ChatGPT may be able to alleviate these issues by taking patient histories and exploring their symptoms comprehensively, supporting physicians’ education and continuous learning, and helping with preventive medicine, such as recognizing disease outbreaks by analyzing global health data. ChatGPT

could also help physicians with the emotional side of the job: one study⁶ showed that on average, ChatGPT's responses were 9.8 times more likely to be empathetic than physicians' when interacting with patients, which could help physicians have difficult conversations and deliver bad news to patients.

Right now, ChatGPT can't be the "boss" because it cannot fully automate the clinical workflow. As we saw in the case study, the most challenging part of automating clinical workflow is generating correct medical diagnoses and treatments, a complicated task that includes interpreting imaging and lab results, determining differential diagnoses with the likelihoods of each possibility, and deciding on the best treatments based on individual patient characteristics. This is a high-risk, high-reward problem: if ChatGPT can accurately diagnose and prescribe appropriate treatment, it would significantly change the landscape of medicine.

There is still much progress needed before it can reliably rival an experienced human physician in the clinical workflow. Instead of understanding mechanisms of disease, ChatGPT just infers the most plausible responses based on probability scores produced by its neural network.⁷ In other words, ChatGPT will sometimes make up information like an eager child who doesn't seek to learn and understand, but rather just wants to finish their homework so they can go out and play. As a result, ChatGPT is severely limited when it comes to rare and complex diseases; because it does not actually comprehend information, it cannot make connections between presented symptoms and underlying causes when the literature on certain diseases is much less comprehensive. Instead, it will likely default to the most probable diagnosis or management strategies but miss the correct ones because ChatGPT infers information based on the probabilistic models.

The future of AI in medicine

Although scientists in OpenAI are working hard to increase the accuracy of the responses, right now ChatGPT is better suited to be a physician's secretary

instead of replacing them as the boss in the clinical workflow. The bottleneck that AI research faces is how to design large language models that fundamentally comprehend knowledge instead of making educated guesses based on probability. Even if ChatGPT can be safely used in low-risk settings such as charting and patient communication, physicians will still need to act like teachers to check ChatGPT's "homework." In addition, ChatGPT can't perform physical exams, meaning ChatGPT will need to notify doctors so they can provide careful examinations when patients have symptoms like shortness of breath, cough, pain, or weakness. Lastly, ChatGPT may not be able to provide sufficient empathy—when one is sick and vulnerable, meeting the doctors in person, hearing their encouragement, and holding their hands can make a big difference that AI simply cannot replace.

Despite these limitations, ChatGPT can still have a major impact on the medical world. It is likely that AI "doctors," such as an upgraded ChatGPT, will have human-comparable understanding, a large knowledge base, and powerful computing resources, all of which could revolutionize healthcare. If AI can make optimal medical decisions in various complex situations, human doctors will be freed from tedious administrative responsibilities and can spend their time on more meaningful tasks such as prioritizing their mental health and work-life balance or expanding their knowledge of new drugs, rare diseases, and improved surgical procedures. Until then, we must continue to develop ChatGPT so that it can realize its potential in the medical field and, perhaps in the future, be promoted from secretary to boss.

* * *

Peijin is a grad student in computational medicine and bioinformatics, where she researches how to predict disease development using patient health data. She was previously trained as a medical doctor in China and hopes to see how AI benefits healthcare providers, patients, and researchers in the near future.

Illustrated by Zoe Yeoh



Sight beyond light

Kate Giffin¹, Katie Bonefas², Chami Amarasinghe³, Frances Gu⁴, Jennifer Baker⁵

1. Author 2. Illustrator 3. Peer editor
4. Content editor 5. Senior editor

Abstract

There is light beyond light: above and below. The smallest, most ancient parts of us know this. In summer, freckles proclaim communion with this light. DNA twists in its presence. We all know of this light. But we do not, can not, see.

Kate is a poet, mandolinist, and professional nerd. In the lab, she studies how severe infections can lead to long-term brain issues like dementia. When Kate is not marveling at the brain, she is probably outside marveling at some strange plant.

Introduction

To see the world through the eyes of another—is that not the great human endeavor? To know what the birds know. To look through the million eyes of an insect. “What is it like to be a bat?”¹

How far can we push the body?

A kitten with a patch over a healthy eye will be blind in that eye as a cat.² Even the bones will mold, will stretch, given the pressure of shaping boards³ and neck rings.⁴ We do not have to accept that which we are given. We are, after all, dirt. And dirt may be dug.

Hypothesis

I plunge my hands into the still-warm compost, grit my teeth against the naysayers. What use is all my scientific training if I cannot apply it, cannot change the world? The knowledge gained in this wild endeavor will far outweigh the risk. I trust my science, I trust the tangle of electricity between my ears and behind my eyes. I believe the testimony of creatures who have seen the world this way since before we moved into caves. I will see for myself and then, I will see for you.

Methods

Roots will grow towards the sound of water.⁵ So too, will the brain crawl towards the information it receives. It is an easy enough connection to make: ultraviolet sensor to electrical signals to the sensory centers of my brain. With this sensory prosthesis, the eyes are entirely unnecessary, though to keep things consistent, the sensor is placed on the small pink membrane in the corner of my eye, this vestigial remnant of reptilian years.⁶ I let the bandages fall away gently, as a child taking a step, and the world is a soap bubble.

Results

The world as it is, the world as it could be—there is no definition, only subjective perception.⁷ We learn as children that white light is made up of all colors, all rainbows a gift hidden within each sunbeam. Now, I have shattered the visible spectrum, blown a shimmering bubble around my mind. Nothing is white anymore. There are no pure tones. The universe is a glittering, clashing thing, and I grow so full of awe I am not sure this body can hold it all.

It is discordant, too many overlapping pitches. The desire to gouge out my eyes grows as the headaches increase. I had forgotten how painful growth is, how the body howls as it stretches. Closing my eyes is no relief as my brain struggles to integrate all that is new with the familiar. Even the sand tracked in on my shoes is brilliant, is loud, is overwhelming. At night, as in day, I walk the line of dream and nightmare and wake exhausted. Sometimes, a scientific breakthrough is more like an erosion.

Only my stubborn faith in the plasticity of the human brain keeps me going. I train this new vision on art: shadow-wrought masterpieces of the Renaissance, expressionist swirls of color, Indigenous thick lines and patterns. On a pilgrimage to the modern art museum I encounter a red Rothko⁸ canvas and suddenly it shatters before me, expanding and contracting into a million colors beyond red, a bold, exhilarating universe stretched over a few feet. I weep, and the tears themselves glitter.

Discussion

Have you ever looked closely at the grackle, black bird from afar? The feathers morph into a black iridescent mother-of-pearl: the purple of mulberry stains in the summer, the green of pond algae, the speckled yellow and white of wildflower seeds scattered across the ground, a dark rainbow.

I was interviewed by every major newspaper. In each story, they manipulated images to show what I see, but it is the saddest of funhouse mirrors. Here is the Truth: you will never see what I see, never know what I know, never feel what I feel. And I am no closer to that for you, or for the grackle, or for the mantis shrimp.⁹ All these colors are merely perceptions: “such stuff as dreams are made on,”¹⁰ indescribable in the graphs and tests of science that attempt to distill the patterns of the world into bite-sized headlines.

Ultimately, the true risk was not to my physical health. Such are the limitations of this study—I cannot see for you. Imagination will have to suffice:

This soap-bubble world is expansive, beauty beyond beauty. Snow becomes a mirror, a prism, light broken and put back together again as foreign rainbow. Here is the color of tears on your best friends’ face, here the warmth of sunshine hanging onto a garden tomato, here the deepness of loneliness—the closest to black. The brightness of a child’s footsteps, the blurriness of your grandmother’s, the ever-evolving Jackson Pollock of strangers’. There are patterns on every flower,¹¹ every songbird,¹² even the bones of the chameleon glow.¹³

I have passed from the cave into the jungle.¹⁴

Conclusion

There is light beyond light, and color beyond color. There are no words for what I see.

Author Disclosure

As science progresses, I believe people will continue doing what they have always done: pursue their curiosity, attempt to understand themselves and the world better, and use science to solve both personal and societal problems. The biggest difference will likely be technology.

This piece imagines a future where technology used in rodents is applied to humans. In “Embedding a Panoramic Representation of Infrared Light in the Adult Rat Somatosensory Cortex through a Sensory Neuroprosthesis,”¹⁵ researchers gave rats the ability to “see” infrared light by connecting an infrared sensor to their brains. This study highlighted the remarkable ability of the brain to change in response to new information (neuroplasticity¹⁶) and suggested that sensory prostheses could enhance existing senses. Sensory neuroprostheses already exist to improve hearing (cochlear implant¹⁷) and vision (visual prosthesis¹⁸). Would it be possible to use a visual prosthesis to see ultraviolet light, too?

—Kate

Engineering a Future for Women: The Role of Medical Device Design in Gender and Health Equity

Ilka Rodríguez-Calero, Ph.D.

In my twenties, I was put on a hormonal intrauterine device (IUD)—a safe and effective medical device—as a form of birth control.¹ Soon after, I developed pelvic pain, a known side effect of the IUD. The pain, combined with other issues, could be difficult to manage, but my healthcare providers couldn't find an underlying cause. Consequently, pain management was limited to self-care through exercise, mindfulness, and over-the-counter medications. I assumed that living with pain was the price to pay for reliable birth control.

Years later, I developed a nagging pain that was more intense than usual, though familiar enough I dismissed it at first. After a few weeks, I decided to get my symptoms checked. At that point, my provider said, “I wish you had come earlier, but I’m glad you’re here and we’re going to take care of it.” I was confused. Had I not anxiously asked if my pain was normal at every opportunity during the first year with the IUD?

Shortly after that visit, I decided I wanted to have the IUD removed. Hormonal IUDs can last 3 to 8 years, depending on the device. Because IUD removal per the manufacturer was not yet due—and despite what I had just experienced—my provider insisted there was no reason to remove the IUD, a recommendation consistent with available evidence. It took three separate and desperate requests for my provider to accept my choice to have the IUD removed early. At the time, I delved into the academic literature, which I knew how to do as a Ph.D. candidate with experience in medical device design. I was surprised to find an overwhelming absence of studies describing relationships between IUDs and patient-reported experiences like pelvic pain and irregular bleeding, particularly as these can vary so widely in intensity.

Medical devices encompass machines, implants, software, and other artifacts intended to be used for medical purposes, making them indispensable tools for advancing individual and population health.² From a tongue depressor to a mechanical ventilator, medical devices are constantly and directly involved in patient experiences, and engineers are engaged at all stages of their lifecycle. However, when things go wrong, the limited evidence available for women like me can be leveraged to deny us agency as patients and to dismiss experiences or symptoms that are not thoroughly understood. This individual experience mirrors broader patterns about who is given a voice in

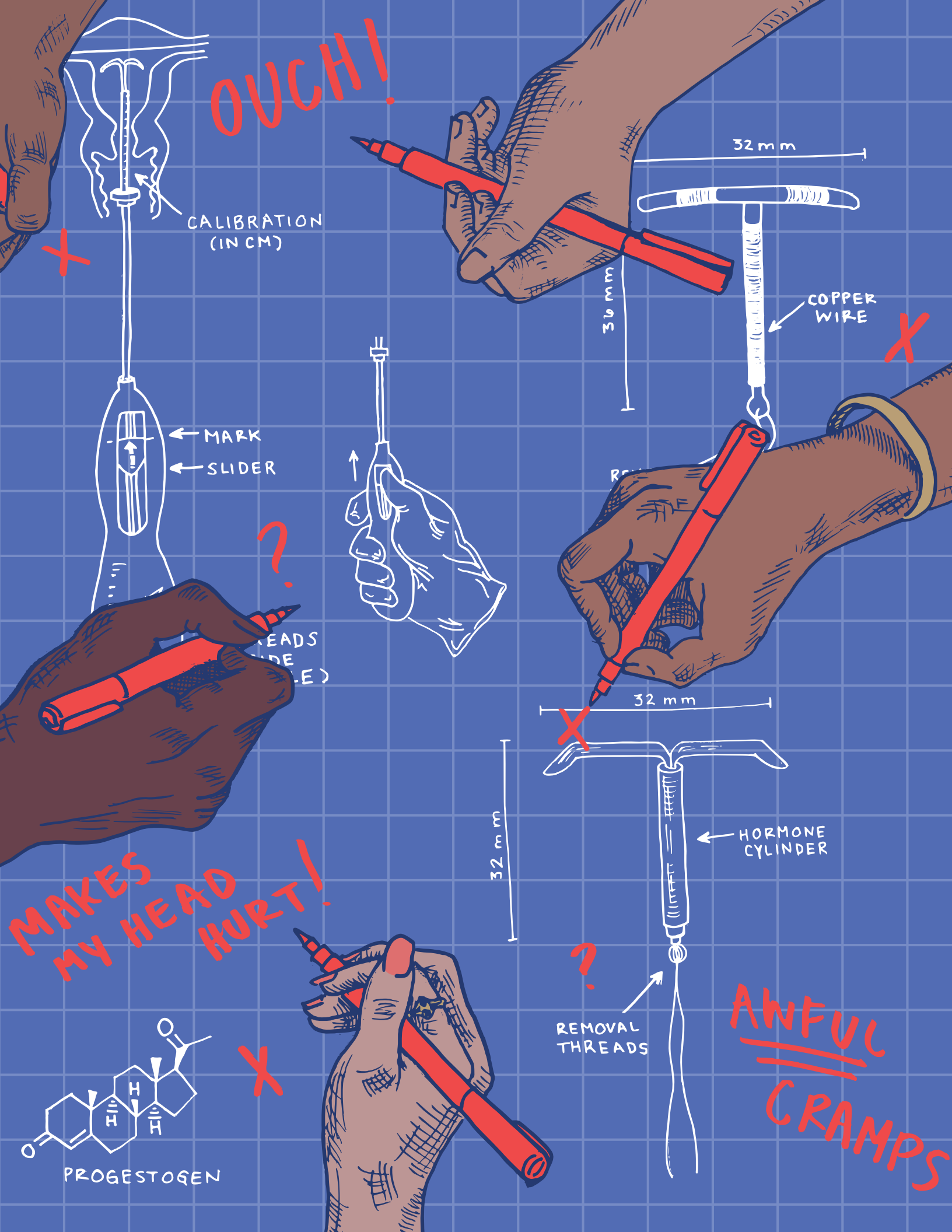
medical device safety and decision-making: the input of patients holds less weight than input from researchers and manufacturers in regulatory decision-making,³ which drives much of medical device innovation. Therefore, many engineering solutions have failed women, putting us at higher risk of harm, contributing to marginalization, and exacerbating health inequities.

Medical device design falls short on meeting the needs of women

Engaging with stakeholders—patients, physicians, nurses, and others who impact and are impacted by design outcomes—is critical if a medical device is to be safely used. Engineering solutions benefit from stakeholder input if they are to define product requirements that correspond to user needs. Medical device manufacturers are expected to perform user needs analyses, human factors evaluations, and field trials consistent with regulatory guidance by the Food and Drug Administration (FDA). Even so, engineers have articulated barriers to engaging with stakeholders, which include: managing conflicting opinions among users, balancing product development and regulatory timelines, and navigating implicit norms regarding who within a company has access to these stakeholders.⁴ Further, the lack of systems and processes for integrating user input in design decisions can lead to technically sound products that inadequately address user needs.⁵

One formal mechanism for user engagement in medical device design is clinical trials. However, trials are limited, as they are conducted after most design decisions have been made. Until recently, scientists avoided using female rodents in animal studies^{6,7} which often preclude studies with human subjects. And while progress has been made towards the inclusion of women in research, it has not been sufficient to address gender disparities in health outcomes.⁸ When examining the burden of disease—the quantified impact of a health issue—women are underrepresented in clinical trials in areas such as oncology, neurology, cardiology, and pediatrics.⁹ This same study also highlights types of clinical trials, including musculoskeletal disease and trauma, in which men are underrepresented relative to how these conditions collectively impact them. Therefore, collecting data separated by sex and gender in clinical trials may improve women's health outcomes and address clinical needs across genders.

The range of women's unmet clinical needs is difficult



to define due to the gender data gap, although there are salient examples. Caroline Criado Perez, author of *Invisible Women*, defines the gender data gap as the absence of women and women's roles throughout the biological and cultural evolution of humanity. One example of the gender data gap's impact in medical device design is that women are more likely to suffer complications after receiving cardiac implantable electronic devices like pacemakers.¹⁰ Heart disease is the leading cause of death in both women and men,¹¹ but some implantable devices used to treat heart disease differ in performance by sex.¹² The gender data gap also extends to surgeons themselves. Surgical instruments are typically designed for male surgeons,¹³ which can result in workplace hazards to women. Adapting to bed heights designed for taller people by performing surgery standing on benches and body aches due to other mismatched device ergonomics are just two hazards women surgeons face.¹⁴ Due to historical and sociocultural factors, it would not be surprising to find the impact of the gender data gap in medical devices in other specialties too.

Engineering's technology-centric ethos has social costs

Despite these gender gaps, engineering solutions have enormously benefited large portions of society. Global life expectancy has increased over the past 20 years.¹⁵ Appropriate medical devices certainly have an important role in promoting health by assisting in the diagnosis, monitoring, and treatment of illness. However, engineering design work is deeply intertwined with the state of scientific research,¹⁶ including the lack of prioritization of women's needs and safety. Research funding from the National Institutes of Health (NIH) is awarded least often to early-career obstetrics and gynecological (OBGYN) researchers compared to other major specialties.¹⁷ Unsurprisingly, knowledge about conditions like endometriosis, fibroids, and polycystic ovarian syndrome is sparse, as are their interventions. Shockingly, one study found that the evidence used to approve high-risk OBGYN medical devices was deficient even for the most strictly regulated devices, sometimes leading to recalls due to safety concerns.¹⁸ Beyond gynecological and reproductive health, basic research on diseases that disproportionately affect women tends to be underfunded, and diseases predominantly affecting men tend to be overfunded.¹⁹ Our inadequate understanding of how women are affected by health conditions may lead to more medical device failures in women. In fact, in 2019, failures of post-market devices—devices being used by patients—were found to disproportionately impact women, who made up 67% of over 300,000 examined injury and death reports submitted to the FDA.²⁰

Engineering fields have not traditionally focused on the social, political, and cultural contexts of engineering work. Interrogating problems like inequality is typically considered beyond the scope of engineering design practice. Further, some engineering codes of ethics state that engineers must remain impartial.²¹ Impartiality, which refers to equal treatment of all parties involved, assumes that all members of society have equal standing and enjoy the same benefits and privileges. This is verifiably untrue. By applying an impartiality lens to problems that disproportionately and negatively impact women, particularly women with multiple marginalized identities, engineers may be inadvertently contributing to a system structured to amplify inequities and experiences of marginalization.

More equitable solutions can emerge with an inclusive design lens

Individual solutions cannot and will not single-handedly address the systemic, deeply interconnected nature of problems underpinning the inequitable risks and benefits of medical device innovation. However, individual and collective action can certainly begin to make a difference.

Policy solutions: regulations and research funding changes

The FDA's Centers for Devices and Radiological Health, which regulates medical devices, has put together a strategic plan outlining priorities to protect the health of all women.²² Meeting these goals will require a collective effort from scientists, clinicians, regulators, engineers, marketers, patients, and advocates. In addition, the FDA has established processes for public participation, including petitions and public comments on proposed rules. Their website²³ has instructions on how to provide input about the way the agency regulates medical devices. Comments and petitions may require extensive preparation with scientific and legal rationale, which creates a substantial barrier for non-technical audiences to participate. However, the public deserves to know how their government makes decisions and how they might participate in such processes, including processes to strengthen regulatory frameworks in matters of women's safety.

There is no shortage of calls to action for increased research funding for health conditions that predominantly affect women, which surely will inform device design activities, and, importantly, help address the documented medical device performance differences by sex and gender. Government stakeholders recognize that health conditions which mostly impact women or manifest differently in women have been historically understudied, as evidenced by biennial reports published by the National Institutes

of Health Office of Women's Health Research²⁴ and a 2022 bill introduced in the U.S. Senate specifically seeking "to close persistent gaps in funding for sex- and gender-based biomedical research."²⁵ Some analyses suggest that increasing research funding in some areas of women's health may result in slight health improvements that, in turn, have dramatic quality of life benefits for women and reduce disease-associated costs.²⁶ Continued advocacy will be necessary until research funding is more equitably distributed across genders relative to the corresponding impact of different health conditions.

Industry efforts: devices designed for and by women

The market size for technology-enabled and consumer-centric women's health products and solutions—FemTech—is between \$500 million to \$1 billion USD, according to some estimates. There has been increased entrepreneurial activity in FemTech over the last decade, with new startups and investment opportunities emerging every year.²⁷ The increased interest could be an unprecedented opportunity to address historically neglected health needs of women. However, FemTech might not ultimately address the most pressing women's health challenges because so many of these challenges are not simply technological.²⁸

FemTech startups present substantial shifts in who gets to innovate. Women account for only 21% of executives in large medical device companies, although they make up 40% of the industry's workforce.²⁹ Further, the engineering workforce more generally—the people who design, build, and test devices—tends to favor people who already hold relative privilege in society due to gender, race, socioeconomic status, and disability.³⁰ However, a report by McKinsey & Company highlights a promising demographic shift in the distribution of FemTech leadership: among the FemTech startups analyzed, 70% had a female leader, in contrast to a 20% female leadership norm for new startups more broadly.²⁷ Highlighting these patterns is not meant to demonstrate a causal path or a solution. Instead, this is meant to illustrate a complex dynamic: the people who make decisions regarding whether engineering solutions can equitably fulfill benefits and mitigate risks are not always the ones closest to the problem.

Innovator decisions: recognizing sociotechnical aspects of problems

Medical devices are defined by their intended use, users, and use environments. These have largely reflected the preferences, priorities, and needs of people who historically held the power to make design, financial, and regulatory decisions. Within those bounds, it is critical that innovators engage in

a reflective practice. When deciding on the intended use, users, and environments, innovators can adopt an inclusive design approach by asking, "*Who is excluded?*" Recognizing and making exclusion visible is the first step to mitigating it³¹—how can someone design for a problem that "doesn't exist?" By determining who is excluded, innovators can engage typically excluded stakeholders in design decisions and outcomes along gender, racial, and socioeconomic lines.

Technology on its own will not provide incremental benefits to society, but interventions that recognize and address exclusion might help fulfill that promise. To build futures in which the health and well-being benefits of engineering solutions are equitably distributed across women with diverse intersectional identities, engineers must engage with both the technical and the social dimensions of problems, which are often overlooked. That needs to change. To this end, design frameworks that are people-, community-, and equity-centric can support engineers and innovators in considering people and their contexts when implementing engineering solutions.

Towards more equitable futures in medical device innovation

If we do this right, patients' lived experiences will inform safe and effective medical devices in the future. We will be able to address, rectify, and repair the harms associated with the known absences of women in biomedical research and medical device design. If we do this right, women's healthcare experiences will be better understood and appropriately addressed, as *absence of evidence* will be increasingly harder to use as *evidence of absence*. If we do this right, medical device design processes and the professional fields that support them will be equipped to respond to the needs of people whom these devices serve, as innovation will be driven by meaningful and equitable stakeholder engagement. Collective and individual efforts will make a difference in how devices are designed, developed, regulated, and distributed such that protecting the health and safety of women has rippling impacts on the overall population's health. If we do this right, more equitable futures can be possible.

* * *

Ilka is an engineering design researcher whose work investigates how engineers make decisions when engaging stakeholders in early project phases. She hopes her piece helps innovators and the people they serve gain a broader understanding of medical device design challenges and, more importantly, helps them envision participating in more equitable futures.

Illustrated by Katie Bonefas

Homegrown Guardians: Harnessing the Power of the Immune System to Fight Breast Cancer

Kassidy Jungles

Cancer is an enemy of your body, starting when your cells turn against you, rapidly divide, and spread. Cancer is clever and conniving. Cancer can rapidly mutate over time, making it difficult for your body to notice and even more difficult to treat. Because of this, it might be hard to imagine your body as the answer to ridding itself of its homegrown enemies. However, this is precisely the future of cancer treatment that scientists are imagining. What if the answer to treating cancer is using homegrown guardians derived from your immune system to beat cancer at its own game?



Meet immunotherapy: a revolutionary anti-cancer tool and the future of cancer care. The term immunotherapy encompasses many therapeutic strategies that have one thing in common: they train your immune system to kill cancer cells. Multiple types of immunotherapies are in various stages of development, including first-generation approaches like immune checkpoint inhibitors and cell transfer therapies, and the more futuristic cancer vaccines. Cancer vaccines specifically may have fewer side effects like hair loss, nausea, and diarrhea, and are currently being developed to prevent people from developing cancers in the first place. While immunotherapy has potential for all types of cancer, it is especially promising for the treatment and prevention of breast cancer, for which studies are currently underway to help bring these therapies to the patients that need them the most.

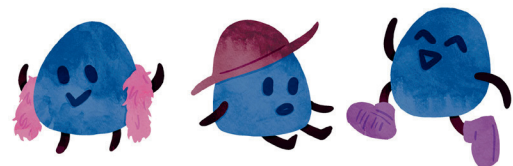
Current breast cancer therapies have major drawbacks and fail to treat all patients

Breast cancer is a leading cancer diagnosed among females and occurs when malignant cells in the breast uncontrollably divide. In 2023, nearly 300,000 females will be diagnosed and approximately 43,000 will die from breast cancer.¹ Treatment outcomes for breast cancer patients have improved significantly in recent years due to advancements in screening for high-risk variants in genes like BReast CAncer (BRCA), allowing at-risk patients to receive treatment earlier or before their cancer develops. Targeted therapies that attack specific components of a patient's tumor have also

significantly improved survival rates. However, breast cancer is complex and varies in how it spreads, what genetic mutations it has, and how well patients respond to therapies. Thus, breast cancer is not just one disease, but many.

Currently, breast cancer is treated using a combination of surgery, radiation, chemotherapy, and, more recently, targeted therapy. The first step in breast cancer treatment is usually surgery to remove either a lump of cancerous tissue (lumpectomy) or the entirety of one or both breasts (mastectomy). Next, any remaining cancer cells that were not removed by surgery are killed off using a combination of the remaining techniques. Radiation involves the highly controlled delivery of small, charged beams of energized particles to the tumor region to cause cancer cell death. While most breast cancer patients receive radiation therapy, it is not the most effective treatment given the high rate of recurrence, or return, of breast cancer. The other mainstay breast cancer therapy is chemotherapy, which refers to drugs that kill cancer cells. While chemotherapy is effective at killing cancerous cells, unfortunately, it also targets healthy cells of the body. This is why cancer patients receiving chemotherapy often have unwanted side effects like hair loss and gastrointestinal distress, because the chemotherapy targets not just cancer cells but all rapidly dividing cells, like those of the hair and the gut.

Furthermore, cancer cells often employ smart techniques to fight back against chemotherapy, which leads to chemotherapy resistance being common. Targeted therapies, such as anti-hormone therapies, are a newer treatment option for breast cancer patients depending on their subtype. To make it easier to classify and treat, breast cancer is divided into subtypes based upon the presence of various hormone receptors. Hormone receptors are like accessories unique to cancer cells that can promote cell signaling and interactions.



Breast cancer is classified based upon the presence or absence of three cellular accessories: estrogen receptor (ER), progesterone receptor (PR), and human epidermal

growth factor receptor 2 (HER2). Consequently, breast cancer is defined as ER+, PR+, HER2+, or triple-negative breast cancer (TNBC)—a form of breast cancer lacking all of the above hormone receptors, which cannot be treated with targeted hormone therapies.

Because of these drawbacks of available breast cancer treatments, scientists are looking for alternatives to improve the treatment response rates—particularly for triple-negative breast cancer—and prevention strategies to protect people at high risk. One promising answer exists in breast cancer immunotherapy, an emerging treatment option where physicians can use the power of the immune system to not only provide additional immune support but also prevent the development of breast cancer in the first place.

Immunotherapy has begun to address gaps in current breast cancer care

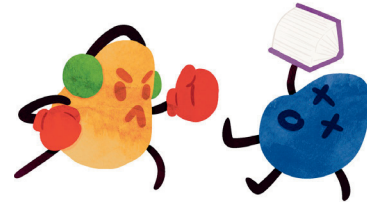
The immune system is incredibly complex and consists of various cells that ultimately aim to fight off both foreign invaders and also local invaders, such as healthy cells that become cancerous. Fundamentally, immunotherapy is a type of cancer therapy that functions to provide extra support to a patient's immune system to help eliminate cancerous cells.

The earliest type of immunotherapy to become available for cancer treatment was immune checkpoint inhibitors, first approved by the FDA in 2011 for the treatment of melanoma. The body has natural checkpoints in place to prevent overactivation of the immune system. Cancer cells can use these checkpoints to their advantage to turn off the immune system, which allows cancer cells to spread through the body unchecked.



Immune checkpoint inhibitors, such as those that target programmed death-ligand/receptor 1 (PD-(L)1), were developed to prevent these checkpoints from being turned off. Consequently, this results in increased immune system activation, which can promote cancer cell killing. Immune checkpoint therapies have revolutionized cancer care and the scientists that discovered immune checkpoint inhibitors, Dr. James P. Allison and Dr. Tasuku Honjo, were awarded the Nobel Prize in Physiology or Medicine in 2018 for this

discovery.² Currently, the immune checkpoint inhibitor pembrolizumab is approved for both early stage (when the cancer is found locally in the breast) and metastatic (after cancer has spread throughout the body) triple-negative breast cancer.

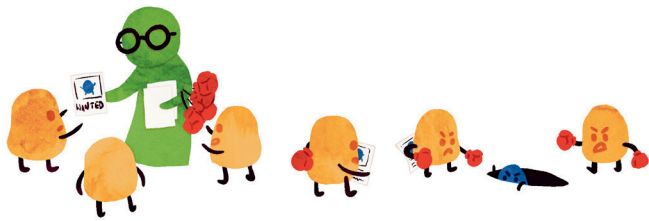


Adoptive cell transfer therapy, such as chimeric antigen receptor (CAR) T-cell therapy, is another type of immunotherapy that involves collecting immune cells from patients, modifying them to recognize and eliminate a patient's cancer, and reintroducing these immune cells into the patients.³ These therapies permit increased immune signaling and promote cancer cell elimination by being modified to express certain signals unique to the cancer. Although these therapies are still in development for breast cancer, they will permit a stronger immune response compared to traditional therapies and train the immune cells specifically against fighting the cancerous cells.



Cancer vaccines are the next generation of breast cancer immunotherapy

One of the most futuristic approaches for treating breast cancer lies in the development of cancer vaccines. In recent years, scientists have made significant advances in vaccine development, such as development in the application of mRNA vaccines for treating COVID-19. These vaccines were the first example of widespread distribution of such new vaccine technology and were proven to be safe and effective in preventing disease progression. Consequently, with these advancements and widespread success of the mRNA vaccines for the treatment of COVID-19, experts predict that cancer vaccines are the future for the treatment and prevention of cancer.⁴



Cancer vaccines function by delivering chemicals or biomolecules to patients that recognize components of a patient's cancer and ultimately promote cancer cell death by turning on the immune system. Specifically, cancer vaccines typically contain two components: a target of the patient's cancer and molecules that promote immune recognition, known as adjuvants. The first cancer vaccine component—the target—can include tumor proteins, carbohydrates, and genetic material like DNA and mRNA, all designed to mimic certain components of a patient's tumor.⁵ Moreover, other cancer vaccines directly target cells of the immune system, like dendritic cells.^{5,6} Dendritic cell vaccines can induce an immune response in the patient by delivering these cells as part of the vaccine to target the patient's cancer.⁶ In these vaccines, dendritic cells are delivered with components of the tumor in order to trigger an antitumor immune response.⁶ The second cancer vaccine component—adjuvants—are added to the vaccine to create inflammation and stimulate a general immune response.⁷ While the adverse symptoms that accompany the inclusion of adjuvants in a vaccine (e.g., fever, body aches) are not always wanted, it is important to cause such inflammation so that the immune system recognizes the signal being delivered by the vaccine as one that is meant to introduce an immune response, instead of simply destroying the foreign particles from the vaccine.

Scientists are starting to conduct extensive studies on breast cancer vaccines due to an increase in breast cancer prevalence and the unmet clinical need for breast cancer therapies, particularly for triple-negative breast cancer. A myriad of preclinical studies—using animals and cells in the lab—and clinical studies—assessing patients with breast cancer—are underway to study the effects of breast cancer vaccines. These vaccines are being developed to work in two different ways. The first strategy, like many other vaccines, is to prevent breast cancer from occurring in high-risk individuals.

Like the development of human papillomavirus (HPV) vaccines that prevent the development of HPV-induced cancers, researchers are currently studying novel ways to prevent the development of breast cancer. Currently, a first-of-its-kind phase 1 clinical trial out of Case Western Reserve University is studying the effects

of a preventative breast cancer vaccine for healthy individuals who are at high risk for developing breast cancer.⁸ This vaccine specifically targets a molecular signature expressed in triple-negative breast cancer, and, like discussed previously, contains an adjuvant to activate the immune system.⁹



While preventative breast cancer vaccines are still in early stages of clinical development, more research has been devoted to studying breast cancer vaccines for treating patients once they get breast cancer—the second cancer vaccine strategy. Unlike preventative breast cancer vaccines, these vaccines are designed to treat breast cancer, similar to the rabies vaccine, which can be delivered to rabies-infected individuals after exposure. Currently, researchers are trying to find ways to make cancer vaccines more effective at activating the immune system, since the vaccines being examined have not always been able to elicit long-term effects.⁵ Consequently, scientists are working to determine the optimal dosage and timing of delivery and develop boosters to make these vaccines more effective.⁵ If successful, these preclinical discoveries may translate into helping treat breast cancer patients in the clinical setting and may have less adverse side effects than the normal treatment regimen.

Much research remains to be done before rolling out breast cancer vaccines

While breast cancer vaccines will revolutionize how we treat and prevent cancer, there is still significant work needed to bring such therapies to patients. Numerous studies have assessed the effects of breast cancer vaccines in clinical trials; unfortunately, there has been little success in moving such therapies into treating patients due to limited improvement in patient survival.^{5,10}

One promising way for improving patient outcomes may be combining cancer vaccines with other available therapies like immune checkpoint inhibitors and hormone receptor-targeted therapies.^{4,5,17} In a preclinical study, immune checkpoint inhibitors combined with a cancer vaccine were found to prolong survival in mouse models of breast cancer.¹⁵ Additionally, in a clinical trial combining cancer vaccines with anti-HER2 targeted therapies in patients with triple-negative breast cancer,¹⁶ researchers observed improved survival and decreased cancer recurrence, even though these patients did not express the HER2

receptor!¹⁵ It is believed that this combination was the most effective in this subgroup due to triple-negative breast cancer having the most immune cells present that can consequently be targeted via immunotherapy, but more research is needed to understand these complex interactions.

Furthermore, more work is warranted to address healthcare disparities and what patients have access to immunotherapy treatment options. There are significant disparities in the field of breast cancer; for example, triple-negative breast cancer disproportionately impacts women of color.¹¹ However, of the existing clinical trials for breast cancer immunotherapies, the patients that enroll are often white and do not reflect the patients of color that are often most affected.¹² Additionally, while immunotherapies like adoptive cell therapies are promising, they are incredibly costly and only available to select patient populations that can afford the high costs.¹³ While cancer vaccines hold the promise of being more widespread and more cost-effective than adoptive cell transfer therapies, additional research is needed to not only study these vaccines in diverse patient populations, but also determine how to best promote accessibility of such therapies to the patients that desperately need them. Finally, there is the issue of educating the public on the safety of and scientific support for vaccinations. Existing vaccines undergo rigorous studies to prove safety and efficacy before being given to patients in the clinical setting. However, more discussions are needed to inform the public on the benefits of vaccines, help eliminate the

stigma of vaccinations, and educate patients to prevent vaccine hesitancy.¹⁴ These discussions will be vitally important considering the ongoing public discussion and misunderstanding originating in the anti-vaccine movement and stimulated by the COVID-19 pandemic.

Cancer vaccines are incredibly promising for fighting off breast cancer. In the future, patients may no longer have to suffer from toxic side effects of chemotherapy or recurrence after radiation. Instead, they could receive a vaccine to rid the body of its homegrown enemies using its homegrown guardians. Furthermore, in the future, healthy patients who are at increased risk for developing breast cancer will be able to rest easy knowing they can receive a simple vaccine to prevent cancer development. While there is still much work to be done to bring these futuristic therapies to patients, cancer vaccines are incredibly promising treatment options that could help alleviate healthcare disparities and bring relief to cancer patients and at-risk individuals across the world.

* * *

Kassidy is a pharmacology grad student whose work aims to discover novel therapies for the treatment of aggressive breast cancers. She is passionate about social justice and advocacy and the promotion of STEM to underserved groups – and also reading, thrift shopping, and traveling.

Illustrated by Jessica Li

A Dark Science

Chami Amarasinghe

For a hundred years now, evidence for invisible matter has been piling up.¹ Eighty-five percent of the mass in our cosmic neighborhood is transparent.² We are completely awash in this invisible substance, dark matter. It far outweighs the stars, planets, asteroids, gas, dust, and us.³ The evidence lies plainly in the night sky. Stars and galaxies are accelerated by the gravity of dark matter.^{4,5} Light emitted from distant objects bends in its presence.⁶ But, despite its ubiquity, nearly nothing is known about the fundamental particles that make up dark matter.⁷ How heavy are they? Why are they so prevalent? If they are everywhere and interact with the atoms of our world, could we detect them as Earth travels through space? Dark matter particles have long been searched for in experiments but none have been found.⁸ The devices built to detect them are the most sensitive ears we have opened to the skies, and they continue to grow in size and complexity as scientists continue their search.⁹ Discovering the nature of dark matter would upturn our understanding of the universe, but history warns of dead ends. It is not predetermined that dark matter particles will be discovered.¹⁰

* *

All of space is filled with a specter, pervasive but discreet, and as old as the universe. We know this because it left imprints in the ancient light created by the first atoms.¹¹ Having left its mark, this substance flowed under gravity into patterns, assembling congregations of mass.¹² It ushered the newly formed atoms along and spun them into galaxies, soon to spark life with the birth of the first stars.

Dark matter. The enigmatic essence, once a sculptor of the cosmos, now binds together the structures in our cosmic habitat: stars, galaxies, and clusters of galaxies, opposing the expansion of space.¹³ Dark matter swirls with the Milky Way round and around, its heft evident in regions bereft of stars. It is everywhere, and yet we are unable to detect the particles it is composed of. We have observed and admired its handiwork, and yet we do not know its nature.

Pooling streams of time bring you, traveler, to the year 3023 C.E.

Generations of theoreticians and experimentalists have transformed dark matter research into an august tradition. Much more is known about how this invisible shroud wreaths around every galaxy in the universe and about how it molded the largest cosmic structures.



The age's wealth of astronomical data has convinced every skeptic of its existence, and there is no doubt that it is everywhere, around you and distant galaxies alike. Yet still, as it was a millennium ago, you are not privy to its nature, and the mystery runs ever deeper.

These are the ending stages of the lunar gold rush. Having stripped the moon of its minerals, the last of the prospectors are moving on to the outer planets, leaving behind a drilled and hollowed rock. Concordant with a long history of Earthly, underground laboratories that started as mines,¹⁴ the desecrated moon has perfect conditions for a dark matter detector, which has finally been built.¹⁵ A giant ocean floats in the center of the moon, unbothered by gravity. Capillaries of sensors penetrate this liquid core, recording the faint sparks and crackles it makes each time a particle passes through. Such tell-tale signatures are rare. The rock shell entombing the detector stops nearly everything, creating a quiet environment to listen for dark matter particles.¹⁶

You submerge into the current of space-time and flow

into the moon's artificial core. The sensor bays latch on to your presence as you settle in, suspended in a drop, to listen. All is quiet at first as you learn to hear with your new ears. Then, softly, a quiet roar rises into focus, from the direction of the sun. Neutrino particles, nature's swiftest messengers,¹⁷ come pouring from our star, through the lunar rock and make the detector hum in static, reminding you of light rain in the forests of old. You occupy the sound, reassured in its seeming constancy. Below the hum, the liquid core quivers with tremors from deep space, sounding like whale song that has been forgotten to time. These tremors are from ancient stars exploding; their quakes are conveyed in all directions by neutrinos. Energetic bolts from the supernovae hit the detector and spritz the soundscape with cracks, faint and sharp.

The sound of the thunderstorm is the music of the universe. You hear it from inside the most titanic instrument operated in these rivers of time. Yet despite its sheer size and ingenuity of design, the detector at the core of the moon has not recorded a single crackle, fizz, or buzz from the passage of dark matter.

You retreat to the dying Earth and hold your fists to the night sky like skinny antennas. Thousands of dark

matter particles are flowing through them each second, and you are completely, blindly, attuned. As you raise your gaze beyond your clenched fists, you notice that Polaris, the once steadfast north star, is no longer occupying its familiar location.¹⁸ The gradual shift of the Earth's equinoxes has dethroned the beacon that once guided civilizations. With this realization fear surges through your trembling fists: a fear that science itself may be imperiled by the mechanics of the universe.

* *

While it is true that in the history of physics, new generations bring paradigm shifts—like the revolutions of relativity and quantum mechanics—it is uncertain if this trend will continue. Predicting major shifts in thinking is a futile endeavor because much of scientific progress is made through incremental advances.

*Disciplines of discovery are steeped in murky scientific waters where incremental progress is difficult to contextualize. This difficulty is best expressed through the doctrine of falsifiability, which guides us to use frameworks that can be easily disproved by empirical observation.*¹⁹



In the case of dark matter, your instruments will only ever have two logical responses to the question: "Are we able to detect it?"

- i) An uproarious "YES", or*
- ii) "Not yet," which invites the question to be asked the next decade, and if negative again, the next century, and many times more again.*

We may be trapped in this loop, but a kind of progress can be made, slowly. We will keep discovering not what dark matter is, but what it cannot be. The decades and centuries of null results will have firmly established that dark matter does not belong to any particle type detectable by past experiments.

Will the questions being posed to nature have morphed into something more satisfactorily falsifiable? If so, how will the future scientists have come to accept their lot? They will have been solemnly bested by the universe; the pursuit of knowledge for the sake of knowledge wrested from them. The interaction of dark matter with ordinary matter is not required by any law to be substantial enough for human observation. It may be arbitrarily reclusive. Currently, our capacity to deal with such facts is limited because the scientific endeavor is still in its adolescence. Like the obstinate hydra, human curiosity will continue to raise its numerous probing heads. But some day, one head may decide to slump down and refuse to rise. After all, it is difficult to think of dark matter ever being materialistically valuable to a creature. Maybe, when the weight of a history of null results disincentivizes progress, curiosity will morph into another tendency of our descendents: our drive to mythologize.²⁰

* *

Drying rivulets of time bring you to the end of the universe. The end of everything, the age of great cosmic rips.²¹

Deep in the far future, the star systems of Aldebaran, Fafnir, Rukbah, Zhu Shi, Thaharu, Jyestha, and Wasat flash by you in a loop. You come to rest on Thaharu, formless, not needing to ossify your body into space. Just as well. The council of atomic elders whom you came to witness are disembodied. They have dispersed onto these seven asterisms and built shrines on hollow-cored derelict planets, following darkness, their inky god, Karuwal. The shrine planet of Thaharu is smothered in a dense smog through which its coral structures protrude, ornate even in ruin, a beacon in

an expanding waste. You flow into its center and hear the elders pray and weep.

Karuwal...Thou dost dwell deep!
In stars and galaxies vast.
We ask your solace, Cosmic Weave,
For this our final cleave.

Vines have sprung loose from the temple at the planet's core. The empty Thaharu shrine, once a prime pilgrimage site, reverberates with the elders' sobs. The elders are weeping for Karuwal. They weep longingly for the misguided beliefs and futile science of their Milkedromedan ancestors. They lament the time when Karuwal was a source of puzzlement, and later, religious fervor. Time has run out. The great Disconnect is upon Thaharu, separating it from the other stars and isolating it in the tattered universe. The elders weep for their god that was splintered by the expansion of space, a god they will now never understand.

You gush, wakeless, into the home system before it too is Disconnected.²² The Earth has vanished in some ancient war, and the once-vibrant sun has long been extinguished. In the abandoned detector at the center of the moon, the rain has stopped. Distant stars, the survivors, are methodically silenced one at a time, as they expand away too fast for their messengers to reach the moon. And then, there reigned silence and darkness, more profound than it ever was. The unknown finally replaced by the unknowable.

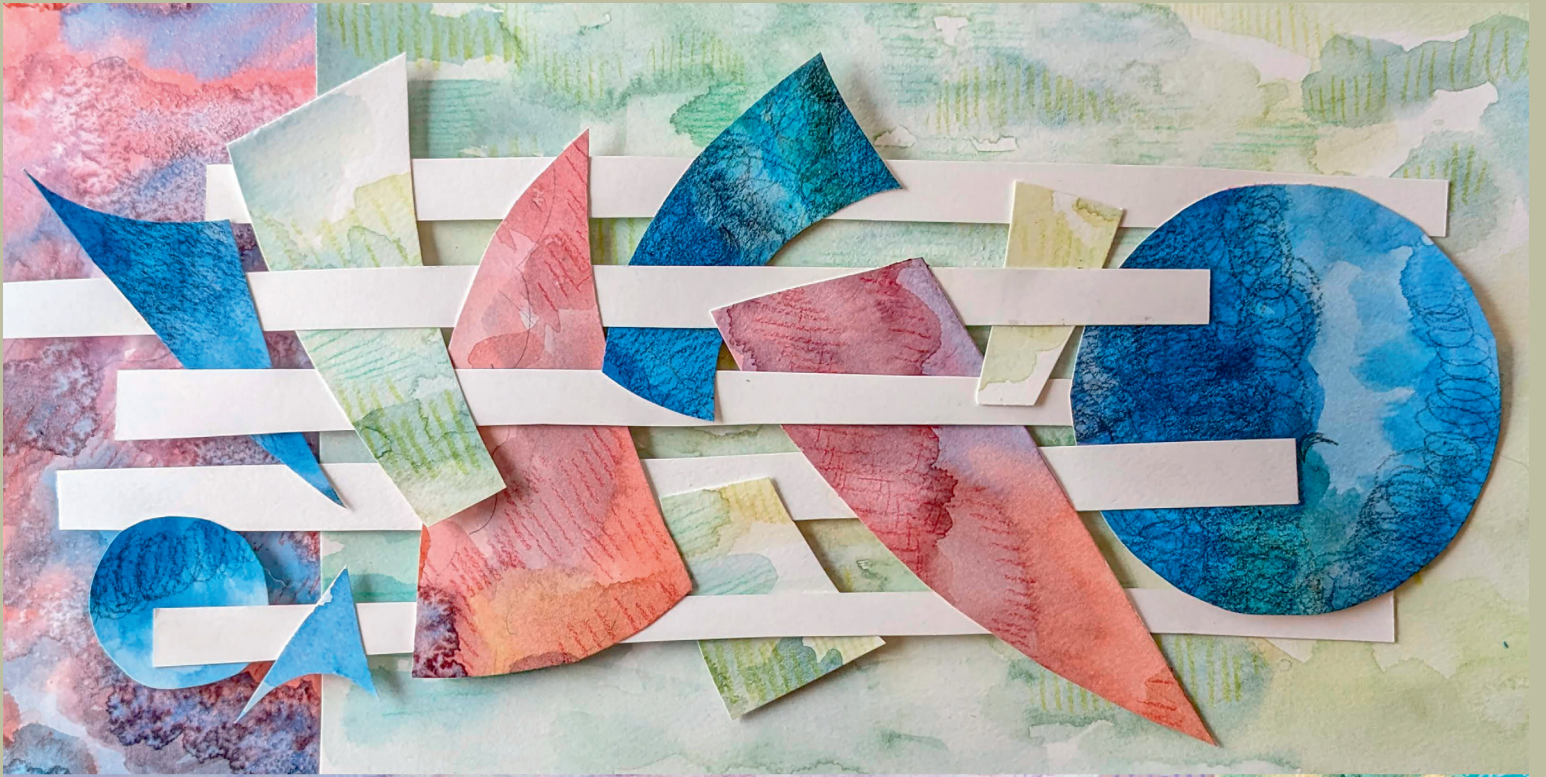
* *

Today, the spirit of the search burns bright as we delve wide and deep into the dark matter mystery. The quest to understand it remains compelling and we learn more with each year. Our detectors await, dormant and deep underground on Earth. They convey to us the sounds of stars echoing throughout the universe. Although it gives pause to know that we may never hear the dark wind no matter how keenly we listen, the unknown captivates us, and the journey itself remains an adventure.

* * *

Chami is a grad student and physicist involved in a search for dark matter particles. He likes reading science fiction and its parallel in the real world, history. He is easily obsessed with the unknowable, and hopes that this article won't cost him his job.

Illustrated by Zoe Yeoh



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Cytotropolis: Life at the Cellular Level

We believe that in the future, we will have an intimate understanding of what the inside of a cell looks like on a molecular—perhaps even atomic—level. This has been enabled by recent advancements in structural biology through artificial intelligence and machine learning. In combination with virtual reality technology, we envision that one day we'll be able to “step inside” a cell to observe these molecular details, reimagined as a thriving city neighborhood. The Golgi Luxury Apartment complex features incredible amenities such as a mitochondria gym, a vacuole pool, and endoplasmic reticulum meeting rooms. Located steps away is The Nucleus, a Michelin Star establishment known for its four-course dNTP mystery menu. Actin and tubulin filaments crisscross above, forming sky bridge walkways and a convenient high-speed metro line to get around the cell with ease. Neatly manicured ribosome trees dot the public park below.

Cover Concept and Art

Zoe Yeoh and Jessica Li