# Missouri Medicine

The Journal of the Missouri State Medical Association www.msma.org/missouri-medicine November/December 2025


MSMA 175 Years 1850-2025

# The Premier Advocate for Missouri's Physicians & Patients

## JOIN-RENEW-RECRUIT



Brain Implants in the Age of Artificial Intelligence

Transcranial Magnetic Stimulation for Major Depression

Threats Against Physicians & Scientists? You Bet Your Life

Dermatologic Tattoo Disorders in this Era of Body Art

# MSMA Patient Advocacy and Education Campaign: "Your Care is at Our Core"

Your Missouri State Medical Association encourages you to join our "Your Care is at Our Core" campaign, a statewide patient advocacy and education program to restore and protect the physician-patient relationship. The campaign is in partnership with the American Medical Association and more than half the states in the nation.

MSMA believes that care begins not with paperwork, but with trust, compassion, and time spent face-to-face. Missouri's physicians, in all medical specialties and in all 114 counties, are facing administrative overload, prior authorization delays, and third-party interference. Our physicians are increasingly constrained by decisions made by insurance companies, pharmacy benefit managers, and other bureaucratic interventions.

Your Care is at Our Core isn't just a slogan—it's a call to action. We are standing with physicians nationwide and the AMA to restore the time, autonomy, and respect that every patient and physician deserves. Join us!




"I am committed to breaking down the barriers that currently exist in the patient-physician relationship, restoring mutual trust, and providing excellent, individualized primary healthcare."

*-Jennifer Powell, MD, Family Medicine, Osage Beach and Lebanon*



Donna Corrado, RN, and Joe Corrado, MD, General Surgery, Mexico, plan to wear their YCOC pins while seeing patients to explain why their core is at their patients' care.



Carlin Ridpath, MD, Radiology, Springfield, (left), receives her YCOC pin from Joanne Loethen, MD, Internal Medicine/ Pediatrics, Kansas City.

**The Your Care is At Our Core campaign amplifies physician voices across Missouri, engages patients in advocacy, and calls on lawmakers to prioritize reforms that protect physician-led, patient-centered care.**

***Contact MSMA at advocacy@msma.org to receive your Your Care is at Our Core pin to wear on your white coat.***

MSMA 175 Years 1850-2025 Protecting the Health of Missourians for 175 Years

# Missouri Medicine

*The Journal of the Missouri State Medical Association – Since 1904*

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*MSMA member authors are bold in Table of Contents and throughout the Journal. MSMA member authors whose manuscripts are accepted to Missouri Medicine receive priority in the publication queue. Scan to join!*

*Journal of the Missouri State Medical Association - Since 1904*

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Submission packets must follow Instructions for Authors available at www.msma.org/Instructions-for-Authors. Manuscripts without the Copyright, Graphic and Photography form, and a Disclosure of Relevant Financial Relationships form delays the peer-review and publishing process. All Authors must disclose if artificial intelligence was used and if so for what purpose. The policy is based on *JAMA* criteria. Incomplete submission packets are returned until correct. Authors receive notification of receipt within 10 days. Peer review is usually completed within 30-45 days of receipt. Submission of article packet does not guarantee publication. *Missouri Medicine* does not charge or collect fees for manuscript processing and/or publishing materials.

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- Corrections are published when deemed necessary
- Feedback and correspondence is encouraged

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# Missouri Medicine Moments The 2025 Chronicle

*by John C. Hagan, III, MD*

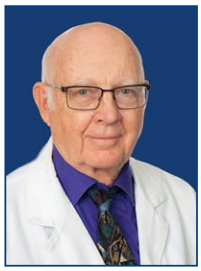
2025 Been there, done that. In the 121-year-life of *Missouri Medicine: The Journal of the Missouri Medical Association* a.k.a *Missouri Medicine*, 2025 was an excellent year. No COVID, no pandemic of writer's block, and the trial lawyers not especially happy with the 2025 Missouri legislative session. A distraught trial lawyer always makes for a good day.

For well over two decades, the heart and soul of *Missouri Medicine* have been medical themes subscribed by departments at one of Missouri's six distinguished medical schools on eight campuses. It is a rich and deep trove of state-of-the-art clinical medicine from which to draw. The themes have become very popular with School of Medicine Department Chairs.

In 2025, we featured Washington University's, Institute of Clinical and Translational Sciences (January/February); Saint Louis University Division of Geriatric Medicine (March/April); University of Missouri's Department of Physical Medicine and Rehabilitation (May/June); Children's Mercy Hospital, Department of Pediatric Psychiatry Kansas City, Missouri, (July/August); and last, but not least the estimable Family and Community Medicine Department, University of Missouri-Kansas City School of Medicine. The November/December issue has no theme in order to try and whittle down our extended publishing queue. Our theme issues are fully subscribed through March 2027. A huge thank you to department chairs, theme coordinators, and faculty.

Foundationally speaking, another journal pillar is our editorial board of experts in the various disciplines of medicine and surgery. Jeffrey Coughenour, MD, Medical Director of the Frank L. Mitchell, Jr., MD, Trauma Center, Associate Professor of Emergency Medicine, Associate Professor of Surgery (Acute Care Surgery) is our new General Surgery expert. He replaces Joseph A. Corrado, MD, who held the position for over 25 years. Dr. Corrado was awarded the Distinguished Service Award. Julie M. Marshall, MD, FASA, Professor of Anesthesiology, Interim Director of Research, University of Missouri Health Care, Columbia, Missouri, onboarded in Anesthesia. This position has been admirably staffed by Kathy Perry, MD, Associate Professor of Anesthesiology, University of Missouri - Kansas City. Kathy has retired from clinical practice. Urologist Elizabeth A. Piontek, MD, Saint Luke's Health System, Kansas City, relinquished her journal duties after more than a decade of service. Mark R. Wakefield, MD, Director of the Renal Transplant Program, Division Chief of Urologic Surgery and Professor of Medicine, University of Missouri Healthcare, assumed the position. We welcome our new physician experts, thank our departing physician authorities, and appreciate those expert physicians continuing to serve on our editorial board.

It is with great sadness that I inform you that Arthur H. Gale, MD, an extraordinary physician, died September 17, 2025. Art served MSMA and *Missouri*



**John C. Hagan, III, MD,** is *Missouri Medicine* editor since 2000 and Contributing Editor to *Kansas City Medicine journal*. Active in many organizations, he is a former President of Kansas City Medical Society, the Missouri Society of Eye Physicians & Surgeons and the Clay-Platte Medical Society. He is a retired ophthalmologist and involved in medical research and journalism in Kansas City, Missouri, USA. Learn more at www.msma.org/MoMed-Editor.

*Medicine* perhaps longer than any other physician. No one at our journal remembers exactly when he joined the editorial board, first as our Internal Medicine expert and later as a Contributing Editor. He was a fixture here when I became Editor in 2000. Art had many talents: he was a consummate writer, an extraordinary teacher, a compassionate physician, and loving husband and father to his family. Art was my Oracle that I turned to for direction and advice. His sagacity continually amazed me. He will be greatly missed. His memorial was printed in the September/October 2025 issue on page 376.

Yearly our volume of unsolicited manuscripts increases, this year was no exception. Our acceptance rate is about 20%. We received papers from three foreign countries; however, none made the journal. With the down-sizing of our journal due to production costs, our publication queue has unfortunately grown to 8 to 10 months for non-prioritized articles. I thank all exasperated authors for their understanding; I tell them I share their pain.

Starting in 2026 we are adding key words as a prerequisite for authors to furnish on scientific articles. Key words make articles more likely to be retrieved in literature searches. A poorly thought-out resolution to make the paper issue of *Missouri Medicine* a mandatory opt-in was thankfully rejected by MSMA Council; instead dues-paying members can opt-out of a paper copy by contacting the MSMA office.

I no longer remember what people talked about before we started talking about artificial intelligence (AI). Writing of all sorts—medical, scientific, commercial, fiction and non-fiction books—have been co-opted as a skill by anyone with even entry level AI competency. With proper prompts the quality of AI writing is extraordinary. AI is and will continue to put many jobs and professions out of work. Human editing may be 'dead man walking.' I have taken every course I could on technical and scientific writing, narrative and business writing. Immodestly, I say I have gotten good at it; I have won several national writing competitions. It will typically take me about three to five hours to write and polish an editorial. AI can write a reasonably facsimile in about 10 seconds. The value of student essays has fallen to zero as most, maybe all, of their writing assignments are completed with AI, frequently undisclosed.

Witness what has happened to elite computer programmers. Graduates from top university programs were highly sought, and enticed with large salaries and generous benefits. Now, due to AI's ability to write code, most graduates cannot find a job. Whether AI will let us satisfactorily address the existential problem of physician shortages remains to be seen. I am deep in research but my working hypothesis is that greatly improved and perfected medical AI is the only way to address the many failings of our present system including availability, quality, and costs.

The book I've just finished reading (T*he Intelligence Explosion. When AI Beats Humans at Everything* by James Barrat, St. Martins Press, 2025) says within five years and no longer than fifteen years, AI will have exterminated humankind or will be using AI-directed smart robots to enslave everyone. Gulp.

So, is there anything else I can say nice about AI? Glad you asked! As reported in the May/June 2025 journal issue, three of the largest (and smartest?) AI programs, ChatGPT, Perplexity, and Copilot ranked *Missouri Medicine* in the top three state medical journals in the United States. Actually, all three AIs ranked *Missouri Medicine* as the top state journal but I'm far too modest to share that.

Being #1 is a tough act to follow so I'll conclude by thanking MSMA and its dues paying members for their 121-year support of *Missouri Medicine*. For all of its national prominence our journal is only a two-horsepower engine. Lizabeth "Liz" R. S. Fleenor, BJ, MA, is our managing editor and a consummate electronic wizard. She puts each issue together with great exactitude and consistent visual appeal. Liz is a joy to work with. Our skills are complementary and supplementary. We are yet to have our first disagreement. AI will never replace Liz.

I have been editor of this esteemed journal for a quarter of a century. The pay isn't great (zero dollars and I personally pay full MSMA active dues). Especially since I retired from clinical ophthalmology in 2023, it is an enormously intellectually stimulating and rewarding position. I thank MSMA and its dues paying members for the great honor of being the editor of your esteemed medical journal. As editor I also feel vaguely uncomfortable about AI commandeering my job.

2026? Bring it on! We're number 1!

**AI was not used for any part of this editorial, but I have about three and a half hours of my time invested in it.* **MM**

# When the Messengers Are Targeted: Protecting Physicians and Scientists in an Era of Public Distrust



*by Shikha Jain, MD*

***When physicians and scientists feel safe to speak truthfully, patients benefit, communities thrive, and society grows stronger.***

## When Science Feels Under Siege

For most of modern history, physicians were among the most trusted professionals. When we spoke, people listened—not because of who we were, but because of what our training represented: expertise, evidence, and service. In recent years, however, that relationship has changed. The rise of social media, the politicization of health, and the rapid spread of misinformation have transformed the way the public engages with science.

The conversation about health has moved online—and with that shift has come new visibility and new risk. Physicians and scientists who share research findings or clinical insights now face an unexpected hazard: personal attacks, online abuse, and harassment.



Shikha Jain, MD, FACP, is Associate Professor of Medicine, University of Illinois Hospital, Associate Director of Communication Strategies, University of Illinois Cancer Center and Founder, Women in Medicine®.

And while these types of attacks and heated rhetoric are often categorized under a political umbrella, in truth this is not about politics. It is about professionalism, civility, and the growing challenge of communicating science and upholding our Hippocratic Oath to "Do No Harm" in a skeptical and often hostile environment. What previously felt like a necessary part of our professional careers—educating the public and advocating for the health of all—has now become a space many feel unsafe participating in.

And this extends beyond the public sphere and can sometimes even infiltrate the exam room, when providing medical advice based on science to a patient can itself turn into a battlefield.

## When Publishing Makes You a Target

When I first began writing about gender equity in medicine, I expected disagreement. What I did not expect were emails calling me a fraud, or messages questioning whether women belonged in leadership. None addressed the data; they were designed to silence. At first, I thought my experience was rare. But in 2021, I coauthored a *JAMA Network Open* study, "Prevalence of Personal Attacks and Sexual Harassment of Physicians on Social Media," which was one of the first peer-reviewed investigations to quantify the extent of online harassment targeting physicians.[1] We found that nearly one in four physicians surveyed had experienced personal attacks, and one in six had faced sexual harassment.

That same week, our team published a companion op-ed in *STAT News* to humanize those findings, sharing firsthand stories of physicians—particularly women—who had been targeted after posting about vaccines, equity, or public health.[2] The response was immediate and sobering. Dozens of clinicians reached out describing similar experiences: threats after publishing research, abusive messages following media appearances, and personal attacks for simply sharing accurate medical information. What began as an effort to document online behavior revealed something deeper—a growing hostility toward those who speak publicly for science.

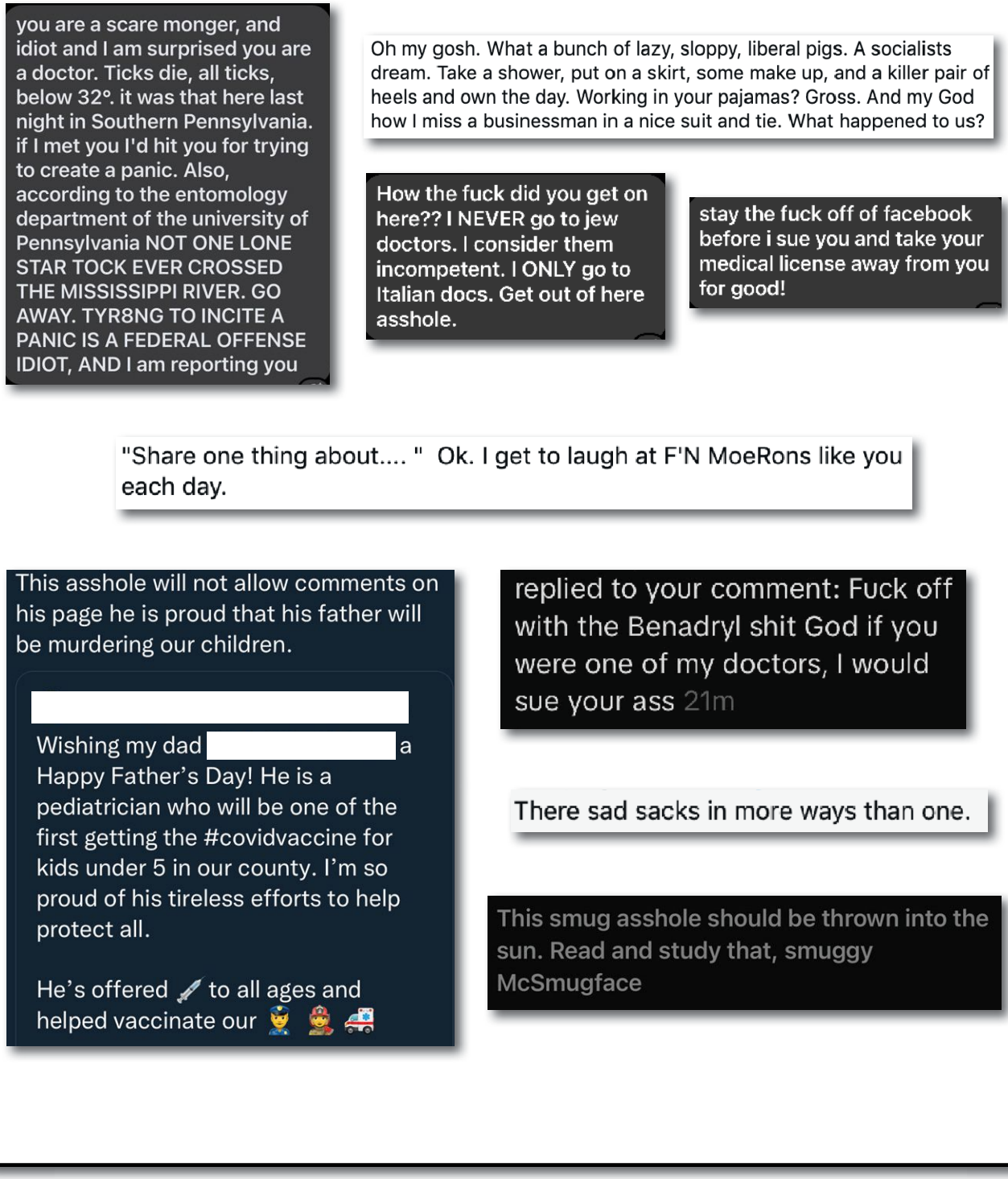
In 2023, our team expanded on this work in another *JAMA Network Open* study, "Physician and Biomedical Scientist Harassment on Social Media During the COVID-19 Pandemic."[3] Among more than 350 respondents, two-thirds reported harassment and one in four women reported sexual harassment. Those who regularly communicated about public health or misinformation were the most frequent targets. Together, these studies confirmed what many of us already sensed: public communication—once viewed as an extension of academic service—now carries both professional and personal risk.

## A New Kind of Hostility Toward Science

Harassment of scientists is not unique to medicine. A 2022 *Nature Human Behaviour* analysis found that researchers in many fields have faced online abuse, coordinated smear campaigns, and even threats of violence after sharing their work publicly.[4] In medicine, this hostility has taken on a deeply personal dimension.

Physicians like Dr. Peter Hotez, Dr. Rochelle P. Walensky and Dr. Anthony Fauci—individuals who have spent their careers advancing science and public health—have become lightning rods for vitriol. All have endured threats, harassment, and misinformation campaigns simply for communicating evolving data. Their experiences are emblematic of what happens when experts become targets rather than trusted guides. At the same time, false claims have circulated suggesting that physicians receive "kickbacks" for recommending vaccines and other evidence-based treatments. There is no factual basis for these accusations. Yet these myths persist and spread rapidly online—while many of those promoting anti-science narratives profit from books, supplements, and unscientific "alternative health" products that in some cases are dangerous and detrimental to health. The result is a troubling inversion: those promoting misinformation are rewarded, while those advancing evidence are attacked.

## Selected Screenshots Contributed by Author: "Prevalence of Personal Attacks and Sexual Harassment of Physicians on Social Media"



## When Dialogue Turns to Vitriol

Scientific disagreement has always been part of progress. Debate refines ideas, strengthens methodology, and clarifies truth. But what we are witnessing now is not debate—it is contempt. The tone of discourse has shifted from inquiry to outrage. Physicians who share clinical data may be accused of bias or corruption. Scientists who advocate for evidence-based interventions are dismissed as elitist or self-serving. Social media magnifies these attacks. A *JAMA Network Open* analysis of physician tweets found that women physicians received significantly more hostile or sexualized comments than men posting similar content.[5] Another study noted that female scientists are more than twice as likely as men to experience targeted online harassment.[6] This escalating hostility undermines trust not only in individual experts but in the scientific process itself.

## The Toll on Individuals and On Science

The consequences are far-reaching. Individually, harassment creates fear, anxiety, and fatigue. Physicians report deleting accounts, avoiding public appearances, or declining to publish on controversial topics.[7] It silences not only their voices but their contributions to the scientific record.

Systemically, this erosion of participation distorts the conversation. When thoughtful experts withdraw, misinformation fills the void. Research shows that simply witnessing harassment of scientists diminishes public confidence in science.[8] The cumulative effect is a feedback loop of distrust: fewer experts speak publicly, misinformation spreads more easily, and the public grows more skeptical of expertise.

## Why Certain Voices Face Disproportionate Risk

Harassment does not affect all scientists equally. In medicine, gender and race amplify the risk. Surveys published in *Annals of Internal Medicine* and P*sychiatric News* reveal that women physicians experience harassment at nearly double the rate of men.[9,10] Online, that imbalance becomes even more visible. Women and minority physicians are more likely to face personal or appearance-based attacks when presenting data or offering expert commentary. This is not merely unfair—it is dangerous. A lack of diverse voices weakens the scientific conversation, limits perspectives, and diminishes the quality of care we provide to patients. When harassment drives certain groups out of the public sphere, we lose both representation and innovation.

## The Institutions That Shape Science Must Adapt

Academic centers, journals, and scientific organizations were built to safeguard the integrity of research. Today, they must also protect the people who produce it. Few institutions have clear procedures for addressing harassment of authors or faculty. Victims are often told to "ignore it," or to take a break from social media—responses that place the burden on the individual rather than the system.

Science cannot thrive in an environment where its contributors feel unsafe. Protecting researchers is not a public relations concern; it is an ethical obligation.

## Constructive Steps Forward

This challenge demands a collective response. Every stakeholder—scientists, journals, institutions, and the public—has a role to play.

### *What Scientists Can Do*

- Communicate clearly and transparently. Avoid jargon, share context, and acknowledge uncertainty. Precision builds credibility.
- Engage respectfully, even under pressure. Model the tone we wish others would adopt.
- Seek community. Support networks—both formal and informal—can reduce isolation and offer guidance when harassment occurs.[10]
- Document and report threats. Silence emboldens aggressors; documentation empowers action.

# *Missouri Medicine* Author Repeatedly Threatened

*by John C Hagan, III, MD, Editor*

> ***"Dr. Hagan, people are calling my office and threatening me and my staff about that article I wrote for Missouri Medicine. They send me emails and letters. I'm very frightened."***

The previous article written by Dr. Shikha Jain, MD, is on the subject of harassment of authors.

*Missouri Medicine* has had one very disturbing incident in which an author was repeatedly threatened following her article's publication in our journal. The vehement actions were triggered by primitive and violent religious practices at odds with gender equality and modern medical care.

The *Missouri Medicine* author's office received numerous obscene and intimidating calls threatening physical harm. Emails and letters were also sent to the author's home.

Prior to this incident, our journal regularly published email addresses of the corresponding author. After learning of the threat, *Missouri Medicine* immediately halted the publication of author email addresses.

*Missouri Medicine* also contacted PubMed explaining the situation. The author's name and email address were removed from PubMed's indexed copy. And, in view of on-going concern about the author's safety *Missouri Medicine* will not disclose either the article or the author.

For articles likely to draw vitriol, we may need to start using pseudonyms. This is another sad commentary on the violent world in which we live.

### *What Journals Can Do*

• Adopt and publicize anti-harassment policies. Clear procedures reassure authors that their safety matters.

• Provide editorial guidance. Help authors frame sensitive findings responsibly and anticipate misinterpretation.

• Stand with authors. When harassment occurs, public statements of support send a powerful message that facts are not up for intimidation.

### *What Scientific Institutions Can Do*

• Treat harassment as a workplace safety issue. Create dedicated reporting mechanisms, rapid-response teams, and access to counseling.

• Educate leadership. Chairs, deans, and editors should understand how online abuse manifests and how to respond.

• Reward responsible public engagement. Academic promotion criteria should recognize evidence-based communication as a form of scholarship.

### *What the Public Can Do*

• Seek credible sources. Follow professionals and peer-reviewed outlets rather than influencers or unverified accounts.

• Pause before sharing. False information spreads faster than truth—but only if we enable it.

• Value civility. Asking hard questions is part of progress; attacking those who answer them is not.

• Remember intent. Most scientists and physicians enter public dialogue to help, not to profit or divide. They are our neighbors, educators, and caregivers.

### *What We Can All Do*

• Promote empathy. Behind every article, post, or policy recommendation is a human being trying to make the world healthier.

• Rebuild trust through transparency. Acknowledging uncertainty does not weaken science—it strengthens it.

• Refuse to normalize hostility. We can disagree passionately without demeaning personally.

## Restoring Civility and Trust

Civility is not a sign of weakness; it is a professional discipline. Physicians and scientists must continue to model what evidence-based, respectful disagreement looks like. The public's faith in medicine will not be rebuilt overnight. But every act of professionalism—every measured explanation, every transparent correction, every respectful interaction—helps restore confidence.

Trust is cumulative, and so is its erosion. Each conversation matters.

## A Culture Worth Protecting

Every physician, scientist, and educator are part of a centuries-long tradition of inquiry and service. That tradition depends on the free exchange of ideas and the safety of those who share them.

Harassment—whether in person or online—undermines that foundation. It replaces dialogue with intimidation, and collaboration with fear. The remedy is not silence, but solidarity. We must reinforce the culture that makes medical progress possible: one grounded in respect, transparency, and a shared commitment to truth. We can disagree without disparaging, debate without demeaning, and communicate without attacking. And when a colleague is targeted for contributing to that dialogue, we can—and must—stand beside them.

## Speaking Safely, Speaking Together

The challenge of our time is not that the public has questions about science. It is that those best equipped to answer sometimes no longer feel safe doing so. We can change that. By supporting the people who speak for science, rejecting hostility, and recommitting to civility, we can ensure that evidence—not outrage—guides public dialogue.

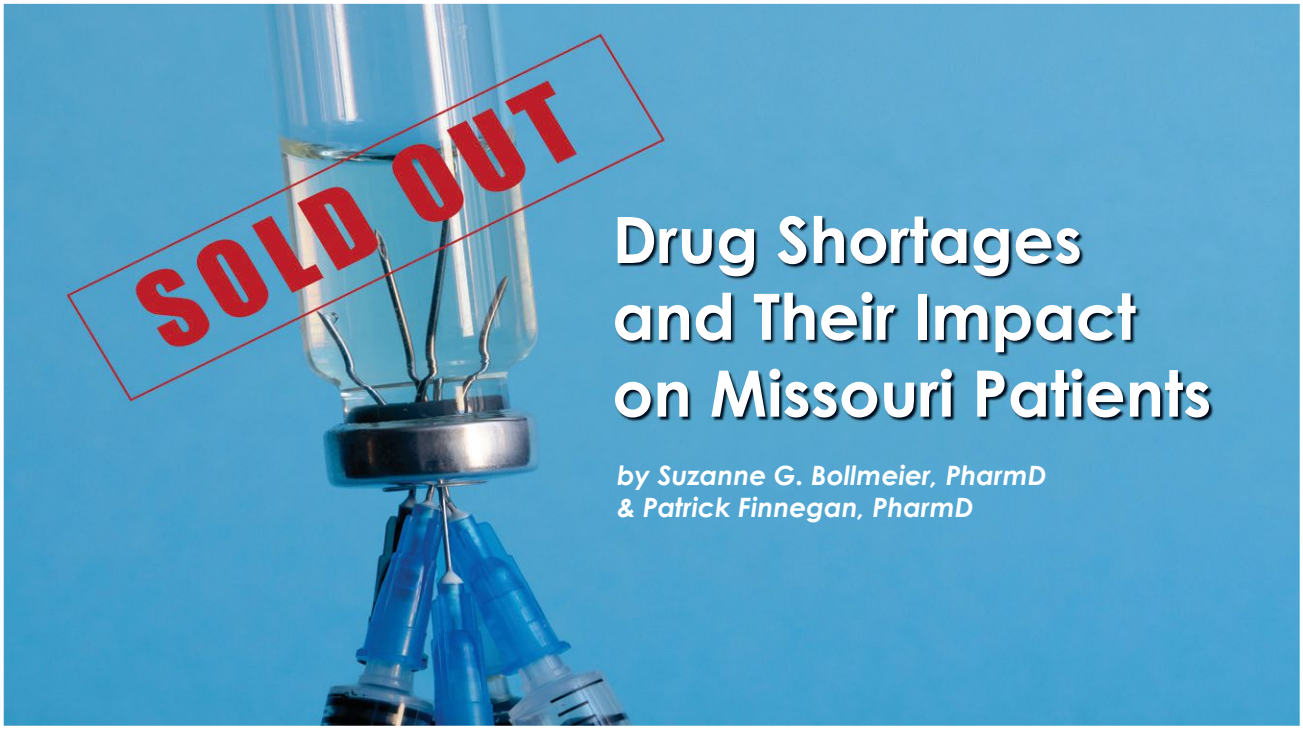
When physicians and scientists feel safe to speak truthfully, patients benefit, communities thrive, and society grows stronger. The future of public health depends not only on innovation, but on the safety of those who dare to share it. Protecting science begins with protecting its messengers.

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## Editor's Note

Social media examples are actual screenshots from the author, and author's research. Actual verbiage is displayed from the screenshots. Identities and avatars are blocked. **MM**




# Drug Shortages and Their Impact on Missouri Patients

*by Suzanne G. Bollmeier, PharmD & Patrick Finnegan, PharmD*

**On a global scale, there is a need for a better organized management system to regularly monitor, update key stakeholders, and better direct the global drug supply.**

## What is a Drug Shortage and What Causes Them?

A drug shortage is an issue affecting how a pharmacy prepares or dispenses a drug or influences patient care (because the prescriber must use an alternative agent) due to limited supply.[1] The Federal Food, Drug, and Cosmetic Act defines a drug shortage as a period of time when the demand or projected demand for a drug within the United States (US) exceeds the supply of the drug.[1] When a drug shortage happens, drug therapy can be compromised, medical procedures can be delayed, and even medication errors can happen.[2]



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Drug shortages can occur for a multitude of reasons.[3] The most common reason for a drug shortage is manufacturing quality issues. Other reasons include production delays, or delays in getting raw materials and components of the drug from their suppliers. Sudden or unexpected increase in demand can also cause a shortage. Manufacturers can also discontinue production of drugs making them in short supply.[4] Natural disasters can also impact production facilities which can impact drug shortages. This was seen most recently with Hurricane Helene and Baxter's North Carolina facility that produced IV fluids.[5]

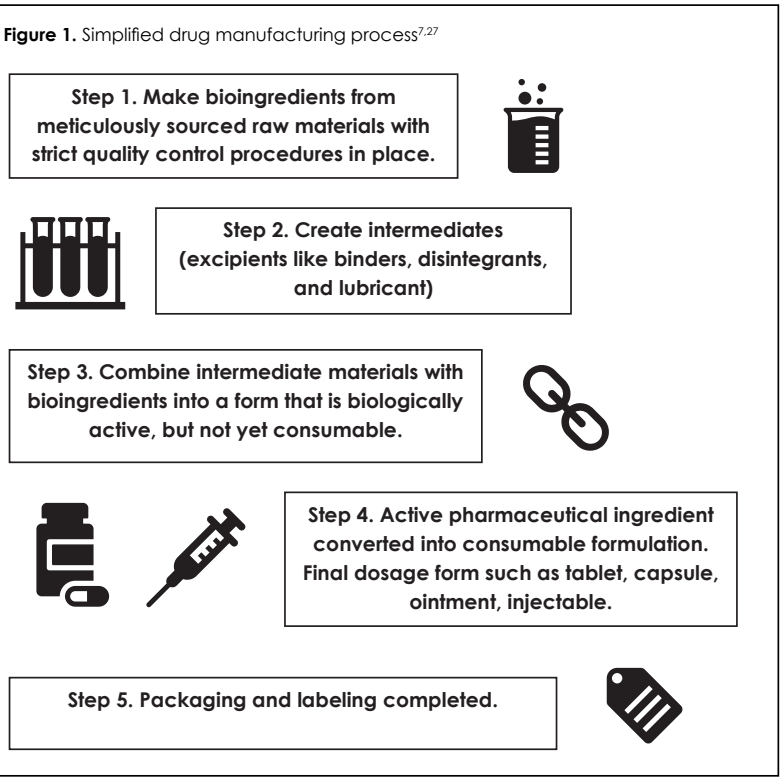
## Are Drug Shortages Common and Why Do They Matter?

The Food and Drug Administration (FDA) keeps track of drug shortages. They routinely receive information from drug manufacturers about their ability to supply the market. The FDA considers a drug in short supply when it is not meeting needs of current demand, or if the supply is not forecasted to meet a projected demand for a drug.

According to the American Society of Health Systems Pharmacists (ASHP) the US is experiencing an active drug shortage for approximately 270 medications. This is down from 323 in the first quarter of 2024.[6] More than a third of these shortages (41%) began in 2022 or earlier. Shortages of critical lifesaving fluids still remains a concern following the Baxter manufacturing issues experienced after Hurricane Helene.

Drug shortages matter to Americans because we are the world's largest pharmaceutical drug market. Nearly 70 percent of Americans are on at least one prescription drug, and more than half take two.[7] The US has less than five percent of the world's population, yet funds roughly 75% of global pharmaceutical profits.[8]

**Figure 1.** Simplified drug manufacturing process[7,27]




## Where Does America Get Its Prescription Drugs?

It is no secret that the US relies on foreign countries to import prescription drugs. Drug manufacturers are not required to inform the public where drugs, or their active pharmaceutical ingredient (API) originates from. The FDA, does however, regulate which drugs can be imported.[9] To do so, prescription drugs must meet or exceed minimal but stringent regulatory standards for safety, purity, and efficacy set by the FDA.[7] Customs and Border Protection, along with the FDA, regulate the physical importation of drugs; however, they have differing definitions of where a drug originates. The FDA states the country of origin is where the drug is packaged. Customs and Border Protection states the country of origin is where the active pharmaceutical ingredient is produced. As mentioned, the vast majority of drugs consumed in the US are produced abroad and imported from foreign countries by their manufacturers.[9] Of the top 100 Medicare Part D drugs, a majority are produced outside the US (68% of finished drug formulations (FDFs), and 78% of APIs.[9] This really poses no health threat to Americans; almost all imported brand name drugs are made in countries with manufacturing safety practices equal or superior to those found in the US.[9] Countries that import the majority of Medicare Part D medications include: countries in the European Union, Canada, Japan, Singapore, Switzerland, and the United Kingdom.[9,10] The single largest exporter of branded pharmaceuticals to the US is Ireland.[11]

The generic drug market is booming. It is thought that more than 90 percent of prescriptions in the US are currently dispensed as generic drugs.[7] Numerous reports have suggested the manufacturing of generic drugs intended for US consumption is increasingly occurring abroad, particularly in China and India. To protect American consumers, the FDA mandates that drugs must meet legal requirements for safety. They also must possess the quality, purity, identity, and strength that they are represented to have.[7]

See Figure 1 for a summary of how a drug is produced before importation to the US.

## Overview of the Problem

Most providers will be impacted by drug shortages. The most recent shortage of GLP1 receptor agonists in the past few years is in the forefront of most of our minds. This is due to this class of drugs having an explosion of popularity due to their clinically significant effects on weight. It is important to remember, many more drugs are in shortages, including anti-cancer drugs, and IV medications.

With the GLP1 agonists like Wegovy, Ozempic, and Mounjaro, efficacy was like nothing the public had ever seen. More and more, patients became interested in these blockbuster weight loss and glucose lowering drugs, so demand spiked. Even before some of these agents had an FDA approval for weight loss (semaglutide), providers were writing off-label prescriptions so patients could use the drug for weight loss. This put pressure on supplies not only for weight loss, but for the patients it was originally intended; those with diabetes. The demand for these drugs was higher than supply. A semaglutide shortage started in 2022[12] due to increased demand. Luckily, by February 21, 2025 the FDA confirmed with the manufacturer of semaglutide that this shortage has resolved.

While these drugs were in short supply, the FDA allowed pharmacies and prescribers' offices to "compound" semaglutide. That allowance has now also ended. Compounders had until May 22, 2025, to stop compounding this medication for patient use.[13]

## Current Shortages

There will always be ongoing challenges with drugs on the shortage list. The most significant and recent shortage hospitals have had to deal with was the IV fluids shortage following Hurricane Helene in 2024. Baxter International's North Cove plant was flooded and rendered inoperable following the storm. This plant was responsible for manufacturing about 1.5 million intravenous (IV) bags which constitutes an estimated 60% of the IV bags used in the US. This led to critical shortages in a variety of solutions, but mostly lactated ringers, concentrated dextrose solutions, and peritoneal dialysis solutions. Many hospitals were reporting having no more than 10 days of IV fluids on hand during this shortage. While Baxter was able to quickly get the plant up and running again, the restrictions and shortages on IV fluids lasted into the summer of 2025.[14]

At the time of the drafting of this report, a shortage of another popular medication used in the hospital setting—injectable lorazepam—looms on the horizon. There are a series of events that led to this shortage. The primary cause was the closure one of the primary manufacturers of the medication. This led to supply/demand mismatch with the remaining producers. Added to this pressure were manufacturing delays as companies retool their production to try and meet demand. As this is the primary medication used for both inpatient seizure management and for alcohol withdrawal, this has the potential to have significant effect on Missouri's medical centers. ASHP has encouraged the identification of therapeutic alternatives and restricted use to help to mitigate the impact of the shortage.[15]

Another emerging shortage that is sure to be felt by both providers and patients across Missouri is glargine insulin. Lantus insulin and it biosimilars Basaglar, Rezvoglar, and Semglee remain the most prescribed long-acting insulin in the US.[16] Products listed in this shortage include both Lantus and Semglee in both of their dosage forms; vials and pens. Reasons given for this include increased demand due to the withdrawal of detemir insulin from the market in 2024, and construction of expanded production facilities which will limit production through the remainder of 2025. For now, Basaglar and Rezvoglar supplies remain stable. Hospitals have already begun to anticipate variable availability, utilizing alternative long-acting insulins like insulin degludec.

Both of these shortages illustrate how fragile the pharmaceutical supply chain in America is. As companies limit or stop production of low margin drugs, remaining companies have little capacity to absorb the increased demand, and pharmacies are left having to navigate these shortages.[16]

## Practical Approaches to How to Deal with a Shortage

In response to the constant threat of significant drug shortages, ASHP has developed guidelines to assist hospitals and healthcare systems to plan for and navigate the disruptions in supplies. While there are a number of recommendations provided in the guidelines, the most important is to establish a multidisciplinary team to handle the shortages. These teams will look slightly different from hospital to hospital and system to system, but the task is the same: to develop policies and procedures for identifying, assessing, and ultimately mitigating the shortage. They also stress the importance of inventory management, as knowing usage patterns will allow you to assess the supply at hand.[17]

The committee will, through their assessments, develop impact reports and recognize therapeutic alternatives. They will then be responsible for identifying and communicating procedures to help providers navigate these new restrictions. This group should also monitor use patterns to be sure that shortages have minimal impact on patient care, and quickly adapt any restrictions based on

this ongoing review. ASHP also recommends that this committee report any shortages using the Food and Drug Administration's Drug Shortage Program along with any necessary regulatory bodies.[17]

While ASHP has a plan to manage shortages as they occur, what is lacking is a plan to manage the supply chain in order to limit the frequency and severity of these shortages. In order to do this, the US will need to increase supply chain transparency by maintaining a national database of vulnerabilities to the supply chain for critical drugs (defined as widely used agents where there are limited to no therapeutic alternatives). These vulnerabilities stem from a lack of diversity in the countries who supply medications. By incentivizing domestic production, ensuring redundancy of those facilities, and better identification of potential bottlenecks to supplies can provide some protection from critical shortages.[18] In addition to manufacturing changes, the US government should undertake a thorough revision of the Strategic National Stockpile.[19] This would involve changes to what is included along with changes to how healthcare systems can access the stockpile in times of need.[19]

## What Role Will Tariffs Play?

In April 2025, President Trump threatened to impose a 25% tariff on any pharmaceuticals imported into the US. His incentive was to 1) create jobs, 2) bring manufacturing back to the US, and 3) potentially improve national security by relying less on foreign countries for such products.[20] It is unclear whether these incentives will be realized by imposing tariffs on pharmaceuticals. Experts mostly agree that tariffs will increase drug prices. It can be quite complex with an industry—like the pharmaceutical industry—that has a product (pharmaceutical) that has to go through many steps to be produced (Figure 1). Also, besides manufacturing, drugs go through importation, distribution, and transport to a retail pharmacy. All of these steps can potentially absorb some of the cost of a would-be tariff and this can potentially lessen the effect felt by the patient or consumer.[21]

It is still unknown, however, if this will be the case, as a large percentage of APIs for common generic drugs such as many antibiotics are sourced from China, while much of the final pill production (Finished Dose Form, FDF) is done in India.[21] Another unknown in this: is what, if any, increase will be passed on to those insured in the form of a co-payment. Insurers typically set contract prices for drugs a year ahead. So, until there is more certainty over tariffs, we may not see price changes being reflected until 2027. [22]

The effects of tariffs on pharmaceutical prices will be contingent on how those throughout the supply chain react. Each step in the chain must choose how much increase in cost to pass on, but also how to pass it on. This could be through increased pricing, a surcharge, redesigning a product, or a shift in supplier (i.e., getting product from a country not involved in the trade war or that can supply it cheaper).[21]

Nearly everyone involved in getting a drug manufacturered and to a patient are opposed to tariffs. This includes drugmakers, pharmacies, and wholesalers.[23]

## What Effect Will All This Have on Drug Shortages?

Again; unclear. A reduction in importation of drugs could trigger shortages. It is thought that even if drug manufacturers pledge to bring more pharmaceutical manufacturing to the US, this will take time. For example, NovoNordisk recently announced a $4.1 billion investment in its current North Carolina plant to boost production of Wegovy and Ozempic. However, this isn't expected to be open for several years.[24] Others estimate it could cost $1 billion to build a drug manufacturing plant and take three to five years to set it up.[23] This would mainly be for branded items; not generic. With higher tariffs on generic drugs, shortages of essential medications will worsen. This can affect patient's health and livelihood.[22] Generic manufacturers face a lot of competition and low margins. The price of a generic drug is very close to the cost of production. To build a manufacturing facility in the US for generic drugs would be high and certainly higher than to do so in India or China. We may end up with more drug shortages for these medications as generic manufacturers choose to simply leave the US market.[22] This was seen with the generic cancer drug, Cisplatin. In 2023, Cisplatin experienced a significant shortage due to the closing of the main plant that produced this generic drug in India in 2022. This was due to quality control issues. Many cancer patients across the country had their treatments modified due to this unfortunate shortage.[25]

It is thought that tariffs will also impact injectable generic product supply because a small ripple, or disruption, in supply can have a big effect. It will be difficult for injectable generic manufacturers to pass the

tariff cost on, however because of inflation penalties. For Medicaid programs, you can't increase the cost of a drug faster than the rate of inflation. Also, if you are using a group purchasing organization (GPO) or a contract through a distributor, the price may be set for quite some time. Again, the answer may be for that generic manufacturer, to simply leave the US market.

This could leave an even smaller number of companies producing generic drugs, exacerbating shortages and supply.[26]

## Conclusion

Drug shortages have always been a part of pharmacy. As prescription drug use among Americans continues to rise, the impacts of these shortages are felt on a much broader scale. A much less reliable supply chain coupled with fewer manufacturers extends these shortages from weeks to months. Add influences from tariffs, embargos, and/or sanctions and the risk to the overall drug supply is even further increased. While individual pharmacists and health systems have little impact on the cause of shortages, it is the responsibility of these providers to plan and react swiftly to mitigate their impact. Organization of committees where interdisciplinary teams can answer these challenges through the use of restrictions and therapeutic alternatives will minimize the effect on patient care. On a global scale, there is a need for a better organized management system to regularly monitor, update key stakeholders, and better direct the global drug supply.

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MM

# The New Landscape of Medicine

*by Brian Biggers, MD*

***We must move beyond passive frustration and become active stewards of our own future.***

I am now more than halfway through my presidency, and just as I mentioned in my acceptance speech, a year passes far faster than one expects. In recent months, I have participated in candidate receptions, attended the MSMA Council Meeting, and made my inaugural visit to Washington, DC for the American Medical Association Interim Meeting. Hard to believe it took me 50 years to make it there. I spent a beautiful fall day walking the Capitol Mall, taking in the monuments—an ideal backdrop for reflection.

At the AMA Interim Meeting, two moments stood out and made me step back to consider the current landscape of medicine. The first was the AMPAC session, where we discussed today's volatile political environment and what it means for us as a profession. The second was hearing Mehmet Oz, MD, Administrator of the Centers for Medicare and Medicaid Services, address the AMA's House of Delegates. Both experiences were thought-provoking, and both forced me to consider how we move forward as physicians.

This is not an article advocating for any political party. Each person has the right to their own beliefs. But whether we acknowledge it or not, advocacy is part of medicine. Advocacy is a subject that medical schools seldom highlight or teach unless students actively pursue it themselves. And because advocacy can feel uncomfortable, or even contrary to our nature, we often avoid it. Yet avoiding it has consequences.



**Brian D. Biggers, MD, FACS,** is a breast surgical oncologist and general surgeon with CoxHealth in Springfield, Missouri, USA, and the 2025-2026 MSMA President.

When we do not participate, others make decisions for us. A considerable number of contemporary medical challenges stem from insufficient engagement. Call it apathy. Call it fatigue. The result is the same.

We have also allowed ourselves to become divided. Too often I hear physicians criticize organized medicine over a single issue or a vote that did not go their way. That fragmentation weakens us all. No system is perfect, and the House of Medicine is no exception. I remind my medical students that it takes all of us to make this profession function. We choose our specialties based on our interests and thank goodness we do. I am grateful for my colleagues who chose specialties I did not!

Consider this: attorneys in Missouri must join the Bar to practice. That is approximately 30,000 unified member voices. That strength translates into real influence when they advocate. Meanwhile, medical organizations across the country are struggling with membership. And it is not simply about cost. Even if their organization pays for their membership fees, some physicians choose not to participate.

But nothing in nature, or medicine, remains stagnant. We must adapt. Our profession is facing significant threats: expanding scope-of-practice battles, the need for meaningful Medicare reform, and the endless headaches of prior authorization. The time to engage is now.

We must move beyond passive frustration and become active stewards of our own future. Either we advocate for our practices and the policies that shape them, or we leave those decisions entirely in the hands of others. And if we choose the latter, we will have no one to blame but ourselves. **MM**



# Missouri's 2026 Legislative Session: A Pivotal Year for Physician-Led Care

*by Rachel Bauer, MPA & Jacob Scott, MA*

***We urge all members to stay engaged—your voice is essential in shaping policy that affects every corner of our state.***

As Missouri prepares for the 2026 legislative session, the landscape of healthcare policy is shifting in profound ways. With the federal Rural Health Transformation Program (RHTP) now officially submitted to the Centers for Medicare & Medicaid Services (CMS), the state stands at a crossroads. The decisions made in Jefferson City this year will shape not only the future of rural healthcare, but the integrity of physician-led care across Missouri.

For members of the Missouri State Medical Association (MSMA), this session presents both significant challenges and unique opportunities.





Rachel Bauer, MPA, is Director of Government Relations. Jacob Scott, MA, is Director of Legislative Affairs. Reach them at advocacy@msma.org

Our legislative priorities remain rooted in protecting patients, preserving professional standards, and ensuring that physicians remain at the helm of care teams. But with new federal funding streams, evolving care models, and aggressive scope-of-practice campaigns from mid-level providers, the stakes have never been higher.

## Building on Previous Years' Momentum

MSMA will reintroduce and be pivotal players in several key ideas from previous sessions that ultimately failed to cross the finish line. These proposals reflect our commitment to strengthening Missouri's healthcare system through smart, physician-led, patient-centered policy. Among them:

- Title protection legislation to ensure transparency in provider credentials and prevent misleading representations of training and expertise.

Patients don't need to play a guessing game on who is taking care of them in a clinical setting. We are filing legislation to ensure only physicians can use the title of doctor or physician in a clinical environment.

• Reforming the use of covenants-not-to-compete and other restrictive contract tools for nonprofit hospitals.

Fixing this issue will help keep physicians in the communities they are committed to serving.

• Medical licensure protections to uphold the rigorous standards that define the physician profession and safeguard public trust.

We will also be a part of other ideas to grow and protect the physician pipeline, such as GME funding, monetary incentives for rural physicians, as well as taking a serious look at the role IMGs can play.

• An amplified interest in expanding telehealth and AI usage in the Missouri Rural Health Transformation Program (RHTP) application.

We will work to see that telehealth remains anchored in physician oversight, ensuring that virtual care maintains the same quality and accountability as in-person visits.

These bills are not just legislative housekeeping—they are foundational to preserving the integrity of the practice of medicine in Missouri. Refiling them is a strategic move to build on existing momentum and keep patient safety at the forefront of policy discussions.

## Scope of Practice: A Renewed Push from Mid-Level Providers

This session is expected to bring an intensified push from nurse practitioners, certified registered nurse anesthetists (CRNAs), optometrists, and other non-physician groups seeking to expand their scope of practice. Their arguments will be amplified by the RHTP's emphasis on rural access and workforce flexibility.

MSMA will vigorously oppose any legislation that compromises patient safety by removing physicians from the care team. We believe that expanding scope without equivalent training or oversight risks fragmentation, misdiagnosis, and lower standards, especially in underserved areas where clinical complexity is high and resources are limited.

Our position is clear: team-based care must be physician-led. The title "doctor" carries weight for a reason. Years of medical education, residency training, and board certification are not interchangeable with other pathways like online courses or programs. Patients deserve clarity, accountability, and the highest standard of care—regardless of geography.

That being said, we have seen a shift in the legislative mood. It is no longer acceptable to simply say no without alternatives. So, buckle up as we are going to be throwing out some ideas in the scope-space that we think are perfectly reasonable and are a must if lawmakers want to let folks with less education and training play doctor. These ideas include those who wish to engage with patients like doctors to be licensed and accountable to the Board of Healing Arts. We also believe that patients deserve to know exactly who they are entrusting with their health. We will require all mid-levels to obtain informed consent from patients. We may also tie their ability to play doctor to service in a truly rural community.

## RHTP: Reforming Rural Care—With Guardrails

Governor Mike Kehoe's submission of Missouri's RHTP proposal marks a major milestone in the state's healthcare transformation. The RHTP will be the litmus test for healthcare policy moving forward. Backed by up to $250 million annually in federal funding, the program seeks to reimagine rural healthcare delivery through:

- Expanded access to primary, behavioral, and maternity care.
- Incentives for care coordination and sustainability.
- Promotion of telehealth and technology adoption.
- Workforce development across rural communities.

While the program offers transformative potential, it also introduces risks. Flexibility in staffing models and care delivery could be exploited to sideline physicians in favor of less-trained providers. MSMA is committed to shaping the implementation of RHTP to ensure that reforms enhance—not erode—quality and safety. You should be aware that part of the scoring criteria for how the funding will be awarded is based on how expansive scope of practice laws are for mid-levels. Though it is only a fraction of the total points, the perception will be that scope expansion is a must for us to get as much of the RHTP funding as possible. Unfortunately, perception is reality.

We see this moment not just as a defensive posture, but as an opportunity to lead. MSMA will advocate for physician-led innovation in rural care models, ensuring

that new funding streams support sustainable, high-quality care—not shortcuts or cost-cutting measures that compromise outcomes.

## Advocacy in Action: Shaping the Future, Not Just Defending It

MSMA's advocacy strategy this coming session will be proactive, coordinated, and member-driven. We're engaging lawmakers early, building coalitions with patient safety allies, and offering solutions that align with RHTP goals while protecting care quality.

Part of our approach has always been and will continue to focus on legislative outreach, educating policymakers on the value of physician-led care. We are also mobilizing our grassroots to activate physicians and patients across the state.

Please let us know if you are interested in joining our advocacy efforts! There are many ways you can help including participating in our Physician Advocacy Day on Tuesday, March 3, 2026, volunteering as Doctor of the Day during session, attending and testifying at hearing, or emails or calling your legislators. We are excited to announce this year we are engaging in strategic partnerships with organizations that share our commitment to safety and professionalism. We are forming a coalition with other highly regulated professionals (such as engineers, CPAs, architects just to name a few) who are also under a scope attack.

We urge all members to stay engaged—your voice is essential in shaping policy that affects every corner of our state. Whether through legislative visits, testimony, or community outreach, your involvement strengthens our collective impact.

## A Defining Year for Medicine in Missouri

Missouri's 2026 legislative session is more than a policy cycle—it's a defining moment for the future of medicine in our state. With federal reform underway and scope-of-practice battles intensifying, MSMA stands ready to lead with clarity, conviction, and a deep commitment to the physicians we serve as well as their patients.

We will not be passive observers of change. We will be architects of a healthcare system that values expertise, demands accountability, and puts patients first. With your support, MSMA will continue to be the trusted voice for physicians—and the standard-bearer for quality care in Missouri.






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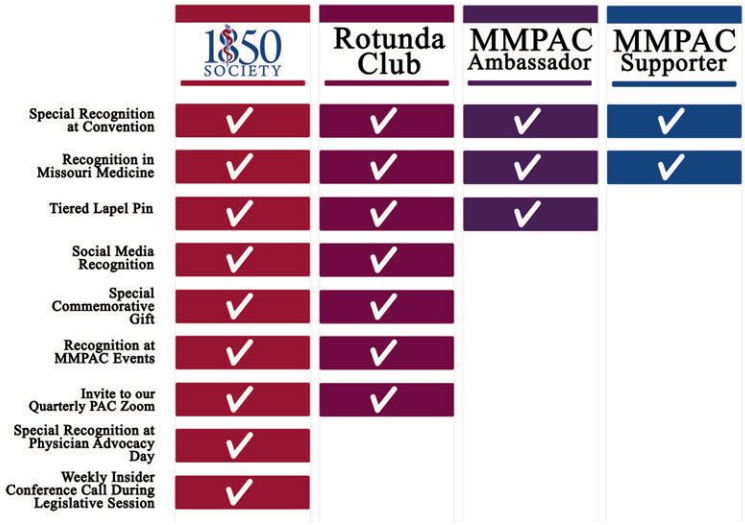
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# Report of the American Medical Association Interim Meeting

*by Charles W. Van Way, III, MD & the Missouri AMA Delegation*

The 2025 Interim Meeting of the American Medical Association (AMA) House of Delegates (HOD) was at the Gaylord Plaza Hotel in National Harbor, MD, near Washington, DC, November 14-18. The Interim Meeting focuses on advocacy, particularly on current and pending legislation, other urgent issues, and ethics.

The AMA president, Bobby Mukkamala, MD, spoke at the opening session. He praised the HOD as representing the best of American medicine. He spoke about the extraordinary pressures put on the physicians on the front lines. He applauded pre-authorization reform. He has a lot of hope about physicians. But we are challenged. Cracks in the healthcare system are affecting physicians. Rural hospitals are struggling. We need a system which promotes preventive health. We need a sustainable payment model, to meet the cost of running practices. We need an adequate workforce. We need to spend less time on administrative tasks and more time with our patients. We need to take care of our own health and mental health. He alluded to his own struggle with brain cancer, and his continuing fight for his own health. Our mission is to restore the health and respect of the medical profession. We must fight for the future of medicine.

The new Executive Vice President of the AMA, John White, MD, talked about our future. What we do here and now at the meeting will shape our future. Our future depends on our credibility. But to solve the problems of healthcare, we must be allowed to do our jobs. Technology is changing our world. But innovation without compassion is the opposite of progress. To unlock the potential of these technologies, physicians must lead the conversation about AI, education, training, and workforce integration in health care. We honor our past by planning our future.

As is usual, the meeting of the Organization of State Medical Association Presidents (OSMAP) was held on Friday afternoon before the opening session. This meeting is always focused on issues of particular importance to the states. Dr. Mukkamala spoke on the challenges of advocacy in a changing political environment. He was supported by David Aizuss, MD, Chair of the Board of Trustees (BOT), and Mr. Todd Askew, Senior Vice President for Advocacy. Shannon Constant, MD, from California, discussed new legislation which gives the Attorney General authority to police the corporate practice of medicine. Steven Davis, from Pennsylvania, reported on a trial of global budgeting of rural hospitals. Gary Price, MD, Chair of the Physicians Foundation, presented results of the latest physician survey. Results were discouraging overall. Physicians reported concerns of stress and symptoms of burnout. There were small improvements in specific areas, such as availability of mental health counseling. Results of the survey can be examined at https://physiciansfoundation.org/newsroom.

Leonard Nelson, the director of the Litigation Center, spoke at OSMAP and at the Litigation Center on the Multiplan litigation. The MSMA has joined this litigation. Determining reimbursement for out-of-network services is a critical issue for insurance companies. MultiPlan, Inc., is a data management



**Charles W. Van Way, III, MD, FACS, FCCP, FCCM**, Missouri/AMA Delegate, and *Missouri Medicine* Contributing Editor, is Emeritus Professor of Surgery, University of Missouri – Kansas City, Kansas City, Missouri, USA.

company which most insurers use to determine reimbursement for out-of-network services. Because the insurers all share data with the company, its recommendations tend to standardize reimbursement and minimize competition. The suit contends that this is an anti-trust (Sherman Act) violation and should cease. The suit will be heard in Federal court in early 2026 and will work its way through the court system.

Dr. Mehmet Oz, Administrator of the Center for Medicare and Medicaid Services (CMS), addressed the HOD. He discussed his administration's priorities in addressing the many problems in Medicare and Medicaid, and in the health system in general. He had encouraging words about the importance of physicians to the system, saying that the new technological tools can improve prior authorization.

The new WISeR (Wasteful and Inappropriate Service Reduction) model for prior authorization will start in January 2026. It is an AI-based system for prior authorization. The AMA has had input in this system. Resolution 827 was adopted to support the development and evolution of this system with continued AMA input.

The HOD considered more than 120 resolutions and reports. The HOD drew 689 of 733 delegates (94%). The review and debate process has improved, making the HOD sessions shorter and more efficient.

"Fix Medicare Now" continues to be an initiative. Congress has indexed physician payments to inflation, although only partially. Go to the website at https://fixmedicarenow.org.

Medical education is a continuing concern of the AMA. Resolutions advocated special treatment for pregnant residents (306, 309), improved work requirements for medical students (301), special mentoring for black male students (308), and equalizing volume of surgical cases and medical procedures with regard to gender and URiM (under-represented in medicine) trainees (311). This last item would represent a significant change in the management of residency programs. The ACGME would have to be involved, as it both sets the rules and collects the data. Resolution 310 addressed the harm resulting from the Flexner Report of 1910, calling for support for establishing medical schools in historically Black and tribal colleges and universities and other minority serving institutions. The objective is to restore opportunities and to increase diversity in the physician workforce.

There was much emphasis on the future of augmented intelligence (AI) in medicine. In 2025, the AMA established a Center for Digital Health and Augmented Intelligence. A three-hour seminar encompassed education, ethics, and medical practice. Resolution 307 called for integration of AI into undergraduate school, residency, and continuing medical education. Other resolutions and presentations addressed implications of various aspects, including ethical questions and use of AI in prior authorization (327) and accountability (823).

A recurring issue is access by International Medical Graduates (IMGs) to resident training and practice in the US. Resolution 304 called for transparency among residencies which use filters in the matching plan to exclude applicants from certain countries or groups of countries. Council of Medical Education (CME) Report 1 discussed alternate pathways available to international physicians. IMGs seeking to start residency in the US on J-1 Visas, or post-graduate employment on H-1B Visas, often find themselves subject to bureaucratic delays. Resolutions 213, 214, and 216 called for streamlining physician immigration. Resolution 313 called for modifying requirements for physicians trained in Gaza, as the AMA recommended for Ukrainian-trained physicians. Both groups from war-torn countries are often unable to provide required documentation. More generally, there were calls to eliminate H1B visa fees and even to advocate a separate visa pathway for physicians.

There was continuing concern for the problems of rural health care, including inadequate payment, physician shortages, hospital closures, and excessive reliance on Medicaid. The AMA is already strongly in support of improving rural care. Rural health systems continue to struggle. Resolution 237 called for protecting and improving rural health. The AMA participates in planning for the new $50 billion Congressional initiative to improve rural health over the next five years.

Emergency departments, particularly in rural areas, are often staffed by non-physicians. The House of Delegates considered Resolution 226, calling for transparency with the term "Emergency Department," and advocating alternative nomenclature for facilities without physicians on duty, such as acute care units or stabilization units. Your delegation stood in principle with the spirit of the resolution, but recognized the legal, regulatory, and financial implications of removing the Emergency Department labeling from certain

facilities. The Board of Trustees will study this complex and multifaceted issue.

Another perennial concern is Medicaid reform. Council for Medical Services (CMS) Report 1 discussed using health savings accounts (HSAs) in Medicaid. However, Resolution 827 called for opposing shift of money within Medicaid to fund HSAs. Clearly, there are arguments against using the HSA model for Medicaid. BOT Report 16 discussed how to preserve Medicaid. While no new solutions were advanced, there was general support for giving more options under Medicaid. But HSAs, tax credits, benefit cuts, and reallocation of resources remain controversial.




MSMA thanks the members who represented Missouri at the American Medical Association Interim Meeting. From left: Drs. Brian Biggers, Elie Azrak, Peggy Barjenbruch, Ed Cabbabe, Charlie Van Way, Ravi Johar, Joe Corrado, Geroge Hruza, Lacey Capetti, Mason Tuttle, and Jay Devineni. Not pictured: Drs. Betty Drees and Joanne Loethen.

More broadly, Resolution 601 called for a study by an AMA-appointed task force to draft in an overall plan for the American health care system. There was a consensus that physicians should lead the effort, although input from other disciplines would be essential. This would put the AMA in a position to set the national agenda. Previous such efforts have failed (consider Clinton Care), but the HOD felt the effort is worthwhile.

Resolution 225 called for the AMA to support Federal legislation prohibiting the corporate practice of medicine. There was a presentation at OSMAP from California, detailing that state's experience with this issue. Laws vary among the states and are often poorly enforced. There was strong agreement that Congress should act. Resolution 230 called for legislation or regulations to prohibit non-compete covenants for physicians.

Council on Ethical and Judicial Affairs (CEJA) Report 1 offered a set of guidelines for unionization and collective action. A majority of the HOD felt that these guidelines were too restrictive. With well over half of physicians being employed, unionization is a sincere consideration. The MSMA is also actively considering this issue.

The HOD considered other issues. BOT Report 8 discussed the possibility of human life extension, emphasizing the ethics of such efforts. Resolutions 603 and 604 dealt with stopping publication of the AMA Journal of Ethics and with maintaining education and fellowships on ethics. Resolution 919 and 925 called for setting standards for the use of vaccines in the face of changing Federal guidance.

Missouri physicians continue to serve in leadership roles. David Barbe, MD, continues to serve as AMA Past President. Jerry Kennett, MD, is on the AMA Foundation Board. Marc Mendelsohn, MD, serves on the Council on Science and Public Health. Charles Van Way III, MD, is President of OSMAP, the Organization of State Medical Association Presidents.

This was the final meeting for Ed Cabbabe, MD, who has led the Missouri AMA delegation for the last 20 years and who is now retiring from the delegation. He will continue to be active in the MSMA.

Your AMA delegation would very much like to hear from physicians throughout Missouri about the issues discussed at the meeting. Records and highlights of the meeting are available on the AMA website, https://www.ama-assn.org/house-delegates/hod-organization/archive-house-delegates-meetings The Annual Meeting of the HOD will be in Chicago, June 5-10, 2026. The AMA continues to advocate for physicians and their patients across the country. **MM**

# Navigating Liability in Virtual Care: Risk Management Strategies for Physicians in a Rapidly Evolving Landscape

*by Kimberly Chew, JD, Colleen Pert, JD & Kathleen Snyder, JD*

***By embracing robust clinical protocols, operational safeguards, and ongoing regulatory compliance, clinicians can mitigate these risks while delivering safe, effective, and patient-centered virtual care.***

## The Transformation of Virtual Care

The COVID-19 pandemic catalyzed a seismic shift in the delivery of healthcare across the United States (US), propelling telehealth and virtual care from niche offerings into mainstream, essential services.[10-12] Practically overnight, physicians and healthcare organizations were required to adapt to new modalities of patient interaction—leveraging video visits, secure messaging, and remote monitoring to maintain continuity of care while minimizing infection risk.[13,14] What began as an emergency response has since evolved into a lasting component of the healthcare landscape, supported by rapid advancements in digital health technologies, clearer regulatory frameworks, and expanded coverage from both public and private insurers—even as certain Medicare telehealth flexibilities enacted during the COVID-19 pandemic expired on October 1, 2025.[15-17, 66]

Today, virtual care is not only here to stay but is also expanding in scope and sophistication. Physicians are using advanced digital tools, FDA-approved remote monitoring devices, and integrated telehealth platforms to deliver care beyond the traditional clinic walls.[18,19] At the same time, federal and state regulators have worked to clarify licensure requirements, reimbursement policies, and privacy protections—creating new opportunities as well as new responsibilities for clinicians.[15-17, 24, 67]

However, this transformation has also introduced a host of novel liability risks. Physicians must now navigate the unique challenges of remote diagnosis, documentation, and patient engagement, all while ensuring compliance with evolving legal and regulatory standards. Understanding these risks—and adopting effective risk mitigation strategies—has become imperative not only for protecting patients but also





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for safeguarding physicians' own professional and legal interests. This article will explore the current landscape of virtual care, highlight key liability exposures, and provide actionable risk management strategies to help physicians thrive in this rapidly evolving environment.

## The Virtual Care Landscape: Modalities and Regulatory Developments

The landscape of virtual care has rapidly expanded, offering a diverse array of technologies and interaction models that enable clinicians to deliver care remotely. For physicians, a clear understanding of these modalities—as well as the shifting regulatory environment that governs them—is essential to providing safe, effective, and compliant virtual care.

Virtual care can be broadly categorized into three principal modalities.[20,21] First, synchronous care involves real-time interactions between patient and provider, most commonly through video or telephone visits. These encounters closely resemble traditional office visits, allowing for immediate communication and clinical decision-making. Synchronous telehealth has become a cornerstone of remote care delivery since the onset of the COVID-19 pandemic, supported by expanded reimbursement and increasing patient acceptance.[6,15,16,17,22,23,24]

Second, asynchronous care encompasses methods such as e-consults, secure messaging, and store-and-forward technology, which allow providers to review patient information and respond at a later time. Asynchronous modalities are often tied to an EHR through patient portals and are valuable for follow-up and the exchange of images or data that do not require live interaction.

Third, remote patient monitoring (RPM) leverages FDA-cleared devices to collect and transmit patient health data—such as vital signs, glucose levels, or cardiac rhythms—from the home to the clinical team.[6,22-25] RPM technologies support proactive management of chronic conditions and facilitate early identification of complications. The Office of Inspector General from the US Department of Health and Human Services (HHS OIG) reported that 94% of Medicare enrollees who used RPM in 2022 did so for chronic condition management.[67] The expansion of RPM has been driven by both the availability of FDA-cleared RPM tools and also new reimbursement pathways. However, there are important questions about device reliability, data management, and clinical oversight that must be considered.[15, 16] Additionally, the HHS OIG has identified risks of fraud associated with RPM.[67]

Alongside these evolving care modalities, the regulatory landscape governing virtual care has undergone significant transformation. After the success of expanded access during the pandemic, many private insurers broadened coverage for telehealth and RPM services, with many of these expansions now permanent or extended, although certain Medicare telehealth flexibilities have expired recently.[6,15,16,66,68]

### *State Licensure*

Physicians must also be mindful of state licensure requirements, which generally mandate that a provider be licensed in the state where the patient is located at the time of the virtual encounter. The Interstate Medical Licensure Compact (IMLC) has helped streamline the process for obtaining multiple state licenses, facilitating cross-state practice for eligible physicians, though participation and requirements can vary by state.[6,8,27,28]

The US Food and Drug Administration (FDA) plays a central role in regulating digital health technologies, particularly those medical devices used in RPM.[31-36] The FDA provides guidance on device approval, post-market surveillance, and software as a medical device (SaMD), ensuring that tools used in virtual care meet rigorous safety and efficacy standards.[37-41] Physicians should confirm that any RPM devices they utilize are FDA-cleared or approved and should remain aware of their responsibilities regarding device-related adverse events.

Data privacy and security are foundational obligations in virtual care, governed by HIPAA and FTC requirements.[1,34,43,44] Physicians must ensure that their technology partners comply with these regulations.[42,43,45] (See Data Privacy and Security section for a detailed discussion of privacy and security risks and mitigation strategies.)

Given the speed of change in this field, physicians must proactively monitor regulatory updates and adapt their practices accordingly. Verifying licensure for all states in which patients are located, using only FDA-cleared or approved RPM devices, ensuring vendor compliance with privacy laws, staying current

on reimbursement policies, and documenting patient consent for virtual care are all actionable steps to minimize liability and optimize patient outcomes. As virtual care continues to evolve, ongoing vigilance and adaptation are essential for both legal compliance and high-quality patient care.

## Key Liability Risks in Virtual Care

### *Medical Malpractice in Telehealth*

As telehealth becomes an increasingly integral part of healthcare delivery, physicians must recognize that the risk of medical malpractice remains ever-present—albeit in new and evolving forms. While virtual care offers unprecedented convenience and access, it also presents unique challenges that can contribute to adverse outcomes and, consequently, liability exposure.

One of the most significant risks in telehealth is the potential for missed or delayed diagnoses due to the inherent limitations of remote assessment.[2,69] The inability to perform a comprehensive physical examination, reliance on patient-reported symptoms, and incomplete or fragmented medical histories can all compromise diagnostic accuracy.[2,5,69] These limitations may be further compounded by the challenges of establishing rapport, assessing nonverbal cues, and ensuring clear communication through digital platforms. In addition, documentation in virtual settings can be inconsistent or incomplete, increasing the risk of miscommunication and undermining the legal defensibility of clinical decisions. The HHS OIG has recommended more thorough documentation for RPM claims, including details on patient education about device use and evidence that providers reviewed the health data to manage the patient's condition.[67] A particularly critical area of liability arises when there is inadequate escalation from virtual to in-person care.[2,69] The failure to recognize or act upon "red flag" symptoms that warrant immediate evaluation can have devastating consequences. The high-profile case of Philip Tong in December 2023 illustrates these risks vividly. Mr. Tong, a patient with complex chronic illness, died following a virtual visit in which his emergent symptoms were not adequately recognized or escalated. The lawsuit against One Medical alleges that clinicians failed to appreciate the severity of his condition, resulting in inadequate triage and insufficient follow-up.[2,3,4,5] This case underscores that the standard of care does not diminish in virtual settings; physicians are held to the same clinical expectations as they would be in-person.[2,70]

Such cases allege several systemic contributors to adverse outcomes in telehealth.[2,69] Staffing shortages, inadequate clinician training in virtual care protocols, and productivity pressures can all play a role in missed or delayed recognition of critical symptoms.[2,5] These examples highlight the importance of robust protocols for identifying and escalating emergent symptoms in virtual care environments.[2] Documentation of clinical reasoning, clear communication with patients regarding limitations of virtual visits, and timely referral to in-person care when indicated are all essential practices for mitigating liability.

Ultimately, the lessons from both litigation and regulatory scrutiny are clear: physicians must approach telehealth encounters with the same diligence and attention to detail as traditional visits. This includes thorough documentation, careful assessment of symptoms, clear communication of follow-up instructions, and the development and implementation of protocols to ensure that urgent conditions are not overlooked. As telehealth continues to evolve, ongoing education, training, and quality improvement efforts will be vital for maintaining patient safety and minimizing malpractice risk.[5,46,47]

### *Remote Patient Monitoring (RPM) Risks*

Remote patient monitoring (RPM) has emerged as a cornerstone of modern virtual care, enabling physicians to track patient health metrics such as vital signs, blood glucose, and cardiac rhythms in real time using FDA-cleared devices.[6,22,24,48] RPM offers significant benefits for chronic disease management, early detection of complications, and patient engagement.[22,23,24,49,50] However, its rapid expansion has also introduced a new set of liability risks that physicians must proactively address.

A risk associated with RPM is the reliability and accuracy of the devices themselves. Device malfunction, software or user errors, or inaccurate readings can result in missed or delayed identification of clinically significant changes, potentially leading to patient harm.[22,51,52-56] Physicians who rely on these devices should verify that they are FDA-cleared and should remain vigilant for device recalls or post-

market safety alerts.[6,57] In addition, clinicians must be prepared to respond to device-generated data in a timely and clinically appropriate manner.

Another concern is the phenomenon of data overload. RPM platforms can generate high quantities of patient data, including frequent alerts and abnormal readings. When practices lack robust protocols for triage and review, there is a substantial risk that clinically important alerts may be missed or not acted upon promptly.[58,59] Allegations of delayed physician response to abnormal data have been seen in recent litigation involving RPM, with lawsuits alleging that providers failed to intervene when remote monitoring indicated acute deterioration or emergent symptoms.[6,60,71] Such cases underscore the need for clear workflows, adequate staffing, and defined escalation pathways to ensure that actionable information is not lost amid the volume of incoming data.

Patient misuse or misunderstanding of RPM devices represents a potential risk to accurate monitoring. Inadequate patient education regarding device operation, troubleshooting, and the limitations of remote monitoring can compromise data integrity and clinical decision-making. Physicians should provide thorough instruction and clear expectations for patients when and how to seek urgent in-person care if concerning symptoms arise.

Lawsuits further illustrate the complexity of RPM liability. For example, allegations of device malfunction, missed alerts, or delayed clinical response were central to claims of negligence and patient harm.[6,71] Issues that are increasingly scrutinized include not only the choices made by individual clinicians, but also the adequacy of system-wide protocols for monitoring, response, and patient communication.[6,71]

To mitigate these risks, physicians should implement comprehensive protocols for device selection, data review, and escalation of care.[60] This includes regular training for clinical staff, collaboration with RPM vendors to ensure HIPAA compliance and data security, and ongoing review of workflow effectiveness. Furthermore, clinicians should stay informed about FDA guidance on RPM device approval and post-market surveillance, as regulatory expectations continue to evolve.[6,9,57,67]

In summary, while RPM holds great promise for enhancing patient care, it also demands heightened attention to device reliability, data management, patient education, and regulatory compliance. By addressing these factors proactively, physicians can reduce liability exposure and ensure that the benefits of remote monitoring are fully realized.

## Data Privacy and Security

The expansion of virtual care has brought data privacy and security into sharp focus, as physicians and healthcare organizations increasingly rely on digital platforms and remote monitoring devices to collect, transmit, and store sensitive patient information. The risks associated with breaches of protected health information (PHI) are significant and multifaceted. Telehealth platforms and RPM devices are attractive targets for cyberattacks, and even inadvertent lapses in security protocols can result in unauthorized access, exposure, or loss of patient data.[1,46,61,62] Such breaches not only compromise patient trust but also expose providers to regulatory enforcement actions, civil liability, and reputational harm.[46,62]

Beyond technical vulnerabilities, inadequate patient consent and transparency regarding data use present additional liability risks.[60,63] Patients should be clearly informed about how their data will be collected, transmitted, stored, and potentially shared with third-party vendors. Failure to obtain and document appropriate consent can lead to legal challenges and undermine compliance with federal and state privacy laws.[60, 63,67] This is particularly relevant in the context of virtual care, where the use of third-party vendors, cloud-based storage, and tracking tools is commonplace. Not all vendors may be fully compliant with the Health Insurance Portability and Accountability Act (HIPAA) or the Federal Trade Commission (FTC) Act Section 5, which prohibits unfair or deceptive practices in the handling of consumer data.[1,46,62]

Physicians should vet the privacy and security practices of all telehealth and RPM vendors they want to partner with, confirming that vendors adhere to HIPAA and FTC requirements.[46] Regular review of vendor compliance, ongoing staff training, and periodic audits of security practices are recommended operational safeguards.[46, 62] Moreover, physicians

should stay abreast of evolving federal and state regulations, as well as guidance from regulatory agencies, to ensure continued compliance in a rapidly changing digital landscape.[46,60,64]

In summary, safeguarding patient privacy and maintaining robust data security are foundational obligations in virtual care. By prioritizing transparency, informed consent, and vigilant oversight of technology partners, physicians can mitigate the risk of data breaches and regulatory violations, thereby protecting both their patients and their practices.

## Risk Mitigation Strategies for Physicians

As virtual care becomes increasingly embedded in clinical practice, physicians must adopt comprehensive risk mitigation strategies to protect both their patients and their professional standing. The evolving legal landscape and the particular challenges of telehealth and remote patient monitoring (RPM) demand a proactive, multi-faceted approach. Key strategies fall into three domains: clinical best practices, operational safeguards, and regulatory compliance.

### *Clinical Best Practices*

Clear, thorough documentation remains a cornerstone of effective risk management in virtual care.[67] Physicians should meticulously record all virtual encounters, including clinical reasoning, patient-reported symptoms, and the rationale for treatment decisions.[5,67] Given the unique nature of telehealth and RPM, it is essential to obtain and document informed consent that specifically addresses the limitations and risks of virtual modalities.[60,67] This consent process should include discussion of potential technology failures, privacy considerations, and the circumstances under which escalation to in-person care is necessary.[60]

Robust protocols for recognizing and escalating "red flag" symptoms are critical, as demonstrated by recent litigation such as the Tong case.[2,5] Physicians should be trained to identify symptoms or situations that warrant immediate in-person evaluation and ensure that patients understand when and how to seek urgent care.[2] In the context of RPM, clinicians must also educate patients on the correct use of monitoring devices, the importance of accurate data input, and the limitations of remote monitoring in detecting all potential health concerns.[2,5,46,60,65]

### *Operational Safeguards*

Operational safeguards are essential for minimizing liability in virtual care environments.[2,5] All clinicians and support staff should receive regular training on telehealth and RPM protocols, including the recognition and management of critical symptoms.[5,46,47] Practices should vet telehealth and RPM vendors for compliance with HIPAA and Federal Trade Commission (FTC) requirements, as well as review vendor security practices to protect patient data.[1,46] Periodic audits of virtual care workflows and outcomes can help identify vulnerabilities, track adherence to protocols, and support continuous quality improvement.[46 62]

Effective data management systems should be in place to handle the volume of information generated by RPM, including reliable triage processes and clear escalation pathways for abnormal findings.[2,58,59] Establishing clear lines of responsibility for data review and patient follow-up is vital to ensuring that no critical alerts are missed.[2]

### *Regulatory Compliance*

Staying abreast of regulatory developments is fundamental to risk mitigation. Physicians, or their advisors, should monitor updates and guidance from the Centers for Medicare & Medicaid Services (CMS), the FDA, state medical boards, and relevant professional societies.[6,57] This includes understanding the requirements for licensure in all jurisdictions where patients are located, especially in light of how the IMLC is evolving.[6,8,27] Ensuring that all RPM devices in use are reliable, well tested, FDA-cleared, and that device-related adverse events are reported as required, further reduces regulatory risk.[6,9,57]

By integrating these clinical, operational, and regulatory strategies, physicians can reduce their liability exposure while delivering high-quality, patient-centered virtual care. Proactive risk management not only safeguards individual practices but also strengthens patient trust and the sustainability of virtual care as a central component of modern healthcare delivery.

## Conclusion

As virtual care cements its role in modern healthcare, physicians must remain vigilant to the unique liability risks it presents. By embracing robust

clinical protocols, operational safeguards, and ongoing regulatory compliance, clinicians can mitigate these risks while delivering safe, effective, and patient-centered care. The landscape will continue to evolve, making continuous education and adaptation essential for protecting both patient well-being and professional integrity in this rapidly changing environment.

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MM

# Embracing Opportunities, Making Choices, and Focusing on the Mission

*by Karen Edison, MD*

***"I would encourage any physician, young or old, to consider academic medicine. You can be creative, innovative, work with young people, and serve those in need."***

Medicine has been the right choice for me though not without challenges. Reflecting on my professional career, I am aware of important and sometimes difficult choices that, for the most part, defined my career and left me feeling grateful and fulfilled. This involved embracing opportunities, having superb mentors, and remaining committed to my personal mission of improving health and health care for Missourians.

I graduated from William Jewell College (WJC) in my hometown of Liberty, Missouri, largely because my mother was on the nursing faculty, which made it affordable. I was interested in both science and the humanities; I majored in biology and English. I greatly enjoyed the humanities and am convinced that part of my education was essential and made me a better physician.

I must admit that my education at the University of Missouri School of Medicine (SOM), was a letdown. The preponderance of memorization and regurgitation required was a slog after having been immersed in reading, writing, and critical thinking at WJC, where even my science classes were essay-based. Thankfully today, the curriculum at MU School of Medicine is much improved using Problem Based Learning (PBL).

After medical school, and dermatology residency at Mizzou, I joined the MU dermatology faculty in 1993. I chose academic dermatology primarily because I was inspired by the stellar faculty and the challenges offered. I wanted to care for complicated patients, teach, and make change where change was needed. I embraced the role of clinician/educator and part-time research collaborator. I became Residency Program Director after a few years and was happy to be supported by the Dean's Office for my efforts in Medical Education.

After six years, I needed a change and looked at opportunities at other universities across the country. Pleased, I found we had a favorable situation at Mizzou in support of our clinical and educational programs. Still, I was restless.



Dr. Edison provided teledermatology in rural Missouri providing a platform for a future in telemedicine.

Mentors are important and I have had great ones along the way. Paramount in my life, personally and professionally, is my extraordinary mother. She was the first pediatric nurse practitioner in Missouri. Gary Phelps, Dean of Students at WJC, had a major impact on developing my leadership skills as an undergraduate. In Dermatology, Philip Anderson, MD, and Ronald Swinfard, MD, helped broaden my perspective as physician, educator, and leader. Later in my career, my husband, David Fleming, MD, was a steady advisor and mentor in many ways.



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Dr. Edison and her class of recipients of the Robert Wood Johnson Health Policy Fellowship.

After six years on faculty, Dr. Anderson sensed my need for challenges beyond academic medicine and suggested that I apply for a Robert Wood Johnson Health Policy Fellowship (RWJ HPF). I made a leap of faith, applied, and was accepted. I had been providing teledermatology in rural Missouri for several years and expertise in telemedicine became my policy platform for that experience. I was off to Washington DC for a life changing immersive experience! I learned about federal health policy, met with leaders of nearly every health-related think tank, trade association, and federal agency, and ultimately served in the US Senate's Health, Education, Labor, and Pensions (HELP) Committee for two years, one as RWJ HPF and one as senior policy analyst. During this time (1999 to 2001) I worked on patient safety legislation, the Safety Net Reauthorization Act, and sundry hospital and physician issues.

My most impactful experience was working with a small group of dedicated individuals in developing telemedicine legislation. I worked with leadership in both the House and the Senate, as well as each of the relevant Committee Chairs, both authorization and appropriations. Through much effort we were able to expand Medicare reimbursement for telemedicine in the Medicare, Medicaid, and SCHIP Benefits Improvement and Protection Act (BIPA) 2000 for rural, underserved patients across the US. My key role in these efforts remains the health policy accomplishment about which I am most proud.

One of my most memorable experiences was in May 2001 when my boss, Senator Jim Jeffords, left the Republican party causing the balance of power in the nearly evenly divided Senate to shift. Chaos ensued in the Senate Hart building. A wall of reporters and cameras blocked the way out of our offices for a week. Hostile calls poured in, and we stopped letting the young staffers answer the phones. In the midst of this Jane Fonda sauntered in and laid a wet kiss on the Senator! Each of the Committee staff had to either quit immediately or never work for the Republicans again.

The day he announced his change in party from Republican to Independent, we were holding a patient safety hearing. After this hearing, Tommy Thompson, then Secretary of the US Department of Health and Human Services (DHHS), asked me to be his "patient safety czar" as Assistant Deputy Director. I gave it much thought and started down the interview pathway but then reconsidered. This was a watershed moment in my career. Was I going to stay in DC and become a "Policy Wonk/Bureaucrat" or return to Mizzou as "Doctor/Teacher?"

I decided to return to Mizzou in hopes of using my newfound knowledge and skills in health policy to improve health and health care for all Missourians, particularly those with greatest need. In 2002, I co-founded the Center for Health Policy (CHP), partnering with Kristofer Hagglund, PhD. He had been a RWJ HPF a year after me and had worked for the Democrats under Senator Tom Harkin. We worked to create a non-partisan Center developing policies to serve the best interests of Missourians.

I also became the Medical Director for the Missouri Telehealth Network (MTN), a position I have held for many years. In this role, I have spent much time convincing and cajoling MU physicians to use telemedicine. By 2013, we had 31 specialties using telehealth from Mizzou and were serving most Missouri counties. I personally enjoyed offering weekly teledermatology to rural Missourians for 26 years.

In early days, CHP had funding from the Missouri Department of Health and Senior Services (DHSS) for working on health insurance access, from the Missouri Foundation for Health (MFH) for working on Health Literacy and Health Equity, and from the Missouri Department of Social Services (DSS) for the MO HealthNet Data project, among others.

When I returned, I also worked with the state and MU medical school, to increase our service to MO

HealthNet (MHN), Missouri's Medicaid program. It took several years, but in 2005, we signed a service contract to receive the MHN Administrative Claims data from the state on a continual basis and home it securely at CHP. For 20 years, we have been serving the state through the retrieval, analysis, and reporting of these data, in various forms for various purposes. With multiple partners, we initiated work on the Missouri Healthcare Workforce data. This project came to CHP in 2018, when Tracy Greever-Rice PhD joined CHP in leadership.

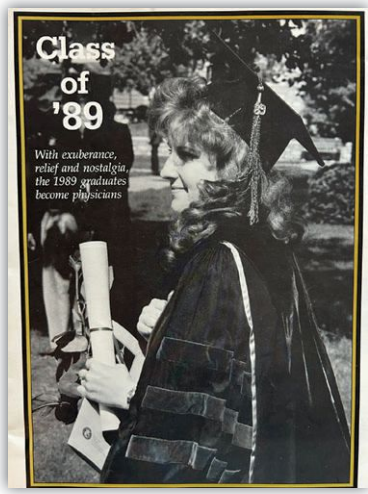
On my return from DC, I resumed my dermatology practice and my first day back in the clinic was the tragic 9/11/2001. May our country never again experience such tragedy.




Dr. Edison as the first female Chair (Dermatology) in the history of MU's School of Medicine.

At that point, the MU Dermatology Division had become a department and there had been major turnover in leadership and faculty. In 2003, I was asked to serve as Chair and was in that role for the next 16 years. This was impactful for the MU School of Medicine as I was the first female Chair in the history of the medical school, and the only female Chair for many years. Today, there are nine female Chairs. The Department of Dermatology grew by adding faculty, residents, surgical fellows, clinic sites, and programs in pediatric dermatology and dermatopathology. I retired from clinical practice and departmental leadership in 2019. By the time I retired I was happy to see MU Dermatology flourishing academically and clinically.

I have had the privilege of educating and mentoring faculty, residents, and students and have found these shared experiences extremely rewarding. Upon retirement, I received a letter from a successful young clinical faculty member who shared her story.




Dr. Edison graduated from the MU SOM Class of 1989, Mizzou's 150th year.

She grew up in a small town in Missouri and wanted to be a physician, but her family and teachers told her it might be too hard as a woman, and she considered pharmacy school. Her parents were Mizzou alumni and when the MU alumni magazine was mailed to their home, there was a picture of me in full regalia the day I graduated from medical school. Her father suggested she drive to Columbia and meet with me, and so she did. I have no memory of that meeting, but she said I encouraged her, and that made all the difference. Now that young woman is an academic physician, serving as role model encouraging and mentoring others. This is an example of the "influence we have during the daily interactions with learners" that Betty M. Drees MD, reflected on in her Perspective: Inspiring Lives and Careers (*Missouri Medicine*, July/August 2025).

Following retirement, I returned to serve as Senior Medical Director for both MTN and CHP, in the "half-time position" that I hold today. The amazing leaders of these organizations had been reporting to the Dean of the MU SOM through me when I served as Chair. Now I report to these leaders, Tracy Greever-Rice, PhD, at CHP and Rachel Mutrux at MTN, both trusted friends and colleagues.

At CHP, our projects have grown to include No Kid Hungry, Kids Count, Senior Count, and our MO HealthNet Data Project has begun to develop required Core Set measures for the state. Dr. Greever-Rice has provided strong leadership over all our programs.

At MTN, Rachel and I learned about Project ECHO in New Mexico in 2013, immediately saw its value, and started Show-Me ECHO (SME) in Missouri in 2014. ECHO stands for Extension for Community Healthcare Outcomes and is a video-based educational program that creates multidisciplinary specialty teams that partner with primary care clinicians and others to



Dr. Edison receiving the Citation of Achievement with Drs. Richard Barohn (right), and Jonathan Dyer (left), shortly after her retirement.



Dr. Edison with her family.

create learning collaboratives around various clinical topics. We worked with two state representatives, Wayne Cooper, MD, and Diane Franklin, and were able to procure a promise of $1.5 million in one year. That year, the Governor vetoed all new funding, but we found some funding and started Chronic Pain and Autism ECHOs. Since that time, we have received this funding from the state of Missouri, along with additional funding from Missouri's three Medicaid Managed Care organizations and have grown our ECHO programs from two in 2014 to 40 in 2025. We have ECHOs in chronic conditions like Diabetes, Hypertension, Kidney Disease, Cardiovascular Disease, Hepatitis C, and HIV; mental and behavioral health such as Eating Disorders, Suicide Prevention, Certified Peer Specialists, and Adult Psychiatry; child health conditions like Asthma, Autism, Neonatal Abstinence Syndrome, Child Psychiatry, Foster Care, and Pediatric Weight Management; and many others. See www.showmeecho.org. I remain passionate about SME and have the privilege of seeing lives saved, suffering prevented, and money saved through our ECHO programs.

I am blessed, in partial retirement, to work with amazingly capable teams in both CHP and MTN/SME working every day to improve health and health care for all Missourians, particularly those with greatest need. It warms my heart that we are using the MO HealthNet Claims Data (housed at CHP) to help evaluate our Show-Me ECHO programs' impact on Missouri's clinicians and patients.

There are many benefits to creating a new and rewarding post-retirement life. I continue to learn and do new things, nurture quality connections with family and friends. I work at being in touch with myself as life and circumstances change. When I am not working for MTN/SME or CHP, my life is full of yoga, weight training, biking, walking with friends, and puzzling. I am trying to learn a new language, and I got my first public library card, already well used. We travel when the weather is good and stay home when it is not.

I have loved my career, and I love this season of life where I can spend more quality time with my wonderful husband, David Fleming, MD, and our beloved dog, Sophie. I am also blessed to be "MiMi" to nine amazing grandchildren.

I would encourage any physician, young or old, to consider academic medicine. You can be creative, innovative, work with young people, and serve those in need. What could be more fulfilling? **MM**

# Running-Related Silent Atrial Flutter Presenting as a Stroke: A Marathoner's Tale

*by Philip R. Cohen, MD*

***Moderation is simple to propose, yet much more difficult to incorporate.***

Atrial arrhythmia, most commonly atrial fibrillation, has been observed to occur in long distance (particularly full and half marathon) runners.[1] Physician runners have reported their own running-associated atrial fibrillation.[2-5] Like these individuals, I developed a running-related arrhythmia (atrial flutter) which remained asymptomatic until it clinically presented as a large right frontal cortex stroke.[6] The purpose of this writing is not only to share my personal experiences, but also to discuss running-associated potential cardiovascular events (including atrial fibrillation and elevated computerized tomography coronary artery calcium score) and the possibility that long distance runners consider moderation in their approach to exercise.

## My Tale

I was born in 1958. As a child I was overweight and non-athletic. I always remember having to buy 'husky' (a euphemism for 'fat') pants at the store.

There were periods of time when I was thinner; this initially occurred when my math teacher (who was the track coach) challenged me to join the high school track and field team in tenth grade. I was too slow to be a sprinter; therefore, I was destined to be a long-distance runner. I was awarded varsity letters for my participation.

At Franklin & Marshall College in Lancaster, Pennsylvania, I continued my running; in the fall on the cross-country team and in the spring on the track and field team as a three-miler. On both teams, I was either the slowest runner or one of the slower runners. Again, during my senior year, I was awarded varsity letters in both sports based on my participation.

Medical school was at New York Medical College; I lived in Vallaha, New York, for my first two years and moved to Manhattan for the latter two years, which allowed me to jog the six-mile loop around Central Park. My next three years were in Houston, Texas, (internal medicine internship, an internal medicine residency, and laboratory research in dermatology each for a year); I ran a few races during that time (Figure 1). During the next three years, I completed a dermatology residency at Columbia University in New York City. Occasionally, I did some leisure running on the weekends.

## My First Marathon

I returned to Houston, Texas, in July 1989. I was six feet and two inches and nearly 200 pounds. I signed up for the 18th Houston Marathon which was being held in January 1990 and began training. Many daily runs were a minimum of five miles with longer runs on the weekends. The popularity of marathon running was still in its infancy. I successfully completed my first marathon. It was my best performance in the race.

## More Marathons and Half Marathons

During the next 25 years, I ran the same race in Houston 19 more times (Figure 2). During these years, I was working full time and raising four children with my wife. I would exercise year-round for running the marathon with my training consisting of between five to seven miles, one or two days during the week, and shorter



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runs or a longer run of 12 to 14 miles on one or both days of the weekend. I also encouraged my family to run the half marathon on that race day or with me two weeks later in Sugar Land, Texas.

It is rather amazing; with all of that running, I was not (and am not) a thin person. Most of the races, my running weight was significantly over 200 pounds. In Texas, runners who weigh more than 200 pounds were affectionately referred to as Clydesdales.

In 2013, I moved to San Diego, California. Since then, my wife and I have returned to Houston each year to participate in the races. I also ran a few half marathons in San Diego, California, and in Northbend, Washington.




Figure 1. Dr. Cohen during the Monument 5-mile run in Pasadena, Texas on April 19, 1986.

## Was My Heart Whispering To Me?

By 2017, I was experiencing back pain and sciatica symptoms. My pace per mile had significantly slowed from 12 minutes to nearly 15 minutes. Eventually, I realized that I was progressively losing motor strength in both legs. My MRI of my lumbosacral spine showed severe spinal stenosis at multiple levels. On November 17, 2017, I had back surgery; there were numerous postoperative complications.[7]

On the fourth day following surgery, I developed atrial fibrillation.[8] I was also experiencing oxygen desaturation. My heart spontaneously returned to normal sinus rhythm after a single 30 milligram dose of diltiazem. The episode was attributed to postoperative atrial fibrillation.

The computer reading of the electrocardiogram that was performed commented that I had experienced a prior myocardial infarction. This was not addressed during the hospital stay, but a repeat electrocardiogram as an outpatient was normal. I had been the victim of a MISFIT (myocardial infarction simulated from incorrect telemetry); the technician had inadvertently incorrectly placed the leads during the procedure.[8]

I never regained the motor strength of my lower extremities after surgery. There were no additional symptomatic cardiac events.

## A Stroke of Bad Luck

On July 27, 2023, I was going to sleep after midnight. I was unable to call (vocally) the dogs back into the house; they came in on their own. I had no other symptoms and went to sleep.

When I woke up later that morning, I still could not speak. I looked in the mirror; there was no facial drooping, and I was able to smile and show my teeth. There were no other deficits of motor function.

I shaved. I replied to a few emails. I still could not talk. I accepted the realization that I had a stroke. I texted one of my adult sons, since my wife was out of town, to take me to the hospital.

## Discovery of Asymptomatic Atrial Flutter

Within fewer than 15 minutes from my arrival to the emergency department, I had received a computerized tomographic scan of the brain that demonstrated a large ischemic cerebral vascular accident of the right frontal cortex. My stroke had presented with isolated dysarthria.[6]

What was completely unexpected was the result of the electrocardiogram. I was in atrial flutter. I was asymptomatic. However, this abnormal heart rhythm was the etiologic risk factor associated with my stroke. I later realized that the heart rhythm was likely the consequence of all my years of exercise and running.

I was initially anticoagulated with heparin and subsequently remain on apixaban for the rest of my life. The atrial flutter came and went; however, since I was anticoagulated, there was no urgency to have me converted to normal sinus rhythm. Overnight, I went from being non-medicated to having to take several daily medicines. My blood pressure and cholesterol were elevated; an antihypertensive (amlodipine besylate which was eventually changed to valsartan to resolve the new leg edema) and a lipid-lowering medication (ezetimibe, since I am allergic to statins) were also added. After two weeks, an antiarrhythmic (amiodarone) and a beta-blocker (metaprolol succinate ER) were also added.

## Returning to Status Quo

Follow up electrocardiogram demonstrated that I was in normal sinus rhythm. Within five months I underwent atrial ablation of both the left and right atrium. The amiodarone

was discontinued after the procedure.

My limited recollection (before the intravenous anesthesia had accomplished its task) of the operating room was a combination of the board game Battleship and the movie Star Wars. Two large screens were suspended from the ceiling to map the target sites; I imagined that the cardiologist would be calling out the sites "B4, B5, B6, and B7" and the corresponding screen showing obliteration of an arrhythmic focus and another colleague announcing, "battleship sunk." Again, as I began to drift asleep and prior to the placement of the cardiac catheter in my right femoral vein, I also imagined that my cardiologist had transformed into Luke Skywalker with his light saber striking and destroying atrial flutter foci.

A follow-up two-week Holter monitor did not show any episodes of either atrial flutter or other supraventricular tachycardia such as atrial fibrillation. However, I developed allergic contact dermatitis from the adhesive tape used to secure the monitor to my chest which resolved spontaneously once the monitor was removed. Subsequent electrocardiograms demonstrate that I remain in normal sinus rhythm.

Extensive endurance exercise and marathon running in men can be associated with an elevated computerized tomography coronary artery calcium score. This was also evaluated. My computerized tomography coronary artery calcium score was 162.3 and the percentile was 63 percent; the report identifies scores of 101 to 400 as moderate identifiable disease and an associated moderate risk.




Figure 2. Dr. Cohen at the 34th Chevron Houston Marathon on January 15, 2006. This was one of the three marathons he completed in under four hours (03:58:01; running pace approximately 9 minute/5 second mile). He would listen to music on a Sony Sports Walkman. Headgear was unique using a sock to cushion ears from being irritated by the Walkman. Reluctant to permanently discard any clothing, he would tie long-sleeved t-shirts around the waist.

## Do I Still Run Marathons? NO! Do I Participate in Half Marathons? YES! But I Walk...

My last marathon (# 20) was January 18, 2015. I currently complete two half marathons each year. I walk the 13.1-mile distance; sometimes, I jog the final mile. It now takes me longer to complete a half marathon than my best time when I ran my first full marathon.

My training is also different; I alternate the walking with swimming. I am the proud co-human to three willful and wonderfully independent-thinking Basenjis who join me for a five-mile walk around Lake Miramar in San Diego, California, three times each week. In 2013, I would run the lake loop in 50 minutes; now I walk the loop with the dogs in about 1 hour and 45 minutes and sometimes my wife joins me. I also swim (freestyle) a mile three nights a week in an indoor pool; this usually takes me between 46 to 54 minutes.

## Would I Have Listened 35 Years Ago?

If a young endurance athlete (marathon runner) in their early 30s reads this perspective, will they change their approach to fitness and exercise? Probably not. Honestly, if I was told to not run marathons or half marathons when I was 30 years old, I would have not heeded the advice. At that age, I was very healthy (albeit overweight) and considered myself to be immortal.

In summary, healthy longevity is multifactorial. Heredity and telomere length is one factor. A conservative lifestyle regarding diet and limitation of alcohol is helpful. In addition, preventive health care maintenance with physical fitness, by routinely exercising in moderation, is a good approach.

## Discussion

Marathon running can be lethal. Death can occur from cardiovascular toxicity. Fatality can be caused from sudden cardiac death, arrhythmias, and other complications from extreme endurance exercise.

### *Marathon Runners Are Not Immortal*

According to legend, the first recorded death of an ultra-long-distance runner was the Greek messenger Pheidippides in 490 B.C. He supposedly died after

completing a 25-mile run from the battlefield in Marathon to Acropolis, Athens. However, prior to the run from Marathon to Athens, he had not only run from Athens to Sparta (approximately 150 miles in about two days) and back to Athens beginning the morning after his arrival to Sparta (approximately another 150 miles, again in about two days). From Athens, he then traveled the 25 miles to the battlefield of Marathon and then back from Marathon to Athens. Although there is some debate as to whether Pheidippides or a different messenger died suddenly after completing the run from Marathon to Athens, Pheidippides death is most acknowledged in the literature.[3,9,10]

The running world of marathoners was more recently stunned by the unexpected death of running author Jim Fixx at 52-years of age. He died during a distance run on July 20, 1984; his body was on the side of the road. His autopsy revealed severe atherosclerosis of his coronary arteries with significant occlusions of their lumens.[3,9]

Noakes, from South Africa, published perhaps the first paper in 1987 that summarized the marathon runners who had died from heart disease. The review showed that there were 36 cases of heart attack or sudden death in marathon runners in the world literature at that time. In 75 percent (27 of 36) of the runners, coronary artery disease had been objectively confirmed. Premonitory symptoms were noted in 71 percent of the runners with coronary artery disease and death occurred either during or within 24 hours of the competitive running event or long training runs in 50 percent of the runners.[11]

### *Cardiac Risk in Long Distance Runners*

There is an increased risk for sudden cardiac death in long distance runners who experience sustained vigorous exercise such as running for three or four hours without stopping or running 20 or more miles at one time. Indeed, the occurrence of cardiac arrest was 1 in 100,000 marathon runners and 0.27 per 100,000 half-marathon runners. Two groups of individuals are at higher risk for cardiac events include runners who train for a marathon by running fewer than 30 miles per week and the group of individuals over the age of 35 years who train and run marathons.[9]

Exercise-induced structural changes of the heart and coronary arteries also occur. These include hypertrophic cardiomyopathy which is estimated to occur in 36 percent of marathon runners. In addition, the structural heart disease may result in atrial or ventricular arrhythmias.[9]

Strenuous endurance exercise has been observed to potentially result in multiple adverse cardiovascular consequences. Acute increase in cardiac chamber size, particularly the right-sided chambers can result from the volume and pressure overload. Other morphologic changes can include aortic stiffening and myocardial fibrosis.[12]

### *Atrial Fibrillation in Long Distance Runners*

Moderate physical activity has been associated with a decreased risk of atrial fibrillation.[13] However, long distance running-related atrial fibrillation was previously referred to as 'lone' or 'idiopathic' atrial fibrillation.[1] Indeed, endurance training in athletes with long-lasting vigorous sports engagement (such as marathon and half-marathon running) places these individuals at increased risk of developing running-associated atrial fibrillation.[14]

The amount of time and the intensity of endurance training are both factors that influence the development of cardiac function impairment and atrial fibrillation. The intensive exercise, such as long-distance running, alters the structure of the heart (including fibrosis of the myocardium and thickening of the atrium) and results in significant increase in vagal tone (not only with imbalances in sympathetic and parasympathetic activation, but also bradycardia). In athletes, the cardiac structure variations and the changes in vagal tone serve as ectopic triggers that can lead to atrial fibrillation, induce the onset of re-entrance mechanisms, and shorten the refractory period shortening.[14]

Atrial fibrillation is not the same as atrial flutter. However, with regards to extensive endurance exercising, both atrial dysrhythmias are running-associated supraventricular arrhythmias. Indeed, although my preoperative prognosis for atrial ablation was much improved since I had atrial flutter instead of atrial fibrillation, the risk of arrhythmia-related severe adverse sequalae (such as another stroke) was similar. Like atrial fibrillation, the cardiologist strongly encouraged me to give him my consent to puncture the atrial septum so he could enter the left atrium and treat the arrhythmia-eliciting foci in that atrium before he returned to ablate the arrhythmia-causing foci in my right atrium.

### *Coronary Artery Calcium Score and Coronary Artery Plaque Volume in Marathon Runners*

The computerized tomography coronary artery calcium score or coronary artery plaque volume or both have been demonstrated to be increased in many male marathon runners;[15,16] this may be related to exercise-induced hypertension.[17] Indeed, a potential increased risk of coronary artery disease, myocardial fibrosis, and sudden cardiac death was postulated in those runners with 25 or more completed marathons.[18] In contrast, long-term marathon running was associated with low coronary plaque formation in women.[19]

## Moderation May Ge the Best Recommendation for Exercise

Moderation of exercise training and physical activity, particularly for long distance runners, is the dogma of choice.[20] Cross-training, with swimming is recommended; other activities such as yoga or walking are also suggested.[21] In addition, gardening or entertaining your dog is proposed.[21]

A 'Goldilocks' zone has been proposed with conservative quantitated guidelines for optimal exercise.[22-25] The zone limits exercise to either vigorous-intensity aerobic activity of 75 minutes or moderate-intensity aerobic exercise of 150 minutes; one day per week of no exercise and additional limitations for individuals over age 45 years.[24] In addition, cardiac testing (such as computerized tomography scanning for coronary artery calcium, or exercise testing and/or echocardiography) is recommended for very high exercisers over 50 years of age.[24]

## Conclusion

I have been a participant of long distance ambulatory athletic sports since age 15 years. Even though I was never the best competitor on any race day, I have always enjoyed the competitive atmosphere. Honestly, I still derive significant pleasure hanging the medal that I earn after successfully finishing a half-marathon. However, moderation is now my mantra.

In conclusion, moderation is simple to propose, yet much more difficult to incorporate. It is a personal decision that each individual needs to make for themselves. Knowledge is essential for a person to be able to make an educated choice. However, in youth, the heart often overrules the brain; a healthy individual may not be willing to sacrifice the short-lived, yet significant, personal benefit of training and completing a marathon or a half-marathon. Each person needs to make their own best choice; however, moderation is always an available option that can be chosen.

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**MM**

## Feature Correspondence

# The Travesty of Physician Unavailability—Triaging Concurrence

*by Farzana Hoque, MD, Juan C. Corvalan, MD & Steven Shields, MD*

### Physician Shortage: A National Crisis Threatening Patient Care

An insightful editorial by John C. Hagan, III, MD, *Missouri Medicine* Editor in the September/October 2025 issue highlights a troubling reality in American health care: long waits for appointments, fragmented access, and the erosion of timely physician care.[1]

These anecdotal experiences echo broader workforce projections from the Association of American Medical Colleges (AAMC), which estimates a national shortage of up to 86,000 physicians by 2036.[2] Without urgent intervention, patients will increasingly confront delays and diminished access—especially in underserved communities. The population aged 65 and older is projected to increase by more than 30 percent in the next decade, raising demands for physician-led care across complex, chronic conditions.[3]

At the same time, a significant portion of active physicians are approaching retirement age and training slots for new physicians remain capped.[4] The convergence of aging patients, rising medical complexity, and static physician supply forms the core of the impending workforce crisis.

My personal experience underscores the stakes of this workforce reality. Earlier this year, my husband called multiple primary care offices and was told he could not be seen by a physician for nearly one year, and that his only available option was a clinic, led exclusively by a physician assistant. As a physician myself, I was eventually able to secure a physician appointment through professional connections—but most patients lack that advantage.

International medical graduates (IMGs) play a central role in mitigating this skilled physician gap. Nearly one in four active US physicians is an IMG per the Federation of State Medical Boards.[4] Sixty-four percent of physicians practicing in medically underserved or shortage areas, and nearly 46 percent located in rural regions, are internationally trained.[4] Nearly 21 million Americans live in areas where internationally-trained physicians make up at least half of the workforce. Many IMG physicians fill critical gaps in specialties that US-trained physicians often avoid, such as primary care, psychiatry, and pediatrics. As an internationally-trained physician serving in a safety-net hospital in East St. Louis, I treat some of the nation's most vulnerable patients—individuals with high medical complexity compounded by homelessness, food insecurity, lack of transportation, and limited social support. Timely access to a physician is fundamental for survival of underserved vulnerable populations. Dr. Hagan's depiction of a patient waiting months for care is more than anecdote—it is a symptom of a system under strain.[1] Advanced practice providers deliver valuable care, yet older Americans with multimorbidity, polypharmacy, frailty, and functional decline require advanced physician clinical reasoning and diagnostic skills. Rural hospitals and urban safety-net clinics, unable to recruit enough US graduates, rely on IMGs to serve high-need communities.[4] To safeguard patient access—especially in rural and safety-net communities— the American Medical Association (AMA), along with multiple medical societies have urged policymakers to ensure that internationally trained physicians can continue to be a healthcare workforce pipeline that serves US patients.[4]

On the other hand, to mitigate the physician shortage some states have enacted legislation that allows qualifying internationally trained physicians to gain full licensure without completing an ACGME-accredited postgraduate residency.[5] While this may seem like a solution, it exposes US patients to practitioners who have not completed the rigorous, supervised, hands-on clinical training that residency provides. Federal funding for graduate medical education (GME) must expand if the United States intends to build a sustainable physician workforce—particularly in rural and underserved regions where the physician shortage is most acute. Residency training is the foundation of safe, high-quality medical practice.

As an international medical graduate who completed US residency training and now serves as a medical educator in an academic medical center, I have seen firsthand how physicians grow—from early trainees to confident, independent clinicians—through structured supervision, high-acuity patient care, and progressive responsibility during residency. All of us are aging, and any one of us may become a patient at any moment. The shortage of board-certified physicians imperils not just access—but quality and safety of care. Patients deserve access to physicians trained at the highest level, available when and where care is needed. Physician shortages endanger patient care, making it essential for the nation to invest in training enough competent doctors to ensure timely, high-quality care for all.

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***Farzana Hoque, MD**, is Associate Professor of Internal Medicine, Saint Louis University School of Medicine, St. Louis, Missouri, USA.*

## It Is Beyond Sad What Medicine Has Become

The editorial of *Missouri Medicine* Editor John C. Hagan, III, MD (122(5); 2025:348-350), on the sorry state of medical care in the United States is excellent and in my experience is grounded in fact. I am also a physician dismayed at what has become of our previously proud medical profession. It seems Dr. Hagan and I practiced in the Golden Age of Medicine. Physicians owned their practices; they knew their patients and promptly answered their calls for service. Physicians took pride in the quality of the care they rendered. Patients knew their physicians and the physicians knew their patients and their families. No more!

For almost all of my career I practiced in a medical office with dedicated physicians, nurses, and staff. Calls were quickly answered and promptly returned. Routine appointments were generally available within a week. Office calls were triaged and urgent problems were seen same day, even if it meant physicians staying "after closing hours." I did not go home until all my patients' calls were personally answered. When my patients were hospitalized, I continued to take care of them, calling in appropriate specialists when needed. I came in early or stayed late to make hospital rounds, never thinking physicians would abandon their patients to 'hospitalists' when admitted as is done now.

I watched with concern, then with dismay, at the transformation of medicine from a profession into a lucrative business. Hospitals bought practices and treated physicians as if their sole purpose was to generate profits. Hospitals and

corporate overlords compelled physicians to churn patients through the profit mill—one every fifteen minutes. Physicians know little of their patients except for the chief complaint on the electronic medical record. Eye to eye contact and projection of concern are replaced by the doctor's mesmerize stare at the computer monitor.

Like Dr. Hagan, my wife is seriously and chronically ill. At first, I could bypass the many inexcusable delays in getting care for her by asking for help from physicians I had known and worked with during my career. As they retired, the reality and short comings of present-day medical care set in. I incrementally realized how much medical care has changed. It has deteriorated into a profit generating business seemingly not interested in the quality or availability of what used to be called medical "care." Most physicians are employed by outsiders. They are subjected to pressures that don't have much to do with excellence or compassionate care, but with producing the greatest profit. Even more lamentable is the intrusion of Private Equity (PE) into medicine. All studies indicate when PE buys a practice or a hospital costs go up and quality goes down. What PE values is a good P/E ratio.

Lest you think I'm exaggerating let me tell you of some of the experiences I have encountered over the last few years while navigating my wife's care. Referrals to specialists often take months when quality care would necessitate a week at most. Calls to physician offices go through 'central scheduling' i.e., clerks with little expertise in triage. Calls for appointments for urgent or relatively urgent problems are referred to the ER or 911. Requests to speak with the physician are referred by central scheduling to the doctor's office. The call then goes to the nurses' voice mail, or the nurse practitioner's voice mail. "Leave a message and we will get back with you." If they call you back it is the nurse or PA. There is little, if any, direct contact with the doctor. Apparently medical offices' phones only do incoming not outgoing calls.

At hospitalization, patients are turned over to a hospitalist that is not familiar with the patient. Coordination is so bad that I ask: "Who is in charge of the care?" No one seems to know as all are under pressure and understaffed. It is terrifying to see there is no coordination of procedures, labs, and meds. Patients have sometimes been reduced to bringing in home medicines to assure essential medicines are given.

How did this happen? Who is to blame? What has Medicine become? How do we keep ourselves and our ill family members from being neglected, ignored, and mistreated by a failing system? Like Dr. Hagan I don't know the solution. I do know that his ill wife deserves better care, and my ill wife deserves better care. In fact, all patients deserve better care from our broken health care system.

My experience with some doctors has been good, even excellent at times. It is important to remember that doctors are under extraordinary pressure given the structural limitation and high demand. Some have even resigned overwhelmed by the high volume of patients and requirements set by others—usually not physicians.

The gold in the Golden Age of Medicine has been replaced by the basest of metals. Is it too much for hospitals, corporations, and private equity to provide quality, accessible, patient-oriented medical care? Apparently so! That is sad beyond words.

***Juan C. Corvalan, MD**, is a retired psychiatrist and Missouri Medicine Editorial Board member Section of Retired Physicians, St. Louis, Missouri, USA.*

## The Travesty of Physician Unavailability—My Thoughts Exactly

I read the editorial by John C. Hagan, III, MD, in the September/October 2025 *Missouri Medicine* issue with a feeling of anxious familiarity. His experiences with physician inaccessibility closely parallel my own. I share his concern about the future of health care access. I am grateful for bringing this immense concern to the membership's attention.

***Steven Shields, MD**, is Assistant Professor of Ophthalmology, Washington University School of Medicine, St. Louis, Missouri, USA.*

# In the News

## *Missouri Medicine* Announces New Board Members

*Missouri Medicine* announces new Editorial Board members. Board members are selected on the basis of exceptional professional accomplishment and expertise in their specialty.



**John B. Holds, MD, FACS,** an internationally known oculoplastic surgeon and world lecturer practicing in St. Louis, Missouri, has joined *Missouri Medicine's* Contributing Editors and Committee on Publication Board. He has served as our Ophthalmology Editorial Board member for over a decade.



**Blake Cooper, MD, MPH, FACS**, has joined the *Missouri Medicine* Editorial Board in Ophthalmology, beginning in January 2026. Dr. Cooper is an ophthalmologist at Retina Associates in Kansas City, Missouri. He is also President of Kansas City Society of Ophthalmology and on the Board of Directors of Missouri Society of Eye Physicians & Surgeons. He replaces John Holds, MD, who has accepted a position as a Contributing Editor to *Missouri Medicine*.



**David O. Barbe, MD. FAAP,** will be joining the *Missouri Medicine* Editorial Board in the newly created position of Physician Advocacy. Dr. Barbe retired in 2025 from a 40-plus year career in Family Medicine. He now sees patients at MSU Care Clinic in Springfield, Missouri. Long active in local, state, national, and international organized medicine, he served as the Physician Executive for Mercy Southwest Missouri, President of the Missouri State Medical Association, President of the American Medical Association, and President of the World Medical Association.



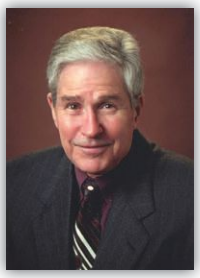
**William 'Russ' Carpenter, DO, FASAM**, has joined *Missouri Medicine* Editorial Board in Physician Wellness, beginning in January 2026. Dr. Carpenter is a psychiatrist at the Center for Mental Wellness at Capital Region Medical Center in Jefferson City, Missouri, and also the Director of the Missouri Physician and Health Professional Wellness Program (MOPHP). He replaces Stephen T. Keithahn, MD, who is retiring. We thank Dr. Keithahn for his

### Thank You Invited Peer Reviewers for 2025

*Missouri Medicine* would like to thank these invited peer-reviewers for their time and expertise this past year: John Vukich, MD, Vance Thompson, MD, Steve Slade, MD, Christian Rojas-Moreno, MD, Carissa van den Berk-Clark, PhD, Kenneth Haller, MD, Sarah S. Procknow, MD, Farrin Manian, MD, Carl V. Migliazzo, MD, Charles Lederer, MD, Brenda Rogers, MD and Catherine E. Hagan, PhD, DVM.

**MM**

# In Memoriam



## Thomas C. Sparkman, MD

**November 2, 1931 – October 13, 2025**

Thomas Carroll Sparkman, MD, family physicians and MSMA's 151st President, passed away on October 13, 2025, at the age of 93.

He was born on November 2, 1931, and was raised on a small family farm near Poplar Bluff, Missouri. His deep Christian faith, instilled early and carried throughout his life, guided every aspect of his personal and professional journey. As a longtime member of the Church of Christ, and later of St. Andrew Lutheran Church and Zion Lutheran Church, Tom lived by the example of Christ-selflessly serving his fellow man with gentleness, sacrifice, wisdom, dedication, and compassion.

After finishing his high school studies at age 16, Dr. Sparkman then studied at Harding College, David Lipscomb University, and then Southeast Missouri State University, earning a degree in education. He taught for four years in the rural Rushville Schools, a one-roomed school, before joining the Army during the Korean conflict. It was there he was trained as a medical specialist and his love for medicine was born.

Following his military service, he earned his medical degree from Baylor College of Medicine in Houston, Texas. In 1963, he began what would become a six-decade career of serving the Cape Girardeau area in family medicine. He was one of the first board-certified family physicians in Cape Girardeau, and a founding member of the Cape Girardeau Doctors' Park, where he served on the board as president for many years.

In 1979, he married Carol Wessell-Hahn. In his later years, Dr. Sparkman extended his care to the elderly and vulnerable, working with the Community Counseling Center, Crown Hospice, and serving as Medical Director for several nursing homes in the surrounding area, and even participated on a medical mission trip to Africa at age 80.



He was President of the Cape Girardeau County Area Medical Society and Missouri State Medical Association. He was an Alternate Delegate to the American Medical Association and an Associate Councilor for the Southern Medical Association. He was a member of the American Academy of Family Physicians, the Missouri Academy of Family Physicians, and the American Geriatrics Society. He participated in numerous medical research trials and introduced Cape County's first dialysis machine—an innovation that would later extend his own life. Dr. Sparkman also supported countless causes, including the Southeast Showcase, Saint Louis University, the American Cancer Society, and Southeast Missouri Hospital. **MM**






# NEW MSMA MEMBERS!

** = Resident/Fellow

* = Medical Student

Ali Ali, MD – Psychiatry – Cape Girardeau
Salamat Aliu-Ibrahim, MD – Pediatrics – Joplin
Aedra Andrade, MD – Family Practice – Joplin
Linda Barbour, MD – PMR – Kansas City
Christopher Brenner, DO – Anesthesiology – St. Louis
William Carpenter, DO – Addiction Medicine – Jefferson City
Emily George, MD – Pediatrics – Jefferson City
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Julie Riley, MD – Urology – Columbia
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Riya Parikh*
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Akhila Swara*
Elle Wilbers*




# Long COVID: What is it? Who has it? What Are Treatment Resources in Missouri?

*by Abby L. Cheng, MD, Ryan Barker, MSW, David von Nordheim, MS & Amy McQueen, PhD*

**A primary care clinician who completes 20 patient visits per weekday is likely interacting with five to six patients each week who are living with manifestations of Long COVID, whether recognized or not.**



Abby L. Cheng, MD, MPHS, (pictured), is Associate professor, Division of Musculoskeletal Physical Medicine and Rehabilitation, Department of Orthopaedic Surgery, Washington University School of Medicine, St. Louis, Missouri, USA. Ryan Barker, MSW, MPPA, is Chief Program and Policy Officer, St. Louis Integrated Health Network, Adjunct Professor, Washington University School of Public Health, St. Louis, Missouri, USA. David von Nordheim, MS, is Statistical Data Analyst, Department of Biostatistics, Washington University School of Medicine, St. Louis, Missouri, USA. Amy McQueen, PhD, is Professor, Washington University School of Public Health, St. Louis, Missouri, USA.

## Abstract

**As we pass the five-year mark since the COVID-19 pandemic hit, the prevalence of persistent (and often disabling) symptoms from the SARS-CoV-2 virus is estimated to be on par with the prevalence of heart disease. Yet, these Long COVID symptoms can masquerade as other conditions and/or normal aging, so it is believed that Long COVID is under-diagnosed and, as a result, under-treated. Although there is not yet a true cure for Long COVID, many patients benefit substantially from rehabilitation strategies, medications, and social support resources that are available in Missouri. The purpose of this article is to review the definition and epidemiology of Long COVID, provide practical guidance for Long COVID assessment and management especially in the primary care setting, and increase awareness of regional resources for people in Missouri who are living with Long COVID and for the clinicians who are caring for them.**

## Key Words

Long COVID, Postacute sequelae of COVID (PASC), SARS-CoV-2, assessment, management.

## Introduction

The five-year anniversary of the COVID-19 pandemic has passed, but the pandemic's effects have persisted. While many people have essentially returned to "life as normal," a significant number have been living with persistent and often disabling COVID-related symptoms for five years, and still others have developed persistent symptoms that were onset after a SARS-CoV-2 infection in just the past year.[1,2] Symptoms often include some combination of extreme fatigue, post-exertional malaise (PEM), difficulty concentrating or remembering (brain fog), lightheadedness and palpitations, breathing discomfort, and others, often despite normal findings on standard clinical tests.[3] The entity of Long COVID was first identified by patients and has subsequently been proven by numerous basic science and epidemiological studies.[4-9] Nevertheless, awareness that Long COVID exists and that management strategies are available has lagged behind, both in the healthcare community and in the general public. Furthermore, the COVID-19 pandemic disproportionately impacted racial minorities, so it would be expected that these populations are also disproportionately impacted by Long COVID; yet, they are also

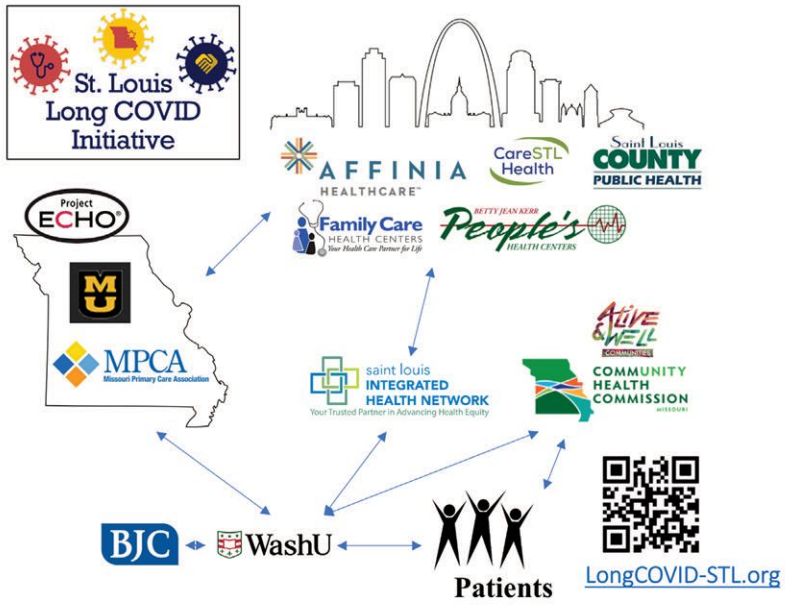



Figure 1. The St. Louis Long COVID Initiative is a community partnership whose goal is to support Long COVID care in Missouri. The QR code links to the Initiative's resource website, LongCOVID-STL.org.

the least likely to be aware of resources and options for care.[1] In 2023, a group of Missouri-based organizations created the St. Louis Long COVID Initiative and received federal funding to raise awareness about Long COVID and to develop Long COVID-related resources that support patients and primary care teams in our region (Figure 1).[10,11] The purpose of this article is to review the definition and epidemiology of Long COVID, offer practical guidance for Long COVID assessment and management especially in the primary care setting, and raise awareness about regional resources for people in Missouri who are living with Long COVID and for the clinicians who are caring for them.

## Definition and Pathophysiology

In 2024, the National Academies of Sciences, Engineering, and Medicine (NASEM) published the most widely accepted definition of Long COVID to-date, which is "an infection-associated chronic condition (IACC) that occurs after SARS-CoV-2 infection and is present for at least three months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems."[12] This definition was intended to promote ongoing Long COVID research and clinical care as the scientific community learns more about the condition and how to diagnose it. As such, the definition was intended to be highly sensitive, with the known tradeoff of lower specificity. The definition of Long COVID will likely evolve as clinically usable biomarkers become available.[7,13,14]

Long COVID pathophysiology is suspected to be multifactorial, which likely contributes to the variability of symptom constellations between patients. Leading pathophysiological contributors include: persistent reservoirs of SARS-CoV-2 virus in the body; autoimmunity and other immune dysregulation including reactivation of latent pathogens; dysfunctional brainstem signaling; impact on the microbiome; and endothelial dysfunction and microvascular clotting.[4-9] Although a reliable diagnostic test for clinical use has not yet been identified for Long COVID, cellular and signaling abnormalities have consistently been identified in basic science studies that have compared samples from people with Long COVID versus healthy controls. One example is that severe exercise-induced myopathy and amyloid-containing deposits in muscle tissue have been disproportionately found after exercise in people with post-exertional malaise related to Long COVID, when compared to people who symptomatically recovered after a SARS-CoV-2 infection.[15]

## Long COVID in Missouri

As of the final national COVID-19 Household Pulse Survey in September 2024 by the US Centers for Disease Control and Prevention, approximately 5.3% of US adults and 6.3% of adults in Missouri reported having symptoms "lasting three months or longer that [they] did not have prior to having COVID-19" (n=45,717).[1] About one in five of these adults reported that their symptoms resulted in significant limitations carrying out their day-to-day activities.[1,2] Anyone of any age or preexisting health status can develop Long COVID after a SARS-CoV-2 infection, but the recorded prevalence of Long COVID is relatively higher among females, middle-aged adults, and people who are not fully vaccinated or up-to-date on

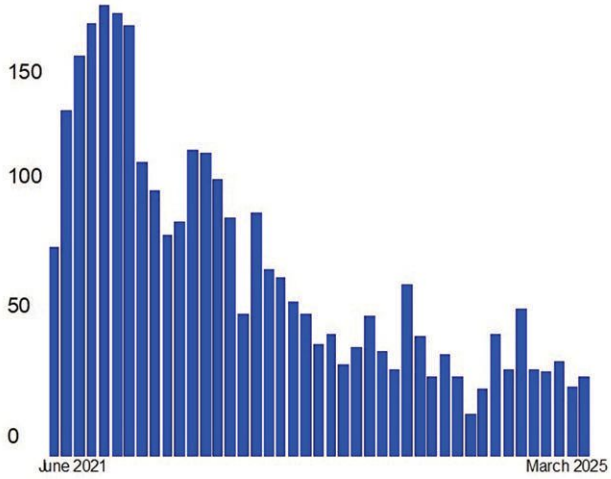



Figure 2: Number of unique patients diagnosed with Long COVID at WashU/BJC HealthCare facilities from June 1, 2021 through March 31, 2025.

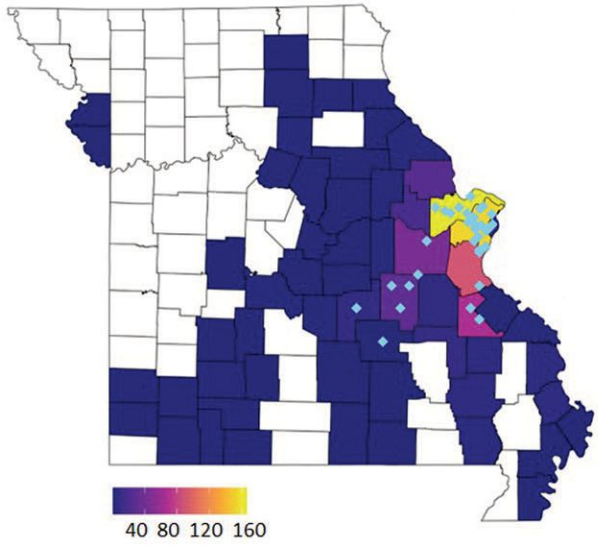



Figure 3: State-wide distribution of patients diagnosed with Long COVID at WashU/BJC HealthCare facilities from June 1, 2021 through March 31, 2025. The heat map colors represent the number of patients diagnosed in each county. The blue diamonds represent clinic locations within the health system.

boosters.[1,16-21] Although more recent estimates are not currently available on a statewide or national level, the prevalence estimates have been relatively stable since late 2022.[1,2,16,17,22,23] Compared to other well-known chronic diseases, the prevalence of Long COVID is comparable to the prevalence of coronary artery disease and cancer in US adults.[1,24-26] In other words, a primary care clinician who completes 20 patient visits per weekday is likely interacting with five to six patients each week who are living with manifestations of Long COVID, whether recognized or not.

From one health system alone in Missouri (WashU/BJC HealthCare), 4,776 unique patients were diagnosed with Long COVID between June 1, 2021 and March 31, 2025, using the International Classification of Diseases (ICD)-10 diagnosis code of "U09.9: Post COVID-19 condition, unspecified." Fewer than 20% of these patients were evaluated by the institution's dedicated Long COVID clinic, which affirms that most patients are being diagnosed and managed by primary and specialty clinicians who do not necessarily dedicate their practice to Long COVID care. New diagnoses peaked after the omicron variant and have declined over time, but new cases continue to occur and add to the ongoing disease burden of patients who have had persistent symptoms for years now (Figure 2). Figure 3 depicts the relative number of people from each county in Missouri who have been diagnosed with Long COVID at a WashU/BJC HealthCare clinic (shown as blue diamonds on the map). Not surprisingly, diagnoses tend to concentrate around clinic locations, and we strongly suspect that other people with Long COVID symptoms, particularly in northern and western Missouri, have sought care through other health systems, as well. These data from a single health system are not intended to be representative of all Long COVID cases in the state, but they do suggest that Long COVID is impacting residents across Missouri.

## Clinical Care Guidance

### *Evaluation and Diagnosis*

The first and most important step for clinicians in diagnosing Long COVID is to include it on the differential diagnosis for any patient who has a relatively sudden onset of new or significantly worsened symptoms without a clear cause, even if the patient does not recall a preceding symptomatic SARS-CoV-2 infection. Patients with undiagnosed Long COVID may present with concerns such as fatigue, brain fog (e.g., difficulty focusing or remembering), palpitations, headaches, dizziness, abdominal pain, sleep disruption, or other common symptoms, and they may make statements such as, "I don't have the energy that I used to," "I can't remember things anymore," "I don't

feel like myself," or even, "I'm just getting older." Long COVID is currently a clinical diagnosis made from a standard history and physical examination, and no confirmatory clinical diagnostic test exists yet. Nevertheless, symptom-based laboratory and imaging workup is warranted to evaluate for competing and/or coexisting conditions which may have different treatment paths.[3] When the diagnosis of Long COVID is made, the patient should be assigned a primary ICD-10 diagnosis code consistent with their primary symptom(s) and a secondary ICD-10 code of "U09.9: Post COVID-19 condition, unspecified." Use of this accepted documentation convention contributes to large-scale Long COVID monitoring efforts, and it could facilitate notification to the patient of novel relevant treatments that are approved in the future.

### *Experience Validation*

A key, and often overlooked, element of Long COVID management is to first validate the patient's symptoms and experience. Long COVID is still a relatively novel condition with numerous unknowns and variable awareness among the healthcare and general community, alike.[27] As a result, many people with Long COVID have been told by family members, friends, and healthcare practitioners that they are exaggerating or fabricating symptoms, or that their symptoms have been misattributed to preexisting conditions, "stress," "not exercising enough," or "being all in their head." These assertions can compound distress that the person is already experiencing due to their symptoms and their subsequent difficulty keeping up occupationally, financially, and at home. These misattributions can also undermine patients' trust in the healthcare system and lead to delays in proper diagnosis and management. Furthermore, these assertions are untrue and contrary to existing evidence.

### *Symptomatic Management*

There is currently no cure for Long COVID, although multiple pathobiology studies and clinical trials are in process.[28] For now, the mainstay of Long COVID treatment is to alleviate symptoms by:

- Managing symptom triggers by pacing and prioritizing activities, employing energy conservation strategies, and implementing workplace and school accommodations;
- Addressing modifiable risk factors related to nutrition, sleep, risky substance use, social isolation, re-infection mitigation, and coexisting medical conditions;
- Optimizing medications with slowly titrated, symptom-based medication trials and de-prescription of medications that could be exacerbating symptoms;
- Referring to rehabilitative services as needed, including physical therapy, occupational therapy, speech therapy, and vocational rehabilitation.

When referring to therapists who may not be familiar with Long COVID management, a "chronic fatigue syndrome" and/or "dysautonomia" type of approach should be recommended. For instance, physical therapy for Long COVID should focus on identifying symptom triggers and learning to pace activities and modify activities, rather than immediately working on strength or endurance training which can trigger exercise-induced myopathy and amyloid deposition in muscle tissue.[15]

## Point-of-Care Guidance

The sheer prevalence of Long COVID is resulting in increasing burden on primary care clinicians to diagnose, educate, and initiate management and referrals for patients with Long COVID. This increasing burden is compounded because: 1) clinical encounters for patients with Long COVID can be time-intensive since Long COVID often manifests as multiple bothersome symptoms that can masquerade as, or coexist with, other medical conditions that must be investigated during evaluation; 2) patients with limited knowledge of Long COVID may have numerous questions for their clinician; and 3) insufficient management of Long COVID symptoms can result in repeated outpatient and emergency department visits.[29,30] In response, the American Academy of Physical Medicine and Rehabilitation (AAPM&R) Multi-Disciplinary Long COVID Collaborative recently published a compendium guidance statement which features succinct, actionable tables that are designed for primary care, rehabilitation, and other front-line clinicians to use for real-time reference during clinical care as needed.[3] The compendium content includes: common symptoms (and differential diagnoses) for

**Table 1. Patient- and clinician-facing Long COVID resources in Missouri.[a]**

| Resource | Description | Details |
|---|---|---|
| ***Informational Resources*** | | |
| LongCOVID-STL.org | Patient- and clinician-facing website | Patient-facing content:<br>• General information<br>• Self-management strategies<br>• Links to regional organizations that offer social & financial support<br>• Flyers for research studies recruiting from Missouri<br><br>Clinician-facing content:<br>• Referral instructions for regional clinics<br>• Links to published guidance statements (e.g., AAPM&R Long COVID compendium guidance[3])<br>• Templated text for notes and therapy referrals<br>• Quick tips for supporting patients through disability applications |
| Long COVID ECHOs[32] | Clinician-facing education | • One hour of didactics and case presentation<br>• Free CME credits available<br>• Schedule and recordings of previous sessions available at https://ShowMeECHO.org/special-echo-sessions |
| Printed materials | Patient- and clinician-facing education | • General information to raise awareness about Long COVID<br>• Recommendations for completing disability applications<br>• Available for download at LongCOVID-STL.org |
| ***Clinical Care Resources*** | | |
| Multidisciplinary Long COVID clinic[b] | Comprehensive evaluation and management initiation | • Includes medical consultation and patient education, social work support, and referral for subspecialty and rehabilitation services as needed<br>• In-person and telehealth options |
| Shared Medical Appointments (SMAs) for physical, occupational, and speech therapy[b31] | Rehabilitative care | • "Group visit" format for patients to learn and practice rehabilitative strategies (e.g., pacing, energy conservation, activity monitoring, memory/attention strategies) with a physical, occupational, and speech therapist<br>• Telehealth format<br>• Covered by Missouri Medicaid and other insurers<br>• Secondarily provides peer support and social connection |
| ***Social Support Resources*** | | |
| Case management support | Patient advocate and guide | • Phone, e-mail, and/or in-person connection with a community health worker (CHW) or community referral coordinator (CRC) to assist with identifying clinical and social support resources, arranging medical appointments, applying for financial assistance and disability, etc.<br>• Contact information at LongCOVID-STL.org<br>• Free to all |
| Peer support group[c] | Peer interaction, validation, and learning | • Facilitated by a behavioral health counselor<br>• In-person and virtual options; 1 hour/week<br>• Free to all |

[a]This list is not necessarily all-inclusive and will likely evolve over time.
[b]Referral instructions for these clinical care resources can be found at LongCOVID-STL.org by navigating to "For Clinicians" and then "Referral Process for Regional Long COVID Clinics."
[c]Sign-up information for the peer support group can be found at LongCOVID-STL.org by navigating to "For Patients" and then "Community Resources," "Long COVID peer support," and "St. Louis Long COVID Initiative peer support group."
Abbreviations: AAPM&R (American Academy of Physical Medicine and Rehabilitation), ECHO (Extension for Community Healthcare Outcomes), CME (Continuing Medical Education).

Long COVID; key history and physical examination elements to consider; symptom-specific laboratory and imaging studies to consider; rehabilitation- and medication-based management options; and example phrases that clinicians can use to counsel patients regarding what Long COVID is, what to expect regarding treatment and prognosis, and persistent unknowns related to Long COVID. This compendium can serve as a "pocket guide" for on-demand reference.

## Missouri Resources for Long COVID

Funded by a grant from the Agency for Healthcare Research and Quality (AHRQ) in 2023,[10,11] the St. Louis Long COVID Initiative was created as a community partnership of existing healthcare organizations to raise awareness about Long COVID and develop Long COVID-related resources that support patients and primary care teams in Missouri and the surrounding region (Table 1). Resources have been co-developed in collaboration with regional leaders and people with lived experience with Long COVID, with intentionality to reach as many communities and people in need as possible. Continuation of Long COVID related grant funding is necessary in order to continue providing some of these resources (e.g., case management, development and face-to-face delivery of educational information); nevertheless, many of the resources that have so far been developed by the Initiative have been archived for future use and/or will continue to be available for the foreseeable future, at least in some form.

Patient-facing Long COVID regional resources that have been developed, supported, or expanded by the Initiative so far include: multidisciplinary clinical consultative care, access to group rehabilitative (physical, occupational, speech) therapy that is covered by Missouri Medicaid,[31] case management support, a peer support group with in-person and virtual attendance options moderated by a behavioral health clinician, and an informational website at LongCOVID-STL.org (Table 1). The website's patient-facing section includes: contact information for the case managers; general information about Long COVID; recommendations and worksheets to prepare for a medical visit related to Long COVID; links to workbooks and videos for self-management of common Long COVID symptoms such as energy crashes, dysautonomia, brain fog, and sleep difficulty; regional community resources for social and financial assistance; guidance to obtain school accommodations for children with Long COVID; and flyers for regional Long COVID research studies that are open to recruitment.

Clinician-facing Long COVID regional resources include: free education sessions via the University of Missouri's Show-Me ECHO program (also recorded and freely available for asynchronous viewing),[32] patient referral options for in-person or telehealth Long COVID specialty medical care and rehabilitation, and an informational website (LongCOVID-STL.org) (Table 1). The website's clinician-facing section includes: detailed referral instructions to Long COVID specialty care in the region; links to symptom-based management algorithms; clinical efficiency tools such as templated text for notes and therapy referrals; tips for supporting patients through disability applications when appropriate; printable flyers with information on Long COVID symptoms, regional resources, and disability considerations; and links to other national resources.

Additional resources for Long COVID clinical care may be available in Missouri. Of note, however, many multidisciplinary Long COVID clinics across the state and country have closed in recent years, especially if not grant-supported. This landscape may well continue to evolve.

## Conclusion

There is currently no cure for Long COVID. Nevertheless, we can make a positive impact in patients' lives by identifying those who have Long COVID, evaluating for potential coexisting conditions, validating their experiences, and directing them to supportive treatments which can improve their quality of life (e.g., pacing and energy conservation strategies for post-exertional malaise, rather than graded exercise programs). By making the appropriate diagnosis of Long COVID in the approximately one in 20 adults who have it, these patients and their healthcare providers can also stay alert for evidence advances and potential new treatments that are developed in the future. For the time-being, Missouri clinicians can leverage national guidance such as the AAPM&R Long COVID compendium statement and refer to regional resources such as the St. Louis Long COVID Initiative's LongCOVID-STL.org website to assist with delivering high-quality Long COVID care within a busy clinical environment.

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# Tattoo-Related Skin Reactions: Clinical Complications, Emerging Trends, and Management Strategies

*by Zainab P. Mohammodu, MD, Damien Abreu, MD, PhD, Kandice Bailey, MD & M. Laurin Council, MD*

**Despite their popularity, tattoos are not without clinical implications, including inflammatory reactions, infections, scarring, and even associations with cutaneous malignancies.**



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## Abstract

**Tattoos have been culturally significant throughout history and continue to serve as an avenue for self-expression, cosmetic enhancement, and medical applications in the modern era. Despite their popularity, tattoos are not without clinical implications, including inflammatory reactions, infections, scarring, and even associations with cutaneous malignancies. This review explores the natural course of tattoo-related skin reactions, focusing on the acute and chronic inflammatory responses to pigment deposition, including allergic contact dermatitis, lichenoid reactions, and granulomatous inflammation.**

**Tattoo-related infections, ranging from bacterial to viral and fungal, are also discussed, highlighting the importance of sterile tattooing practices. Further, the potential for scarring, including hypertrophic scars, keloids, and dermatofibromas, is evaluated, particularly in individuals with a predisposition for abnormal wound healing. Although no direct causative link between tattoos and skin cancers has been established, tattoos can obscure early detection of malignancies, potentially delaying diagnosis and increasing morbidity.**

**This article also examines emerging trends in cosmetic tattooing, such as scleral tattoos, microblading, and scar camouflage, noting both the benefits and potential complications. Management strategies for tattoo complications, including medical and procedural interventions, are outlined. Treatments include corticosteroids for inflammatory reactions, laser therapy for pigment alteration, and surgical options for severe scarring. The growing field of cosmetic tattooing requires continued research into the long-term outcomes and management of tattoo-related complications to ensure both aesthetic and medical safety for individuals seeking these modifications.**

## Key Words

Tattoos, dermatology, dermatitis, lichenoid reactions, granulomatous inflammation.

## Introduction

Tattoos have historically rendered significance that spans

**Table 1.1 – Summary of Tattoo-Related Reactions**

| Tattoo-Related Reaction | Clinical Findings | Histopathologic Findings |
|---|---|---|
| ***Inflammatory Reactions*** | | |
| Allergic Contact Dermatitis (ACD) | Erythema, edema, papules, nodules, vesicles/bullae localized to tattoo site, itching<br><br>*Red tattoos commonly implicated* | Epidermal edema, eosinophils |
| **Lichenoid Reactions** | Erythematous, scaly, flat-topped papules or plaques<br><br>*risk of Koebner phenomenon in pre-existing lichen planus* | Dense lymphocytic band along dermal-epidermal junction; necrosis of basal keratinocytes |
| **Foreign Body Granulomas** | Erythematous papules or nodules, localized to tattoo site; +/- tenderness or itching | Multinucleated giant cells containing tattoo pigment |
| **Sarcoidal Granulomas** | Erythema, nodule formation at the tattoo site; may represent localized cutaneous or systemic sarcoidosis | Epithelioid histiocytes aggregates, few lymphocytes ("naked granulomas"); further evaluation for systemic sarcoidosis needed |
| **Tattoo-Related Uveitis** | Eye pain, redness, blurred vision | No specific histopathologic description provided, but linked to systemic sarcoid-like processes |
| **Infectious Granulomas** | Red papules, nodules, pustules, abscesses; necrosis or systemic infection may occur, especially in immunocompromised individuals | Tuberculoid granulomas: histiocytes with or without central necrosis surrounded by lymphocytes<br><br>Suppurative granulomas: epithelioid histiocytes with central neutrophils (abscesses) |
| **Bacterial Infections** | Impetigo, cellulitis, erysipelas, abscesses; may be localized or systemic | Varies based on clinical presentation and causative organism |
| **Viral Infections** | HSV, HPV, molluscum contagiosum; systemic and localized presentations | Varies based on clinical presentation and causative organism |
| **Fungal Infections** | Varies based on causative organism | Varies based on clinical presentation and causative organism |
| **Scarring** | Keloids, hypertrophic scars, dermatofibromas (firm nodules, "dimple sign") | Varies depending on the type of scar |
| **Cutaneous Malignancies** | Skin cancers like SCC, BCC, malignant melanoma; tattoos may obscure early detection | Varies depending on the neoplasm |

across various modalities of cultural expression. In our most ancient civilizations, tattoos were used as symbols to commemorate the dead, as a means of adornment, and under grave circumstances, could even be used as a form of punishment. In our modern era, tattoos continue to be an avenue of self-expression for many individuals and have taken on new practical uses through cosmetic (including permanent makeup and scar camouflage) and medical applications (Figure 1).Tattoos are often composed of organic or inorganic dye compounds suspended in an antimicrobial solvent that allows for smooth subcutaneous application.

## Natural Course of Cutaneous Tattoo Reaction

The deposition of exogenous particles below the dermo-epidermal junction for tattooing causes disruption of the epidermal barrier leading to an acute inflammatory response. This manifests histologically as transient edema and polymorphonuclear leukocyte phagocytosis of pigment.[1] By 24 hours, pigment is found in cytoplasmic phagosomes of keratinocytes, histiocytes, mast cells, fibroblasts and Langerhans cells, with transepidermal elimination of pigment occurring up to one month after tattooing as the basement membrane heals.[2,3] Tender lymphadenopathy may also occur due to smaller pigment particles draining to regional lymph nodes.[4]

## Inflammatory Reactions

Tattoos hold clinical importance for physicians due to the various complications that may occur due to placement of external pigments into the skin. These include inflammatory reactions, infections, scarring, and neoplasms. The clinical and histologic presentations of these complications are summarized in Table 1.

Inflammatory reactions associated with tattoos vary widely in both clinical appearance and histopathological presentation. The most common of these reactions is an allergic reaction, which commonly manifests as allergic contact dermatitis (ACD).[5]

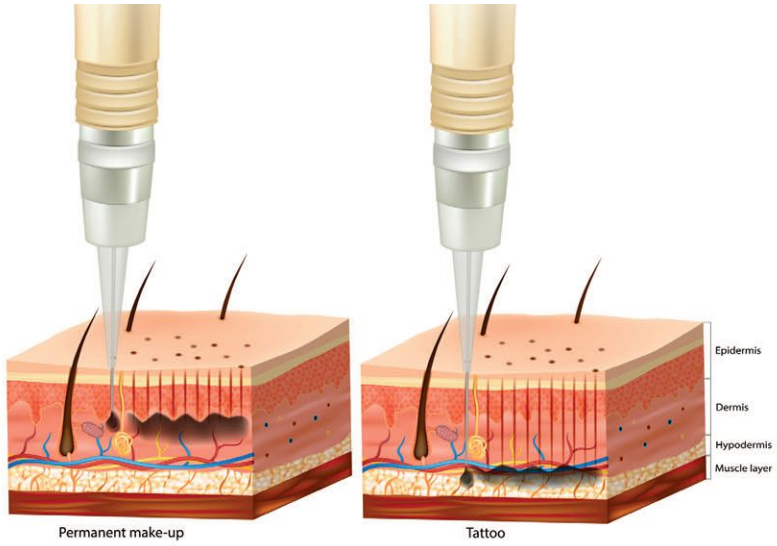



**Figure 1.** Difference between tattoo and permanent make-up process. Pigment under layers skin of Epidermis, Dermis and Gipodermis.

Clinically, ACD typically manifests as erythema, edema, papules, nodules, and/or vesicles/bullae in areas of pigment; however, more generalized rashes and even systemic manifestations of lymphadenopathy have been reported.[6,7] Histologically, contact dermatitis demonstrates variable spongiosis and dermal edema along with a dermal infiltrate composed of eosinophils, lymphocytes, and histiocytes. Red tattoos remain the most common ink pigment implicated in tattoo-associated ACD due to mercury sulfide or cinnabar. Even with its popular replacement with organic dyes, such as azo pigments, this has not decreased the association between red pigment and ACD.[8] Other ink components, such as nickel, cobalt, and cadmium are also known to cause ACD. Knowledge of this tattoo complication is valuable to avoid misdiagnosis and delay of appropriate treatment.[9]

Lichenoid reactions are clinically characterized by erythematous, scaly, flat-topped papules or plaques. This reaction may represent an allergic response or idiopathic lichen planus (LP).[10,11] Histologically, these lesions show dense lymphocytic band along the dermal-epidermal junction, which may obscure the junction and cause necrosis of basal keratinocytes. Individuals with pre-existing lichen planus should be cautioned against tattoos to prevent the exacerbation via Koebner phenomenon, new skin lesions at sites of skin trauma or injury in individuals with certain inflammatory skin conditions.

Granulomatous reactions must be confirmed via histology due to their varied clinical manifestations. Foreign body granulomas show multinucleated giant cells containing tattoo pigment on histology, presenting as erythematous papules or nodules localized to the tattoo site.[12]

Sarcoidal granulomas in tattoos may indicate either localized or systemic disease.[13-15] Histologically, sarcoidal granulomas, sometimes referred to as "naked" granulomas, consist of aggregates of epithelioid histiocytes without surrounding lymphocytes. The presence of tattoo-induced sarcoidal granulomas should prompt further investigation for systemic sarcoidosis for appropriate long-term management.[16-19]

Infectious granulomas are caused by introduction of infectious organisms during the tattooing process.[20] Ink may become contaminated either before or immediately before use. Clinically, infectious granulomas can present with mild inflammation (red papules, nodules, or pustules), abscesses, necrosis, or even systemic infection especially in the immunocompromised. Suppurative granulomas often indicating a non-tuberculoid mycobacterial or deep fungal infection.[21] Tuberculoid granulomas commonly seen in mycobacterial infections.[22,23] Both tuberculosis and leprosy have been linked to tattoos.[24]

## Infections

Tattoos involve breaking the skin's barrier, leading to risk of infectious agents, such as bacteria, viruses, and fungi, most significant being hepatitis B and C, HIV, and syphilis.[25] The CDC notes that while the risk of HIV and transfusion-related infections is low due to strict hygiene regulations, the risk increases considerably when tattoos are performed in unregulated or unsanitary environments by unlicensed individuals (Centers for Disease Control and Prevention. HIV transmission).

Rarer complications like toxic shock syndrome and infective endocarditis have also been reported post-tattooing.[26,27] Viral infections such as herpes simplex virus, HPV, and molluscum contagiosum have been linked to tattoos, along with a reports of fungal infections after tattoo procedures.[28-30]



**Figure 2.** Keloid from a tattoo.

## Scarring

The physical trauma from tattooing often leads to scarring putting individuals at risk for developing a specific type of scar called a dermatofibroma, a firm subcutaneous nodule.[31] Other forms of scarring, such as hypertrophic scars and keloids, are also common complications from tattoos.[32-,33] Individuals with a history of abnormal scarring, such as keloid formation, should be cautioned prior to obtaining tattoos due to increased scarring risk (Figure 2).

## Cutaneous Malignancies

There have been several reports of skin cancers, such as squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and malignant melanoma, arising within a tattoo. Diagnosis of these malignancies requires skin biopsy and histologic evaluation.[33-36] However, previous studies have not demonstrated a causal relationship between tattoos and the development of cutaneous malignancies. Despite this, physicians should be aware of the appearance of cutaneous malignancies within tattoos during skin evaluations. The presence of tattoo pigment can obscure the early detection of underlying skin cancers, potentially delaying diagnosis and increasing associated morbidity.[36,37]

## New Trends in Cosmetic Tattoos

### *Scleral Tattoos*

While cosmetic tattoo enhancement of periocular structures has a long global history, the realm of extreme body modification grew in 2007 with the advent of scleral tattooing.[38] (Figure 3). This practice, colloquially termed "eyeball tattooing," has been associated with a wide spectrum of severe ocular complications ranging from globe penetration, orbital cellulitis, and inflammatory foreign body reactions to rare case reports of cutaneous sarcoidosis at distant sites.[39,40] Given that the dyes used for subconjunctival application are the same as those used for skin tattoos, it is not surprising that allergic contact conjunctivitis and periocular dermatitis have also been reported as complications.[41] Long-term effects of scleral tattooing will require further monitoring, but the known risk profile of this cosmetic practice has already garnered legislative bans in Oklahoma, Indiana, and Washington.

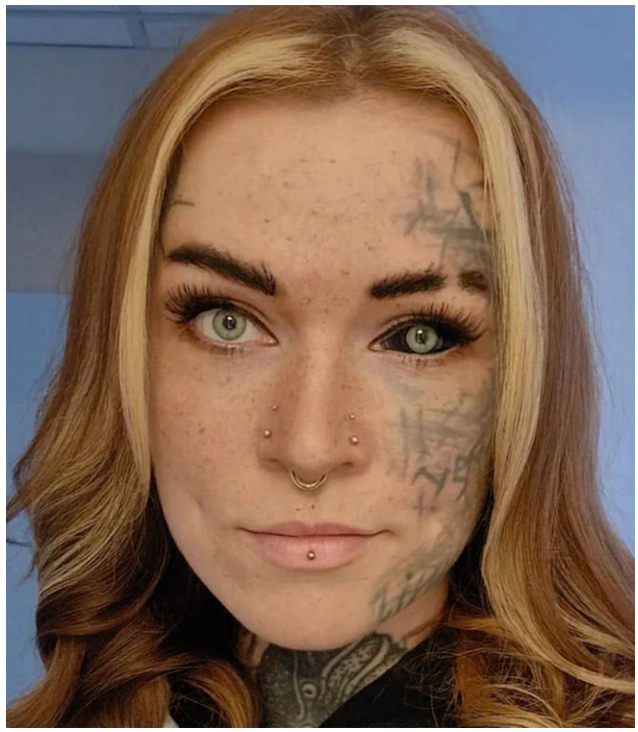


**Figure 3.** Scleral tattoo.

### *Microblading*

Cosmetic tattoos have gained popularity because of their use for superficial enhancement. Microblading is the practice of using a multi layered blade to introduce hair stroke- like pigment to the papillary dermis of the eyebrows for the appearance of increased density. Pigmentation used for this practice often requires a unique blend of multiple colors to mimic the shade of natural hair color.

### *Scar Camouflage*

The utility of scar camouflage has proven beneficial for people with long-standing scars resulting in discoloration. Iron oxides have shown to be the pigmentation of choice as they are most likely to mimic the natural undertones of skin color and are less likely to cause an allergic reaction. Cosmetic options for dyspigmentation management come with its limitations as with all tattoos, as multiple environmental processes such as the breakdown of dye in the setting of ultraviolet light exposure and the role of macrophages of the skin's immune system engulfing deposited pigment overtime can lead to faded and undesired results.

## Management of Tattoo Complications

Inflammatory tattoo reactions can be managed using both medical and procedural interventions. For granulomatous tattoo reactions, therapy using intralesional steroid or topical high potency steroid are mainstays treatment. The anti-inflammatory effects of tetracyclines have also proven useful for treatment of granulomatous tattoo reactions.[42,43] For systemic manifestations, referral to appropriate specialists is recommended. Lichenoid tattoo reactions can also be managed with high potency topical corticosteroids and have had treatment efficacy with topical non-steroidal medications such as tacrolimus or pimecrolimus. Lastly, surgical excision can be used for secondary keloid scarring or recalcitrant granulomatous reactions.

A common complication of cosmetic tattoos is the discoloration they inevitably undergo over time. Utilizing lasers of varying wavelengths to target customized pigment mixtures for cosmetic pigment has become standard therapy for removal (Figure 3).

Lasers at 1,064 nm have proven to be an effective wavelength for removing dark brown and black pigment along delicate and sensitive areas of the face such as the lips, eyelid margins, and eyebrows.[44] The endpoint of laser treatment is defined by whitening of the skin with mild pinpoint bleeding. It is important to keep in mind this therapy may require multiple sessions using varying appropriate wavelengths for corresponding hidden undertones that become more prominent during the treatment course. Other treatment-induced color changes include paradoxical darkening which can be seen in the chemical reduction of ferric oxide to ferrous oxide in brown pigment and transient hyperpigmentation.[45] This phenomena should be disclosed to patients seeking treatment of sensitive cosmetic areas such as the eyes and lips.[46] There are additional case studies where the option of using both 532nm/1064nm picosecond wavelengths have shown to have superior results as the higher peak frequency allows for pigment target versatility and quick dissolution of pigment particles.[44]



**Figure 4.** Results of tattoo removal.

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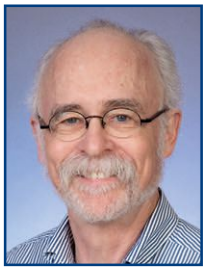
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# Autism Spectrum Disorder: Nature vs. Nurture

*by Joel C. Eissenberg, PhD*

**A better understanding of the gene-environment relationship in ASD will likely lead to more effective interventions.**



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## Abstract

**Autism Spectrum Disorder (ASD) is associated with a variety of inherited disorders, but most diagnoses have no identifiable genetic etiology. There has been a significant increase in the incidence of ASD diagnoses in the past three decades. The now-discredited vaccine theory of ASD causation has driven concerns over environmental exposures that may or may not lead to ASD. Here, I discuss the evidence for an underlying genetic basis for ASD, the evidence that environmental inputs could play a significant role ASD and potential treatments for associated symptoms.**

## Key Words

Autism spectrum disorder, autism genetics, microbiome, autism therapy.

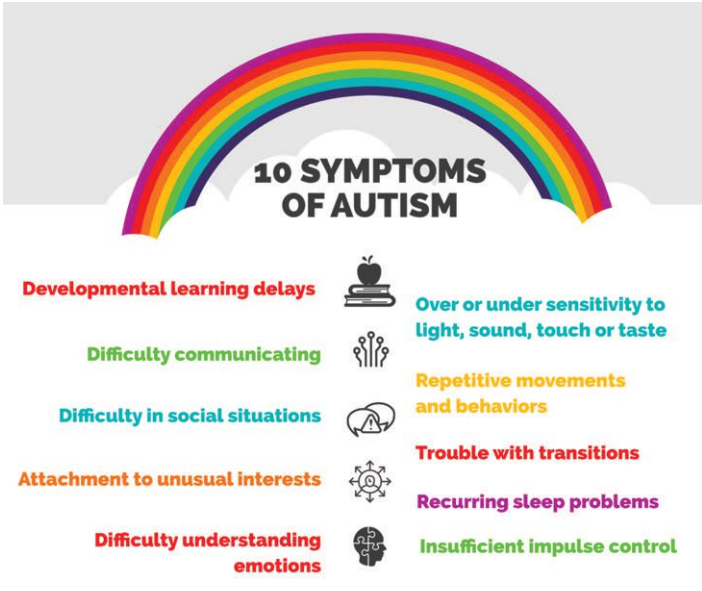
## Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that typically emerges early in life and is characterized by impaired social communication and interaction as well as by restricted, repetitive or stereotypical behaviors and restricted interests (Figure 1). While symptoms of ASD often develop early in life, they typically become evident between the age of one to two years, when social and emotional development progresses rapidly and delays become conspicuous. Symptoms may also be masked by adaptive strategies or cultural norms which may bias diagnosis in certain groups. One to one-and-a-half percent of the global population is believed to be affected by ASD,[1,2] with a 3.5-5-fold percent higher prevalence among males.

The incidence of ASD diagnosis has increased dramatically in the past 20 years (Figure 2), leading to questions about changes in environmental exposures driving this increase. While this is possible, it is important to stress that while the diagnosis of ASD has increased, the prevalence of ASD has not necessarily changed. For example, changes in diagnostic criteria, widespread use of screening tools, and increased recognition of symptoms have all contributed to the increase in ASD diagnosis.[3]

The diagnostic criteria for ASD have changed with the release of the fifth edition of the Diagnostic and Statistical Manual of Mental Illnesses (DSM-5) in 2013, which collapsed previously distinct diagnoses like autistic disorder, Asperger's, and pervasive developmental disorder not otherwise specified into a single diagnosis of ASD.[4] The DSM-5 diagnostic criteria include persistent deficits in social communication and social interaction, restricted, repetitive patterns of behavior,

**Figure 1.** 10 Symptoms of Autism




*Source: https://www.appliedbehavioranalysisprograms.com/lists/5-symptoms-of-autism/*

interests, or activities with symptom onset in the early developmental period. Consolidation of various autism subtypes into a single diagnosis likely contributes considerably to the increase in ASD diagnoses, since the broader criteria in DSM-5 may include individuals who would not have been diagnosed under the DSM-IV criteria. That said, a real increase in ASD rate cannot currently be excluded.

## The Refrigerator Parent Theory and ASD

Early theories surrounding autism centered on environment. Kanner[5] invoked "parental coldness, obsessiveness, and a mechanical type of attention to material needs only.... They were left neatly in refrigerators which did not defrost." This idea was also promoted by the well-known Freudian psychologist Bruno Bettelheim.[6] The hypothesis that autism was due to "refrigerator parents" who were cold and rejecting was popular in the psychiatric community through the 1960s in the absence of an alternative biomedical mechanism.

This theory placed blame on parents of children with ASD, leading to a sense of guilt and shame and stigmatizing the diagnosis, despite the fact that no one can control their genetics.

## Genetics and ASD

The main risk factor for ASD is genetics. However, it's important to stress that there is no such thing as "the gene for ASD." There are variants ("alleles") of approximately 800 genes and genomic regions that increase the risk for ASD.[7,8] The risk for ASD and the severity of symptoms is dependent on the gene(s), variants, and the individual's genetic background (polygenic effect) on the individual. Manifestation may also be affected by environmental inputs.

### *Twin-Pair Studies and Autism Heritability*

Several familial and twin-pair studies demonstrate a heritability of 60-90% for ASD.[9-11] Both rare and common genetic variants are believed to contribute to risk of ASD in an additive fashion. But what about the other 10-40%? Some cases are explained by *de novo* variants that occurred during spermatogenesis or oogenesis. For many syndromes that include ASD—for example Rett syndrome—individuals rarely have descendants, so nearly all cases of Rett syndrome-associated ASD are due to *de novo* variants.

### *Allelic Associations with ASD*

There are a number of syndromic neurodevelopmental disorders that are associated with ASD including Fragile X syndrome, Rett syndrome, Tuberous Sclerosis Complex, Angelman syndrome, Phelan-McDermid syndrome, Cornelia de Lange syndrome, Down syndrome, Smith-Lemli-Opitz syndrome, Smith Magenis syndrome, Sotos syndrome, CHARGE syndrome, Snijders Blok-Campeau syndrome, Neurofibromatosis type I, and Prader-Willi syndrome. Note, however, that the occurrence and severity of ASD can vary between disorders and even within families.

In genomic studies of syndromic and non-syndromic ASD in humans, as well as in mouse studies, there are variants in numerous genes involving various pathway that have been implicated in ASD[12] (Table 1 for a small sample). As of this writing, no unified theory exists for how ASD-related variant molecules drive abnormal synaptic connections and in which specific brain regions or circuits they operate.

## Environmental Inputs to ASD

While current research points to an underlying genetic mechanism for most or all cases of ASD, environmental factors can influence the phenotypic

**Table 1.** Selected Genes with Alleles Implicated in ASD

| Gene | Gene product |
|---|---|
| ***FMR1*** | Multifunctional polyribosome-associated RNA-binding protein that regulates alternative mRNA splicing, mRNA stability, mRNA dendritic transport and postsynaptic local protein synthesis of target mRNAs; implicated in Fragile X syndrome |
| ***MECP2*** | Chromosomal protein that binds to methylated DNA and mediates transcriptional repression; implicated in Rett Syndrome |
| ***SHANK3*** | Scaffold postsynaptic density protein that orchestrates dendritic spine and synapse formation, maturation and maintenance; variants are linked to Phelan-McDermid syndrome |
| ***MEF2C*** | Transcription activator that plays an essential role in hippocampal-dependent learning and memory by suppressing the number of excitatory synapses |
| ***CHD3*** | ATP-dependent helicase that participates in the remodeling of chromatin for gene transcription; variants are implicated in Snijders Blok-Campeau syndrome |
| ***CHD7*** | Contains several helicase family domains; implicated in CHARGE syndrome |
| ***DDX3X*** | ATP-dependent RNA helicase involved in protein biosynthesis and cell signaling |
| ***SENP1*** | Cellular enzyme that regulates protein turnover |
| ***GIGYF1*** | Adaptor protein that binds growth factors and regulates cell signaling |
| ***TAOK1*** | Enzyme that phosphorylates proteins and plays an essential role in the regulation of neuronal development in the central nervous system |
| ***SRCAP*** | Protein that remodels chromatin for transcription of genes implicated in neurogenesis and several behavioral abnormalities; variants are associated with Floating Harbor syndrome |
| ***NF1*** | Negative regulator of cell proliferation through the *ras* signaling pathway; variants are implicated in Neurofibromatosis, Type I |

variability of ASD.[13,14] The list of hypotheses and speculations for environmental inputs to ASD is far too long to cover exhaustively here. Discussed here is a short list of examples that lend themselves to intervention and/or therapies, as well as highlighting theories that are discredited or implausible but have been mentioned in the press and might be on the minds of individuals with ASD or their guardians

## *ASD, Diet, and the Gut Microbiome*

Diet can influence the expressivity of genetic traits and disorders. A dramatic example of how environment can affect symptoms of a genetic disorder is phenylketonuria, (PKU), which is caused by a deficiency of phenylalanine hydroxylase, an enzyme essential for breaking down the amino acid phenylalanine. In individuals with PKU, toxic phenylalanine metabolites build up in the blood, leading to brain damage. A life-long diet that minimizes phenylalanine can mitigate this damage. Thus, while dietary phenylalanine doesn't cause PKU, it is required for manifestation of the disease symptoms.

Diet has strong effects on the identity and diversity of gut microbes in individuals with ASD. These individuals often have food aversions and dietary selectivity that result in an unbalanced diet, disrupting the microbiome, the gut-brain axis, and causing nutritional deficiencies. ASD is also associated with an increased incidence of immune dysfunction, leading to increased prescription of antibiotics that also disrupt a healthy gut microbiome. While there is no consensus in the literature as to which microbes and in what proportions define a healthy microbiome,[15] disruption of the normal gut flora has been implicated in numerous gastrointestinal symptoms (constipation, diarrhea, abdominal pain, bloating, gastroesophageal reflux, vomiting, and food sensitivities). Microbially-derived metabolites such as trace amines and short chain fatty acids could contribute to ASD symptoms via gut-brain signaling.[15,16] Microbiota transplant therapy (MTT)—transplanting gut microbiota from a healthy donor into a patient to modify their gut microbiota—has been suggested as a therapy to normalize gut microflora in individuals with ASD,

possibly blunting the ASD symptoms.[17] Several small-scale studies and case studies of MTT in individuals with ASD have reported significant improvement in both gastrointestinal and behavioral symptoms (reviewed in Ref. 17), but larger scale randomized, double-blind, placebo-controlled studies are needed to confirm these findings. However, the use of antibiotics after MTT may well affect its long-term durability.

### *Prenatal Valproate Exposure*

Valproate is a commonly prescribed drug used to treat epilepsy, bipolar disorder, and other neuropsychological disorders. It acts by enhancing inhibitory neurotransmission and modulating voltage-gated ion channels. However, valproic acid is also a potent teratogen[18] and valproate exposure during pregnancy is associated with a high risk for ASD in humans and in rodent models.[19-21] *In utero* exposure in rodent models showed that valproic acid impairs neural development by increasing the ratio of excitatory/inhibitory synaptic transmission, neuroinflammation and oxidative stress, and by stimulating Wnt/β-catenin signaling.[22,23] Accordingly, valproate therapy should be avoided during pregnancy.

### *Selective Serotonin Reuptake Inhibitors*

Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed during pregnancy. They can cross the placenta and are secreted in breast milk and thus could have adverse effects on fetal and infant neurological development. Indeed, several studies report a correlation between gestational SSRI exposure and increased risk of ASD in children.[24-28] However, it is important to note that maternal psychiatric conditions themselves could be a risk factor, independent of SSRI use.[29] Most SSRIs are FDA pregnancy class C and lactation class L2-L3; thus, caution should be used in prescribing SSRIs in pregnant and nursing individuals.

### *Air Pollution and ASD*

Exposures to air pollution particulate matter with an aerodynamic diameter of ≤2.5 μm in the first two gestational trimesters were associated with increased ASD risk in children, with stronger associations observed for boys.[30] Ozone, a major component of smog, has been implicated in ASD risk/severity among children with high DNA copy number variation.[31]

### *Lead-Autism Claim*

Some of the symptoms of lead poisoning overlap with autism. However, there is no convincing evidence that childhood lead poisoning causes ASD.[32,33] While lead exposure could further ASD comorbidities,[34] there's no indication that environmental lead exposures across the US have increased concomitant with the increase in ASD diagnoses.

## Specious and Doubtful Environmental Links to ASD

Normally, this author would not devote precious journal space to discussing specious or questionable claims, but because of the politicization of ASD, individuals with ASD and their loved ones may be apprehensive and may seek guidance from their doctor. Their concerns should be met with compassion and understanding, buttressed by facts. Accordingly, here is a brief discussion of claims that have found their way into the popular press.

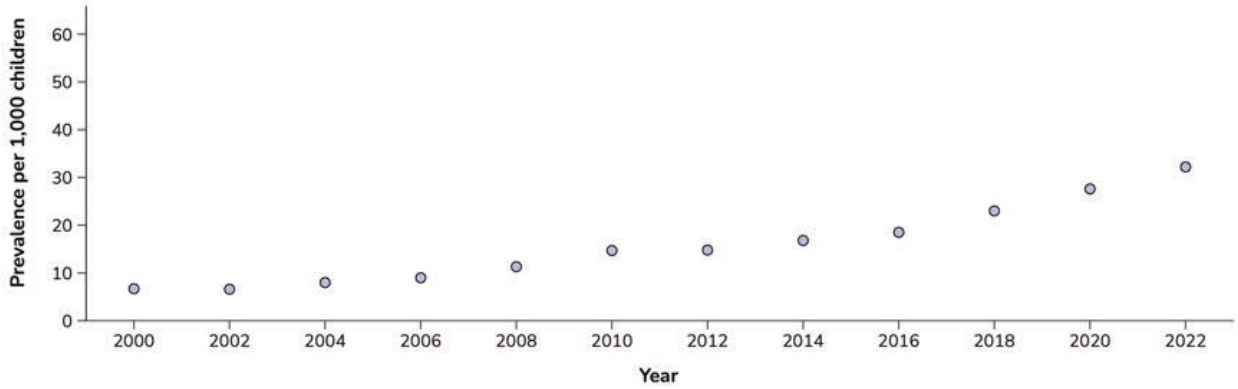
### *Vaccine-Autism Claim*

In 1998, a group led by the British physician Andrew Wakefield published a paper in the journal *Lancet* claiming to have found a connection between colitis and autism and exposure to the measles, mumps, and rubella vaccine. This report was subsequently retracted by the journal after it was found to be fraudulent due to data selection and manipulation. Since that time, numerous large-scale and high quality studies have failed to find a connection between vaccines and ASD.[35-39] None the less, such claims are still being repeated on the internet and by the current Secretary of Health and Human Services. It is worth noting in this connection that children who are vaccinated are more likely to be under the care of a physician who could recognize and diagnose ASD, compared to children who are not vaccinated.

A subsequent report[40] suggested a connection between autism and Thimerosal, the thiosalicylate salt of ethylmercury used as a preservative in vaccines. This idea gained saliency as there are data linking organomercury exposure and neonatal neurotoxicity.[41] However, two considerations weigh against the speculation that mercury-based vaccine preservatives cause autism.

Firstly, Thimerosal was removed from most routine childhood vaccinations in 2001. However, as Figure 2 shows, the incidence of ASD has continued to increase rather than decline. It is important to note that neither

Figure 2. The incidence of ASD has continued to increase rather than decline.




Source: https://www.cdc.gov/autism/data-research/autism-data-visualization-tool.html

the MMR, Varicella, IPV, nor pneumococcal vaccines have ever contained Thimerosal. The only remaining commonly utilized vaccination containing Thimerosol is multi-dose flu vaccines. Second, the amount of ethylmercury previously contained in vaccines was miniscule and cleared rapidly from the body after injection.

### *Fluoride-Autism Claim*

Fluoridation of public water supplies, which reduces dental caries, tooth decay, and dental health disparities,[42] is one of the 20th century's great public health achievements. The notion began with the observation, in early 20th century, that communities with high natural levels of fluoride in the water had unusually low levels of dental decay. While natural fluoride concentrations vary from zero to more than four parts per million, the currently recommended level for community water fluoridation is 0.7 parts per million (0.7 mg/L).

Recently, provocative articles have appeared implicating water fluoridation in decreased IQ.[43-45] While this association was moderately strong at high fluoride concentrations, the effect was at best uncertain when drinking water exposure was at or below recommended levels for artificial fluoridation. A specific link between fluoridated water and ASD has been proposed,[46] although the argument for such a link at current recommended drinking water levels is speculative and unsupported by current data. On this point, further research is needed.

It is worth noting that current water fluoridation levels don't explain the increase in ASD diagnoses in the past 20 years, since in most municipalities, fluoridation levels in water supplies have been unchanged since 1945. That said, the possibility that early developmental fluoride exposure enhances underlying genetic risk for ASD cannot be ruled out.

## Animal Models of ASD

Animal models have proven useful in identifying candidate genes and pathways that are deficient in ASD, as well as elucidating mechanisms for and mapping brain regions implicated in ASD pathophysiology and for testing possible pharmacological interventions. Rodent models have been developed for these purposes.

## ASD Treatment

A critical issue for ASD therapy is whether the behavioral symptoms can be reversed in adulthood or if they become fixed and irreversible. The potential for therapeutic intervention is suggested by experiments in a mouse model of Rett syndrome, in which re-introducing wild-type MECP2 reversed neurodevelopmental deficiencies in adult MECP2 null mice.[47] While promising results are being reported for genome-editing approaches to Rett syndrome,[48,49] it's far from clear how effective this approach will be for the many different loci that have been implicated in ASD.

Psychoactive drugs are being tested as potential therapy for ASD. In particular, the dissociative anesthetic Ketamine has been shown to be effective in a mouse model for Rett syndrome[50,51] and is being pursued in clinical trials.[52,53]

A humanized chimeric mouse model of valproate-induced ASD was used to test potential therapeutic interventions.[54] In this model, VPA-pretreated human neural progenitor cells were engrafted into the cortex

of immunodeficient mice. These mice present with the core ASD symptoms of reduced sociability, interactions and communication, and increased repetitive and anxiety-like behaviors. Interestingly, targeted transcranial magnetic stimulation (TMS) for one week significantly increased social preference, social novelty, and vocalization. These improvements were complemented by normalization of neuronal differentiation and axonal projections.

While the TMS results in a mouse model for VPA-induced ASD are encouraging, the experiences in ASD humans so far have been uneven.[55-57] A limited but promising study of TMS in humans implicated the right parietal lobule as a seat of neural rigidity.[58] The study collected data from 50 participants with ASD and 50 sex-, age- and intelligence-matched neurotypical volunteers. To encapsulate the detailed and thorough measurements, the authors report evidence that TMS mitigated neural rigidity associated with autism, altering different ASD-associated behaviors in different neural processes. The results suggest that TMS could provide a noninvasive strategy to modify behaviors associated with ASD in humans. However, it seems unlikely that a single TMS protocol would target all clinical domains that are affected in a complex and heterogeneous disorder like ASD, highlighting the need for a multidimensional approach to treatment development.

## Conclusion

The evidence that ASD has a genetic basis is very strong. As with many genetic disorders, environmental effects can magnify an underlying clinical presentation without being the cause. Research into the major genes in which ASD risk alleles are well-established and the structures and processes controlled by those genes are known will be key to understanding ASD and the potential for therapeutic intervention. While specific environmental causes of ASD cannot be disproven, the current evidence suggests that environmental inputs exert their effects as modifiers of underlying genetic risk. A better understanding of the gene-environment relationship in ASD will likely lead to more effective interventions.

In discussing a diagnosis of ASD, caregivers should be reassured that they are not the "cause" of their child's ASD. Further, they should be confident that vaccinating their child did not cause ASD. While there is still much to learn about the interaction between ASD genetics and environment, there are interventions that could be tried with minimal risk as long as false hopes of a "cure" are not raised. An ASD diagnosis opens a door of understanding as well as an opportunity for the community to help each individual to maximize their success and happiness.

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# What the Non-Psychiatrist Should Know About Transcranial Magnetic Stimulation for Major Depression

*by Pilar Cristancho, MD, Jeanne Therese Hagemeister, MS, Darin Quach, DO, PhD & Eric J. Lenze MD*

**In the sequential treatment algorithm of depression, transcranial magnetic stimulation shows greater benefit than medication and should be considered after two failed antidepressant medications trials.**



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## Abstract

**Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation treatment for major depressive disorder. Randomized controlled trials show response rates twice times higher for TMS (23.9%) than placebo (12.3%) in adults with depression. Real world studies showed increased response rates up to 58% in clinically heterogenous adult patient populations.**

**TMS is safe and well tolerated with a benign side effect profile and high adherence. Standard TMS protocols include left dorso-lateral prefrontal cortex stimulation using a fixed stimulation protocol or burst-patterned protocols such as intermittent theta burst delivered over six weeks. Novel accelerated protocols using high daily dosing and functional MRI targeting provide increased precision and improved treatment outcomes. TMS shows effectiveness in patients with comorbid anxiety, older adults and adolescents for which received FDA approval in 2024.**

**Future studies incorporating neuroimaging techniques may help to refine protocols leading to improved outcomes across different patient populations.**

## Key Words

Transcranial magnetic stimulation, brain stimulation, neuromodulation, depression, depression treatment algorithm

## Introduction

TMS is an office based, non-invasive brain stimulation technique that uses strong (1.5 – 3 Tesla) but focused magnetic fields to modulate brain activity. TMS devices use the electromagnetic induction principle in which passing an electrical current through a coil of wire generates a magnetic field. The dynamic, rapidly changing magnetic field originated in the TMS coil in turns generates electrical activity on a nearby conductor. When the TMS coil is in contact with the scalp it induces neuronal depolarization on a focal area of the brain cortex; these effects propagate downstream affecting neural pathways in distant brain regions.[1]

TMS was first introduced in the UK by Antony Barker,[2] after years of active research TMS received approval by the US FDA in 2008 for treating Major Depressive Disorder (MDD) in adult patients who have not responded to antidepressant medications, or those with medication intolerance.[3] In March, 2024 TMS was also approved for the treatment of




**Figure 1.** Clinical administration of Transcranial Magnetic Stimulation at Washington University's Treatment-Resistant Depression Program in St. Louis, Missouri, USA.

adolescent depression.[3] Other FDA indications also include Obsessive Compulsive Disorder and smoking cessation, although these involve different TMS coils and protocols (Figure 1).

We provide an overview of TMS for the non-psychiatrist to increase their knowledge about the use of this treatment in major depression. We emphasize TMS use in common patient populations and discuss the place of TMS in the treatment algorithm of treatment-resistant depression (TRD).

## TMS Studies in Depression

TMS has been studied and is widely utilized to treat MDD with a large body of evidence supporting its efficacy.[4,5] Three main large randomized controlled clinical trials support the efficacy of TMS for adult patients with major depression. O'Reardon and colleagues examined the efficacy of high frequency TMS in medication free patients with severe major depression (n = 301) with previous medication resistance or medication intolerance. Response rate for TMS was 23.9% versus 12.3% sham (placebo) response (p<.01). Remission rate was 12.2% for TMS and 5.5% for placebo (p = <0.1).[6] This study led to the FDA approval of the first TMS protocol in 2008. A NIH-sponsored study using the same protocol in medication-free patients with a history of medication resistance (n = 190) found a 15% response for rTMS and 5% response for sham.[7] Remission rates were 14.1% for TMS and 5.5% for sham.[7] In 2015 Levkovitz and colleagues examined high frequency Deep TMS, using the H1 coil (n=212). This coils allows for deeper but less focal stimulation in the prefrontal cortex and fiber tracts connecting with subcortical regions. They found a 38.4% response for Deep TMS versus 21.4% for sham in medication-free patients with treatment resistance or treatment intolerance. Remission rates were 32.6% and 14.5% respectively for active deep TMS versus sham deep TMS.[8]

Studies conducted post-marketing approval in naturalistic settings yielded improved clinical outcomes. Conolly and colleagues examined 100 patients with treatment-resistant depression treated at an academic center. They reported 50.6 % response and a 24.7% remission rate. Notably, this study included a subgroup of patients who previously received ECT, of which 47% responded to TMS.[9] Carpenter et. al examined patients with TRD in a multisite naturalistic study (n = 307) and found a 58% response and 37.1% remission rates. In this study, younger age ( < 55 y/o) and lower depression severity at baseline were moderators of

TMS response. Interestingly, study patients with high medication resistance were as likely to respond to TMS as those with lower medication resistance. Regarding adherence, the study reported 83% of adherence which is comparable with a 7.7% drop out in the pivotal randomized controlled study.[10] Clinical characteristics of this patient population including heterogeneity of illness severity, levels of treatment resistance, greater comorbidities, as well as concomitant antidepressants, may have contributed to the improved outcomes seen in these patients.

In sum, TMS is efficacious for major depression as demonstrated in multiple RCTs and has demonstrated effectiveness in large real-world studies.

## TMS in Special Patient Populations

### *TMS in Patients with Depression and Anxiety*

Clinically significant anxiety is a common co-traveler in patients with MDD. Comorbid anxiety may present either as a prominent symptom of the depressive episode, such as complaints of tension, restlessness, worrying, fearfulness of something awful happening, or feelings of loss of control; or as a comorbid anxiety disorder such as generalized anxiety disorder, panic disorder, or social anxiety disorder. In both cases, anxiety is highly common in patients with depression. Furthermore, depression with concurrent anxiety has been associated with greater depressive symptom severity, higher suicide risk, polypharmacy and greater use of benzodiazepines.[11] The treatment of MDD with anxiety is challenging in part because these patients experience a greater burden of medication side effects[12] and may be anxious about taking their antidepressant medications.

Initial TMS studies found anxiety as a negative predictor of antidepressant response.[13] However, recent TMS studies have shown improvement of both depression and anxiety in patients with concurrent anxiety. In a large naturalistic study (n = 248) Clarke and colleagues reported 39.5% antidepressant response for patients with comorbid anxiety disorders treated with TMS. No differences were found between antidepressant response rates in those with or without anxiety comorbidities and symptomatic improvement in anxiety in patients with anxiety disorders was seen.[14] An analysis of the randomized non-inferiority THREE-D trial in patients with TRD (n = 288) reported improvement in anxiety symptoms with either standard 10 Hz TMS versus intermittent theta burst TMS (iTBS) to the left Dorsolateral Prefrontal Cortex (DLPFC). Importantly. The study showed depression and anxiety symptoms followed the same trajectory of improvement. The authors posited that modulation of brain structures including the amygdala in the mesocortico-limbic reward circuit may be involved in the anxiety effects of TMS over the DLPFC.[15] Recently, a large multisite registry study (n = 1820) showed 50% improvement in generalized anxiety symptoms using the GAD-7 Scales in patients with anxious depression treated with TMS. The study reported the use of off- label TMS protocols consisting of bilateral stimulation to the right DLPFC (using inhibitory frequency) and the left DLPFC ( using excitatory frequency) in patients with anxious depression.[16]

Conflicting evidence has been reported in the US military veterans population, partly attributed to comorbid Post-Traumatic Stress Syndrome (PTSD). TMS treatment did not separate from placebo in a Randomized Controlled Trial (RCT) in veterans with TRD (n= 164). In this study, PTSD was a moderator of treatment effects with higher remission rates for MDD without comorbid PTSD for active treatment versus sham and lower remission rates for MDD with PTSD.[17] By contrast a multisite naturalistic study (n = 770) of veterans with MDD and PTSD found depression improvement with TMS with a large effect size Cohen's 1.21 (95% CI 1.04- 1.21). The presence of PTSD did not impact antidepressant response.[18]

In summary, TMS is efficacious for major depression with comorbid anxiety with improvement in both depressive and anxiety symptoms. The evidence of TMS in veteran populations with comorbid PTDS is conflicting.

### *TMS for Adolescent Depression*

Similar to MDD observed in adults, adolescent major depression is a major public health problem with immense morbidity and mortality. Suicide is the second leading cause of death for individuals in the US between the ages of 15-24, with most of those cases likely due to MDD. Given the almost two-fold increased prevalence from around 8% to nearly 16% of adolescent depression over the past decade[19] and the relatively limited options of FDA-approved treatments for MDD namely fluoxetine and escitalopram, the need for novel therapeutics is at an all-time high.

In early 2024, the FDA granted TMS clearance for depression in adolescents aged 15- to 21-years old.

This decision stemmed from real world data on 1,200 adolescents with MDD treated with a specific TMS device. The study showed that 78% of patients had depression improvement and 48% achieved remission with TMS.[20] While promising, one limitation includes this analysis being drawn from naturalistic observation as opposed to a rigorous RCT study design. To date, the two RCT of TMS in adolescents produced conflicting results: (1) A study by Pan and colleagues observed treatment-naive MDD patients benefiting from active rTMS with significantly reduced depression scores on the Hamilton Depression rating scale and the Montgomery Asberg Depression scale in comparison to sham rTMS[21]; whereas (2) data from another randomized trial suggests that TMS is not more effective than sham in a treatment-resistant depression adolescent population.[22]

From a safety perspective, studies in adolescent patients showed similar to adults that TMS is generally well-tolerated but mild and transient side effects such as headache, scalp discomfort, muscle twitching, fatigue, and tinnitus are common.[23] More serious, but rare, side effects include seizures and hearing loss. The seizure risk, estimated to be around 0.6%, is not dissimilar to what is observed in adults receiving TMS or the incidence of spontaneous seizures with antidepressant medications.[24]

Despite gaining FDA clearance for adjunctive treatment of adolescent depression, there is still need for further investigation of optimal treatment parameters and study design for young patient populations. A majority of studies have localized the treatment region to the dLPFC. However, this does not take into account heterogeneity in depression, severity or specific neurodevelopmental trajectories in this population.[21,22] Thus, future studies incorporating the use of brain imaging may promote the identification of other brain regions of interest and pave way for better target engagement in the young. There remains an FDA black box warning for increased suicidality related to antidepressant use in young patients[25] which may offer an advantage for utilization of brain stimulation treatments in adolescents. Ultimately, TMS gaining FDA clearance is a pivotal step in expanding upon the limited treatment options for depression adolescents.

### *TMS for Depression in Older Adults*

Late-life depression (LLD) is defined as major depression in adults aged 60 and older. LLD affects a significant portion of the aging population with a reported prevalence of 2.7% in elderly men and 4.4% in elderly women.[26] Notably up to 30% of patients with LLD do not achieve response to conventional antidepressant therapies.[27] This highlights a substantial need for more safe and effective treatments. TMS is particularly appealing in this population due to its favorable safety profile and non-pharmacologic mechanism, which is critical given the increased risk of adverse drug interactions from polypharmacy and age-related physiological changes.[3]

LLD is a multifactorial disease with marked biological heterogeneity; some individuals with LLD have preserved brain structure, while many—particularly those with resistant depression—have age-related changes, such as vascular and metabolic dysfunction, chronic inflammation, stress, and the accumulation of iron and beta-amyloid.[28] These changes contribute to accelerated brain aging, structural and functional brain alterations.[29] Cognitive impairments, particularly in executive function, are also common in LLD and are associated with reduced responsiveness to oral antidepressants, greater risk of treatment discontinuation, and higher likelihood of symptom recurrence or early relapse.[27,30] In contrast, preliminary evidence suggests that comorbid cognitive impairment does not reduce the response rate in LLD from TMS.[31] Treatment of LLD is further compounded by medical comorbidities including cardiovascular disease, diabetes, cancer, and neurologic and other comorbid psychiatric conditions observed in this population.[32] These overlapping biological, cognitive, and systemic processes make the pharmacological treatment of LLD particularly challenging.

It has been posited that TMS mechanism entails modulation of activity on brain networks disrupted in depression.[33] Such networks have been identified using modern resting state functional MRI techniques measuring the blood oxygen level dependent (BOLD) signal.[34] Key resting state networks thought to be dysregulated in geriatric depression include: the Cognitive Control Network (CCN) a fronto-parietal circuit involved in top-down attention dependent-executive control which has been associated with the executive-dysfunction syndrome in LLD,[35] and the Default Mode Network (DMN) implicated in self-referential processes and thought to be overactive in depression.[35,36] Low resting state connectivity in the CCN and high resting state connectivity in the DMN have been reported in LLD.[37] However, initial data

examining the effects of intermittent theta burst TMS (iTBS) on the CCN and the DMN did not detect changes before and after iTBS in older adults with depression.[38]

TMS is FDA-approved for the treatment of geriatric depression up to age 68, with one device cleared for use in up to age 86.[3] Initial open-label studies reported response rates to TMS ranging from 20-50% in geriatric populations.[39] Newer protocols show improved outcomes. Trevizol and colleagues analyzed data from RCTs and reported remission rates of 40% using bilateral TMS with stimulation over both left and right dorsolateral prefrontal cortices compared to unilateral TMS (0%) and sham TMS (0%).[40] A randomized non-inferiority trial showed non-inferiority of bilateral iTBS compared bilateral standard TMS, with remission rates of 35% for bilateral iTBS versus 32.9% remission rate for bilateral TMS.[41] Additionally, deep TMS (using the H1 coil) has shown significantly greater remission (40%) rate compared to sham 14.8% and no serious adverse events.[42]

Overall while current data and FDA approvals support the effectiveness of TMS in LLD, additional research can help optimize treatment outcomes. These include addressing coil to cortex distance in individuals with marked cortical atrophy, stimulation parameters and laterality and target engagement precision using resting state brain connectivity.[43]

## Overview of TMS Safety

TMS is generally considered safe and well-tolerated when standard procedures and guidelines are followed. The most common side effects are stimulation site pain (39%), tension-type headaches (28-65%), nausea (7-11%), and dizziness (4-9%). Severe adverse effects including seizures, syncope, and hearing impairment are uncommon.[3] The incidence of seizures with TMS is low (less than 1%) and primarily occurs in individuals with known risk factors such as severe head trauma, non-treated epilepsy, heavy alcohol use, severe cardiac disease, medications that lower seizure threshold, sleep deprivation, and electrolyte disturbances.[44] Those administering TMS should be educated in seizure recognition and trained in basic life support to maintain the safety of the patient in case of seizure, besides clinical practices should develop and follow standard protocols to manage for this serious but rare event.[3] Syncope which can also present with motor phenomena such as tonic postures of myoclonic jerks has also been reported in some patients and is a benign occurrence typically related to anxiety, vasovagal response, or discomfort.[3]

Hearing protection (eraplugs) is required due to the loud acoustic artifact produced by TMS.[45] Permanent changes in hearing threshold were observed in an individual without hearing protection, by contrast in the majority of studies where hearing protection was used, no changes in hearing were observed.[45] Reported side effects were generally limited to discomfort and transient tinnitus, with no permanent hearing damage noted.[46]

Compared to electroconvulsive therapy, TMS has a more favorable safety profile, particularly regarding cognitive effects.[47] Most studies report no significant cognitive impairment associated with TMS and some patients may experience transient improvements in both short and long term memory.[47] Although rare (0.84% per year), cases of TMS-induced mania or hypomania have been documented, especially in patients with a history of bipolar disorder.[3] No consistent pattern of long-term side effects has been identified with the use of TMS.[3] TMS is contraindicated in patients with metallic implants in or near the head, including cochlear implants or medication pumps.[48] While initially thought to be a contraindication, pacemakers and ICDs are considered safe if there is sufficient distance (> 10 cm) between these devices and the TMS coil.[46] Great caution is taken in patients with pacemakers or ICDs to mitigate risk of TMS disrupting these devices' function. Those with a personal history of epilepsy or traumatic brain injury are at higher risk of epileptic seizure.[45]

Overall, TMS is associated with minor side effects that typically resolve within a few days; more serious adverse effects are uncommon and can be minimized through proper patient screening and adherence to established protocols.

## Clinically-Used TMS Protocols

The effects of TMS on the brain vary widely depending on the stimulation protocol, which refers to the specific set of parameters used during treatment.[3] These include pulse frequency (pulses per second), pulse pattern, intensity (typically relative to the motor threshold), number of pulses continuously before a pause (pulse train), duration, and treatment schedule.[3,46] TMS is usually delivered in trains of stimulation for clinical purposes, therefore it is also known as repetitive TMS or rTMS. Broadly, TMS

protocols fall into two categories: fixed-frequency stimulation (either high- or low- frequency) and patterned protocols such as theta burst stimulation (TBS), in which pulses are delivered in bursts. These variables influence the excitatory or inhibitory effects on the brain of TMS and are tailored to specific clinical and research goals.[46,49]

The conventional FDA-approved TMS protocol for the treatment of MDD involves high-frequency stimulation delivered to the left dorsolateral prefrontal cortex (DLPFC). This standard regimen consists of 10 Hz stimulation administered over a 37.5-minute session delivering 3,000 pulses per session, typically five days a week for four to six weeks.[6] High-frequency TMS (greater than 1 Hz) is thought to exert an excitatory effect on cortical neurons. In contrast, low-frequency TMS (1 Hz or less) is typically associated with inhibitory effects.[49] While effective, the conventional high-frequency protocol (37.5-minute duration per session) is time-intensive, restricts capacity, and contributes to higher treatment costs.[50] These logistical challenges have spurred interest in the development and adoption of shorter protocols such as Theta Burst TMS (TBS).

TBS is an efficient TMS protocol that substantially reduces treatment duration from 37.5 minutes to three minutes per session while producing equivalent antidepressant responses. TBS is designed to mimic endogenous theta rhythms, which can induce synaptic long-term potentiation. One form of TBS, intermittent TBS (iTBS), delivers 600 pulses over a three-minute period and has demonstrated non-inferior response (49%) and remission (32%) rates compared to conventional 10 Hz stimulation (47% response and 27% remission).[50] Compared to 10 Hz rTMS, iTBS had no significant differences in self-reported adverse events following treatment and had similarly low dropout rates.[50]

Recently developed, the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) is an innovative, accelerated TMS protocol that intensifies the delivery of iTBS. The protocol administers a total of 90,000 pulses over the course of five consecutive days, with patients receiving 10 iTBS sessions per day. Each session is brief, three minutes, with 50-minute intersession intervals.[51] A key component of SAINT is its use of functional connectivity MRI (fcMRI) personalized targeting. Utilizing fcMRI data for each individual, this approach identifies a region of the DLPFC that is functionally anti-correlated with the subgenual anterior cingulate cortex,[51] which is thought to be dysregulated in depression.[33] This innovative protocol tested under open label conditions resulted in high remission rates (80-90%) with minimal side effects and no reported seizures[51] and subsequently obtained FDA clearance (09/2022) for the treatment of MDD.

## TMS in the Depression Treatment Algorithm: Addressing the Challenge of Treatment-Resistant Depression

A treatment algorithm is helpful for directing treatment of depression; for example, start with an SSRI and then if no response, move to a medication from a different class (e.g., serotonin norepinephrine reuptake inhibitor such as duloxetine). Challenges arise in the case of treatment resistant depression (TRD); i.e., two failed trials of antidepressants in the current episode of major depression. TRD is common, with an estimate of about one-third of all individuals with major depression being treatment resistant.[52] TRD it also is associated with persistent suffering, suicide risk, and high societal costs including burden on the health care system, unemployment, and individual productivity.[53] Increasing evidence suggests that further pharmacological strategies are insufficient to address this problem. In the Sequenced Treatment Alternatives to Relieve Depression STAR-D trial—the largest clinical trial of antidepressant—after two failed trials of different antidepressant classes, only 13.7% and 13.0% of patients remitted from a third or fourth trial, respectively.[54] More recent data in LLD show a similar diminishing rate of returns: in people with TRD, remission rates from augmentation and switch strategies ranged from 19-29%, with further diminished response in patients with three or more failed trials.[55,56] Patients with TRD need better options than additional medication trials that are likely to be futile.

Many studies support the use of TMS in TRD. The FDA cleared TMS for patient with previous antidepressant failures as well as for those with medication intolerance. Given the increased complexity in the treatment of depression an important question remains: when TMS should be considered? Two recent studies have informed on the comparative effectiveness of TMS and other treatment options. The first is the ASCERTAIN-TRD study which

## Clinical Vignette

### *Initial presentation and Treatment Resistant History*

A 72-year-old, single male academic musician was referred for TMS evaluation for worsening depression for over a year. He reported persistent depressed mood most days, he had lost interested in music and in reading, and stopped going to the gym. He experienced frequent thoughts of death, and he was feeling increasingly isolated. He endorsed fatigue, hypersomnia, and poor concentration which interfered with his job. He reported frequent worries and vasomotor symptoms including hot flashes. He had been planning on retiring from his academic position, his long-term partner moved to another city and he had acquired additional responsibilities in caring for his elderly mother.

The patient had a previous diagnosis of depression and anxiety. He has been attending psychotherapy for over a decade. His primary care physician prescribed fluoxetine and paroxetine for years but they ultimately stopped working. His psychiatrist prescribed bupropion 300mg/day and Cymbalta 60mg/day. Bupropion was discontinued due to irritability. Cymbalta was increased to 90mg/day and buspirone 30mg BID and lorazepam 0.5mg PRN were added. His history was notable for a period of increased alcohol intake (several days a week) during the COVID pandemic. In the last year he managed to reduce his drinking to two to three times per week. He had never blacked out or had withdrawal symptoms.

He was in good physical health but had controlled hypertension, hyperlipidemia, coronary artery disease post-stenting 20 years ago, paroxysmal atrial fibrillation, sleep apnea using CPAP. He had no history of seizures, head trauma or implanted metallic devices on the head.

On mental status he presented neatly groomed with normal psychomotor activity, his mood was described as "not so good" and exhibited a dysthymic affect. There was no evidence of suicidal ideation or psychosis. He was fully oriented, and no cognitive deficits were noted.

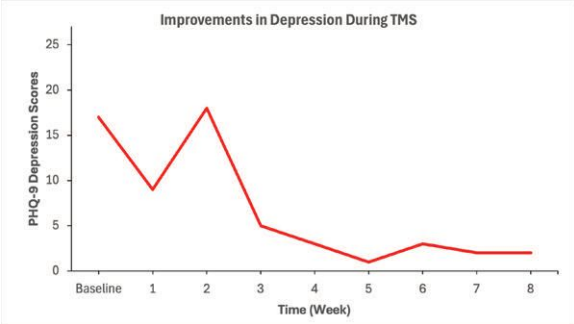



**Figure 2.** Depression scores during TMS treatment using the Patient Health Questionnaire PHQ 9 (decreasing scores denote improvement)

### *Treatment and Outcome*

The patient underwent intermittent theta burst stimulation with triplet 50Hz burst repeated at 5Hz, delivering 600 pulses for over three minutes, with sessions five days/week for six weeks (30 sessions) and a taper over the next three weeks. Medications were held fixed without changes during TMS.

At the end of treatment, he reported improved mood and motivation. He had a better outlook on his retirement plans and was at ease with the timeline and was exploring potential commitments in his field for after his retirement. He was more social, going out for dinner, and reaching out to friends by phone. He reported improved energy and concentration describing this as if "the brain fog is being lifted." He no longer had thought of death and felt more hopeful about the future. Notably He was able to further reduce his alcohol intake.

randomized patients with TRD to three conditions: antidepressant medication switch, antidepressant augmentation with the atypical antipsychotic aripiprazole (a popular augmentation option in major depression), or addition of TMS. TMS showed greater depression improvement than medication switch. TMS had also higher response and remission rates than aripiprazole augmentation.[57] In the second study, Dalhuisen and colleagues randomized patients with TRD to TMS versus algorithm-based pharmacological treatment (i.e., switch to a tricyclic, augmentation with lithium, or atypical antipsychotic). Both groups received psychotherapy. TMS showed greater depression improvement than the pharmacotherapy group with large effect size (Cohen's d = -0.77).[58] Headaches, tiredness, and local pain were reported with TMS, whereas headache, tiredness, dizziness, dry mouth, sleep problems, weight gain, and diarrhea occurred with medications.[58]

As a whole, these studies in TRD show that, when compared to pharmacotherapy TMS leads to clinically meaningful outcomes and shows a favorable side effect profile. TMS should be considered after two failed antidepressant treatment trials and certainly after three failed trials. ECT can also be considered for TRD or for those in need of a rapid antidepressant

response (e.g., suicidal ideation, weight loss) or with psychosis. Additional studies are needed to refine and test treatment algorithms in TRD including the role of psychopharmacological and neuromodulation interventions. (Figure 2 and Clinical Vignette).

## Conclusion

TMS is an effective, a safe and well-tolerated brain stimulation treatment for MDD. Its use is supported by a large research evidence including RCTs and effectiveness data in real world patients. TMS in special populations shows improvement of depression and anxiety in these comorbid conditions. TMS is safe and effective in adolescent depression with recently granted FDA approval. Older adults with depression respond to TMS with bilateral and deep TMS protocols showing improved responses. Novel protocols such as iTBS have comparable efficacy to standard TMS with improved efficiency. Accelerated protocols such as SAINT offer a highly precise treatment approach with improved outcomes. In the sequential treatment algorithm of depression, TMS shows greater benefit than medication and should be considered after two failed antidepressant medications trials.

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# Brain Implants in the Age of Artificial Intelligence

*by Bornali Kundu, MD & Jamir Pleitez, MS*

**Ethicists are needed now more than ever to help physicians, scientists, industry partners, and legislators navigate this new era to ensure responsible, secure, patient-centered, and human-centered care.**



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## Abstract

**Brain implants are routinely used to treat movement disorders and other network disorders such as obsessive-compulsive disorder. Closed-loop intracranial brain stimulation systems can now detect neural biomarkers of disease in real-time and therapeutically stimulate the brain based on these signals. Research devices can measure neural data on the order of single neurons and transform these data, via machine learning algorithms, into cursor movements and keyboard clicks, so that a quadriplegic patient can control a robotic arm. It is still a challenge to find the important brain signals of interest, that encode a patient's intentions or needs. Furthermore, the ethics of developing devices that allow for human cognitive and physical enhancement should be a part of societal discussion. The hope is that artificial intelligence (AI) will continue to advance neurotechnology's role in human health.**

## Key Words

Brain-machine interface; deep brain stimulation; epilepsy, artificial intelligence.

## Introduction

Recently, two additional spinal cord injury patients were implanted with Neuralink's N1 chip brain machine interface device. Both were young men who were tetraplegic as a result of their injuries. The surgery was done in four hours, and the patients went home the next day. But now, they have a device that allows them to interact with a computer to perform computer cursor movements and read out their mental intentions. Such stories sound sci-fi but are now becoming part of a progressive technological movement to improve brain-based therapies. Brain implants play a major role in standard clinical practice. But now artificial intelligence (AI) is becoming important to allow such devices to interface with the biological nervous system.

First, what is a "brain implant?" Technically, it is anything that is implanted in the brain, which could include biological and/or non-biological materials. Electronic brain implants are generally devices that are partially or completely implanted into the body and interact with a part of the biological central nervous system. The first of such devices was the deep brain stimulation (DBS) system used to treat medically refractory essential

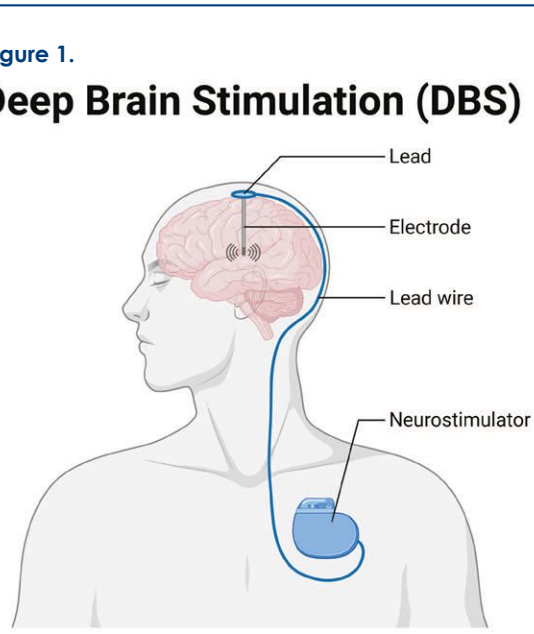
tremor.[1] This system consists of macroelectrodes that deliver current through cylindrical metallic contacts mounted at the tip of an insulated wire and that wire connects to a battery that generates current (Figure 1). The electrodes are surgically placed into the brain at particular targets based on the disease being treated. In the case of essential tremor, that target is generally the ventral intermediate nucleus of the thalamus. In the case of Parkinson's disease, the target is usually the subthalamic nucleus or globus pallidus.

When stimulation is applied through the electrodes, via an implanted battery, there is an electrical field generated by the electrodes referred to as a 'volume of tissue activation," which then results in potential changes in the brain tissue.[2–5] DBS systems are also used to treat dystonia,[6,7] epilepsy,[8] and psychiatric disorders such as obsessive-compulsive disorder[9,10] and Tourette's syndrome.[11,12] It also has experimental applications such as depression,[13] post-traumatic stress disorder, pain,[14] Alzheimer's disease,[15,16] coma,[17,18] and anorexia nervosa.[19] These disorders all have one thing in common: they are network disorders such that two or more brain areas are generally implicated in the disease, and how those areas are connected, is abnormal in the diseased state.[20] By targeting certain network 'hubs,' DBS can modulate the activity of a network node or connection and this may be a mechanism that allows stimulation to improve symptoms.[21,22]

## History of Brain Implants

Electrical brain stimulation was first used by German physiologists Edward Hitzig and Gustav Fritsch in 1870 to move the limbs of a dog. [23] Later in 1874, Dr. Robert Barthlow electrically stimulated the brain of a patient with exposed motor cortical tissue, as a result of cancerous ulcer, that caused her limbs to move systematically.[24] These demonstrations showed that certain brain areas perform certain functions, and those functions can be recapitulated with brain stimulation. This revolutionary concept in neuroscience of 'cerebral localization' has been critical to the conception and design of brain implants because we expect, for example, that motor areas consistently show activation with consistent motor movements—thereby providing a reliable control signal from the brain that can be used to run a machine.

**Figure 1.**



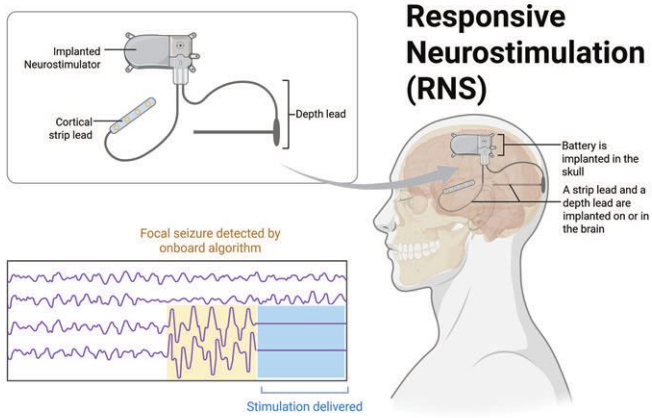

The first demonstration that a brain implant could be wirelessly controlled and influence behavior was famously demonstrated by Dr. Jose Delgado, MD, PhD, in 1964. Dr. Delgado implanted electrodes into the presumed caudate nucleus of a bull ("presumed" because there were no stereotactic atlases of bull brains at that time). He showed that applying stimulation to the caudate while the bull was charging caused the animal to stop in its tracks.[25] From there, the modern applications of DBS for treating essential tremor and Parkinson's disease were born. Dr. Alim Louis Benabid, MD, PhD, a neurosurgeon in France, brought this method into clinical practice in the 1980s, introducing the electrodes and internal pulse generator battery concept that is used in DBS systems today. DBS for tremor was approved by the FDA in 1997 and for Parkinson's disease in 2002.[26] Notably, the surgical method and devices for deep brain stimulation have not changed significantly since then.[27–30] The battery used to power these devices was based on pacemakers.

## Mechanism of Action

At the cellular level, the mechanism by which brain stimulation works is not completely known. One theory is that high frequency stimulation

acts by injecting noise into a circuit that has aberrant firing, so called "jamming" the signal.[31–34] Another theory is that stimulation creates a 'virtual lesion' that reversibly knocks out brain activity. Other theories exist with supporting and refuting data, proving that at the cellular level, the mechanism by which brain stimulation works is anything but simple. When the activity of thousands of neurons is summed, the output is a local field potential or LFP. LFP based oscillations in different frequency bands, the so called 'brain waves,' have come to the limelight as systematic relationships between the amplitudes of these waves and clinical symptoms or cognitive functions are found. For example, the amplitude of the beta (12-25 Hz) band power in subthalamic nucleus of Parkinson's patients is found to be related to symptom severity.[35,36] Moreover, the degree to which DBS suppresses beta power leads to better symptom control. Thus, beta power is considered pathological in this case and a neural biomarker that AI can tackle.[37]

**Figure 2.**



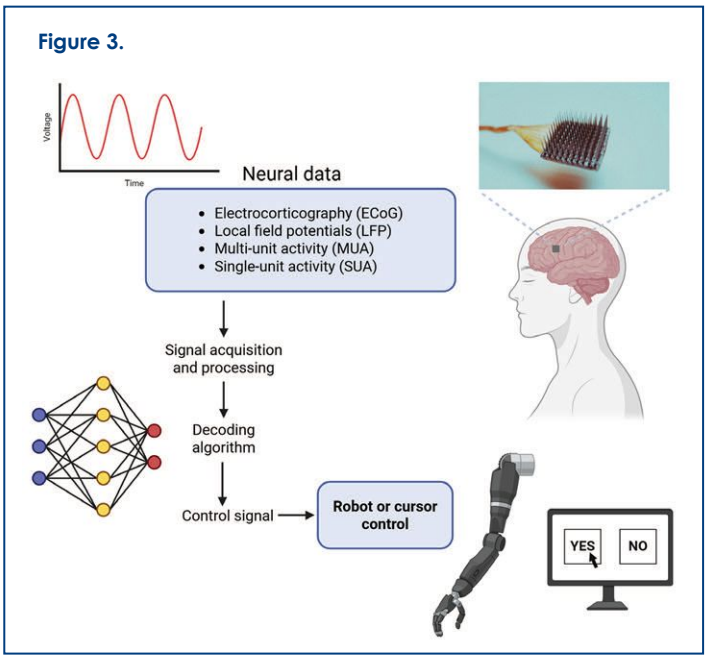

## Devices in Clinical Use

How can AI play a role when we have a useful neural biomarker for a disease process? AI essentially provides an algorithm that can pick up on patterns of signal change and guide changes in stimulation parameters. This can be integrated into the concept of a 'closed-loop' system in which there is a component that senses signal changes, interprets them based on e.g. an AI-based algorithm, and then stimulates the network based on known effects of stimulation.

The first closed-loop brain implant on the market was the Responsive Neurostimulation System (RNS) made by Neuropace Inc. (Mountain View, CA). This device is used to treat multifocal epilepsy and applies closed-loop stimulation to sense epileptic signals in a patient and stimulate based on those signals, i.e. closing the loop (Figure 2). Data shows that over time stimulation may reshape the entire seizure network, decreasing seizure frequency.[38] The RNS device was initially FDA approved for multifocal epilepsy but is now being investigated for other epilepsy conditions such as generalized seizures.[39] In the case of Parkinson's disease, Medtronic recently came out with the second FDA-approved closed-loop brain stimulation system to treat symptoms. Here, the onboard algorithm in their Percept battery tracks the amount of power in a frequency band in real-time and adjusts the DBS current delivered to the patient accordingly. Additionally, a recent pilot study showed a second potential biomarker to run DBS, which is stimulus-entrained narrow band gamma (65-70 Hz) power. This signal had better symptom control than conventional continuous DBS.[40] Thus new scientific efforts are being focused on finding predictive biomarkers of network disorders, since those markers could guide therapeutic stimulation.

## Research Devices

While RNS and DBS are brain implants on the market with on and off label usages, there is also a class of brain implant devices which are purely in the clinical research realm. These brain machine interfaces use microelectrodes which record cellular level data and allow machine learning algorithms to control computer cursors and robotic arms. The first demonstration of this type of device's efficacy was in non-human primates by the seminal work of Drs. Dawn Taylor, Andrew Scwartz, and colleagues.[41] The microelectrode array, the 'Utah array,' was created in Salt Lake City, Utah, by the pioneering implant company, now called Blackrock Neurotech (Salt Lake City, Utah). This 4 x 4 mm array resembles a pin cushion that gets impacted into the cortical tissue with a precise pressurized insertion device




(Figure 3). The adaptive-learning algorithm was engineered to sense neuronal firing patterns from the brain tissue and then uses those signals to control a device such as a computer cursor or robotic arm based on these patterns. The concept of 'decoding neural data' using machine learning is the foundation of BMIs and came from work by Dr. Schwartz and his mentor Dr. Apostolos Georgopoulos. Amazingly, animals and patients can adapt their own neural activity in motor cortex or parietal cortex through training an adaptive computer algorithm to learn the patient's brain signals related to the intention to move, and then moving a robotic arm with varying degrees of freedom accordingly. Here AI is the computer model that trains on neural activity related to the desired output such as a robotic arm movement. This model learns a 'transform function' which it uses to predict when and how the patient wants to move the robotic arm in a future planned movement. Once trained, the patient can control a machine using the brain implant with their mind. The machine is effectively "mind-reading" via the learned transfer function. This concept opens the door to treating patients who are tetraplegic or otherwise locked-in and unable to communicate or interact with the world. It also leads to some interesting privacy issues such as, should and could there be controls in place for the computer not to read certain types of neural signals?

The first use of brain implants to treat such patients was led by Drs. John Donoghue, Leigh Hochberg, and their team at Brown University and Massachusetts General Hospital, via the BrainGate clinical trials.[42,43] The BrainGate2 clinical trial (NCT00912041) is currently active and recruiting patients with tetraplegia from amyotrophic lateral sclerosis or spinal cord injury. These patients have a Blackrock NeuroPort electrode-based BCI device implanted into the motor cortex or other cortical areas. Patients use their brain activity to train a machine learning algorithm to then control an assistive device. While these clinical trials are certainly tailored to the individual patient, these trials help researchers develop better control algorithms for other BCI applications and helps researchers gain insights into how the human brain works, which they otherwise would not be able to learn. For example, in a study with stroke patients at Washington University in St. Louis, it was noted that patients could control the limb ipsilateral to a control device in motor cortex, when generally we do not think about possible ipsilateral limb control capabilities of motor cortex.[44] Note that the Blackrock NeuroPort electrode (which is the human version of the Utah array) is not fully implanted. It requires a head-mounted pedestal to transfer data and that piece is exposed outside the skin which may carry a higher risk of infection than a fully implanted device.[45] Neuralink's (Fremont, California) N1 Chip mentioned above, is fully implantable and has 1,024 electrodes. Several patients with tetraplegia or tetraparesis have been implanted with this research device in the ongoing PRIME clinical trial (NCT06429735). Paradromics (Austin, Texas) has the Connexus BCI interface that is also fully implantable and supports 1,600+ channels of data, again supporting AI models that require large amounts of data and has also been implanted in humans. Precision (New York City, New York) has a thin seven-layer film designed to

capture data at the level of LFPs (NCT05182437) and is designed to treat epilepsy. It is also fully implantable with a battery in the chest and can capture wave phenomena on the brain and has been implanted in several patients. Finally, Synchron (Brooklyn, New York) has created the Stentrode, which is a device with electrodes mounted on a stent that is then implanted in a cerebral vessel near motor cortex. The device records cortical neural activity that is rich enough to run an AI algorithm to control a touchscreen device. The potential advantage here is perhaps a lower rate of infection by being intravascular, as opposed to the immune sheltered environment of the brain. The SWITCH trial (NCT 03834587) enrolled five patients with results pending.

Aside from motor control, speech prostheses designed for communication have also emerged. Here the concept is to decode speech directly from speech-related motor areas including ventral sensorimotor cortex and midprecentral gyrus using a brain implant.[46] Patients most appropriate have motor paralysis causing dysarthria or anarthria, which is the total inability to produce speech. This could be a result of stroke or amyolateral sclerosis. First demonstrations of speech decoding came from the lab of Edward Chang, MD, followed by others.[46] This does require that the patient's ability to understand speech is intact. The control signal is generated usually by imagining the speech. Most recent iterations involve a patient having an avatar perform realistic facial movements as well as generate something similar to the patient's voice.[47] Here you can imagine that if the decoding is accurate, any words the patient imagines would be projected, which may compromise patient privacy to some degree. Efforts are being made to try and separate which signals the BCI should translate.[48] DBS for depression has had several clinical trials and while the main results of earlier trials were negative, much has been learned post hoc from those data yielding better biomarkers of mood.[49–52] Closed-loop DBS of the orbitofrontal cortex in a patient showed consistent improvement in mood.[53,54] This AI algorithm decodes mood states from a patient's neural data and stimulates based on those control signals. Another study showed stimulation of subcallosal cingulate and ventral capsule/ventral striatum at model-derived parameters resulted in symptom improvement.[55]

## Limitations of BCI

There are numerous limitations to this technology. One is having acceptable biocompatibility between a device and brain tissue so that an inflammatory reaction does not destroy the tissue environment of the neurons providing the control signal. A related issue is the tradeoff between having a fully implanted device and having the onboard computing capability to transfer and then decode a complex control signal. Large amounts of real-time data transfer are required, i.e. the 'bandwidth' of the data, to run complex AI models because these models generally have numerous degrees of freedom or number of parameters to estimate. This requires efficient data collection and transfer which is an important engineering problem companies like Neuralink and others are working to optimize. Moreover, neuronal population selectivity can be dynamic, and so finding stable patterns that an AI algorithm can consistently use over a long period of time such as years the patient may have the device is challenging. These algorithms generally must be retrained periodically. One solution to this is using AI to derive 'manifolds' or lower dimensional trajectories these cell populations may work along so single cell activity becomes less critical as a control signal, and what is more important is learning the neural population manifold.[56] One can think of this as a summary measure that captures important components of the neural data that are informative for the BCI application.

There are other implants which do not physically contact the brain but interface with the nervous system. A cochlear implant interfaces with the cochlear apparatus in the ear to bypass the body's biological tympanic membrane to transfer the sensory acoustic information directly to the central nervous system. A single channel device was first implanted in humans by Dr. William House, MD, and Dr. John Doyle, MD, in 1960s and 1970s and later multichannel devices came to market that offered better tonal resolution. Similarly, the Argus 1 and Argus 2 retinal implants

created by Second Sight Medical Products (Los Angeles, California; and now acquired by Vivani Medical Inc, Alameda, California) allow patients with retinitis pigmentosa to be able to perceive shapes. Argus 2 uses a camera mounted on glasses to sense and transform the actual scene in front of the patient to a low-resolution version that is projected to retinal neurons directly via the retinal implant. The implant has a grid of photoelectrodes which flash light onto the retinal cells thus bypassing the nonfunctional photoreceptor cells in this disease. Finally, there are implants which interact with the peripheral nervous system, i.e. the nerves after they exit the brainstem or spinal cord. Among them are spinal cord stimulators, vagal nerve stimulators, and peripheral nerve stimulators. The vagal nerve stimulator consists of an electrode placed on the vagus nerve in the neck and a battery in the chest and is FDA approved for treating epilepsy.[57] It has also been used in the clinical trial setting for other disorders including depression,[58] stroke,[59] and even arthritis.[60,61] Spinal cord stimulators are generally used for failed back syndrome, refractory angina pectoris, or complex regional pain syndrome. The Inspire device uses stimulation of the hypoglossal nerve to treat sleep apnea.[62] Finally, there are nerve machine interfaces that power prosthetic devices to allow patients who might have lost control of a limb to interface with a robotic arm to perform tasks,[63] though many of these devices are in experimental stages.[64]

Primary care referral for a brain implant to treat movement disorders, epilepsy, and psychiatric disorders are generally to a neurologist or psychiatrist for initial evaluation. Specialists in movement disorders, epilepsy, pain, and mental health disorders are familiar with the array of medical and surgical options available to these patients including potentially brain implants. Drug resistant Parkinson's disease, essential tremor, OCD, Tourette's disease, dystonia, and epilepsy may warrant a brain implant and generally require evaluation by a multidisciplinary team as is present in university hospital settings, such as the University of Missouri – Columbia for example.

## Ethical Considerations

Finally, while we are far from implants that can potentially enhance normal functioning, like allowing someone to play piano at a virtuoso level or perform athletic feats, there are significant ethical considerations surrounding the use of brain implants to change brain function.[65–67] Some immediate concerns are how to determine who is responsible for maintaining research devices after a research study is complete. Batteries for these devices are costly, and software on devices are subject to possible failure, but is it right to take away a device that is potentially helping a patient function?[68,69] And who should bear the cost of this research and device maintenance? Finally, should brain implants be created for performance enhancement? Is there any issue to offer a device that has risks to someone who is otherwise healthy so that he or she may improve their mental and/or physical functioning to gain an advantage? Additionally, since decoding algorithms can decode mental states, is mental privacy then at stake with the use of brain implants and could mental privacy ever be protected? These issues are being considered internationally, and first steps may be to encrypt data and treat 'neurodata' as we do other patient health information.[70] This would apply to all entities including neurotech companies who may currently hold repositories of human neural data.

## Conclusion

It is an exciting time for neurotech and neuroscience. With advancement in computing power and data sharing practices, the ability to make breakthroughs in device development and AI algorithm development improves. However, there should always be a consideration of the ethical issues at hand to protect these patient data and maintain privacy both in the clinical and research settings. Brain implants have and will continue to improve quality of life for patients with neurological and psychiatric conditions. A time may come when they also play a role in enhancing human performance, though that seems a distant future, and outside the realms of standard medical practice. With interested industry partners and the advancement of AI, society will hopefully be able to direct where it wants these applications to go. Ethicists are needed now more than ever

to help physicians, scientists, industry partners, and legislators navigate this new era to ensure responsible, secure, patient-centered, and human-centered care.

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