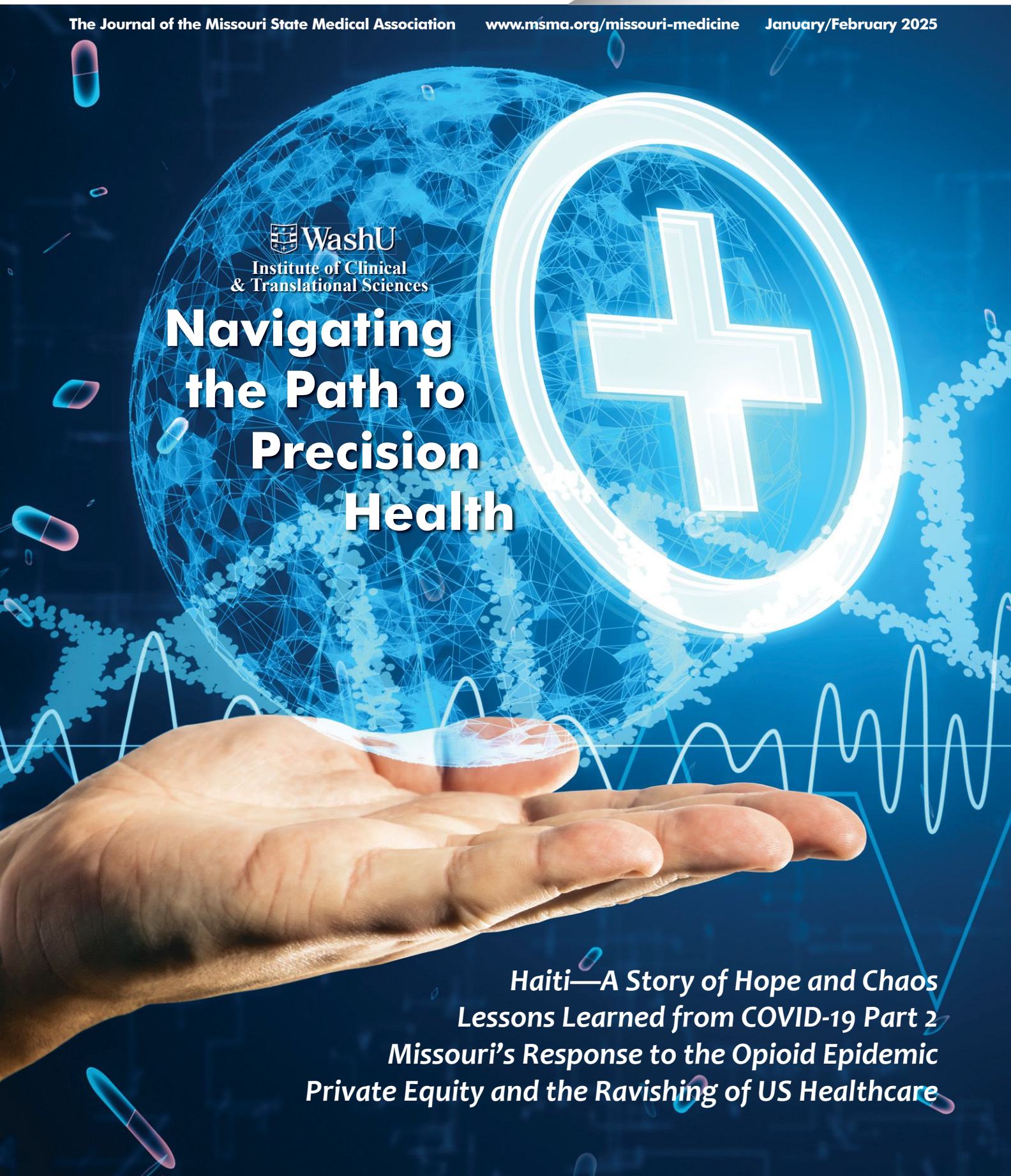
Missouri Medicine

MSMA 175 Years 1850-2025

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



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Haiti—A Story of Hope and Chaos

Lessons Learned from COVID-19 Part 2

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PRELIMINARY SCHEDULE

FRIDAY, APRIL 4, 2025

3:00-6:00 pm	Registration
2:00-4:00 pm	MSMA Executive Board Meeting
4:15-5:15 pm	General Session
5:30-7:00 pm	MSMA Opening Reception
7:00-8:00 pm	Mixer: WPS/YPS/IMG/RFS
7:00-8:00 pm	MSS Business Meeting

SATURDAY, APRIL 5, 2025

7:00 am-5:00 pm	MSMA Registration
7:30-8:30 am	Moneta Product Theater Breakfast
8:30-9:30 am	MSMA House of Delegates
9:30-11:30 am	MSMA Reference Committee
11:00 am-Noon	Caucus Meetings: St. Louis Metropolitan Medical Society & Kansas City Medical Society
11:30 am-12:30 pm	Product Theater Lunch
12:45-1:45 pm	MSMA General Session
2:00-3:00 pm	MSMA General Session
3:00-4:00 pm	MMPAC Business Meeting
3:15-4:15 pm	MSMA General Session
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7:30 pm	MSMA Presidential Reception

SUNDAY, APRIL 6, 2025

7:00-8:00 am	District Breakfasts
8:15 am	MSMA House of Delegates
After HOD	MSMA Council Meeting

175 Years 1850-2025

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GENERAL SESSIONS

Friday, April 4 4:15 pm

Enhancing Physician Power: A Look at Non-Competes and Collective Bargaining



Diomedes Tsitouras, JD, MPA
Executive Director of the American Association of University Professors - Biomedical and Health Sciences of New Jersey, a labor union of 1,500 faculty at Rutgers and Rowan Universities who teach the next generation of doctors, nurses, scientists, and health professionals.

Saturday, April 5 12:45 pm

Long COVID: An Overview for Clinicians



Abby Cheng, MD, MPHS
Assistant Professor and physical medicine and rehabilitation physician at the Washington University School of Medicine in St. Louis. As a member of the AAPM&R Long COVID Collaborative, she is co-lead on the Collaborative's consensus guidance statements on mental health and on the holistic assessment and management of Long COVID. She is also the lead principal investigator of an AHRQ grant to improve equitable access to Long COVID care.

Saturday, April 5 2:00 pm

The New Paradigm for Acute Migraines: Nasal Spray Timolol



John C. Hagan, III, MD, FAAO
Retired ophthalmologist and a current editor of *Missouri Medicine* medical journal. For for over a decade, Dr. Hagan has studied the successful use of timolol 0.5% for acute migraine. He has published more on this subject than any other physician world-wide. In 2014, with another physician, he first reported success using timolol eye drops and in 2024, with headache specialist Steve Kosa, MD they first reported the preferred use of timolol by nasal spray for refractory acute migraines. Using this same delivery method they also first described the first successful treatment of essential tremor in a patient who could not tolerate oral beta blockers.

Saturday, April 5 3:15 pm

Trauma and Violence Caused by Mental Health Disorders



Erick Messias, MD, PhD
Chair of the Department of Psychiatry and Behavioral Neurosciences for the Saint Louis University School of Medicine. Previously, he was medical director of the Walker Family Clinic and responsible for the House Staff Mental Health Service at the University of Arkansas for Medical Sciences in Little Rock and Vice President and Medical Director for Beacon Health Options, overseeing the mental health care received by Arkansas Medicaid recipients.

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Missouri Medicine

The Journal of the Missouri State Medical Association – Since 1904

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Mission—Submissions—Peer Review—Polices

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Get Your DTaP and Avoid This Misery

Whooping Cough: No Longer Just Kid Stuff

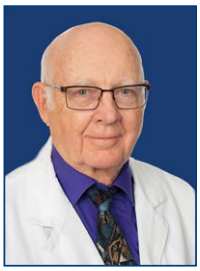
by John C. Hagan, III, MD



Kid (enthusiastically):
"Excuse me mister, my mom wants to know if you would move to a table further away from us? She doesn't like the way your cough sounds."

Me (grumpy but understanding):
"Sure kid, tell your mom I don't like the way it sounds either."

I know what Job felt like. The last four months have given me a deeper, and more sympathetic, understanding of the trials and tribulations of chronic coughers. If you wonder where I'm going with this, much to my bewilderment, I have joined the thousands of adults suffering from pertussis, AKA 'Whooping Cough." 'Suffering' does not begin to describe my pertussis misery.



John C. Hagan, III, MD, (pictured) is an ophthalmologist and editor of *Missouri Medicine* in Kansas City, Missouri.
This manuscript is co-published by Kansas City Medicine and Missouri Medicine: The Journal of the Missouri State Medical Association

Currently, there is an epidemic of pertussis in adults, especially we "folks of a certain age." I became a 'whooper' four months ago and am still coughing like a consumptive. My hacking has drawn so much unwanted attention that I have remodeled the truth and tell concerned onlookers "I have asthma and I forgot my inhaler."

Pertussis in grown-ups has increased 500% since this time last year. A significant part of this increase is due to decreased rates of vaccination. To this I plead guilty as charged. I believe my last DPT, also known as DTaP (diphtheria, pertussis, tetanus) vaccination was way back in the days when I had a full head of curly blond hair. And that was very, very long ago when dinosaurs roamed the earth.

Known by many names over the centuries, (my personal favorite 'The 100 Day Cough') etymologically "pertussis" comes from Latin per (intensive) and tussis (cough). It was first described in the 1578 Paris epidemic. In 1906, Jules Bordet and Octave Gengou isolated the bacterium *Bordetella pertussis* (Figure 1),

which causes pertussis. This led to a whole-cell vaccine in 1914. In the 1940s pertussis vaccine was combined with tetanus and diphtheria (Figure 2). Now known as DPT or DTaP, the number of deaths declined dramatically after vaccines were available. Subsequent published studies noted that protection from the vaccine wanes after four to twelve years.

I recall my grandparents talking about grim pre-vaccine pertussis times. They called it "The death cough" (Figure 3). As in many families of that early 1900s era, pertussis killed two of my grandparents seven children. My grandmother said that parents of their generation fully expected one or two children to die in infancy due to pertussis or infections. A 2014 publication estimated 24.1 million pertussis cases and 160,700 deaths in children younger than five years worldwide. In 2018, the World Health Organization (WHO) reported 151,074 pertussis cases globally. Based on 2008 data WHO estimated that there were 89,000 deaths."



Figure 1. *Bordetella pertussis* is a gram-negative, aerobic, pathogenic, encapsulated coccobacillus bacterium of the genus Bordetella, and the causative agent of pertussis or whooping cough.
Source: Wikipedia

Vaccination recommendations for infants, children, and adults have changed over the years and continue to evolve. The most current can be found at https://www.cdc.gov/pertussis/hcp/vaccine-recommendations/index.html. From those recommendations: "Adults do need booster doses every 10 years to maintain protection against tetanus and diphtheria." Don't be like yours truly and ignore these recommendations; Whooping Cough is nothing to sneeze at.



Figure 2. Pertussis vaccine was heavily promoted by public health officials and readily accepted by fearful parents.
Source: Office of NIH History and Stetten Museum

My case began innocently enough with very mild coughing. Seems like three to four years ago but really three to four months ago. When I have a upper respiratory infection, I often cough weeks after the acute process has cleared. "Here I go again," I thought. Then the coughing morphed into something I have never experienced before and hope to never experience again. Fits of coughing and gagging so severe and violent that I thought I was going to heave or black out. They occurred so often the muscles (what few I have left) of my back and chest hurt. When talking on the phone I always kept one finger on the mute button. When out socially, feeling cough spasm coming on, I would head for the bathroom as quickly as possible. More than once my wife was asked, "Does John have diarrhea?"

I was afebrile and my sputum mucoid. I contacted my cardiologist and explained my predicament. He

ordered chest and sinus X-rays which were normal. Use of Robitussin anti-tussive came a cropper. I tried Smith Brothers Cough Drops, which has been "Trusted Since 1847" and were a favorite childhood nostrum of my RN mother. Zilch on the Smith boys also.

I am used to calling physicians' offices for both acute and chronic problems for my wife and I only to be told, "The doctor can see you in (three weeks to six months). The nurse practitioner can see you this afternoon or tomorrow." With appointment delays like that, no mystery why non-physician scope of practice is expanding so quickly into traditional medicine. As a profession and in our practices, we have to do much better on outlandish wait times.



Figure 3. According to the Centers for Disease Control and Prevention (CDC), there are an estimated 24.1 million cases of whooping cough and about 160,700 deaths in children younger than age 5 years worldwide annually.
Source: Wikipedia

As a physician, I have options our patients don't. Bypassing the gate-keeper nurse, I call a physician friend or colleague and ask them to see me or get me in quickly to the specialist's office. A colleague got me in to see Vincent Lem, MD, an esteemed pulmonologist in 48 hours.

That visit started with "Tell me about your cough." I proceeded to tell him what I have just told you. "Does it feel like your cough could make you vomit or pass out?" I answered: "Roger that! I am afraid I am going to cough up a lung." Without picking up his stethoscope, he said, "I think you have adult pertussis, you know Whooping Cough." Me: "What?" He continued, "Very few things will make you cough that bad except pertussis and we are seeing a big increase in adult cases. When was your last booster?" Once again, I came clean, "A long time ago when Madonna and Cher were young."

He told me, given the time frame, I was probably not infectious but recommended I do the hermit thing for a week. He prescribed two weeks of azithromycin. He ordered B pertussis IgA, G, and M. The IgA and IgM were extremely elevated confirming his diagnosis. Telling me again nothing worked well for the cough, he prescribed hydrocodone. That didn't work and I stopped after four days worried about withdrawal symptoms. I tried a steam vaporizer and burned my nose and lips; I used a hypertonic saline nebulizer. It was no help and filled my nostrils with brine. I haven't drunk alcohol in over 40 years but much more of this and I might reconsider.

As of press time I'm still having major league coughing. Don't put yourself through this, get your DTaP booster, recommend it appropriately for your patients.

I may never be the same. Recently, I bumped into an old acquaintance. After a pleasant conversation, I meant to say, "I enjoyed talking to you." What came out was: "I enjoyed coughing on you." A week later I was inducted into the Freudian-Slip Hall of Fame.

Excuse me, I feel another coughing jag coming on. I'm out of here.

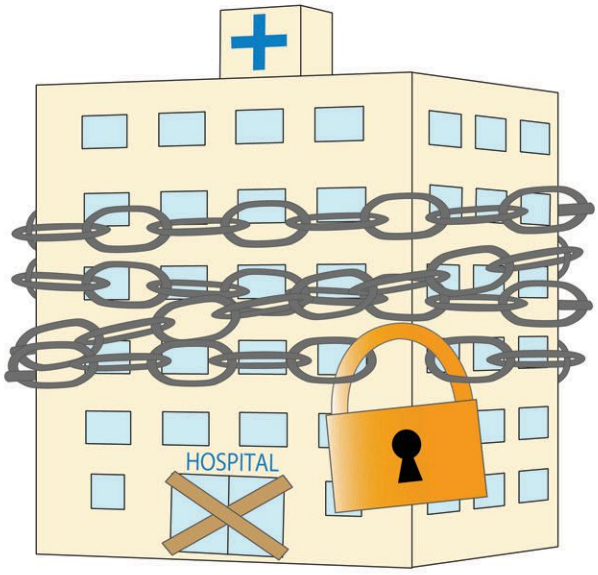
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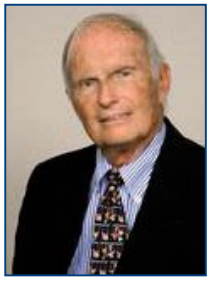


Private Equity and the Ravaging of United States Health Care

by James R. Webster MD

Strategies and tactics used by Private Equity include but are not limited to: cutting costs by reducing staffing positions, hiring less skilled and less costly providers, e.g., physician assistants replacing MDs, nursing aids replacing nurses, totally untrained individuals replacing aids, and mandating fewer home health or hospice visits.

In 1914, William Osler advised graduating medical students that they were joining a calling involving their head and heart, not a business. He, like some contemporary American physicians, such as the leadership of the American College of Physicians,[1] would probably be appalled that in 2023 private equity (PE) firms are involved in completing the "financialization" of health care.[2,3] Their goal is to maximize profits by manipulating the fiscal opportunities in the management of business dealings surrounding care without providing any actual care for patients. Rather than being a social good, health care becomes a series of market driven financial transactions.



James R. Webster MD, MS, MACP, is retired Gertz Professor of Medicine at Northwestern School of Medicine, Chicago, Illinois.

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This trend began 50 years ago with the onset of national for-profit hospitals led by Health Corporation of America (HCA) and Tenet Healthcare. In the past decade, PE investors Kohlberg, Kravis and Roberts (KKR), Bain Capital (a major supporter and investor in HCA), The Blackstone and Carlyle Groups, and 136 others have become major players in health care financing.[2] As such they bring with them access to huge financial resources, arcane financial engineering strategies that benefit only their bottom line and some of the sharpest elbows in capitalism. Their strategic interventions are theoretically promoted to magically improve efficiency and reduce costs.

However, whether acquiring hospitals,[4] physician practices,[5,6] nursing homes,[7] mental health entities,[8] home care services, hospices,[9,10] or ambulance services,[11] the effects are the same. Under their stewardship, costs routinely increase,[12-15] while quality and quantity of care decreases. The idea that introducing into the health care equation, a strictly for-profit middleman that promises its investors a 20 percent annual return as its primary goal would improve care is prima fascia unrealistic.

The strategies and tactics used by PE are basically the same no matter which of the above care delivery sites or disciplines they touch. These include but are not limited to: cutting costs by reducing staffing positions, hiring less skilled and less costly providers, e.g., physician assistants replacing MDs, nursing aids replacing nurses, totally untrained individuals replacing aids, etc.,[7] and mandating fewer home health or hospice visits.[8-10]

Diagnostic and therapeutic options are limited by denying them at the front end of care. Lucrative leaseback arrangements are common, as PE sells real estate holdings and equipment of the entity they have acquired, pockets the money, resulting in the hospitals, group practices, nursing homes left paying rent on what they used to own.[15]

Using their financial backing large debts are loaded by PE onto the hospitals, nursing homes, and other clients. These funds are then short-circuited to the PE owners.[1,3] Meanwhile the PE group also charge and pay themselves hefty consulting fees while undertaking dividend recapitalizations.

Once a PE hospital, nursing home, or home care chain can establish local market monopoly power, prices can easily be increased. Profitable procedures can be referred to affiliated hospitals, and underperforming units such as Medicaid, obstetrical, and mental health units can be closed. For-profit hospices (once considered an oxymoron) can be further gamed; cherry-picking less ill patients who will live longer than the usual several weeks of intensive end of life care thus prolonging collection of the daily stipend. They can also use Medicare Part D to pay for expensive medications, and convince families to take the patient to the hospital emergency room if they get too sick for home care.[10]

Studies show how vulnerable nursing home patients experience double jeopardies in PE-owned facilities.[7] Excess mortality, decreased mobility and overall quality of life occur at the same time staff and care are being cut. Costs are being shifted to cover fees, interest, and lease payments as charges per episode of care are significantly increased.[7]

To allow all this to occur, government has, over the years, loosened anti-trust regulations, deregulated the financial industry and reduced oversight.[2,12,16] Much of the money that PE captures comes from government programs, with taxpayers being the ultimate source of such funding.[2] Most of the above PE targets for mergers and acquisitions fall below the $200 million mark so they avoid federal anti-trust attention.[2]

From a strictly investment standpoint all these strategic and tactical activities are financial genius, with devastating results for families and providers. Health care is reduced to a complex, endless pirouette of financial transactions.

Financial Engineering

PE financial engineering was promoted as the cure for cost containment through proven business tactics.[12] What were the alleged benefits for partner hospitals, doctors, and nursing homes who collaborated? In truth, there often are some improvements in back office billing procedures, but the efficiencies primarily come at the sharp end of care.[14-17] Profitable specialty practices, especially radiology, dermatology, anesthesiology, ophthalmology, emergency medicine, urology, gastroenterology, and orthopedics, were bought early in the organizational process using leveraged buyouts.[5] They then were made more procedurally efficient with higher fees, staff reductions, and emphasis on physician productivity as the PE group manages the business aspects. Physicians often find that they are no longer in charge and have made a Faustian bargain causing patients harm on a routine basis.[3,4,12]

When feasible, such specialty practices are consolidated into national "Physician Practice Management" organizations, owned by the PE groups such as Oak Street Health and Agilon Health.[6] is fragments care and raises costs at a time when more support of local systems of care is needed, particularly in non-urban settings. It

is estimated that up to 35 percent of all physicians in the US are now employees of PE sponsored management firms[18] such as KKR (Envision Physician Services) and The Blackstone Group (Team Health).

Through all these complicated, hidden dealings, the promised profits of 20 percent annually for the PE groups and funding partners are maintained.[14,15] Favorable exits for all the health pieces of the PE investments are a buy-to-sell strategy negotiated as part of the original plan, often selling to other PE groups. Usually this occurs at five years to six years.[1,14,15]

Complex Contracts

An example of the effect of PE is the collapse of Steward Healthcare, owned by Cereberus Capital Management, based in Dallas, TX. They ran 31 hospitals in eight states and filed for Chapter 11 in May 2023,[19] admitting that they were out of operating funds for their hospitals. Attempts to sell their facilities and physician groups were unsuccessful[20] when the potential buyers, primarily other PE entities, found that all the assets were involved in complex buy-back/lease contracts. These are financial transactions where tangible assets are sold to a new owner who then leases them back to the seller who ends up paying rent on what they used to own.

In 2016, Steward had sold these assets to Medical Property Trust, which Cereberus also owns, for $1.75 billion, generating more than $100,000 in profits for Cereberus. As of August 2024, the final outcome of these machinations is unclear.

What If...

An issue of particular interest to physicians should be what happens to PE employees if their owner folds and declares bankruptcy? Not a theoretical question. The two biggest PE physician employers, who cover a large portion of employed physicians—Envision Health Care (KKR) with $7.7 billion in debt, and Team Health (Blackstone) with $5 billion in debt—have recently filed for bankruptcy relief. American Physician Partners (APP, owned by Brown Brothers, Harriman) which provided emergency room staffing for 150 US hospitals had $472 million in debt, but could not find a buyer and went out of business as of August 1, 2023.[19] This left 2,500 physicians and numerous nurses and technicians without several months of back pay and even worse, no malpractice tail coverage.[21]

The two largest physician staffing groups, which cover 40 percent of employed US physicians,[18] are in serious financial difficulties. Envision, previously owned by KKR and now in the hands of creditors, with debt of $7.7 billion filed, and was approved for, Chapter 11 bankruptcy in 2023.[21] In addition, Health Partners, property of Blackstone with greater than $5 billion in debt, is trying various solutions to avoid bankruptcy.[22]

Leaders in medicine are aware of these very disturbing, threatening trends,[1] and the fact that PE involvement in medicine is growing each year. However, they lack significant financial enforcement capabilities, or the legislative power, to institute needed changes. The logical remedy for this health care disaster seems to require government involvement to bring full transparency and oversight, with a major goal of turning off the PE money sources. These include, but are not limited to:

- Support by physician organizations of new federal laws to prevent the predatory, unethical, and often legally questionable financial engineering strategies and attempts to develop local provider monopolies.

- Legislation such as:
  - Full restoration of the Investment Company Act of 1940 without exceptions.
  - Enforcement for joint liability of PE firms for debt that is loaded onto their acquisitions such as those for leveraged buy-outs.
  - Tracking all PE merger ventures with vigorous anti-trust prosecutions as indicated.
  - Reviews of purchased and merged assets.

  - A dividend moratorium for two years after any purchase.
  - An immediate lowering of the financial limit for the review of medical M and A activities.
  - An end to the favorable tax break loopholes, e.g., carried interest.
- Legal enforcement of local standards of care for staffing, and patient safety by federal and local governments, and the aggressive pursuit of false claims. Such plans are starting to have traction led by Health and Human Services, and the White House.[23]

While awaiting these political actions, an important strategy at a local level could be enhanced educational and informational programs for health professionals (physicians, nurses, medical social workers, etc.) who advise patients and families about where and how to receive care. They could be informed by both community and medical organizations to become, and stay, continuously informed about the care quality, staffing, management, and funding of their recommendations regarding nursing homes, hospices, and home care services. Local activism can be powerful.

The medical establishment should provide support—financial and in-kind—of academic health economic experts[2,3,11,23] who provide help and guidance for effective patient funding.

While these legislative and legal solutions are easy to propose—and some are actually coming under consideration—implementation would be challenging. Multiple forces would align against even having a serious discussion of the topic. With profits at risk, some physician and hospital organizations would undoubtedly demure. The PE players would mobilize their political enablers and resources in opposition. The battle would be contentious, but well worth having in order to maintain and improve access[23] to quality, safe, and affordable health care for Americans.

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Excellence ... and Other Random Thoughts

by David L. Pohl, MD

Excellence is not an act, but a habit. We are what we repeatedly do. This phrase (or a variant of it) reportedly comes from Aristotle, but more likely derives from Will Durant's interpretation and summary of Aristotle's philosophies. It is something which we as physicians should aspire to, and likely, are already doing, since this philosophy is also rooted in the concept of the physician-patient relationship (one of the central cores of medical philosophy) in which we have a personal and fiducial responsibility to our patients to always do what is best for them.

This is not to say that we always do or recommend what our patients want or wish to hear, but that their benefit is the most important consideration that physicians have when we care for our patients. In many cases, the patient may not feel this way about their physician, since we often hear that "my doctor won't listen to me," "my doctor won't order this test for me," "my doctor won't prescribe this drug for me," or any of a variety of statements that, in the patient's mind, indicate that their physician has put his or her personal gain and interests above that of the patient.

As is often the case, communication lies at the root of the misunderstanding. When our patients seem upset and do not understand as to why we recommend certain actions or items, our rationale may need to be reviewed with them. Underpinning that discussion is the element of trust between the physician and the patient. In modern medicine, those relationships are being sorely tested. We have "one-stop" clinics where physicians and patients are meeting for the first (and often only) time; and other situations where the physicians and patients are randomly thrown together to address the "inefficiency" of patient care. I think we all need to be reminded that good patient care means effective care, which is not necessarily "efficient" care, since such care and personal attention will often seem ineffective from a systems point of view with its goals centered on the efficiencies of "cutting costs" and "saving time."

We now come to the conundrum of modern medicine. Are we working to do our best for our patients, or for the system (which all too often is also our employer). Understandably, this can be a difficult decision. It is amazing how often physicians have put themselves at risk for their patients, historically from the times of the bubonic plague to the more recent COVID pandemic, physicians have fought for their patient's well-being at their own personal risk. For that, all physicians should be commended. With all said, we can seek guidance from a well-known meditation (often known as the "Serenity Prayer"). *Grant us the Serenity to accept those things we cannot change; the Courage to change those things we cannot accept; and the Wisdom to tell the two apart.*

And now on to other random thoughts and observations.

With the New Year (and the new legislative session) now begun, we need to consider those things we wish to address as our higher priorities, since "political capital," while intangible, does have it limitations.

The state legislature has many new members. If one of them represents your district, please contact them to offer yourself as a resource for medical issues. Your contact may be the one that points them in the right direction on complex items up for consideration (you may be one of the few, or sometimes the only physician, from their district who has contacted them; and the phrase "from your district" means more to them than you might think). While a particular issue may not directly affect you or MSMA, it will almost certainly affect at least some of your patients— advocate for them.

Remember to sign up, and show up, for the Physicians Advocacy Day on Tuesday, March 4, 2025. With so many new legislators, we can show them how important our patients and our concerns mean to us.

With the plethora of introduced bills, we need to analyze their intended actions and, more importantly, anticipate their actual actions so we can avoid the unintended consequences when we are only being told "how great" things will be if we just pass the bills as the authors have written.

Again, we are looking forward to your participation on Physician Advocacy Day on Tuesday, March 4, 2025.



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The Pandemic of Our Lifetime



Optimizing Missouri's Preparation for the Next Pandemic: Lessons Learned from COVID-19: Part 2

by David S. McKinsey, MD, Joel P. McKinsey, MD, Julie R. McKinsey, BS & Maithe Enriquez, PhD

Now is the time to seize the opportunity to act upon one of the most important lessons from the pandemic: we need to re-empower and strengthen our public health system. Future generations will be counting on us.

From March 2020 to May 2023 our public health system and its workers, who had previously labored in relative obscurity, were thrust into the spotlight during the once-in-a-lifetime COVID-19 crisis in Missouri. Public health actions to reduce the spread of disease saved lives, as discussed in the first article in this series, but became deeply unpopular and generated heated opposition as the pandemic persisted. This second article will assess the history and structure of the public health system, the many barriers that stymied optimal implementation of its pandemic mitigation best practices, and lessons learned regarding areas for improvement.



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The History of Public Health

The field of public health is rooted in the seminal work of Dr. John Snow who in 1856 investigated a cholera epidemic that had killed hundreds in the Soho neighborhood of London, England. By mapping the location of cases and municipal water pumps, Dr. Snow determined that persons who used the Broad Street pump for their water supply had a 14-fold higher risk of mortality. He removed the pump's handle, ending the epidemic[1] (Figure 1). Of note, England's General Board of Health rejected his correct conclusion that cholera was a waterborne illness, instead opining that the disease was spread through airborne miasmas.[2] This was not to be the last time that public health workers' efforts to interrupt epidemics would spur controversy.



Figure 1. Broad Street pump, London, England.
Source: Alamy

In the United States the concept of the need for organized public health programs arose from the belief that wellness of the population is a shared social responsibility.[3] As urbanization and industrialization led to overcrowded living conditions in the late 1800s, infectious diseases proliferated. In 1900 tuberculosis, pneumonia, and infectious enterocolitis accounted for one-third of deaths in the US.[4] The efforts of the first American public health agencies, founded in the late 19th and early 20th centuries, focused on sanitation reforms and the establishment of health departments.[3] As these initiatives gained traction and their effectiveness became evident, the role of public health expanded to include overall health promotion. Major accomplishments in the 20th century included recognition of the hazards of tobacco, fluoridation of drinking water, improvements in sanitation and food safety, and vaccination campaigns that eradicated smallpox from the planet and polio from the US.[4]

Paradoxically, despite its major triumphs, the field of public health has received limited recognition.[5] A major goal of public health has been to prevent infections. Successful outcomes, i.e. when nothing has happened as the result of effective interventions, have been dubbed "silent victories."[6] Further, although extraordinarily impactful, initiatives such as smoking bans and mandatory vaccination raised controversy regarding the balance between collective health and individual autonomy.[3]

Structure and Functions of the Public Health System During the Pandemic

The COVID-19 pandemic highlighted the complicated, evolving, and difficult-to-understand interfaces among our national, state, and local public health agencies, elected leadership, and the judiciary system (Figure 2). Certain decisions for implementation of the control measures described in our first article (e.g. business closures) were issued as public health orders. Some restrictions were issued as mandates and others as non-binding guidance left to the discretion of the public. For example, citizens in the private sector often had the latitude to decide whether to require mask use in their businesses. Adding to the confusion, responsibilities for implementation of control measures evolved during the pandemic as public health's role declined and elected officials and judges seized greater authority including the unprecedented ability to overturn public health orders. This complex milieu during one of the most lethal pandemics in recorded history set the stage for intense disagreement and conflict and suboptimal implementation of public health measures.

In the US most public health powers are vested in the states and their local health departments, not in the federal government. This decentralized system prioritizes local knowledge and contacts; operations are supported by national level expertise. The federal Centers for Disease Control and Prevention (CDC) was established in 1944 (Figure 3). CDC is authorized to take regulatory actions to prevent the introduction and spread of infectious diseases.[7] Although for decades

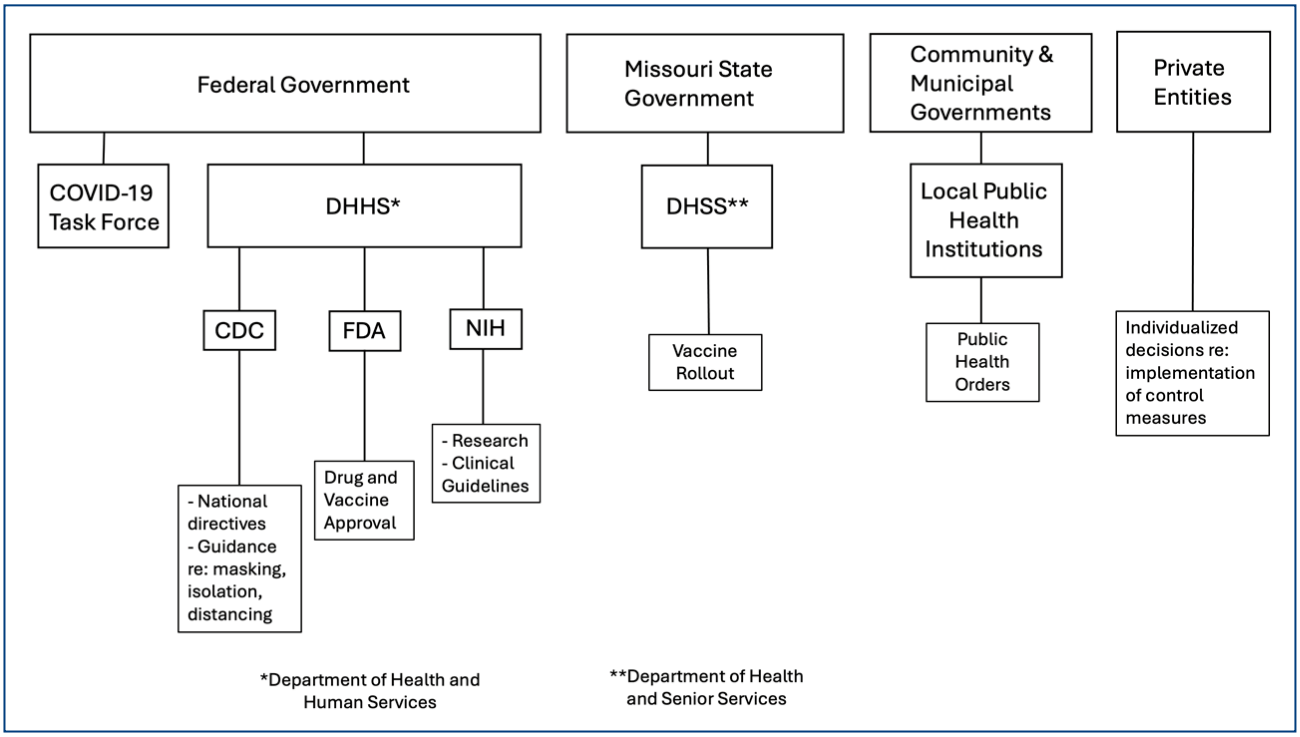


Figure 2. U. S. public health system structure during COVID-19 (abbreviated)

CDC has been the world's preeminent public health organization, and its guidance has been the gold standard, CDC has relatively limited statutory powers focused on prevention of importation or interstate spread of infections.[7] At the onset of the pandemic, when critical public health decisions were being made, CDC's primary role was to issue guidance to the states rather than to implement specific control measures.

Each state had the latitude to manage the pandemic within its borders independently with guidance from CDC. Prior to COVID-19 there were two established models for state and local leadership during public heath crises: the leader either delegated decision-making authority to the public health expert or retained authority and followed guidance of the expert.[8] During the pandemic a new third model emerged: some state government officials took a minimalist approach and delegated most decisions to local officials.[9]

In Missouri, a critically important question in March 2020 was whether the Department of Health and Senior Services (DHSS) would assume control of the pandemic response as was done in some other states. DHSS, which has 1,900 employees, instead made the consequential decision to play a back-up role and to place responsibility for implementing CDC guidance primarily in the hands of the state's 115 county and city public local public health agencies (LPHAs).[10]

Missouri's LPHAs are independent entities that do not report to the DHSS.[11] Among their multitude of responsibilities, which vary to some extent from county to county, are restaurant inspections, rat control, lake water testing, immunizations, maintaining vital statistics, disease surveillance, reduction of opioid overdoses, and administration of Women, Infants, and Children (WIC) programs. Although the LPHAs benefit from a communications network provided by DHSS and receive technical support and government contracts, many LPHAs have limited resources.[10, 11]

Missouri's per capita spending on public health in 2020 ranked last in the country.[12] In the decade prior to the pandemic the state's LPHA staffing dropped by 8%.[13] LPHA capacity in 2020 varied widely throughout the state. For example, the St. Louis County Department of Public Health has 518 employees, some of whom have doctoral degrees.[14] In contrast Reynolds County, population 5,950, has only seven employees in its LPHA.[15]

Thus, in early 2020 primary responsibility for Missouri's pandemic control fell on the state's LPHAs, most of which already were over-worked and under-

funded. There were several urgent priorities: locating and distributing personal protective equipment which was in short supply; establishing and implementing testing sites; investigating cases and tracing their contacts; building data infrastructure; and answering myriad unceasing questions from the public, news media, and health care personnel. During these frantically busy days, many public health employees slept at their offices. As the pandemic progressed Missouri's LPHA employees were to face unrelenting opposition not only from their deadly viral foe but also from many of the citizens they were endeavoring to protect.



Figure 3. Centers for Disease Control and Prevention (CDC), Atlanta, GA.
Source: Alamy

Public Health Faced Pushback From All Three Branches of Bovernment

In 1918, the *Kansas City Star* editorial board expressed despair about the "utter futility" of the public health board's efforts to manage the devastating influenza pandemic "as long as it is a politically controlled body."[16] A century later history repeated itself. As the COVID-19 pandemic surged, tensions directed at public health rose to a boiling point and agencies' longstanding powers to close businesses and schools and to limit or prohibit public gatherings were stripped by government officials and the courts.

At the federal level, CDC issued guidance on mask use and social distancing throughout the pandemic. Only five COVID-19-specific public orders were implemented. Two were overturned: a no-sail order for cruise ships by the White House Coronavirus Task Force; and a public transportation mask requirement, by a federal judge in Florida.[17] In Missouri, in March 2020 when COVID-19 cases were first reported in the Kansas City metropolitan area, the CORE 4 consortium comprised of Kansas City, Jackson County and neighboring Wyandotte and Johnson Counties, KS, closed businesses and banned public gatherings, likely saving many lives.[18] In response to this and other closures the Missouri legislature passed House Bill 271 which limited the duration of restrictions on schools, churches, businesses, or public gatherings to 30 days unless extended by a local governing body. [18] The bill's signing ceremony in July 2021 was hailed as a victory for individual rights and was attended by representatives of the restaurant industry which stood to benefit financially.[19] During the next two months disease incidence more than doubled and hundreds of Missourians died during the lethal Delta variant surge which began shortly after the law was enacted.[20]

In summer 2020, the Missouri legislature determined that a portion of pandemic relief funds received from the federal CARES Act, designed to stimulate the reeling US economy, should be designated for local public health departments to aid in pandemic control efforts. However, some county commissioners, angered by business restrictions imposed by the LPHAs, not only delayed payments for months but also slashed public health funding far below the recommended figures, as punishment for unpopular actions.[10, 21]

Further complicating matters, the judicial system intervened. The state of Missouri initiated dozens of lawsuits to overturn mask mandates enacted by local school districts and one to require cessation of governmental actions to prevent dissemination of dangerous misinformation on social media sites. (Figure 4) None of these lawsuits were prosecuted successfully. A Jackson County judge ruled that the state did not have the right to "insert (itself) into the school district's efforts to manage the COVID-19 pandemic."[22]

In a devastating blow to pandemic control efforts the Cole County Circuit Court ruled in November 2021 that all public health orders in the state were unconstitutional and were "null and void." [19] Following the ruling multiple health departments in rural areas of the state immediately ceased their COVID-19 response efforts.[10,19] Mortality in the month after the judge issued this decision was the third highest in the three-year pandemic.[20]

The Impact of Opposition to Public Health

During a worlwide health crisis that cost more than a million American lives, one would have hoped for a World War II-like response, "we're all fighting together against a common enemy." To the contrary, the US population was bitterly divided with many choosing to oppose pandemic control measures.



Figure 4. Tension between public health and the judiciary system.
Source: Alamy

The public health community was seriously outnumbered by its numerous outspoken, albeit vastly less knowledgeable and experienced, opponents. LPHAs, whose resources already were scarce at the beginning of the pandemic, faced nearly insurmountable challenges including reduction of powers, lack of affirmation from their local governments, and public harassment. A study of LPHA communications officers in Missouri, Oklahoma, and Kansas identified several recurring themes. Multiple LPHA officials were "trolled" online and were met with hostility in their communities. Long hours, inadequate funding, limited resources, and bureaucratic barriers all contributed to burnout. [3]

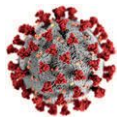
In Jefferson City, public health workers (PHWs) were threatened with sexual assault and there was online chatter about "chasing the (director) out of the county."[19] In Kansas City a social media post opined that "health inspectors should be strung up or killed."[24] The Director of the St. Francois County public health department and her family were doxxed.[24] PHWs sometimes changed clothes when leaving work at the end of the day, attempting to go incognito and thus to avoid harassment. Of note, 15 states, not including Missouri, have statutes protecting public health workers from threats or intimidation.[25]

Some public health officials kept their noses to the grindstone and took comfort from the phrase *illegitimi non carborundum* ("don't let the (opposition) grind you down"). However, in the face of constant and extreme adversity, turnover in LPHAs was high, exacerbating pressures on those who remained in their positions.[23] Between 2020-22 the leadership of the Missouri DHSS changed four times, and a fifth potential leader appointed by the Governor was blocked by the legislature following protests from anti-vaccination activists. [26] Nationwide in the first nine months of the pandemic more than 300 state and local health department leaders voluntarily left their jobs or were fired, including the directors of the LPHAs in Audrain, Christian, Howard, St. Francois, and St. Genevieve Counties; Tri-County (Dekalb, Gentry, and Worth Counties); and Joplin, Missouri.[24]

Misinformation and Disinformation Poured Fuel on the Fire

As health care workers we are trained to follow the scientific method. If a valid study is done, a hypothesis proven, the manuscript subjected to peer review, the results published in a reputable journal, and the observations confirmed, the findings should be accepted. Conversely, non-evidence-based anecdotes and opinions, especially from those without scientific training and expertise, should be met with healthy doses of skepticism. In the early 2020s proponents of the scientific method were in the minority.

Much blatantly incorrect and harmful information was spread, seemingly with the aim of sowing distrust of esteemed academic experts and national and local public health agencies and thereby undermining critically important pandemic mitigation efforts.[27] However, the 13,000-member Infectious Diseases Society of America (IDSA) stood in solidarity with our public health colleagues' actions. Infectious Diseases (ID) physicians traditionally have taken a



keen interest in either confirming or disproving each other's research findings. Notably, during COVID-19 IDSA members did not refute the experts' treatment guidelines and vaccination recommendations. Stated differently, the many naysayers who were so outspoken and influential during the pandemic were not trained ID experts. Although there should always be room for healthy differences of opinion, the authors believe that legitimate questions should be raised regarding the motives of those who sought to undercut evidence-based public health practices during a lethal pandemic.

How Did the Public Health System Perform Under the Dire Circumstances?

Limitations of the public health system were assessed after the pandemic waned. CDC's director concluded that "our performance did not reliably meet expectations."[28] Specifically, during a crisis, new scientific data should not be withheld until after publication; instead, actionable information should be released immediately. Some of the issued CDC guidance was recognized to have been "confusing and overwhelming." Needs were identified to enhance competency training and to permit pre-decisional input by LPHA personnel into new federal guidance. In general, the nation's public health infrastructure was considered to have been "frail" during the pandemic.[28] The CDC was prompted to begin modernizing public health data-sharing systems to improve dissemination of information in the future.[29]

In Missouri, an illustrative example of an area for improvement was the rollout of COVID-19 vaccine in late 2020 and early 2021. Distribution of the limited supply was managed at the state level. DHSS opted mostly to bypass LPHAs and to outsource the work to hospitals, federal programs, and consultants. LPHAs were allocated only 8% of the vaccine supply. St. Louis and Kansas City received 15% less than their shares whereas some rural areas, where there was lower interest in vaccination, had thousands of unused doses.[30] During the first three months that vaccine was available, approximately one-third of Missourians needed to travel outside their home counties to be vaccinated.[9, 30]

A comprehensive assessment of Missouri's public health response during the pandemic was done by the Millikan Institute School of Public Health at George Washington University.[31] Several conclusions were drawn. LPHAs did not receive adequate guidance on new policy issues including masking and school closures. Local workers' decisions sometimes were undermined by the state's actions.[31] LPHA authorities did not perceive the DHSS to be helpful in resolving differences in practices among neighboring jurisdictions.[31] In hindsight LPHAs felt that the decision to place pandemic management in their hands led to confusion, lack of trust, and fragmentation, contributed to low vaccination rates, and created vulnerability to political attacks in their communities when restrictions were imposed on schools and businesses.[10] Given the perceived lack of support from the DHSS and local elected officials, and widespread animosity in the population, "finally most of our (Missouri) health departments just threw in the towel."[10] Kelley Vollmar, chair of the Missouri Association of Local Public Health Agencies, summed up the situation by stating that during the pandemic "public health (was) silenced." [21]

Conclusion

Missourians learned many lessons during the COVID-19 experience. The decentralized approach to public health nationwide and in Missouri created a politically divisive pandemic control strategy with profoundly negative consequences. The federal and state pandemic responses were impeded by incomplete access to data. Some public health efforts were overturned by actions of elected officials and judges without expertise in the field. As summarized by Clay Goddard, Senior Director of Public Health Transformation at the Missouri Foundation for Health, "(the state's) pandemic response was what one would expect when a novel virus shows up … during one of the most divisive periods in history, and after a marked disinvestment in public health."[10]

Of concern, many of the public did not connect the following dots during the pandemic: A) the heroic actions of our public health community saved lives; B) conversely, active efforts to neutralize public health control measures led to substantial mortality that could have been prevented; C) elected officials and judges who overturned public health directives did not have scientific backgrounds and may have been influenced by political considerations; and D) perhaps most alarmingly, there was no apparent accountability for the words and actions of those who intentionally undermined public health with disinformation and thereby led to unnecessary loss of life during an infectious disease disaster.

Our most promising strategy to prevent a repeat of the COVID-19 debacle is to focus on aggressive surveillance and early detection of new pathogens with pandemic potential.[32] The best-case scenario is that the next catastrophic pandemic will not begin for at least another generation, by which time one can hope that the vitriolic opposition to public health we witnessed from 2020-23 will have dissipated, and that cooler heads will have restored the profession's long-held independence and powers that were curtailed.

We must be better prepared for the next pandemic, when once again many lives will be at stake. As we were taught in 2020-23, one of the most important factors that will affect our state's mortality rates during future crises will be the robustness, or lack thereof, of its public health response. Health care workers should stick together with our highly valued public health colleagues who were made into scapegoats during COVID-19 and endured relentless and misguided attacks by so many at great personal cost. Missouri should join other states by enacting legislation to criminalize harassment of public health workers. Now is the time to seize the opportunity to act upon one of the most important lessons from the pandemic: we need to re-empower and strengthen our public health system. Future generations will be counting on us.

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Overdose Data to Action in States (OD2A-S): Missouri's Response to the Opioid Epidemic

by Andrew Hunter, MA, Ashley E. Douglas, PhD, Neann Wedgeworth, BHS, Julie M. Kapp, PhD

Drug overdose continues to represent a challenging public health crisis nationally and locally. Nationally, the landscape of drug overdose mortality has evolved over the past two decades and is characterized as having distinct waves. The first wave began in 2000 and was driven by prescription opioids, the second wave began in 2007 and was attributed to heroin, and the third wave began in 2013 and is driven by illicit fentanyl.[1] Some scholars suggest a fourth wave has begun, driven by increases in polysubstance overdoses combining fentanyl and stimulants or other substances.[2,3] In 2022 in Missouri, an unprecedented 2,180 residents died from overdose deaths with most of the increase being fueled by non-heroin opioids such as fentanyl (Figure 1). Additionally, drug overdose ranked as the leading cause of death for those 18-44 years of age and Missouri's rate of years of potential life lost (YPLL) due to drug overdoses exceeded that of the US (1,258 compared to 1,081 per 100,000).[4,5] In fact, Missouri's YPLL rate has consistently exceeded that of the US since at least 2016.[5]



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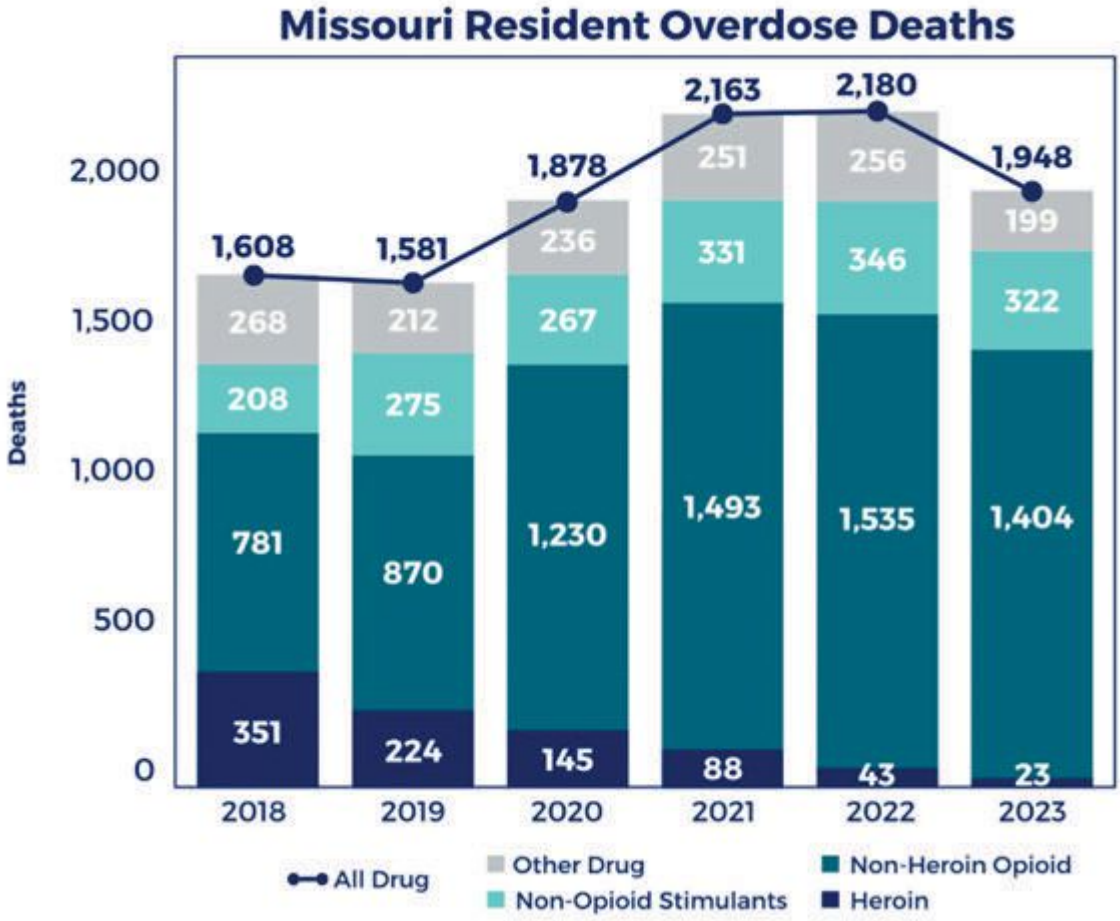
This enduring public health crisis will only be resolved with robust partnerships between public health, public safety, harm reduction programs, and health systems. Missouri's network of hospitals is a crucial ally in responding to the overdose crisis, as hospitals are a key intervention touchpoint for people who use drugs (PWUD). Consequently, the Missouri Department of Health and Senior Services (DHSS) has partnered with the Missouri Hospital Association (MHA) and hospitals across the state to respond to Missouri's overdose crisis collaboratively.

This article describes two overdose response strategies spearheaded by this partnership. First is biosurveillance, i.e., the process of collecting, interpreting, and communicating key information on hazard threats or disease activity so that early detection is achieved and informed decisions can be made.[6] The second is prevention, as implemented through expanded linkages to care and clinical education. These efforts are funded by the Centers for Disease Control and Prevention's (CDC) Overdose Data to Action in States (OD2A-S) program (CDC-RFA-CE-23-0002).

Overdose Data to Action in States

CDC's OD2A-S program is a five-year cooperative agreement with 49 states and the District of Columbia aimed at enhancing states' ability to decrease morbidity and mortality related to opioid, stimulant, and polysubstance use. OD2A-S builds on the work from CDC's prior cooperative agreements related to drug overdose as well as other federal initiatives. DHSS received OD2A-S funding in August 2023, and statewide interventions are underway. OD2A-S focuses on evidence-based and evidence-informed surveillance and prevention strategies, emphasizing health equity.

Figure 1. Missouri Resident Overdose Deaths, 2018-2023



OD2A-S uses a data-to-action framework[7] (analyze, prioritize, implement, and evaluate), under which multiple sources of data are used to select, improve, and scale interventions.

Biosurveillance

OD2A-S funds biosurveillance activities to maintain and improve infrastructure, conduct ongoing surveillance for fatal and non-fatal overdoses, and disseminate overdose analysis to the public in useful and innovative ways. For example, DHSS maintains a publicly available Drug Overdose Dashboard website with trends and interactive charts for overdose mortality and morbidity data (https://health.mo.gov/data/opioids/).[5]

Notably, Missouri was one of 20 states to receive OD2A-S funding for non-fatal overdose biosurveillance. One of the goals of OD2A-S is to enhance DHSS and CDC's ability to monitor changes in drug overdose patterns. To inform biosurveillance, DHSS' Missouri State Public Health Laboratory (MSPHL) has partnered with MHA and hospitals throughout the state to conduct toxicological testing for emergency department (ED) patients suspected of experiencing a drug overdose. Samples are submitted from participating hospitals and analyzed by MSPHL using a liquid chromatograph tandem mass spectrometer (LC/MS/MS). This device is a valuable resource for toxicology testing, as it is highly sensitive in detecting specific drugs rather than just drug classes. It also allows for comprehensive screening to identify emerging fentanyl analogs or other designer drugs.[8]

MSPHL currently analyzes samples for fentanyl and 22 fentanyl analogs (including U-47700). MSPHL will expand the testing panel to include other controlled substances in the future. Fentanyl and its analogs are of interest due to evolving drug patterns, including the growing number of Missouri overdose

deaths involving these synthetic opioids. Missouri's synthetic opioid deaths increased by 140% from 2018 to 2022, while deaths involving heroin declined by 94%.[5] Expanding surveillance to monitor the drugs involved in non-fatal overdoses enables a more comprehensive picture of Missouri's drug supply and overdose risks. Hospital participation is critical to the program's success. DHSS and MHA are collaborating to recruit hospitals and streamline the sample submission process to minimize the associated time and resource burden.

As of July 2024, three hospitals are submitting samples for testing and four additional facilities are being onboarded. MSPHL is currently testing approximately 30 samples per month with the capacity to expand to 85 samples. Nearly half of the samples provided so far have tested positive for fentanyl, with norfentanyl (a major metabolite), despropionyl fentanyl (4-ANPP; an intermediate in the synthesis of fentanyl), and parafluorofentanyl (a fentanyl analog), being commonly detected substances. Confidentiality rules related to facility and personal identity are in place to maintain privacy. The goal is seven hospitals fully participating in the program before September 2025, with the capacity for expansion in future years. Hospital recruitment was designed to represent a cross-section of hospitals statewide. As more hospitals participate and the number of specimens submitted exceeds the lab's capacity, MSPHL will implement systematic sampling to test a representative proportion of all specimens received.

Initially, biosurveillance findings will be shared with MHA, participating hospitals, and OD2A-S staff, while maintaining privacy. Data by age, gender, and race will be analyzed and graphed to highlight percent positivity of samples, compare the fentanyl analogs detected, and show monthly trends. Participating hospitals may use this information for clinical decision-making related to anticipated patient volumes in the state or their region or emerging potent analogs.

By September 2025 enough data will be available to provide a statewide analysis, and DHSS will release a publicly accessible Biosurveillance Fact Sheet summarizing the program. Information about the fact sheet will be available through the DHSS Drug Overdose Dashboard website. This will supplement the website's existing morbidity data related to health care, which includes ED versus inpatient visit types, and visits by county, gender, race, age group, drug type, and estimated ED charges. Recently, DHSS added a tab on the dashboard for emergency medical services (EMS) data.

Prevention

In addition to biosurveillance, DHSS and MHA are supporting a comprehensive, evidence-based response to overdoses within hospitals. One element of this partnership includes increasing linkages to care for PWUD who present to EDs. Linkages to care are facilitated by Engaging Patients in Care Coordination (EPICC)—a program that utilizes Certified Peer Specialists (CPS), or navigators, to link PWUD who present to EDs to community-based treatment and medication for opioid use disorder.[9] Navigators provide support to EDs by making focused connections with patients presenting drug-related conditions, typically within hours of admission. EPICC support extends beyond the hospital and includes helping clients meet needs such as housing, employment, transportation, and childcare, which may support retention in care and recovery. Patient engagement with EPICC has been associated with a reduced 90-day readmission rate among individuals with opioid use disorder and severe injection-related infections.[10] MHA leads EPICC in Missouri's Central, Western, South Central, and Southwest regions, whereas the Behavioral Health Network of St. Louis leads EPICC in Missouri's Eastern region.

DHSS and MHA are also collaborating to provide clinicians with training opportunities on topics such as pain management, screening for opioid use and stimulant use disorder, stigma, and sexually transmitted and blood-borne infections. These trainings aim to enhance clinicians' knowledge of evidence-based practices to prevent and respond to overdoses. Interested clinicians should contact the corresponding author. A recent article introduced Missouri's healthcare workforce to two evidence-based approaches for patients with opioid use disorder: medication-assisted treatment, and harm reduction.[11] Additional information for reducing opioid-related morbidity and mortality in Missouri can be found online at DHSS' Time2Act website (https://time2actmissouri.com/).

Evaluation

OD2A-S is invested in population-level impact. All grantees are required to conduct extensive evaluations

of their programs, including the program's impact on drug overdose mortality and health disparities, implementation opportunities, and barriers. Evaluation efforts are tailored to their populations of focus and prevention activities, including assessment of progress on short-, intermediate-, and long-term outcomes. OD2A-S emphasizes involving partners and people with lived and living experiences in planning and evaluation efforts to provide critical feedback on aligning program activities with the needs of the community. Finally, OD2A-S evaluation guidance includes a targeted evaluation specific to linkages to care through navigation activities. In the data-to-action framework, the evaluators are considered members of the project team and work together as partners.[7]

Conclusion

The CDC-funded OD2A-S program enables Missouri DHSS to implement initiatives aimed at reducing drug overdose mortality across the state. Through a robust partnership with MHA and participating hospitals, DHSS is collecting meaningful biosurveillance data, expanding overdose education, and providing an evidence-based, person-centered approach to linking PWUD to care. These efforts represent a portion of Missouri's plan to combat the overdose crisis. It will take a statewide effort with comprehensive partnerships to rise to this challenge.

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Haiti—A Story of Hope and Chaos

by W. Abraham White, MD & William L. White, MD

The Caribbean nation of Haiti, occupying the western half of the island of Hispaniola, is no stranger to struggle. Over the last five years, the country has descended from abject poverty into lawless chaos.[1] While it is impossible to deal comprehensively with how Haiti arrived at the current state of affairs in a short article, we hope to provide a brief explanation for those readers who may not be as familiar with the nation and its history. We will also discuss the implications for medical care in Haiti, including both indigenously delivered care as well as medical relief work.

The authors have been involved in medical relief work in Haiti since 2001.[2,3] Over the course of that time there have been periods of unrest and struggle, including earthquakes, violent demonstrations, and a cholera epidemic unwittingly unleashed by the international relief effort in 2010.[4] Despite these events, affairs have generally returned to the status quo ante. This cycle of disaster and reversion has more or less dominated Haiti's history from 1804 when the nation gained independence from France until the events of 2019.

Epicrisis for a Failed State

Haiti does not have a centralized power grid that serves much of the country; as such fossil fuel generators are often the only means of electricity, particularly outside of major cities.[5] Beginning in 2018 there was a sharp increase in fuel prices largely due to political turmoil in Venezuela, Haiti's primary supplier of petroleum.[6,7] These price increases set off widespread protests. In early 2020 with the beginning of the pandemic lockdowns and travel bans, Haiti was largely cut off from the foreign visitors as well as the aid that they often brought with them. The rampant inflation that has dominated the world economy for the last four years hit the already chronically weakened economy in Haiti hard, elevating the prices of basic necessities such as food beyond the reach of many families.

Due to the political unrest resulting from the economic crisis, Haiti has not held elections since 2016, leading to the expiration of the terms for Haiti's legislators.[8] Haitian president Jovenel Moise was assassinated in July 2021 and then-Prime Minister Ariel Henry was installed as Acting President of the fraying remnants of Haiti's government.[9] Widespread gang violence filled the void left by increasingly powerless police and security forces, struggling for control of neighborhoods and cities. The power vacuum generated by the economic and political crises created a feedback loop, further weakening the economy and strengthening the gangs.

In order to finance their operations, many of these gangs turned to kidnapping for ransom, leading many to flee the country who had the means to do so. Prior to this time, US citizens were largely overlooked as ransom targets due in part to the low probability of a ransom payment being made and the almost certain response of the US government. This protection evaporated as conditions in Haiti deteriorated, leaving even the gangs increasingly desperate for money. Notable US victims of these gangs include 17 missionaries working with Christian Aid Ministries who were kidnapped and released after two months of captivity in 2021, and Davy and Natalie Lloyd, the son-in-law and daughter of Missouri state representative Ben Baker, who were murdered by gang members on May 23, 2024.[10,11] Beginning in February 2024 gangs including the Revolutionary Forces of G9 Family and Allies, led by former police officer Jimmy Cherizier, began a coordinated effort to



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target infrastructure and strategic targets.[1] They staged a large jailbreak in March 2024, liberating thousands of prisoners, and laid siege to the international airport in Port-au-Prince.

A transitional council was appointed and officially took charge of the country on April 25 following the resignation of Ariel Henry the day before. Despite this step forward, much of the capital and other parts of Haiti remain in the control of armed gangs. A multinational force, led by Kenya and including peacekeepers from the Bahamas, Jamaica, Guyana, Barbados, Antigua, Barbuda, Bangladesh, Benin, and Chad began arriving in May 2024, with financial support from the US government.[12] These police officers and soldiers will be charged with retaking and securing vital infrastructure to stabilize the government and economy. As of the writing of this article, the extent of their success remains unknown. The recent cessation of most commercial flights in and out of Haiti are an indication that the level of violence remains at an unacceptably high level.[13]



David Yi, MD performing cataract surgery with technician Cindy Alborn assisting, July 2022.



David Yi, MD and Cindy Alborn with members of the Northwest Haiti Christian Mission staff.

Implications for Medical Care

The current state of near anarchy within Haiti has been devastating for healthcare delivery within the country. Prior to the current crisis, Haiti spent approximately $13 per capita on healthcare, which is well below average even for low income countries.[14] Medical practice in Haiti was difficult in 2019 and has become nearly impossible at the present time. Staffing shortages, logistical difficulties in acquiring medical supplies and pharmaceuticals and a lack of electricity have stymied the delivery of even basic medical care in much of the country. It is estimated that

as many as 20% of medical professionals had left the country by early 2024.[15]

We last dispatched a major surgical team to Haiti in October 2018. Our most recent clinic team traveled to Haiti in February of 2020. This seven-member team examined 744 patients, treating conditions ranging from refractive errors to glaucoma. After international travel resumed with the waning of the COVID-19 pandemic a three-member surgical team ventured to Haiti in July 2022, testing the equipment and checking on the supplies and instruments that had been left behind by previous teams. For safety, this team traveled in relative secrecy to avoid being targeted for kidnapping, with only a handful of people being aware of their arrival and departure dates. A future trip was planned, though this did not materialize after the evaporation of predictably accessible domestic air travel in April 2023 when Mission Aviation Fellowship suspended operations in Haiti.



Bullet hole in the windshield of a "tap-tap", the local term for a taxi.

Charitable donations from industry are a major component in the success of private international medical relief work. Corporate support for this work depends upon the ability to safely transport both personnel and supplies to the host facilities. The US Department of State has a 4-level travel advisory system that is widely accepted as a benchmark for safety. Haiti is currently classified as a level 4, which is equivalent to a war zone. It is virtually impossible to secure private donations for work in any nation that is at a travel advisory level 4, and it is impossible to fly commercially to Haiti from the US as of the writing of this article.

We are actively supporting Haiti by shipping supplies to our partners there when this is possible. This enables the ongoing treatment of some chronic ocular conditions such as glaucoma. We look forward to the time when we are able to return to continue delivery of surgical care to those we have cared for and deeply invested in.

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John Sappington MD: The Missouri Country Doctor Who Introduced Quinine for the Treatment of Malaria in North America

by Arthur Gale, MD

Symptoms of Malaria were first described in China in 2700 BCE. Hippocrates described the symptoms of malaria in Greece in the fourth century BCE. In the 17th Century Indigenous Indian tribes in the New World used a medicinal bark for the treatment of fevers.

In 1880 Charles Louis Alphonse Laveran, a French army surgeon stationed in Algeria, noted parasites in the blood of a patient suffering from malaria. In 1907, Laveran was awarded the Nobel Prize for his discovery. In 1897, Ronald Ross, a British officer in the Indian Medical Service, was the first to demonstrate that malaria parasites could be transmitted by mosquitoes. For this Ross was awarded the Nobel Prize in 1902.[1]



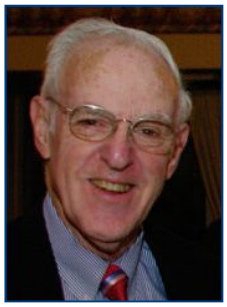
Figure 1. John S. Sappington, MD, from Arrow Rock, Missouri, was the first to use quinine to treat malaria. Born May 15, 1776 and died September 7, 1856 at age 80.

In the 1820s and 1830s long before the cause, mechanism of transmission or even the name malaria was known, a Missouri country doctor named John Sappington, defying standard medical practice, prescribed and sold pills containing quinine to treat fevers (Figure 1).[2]

Malaria was carried to the New World by European colonists and African slaves. In North America the malaria parasite thrived among mosquitoes in swampy waters like those in coastal Carolina, the Mississippi bottom lands and along the Missouri River where Sappington set up his practice. When Thomas Jefferson finalized the Louisiana Purchase in 1803, opponents of the purchase and his political enemies criticized him saying that he had bought "a swamp unfit for human habitation."[3]

In Europe physicians had treated the symptoms of malaria with a remedy from the Andes where Jesuit missionaries had seen the Incas use the bark of the Cinchona tree to treat "shivering." By 1832 Sappington began commercial production of the cinchona bark and mass-produced the pill adding myrrh, licorice, and sassafras to mask quinine's bitter taste (Figure 2).

Sappington sent numerous salesmen across Missouri and mainly the southern states to sell his anti-fever pills. At the time most doctors were still bloodletting and purging for all sorts of illnesses.



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Ahead of his time, Sappington strongly condemned these practices. As a result, the physicians of the "prestigious St. Louis Medical Society" denied him membership in the society and called him a quack.[4]

Despite the criticism of his fellow physicians Sappington remained undeterred. In 1844 Sappington published a book *The Theory and Treatment of Fevers*. This book was the first medical book to be published west of the Mississippi. He gave away all copies. Much to the chagrin of his relatives the book revealed his heretofore secret formula for his anti-fever pills.[5]



Figure 2. Dr. Sappingon flavored the cinchona bark by adding myrrh, licorice, and sassafras to mask quinine's bitter taste.

John Sappington was born in 1776 the same year the Declaration of Independence was signed. He grew up in Tennessee. He was a friend of future Missouri Senator Thomas Hart Benton who encouraged him to come to Missouri. He settled in Arrow Rock Missouri which was on the fur trade route between St. Louis and Santa Fe. Benton lent Sappington $950 with which he bought several thousand acres of land in the Boonslick area of Missouri.

Sappington was born into a family of physicians. He apprenticed to his father, who was a doctor, as was the custom in those days. He married Jane Breathitt the daughter of the governor of Tennessee. Sappington was the patriarch of a family political dynasty that included three Missouri governors—two sons-in laws Meredith Miles Marmaduke and Claiborne Fox Jackson and grandson John Sappington Marmaduke. A more contemporary descendant, the singer, dancer and actress Ginger Rogers, was his great-great granddaughter.

One author described Sappington as follows:

"For over thirty years Sappington traveled horseback on the roads and cow paths of the frontier-a tall, ruddy handsome clean-shaven figure…bearing a remarkable resemblance to his friend Andrew Jackson. In his saddlebags he carried a supply of drugs and a brace of pistols, and in his hip pocket was a long, sheathed knife on whose point he measured out his doses of Peruvian bark and later its extract quinine. He had a quick wit and polished manner, but he often spoke with savage denunciation of the murderous puke, purge, and bleeding which other doctors used in treating malaria."[6]

Sappington became wealthy from his anti-fever pills and from other investments and businesses. He was philanthropic. He was a strong believer in education and established the Sappington School Fund which helped underprivileged children to attend schools. It is still in existence today. In recent years the fund has helped students obtain a college education.

By 1951, malaria was considered eliminated in the United States mainly through the use of better sanitation and the insecticide DDT. However, throughout the world malaria is still a killer. In 2015 it caused 214 million infections and 438,000 deaths 70% occurring in children under five years of age. Cases treated in the United States are mainly in persons who have travelled to or are from Africa. Quinine still remains an effective treatment of malaria and is one of the two main drugs used for the treatment of central nervous system malaria.[7]

Without knowing what disease he was treating or how it was transmitted and relying solely on testimonials from patients, what today we would call anecdotal evidence, John Sappington's anti-fever pills were astonishingly effective.

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Life as a Rural Physician: Many Opportunities for Service and Impact

by Warren Lovinger, MD

I consider myself to be incredibly fortunate! I was blessed to have strong role model parents, was always encouraged to be a servant leader, and spent my career in a profession (medicine) and lifestyle (rural practice) where I could "make a difference."

I grew up on the campus of Central Missouri State University (now UCM), in Warrensburg, Missouri, where my father was the President for 23 years and my mother was deeply involved in community service. I was always stimulated by an environment of learning, enthusiastic people, and a sense of positive purpose. I am sure that I would have also entered the field of education, if it hadn't been for a serious high school football injury that introduced me to an entirely new world—the medical profession.



The young Lovinger family at my medical office in downtown Nevada on February 13, 1992.

The physicians I met impressed me with their knowledge, demeanor, and compassion. I really liked their combination of scientific and communication skills. I soon decided that I wanted to be a part of their profession.

After a great undergraduate experience at CMSU, I was accepted to the Johns Hopkins University School of Medicine, in Baltimore, Maryland. My arrival at this urban hospital and medical campus in August of 1973 was quite a culture shock for a small-town Missourian! However, I soon embraced the invigorating culture, with brilliant teachers and classmates, a strong sense of history (home of Drs. Osler and Halstead), and the challenge of so much new learning. After four years in this intense environment, with many great experiences, I was an optimistic and motivated new MD.

I was very thankful to match into the Internal Medicine residency program at Barnes Hospital, in St. Louis, Missouri. It was exciting to return to the Midwest. Much like Johns Hopkins, the Barnes system promoted high expectations and many opportunities for learning. The hours were long, but my colleagues and mentors were excellent, and I felt that I was at the "cutting edge" of medical knowledge and therapeutics. Yet, as my experience grew, I realized that my greatest joy came from providing comprehensive care to patients, while developing relationships with them. It was apparent that primary care medicine was my calling, and that I would be happiest in a rural, small-town environment. Though I was the only member of my residency class who chose this path, my fellow physicians and program directors were supportive.

During my three years in St. Louis, I had the great good fortune to meet Marilyn Ratzlaff at the



Warren Lovinger, MD, is a retired Internal Medicine physician from Nevada, Missouri. Pictured here with his wife Marilyn.

church we both attended. She was a math teacher and McDonnell Douglas IT employee, having grown up in rural Illinois. We were married on August 11, 1979. Her exemplary faith and advocacy have since guided me toward being the best person that I can be. As newlyweds, during my final year of IM residency, we visited several communities and practice settings —seeking a permanent home. We eventually chose Nevada, Missouri, a rural town of 10,000 in the southwest part of the state. We moved to Nevada in July 1980, and it has continued to be our home for 44 years.



Warren and Marilyn Lovinger leaving the office for travels to 114 Missouri counties as MSMA President, 2017.

Upon starting practice on July 14, 1980, I was immediately expected to provide the full spectrum of care to a diverse group of patients. There proved to be many additional skills and insights that I had to "learn by doing." I benefitted greatly from the advice of older, experienced physicians. During the next 40 years, I practiced Internal Medicine in the office, in the hospital (Nevada Regional Medical Center), in the nursing home, and in various consulting capacities. My special interest was in cardiologic diagnostics, which gave me the opportunity to interpret more than 40,000 EKGs and to provide thousands of stress tests and echocardiograms during my career. Due to a limited availability of medical office space, I had the educational experience of acquiring properties and building two new medical office buildings.

Another unique role for me was in serving for 17 years as the students' physician at Cottey College of Nevada. Yet, the greatest joy always came from providing medical care to my many long-term adult patients. I considered them as friends, and often cared for multiple generations within families. This gave me the opportunity to favorably impact their lives, and I looked forward to every day that included patient interactions.

I was greatly blessed to spend my entire career as an independent, office-based, private practice physician. Though I routinely worked 60 hours per week, this practice arrangement allowed me to determine my schedule and my practice emphasis. I was still functioning at full capacity when—as was long planned —I retired from medical practice in July 2020. I just missed the COVID-19 pandemic. The practice model that I enjoyed so much is now becoming increasingly uncommon, due to the economic, technologic, and social demands of office-based primary care medicine. It is understandable that most younger physicians seek the financial rewards and lifestyle predictability of an employment model, when they enter the medical field.



Dr. Lovinger thanked for being a Medical Director at Nevada Hospital and Nursing Home, 2001.

A greatly underrated aspect of life as a rural physician is the opportunity to favorably impact other features of the community. Physicians and their families are warmly received and expected to be leaders in civic service and vision. Since Marilyn and I were blessed with four children, all born in Nevada, we were immersed in numerous types of school, sports, church, and other activities for 30 years. This type of nurturing and supportive environment encourages youth to set high goals. It clearly benefitted our children, as three of them are now physicians practicing in Missouri, while the fourth lives in a beautiful part of Switzerland. Eight grandchildren, ages 1 to 11, are a great source of joy for us.

My non-medical service opportunities have been numerous. I served 18 years on Nevada's Board of Education, enjoyed 13 years as a youth soccer coach, co-founded the Osage Prairie YMCA, have been a Presbyterian Elder for over 40 years, and am currently serving as the Governor of Rotary District 6110. Marilyn and I will be particularly busy this year, as we travel to 73 Rotary Clubs in Missouri, Kansas, Oklahoma, and Arkansas. One other family project has been to promote local economic development. We partnered with younger Nevadans to bring a popular new restaurant to town—successfully adding jobs, tax revenue, and food options for our community.

Leadership in the medical profession has been an important priority for me, throughout my career. I served as President (as well as other offices) of NRMC's medical staff for several terms, over 40 years. In 2019, I chaired a committee of Nevada's leaders when we proposed a new sales tax to support our hospital. Thankfully, it passed with an 87% positive vote. I served as the Transitional Governor of Missouri's ACP Chapter in 1999 and 2000. I was humbled to receive the American College of Physicians' national Claypoole Award in 2021 for "devotion of a career in Internal Medicine to the care of patients." After being active in the Missouri State Medical Association since residency, I served as its President in 2017-2018. To emphasize the importance of rural physicians and hospitals, Marilyn and I visited all 114 counties in Missouri, during that year. We put 18,000 miles on our vehicle with this epic adventure. I also enjoyed ten years of service on Missouri's AMA delegation.

As I look back on 50 years of involvement with the medical profession, I have enormous gratitude for the many experiences it has provided for me and my family.

It is a great honor to have treated so many patients, to have had so many leadership roles, and to have made so many community and professional friends. As a rural physician, I have been given innumerable opportunities to serve and make an impact on others. I am eternally thankful to be part of the "world's greatest profession!"

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Left to right: Sarah Florio, MD, Grandson A.J. Florio, Marilyn Lovinger, Warren Lovinger, MD, MACP, Dan Lovinger, MD, and Tom Lovinger, MD.



Current Lovinger Clan: It includes four physicians (all MSMA members), one Dentist, one Dr. of Ministry, and our eight grandchildren (ranging in age from 1 to 11). Taken December 28, 2024.

In the News

Missouri Medicine Announces New Contributing Editor and Board Members

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



Nicholas N. Gier, MD, is a Hospitalist with Gates Hospitalists in Kansas City. He replaces **Emily A. Hillman, MD**, who completed her three-year term, and we thank her for a great job.

After many years of service, both **Jerry Kennett, MD**, and **Joseph A. Corrado, MD**, are leaving their positions in Cardiology and General Surgery, respectively. We thank both for their generous service to our Journal as well as MSMA, including serving as Presidents for our Association.



Jeffrey Coughenour, MD, Medical Director, Frank L. Mitchell, Jr., MD, Professor of Surgery (Acute Care Surgery) with University of Missouri-Columbia, is our next General Surgery Editorial Board Member.



Vrinda Trivedi, MD, Assistant Professor of Medicine at the University Missouri-Columbia, is stepping up as our Cardiology Board Member.



Missouri Medicine welcomes **Abid M. Bhat, MD**, as the new Sleep Medicine Editorial Board Member. He is a Professor of Medicine in the Division of Pulmonary, Critical Care, and Sleep Medicine at University Health Hospital, University of Missouri – Kansas City School of Medicine.

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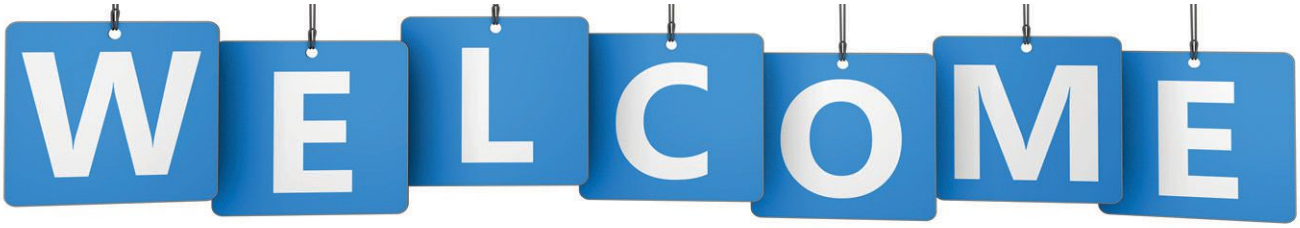
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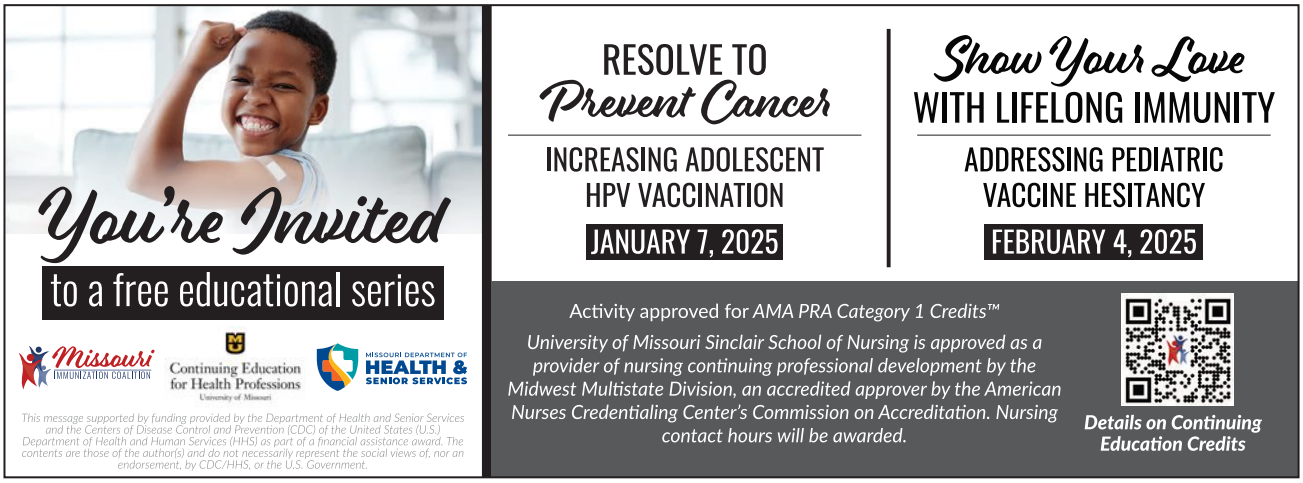
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In this issue we aim to raise awareness of the precision health field and showcase the breadth of topics it covers.

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Looking Forward to AI and Medicine: Where Are We, and Where Are We Going?

by Adam Wilcox, PhD, Malachi Griffith, PhD & Obi Griffith, PhD

We speculate that the integration of AI, particularly generative AI, into medicine is expected to progress at a slower pace than in fields such as research.



Adam Wilcox, PhD, FACMI, (pictured), is Director, Center for Applied Health Informatics, Professor of Medicine, Division of General Medicine & Geriatrics, Washington University School of Medicine, St. Louis, Missouri. Malachi Griffith, PhD, and Obi Griffith, PhD, are both Associate Professors of Medicine (Oncology) and Genetics and Assistant Director of the McDonnell Genome Institute at Washington University, St. Louis, Missouri.

Abstract

Artificial intelligence (AI) has emerged as a significant area of interest in medicine, with the potential to influence various aspects of health care. However, the real benefits of applications of AI to medicine often become obscured by the considerable attention, and hype, around its capabilities. To better understand AI's role in medicine, it is important to contextualize its development and review the stages of AI evolution that have contributed to its present state.

Introduction

My (AW) first exposure to AI was taking a course in the topic as part of my graduate studies in a new field called "Medical Informatics." Most of the students in the class were training as computer scientists, and during that semester were particularly interested in a chess match between then-world chess champion Garry Kasparov and IBM's Deep Blue supercomputer. Though Kasparov won that match, the next year Deep Blue would be the victor, marking the first time a computer program defeated a world champion in a tournament-style match. What I didn't recognize at the time was that I wasn't witnessing the beginning of a new era of AI capability, but rather the apex achievement of a rule-based era in the field that was rapidly declining. By the time I completed research for my dissertation, both I and much of the world had moved on to a new approach to AI known as machine learning.[1] These transition points of different eras in the field are important for understanding both where it has been and the significance of where it may be going.

Artificial Intelligence History

The earliest applications of AI that demonstrated practical capabilities beyond proof-of-concepts were rule-based systems. Initially, such systems used simple rules and logic to simulate human decision-making. By the 1970s, expert systems were developed that used large sets of rules to make decisions in specialized domains. Perhaps the peak expert system was Deep Blue. With a complex but well-defined problem and sufficient computing power to search and apply rules it could outperform any human in that task. However, in general these systems were limited in their ability to handle ambiguity, learn from data, and adapt to complex problems. Their dependence on hand-crafted rules made these systems inflexible and difficult to scale.

Years later, after considerable disappointment in rule-based systems, and disinterest in AI generally, another stage of AI emerged in the 1990s with machine learning. Machine learning allowed systems to learn from data, so that

rules could be created and managed flexibly according to the data that were already collected and expected to be available in their application. To a degree, machine learning is a form of automated analysis of data, where algorithms that mimic different approaches to analyzing data are applied automatically. This made them much more flexible and scalable, though they were dependent on both the availability of training data and processing capabilities of the computers generating and applying the developed models. If sufficient data were not available to indicate patterns for learning, machine learning algorithms were limited in what could be discovered.[2]

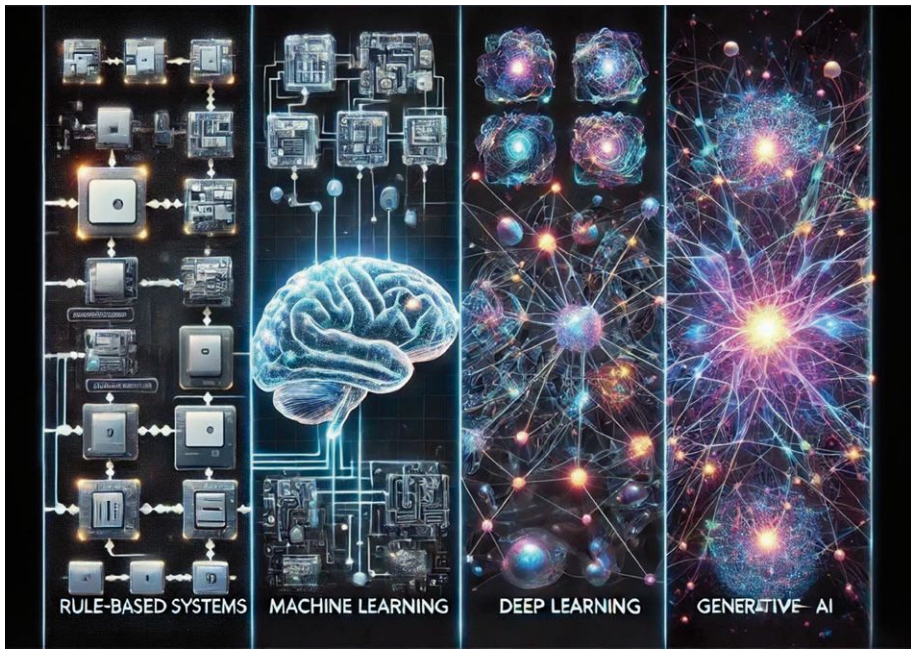


Figure 1. The different stages of artificial intelligence. This image was created (with significant prompt iteration and targeted edit requests) by DALL-E, an AI image generator.

The next major breakthrough came in the 2010s with the rise of deep learning, which is a subset of machine learning.[3] This was in large part due to the rapid growth of available data that could be used for machine learning and increased processing capabilities; deep learning coincided with the era of "Big Data" and the emergence of graphics processing units (GPUs) for processing of data. Deep learning used a particular type of machine learning algorithms, artificial neural networks that were composed of multiple layers. These networks were capable of learning high-level features from raw data, which allowed greater abstraction and more powerful modeling of complex datasets.

In addition, neural network models once developed are highly efficient, because they use direct numeric calculations with the variables among the nodes in the networks. With more data and processing capabilities, deep learning allowed discovery of patterns that could not be identified during the previous machine learning era without substantial use of domain knowledge in the process.[1] Not surprisingly, the areas of greatest impact with deep learning were in the domains with the largest amounts of available data, including image and speech recognition, natural language processing, and autonomous systems like self-driving cars. These data sources were available due to growth of image capture, increase of text information ability, and improved data collection.

The current era of AI, coming to prominence in the 2020s, is defined by generative AI, which extends the capabilities of AI models beyond pattern recognition and prediction to the creation of new data (Figure 1). Generative AI models such as large language models (e.g., ChatGPT) are built on transformer architectures, which are a type of deep learning model that is more efficient and powerful than previous models.[4] This allows higher processing capability, making generative AI algorithms the most advanced that have been applied. Importantly, generative AI provides a different kind of interaction than previous modes of AI like deep learning, which were applied to specialized domains and workflows. Because generative AI creates new content rather than simply classifying content already defined, it can provide more immediate value and assist in tasks that are directly useful to a wide range of users. In fact, almost immediately after its release in late 2023, ChatGPT became the most widely and rapidly adopted technology ever.[5]

Artificial Intelligence in Medicine

The application of AI to medicine has evolved alongside the broader field of AI, though progress has often been shaped by the availability of data, regulatory constraints, and the complexity of medical tasks. Expert systems were widely developed for medical settings because of their potential to standardize complex

Table 1: Previous stages of AI and their impact on medicine. Applications in medicine were some of the earliest examples for Rule-based systems; however, the lack of available data limited AI applications during subsequent stages.

AI Stages	Use in Medicine
Rule-based systems	Antibiotic assistance
Machine learning	Some applications in bioinformatics, but generally only used in research
Deep learning	Image analysis; high-throughput sequencing; NLP

diagnostic and therapeutic recommendations. One of the most notable examples from this period is MYCIN, developed in the 1970s to assist in diagnosing bacterial infections and recommending appropriate antibiotics.[6] While it and other advanced expert systems were limited in practical use, they were significant in advancing the field of AI. In contrast to the low use of rule-based expert systems, rule-based decision support remains the most active use of any electronic health record (EHR) clinical decision support.

During the machine learning era, AI was applied in healthcare to various tasks including diagnostics, predictive modeling, medical language processing, medical imaging and more. However, this was primarily in studies of feasibility, and the actual impact was limited. This is in large part due to the complexity of clinical data and a low availability of data. Most machine learning approaches used supervised learning, which required data that were already curated or had defined outcomes. This meant that datasets would first have to be created by having experts classify the outcomes in order to be used to train machine learning models.[1] Ultimately, due to this curation cost and broader challenges with machine learning performance, most machine learning projects in medicine outside of bioinformatics and genetics failed to move beyond the experimental stage.

The deep learning period achieved some real successes in AI adoption in medicine but only in specific areas. These occurred in areas with high volumes of data, such as medical imaging, or where the data were too complex for human understanding, such as genomics. In medical imaging, deep learning applications have been used to analyze medical images and detect conditions with performance comparable to or even exceeding that of human specialists.[7] In genetics, deep learning through high-throughput sequencing has been used to predict protein structures, identify disease-related mutations, and understand the functional consequences of genetic variants.[8] However, in other areas the application of deep learning lagged behind other fields and had limited adoption. This was in part due to the protection of medical data that limited sharing of clinical data between institutions, making it difficult to gather the large datasets necessary to train deep learning models effectively. Even in areas that appeared to be successful in generating effective models like corpus-based natural language processing (NLP), the cost of creating the datasets and the localization of data limited adoption beyond research demonstrations.[1] In addition, there were concerns about the "black box" nature of deep learning models, which offered limited insight into how those predictions are made. Such applications are difficult for adoption in life-critical healthcare environments.

It is perhaps the limited success of AI applied to medicine during the previous eras (Table 1) that has made the current excitement around the use of generative AI in medicine so interesting. These possibilities have been inspired by the broad application of Large Language Models (LLMs) outside of medicine. Shortly after its release, ChatGPT and its successors were applied to the Law School Admission Test (LSAT) to demonstrate its capability with reasoning and comprehension.[9] It was then applied to the Medical College Admission Test (MCAT) to demonstrate its capability with scientific reasoning and domain-specific scientific knowledge.[10] Later, it was applied to more advanced medical training tests like board examinations.[11] These test results were important to demonstrate capabilities of the LLMs and increased enthusiasm for them; this quickly led to applications in understanding medical information in practice generally. In fact, some have described LLMs as "all-purpose prediction engines" when working with data from a health system.[12] Others have made suggestions that they could transform the use of information in health care, allowing a shift in focus

away from structured data collection and towards more use of narrative text.[13] In a very short time, LLMs have been evaluated in tasks from general prediction, to automated coding for billing, to interfacing directly with patients in clinical communication. Considering the narrow applications of specific AI capabilities in medicine during the past few decades, this rapid acceptance of generative AI tools has been the most significant change, and perhaps the most important (Table 1).

As an example, consider the use of LLMs in medical language understanding. As Kather et al. describe, the performance of LLMs appears sufficient to consider broad use in areas where AI has not previously been applied at scale.[13] Multiple evaluations of LLMs have shown their performance is actually inferior to existing demonstrations of NLP. However, this does not prevent enthusiastic recommendations of their use in areas where NLP was never applied with meaningful success. This is in part due to the ease of use—LLMs require minimal development in comparison to NLP and they can be applied very flexibly—but is also due to the acceptance of their performance as demonstrated. Users know that LLMs are imperfect based on experience in applying them in broad domains, and so their flaws may appear more tolerated than NLP applications that have been developed in niche domains. The acceptance for use and tolerance of mistakes may also be forward-looking, with the expectation that the performance can get better with just more training data, 'prompt engineering,' or configuration; this can also be influenced by the perception of how recently these applications became available.

Looking Forward

While there has been a rich history of AI development and its application in medicine, the current environment appears significantly different in terms of both capabilities and possibilities. There is clearly some overexuberant hype with AI applications, but there are also real expectations that this era will be significant in the value it can bring to medicine. It is reasonable to expect that performance will improve in medicine with optimization—researchers are already demonstrating better performance when language models are trained on medical text at an individual institution. If the privacy of medical data can be effectively managed, barriers to sharing data can be overcome, and these models can be scaled across institutions, we can expect even greater utility than we are now observing. There are likely to be some modest challenges related to incorporating key knowledge sources that may have license restrictions (e.g., knowledge in the Unified Medical Language System or National Comprehensive Cancer Network), but such challenges have rarely remained permanent barriers in the information age. There are also likely ethical challenges that will arise from limitations and flaws of the technology, such as observed issues of "hallucinations" from generative AI systems or concerns that they could enable fraud or disinformation, but such challenges also have generally been transient while solutions are identified. There is also likely to be different perspectives on how such technologies should be regulated, which will result in more deliberate steps to their application.

Regardless of the area of application, flaws in the technology, or regulatory requirements, it will be important in all attempts to apply AI in health care to have the technology evaluated. With the broad capability of generative AI, this era is different in that new uses are proposed that were not specified in the design or development of the application. As a result, end users must be capable at evaluating the actual expected effect of the different uses. This will require both a clear definition of the use case(s) being evaluated, but also a real assessment of the comparators for measuring effectiveness.

The above example of comparing LLMs against NLP is a good illustration. So far, the performance of LLMs has not matched the performance of NLP; however, the simplicity of development and ease of application for LLMs are substantially better in comparison to NLP. On the other hand, the development and implementation costs for NLP have led to it rarely being used beyond research studies.[14] The important comparison for evaluation therefore may shift to comparing the use of LLMs for information extraction against not using the text information, since that represents the "usual care" environment for health care data analysis. Evaluations should focus not just on performance, but also "fit for use" that considers implementation as well.

The application of generative AI to medicine feels like a paradigm shift, because it is one. Rarely, if ever, in medicine has such a flexible technology been made available in such a short time window. We are all

still trying to figure out how it works, where it works, and where it fails, with little relevant history of its application. It can be a transformative technology, if it is applied correctly. There have been other technologies that we thought were transformative in health care, which may provide relevant lessons in this time. Genomic sequencing has proven to be transformative especially when costs of sequencing dropped rapidly to a level supporting broad use. Electronic health records, on the other hand, appeared transformative but have been plagued with issues related to their difficulty in implementation and limited or inflexible capabilities.[15,16]

So, what might we expect with this new paradigm? We speculate that the integration of AI, particularly generative AI, into medicine is expected to progress at a slower pace than in fields such as research. While AI technologies are being rapidly adopted across sectors, the high-stakes nature of healthcare necessitates a more cautious approach. However, it is unlikely that this will follow the traditional 17-year knowledge-to-practice timeline, as AI has already accelerated the adoption of new tools and knowledge transfer. The integration of AI into life outside of medicine may be the most important driver for its acceptance within health care. Patients may increasingly use AI to access personalized health information, and doctors might rely on AI-powered tools to streamline administrative tasks or to support decision-making. Of course, concerns about accuracy, language barriers, and exacerbation of healthcare disparities are significant obstacles to overcome before AI can revolutionize healthcare. In addition, regulatory frameworks will play a critical role in this transformation, likely slowing AI's integration in attempts to ensuring its responsible deployment. The battle we are already seeing over control of AI outside of medicine will influence the strength of these frameworks. However, the key driver for AI adoption in healthcare will eventually be its demonstrated return on investment (ROI), particularly as AI begins to show clear benefits in clinical efficiency and outcomes. In the short term, we expect AI to alleviate some burdens on healthcare providers, allowing for more time in patient care and improving the patient experience. The broader shift towards AI-powered medicine will take time, as healthcare systems and regulatory bodies work through the complexities of implementation. Still, as we saw so many years ago in the tournaments between Kasparov and Deep Blue, technology tends to eventually win these competitions.

In the meantime, the sooner we can identify the ways, which may be many, that AI can now be used effectively in health care, the better we will be able to observe how transformative it is. It will be both important and interesting to watch.

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Advanced Technology Clinic Provides Personalized Approach to Pediatric Epilepsy Surgery: Early Data and Future Directions

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Improvement in seizure burden and quality of life outcomes following epilepsy surgery may be related. Further outcomes research is required.



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Abstract

Objective: Postoperative improvement in seizures may impact quality of life. We examined the relationship between reduced seizure burden and quality of life in a surgical epilepsy clinic.

Methods: We reviewed data from all children who received epilepsy surgery at our center. Surgeries were classified as palliative or definitive based on the seizure outcome goals. We collected demographics, surgical data, Engel classification, and quality of life outcomes.

Results: Between 2016 and 2024, 282 patients underwent 338 surgeries. In the definitive surgery group, 66 patients (58%) attained an Engel 1 outcome at six months and 46 patients (58%) at 24 months. In the palliative surgery group, six patients (7%) attained an Engel 1 outcome at six months. At 12 months, 75% of patients who attained Engel 1 reported lower depression scores.

Conclusion: Improvement in seizure burden and quality of life outcomes following epilepsy surgery may be related. Further outcomes research is required.

Introduction

Epilepsy is the most prevalent long-term neurological condition in children, affecting up to 1% of the pediatric population.[1] Nearly a quarter of children with epilepsy become drug-resistant.[2,3] Children with drug-resistant epilepsy (DRE) have decreased life expectancy and reduced quality of life (QOL).[4] Surgical intervention is an option to eliminate or reduce seizures for children with medication-resistant epilepsy and increases life expectancy.[5-7] However, post-operative reduction in seizure burden may not always improve quality of life, indicating there may be multifactorial risk factors responsible for suboptimal outcomes.[8,9]

The documented rate of seizure control ranges from 41% to 76% following definitive surgery,[10-13] with the majority of studies referencing Engel classification.[14] Seizure-free rates decline over time following epilepsy surgery. A recent meta-analysis of 258 studies on temporal, extratemporal lobe resections, and hemispherotomies demonstrated a decline of seizure-free patients from 64.8% to 60.3% and 39.7% after one, five, and ten years of follow-up.[6]

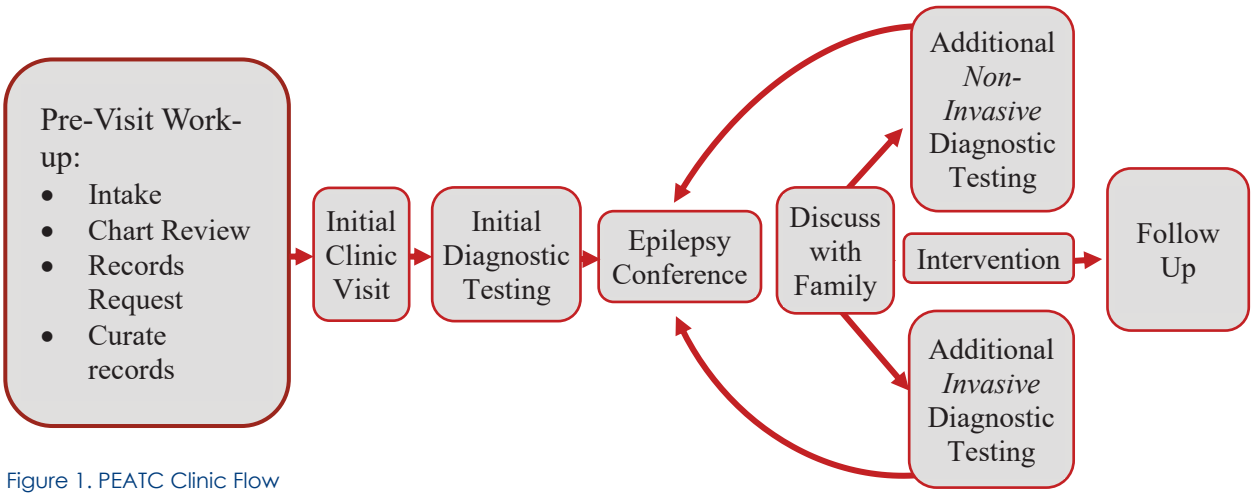


Figure 1. PEATC Clinic Flow

Previous studies have shown a correlation between a favorable seizure outcome and improved quality of life.[1,15,16] With improving diagnostic technologies and more refined, minimally invasive approaches to surgery, the number of patients eligible for surgery or device placement is increasing. In these patients, the goal of epilepsy surgery is "palliative" seizure reduction and improved quality of life. The relationship between decreased seizure burden and improved function and quality of life of individuals who have had surgery is less well defined.[17] In this report, we aimed to evaluate our seizure outcomes for patients undergoing definitive versus palliative surgeries and evaluate early data collected on postoperative functional and quality of life measures.

Methods

Data was collected for all patients evaluated in our Pediatric Epilepsy Advanced Technologies Clinic (PEATC) at the Washington University Pediatric Epilepsy Center at St. Louis Children's Hospital, St. Louis, Missouri. Patients are referred from the greater metropolitan region and surrounding states. The clinic workflow is summarized in Figure 1.

We collected demographic and clinical data in REDCap [18] for patients seen in PEATC from May 2019 to May 2024. This included age at referral, type of surgery, and postoperative outcomes scored by providers (Engel score), as well as a self-reported survey (QOLCE-16) by patients or families. The data was collected from surgery documentations between January 2016 and May 2019. We collected additional clinical data from EPIC, including age, sex, ethnicity, and PROMIS scores. QOL surveys were initiated in 2019, but there was a yearlong gap between 2019-2020 due to the COVID-19 pandemic.

Patients underwent individualized presurgical evaluation that may include scalp electroencephalography (EEG) with video telemetry, high-resolution magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), intracarotid amobarbital procedure (WADA), magnetoencephalography (MEG), high-density electroencephalography (EEG) recordings and neuropsychological evaluation. Patients were followed up as clinically indicated, but typically, occurring at approximately six, 12, and 24 months post-surgery.

Surgery was categorized into two groups: definitive and palliative. The definitive group included all procedures in which the primary goal was curative with an expectation for seizure freedom or freedom from primary seizure type, as would be the case for patients with tuberous sclerosis complex (TSC). The definitive procedures were lesionectomy, temporal and extratemporal resection, hemispherotomy, and disconnections. Surgery types were coded according to the operation note, not related to the pathology of the specimen or independent review of the MRI. Examples of lesionectomy included focal cortical dysplasia, tuberous sclerosis, and low-grade tumors. Temporal resection included mesial temporal and/or hippocampal sclerosis. Disconnections included frontal or posterior-quadrant disconnections.

The palliative group included procedures in which the primary goal was to decrease seizure burden or severity. The palliative procedures were vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neural stimulation (RNS), as well as corpus callosotomy. Radiofrequency ablation (RFA) was included as a separate category, given it was both a diagnostic and therapeutic procedure with anticipation for future definitive procedure as needed.

Following surgery, the patient's primary epileptologist was asked to provide Engel classification at six, 12, and 24 months. The Engel epilepsy surgery outcome scale is extensively used to categorize results after surgical intervention for medically resistant epilepsy. Engel class 1 refers patients who are free of disabling seizures, with 1A considered to have complete seizure freedom. Class 2 is classified as rare disabling seizures. Class 3 represents worthwhile improvement in seizures and Class 4 is described as no appreciable change in seizures. For analyses we considered Engel 1 and 2 as favorable outcome. Engel outcome at 12 months was chosen for group comparisons due to the longer outcome than six months and relatively few responses at 24 months.

Depression and cognitive function scores were evaluated using the patient-reported outcomes measurement information system (PROMIS), a measurement system that evaluates physical, mental, and social health, well-being, life satisfaction, as well as sensory, motor, and cognitive function[19]. The quality of life in childhood epilepsy questionnaire (QOLCE-16) was utilized to assess overall QOL.[20] For QOL and cognitive function, increasing scores suggest improvement while for depression a decrease implies improvement. Patients were sent these surveys to fill out. Subsequent surveys were requested periodically during follow-ups. Due to the small number of QOL metrics, all surgical resections were considered one group for statistical analysis.

Basic statistics were completed, including summary statistics and Chi-square to evaluate for group difference. A p-value of less than or equal to 0.05 was deemed as statistically significant. Statistics were done with Stata version 16 (College Station, TX: StataCorp LLC).

Table 1. Patient demographics

	N= 282 (%)
Sex	
• Female	129 (46)
• Male	153 (54)
Race	
• White	239 (85)
• African/American	26 (9)
• Asian	5 (2)
• Hispanic	10 (3)
• American Indian	1 (0.4)
• Pacific Islander	1 (0.4)

Results

Between May 2019 and May 2024, PEACT received referrals for surgical evaluation from 534 patients, with 209 being selected for surgery. Seventy-three patients underwent epilepsy surgery between January 2016 and May 2019. Between January 2016 and May 2024, a total of 338 surgeries were performed on 282 patients, with the number of procedures per patient varying from one to four. Patient demographics, including sex and self-identified race are reported in Table 1. Patient age ranged from three months to 28 years at the time of referral. Surgery types are summarized in Table 2.

Of the 338 surgeries, 200 were palliative, 130 were definitive, and eight RFA. For neuromodulation, most received VNS therapy 133 (39%), while DBS and RNS were performed on 10 (0.02%) and four (0.01%) patients, respectively. Corpus callosotomy was performed on 53 (16%) patients. Among the definitive surgery group, lesionectomy was the most performed, accounting for 54 cases (16%). This was followed by extratemporal lobe resection, 24 cases (7%) and temporal lobe resection, 22 cases (6.5%). Laser interstitial thermal therapy (LITT) was used in 59 procedures (17%). Eight (2%) radiofrequency ablation was performed.

Engel score was reported for 204 procedures at six months, 179 procedures at 12 months, and 121 procedures at 24 months combined with definitive and palliative procedures. A favorable clinical outcome

Table 2. Surgical intervention and favorable seizure outcome during follow up

	N= 338 (%)	6 mo	12 mo	24 mo
Palliative				
Corpus callosotomy	53 (16)	8 (15)	8 (15)	6 (11)
Neuromodulation	147 (43)			
VNS	133 (39)	7 (5)	7 (5)	3 (2)
DBS	10 (3)	1 (10)	5 (50)	5 (50)
RNS	4 (1)	0	1 (25)	1 (25)
Definitive				
Lesionectomy	54 (16)	29 (54)	25 (46)	20 (37)
Extratemporal resection	24 (7)	21 (87)	14 (58)	13 (54)
Temporal resection	22 (7)	12 (54)	11 (50)	7 (32)
Hemispherotomy	20 (6)	15 (75)	12 (60)	11 (55)
Disconnection	10 (3)	5 (50)	5 (50)	5 (50)
RFA	8	3 (38)		

VNS vagal nerve stimulation, DBS deep brain stimulation, RNS responsive neurostimulation, RFA radiofrequency ablation

(Engel class 1 or 2) was observed in 79 patients (69%) with 66 (58%) patients being seizure-free at six-month follow-up in the definitive surgery group. Engel 1 scores were in 55 (55%) and 46 (58%) patients at 12 and 24-month follow-up, respectively. As anticipated, there was a significant difference in Engel classification between patients in definitive versus palliative surgery groups. The definitive surgery group had an Engel score of 1.9 (SD 1.13), while the palliative surgery group was 3.1 (0.09), ($p < 0.005$) at 12-month follow-up. Engel scores are summarized in Table 3.

Stereo electroencephalography (sEEG) was performed in 55 (47%) of the 118 resective procedures. There was no statistically significant difference between Engel scores for patients who did (mean 2.21, SD 1.14) or did not undergo sEEG (mean 1.84, SD 1.51) ($p = 0.23$). For resective procedures there was no statistically significant difference in Engel score at 12 months between the use of LITT (mean 2.29, SD 1.12) versus open surgery (mean 1.87, SD 1.14), ($p = 0.17$).

Pilot data was collected on patient reported QOL using PROMIS and QOLCE-16 questionnaires. The QOLCE-16 was completed by 39 patients at baseline and 22, 28, and 18 patients at six, 12, and 24 months, respectively. Some patients who had multiple surgeries completed multiple questionnaires for each surgery. The PROMIS was completed by 62 patients at baseline and 43, 49, and 32 patients at six, 12, and 24 months, respectively. QOL, depression, and cognitive function were analyzed as post-operative changes from baseline (increase, decrease, or no change) at six and 12 months due to the few observations with both baseline and 24-month results.

At the 12-month follow-up, depression and Engel scores were available for 18 patients, and QOL and Engel scores for 12 patients. Three out of the four patients with Engel 1 reported a decrease in their depression scores, while one patient reported no change, as their score remained within normal limits. Two of three patients (66%) with Engel 1 reported mild decrease in quality of life. Of the patients who reported a change in QOL, there was not a significant difference in Engel score between increase or decrease QOL (p=0.66). There was also not a significant difference in Engel score between those reporting an increase or decrease in depression (p=0.1), though there was a trend toward higher Engel scores in patients reporting an increase in depression.

Discussion

The Pediatric Epilepsy Advanced Technologies Clinic (PEATC) was created for concierge service to streamline the patient experience and personalize the medical and presurgical workup for pediatric patients with medically intractable epilepsy. A randomized controlled trial of epilepsy surgery in 116 children, found that patients who underwent epilepsy surgery were more likely to be seizure free (77%) than patients that received medical therapy alone (4%).[5] In our cohort, 71% of patients who underwent definitive

Table 3. Engel scores following definitive and palliative surgery

Engel Score	6 months	12 months	24 months
Definitive Surgery, N (%)	N=113	N=99	N=79
1	66 (58)	55 (56)	46 (58)
2	13 (11)	12 (12)	10 (13)
3	19 (16)	19 (19)	12 (15)
4	15 (13)	13 (13)	11 (14)
Palliative Surgery, N (%)	N=88	N=80	N=42
1	6 (7)	6 (8)	2 (5)
2	10 (11)	6 (8)	8 (19)
3	49 (56)	42 (52)	19 (45)
4	23 (26)	26 (32)	13 (31)

surgery attained Engel class 1 or 2 outcome, with these rates persisting to two-year follow-up. As anticipated, seizure outcomes following palliative surgery were less favorable, with 16% having rare or free of disabling seizures at six months with similar rates persisting to two-year follow-up (See Tables 2 and 3). These findings align with previously published surgical outcomes.[6,10-13]

The assessment and interpretation of seizure outcomes demonstrate substantial variability across the country and quality of life outcomes are frequently overlooked.[21] With early data, we sought to better understand whether measures of quality of life and depression improved with variable rates of seizure freedom. There has been increasing emphasis placed on quality-of-life factors in epilepsy management with an association between favorable seizure outcome and improved QOL.[15,16,22,23] Our initial data, deployed on a subset of the population, supports aspects of these findings with greater than half of the patients in the definitive surgery group reporting a decrease in depressive symptoms and 18% in the palliative group. Conversely, 66% of the patients with Engel score 1 reported decreased QOL at 12 months. This finding suggests that seizure control alone does not provide a comprehensive picture of QOL. Patients may have challenges while transitioning from a state of illness to normalcy, and experience frustration if improvements are not fulfilled promptly.[24] In our early data, we also did not find a relationship between cognitive and depression scores and seizure outcome, although these observations are limited by a small sample size.

Many factors compromise QOL, including psychosocial and cognitive outcomes with ongoing work needed to refine these patient-reported questionnaires and surveys. Common assessments of QOL rely on more generic or disease-oriented questionnaires reporting a mean score of QOL for a group that lacks insights into individual factors.[25] There is also the issue of differences that are statistically significant versus those with a meaningful clinical effect size. By addressing the minimum clinically important change (MCIC), investigators may be able to quantify the change in QOL that an individual patient deems significant.[26,27] When applied to medical and surgical epilepsy groups in adults, patients achieving MCIC was not always the same across different QOL questionnaires.[25] Using QOL assessment tools, including MCIC, in pediatric populations is confounded by the difficulty of standardizing assessments across age, developmental level, and self- versus parent-reported measurements. More investigation is needed to determine QOL measures more customized for the pediatric epilepsy surgery population.[28]

Nursing has a profound impact on the care of surgical patients. Early patient information and

education is one of the most critical components of ensuring a positive outcome.[29]

The Pediatric Epilepsy Advanced Technologies Clinic provides a patient centric structure to personalize the approach to epilepsy surgery work-up and tailored management. We have a fully dedicated nurse navigator who directs appropriate referrals and assists with triage, scheduling, record retrieval and review, as well as preparing a summary for providers prior to the patient's visit. Additionally, this individual tracks and coordinates post-op testing and follow up visits and serves as a liaison between the PEATC team, referring neurologist, and child's family, as well as providing patient and family counseling throughout the process.

The recent growth in minimally invasive methods of monitoring, including stereoencephalography (sEEG), have opened the door for patients previously not felt to be surgical candidates. In our cohort there was no significant difference in seizure outcomes among the patients who underwent sEEG and those who did not. A meta-analysis that reviewed the outcomes of 3511 epilepsy surgeries revealed that intracranial monitoring was associated with an unfavorable prognosis.[30] This is likely related to patient selection with increasing numbers of patients, who previously were not resective candidates, but are now more amenable to palliative or staged approaches with less invasive treatment options, including radiofrequency ablation (RFA) and laser ablation. RFA delivers a radiofrequency via single electrodes to heat surrounding tissue and create a focal lesion. RFA has been used for interrupting epilepsy networks, lesioning the seizure onset zone near eloquent areas, and has been used as a treatment predictor of future surgical intervention.[31-33] These less invasive methods of evaluation and treatment also relieve patient and family anxiety and may facilitate earlier referral for surgical evaluation; and earlier epilepsy surgery leads to improvements in QOL and neurocognitive outcomes.[34]

There are several limitations of this pilot study. This is a retrospective study that relied on clinically gathered data. There was incomplete follow-up data that limits the interpretation of the quality-of-life measures collected and underscores the importance of more consistent collection of this data. The PEATC population is heterogenous with a mix of ages, developmental levels, and types of epilepsy. This makes extrapolating meaningful averages or generalizable conclusions challenging. Additionally, we used patient and family reported questionnaires for QOL. Such inquiries can be confounded by many factors not related to epilepsy surgery, including other medical conditions, psychosocial factors, and timing of the responses. We also did not ensure all outcomes and questionnaires were consistently reported at all time points, limiting the sample size and interpretation. Furthermore, the limited sample size in QOL outcomes was likely exacerbated by the interruption in data collection caused by the COVID-19 pandemic.

Future directions for the PEATC team will lean into the strengths of this program and improve on the limitations. We will utilize our nurse coordinator to strengthen our relationships with local neurologists and primary providers to improve coordinated care and provide educational opportunities for patients, families and healthcare providers. We will continue to refine our minimally invasive approach to monitoring and surgery and build-out our palliative surgical options with newer techniques including reactive and deep brain neurostimulation. Finally, we need to continue to work with patients and their families to identify the outcome measures that are the most meaningful to them.

Conclusion

Patients receiving diagnostic work-up and epilepsy surgery through a personalized pediatric epilepsy clinic had rare to no disabling seizures (Engel 1 or 2) over 70% of the time in the definitive seizure group and at least a worthwhile improvement in seizures (Engel 3 or better) in the palliative group 69% of the time at two-year follow-up. Quality of life measures and assessment of depression were less clear with increases and decreases in these scores independent of seizure outcomes. Future epilepsy surgery studies, particularly in the setting of more refined and minimally invasive diagnostic and surgical approaches, need improved assessments of patient-focused outcomes.

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Triumphs, Trials, and Future Considerations in Genetic Therapies for Hereditary Neuromuscular Diseases

by W. David Arnold, MD & Kajri Majithia, DO

It is anticipated that the next few decades will bring advances in gene therapy technologies that will enhance both the accessibility and efficacy of these treatments for patients with neuromuscular and other disorders.



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Abstract

Neuromuscular diseases include conditions that affect the spinal motor neurons, peripheral nerves, neuromuscular junctions, and muscles, and they can result from acquired and inherited causes.

The number of genetic therapies targeting the inherited causes of neuromuscular diseases has surged in the last decade. This review aims to highlight the current state of genetic therapies within the framework of precision medicine, focusing on the achievements and the gaps that remain. A major emphasis is on spinal muscular atrophy, Duchenne muscular dystrophy, and amyotrophic lateral sclerosis, as these neuromuscular diseases have seen tremendous recent advancements. We will also discuss the future considerations necessary to accelerate the development of next-generation genetic therapies and enhance therapeutic outcomes for patients with neuromuscular diseases.

Introduction

Precision medicine integrates biological, environmental, and lifestyle information to tailor medical care and interventions to optimize health outcomes.[1] As part of biological information utilized for precision medicine, genetics inform diagnostic and treatment decisions. Aligned with the concepts of precision medicine, genetic and gene therapy, defined as introducing, altering, or removing genetic material in cells to mitigate disease, is precisely designed to mitigate disease. The term gene therapy is specifically defined by the FDA as therapies that "mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms. The products may be used to modify cells *in vivo* or transferred to cells *ex vivo* prior to administration to the recipient usually used to denote leverage viral vector delivery of treatments to as introducing, altering, or removing genetic material."[2]

The concept of gene therapy, as an approach to treat human disease, dates back at least five decades, though it has been suggested that the possibility of gene therapy was first raised in the 1930s-40s when bacterial

Table 1. Genetic Mechanisms

Category	Representative Disorders	Clinical Features
Loss of Function	Duchenne Muscular Dystrophy (DMD): Mutation of *DMD* gene, most commonly deletions of exons, causing dysfunctional or missing dystrophin protein	Progressive loss of muscle, children presenting with symptoms at 2-3 years of age with an abnormal gait, frequent falls, and difficulty getting up; eventual mortality in patients aged 20-40 from cardiac and respiratory failure
	Spinal Muscular Atrophy (SMA): Deletion (or missense mutation) of exon 7 of *SMN1* gene leading to reduced levels of full-length SMN protein	Progressive proximal muscle weakness by denervation, commonly with the clinical presentation before 6 months of life, hypotonia progressing to respiratory failure and death before 2 years of age
Gain of Function	Amyotrophic Lateral Sclerosis (ALS): Mutation in *SOD1* causing the production of toxic SOD1 protein	Progressive muscle weakness, spasticity, dysarthria, dysphagia, respiratory insufficiency, with eventual paralysis and death typically within 3-5 years of symptom onset

transformation experiments alluded to the possibility of genetic therapies.[3] The first preclinical proof of concept gene therapy in a mouse model was published in 1984, and the first gene therapy clinical trial for severe combined immunodeficiency was performed in 1990 at the National Institute of Health.[4,5] Today we are in an era of rapidly accelerating innovation for gene and genetic therapies. For five decades, gene therapies have evolved and the number of investigational new drug applications and clinical trials investigating gene therapies have skyrocketed. It was recently estimated in the spring of 2024 that more than 2,000 gene therapies are in development and over 600 clinical trials are underway.[6]

The goal of this review is to provide an update regarding the state of the science of gene and genetic therapies for hereditary neuromuscular disorders within the framework of precision medicine and to outline recent accomplishments as well as ongoing gaps and needs for future discovery, including ethical considerations. We will primarily focus on spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD), and Amyotrophic Lateral Sclerosis (ALS) as representative cases to highlight both the successes and the remaining gaps in genetic therapy development.

Genetic Mechanisms of Neuromuscular Disease

Neuromuscular diseases comprise a diverse group of pathologies affecting the peripheral nervous system. These include inherited and acquired disorders that impact spinal motor neurons, peripheral nerves, neuromuscular junctions, and muscles. Hereditary forms of neuromuscular disease are a major target for the development of genetic therapies.[7] Broadly speaking, genetic mutations are grouped into gain-of-function or loss-of-function (Table 1). Loss-of-function mutations result in partial or complete loss of function of a particular gene function, whereas gain-of-function mutations result in an enhanced or new function of a particular gene. Gene therapy approaches include gene addition (replacement), silencing, and editing. Gene therapies can be delivered as localized, systemic, or *ex vivo* applications (e.g. treating cells that are then reintroduced into the patient). The development of genetic therapies is guided by understanding the genetic mechanisms of diseases. For loss-of-function mutations, the approach may involve introducing or replacing a defective or missing gene. For toxic gain-of-function mutations, therapies target silencing the harmful gene or mitigating the consequences of the mutation (Table 2).

The primary focus of this review is on therapies that are designed to directly address genetic mechanisms of disease, but gene therapies have been applied to neuromuscular disorders independent or agnostic of genetic mechanisms or known mutations. An example includes gene therapy for sporadic inclusion body myositis which is the most common acquired myopathy after the age of 50 and lacks a specific known cause or associated genetic mutation.[8] Other examples include gene therapy to express proteins to increase muscle function in the context of genetic forms of neuromuscular junction failure or age-related neuromuscular failure (i.e. sarcopenia).[9,10]

Table 2. Approaches to Genetic Therapies

Approach	Description	Mechanism of Action	Disease (Gene) Application	Examples
Gene Addition/Replacement	Adding a functional copy of a gene to compensate for a defective one	Viral Vectors: Viral capsids modified to hold and deliver a transgene to tissue targets	Spinal Muscular Atrophy (SMA), Duchenne Muscular Dystrophy (DMD)	Elevidys (delandistrogene moxeparvovec-rokl), Zolgensma (onasemnogene abeparvovec-xioi)
		Non-viral Vectors: Polymers, lipids, peptides, inorganic materials, or a hybrid system used to deliver genetic material	No current FDA-approved therapies for neuromuscular diseases	
Gene Knockdown/Silencing	Reducing the expression of a harmful gene product	RNA interference (RNAi), Antisense oligonucleotides (ASOs)	Amyotrophic Lateral Sclerosis (*SOD1*), Myotonic Dystrophy (DMPK), Spinal Muscular Atrophy (*SMN1*), Duchenne Muscular Dystrophy (DMD)	Qalsody (tofersen), Spinraza (nusinersen), Evrysdi (risdiplam), Exondys (eteplirsen), Vyondys (golodirsen), Viltepso (viltolarsen) Amondys 45 (Casimersen)
Gene Editing	Directly altering the DNA sequence in the genome	CRISPR/Cas9, TALENs, ZFNs	Duchenne Muscular Dystrophy (*DMD*)	No current FDA-approved therapies for neuromuscular diseases
Cell-based	Using genetically modified cells to treat or cure diseases	Stem Cell Therapy	Duchenne Muscular Dystrophy (*DMD*)	MyoPAXon (in clinical trial)

Yet, examples of gene-agnostic gene therapies are much more limited and only in earlier stages of development.

Successful and Emerging Genetic Therapies for Neuromuscular Diseases

As a therapeutic approach, gene replacement for loss of function (including SMA and DMD) has shown the most advanced impact in the clinic whereas approaches to reduce the impact of mutations with toxic gain of function, such as forms of ALS, have lagged but are gaining momentum.

SMA and DMD-Loss of Function Genetic Mechanism

SMA and DMD represent two neuromuscular disorders related to loss of function genetic mechanisms. SMA is an autosomal recessive genetic motor neuron disorder occurring in one in 10,000 live births caused by homozygous loss of the SMN1 gene.[11] Historically, SMA was the most common genetic cause of infant mortality.[11,12] However, SMA can present with a wide range of clinical severity (type 0, most severe to the mildest form, type 4).[11] Disease severity is modulated by the retention of a second closely related gene SMN2 which is present in variable doses or copy number across individuals. A single nucleotide difference between SMN1 and SMN2 results in 90% of transcripts from SMN2 being shortened, thus producing an SMN protein that rapidly degrades. Yet, 10% of transcripts from SMN2 are full-length, and thus SMN2 produces some normal, full-length SMN protein, albeit less efficiently. Accordingly, SMA is a disease of SMN protein deficiency but the mechanisms of how SMN deficiency results in motor neuron loss remain to be fully determined.[13] The genetic cause of SMA was determined in 1995, and now there are currently three genetic therapies: nusinersen (Spinraza), an antisense oligonucleotide (ASO) that increases the production of full-length SMN protein from the SMN2 gene; risdiplam (Evrysdi), an oral small molecule drug that increases full-length SMN protein from the SMN2 gene; and Onasemnogene

Abeparvove (Zolgensma), a gene therapy that delivers a normal SMN gene via an adeno-associated viral vector that is delivered by systemic infusion.

DMD is the most common muscular dystrophy affecting approximately one in 5,000 male live births.[14] DMD is an X-linked recessive disorder primarily affecting males, though females can manifest as carriers. DMD is caused by mutations in the DMD gene resulting in loss of dystrophin which is essential for muscle function. This leads to progressive muscle degeneration, cardiomyopathy, and early death. Symptoms typically appear at two to three years of age, with patients typically becoming wheelchair-dependent by age 12 and often requiring mechanical ventilation by age 20.[15] An obstacle in developing gene therapy for DMD was the large size of the dystrophin gene. On June 22, 2023, the FDA approved delandistrogene moxeparvovec (Elevidys), the first gene therapy for DMD in patients aged four to five with confirmed DMD gene mutations.[16,17] The creation of "micro-dystrophins," smaller but effective versions of the DMD gene, enabled the development of delandistrogene moxeparvovec. This adeno-associated virus (AAV) vector-based therapy delivers the micro-dystrophin gene to muscle cells, including the heart and diaphragm.[16]

ALS-Gain of Function Genetic Mechanism

ALS is a neurodegenerative disorder that typically affects individuals in their sixth or seventh decade of life and has an incidence of 1.4/100,000.[18] A distinctive aspect of ALS is that it results in degeneration of upper (cortical) and lower (spinal) motor neurons, resulting in mixed features of lower motor neuron dysfunction (weakness, atrophy, fasciculations) and upper motor neuron dysfunction (slow movements, spasticity, and increased tone). There are hereditary (familial) and sporadic forms of ALS, and, clinically, familial and sporadic forms are indistinguishable. Approximately 10-20% of patients with ALS have a known genetic variant associated with familial ALS, typically expressed in an autosomal dominant manner.[19] More than 30 gene mutations are associated with familial ALS, and there are autosomal dominant and recessive forms with the dominant being more common,[20,21] the clinical syndrome of familial ALS.

Accordingly, genetic therapies are an emerging area for the treatment of ALS. Superoxide dismutase 1 (SOD1) was the first to be found to have variants associated with familial ALS.[21] Tofersen received accelerated FDA approval in 2023 for the treatment of ALS related to mutations in the SOD1 gene.[22] Tofersen is an antisense oligonucleotide-based therapy that reduces (knocks down) SOD1 protein to mitigate the toxic gain of function of mutant SOD1 protein.[23,23] Tofersen is administered intrathecally with three loading doses scheduled at 14-day intervals and then chronically every 28 days thereafter. A phase 3 trial did not demonstrate impact on the decline of the ALS functional rating scale (a measure of function) but did show significant differences, including a reduction of SOD1 levels in cerebrospinal fluid and plasma measures of neurofilament in faster-progressing subgroups. Work is ongoing to investigate the long-term efficacy and tolerance in familial ALS, and a phase 3 study is currently underway.[24,24]

Gaps and Opportunities for the Next Generation of Gene Therapies

Despite the dramatic success of the field of genetic therapies and the associated impacts on neuromuscular disorders, there are a range of ongoing gaps in optimizing the impact of genetic therapies. Some examples of challenges include cargo and delivery limitations, long-term efficacy and safety, limitations of manufacturing and access, and regulatory and ethical considerations. In nearly all ways, the field of gene and genetic therapies is still in early stages with many ongoing gaps and crude approaches.

Cargo Size, Delivery, and Adverse Effects

The promise of gene therapy relies on the efficient and sufficient delivery of genetic cargo for replacement therapy or to knockdown or edit genetic material. One of the major hurdles is the packaging limit, which impairs the development of interventions for disorders involving larger genes, such as DMD. Adeno-associated virus (AAV) is a powerful and effective viral vector, but its packaging capacity is limited to 4.7 kilobases, restricting its use to smaller genes and regulatory elements.

Strategies to overcome these limitations include developing and implementing alternative vectors with

greater capacity, creating "mini" genes that fit within the packaging constraints but still offer therapeutic effects, and delivering dual constructs that express gene fragments recombined in target cells. Additional challenges in gene therapy delivery include ensuring the genetic material is delivered effectively to target cells, managing immune challenges and potential consequences, overcoming distribution limitations for antisense oligonucleotides (ASOs) and small interfering RNA (siRNA), and minimizing off-target effects in gene editing.

Although AAV is non-pathogenic, high doses are associated with severe immunogenic side effects, including systemic inflammation and multi-organ injury affecting the liver, blood, heart, and skeletal muscle, which can lead to organ failure and death.[25,26] Delivering sufficient viral loads to treat larger patients without causing toxicity (such as hepatotoxicity) is a significant challenge.[25] Notably, a recent post-mortem study of gene therapy for SMA revealed that the therapy achieved SMN protein expression at only 25% of the level seen in healthy controls.[27] These challenges necessity limitations patient size and require large doses of corticosteroids and frequent and intense laboratory monitoring.

Long-Term Efficacy and Safety

The long-term efficacy and safety of gene therapy remain incompletely understood due to the relatively short time since these interventions have been in use. Gene therapy is often envisioned as a "one and done" intervention with enduring benefits. However, this perceived advantage has a notable drawback; once a gene therapy is administered, there are no methods to reverse, stop, or modulate the treatment. This irreversible nature of gene therapy means that the therapy cannot be adjusted for optimal dosing or efficiency of gene knockdown or replacement.

Conversely, viral vectors can be considered integrating or non-integrating.[28,29] Integrating viral vectors deliver cargoes into cells with the ability to incorporate them into the genome of the transduced cells. This integration allows dividing cells to pass the delivered transgene cargo onto daughter cells. Non-integrating vectors deliver cargoes as episomes which are stable in non-dividing, post-mitotic cells, but these episomes are lost in dividing cells during cellular proliferation.[28,29] Additionally there are gaps in our ability to monitor therapeutic levels and track the long-term effects of gene therapies. Improved biomarkers are needed to assess the longitudinal effects in treated patients. For example, in SMA, there is currently no reliable method to track SMN expression levels in relevant tissues to ensure therapeutic sufficiency or to monitor for potential toxicity. This points to the necessity for more comprehensive tools and methods to evaluate and balance the risks and benefits of gene therapies.

Scalability/Manufacturing/Access

Gene therapy, as compared with small molecules, is more complex to manufacture due to their biological nature. Producing viral vectors and a high and reproducible quality is difficult and costly. In addition, regulatory processes for gene therapy development continue to evolve and vary between global regions.

Regulatory/Ethical Considerations

From the early conceptualization of gene therapy in the 1970s to the first gene therapy death in 1999, ethical challenges have been prominent.[30] These include protecting genetic diversity, preserving privacy, respecting autonomy, maintaining accessibility, and doing no harm, among other major concerns.[31]

Determining targets for gene therapy can be complex due to the blurred line between normal traits and disabilities.[32] Furthermore, germline editing poses potential ethical concerns regarding its impact on genetic variability in society, raising the specter of eugenics. As genetic testing becomes more capable and accessible, the identification of genetic disorders increases, including rare and ultra-rare disorders that could be candidates for genetic treatments. However, privacy concerns increase with the prevalence of genetic testing, as patients want to preserve their genetic information while still determining eligibility for new treatments.[33]

There is an increasing focus on unique approaches for ultra-rare disorders and precision medicine, leading to innovative study designs such as N-of-1 studies as the ultimate in personalized medicine.[34,35] These studies are becoming more common in genetic therapy approaches like antisense oligonucleotides (ASOs), though viral vector interventions, often

termed "one and done" approaches, are more challenging due to their complexity and cost. The high cost of gene therapies, among the most expensive drugs in the world, raises ethical concerns about equitable access. Another ethical aspect is the decision-making process for one-time therapies in infants and children, which cannot be undone, raising challenges to informed consent and respect for autonomy.[36]

Balancing cost, risk, and potential benefits also adds to the complexity. Conducting clinical trials for ultra-rare disorders and scaling therapies for equitable access are challenging, and often limited by current regulatory frameworks. Financial constraints further hinder equitable access, as the high manufacturing costs can be prohibitive.[37] Access to these therapies remains a moving target, posing a considerable challenge in gene therapy development. Additionally, there is often a lack of motivation for pharmaceutical companies to develop these therapies due to an unfavorable risk-benefit ratio in terms of financial investment and return on investment.

The regulatory approval process for gene therapies also presents significant challenges, and the success of individualized, cutting-edge treatments is often unpredictable, raising concerns about financial accessibility and informed consent. Upholding the principle of non-maleficence—"first, do no harm"—becomes especially difficult in the pursuit of groundbreaking research.

For instance, the recent approval of Delandistrogene moxeparvovec (Elevidys), a gene therapy designed to deliver a shortened version of the dystrophin gene to produce microdystrophin, was granted through the FDA's accelerated approval pathway. This decision was based on the theoretical assumption that a shortened version of dystrophin would offer therapeutic benefits to children with Duchenne Muscular Dystrophy (DMD). However, this benefit remains unproven, despite the treatment's high cost and potential safety risks. Therefore, it is crucial to balance access to new therapies with careful consideration of safety and economic implications.

Integration of Gene Therapy with Current Standards of Care

Gene therapies have revolutionized treatments for disorders such as SMA, which was historically untreatable.[38] Now, individuals who previously would not have been expected to survive past their second birthday are reaching new milestones for the first time in history. Despite these groundbreaking advancements, new challenges and discoveries are expected emerge related to changing natural history and novel phenotypes in previously fatal disorders. This highlights that with the successes of gene therapy come new issues that must be characterized and managed. Additionally, therapeutic exercise and rehabilitation are established standards of care in neuromuscular medicine. However, there is a need for further research to understand how these interventions can be best employed in conjunction with gene therapies.[39,40] Integrating these approaches effectively will require ongoing study and adaptation to ensure the best outcomes for patients.

Conclusion

Remarkable progress has been made in recent years in the development of genetic therapies for neuromuscular and other diseases. However, much remains to be learned to fully optimize the impact of these therapies and improve access to them. Current challenges include limitations in delivery strategies, regulatory hurdles for increasingly rare diseases, toxicity concerns, and limited methods for tracking disease response, among others. It is anticipated that the next few decades will bring advances in gene therapy technologies that will enhance both the accessibility and efficacy of these treatments for patients with neuromuscular and other disorders.

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From Serendipity to Scalability in Rare Disease Patient Collaborations

by Kerry Grens, MS, Judith L. Weisenberg, MD, Robin C. Ryther, MD, PhD & Harrison W. Gabel, PhD

As each rare disease network builds momentum, the integration of research and clinical care across disorders will grow and provide much-needed support for the collectively not-so-rare rare disease patient community world-wide.



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Abstract

As the rate of diagnosis for rare disease increases, so does the need to develop scalable solutions to address patient community needs. Drawing upon our experiences in rare intellectual and developmental disability research, advocacy, and treatment, we present two examples of how collaboration between patient groups, clinicians, and investigators at Washington University in St. Louis have generated invaluable resources to accelerate toward treatments. These successful partnerships serve as models for building research and clinical infrastructure for rare diseases.

Introduction

Although each rare disease affects a small population of patients, collectively these conditions are quite common. Prevalence is estimated at 3-6% of the worldwide population,[1] and 30 million people in the US alone are affected by any of the 7,000 rare diseases identified to date.[2] Rare diseases place an enormous toll on patients and caregivers. And the number is climbing; roughly 200 rare diseases are newly identified each year.[3]

To make progress in finding treatments for rare diseases, it is critical that patient, clinical, and research communities collaborate to share resources and align efforts to the highest priorities for patients and caregivers. Notably, patients and caregivers play a particularly important role in understanding newly defined disorders, as their daily experience affords them a wholistic understanding of the disorder that few clinicians who may see just a handful of patients can develop.

At Washington University (WashU) the colocalization of extensive pre-clinical and clinical research infrastructure together with numerous patients being treated for rare disorders creates a critical mass to foster collaboration between patient advocates, clinicians, and researchers.

Here, we illustrate the power of collaborations with patient organizations at different stages of rare disease progress, from discovery and characterization to clinical research and patient care (Figure 1). We focus on intellectual and developmental disabilities (IDDs) for several reasons: 1) IDDs are a research strength at WashU, which is among 14 sites of NIH-funded Intellectual and Developmental Disability Research Centers (IDDRCs) in the US;[4] 2) clinical features and patient needs overlap among IDDs; and 3) the trajectory from identification to treatments frequently takes a similar path.

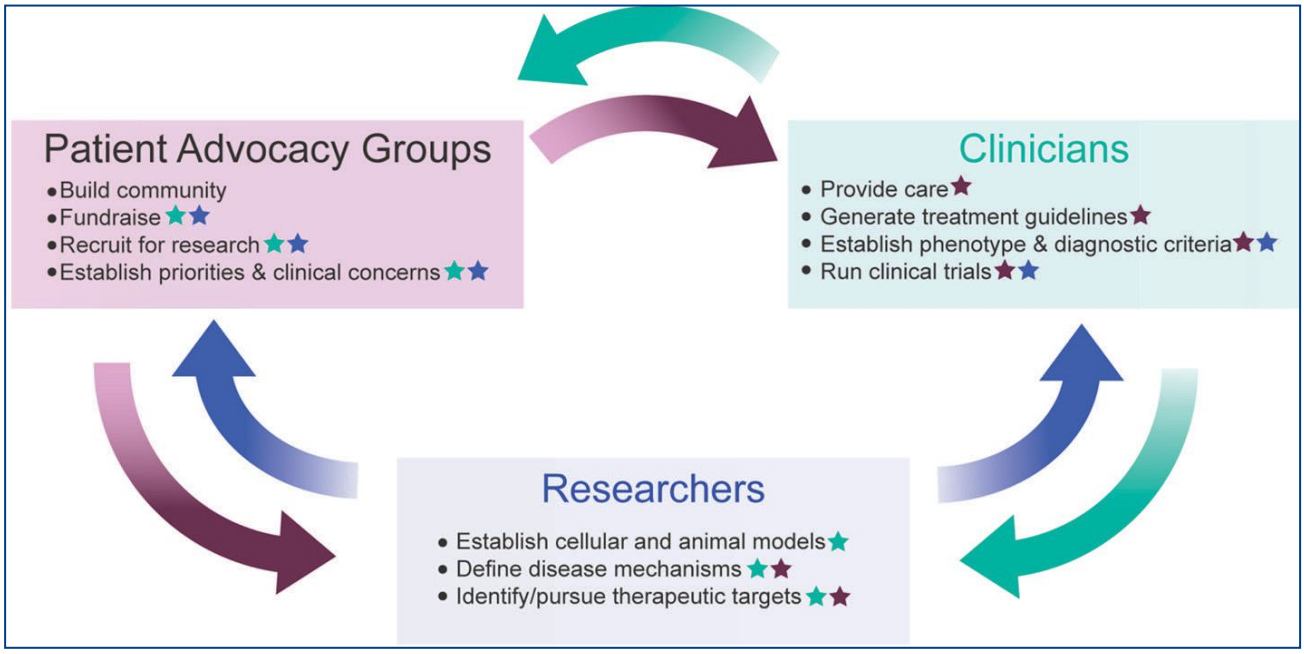


Figure 1. Contributions among rare disease partners toward shared objectives. Each stakeholder can provide valuable resources, information, and support to recipient partners (indicated by colored stars) in the rare disease collaborative network.

Collaboration Between Patient Advocates and Researchers to Understand Emerging Disorders

The increased pace of discovery for rare diseases is creating opportunities to better understand underlying causes of these disorders and to work toward treatments. Because of the small size of patient communities affected, significant challenges exist in launching research programs, and this can only be addressed through active involvement of patient communities themselves. Often a few committed patient caregivers form the nucleus for launching patient advocacy work, and they rely on perseverance and luck to engage researchers and build a roadmap toward treatments for their disorder. The progress made by patient advocates for Tatton Brown Rahman Syndrome (TBRS) in collaboration with WashU researchers and clinicians is an example of how communities formed around newly identified disorders can forge a path toward these goals.[5]

TBRS is a rare disease caused by heterozygous mutations in the DNMT3A gene[6] and is among roughly a dozen overgrowth–intellectual disability (OGID) syndromes. DNMT3A encodes a methyltransferase that establishes DNA methylation patterns during development, and pathogenic DNMT3A variants cause widespread disruption of genetic regulation.[7]

Around 350 people have been diagnosed with TBRS worldwide, and with momentum built by TBRS patient advocates there now is a robust global research community investigating myriad aspects of the disorder, from neurodevelopment to cancer risk to sensory processing and behavior. Intimately connected with the patient advocacy organization, TBRS Community, researchers at WashU have launched collaborations addressing the most urgent aspects of the disorder. We have established mouse and human induced pluripotent stem cell (iPSC) models for the study of disease mechanisms, and reported underlying molecular disruptions of DNA methylation likely driving the disorder. We have further characterized potential genetic underpinnings of differential severity in patients and started testing potential gene therapy modalities.[7–11]

Origins of TBRS/WashU Partnership

Key to the advances we have made in understanding TBRS and developing models of the disorder has been the partnership between researchers, clinicians, and the patient community. It was one family in particular that sparked this collaboration at



Figure 2. The TBRS and Rett syndrome patient communities engaging with researchers and clinicians. Left, Aevary Kiernan (center) and Ayden Isaacs (right) present on their experience with TBRS at the TBRS Community Summit. Right, Ellie McCool (center) is seen by Robin Ryther, MD, PhD, (right) in the Rett Spectrum Clinic at St. Louis Children's Hospital. (Photos courtesy of TBRS Community and St. Louis Children's Hospital).

WashU. The syndrome was first identified in 2014 with the description of 13 individuals.[12] In addition to the characteristic features of overgrowth (height and/or head circumference greater than two standard deviations above the mean) and some degree of ID, those affected by TBRS also have distinct facial features and a host of clinical findings, most frequently: autism spectrum disorder, cardiac defects, hypotonia, kyphoscoliosis, seizures, and obesity.

Within months of that initial report, Marwan Shinawi, MD, professor in the Department of Pediatrics' Division of Genetics & Genomic Medicine, diagnosed another patient: a nine-year-old boy whose father happened to work at WashU Medicine. Like the others diagnosed with TBRS, Ayden Isaacs had a unique DNMT3A gene sequence variant. Remarkably, WashU was already an established leader on this boy's variant; in 2010, Timothy Ley, MD, professor of medicine and chief of the Section of Stem Cell Biology in the Division of Oncology, had identified the R882 variant in DNMT3A as a driver of acute myeloid leukemia (AML) in patients with somatic gene variants.[13] The investigators immediately formed a collaboration, working with the family to obtain patient biospecimens and study the effects of the variant on DNMT3A function. They quickly made headway understanding the molecular alterations that occur in the blood of individuals with TBRS.[5]

Around the same time, co-author Harrison Gabel, PhD, established his laboratory in the Department of Neuroscience at WashU studying genetic regulation during neurodevelopment, with DNA methylation-associated disorders as a central focus. Leveraging this expertise, he began developing TBRS mouse models to understand how altered DNA methylation in the disorder impacts brain function. Dr. Gabel was introduced to Drs. Shinawi and Ley, and the Isaacs family by IDDRC colleagues, closing a loop to create a highly productive research network.

Contributions of TBRS Community to WashU Research

As the WashU team was making inroads into understanding the etiology of TBRS, the patient community was taking shape. In 2017, Jill Kiernan, whose daughter was among the first 13 TBRS patients described, founded the TBRS Community, a patient advocacy group initially centered around family support. The Isaacs family introduced the WashU team to the TBRS Community, sparking fruitful partnerships that continue to this day.

Since this beginning, the TBRS Community has evolved into an important partner in spurring research on the disorder (Figure 2). As part of the organization's strategic research roadmap, the TBRS Community has generated invaluable resources for the research community to use (Table 1). These include:

Patient Registry

More than 100 participants have uploaded medical records and completed comprehensive surveys covering development, quality of life, diagnoses, and treatment.

Table 1. Research resources contributed by Tatton Brown Rahman Syndrome stakeholders

Resource	Patient advocacy group	Researchers and clinicians
Patient registry & natural history study	• Financial support •. Participant recruitment • Analysis/QC of data • Dissemination of data	• Guidance on questionnaires • Clinical data-mining study development
Biorepository	• Financial support • Tissue collection & dissemination • Donor recruitment	• Specimen storage/processing guidance
Cell models / induced pluripotent stem cells	• Financial support • Tissue collection • Donor medical history & phenotype	• Guidance on variants of interest • Financial support- grant acquisition • Development
Mouse models	• Relevant patient phenotype data	• Financial support- grant acquisition • Development

De-identified data are available to researchers at no cost upon approval of an application form by the medical and scientific advisors of the TBRS Community. The survey is hosted by the National Organization for Rare Disorders.

Biorepository

Dozens of diagnosed individuals and their siblings have contributed blood samples to a biobank organized by Combined Brain. Researchers can apply for samples at minimal cost.

Contact Directory

Count Me In for TBRS is an opt-in database the organization manages to track diagnosed individuals and contact their caregivers with relevant information. This directory can be used for outreach to recruit participants to studies.

Patient Priorities Survey

In collaboration with the Overgrowth Syndromes Alliance (OSA), co-founded by co-author Kerry Grens, MS, patients and their caregivers share their top priorities for treatment. OSA has distributed survey findings to the research and clinical communities to direct efforts to address the greatest needs of those living with overgrowth syndromes.

The use of these assets is accelerated by auxiliary initiatives, such as the TBRS Community encouraging study participants to register for the unique, universal Clinical Research ID (CRID), which enables data from research participants to be linked across studies. The TBRS Community also partners with Citizen Health to collect medical records in a database accessible to researchers and clinicians. The TBRS Community has awarded scientists more than $150,000 to pursue research projects aligned with the community's highest priorities.

Contributions of Researchers to Growth of TBRS Community

The TBRS Community is guided by the scientific and medical advisory committees for the organization, which include members of the WashU team. By participating on this committee, researchers, clinicians, and advocates ensure that resources are optimally useful for research and patient priorities alike; for instance, the TBRS Community is investing in the development of additional iPSC lines. They surveyed scientists to determine which disease-related variants would be of most interest to develop. In return, researchers are encouraged to use the cell lines to answer the patient community's most pressing questions. Pilot projects funded by the Community and requests to use TBRS Community resources, such as the patient registry and biorepository samples, must meet these priorities (Table 1).

Researchers and clinicians in turn provide valuable insights into TBRS to the patient community, presenting at family and research conferences organized by the TBRS Community. By connecting scientists across disciplines through a Collaborative Research Network, the TBRS Community has fostered a culture of sharing resources and knowledge among

researchers. The wealth of expertise at WashU on TBRS and how it came together has been referred to as "serendipity,"[5] but the outcomes also reflect the expanse of research and clinical care across the school and the ability afforded to faculty to nimbly address problems that present themselves.

Collaboration in Clinical Care and Therapeutic Development

A goal for each emerging rare disease community is to develop standards of care and implement these in multidisciplinary clinics that optimize patient health management while minimizing multi-visit family burden. Specialized clinics can also facilitate development and accessibility of new therapeutic approaches. However, fiscal realities of establishing specialized clinics for small populations of rare disease patients can limit progress. This is another example where advocates partnering with clinicians can build a critical mass of patients to overcome fiscal challenges and advance rare disease care and research.

The Rett Spectrum Clinic at WashU and St. Louis Children's Hospital has its origins more than a decade ago and 1,200 miles away, in Boston. At the time, co-author Robin Ryther, MD, PhD, was a resident at Massachusetts General Hospital. On her second day, she diagnosed a girl with Rett Syndrome, after other clinicians had missed signs of this rare disease. Rett is caused by variants in MECP2 on the X chromosome, frequently affecting girls—roughly 1 in every 10,000.[14] It leads to repetitive hand movements, limited mobility and speech, and, for some patients, seizures, scoliosis, breathing problems, and disturbed sleep.

Inspired by that first patient, Dr. Ryther sought to form a Rett Clinic at WashU when she arrived for her epilepsy fellowship. Just three Rett clinics existed in the US, and Dr. Ryther wanted to develop multidisciplinary comprehensive care for Rett patients in our region. As part of her fellowship, Dr. Ryther also worked with Judy Weisenberg, MD, who had an interest in CDKL5 deficiency disorder (CDD), a genetic disorder with overlapping clinical features with Rett syndrome. They formed a partnership to bring this care model to all patients with Rett syndrome and CDD, as well as individuals with closely related disorders, MECP2 duplication syndrome and FOXG1 disorder.

The clinic required five elements:

- Built-in time for patients: 1.5-2.5 hours for returning patients and 3-4 hours for new ones
- A dedicated nurse
- An administrative coordinator
- A physician advocate to generate buy-in among specialists to see patients in the clinic
- Support from patients and caregivers who were seeing Drs. Ryther and Weisenberg in their epilepsy clinic.

Families of patients shared the desire to form a Rett Spectrum Clinic on social media and it went viral within the regional Rett community, ultimately getting the attention of the McCool family. Once again, serendipity was on our side. The McCools' daughter Ellie (Figure 2), a teenager age at the time, was being seen for her Rett-related conditions, and their dream—like Dr. Ryther's—was to form a clinic. The partnership between Dr. Ryther and the McCools filled out needed assets and the Rett Spectrum Clinic opened its doors in January 2015, seeing approximately 30 patients that first year.

Family Leadership

It is often the experience among rare disease caregivers that they have to educate clinicians on the disorder. This exhausting process can result in suboptimal care from doctors not familiar with the particularities of that disease. A dedicated clinic means physicians are disorder experts, relieving family burden and ensuring patients receive high quality treatment. Making visits a one-stop shop to see all specialists also eases the considerably logistical, emotional, and financial toll of doctor visits.

Ms. McCool was formerly the lead family liaison to the International Rett Syndrome Foundation and a successful fundraiser. After meeting Dr. Ryther—in a visit that started with a hug—she dedicated the proceeds from her annual fundraiser to support the Rett Spectrum Clinic at WashU. This financial support has been critical to the success of the clinic. The funds enable them to participate in the Rett syndrome natural history study,[15,16,17] which was the foundation for a national network of Rett expertise. The funds also sponsor an education day each year, where families are invited to gather with experts to hear about advances or guidance on particular topics and, equally important, to spend time together. Lastly, it helps the team bring additional research projects to the St. Louis area.

Expanded Operations

Nowadays the clinic sees more than 120 patients annually and has cared for more than 160 patients in total. They see a core team of specialists, including a neurologist who specializes in seizures, nutritionist, physical therapist, equipment specialists, and speech therapist and occupational therapist for augmentative communications. The core clinic for each family lasts around four hours, and the clinical team cycles through patients throughout the course of the day. Patients then might go to see relevant specialists.

Bringing Research to Families

In addition to making it easier for families to access high-quality care, the clinic also brings cutting-edge research to families. Before the Rett Spectrum Clinic existed at WashU, families would have to travel to Birmingham, AL, or Chicago, IL, to participate in research. For instance, for the natural history study families travelled to one of those two sites for 10 years. Now it is closer to home. Support has expanded nationally when the clinic was named a Center of Excellence from the International Rett Syndrome Foundation.

The clinic has also brought clinical trials to St. Louis. Research coordinators update families on data and inform them about new trials that they can participate in. For example, the clinic was a leading site for the Trofinetide trials led by Acadia Pharmaceuticals.[18] They enrolled 15 patients, and these data led to FDA approval of the first treatment for Rett Syndrome patients over two years of age in March 2023. Before the clinic, the closest site for Trofinetide trials was in Birmingham, AL, and only one patient from the region participated.

Work continues for this treatment as side effect management and longitudinal data are needed, work supported by the McCool family's efforts. Dr. Ryther is also currently working on a protocol to assess safety and efficacy of Trofinetide in patients under the age of two years, with the goal of following developmental changes in this group. Dr. Ryther will be working to advance newly initiated Rett Syndrome gene therapy trials as well.

Within CDKL5 research, Dr. Weisenberg has been involved in several studies. She was a lead investigator for the Marigold trial,[19] which started in 2018 and resulted in the first approval of an anti-seizure medication for CDD. Due to the rarity of CDD, this study worked internationally to ultimately screen 114 patients and enroll 101, with WashU's clinic enrolling three. Currently, the clinic is involved in multiple studies to develop better clinical outcome measures more specific to CDD as part of an international CDKL5 clinical centers research network (ICCRN).[20] These measures are essential to ensure that when potential treatments are tested, they can accurately detect benefit as efficiently as possible.

Ultimately, it was a combination of local partnerships with clinicians, researchers, and families such as the McCool family, as well as national partnerships among dedicated researchers, clinics, and advocacy groups such as the International Rett Syndrome Foundation, that have led to progress toward therapies.

Conclusion and Outlook

As the power of partnering with patient advocates in advancing early-stage rare disease characterization is becoming widely acknowledged across funders and investigators, an important next step is to take these interactions from serendipity to scalability. For example, recognizing the incredible efficacy of patient and caregiver champions in rare disease research, the Chan Zuckerberg Initiative Rare as One Project[21] now provides funding and training for patient advocacy groups to expand operations and increase capacity for research, patient community building, and sustainable fundraising.

At WashU, IDDRC-supported initiatives such as The Brain Gene Registry[22] are engaging patients with variants in newly defined disease genes to help collect disease symptom data through mining of electronic health records and development of standardized patient phenotyping

assessments. This project also encourages patient network building and facilitates initiation of pre-clinical studies using patient-derived cell lines.

These types of efforts will build off the lessons learned from partnerships like that of TBRS Community and WashU to bring the power of patient-clinician-researcher collaborations to rare disorders at scale. There is no guarantee that within any given rare disease community there are families with the resources and skills to accelerate research and patient care, as has been the case with TBRS and Rett, but there are countless other ways clinicians can encourage families to be partners in research and loved ones' care. Connecting families with patient advocacy groups—when they exist—can build the camaraderie and trust necessary to advance research, natural history studies, and biospecimen collection. As each rare disease network builds momentum, the integration of research and clinical care across disorders will grow and provide much-needed support for the collectively not-so-rare rare disease patient community world-wide.

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The Pathophysiology of Traumatic Brain Injuries and the Rationale Behind Creatine Supplementation as a Potential Therapy: A Review

by Faith I. Vietor, BS, Kayln Sticher, BS & Komal H. Ashraf, DO

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There is compelling evidence that creatine may act as a potential pharmacological therapy directly targeting the pathophysiologic effects of TBI.



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Abstract

Traumatic brain injuries (TBI) are detrimental to the brain in a variety of ways. Mild traumatic brain injuries (mTBI) are concussions; these are common events that disrupt typical brain functioning and send millions of patients to seek acute care each year globally. Despite the frequency of mTBIs, clinicians have few tools, pharmacologic and nonpharmacologic, to promote recovery and alleviate symptoms. After a TBI, complex biomolecular signaling, diffuse axonal stretching, and glutamate excitotoxicity occur, along with other pathological sequelae. Creatine has been shown to improve cognitive functioning in healthy adults. Burgeoning research is providing evidence that creatine may enhance recovery from TBI, as it directly targets derangements from such trauma.

TBI Epidemiology

TBIs represent a leading cause of morbidity and mortality worldwide.[1] These injuries have garnered more attention from the media and public during the last decade. However, trends show that although overall TBI-associated mortality has decreased by 50% in the last century, there has been no decrease in the mortality rate since 1990.[2,3] Interestingly, despite this finding, updates to evidence-based medicine have led to overall improvements with outcomes for those suffering from a TBI.[2] It is estimated that 50-60 million individuals worldwide are affected by TBIs each year; approximately 50% of the world's population will sustain a TBI in their lifetime.[3] Understandably this disease process places a large burden on the health system. In fact, TBI accounts for more than 2.5 million emergency department visits annually across the globe. In addition to the work required by acute care resources, other facets of the health care system bear this load, such as rehabilitation and therapy services. In fact, 5.3 million people in the United States are living with a TBI-related disability.[2]

Classification of TBI

The diagnosis of TBI comprises a heterogenous array of pathologies. For that reason, it has been difficult to categorize TBIs. The classification system

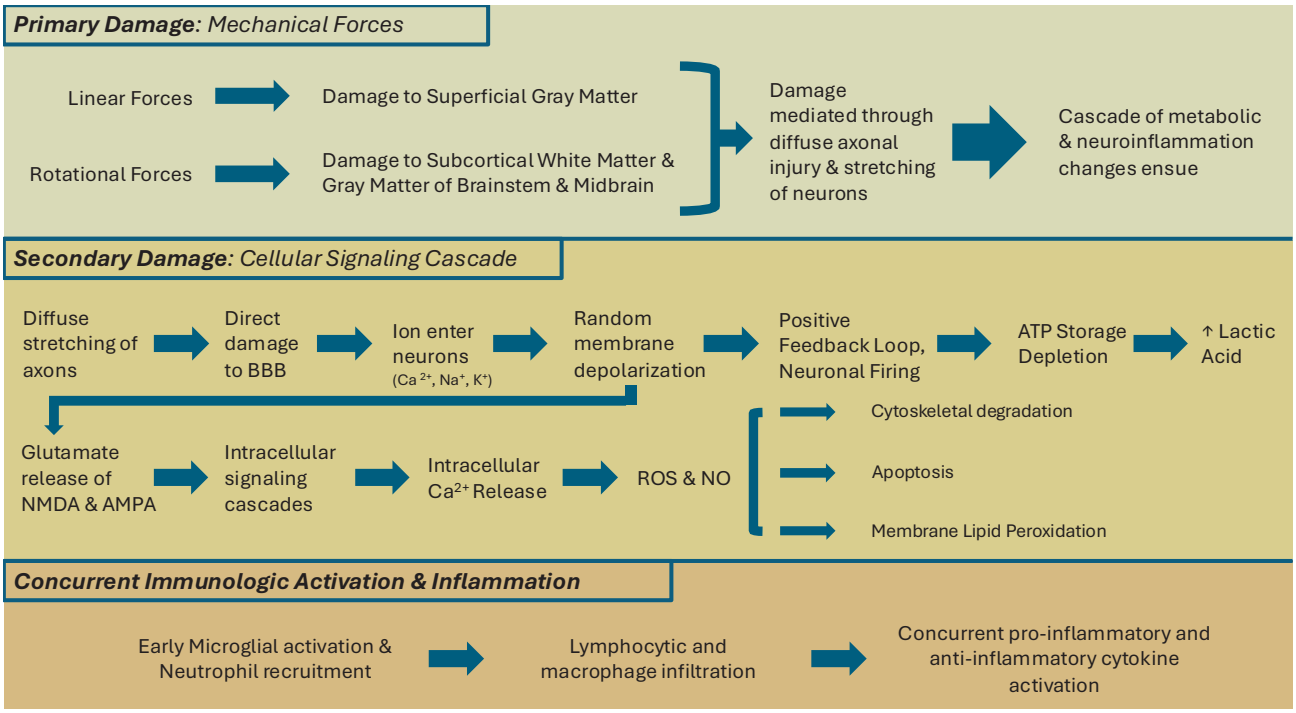


Figure 1. Illustration of complex pathophysiology and sequelae of TBI including direct damage to neurons, cell energy depletion, and cytokine production. Blood brain barrier (BBB); N-methyl-D-aspartic acid (NMDA), ɣ-aminobutyric acid (AMPA), reactive oxygen species (ROS); nitric oxide (NO).

uses three broad categories to guide diagnosis and acute care: clinical, radiographic, and mechanistic.[1] Clinically, and commonly, the Glasgow Coma Scale (GCS) is used. A mild TBI is classified as having a GCS score of 13 to 15, a moderate TBI has a GCS score of 9 to 12, and a severe TBI has a GCS of 8 or less.[1] Radiographic methods characterize structural damage, while mechanistic classification schemes can provide valuable prognostic information.[4] Of note, an mTBI is commonly regarded as a concussion. Other indices of severity can be used to help infer prognosis, such as the Abbreviated Injury Severity Scale (AISS), loss of consciousness, or the presence of posttraumatic amnesia.[5]

mTBI Current Treatment Strategies

Current research shows that the treatment of mTBI should be multifaceted. Early patient education on concussion and treatment strategies has been shown to improve outcomes.[6] While brief rest following an mTBI is warranted (24-48 hours), no research has proven that further rest is required or beneficial. Rather, it is preferrable if physical and cognitive activity is restarted. Return to previous levels of activity should be reintroduced slowly and decreased if there is a rebound of mTBI symptoms.[7] Research on treatment of post-concussive syndrome shows that disturbances in mood and sleep often follow. It is key that these are diagnosed with neuropsychological testing and adequately treated with cognitive behavioral therapy (CBT) and pharmacological agents.[6,8] Cognitive deficits that arise may be addressed with neurocognitive rehabilitation, which uses tasks to improve mental processing or give patients coping mechanisms to navigate through daily activities.[6] Mild TBI sequelae also include damage to the vestibular system and cervical spine. As such, physical, occupational, and speech-language therapy can alleviate this dysfunction, making the return to natural aerobic exercise and typical physical activity more successful.[9,10]

Thus, while many strategies can be employed to ameliorate symptoms following mTBI, there continues to be a dearth of research surrounding pharmacological treatments that directly target the biochemical causes of injury that follow physical trauma to the head.

TBI Pathophysiology

A complex biochemical cascade of inflammatory and cellular processes occurs after the initial traumatic insult to the central nervous system (Figure 1). Largely,

the injuries that ensue can be divided into primary and secondary insults. Linear acceleration forces are more likely to cause superficial brain damage; gray matter that is closest to the surface is most susceptible to developing lesions. Rotational forces can potentiate damage to deep white matter and gray matter nuclei axonal tracts in the brainstem and midbrain.[11,12] The primary mechanism by which damage occurs is through diffuse axonal injury and stretching of neurons. Rather than causing immediate swelling, these shearing forces act as a catalyst for the complicated metabolic and neuroinflammatory changes that comprise the secondary injury, which is more devastating and predictive of clinical outcomes.[12–14]

The secondary insult of a TBI is indolent and progressive, encompassing a vast network of biochemical responses. Initially, there is destruction of the primary brain lesion affected by the physical trauma; however, widespread damage to neurons and glial cells occurs later due to release of molecules and initiation of signaling cascades.[12] The diffuse stretching of axons causes direct damage to the blood-brain barrier (BBB). Subsequently, ions enter the neuron, including calcium, sodium, and potassium. Random membrane depolarization ensues, causing release of excitatory amino acids (e.g. glutamate) from voltage- and ligand-gated ion channels. A positive feedback loop occurs with other neurons firing. This system depletes ATP stores, which are unable to be readily replenished due to the damage of oxidative respiration as cerebral blood flow is compromised.[13] Anaerobic glycolysis will increase but cannot provide adequate energy to the neuron. As such, lactic acid also builds up within the cell.[13] Glutamate release activates receptors, N-methyl-D-aspartic acid (NMDA) and γ-aminobutyric acid (AMPA), to cause intracellular signaling cascades. Calcium is then release intracellularly, promoting generation of both reactive oxygen species (ROS) and nitric oxide (NO). ROS can precipitate apoptosis, cytoskeletal degradation, and membrane lipid peroxidation. These processes can further promote the production of excitatory amino acids and the release of cytokines.[12]

New insights have been made regarding the role of inflammation within the secondary injury process. This neuroinflammation was previously regarded as peripheral immune mediators entering through a fragmented BBB. However, research has since shown that this is a multi-faceted web of interactions, including central and peripheral components. To begin, there is early microglial activation and neutrophil recruitment. Subsequently, lymphocytes and macrophages infiltrate. Natural killer cells, dendritic cells, and T cells also are involved. Overlaying this is concurrent pro-inflammatory and anti-inflammatory action by cytokines to both promote and reduce the neuroinflammatory response.[15–17]

Overall, this orchestration of the immune system is affected by various factors, including mechanism of injury, timing, age, genetics, and sex. All the molecular and cellular participants in the process ebb and flow during the secondary injury timeline. Likely, aspects of the post-injury neuroinflammatory process are both beneficial and harmful.[15]

Biomarkers

There are a variety of biomarkers that are associated with TBI; these are related to the kinetic release from neurons, transfer across the BBB, and clearance from systemic circulation. Diagnostic markers include S100B, UCHL-1, and glial fibrillary acid protein (GFAP).[4] These markers can be used as proxies for imaging, allowing for a reduction in cost and radiation exposure. Furthermore, the *IL-1B* gene can be used with electroencephalography (EEG) to predict risk of post-traumatic epilepsy (PTE).[4,18]

Free fatty acids (FFA) and lactic acid can also be used as markers of cellular injury after a TBI. In fact, animals given creatine for two weeks prior to a TBI had lower levels of FFA and lactic acid; however, these levels were still higher than sham controls.[19] Another study found reversible decreases of creatine, phosphocreatine, N-acetylaspartate (NAA), adenosine triphosphate (ATP), and adenosine diphosphate (ADP) following CNS trauma in rat models; creatine and NAA were decreased by 44.5% and 29.5%, respectively.[20] Later research found decreases

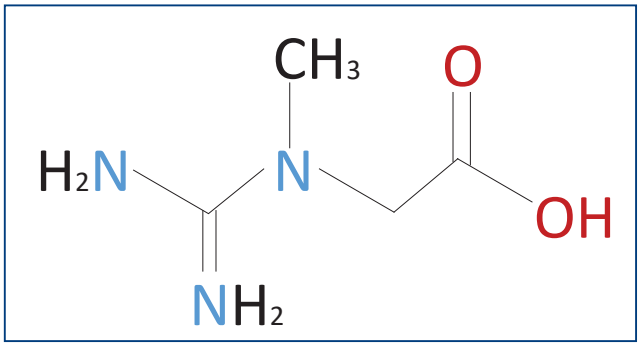


Figure 2. Illustration of the creatine molecule. Creatine is an organic compound and a derivative of glycine. It is methylated and has Nitrogen (N); Hydrogen (H), O (oxygen) and it is found primarily in brain and muscle tissue and is involved in vital physiologic processes.

in NAA and creatine brain levels in concussed athletes using proton magnetic resonance spectroscopy. It was therefore concluded that mTBI may cause accompanying decreases in cerebral NAA and creatine levels. Such derangements make return to baseline neuronal homeostasis more lengthy.[21]

Skeletal Muscle Creatine Compared to Brain Creatine

Creatine is naturally occurring compound that is made endogenously from the amino acids glycine, arginine, and methionine and can be produced by the kidneys, liver, pancreas, and brain. It is a commonly used ergogenic substance that helps support the creation of lean muscle mass and helps increase capacity for high-intensity, short-duration exercise[22] (Figure 2.)

Largely, this compound is stored in skeletal muscle, as it has a critical role in the phosphocreatine shuttle and generation of ATP, without need for oxygen.[23,24] Creatine's main function is to supply energy on an immediate basis for acute needs; creatine is stored as phosphocreatine and the compound's high-energy phosphate bonds allow for fast energy regeneration.[25] Broadly, it helps convert ADP to ATP in addition to transferring energy from the mitochondria to the cytosol.[26]

Over the past decade, research has shown that creatine may play a role in cognition, particularly when the brain is enduring stress.[26] Creatine has also been shown to be neuroprotective with regards to normal aging, brain injury, and neurodegenerative conditions.[27] Logically, this relationship has been translated to a therapeutic strategy for recovery from an mTBI.[13]

As previously mentioned, creatine can be endogenously synthesized by organs in the body, including the kidneys, liver, pancreas, and brain. However, skeletal muscle cannot produce creatine. Rather, the creatine synthesized by the kidneys, liver, and pancreas joins systemic circulation and then enters skeletal muscle cells through the SLC6A8 transporter.[24]

Generation of energy is important for the brain as it consumes 20% of the body's total energy; however, it only makes up 2% of the body's total mass.[24,26] Unlike skeletal muscle, the brain is not fully reliant on circulating creatine from diet or supplementation as it can generate the compound endogenously. Creatine kinase, an enzyme critical to the energy generation of creatine, has a specific brain isoform, located in the cerebellum, hippocampus, pontine reticular formation, red nucleus, cerebral cortex, and choroid plexus. This underscores the fact that creatine is necessary for energy production in the central nervous system (CNS).[25,26] Additionally, the SLC6A8 creatine transporters allow creatine from exogenous sources to be utilized by the CNS.[22,25] These transporters are found on neurons and oligodendrocytes.[26] They are also found at the BBB; there is likely some ability for creatine to cross this complex biomechanical barrier.[24,26] Though, creatine is absorbed at significantly slower rates into the CNS compared to skeletal muscle.[22] This could be a result of low permeability at the BBB or because astrocytes lack expression of the SLC6A8 creatine transporter.[24,26]

Studies have shown that exogenous ingestion of creatine can increase brain levels.[22,28,29] Factors that can influence brain creatine levels include aging, amount of brain activity, amount of physical activity, mood disorders, schizophrenia, and panic disorder.[26] Another difference between skeletal muscle and brain levels of creatine is that, according to several studies, larger amounts of creatine are needed for a longer period of time to increase brain levels compared to skeletal muscle levels.[22,24,29,30]

In a review article, Forbes et al. found that 12 studies in 11 articles showed that brain creatine content changed from -0.7% to 14.6% with oral supplementation; most of those studies reporting a 3-10% increase. Other studies found no change or even decreased brain creatine with supplementation.[24] A large element of brain creatine levels after supplementation depends on basal creatine levels; the potential for increase is inversely related to baseline levels.[25] Researchers theorize that because the brain can endogenously synthesize creatine, it may downregulate this creation when creatine supplementation occurs.[26] Others suggest that simply because the brain can synthesize creatine the neuronal tissue is more resistant to the uptake from systemic circulation.[24]

Creatine Supplementation and Cognitive Function in Healthy Adults

Many studies have examined the effects of creatine on cognition in healthy patient populations. On the whole, creatine has been shown to improve cognitive processing, brain function, and recovery from trauma.[26] Studies have shown that these positive influences are most beneficial when the brain is experiencing stressful situations such as sleep deprivation, exercise, or hypoxia.[22,24,26] With regards to exercise, athletes have been shown to have improved cognitive performance, mental fatigue, and memory.[22]

Further proof in the importance of creatine for the homeostasis of cognitive functioning exists within a variety of genetic creatine deficiency disorders: L-arginine-glycine amidino transferase (AGAT), guanidinoacetate-methyltransferase (GAMT), and SLC6A8 deficiency. Each of these disorders disrupts creatine metabolism or transport, has global effects on development, and causes intellectual disability. Critical to this connection is that the supplementation of oral creatine counteracts the effects of AGAT and GAMT, except with SLC6A8 deficiency.[25]

Creatine Supplementation and TBI

While creatine has been shown to be efficacious for cognitive functioning, particularly in times of brain stress, significant research has shown that it can play a role in directly combating the pathophysiological changes that occur in neuronal tissue after a TBI. In fact, following a TBI, brain creatine levels are reduced.[20,21,24] Furthermore, animal model data indicate that creatine supplementation prior to TBI can decrease damage up to 50%.[31]

Two small clinical trials were performed giving children and adolescents creatine after TBI. In one study, creatine supplementation was initiated within four hours of the TBI and was administered for six months daily at 0.4g/kg in an oral suspension. Of the patients that received the supplementation, less posttraumatic headache, dizziness, and fatigue were reported compared to the group who received no creatine.[32] Another investigation by the same authors with similar methodology showed that creatine could confer neuroprotective effects in children and adolescents post-TBI. In that study, patients who received the creatine supplementation had improved post-traumatic amnesia, decreased duration of intubation, intensive care unit stay, and disability. These children also had improved communication, locomotion, behavior, and cognition.[33] Importantly, both experiments found no deleterious side effects with creatine supplementation.[32,33]

In terms of PTE, creatine supplementation in rat models begun one week after TBI has been shown to increase latency of first myoclonic and tonic clonic seizures. In addition, creatine was found to decrease time spent in seizures and seizure intensity. This neuroprotective effect was demonstrated even one week after creatine supplementation was discontinued.[34] Creatine can reduce cell loss in the hippocampus and protect against GABAergic function in the hippocampus. This is critical, as progressive neuronal damage that follows TBI for months can be related to pathologic excitotoxicity.[34] Another rat model study examining creatine's effects on seizure and biomarkers found that creatine helped to reduce amounts of markers associated with protein carbonylation and lipid peroxidation, thought it did not reverse a decrease in Na^+/K^+ ATPase activity.[35] Rather than protecting against seizures, this study found that rats with creatine

supplementation had decreased seizure latency at four days post-TBI and had a longer duration in tonic-clonic seizures. Therefore, there is mixed proof regarding creatine supplementation and TBI; likely the neuroprotective effects are not able to minimize all the excitatory pathways that create PTE.[35]

After a TBI, random membrane depolarization causes neuronal firing, depleting ATP stores. Furthermore, there is reduced blood flow and hypoxia. Brain metabolism can be dysregulated for years.[26] However, creatine can help restore membrane potentials and act as an energy source for the cells.[13] In a study with induced hypoxic conditions for human subjects, creatine supplementation was found to restore hypoxia-induced decrements in cognitive functioning. These patients also had an increase in corticomotor excitability. This is likely as creatine can delay hypoxia-induced membrane depolarization and maintain neuronal integrity.[23] Creatine supplementation prior to insult can also prevent impaired protein synthesis and axonal damage, protecting against synaptic transmission breakdown and the pathologic anoxic depolarizations that can cause neuronal death. Furthermore, creatine works to help the energy balance by transferring high-energy phosphates to areas of the neuron that need additional energy when oxidative phosphorylation is unable to function during hypoxia.[23] There is also a theorized state of hypermetabolism followed by hypometabolism following TBI. Due to the limited cerebral energy and injury-induced blood flow anomalies, energy supply and demand are unequal. Creatine is beneficial to this problem both prophylactically and immediately following TBI.[24]

The impaired mitochondrial function associated with TBI can also be addressed by creatine supplementation. Creatine has been shown to help increase mitochondrial membrane potential and decrease intramitochondrial reactive oxygen species and calcium.[31] Furthermore, it can help maintain ATP levels produced by the mitochondria. With restoration of functioning mitochondria, creatine kinase is able to catalyze the reversible conversion of creatine and ATP to ADP and phosphocreatine, thus generating energy reserves for the healing neuronal tissue.[31] Creatine is also able to directly stimulate oxidative respiration of the mitochondria and prevent formation of mitochondria permeability transition pores (mPTP).[13]

TBI causes excesses glutamate activation of NMDA receptors. This is one arm of the complex biomolecular signaling cascade previously described that causes increased cellular calcium, neuronal damage, and death.[24] In cultured rat embryonal hippocampal and cortical cells subjected to glutamate or peroxide, creatine was found to act in a neuroprotectant manner. Creatine was able to antagonize the excitotoxic response of glutamate on NMDA receptors, thus preventing calcium influx and sequestration.[27]

In addition to addressing energy, glutamate excitotoxicity, and impaired mitochondrial function, creatine has other ways it can combat TBI pathophysiology. It dampens calcium influx and reduces ROS by directly scavenging free radicals. Moreover, it prevents cerebral edema and can act as an anti-inflammatory agent.[13]

Conclusion

Overall, there is compelling evidence that creatine may act as a potential pharmacological therapy directly targeting the pathophysiologic effects of TBI. Future studies need to elucidate proper creatine supplementation protocols, including dosage amounts and intervals. While some studies have examined the effects of creatine on cognitive function, more trials are needed to analyze the connection. Further examination is also needed on the specific brain conditions that could benefit the most from creatine, in addition to post-traumatic states.[26]

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Enhancing Patient Education on Cardiovascular Rehabilitation with Large Language Models

by Som Singh, MD, Eric Errampalli, BA, Nathan Errampalli, BS & Mohammed Shah Miran, MD

Improving these generative artificial intelligence models can help address barriers preventing patients from adhering to cardiovascular rehabilitation programs.



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Abstract

Introduction: There are barriers that exist for individuals to adhere to cardiovascular rehabilitation programs. A key driver to patient adherence is appropriately educating patients. A growing education tool is using large language models to answer patient questions.

Methods: The primary objective of this study was to evaluate the readability quality of educational responses provided by large language models for questions regarding cardiac rehabilitation using Gunning Fog, Flesh Kincaid, and Flesch Reading Ease scores.

Results: The findings of this study demonstrate that the mean Gunning Fog, Flesch Kincaid, and Flesch Reading Ease scores do not meet US grade reading level recommendations across three models: ChatGPT 3.5, Copilot, and Gemini. The Gemini and Copilot models demonstrated greater ease of readability compared to ChatGPT 3.5.

Conclusions: Large language models could serve as educational tools on cardiovascular rehabilitation, but there remains a need to improve the text readability for these to effectively educate patients.

Introduction

Cardiac rehabilitation has provided patients with an effective way to modify cardiovascular risk factors and reduce the risk of rehospitalization.[1–3] The foundation of cardiovascular rehabilitation is built on a multidisciplinary team of physicians, nurses, advanced practice providers, etc. The longitudinal nature of cardiovascular rehabilitation programs makes adherence and completion of participation imperative for individuals undergoing them to truly receive their beneficial effects.[4,5] Patients who have completed three-month-long cardiovascular rehabilitation have demonstrated a lower risk of heart failure rehospitalization.[6] The literature has also shown that numerous

factors contribute to adherence to cardiovascular rehabilitation, including patient education.[6–8] This has led to an ongoing initiative by clinicians and healthcare providers to educate patients regarding cardiovascular rehabilitation.[9] Moreover, there is a growing body of literature that demonstrates adherence to cardiovascular rehabilitation is improved with the use of personalized interventions using artificial intelligence.[4]

Artificial intelligence has been leveraged in numerous areas to innovate patient care, including electronic medical records, personalized medicine, diagnostic imaging, and histopathology.[10–12] This is in addition to the fact that there has been improved public health information dissemination to patients through generative artificial intelligence models, including answering questions.[13–15] Given the early encouraging results of generative artificial intelligence models, the options for these tools continue to grow.[16] However, there is a lack of data that analyzes the behavior of generative artificial intelligence in how they answer questions asked by patients in cardiovascular rehabilitation. This area of literature may serve as an advantageous tool for clinicians to integrate if the responses by generative artificial intelligence models are accurate and understandable.

Regarding the latter, a key driver in improving a patient's understanding of healthcare is improved healthcare literacy.[17–20] In order to improve healthcare literacy, the text of generative artificial intelligence models would benefit by being readable at the recommended sixth to eighth grade reading level for most individuals.[21,22] This presents a paucity of knowledge that could uncover a key area to improve patient adherence to cardiovascular rehabilitation.

One area which is actively growing in the literature is the use of large language models.

Table 1. Questions asked to large language models to generate response corpus.

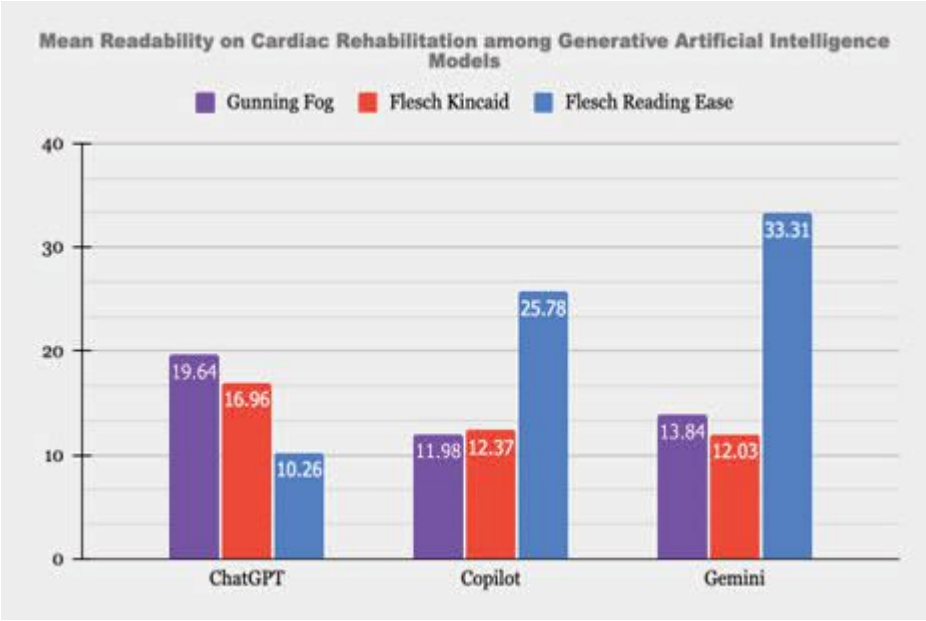
Questions
What is cardiovascular rehab
What is involved in cardiac rehab?
What are the phases of cardiac rehab?
What exercises are best for cardiac rehab?
How long do patients stay in cardiac rehab?
Can I do cardiac rehab at home?
What is the difference between cardiac rehab and regular rehab?
Does insurance cover cardiac rehab?
When is the best time to start cardiac rehab
What does a cardiac rehab nurse do?

These generative artificial intelligence models which are actively trained using neural networking architecture to learn and identify patterns in language data. As a result, these models use this training to generate free-text responses. Furthermore, this characteristic nature of large language models makes them a possible avenue to aid in educating patient over an array of topics. However, the literature regarding large language models in cardiovascular rehabilitation is limited. If participants undergoing cardiovascular rehabilitations can use large language models to as a supplementary education material, clinicians could benefit from a more robust tool in patient education, and it is therefore imperative to better understand the quality of the text content generated by these text models. The objective of this study was to observe the readable quality of the responses created by large language models in addressing frequently asked regarding cardiovascular rehabilitation.

Methodology

Similar to previous literature, this study employed publicly available generative artificial intelligence product which use large language modeling to assess the readability

Figure 1. Mean readability on cardiac rehabilitation among generative artificial intelligence models.



quality of the responses generated to answer the questions asked of the models. Specifically, the generative artificial intelligence models employed in the study were ChatGPT 3.5 (OpenAI®), Copilot (Microsoft®), and Gemini (Google®).[23–25] These models were employed, given the growing body of literature utilizing them.[13,26–30] Following the selection of these models, frequently asked questions generated as based on prior literature.[31–35] These questions were selected if they were: 1) unique and nonrepeating; and 2) pertained to cardiovascular rehabilitation. The questions selected for this study are demonstrated in Table 1. The text responses created by the generative artificial intelligence model were subsequently extracted by the authors of this study and pasted onto a plain text document using Microsoft Word®. These text responses were then calculated for readability using Gunning Fog, Flesch Kincaid, and Flesch Reading Ease scores. The selection of these readability calculations was based on prior literature demonstrating their use in categorizing the readability of digital texts.[22,36–40] The Gunning Fog score was calculated for each text using the following formula: 0.4 [(words/sentences) + 100 (complex words/words)] where a word is classified as complex if it has >3 syllables. The Flesch Kincaid score was calculated for each text using the following formula: 0.39 x (words/sentences) + 11.8 x (syllables/words) – 15.59. The Flesch Reading Ease score was calculated using the following formula: 206.835 – 1.015 x (words/sentences) – 84.6 x (syllables/words). Following readability calculations, descriptive statistics were obtained using the scores of each text response generated by the large language models.

Results

A total of 90 readability scores were obtained for the text responses generated by the large language models. The Copilot model demonstrated the lowest mean Gunning Fog score at 11.98 ± 1.28, a Flesch Kincaid score of 12.37 ± 1.34, and a Flesch Reading Ease score of 25.78 ± 8.85, as demonstrated in Figure 1. The Gemini model demonstrated the lowest mean Flesch Kincaid score at 12.03 ± 1.60 and the highest mean Flesch Reading Ease score at 33.21 ± 10.93. The Gunning Fog score of the Gemini model was 13.84 ± 2.13. The ChatGPT model demonstrated a mean Gunning Fog score of 19.64 ± 2.69, a Flesch Kincaid score of 16.96 ± 1.99, and a Flesch Reading Ease score of 10.26 ± 10.34.

Discussion

This study has compared the readability quality between responses generated by publicly available artificial intelligence models. Readability is an advantageous tool in medical

education to aid in creating and adapting content that can improve patient healthcare literacy. Improving healthcare literacy may improve adherence for patients undergoing cardiovascular rehabilitation as it may address knowledge gaps that patients have, further reducing healthcare barriers. In the current dataset, Copilot and Gemini demonstrated lower Gunning Fog and Flesch Kincaid readability scores compared to ChatGPT. This indicates a possible greater ease of readability using these two models than ChatGPT when considering statistical significance in these two readability calculations. While Flesch Reading Ease was not found statistically significant, the mean scores for Gemini and Copilot were also higher than ChatGPT, indicating greater ease using this readability calculation. These findings may suggest that patients will likely have greater ease in utilizing Copilot or Gemini over ChatGPT when answering their questions about health information. However, the text responses generated by these models must not be considered medical advice or replace formal evaluation by clinical providers.[15,41] Rather, they are used as supplemental information that would benefit from shared discussion with their clinicians. Likewise, it is also worth noting that the mean Gunning Fog and Flesch Kincaid scores do not meet the reading level recommendations in the US. Generative artificial intelligence models have yet to demonstrate the ability to deliver information appropriately on cardiac rehabilitation at a degree that is not too complex or difficult for patients to understand. This should be addressed with a longitudinal evaluation of the changes in the readability scores for these responses over time as deep learning by these models continues to adapt.

The selection of these questions was based on using the frequently asked questions as modeled in previous literature.[33,35] This set of questions has provided early literature on how generative artificial intelligence models can be measured using a standardized set of questions. However, the generated questions are acquired by internet-based machine learning in the Google RankBrain algorithm, so the findings of these studies may not apply to all questions by individuals.[32] Future steps to build upon this investigation could include utilizing a larger set of questions and measuring the difference in responses generated by the artificial intelligence model. Likewise, the development of a robust, large language model trained on clinical evidence may be an area of future investigation.

Conclusion

The mean readability quality of the text responses by ChatGPT, Copilot, and Gemini generated to answer questions on cardiovascular rehabilitation does not meet US grade-level reading recommendations. While Copilot and Gemini demonstrated greater readability compared to ChatGPT, all models may benefit from utilizing improved translation and word choice so that patients can understand better. These findings suggest that future analysis of these generative artificial intelligence models can determine how the models adapt over time. Improving these generative artificial intelligence models can help address barriers preventing patients from adhering to cardiovascular rehabilitation programs.

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Disclosure

The authors of this study report no conflicts of interest. The use of generative artificial intelligence was implemented in the research methodology of this study to curate the dataset as relevant to the primary aim of this study. Artificial intelligence was not used in the writing of this article. Part of this work was presented as a poster presentation at the Texas Cardiovascular Innovations conference in 2024. **MM**

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