

Missouri Medicine

The Journal of the Missouri State Medical Association msma.org/missouri-medicine January/February 2026

Washington University in St. Louis School of Medicine

The Center for Biostatistics & Data Science

From Data to Impact
The New Era in Medicine

National Review: The Scope of Medicare Fraud

Food Expiration Dates: Okay To Eat? Or Pitch?

Of Paramount Importance—Physician Advocacy

The Empty Promise of 'Medical Marijuana'

MSMA
Protecting the Health of Missourians Since 1850

168th Annual Convention

April 10-12, 2026 | DoubleTree by Hilton, Chesterfield, Missouri | www.msma.org/convention

PRELIMINARY SCHEDULE

Friday, April 10, 2026

3:00-7:00 pm	Registration
4:00-5:00 pm	CME Session
5:30-7:30 pm	Welcome Reception: Hosted by MSMA, St. Louis Metropolitan Medical Society, and St. Charles/Lincoln County Medical Society
7:00-8:00 pm	Medical Student Section Business Meeting
7:30 pm	Young Physician Section/Women Physicians Section International Medical Graduate Section/ Resident and Fellow Section Mixer

Saturday, April 11, 2026

7:00 am-5:00 pm	Registration
7:30-8:45 am	Product Theater Breakfast: Sponsored by Moneta Free with Registration
9:00-10:15 am	MSMA All-Member Business Meeting
10:30-11:30 am	CME Session
12:00-1:00 pm	MMPAC Roundtable Fundraiser Lunch $100 lunch per person ticket as donation to MMPAC
1:15-2:15 pm	CME Session
1:30-2:30 pm	MSMA Physicians Health Foundation Board Meeting
2:30-3:30 pm	CME Session
2:30-3:30 pm	Schools of Medicine Deans' Meeting (By Invitation Only)
2:30-4:30 pm	State Specialty Society Board Meetings
3:30-4:15 pm	MMPAC Board Meeting
3:30-4:30 pm	Medical Student Section Meeting
4:30-6:00 pm	Schools of Medicine Receptions
5:30-6:15 pm	Past Presidents/50-year Pin Recipients/MMPAC 1850 Society Members Reception
6:30-7:30 pm	Presidential Inauguration
7:30 pm	Presidential Reception

Sunday, April 12, 2026

8:00-9:00 am	Council Breakfast Meeting (Council Members Only)

**Subject to Change*

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General Information

Convention Registration

Hotel Reservations

GENERAL SESSIONS

Friday, April 10 4:00-5:00 pm

Empowering Health through Lifestyle Medicine



Speaker

Devyani Hunt, MD, MSMA member, is Division Chief, Physical Medicine and Rehabilitation, Department of Orthopaedic Surgery; and Director, Living Well Center, Washington University, St. Louis, Missouri.

Saturday, April 11 10:30-11:30 am

Missouri Public Health Update



Speaker

Heidi Miller, MD, MSMA member and an Internal Medicine physician is the Missouri Department of Health and Senior Services Chief Medical Officer. She was formerly with St. Louis Regional Health Commission and the St. Louis Integrated Health Network, while providing primary care at Family Care Health Centers. She completed her schooling at Yale College and Harvard Medical School.

Saturday, April 11 1:15-2:15 pm

Role of Genetic Counselors and Genetic Testing in the Era of Precision Medicine



Speaker

Erin Beaver, MS, CGC, is a Genetic Counselor in Oncology at BJC Healthcare, Missouri Baptist Medical Center, St. Louis, Missouri. She is the founder of inGENEuity, LLC, a genetic genealogy and counseling company.

Saturday, April 11 2:30-3:30 pm

Beyond the Headlines: Private Equity and the Future of Physician Practice

Panelists



Barton Hamilton, PhD, Panel Moderator, is the Robert Brookings Smith Distinguished Professor of Economics, Management, and Entrepreneurship and Academic Advisor for Experiential Learning at Washington University's Olin School of Business and School of Public Health, St. Louis, Missouri.



George Hruza, MD, MSMA member, is a fellowship-trained Mohs micrographic surgeon at Schweiger Dermatology Group, Chesterfield, Missouri, and Adjunct Professor, Dermatology and Otolaryngology, Saint Louis University, St. Louis, Missouri. Dr. Hruza serves in the Missouri House of Representatives for District #89.



Ryan McDevitt, PhD, is a Professor of Economics at Washington University's Olin School of Business and School of Public Health, St. Louis, Missouri, as well as a Research Associate at the National Bureau of Economic Research, Cambridge, Massachusetts. Dr. McDevitt currently serves as editor of the *Journal of Industrial Economics*.

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The Journal of the Missouri State Medical Association – Since 1904

Volume 123 | Number 1 | January/February 2026 **msma.org/missouri–medicine**

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Missouri Medicine

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Missouri Medicine
Mission—Submissions—Peer Review—Polices

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- Feedback and correspondence is encouraged

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They Stole Your Umbrella: Why Healthcare Professionals Should Support Stronger Fraud Controls

by Malcolm K. Sparrow, PhD

The rain, it raineth on the just and also on the unjust fella:
But chiefly on the just, because the unjust steals the just's umbrella.*



Introduction

Total US National Health Expenditures (NHE)—projected at $5.9 trillion for calendar year 2026, which represents 18.6% of GDP—are expected to rise to an unprecedented 20% of GDP by 2033.[1] The need for effective cost containment strategies is pressing.

Malcolm K. Sparrow, PhD, is Professor of the Practice of Public Management at the John F. Kennedy School of Government, Harvard University, Cambridge, Massachusetts, USA. He is Faculty Chair of the School's Executive Program - Strategic Management of Regulatory & Enforcement Agencies.

**From Matthew Chapter 5, Verse 45, augmented as attributed to Lord Charles Bowen, 1835–94.*

One path would be to launch a more vigorous assault on health care fraud and abuse, assuming that there is plenty of it to be found, that we know how to detect and suppress it, and that we could do so without harming patients' health or rights, or interfering with legitimate medical practice.

Alternative approaches to cost control involve less discriminating methods. Squeeze everything. Reduce benefits across the board. Restrict eligibility. Reduce access to services. Cut provider reimbursement rates. Decrease utilization and shift costs to patients by limiting insurance coverage, increasing premiums and deductibles, and eliminating subsidies.

Providers and their associations have historically been leery of the first approach, scarcely if ever expressing public support for it. Physicians resent medical judgments being second-guessed by investigators and auditors. Some providers are nervous about mobilizing condemnation for even the most blatantly criminal acts of their peers if they cannot draw a bright line separating what the crooks do from what they do themselves. Perhaps they engage in small-fry noble-cause corruption, such as altering diagnoses or fabricating symptoms to help patients qualify for treatments that physicians believe they need. Would they welcome more attention to "False Claims?" Provider associations, defending the financial interests of their members, see only downside risk, especially if controls were poorly directed.

Does the medical provider community prefer the more general methods for ratcheting down costs? In theory, any "broad squeeze" hits the honest and the dishonest alike. In practice, it hits the honest providers and genuinely needy patients hardest. Fraud perpetrators, faced with tighter restrictions and lower reimbursements, enjoy the advantage of being unconstrained by truth; they adjust their billings to fit whatever pays, invent new ways to cheat, and step up their volume of fictitious claims. Honest providers take the pay cut, and their patients suffer the health consequences.

I want to make the case that more rigorous control of fraud and abuse, properly targeted, could cut costs substantially without denying patients necessary services or adversely affecting legitimate medical practice.

How Goes the War?

The Clinton Administration "declared war" on health care fraud and abuse in 1993. Attorney General Janet Reno ranked health care fraud the number two crime problem in America, second only to violent crime—an extraordinary status for any white-collar crime.[2] Attention to health care fraud has waxed and waned over the years since, gaining prominence whenever the annual medical costs inflation rate ticks upwards towards 10%.

How goes the war now? Rather well, one might surmise, based on a number of recent and highly visible signals:

1. "Crushing Fraud, Waste & Abuse"—a banner headline—now tops the Fraud webpage for the Center for Medicare and Medicaid Services.[3]
2. On June 30, 2025, the US Department of Justice announced the largest "National Health Care Fraud Takedown" of all time, resulting in 324 defendants charged with over $14.6 billion in alleged fraud.[4] The press release points out this new record "More than Doubles [the] Prior Record of $6 billion."
3. In January 2025, the Department of Justice reported a record high number, 979, of whistleblower (or qui tam) lawsuits filed in Fiscal Year 2024 under the False Claims Act, with the majority of cases related to health programs. Every year since 1986, when the Act's coverage was broadened to include health care expenditures, health-care fraud cases have made up the majority of cases filed.[5]
4. During FY 2024, the Office of Inspector General (DHHS) excluded 3,234 "untrustworthy" individuals and entities from participating in federal health care programs.[6] The total number of federal exclusions currently exceeds 82,100.[7] Forty-five states also maintain their own state-level health care provider exclusion lists which they use in addition to the federal list to keep bad actors out.

Taken together these signals suggest high levels of determination, record numbers of prosecutions, a plentiful supply of whistleblowers, and an apparently robust system for shutting out identified miscreants. But does that mean fraud and abuse is well controlled?

Invisible Risks

Health care fraud belongs to the class of "Invisible Risks." These risks have detection or discovery rates substantially lower than 100%, and in many cases as low as 10% or even 1%. This class of risks include most white collar crimes which, if well designed, remain invisible in perpetuity; consensual crimes like drug-dealing and bribery, and abuses that occur inside closed institutions (e.g., prisons, nursing homes, locked psychiatric wards, boarding schools).[8]

For such risks, we know the problem exists because we observe some cases and deal with those that come to light. We may make the mistake of assuming that the cases we detect are typical of those that remain hidden. We have little or no idea about the true scale of the problem and, as a corollary, cannot estimate our discovery rate, even roughly. The challenge with invisible risks is to get to grips with the invisible mass, rather than simply dealing with the visible sliver; which means, for starters, discerning the true scale of the problem.

"Invisible Risks" present a variety of operational challenges. First and foremost, massive underinvestment in controls is the norm. Underinvestment is a self-perpetuating reality, as lack of commensurate resourcing guarantees under-discovery, which in turn perpetuates uncertainty and continuing underinvestment. This macro-level circularity trap of underinvestment routinely stifles effective control for risks of this type.

Second, all readily available metrics are inherently ambiguous. If this year we discover twice as much fraud as last year, is that good news or bad? Call this the "find more trouble conundrum:" we found more trouble, so maybe there's more trouble, or maybe we got better at finding it, or both at once. And if we find less trouble, good news and bad stories are similarly available. Unless the ambiguity is somehow resolved, everyone is free to pick the good news or bad news narratives, whichever they prefer.

What should we make of the government's "record fraud take-down" involving $14.6 billion in fraud? It has become an annual ritual for the government to bundle enough cases together to produce impressive hauls like this. They have announced massive "fraud take-downs" every year for the past 10 years, most often in June or July. New records have been set in 2016, 2017, 2018, 2020, and now 2025.[9]

If a fishing boat returning to shore dumps massive and possibly record hauls on the quayside trip after trip, what conclusion might an observer reach? That the fishermen had worked hard and should be applauded? For sure. That fishing methods and technologies were improving? Perhaps. That fishing was close to extinguishing the fish population? Certainly not. That the fishermen were demonstrating their "zero tolerance" for fish? With massive haul after massive haul, one would surely assume that the seas were veritably teeming with fish, and that the number of fishermen was insufficient to alter that reality.

Measurement Studies

To break the circular trap of underinvestment and resolve the ambiguities in the metrics, we need reliable estimates of the true scale of the problem. Then we could base future control investments in some rational way on the actual prevalence of fraud and abuse rather than on the sliver of cases that come to light. We could also interpret output metrics and caseloads more reliably.

The standard approach to measurement of invisible problems involves conducting rigorous audits or inspections on a random, quasi-random, or otherwise representative sample drawn from the relevant population. In the fee-for-service setting, this means conducting fraud audits on a random sample of health care claims recently paid. Such measurement audits need to be rigorous enough to find "the trouble," if present, at least most of the time. Findings from the sample can then be extrapolated to the entire population with statistical validity.

Unfortunately, when formal measurement studies for invisible problems are conducted with the appropriate level of rigor, they typically produce estimates of prevalence so high that nobody wants to believe them. To avoid rocking the boat too much, officials may be tempted to use softer audit or inspection protocols which produce reassuringly low estimates.

Both Medicare Fee-for-Service and Medicaid are designated "High Risk" programs and therefore

required under federal law to measure and publish payment accuracy rates on an annual basis, which they do through the "Payment Error Rate Measurement Program" (PERM) for Medicaid, and the "Comprehensive Error Rate Testing (CERT)" program for Medicare Fee-for-Service.

The figures produced by these programs provide a partial and somewhat patchy picture. Over the last decade improper payment estimates for Medicaid have ranged from a low of 3.13% in 2020 to a high of 21.69% in 2021; and for Medicare, a low of 6.26% in 2021 to a high of 12.09% in 2015.[10] The estimates vary so widely because of the way the studies are conducted, with different review factors either included or excluded year by year, and varying degrees of rigor applied to the audit process.

The audit protocols include standard document reviews to check whether the claim, taken at face value, complies with coverage, coding, and billing rules. Medical records supplied by the providers are then reviewed to see if they match and justify the claim.[11]

Bear in mind that fraud perpetrators, even 30 years ago, had learned how to fabricate medical records to match their fabricated claims. Assuming they bill their lies correctly and back up their fake claims with fake medical records (which is ordinary common sense for fraud perpetrators), any of their claims that fall within such samples will likely be determined "correct."

The audit protocols used make no determinations of fraud or abuse because there is no way to get inside the mind of the claimant to determine the relevant mens rea. Nor do they include enough broader contextual analysis to spot kickbacks and illegal referral schemes, or anomalous patterns of coincidence that might reveal organized scams orchestrated at high levels.

Hence error and overpayment rates, as estimated by the PERM and CERT programs, turn out to be poor proxies for fraud and abuse. (Officials conducting these programs readily acknowledge they are not designed to measure fraud and abuse rates per se, even though many observers assume that they do.)

These measurement programs focus on fee-for service, and we have no equivalent studies attempting to calibrate the full range of abuses under managed care. (More than half of Medicaid and Medicare patients are now enrolled in some kind of managed care plan). We have no aggregate estimates from the private insurance market, which now represent 30% of health care spending; nor for personal out-of-pocket health care spending, which represents another 10%.[12] So we really don't know much at all about the true scale and scope of health care fraud and abuse; at least, not this way.

Characteristics of Cases Uncovered

We can, however, extract some clues about the effectiveness of control systems by examining the characteristics of the cases that come to light. Let us imagine two different worlds. In World One, control systems are well resourced, vigilant, quick to react, and effective. Fraud and abuse has not been completely eliminated but is certainly well contained. In World Two, control systems are inadequately resourced and overwhelmed, with weak detection systems and shortages of investigators, auditors, and prosecutors for follow up.

Consider the characteristics of the cases that might be discovered under these two scenarios, and how they might differ from each other.

In World Two, fraud schemes uncovered would likely be huge. They would have been running for years and caused substantial economic damage before being discovered and shut off. They might involve widespread conspiracies, which take a long time to set up. During many years of operation, the scheme's activities evaded detection. More likely than not, the scheme was uncovered in the end when a whistleblower stepped forward, rather than through the routine operation of detection apparatus. Had the whistleblower not stepped forward, it seems plausible that the scheme could have grown yet further and rumbled on for several more years.

In World One, by contrast, schemes would be discovered in their early set-up stages. They would not yet involve broad conspiracies, nor have done much economic damage. They would be discovered through the operation of routine detection or intelligence systems, and possibly through the operation of multiple, independent, discovery methods each attuned to different aspects of the scam.

Which world do we live in? Consider the following cases, each discovered or settled within the last year.

1. In May 2025, Dr. Jorge Zamora-Quezada, a Texas rheumatologist, was sentenced to 10 years in prison for submitting $118 million in fraudulent claims to public and private insurers. He falsely diagnosed patients with rheumatoid arthritis and then provided tests and unnecessary and potentially harmful treatments over many years. In addition to his prison sentence, he was ordered to forfeit $28 million, 13 real-estate properties, and a private jet.[13]
2. In June 2025, Gary Cox, CEO of a Healthcare software company DMERx was convicted of operating an internet-based platform which generated more than $1 billion in fraudulent claims. Cox and his co-conspirators targeted "hundreds of thousands" of Medicare patients, using false advertising and offshore call centers to persuade them to accept unnecessary medical supplies. Fake doctor's order and kickbacks were used across a vast network of participating pharmacies, DME providers, and telemedicine companies.[14]
3. In June 2025, Tyler Kontos, Joel Kupetz, and Jorge Kinds were indicted for billing more than $1 billion over a 14-month period for unnecessary but expensive amniotic wound allografts. They targeted elderly Medicare patients in hospice care. They were paid more than $600 million.[15]
4. In May 2025, Syed Murtuza Kablazada and Syed Mehdi Hussain were arrested in Illinois having submitted $227 million in fraudulent Medicare claims for COVID-19 test kits supposedly provided to Medicare beneficiaries. Foreign nationals brought in as nominee owners of the laboratories were instructed to leave the country at the first sign of any investigation.[16]
5. In June 2025, the Department of Justice charged Farrukh Jarar Ali, a Pakistani national, in a fraud scheme involving at least 41 addiction clinics in Arizona. False claims totaling $650 million were submitted for services not provided as billed, or medically unnecessary—$564 million was paid. The scheme preyed on native Americans, the homeless, and other vulnerable individuals, enrolling them in the state insurance system and then providing substandard care or no care at all.[17]
6. A broader pattern of fraudulent "sober homes" in Arizona, involving more than 100 facilities, is estimated to have cost the state's Medicaid program at least $2.5 billion dollars.[18] Relatives of the victims (many of whom died in these facilities) have launched a class-action lawsuit against the state for its sluggish response, claiming they failed to intervene earlier when the scheme was apparent in 2019, with estimated losses of $43 million at that time.[19]
7. In December 2024, consulting company McKinsey agreed to pay $650 million to settle allegations that its advice to opioid manufacturer Purdue Pharma resulted in fraudulent claims for oxycontin being submitted to federal health care programs. McKinsey advised Purdue on marketing strategies and how to "turbocharge" sales.[20]
8. In June 2025, 11 defendants were indicted as a result of "Operation Gold Rush." A transnational criminal organization with roots in Russia bought up dozens of existing DME companies and used them to submit $10.6 billion in false claims, using more than a million stolen identities. Fake corporate documents disguised foreign ownership of the companies. Claims totaling roughly $941 million were paid. In announcing the indictments, the Department of Justice seems to celebrate the "Largest Case by Loss Amount Ever Charged by the Department of Justice."[21]

Welcome to World 2. It is astonishing how large such schemes can become and how long they can operate before eventually being exposed and shut down. The medical community needs to understand that these offenders and thousands like them—the majority of which go undetected—are eating your lunch or they stole your umbrella, whichever metaphor you prefer. They are ripping several hundred billion dollars a year out of the health system, huge sums of money for which we could all imagine better uses.

How Many Hundreds of Billions of Dollars?

Suppose we took the broad range of "overpayment" estimates from the PERM and CERT studies—that is, a low of 3% to a high of 25%—and imagined losses to fraud and abuse lying somewhere between these extremes. Applied across the totality of annual health care spending ($5.9 trillion) the range is roughly two hundred billion to 15 hundred billion dollars. That is, for some integer n, most probably in the range n=2 to n=15, the losses would be n followed by eleven zeroes, or $n00,000,000,000. We just do not know n.

Based on 2018 health expenditures, the National Health Care Anti-Fraud Association (NHCAA) floated the possibility—based on what they saw and heard from law enforcement—that n might be three (i.e., annual losses of $300 billion at that time). In 2025, if I had to guess (which I have some qualms about doing), I would guess n was at least 10. Readers can guess too, based on what they see happening around them.

But whether the scale of the problem is $300 billion, or more than a trillion dollars, it makes absolutely no sense that the aggregate national budget for Medicaid Fraud Control Units is less than half a billion (at $396 million). This equates to 0.04% of the Medicaid budget.[22] Or that the FBI only gets $168 million (FY 2024) for its work on health care fraud cases, and the Department of Justice $196 million.[23] The DHHS Office of Inspector General's budget for oversight of the Medicaid and Medicare programs, at $341 million,[24] is equivalent to just 0.015% of the combined program budgets.

These control investments seem impressive until you hold them up against the potential scale of the problem, at which point they appear miniscule. These dollar amounts have the wrong number of zeroes. Total annual federal spending on Health Care Fraud and Abuse control ($2.5 billion) equates to just 0.07% of total government health care spending. False Claims Act recoveries by the Department of Justice (for healthcare matters) totaled $1.67 billion last year, with a clear majority of the cases prompted by whistleblower reports.[25] To make a substantial impact, that number needs to be at least $20 billion.

If we could discover and add up all the investments in fraud and abuse control across the entire US health system, total spending would likely not exceed $5 billion. Given total health expenditures of $5.9 trillion, this means that for every $100 we spend on health care we devote less than 10 cents to checking that we got what we paid for and that it was medically appropriate. Would not any prudent shopper be prepared to spend a whole dollar, or even $5, to assure themselves that their $100 was well spent?

Managed Care and Capitated Systems

Thirty years ago, in the early days of managed care, many hoped that capitation arrangements would eliminate fraud and abuse by removing all the incentives for overbilling and overtreatment. But capitation merely changes the forms of fraud, creating incentives for undertreatment and diversion of funds away from front line service delivery. The locus for fraud also changes, from the front-line providers to the plans themselves.

MCOs can cheat by manipulating risk scores on which capitation payments are based, fabricating enrollments, using selective enrollment and disenrollment practices, improperly restricting access to care, destroying or arbitrarily denying claims, or assigning unreasonably high numbers of patients to providers. They can divert or embezzle capitation funds through fraudulent subcontracts and by paying excessive salaries and fees to executives and close associates.[26]

Most of these practices do not involve false claims per se, hence they do not show up at all in the fee-for-service measurement studies. These are corporate frauds and abuses, hidden somewhere within the complex layers of for-profit enterprise which now separate payers from patients. These illicit practices are especially hard to detect through routine audits, therefore even more "invisible." We have relied heavily on serendipitous disclosure by whistleblowers for discovery.

Manipulating patient risk scores, on which capitation rates are based, seems to have emerged as one favored method for boosting revenues. The last five years have seen a slew of cases brought by the DOJ against major plans (and provider groups that receive risk-adjusted payments) for submitting false, exaggerated, or unsupported diagnosis codes. The Cigna Group paid $172 million in FY 2023 to settle such allegations in relation to the Medicare Advantage program.[27]

In October 2024, the Office of Inspector General published analysis showing that diagnoses reported on Health Risk Assessments, but which did not appear on any other service records, increased Medicare Advantage risk-adjusted payments for 2023 by an estimated $7.5 billion.[28] The vast majority of Medicare Advantage companies (157 of 170) had submitted such uncorroborated diagnostic codes.[29] UnitedHealth Group ($3.7 billion) and Humana ($1.7 billion) accounted for substantial and disproportionate shares of the $7.5 billion.[30] UnitedHealth faces criminal and civil investigations by DOJ, with no final resolution as of October 2025.[31]

Ramping Up, and Returns on Investment

The Office of Inspector General (OIG), in their Spring 2025 semi-annual report, cites a return ratio of $11 for every $1 of their budget.[32] Economists might argue that the efficient level of fraud and abuse control is the point at which marginal costs are equal to marginal benefits. As control investments are currently so small compared with the scale of the problem (i.e., with so many fish in the sea, and so few fishermen), we are nowhere near a point of diminishing returns.

In fact, the 11:1 ratio cited by the OIG is a very modest claim. The OIG base this estimate purely on hard-dollar recoveries and restitution resulting from their enforcement and oversight actions. They do not include specific deterrence effects (shutting off the stream of future billings from a specific provider), nor general deterrence (effects on the behavior of other providers based on actions taken against one). Both of these effects are potentially much greater than the hard-dollar recoveries, but are more difficult to estimate.

Get On Board

There is plenty of room for at least a five-fold increase in fraud and abuse control investments, across the entire US health system, without running any risk of approaching or exceeding an optimal level of control. Not a 5% increase. Five-fold. We need to break the circularity trap of under-investment and under-discovery, and match the scale of control efforts to the scale of the problem.

Officials in the current administration have publicly expressed their determination to "crush" fraud and abuse. Aggressively ramping up controls should pay off handsomely over time, but would of course be politically contentious and take time and cost money up front.

I wonder whether the medical community would support such a dramatic, five-fold, scaling-up of control efforts, or any significant steps in that direction. They should. Other academic commentators have warned against additional fraud control efforts, assuming they necessarily make life more difficult for honest physicians and place obstacles in the way of patients seeking care. Neither is true. It is the big, broad, general, indiscriminate "squeeze" that has those effects; not a properly targeted campaign focused on crooks and crime.

Conclusion

Fraud and abuse harms patients. Patients treated by perpetrators suffer worse medical outcomes.[33] With abuses by managed care plans, patients cannot get the care they need. With fee-for-service fraud and abuse, patients suffer the adverse health consequences of unnecessary and inappropriate treatments, see their insurance benefits exhausted or substantially used up, and end up paying co-pays and deductibles for treatments they do not need and should not have. False diagnoses and fictitious treatments included on their medical records may distort future care decisions and restrict their ability to obtain health insurance, life insurance, and some forms of employment.

Ramping up fraud and abuse controls would benefit all legitimate providers, providing a discriminating way of controlling costs by identifying and removing bad actors and stemming the flow of funds to them. Carefully targeted controls protect the interests of the good by squeezing out the bad, enabling a "pay-on-trust" system to survive by weeding out those who cannot be trusted.

Finally, consider this: last year, qui tam relators (whistleblowers) took home between them $463 million as their share of settlements in cases they brought forward.[34] Whistle-blowing is a painful path to follow, but one sure way to take your umbrella back!

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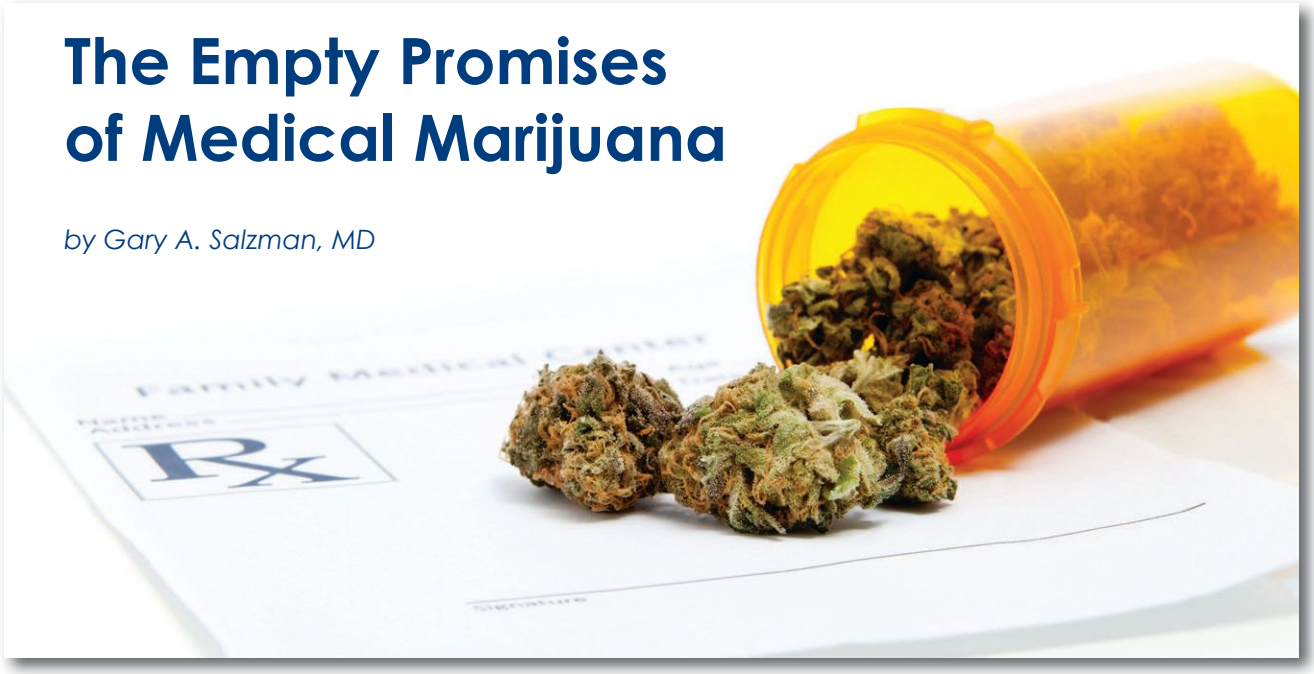
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MM

The Empty Promises of Medical Marijuana

by Gary A. Salzman, MD



The widespread availability and euphoric effect of medical marijuana divert patients away from physicians who can provide an accurate diagnosis and effective treatments.

In 2018 medical marijuana was approved in Missouri for individuals certified by a licensed physician or nurse practitioner. As of early 2025 there were more than 120,000 individuals certified in Missouri.

Promises were made that marijuana purchased from licensed dispensaries would improve symptoms associated with cancer, epilepsy, glaucoma, migraines, HIV, and other chronic debilitating conditions. There is clear evidence from an extensive meta-analysis recently published in the *Journal of the American Medical Association* that these promises were false.[1]

It turns out that medical marijuana sold from dispensaries is not effective and not safe. Inhaled or oral cannabis is not recommended for medical conditions by any evidence-based professional guidelines. It has been reported that 27% of adults in the US and Canada have used Cannabis for medical purposes.

The scientific name for marijuana is *Cannabis Sativa L*. The Cannabis plant contains THC (tetrahydrocannabinol) that has psychoactive properties. CBD (Cannabidiol) comes from the hemp plant. CBD has no psychoactive properties and is thought to have therapeutic benefit for a variety of medical conditions.



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Licensed dispensaries sell Cannabis flower that is smoked; edibles that contain various concentrations of THC and CBD; vape pens containing THC; topical CBD and THC; and THC concentrates that can be vaporized.

Today's marijuana is much more potent compared to the marijuana that was smoked in the past. Many baby boomers underestimate the risks based on their experience of mild euphoria smoking marijuana in their youth. The THC levels in the 1960s and 1970s were 1-3% as compared to 18-30% today. The higher levels of THC today produce significant acute psychoactive effects including confusion, anxiety, paranoia, altered perception, and even psychotic episodes. The delayed effects of edible Cannabis results in multiple doses and increased toxicity.

The FDA has approved pharmaceutical-grade Cannabinoids. CBD oral solution is approved for specific types of seizures. Dronabinol, a synthetic THC, is approved for HIV/AIDS-induced anorexia and chemotherapy-induced nausea and vomiting. Nabilone, a CB1 receptor agonist, is approved for chemotherapy-induced nausea and vomiting. Both of these drugs are designated Schedule II by the DEA. All three drugs are associated with commonly encountered significant adverse effects that limit their use. Other medications for these indications are more effective with fewer side effects compared to these three Cannabinoids.

Cannabis is legal to use for medical conditions in 39 states. In 24 of those states, including Missouri, both medical and recreational use of marijuana are legal. CBD alone is legal to use in 10 states. Purchase of Cannabis illegally from drug dealers is still common. As a pulmonary critical care physician, I commonly encounter drug overdoses in patients purchasing illegal Cannabis that was laced with other drugs and agents including fentanyl, PCP, ketamine, and formaldehyde. Patients are unaware of these additions and thought they were purchasing Cannabis only. Many of these patients end up on mechanical ventilation in the ICU and some patients die from the overdose.

There is no credible scientific data that supports the efficacy of medical marijuana purchased at licensed dispensaries. Most of the support of efficacy is based on anecdotal reports and poorly designed studies. There is likely a placebo effect and high potency THC products result in euphoria that can mask the underlying medical condition. The euphoria often results in daily use and dependence.

There is no valid scientific evidence that Cannabis relieves chronic pain, reduces spasticity due to multiple sclerosis, reduces intraocular pressure in glaucoma, reduces anxiety, or treats insomnia. The widespread availability and euphoric effect of medical marijuana divert patients away from physicians who can provide an accurate diagnosis and effective treatments.

For example, anxiety and insomnia may be due to hyperthyroidism that can be easily treated without the significant risks and lack of benefit associated with medical marijuana. Multiple studies have demonstrated the most effective treatment for insomnia is Cognitive Behavioral Therapy without any drugs. Cannabis has multiple drug interactions with prescribed medications including anticoagulants, CNS depressants, seizure medications, antidepressants, and antihypertensive medications. When combined with alcohol, high potency THC containing Cannabis will produce increased sedation, lethargy, and ataxia.

What are the problems with Cannabis use? Long term daily use of Cannabis with high potency THC may be associated with impaired memory, learning, processing speed, and attention. Cannabis impairs driving, leading to motor vehicle accidents due to impaired performance and attention with delayed reaction times. Cannabis use has been associated with an increased risk of myocardial infarction, strokes, and arrhythmias. As a pulmonologist, I commonly see patients with cough, wheezing, chronic bronchitis, and exacerbations of COPD and asthma in patients inhaling Cannabis from vaping and smoking. Use of Cannabis in pregnancy is associated with low birth weight and increased neonatal ICU admission.

It is now common for patients using marijuana on a daily basis to present to the emergency department with intractable vomiting only relieved by a hot shower. Cannabis hyperemesis syndrome hospitalizations have sky-rocketed after the legalization of marijuana. It has been reported that 17% of individuals regularly using

Cannabis suffer from Cannabis withdrawal syndrome. Observational studies report 29% of individuals using medical marijuana meet the criteria for cannabis use disorder. There has been a significant increase in emergency department visits of children accidentally ingesting edible Cannabis presenting with sedation, lethargy, seizures, bradycardia, hypotension, and hallucinations. Cannabis edibles look and taste like candy.

Proponents of medical marijuana emphasize that this is a safe natural plant-based therapy. Growers manipulate the plant's genetics, lighting, temperature, and nutrients to produce higher levels of THC. Cannabis with high concentrations of THC does not come from plants found in nature. Our environment is full of dangerous substances whether they are manufactured or natural.

President Trump signed an executive order in December 2025 to reclassify marijuana from a DEA Schedule I drug to a DEA Schedule III drug to facilitate needed research on the drug. Who will provide funding for this research? The Cannabis industry will have no interest in funding research that may find their drug is not effective in treating medical conditions.

Currently medical marijuana is readily available in 39 states, and the companies are receiving billions of dollars in revenue from medical and recreational marijuana. Schedule I drugs have no currently accepted medical use and a high potential for abuse. Schedule III drugs have a moderate to low potential for physical and psychological dependence. Examples of schedule III drugs are Tylenol with codeine and anabolic steroids. Reclassifying marijuana sends the dangerous message that this drug is thought to be safe and effective to treat medical conditions. It sends the message that marijuana is as safe as Tylenol with codeine.

With marijuana available for legal purchase in dispensaries and reclassified to Schedule III, young people will not think twice about using marijuana. In Missouri, the individual must be 18 years or older to purchase medical marijuana and 21 to purchase recreational marijuana. Adolescents too young to purchase marijuana from a dispensary will purchase from a drug dealer and face the risk of adulteration with other drugs.

Our patients deserve more than the empty promises of medical marijuana. Physicians have the responsibility to educate our patients on the risks and lack of benefit from medical marijuana and encourage our patients to get a medical evaluation for their symptoms. Once a diagnosis is made by a physician, treatment with proven therapies with appropriate risk benefit ratios can be implemented.



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MM

A 20th Century Historical Perspective on Congenital Syphilis and Lessons for Today

by Jane F. Knapp, MD & Robert D. Schremmer, MD

In the early 20th century, syphilis was a significant public health problem affecting adults and, through congenital transmission, children. Focus on the cutaneous manifestations of the infection gave rise to the linked medical specialty of Dermatology-Syphilology. Charles Clayton Dennie, MD, a Dermatologist-Syphilologist, established a Congenital Syphilis Clinic in 1915 and pioneered the description and treatment of the disease in infants, children, and adolescents (Figure 1). The span of his career coincided with historical breakthroughs, public health challenges and the advent of treatment with penicillin in the 20th century.



Figure 1. Dr. Charles C. Dennie with a patient, circa 1930.
Used with permission by University of Kansas Medical Center Archives, Kansas City, KS

With the current disease resurgence, experience from the past century is newly relevant. The Center for Disease Control (CDC) reported 3,882 cases of congenital syphilis in 2023 including 279 congenital-syphilis related stillbirths and neonatal deaths.[1] Almost all jurisdictions in the United States (US) reported cases. This is the largest number of cases since 1992 and a 3% increase over 2022.[1] The 20th century historical record of congenital syphilis can demonstrate successful approaches and pitfalls to the current surge in cases.

The Congenital Syphilis Clinic

Dr. Dennie graduated from the University of Kansas School of Medicine in 1912. Around this time three significant breakthroughs were made in the recognition, diagnosis, and treatment of syphilis. Fritz Schaudinn and Erich Hoffman demonstrated *Treponema pallidum* as the causative organism in 1905.[2] The Wassermann test for diagnosis was developed in 1906.[2] In 1910, Paul Ehrlich and a team of scientists found that an arsphenamine compound cured rabbits infected with *T pallidum*.[3] Ehrlich termed the new drug Salvarsan (meaning "I save").[2]

As a student, Dr. Dennie first saw patients with congenital syphilis at Children's Mercy Hospital in Kansas City, Missouri. He went on to postgraduate training in Dermatology-Syphilology at Massachusetts General Hospital where he was an instructor of syphilis at Harvard Medical School and participated in research to locate T *pallidum* organisms in cutaneous lesions.[2] In 1914, he studied at l'Hôpital Saint-Louis in Paris. At that time l'Hôpital Saint-Louis was known as "the lighthouse of dermatology throughout the world."[4] Physicians there made the treatment and prevention of syphilis a priority "…not only because of the contagiousness of the illness that was inflicted on the family but also because of the hereditary consequences notably the frightening mortality threatening future generations…."[4]



Jane F. Knapp, MD, is a retired pediatric emergency physician at Children's Mercy Hospital and Emeritus Professor at the University of Missouri-Kansas City School of Medicine, Kansas City, Missouri, USA. Robert D. Schremmer, MD, (pictured), is a pediatric emergency physician at Children's Mercy Kansas City and is a professor of Pediatrics at University of Missouri-Kansas City School of Medicine, Kansas City, Missouri, USA.

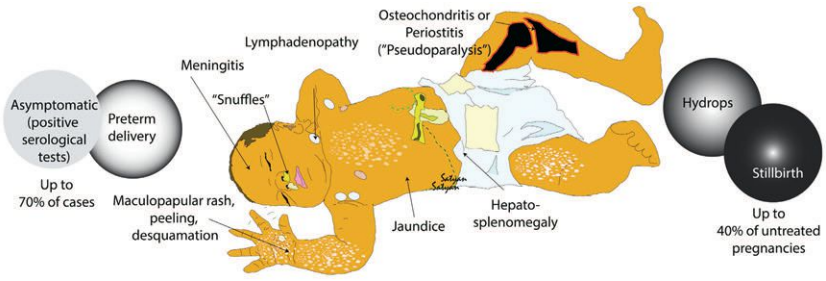


Figure 2. Stigmata of congenital syphilis.
*Deepika Sankaran 1ORCID,Elizabeth Partridge 2 and Satyan Lakshminrusimha 1,*ORCID, CC BY 4.0, via Wikimedia Commons*

In 1915, at Children's Mercy Hospital, Dr. Dennie established what he described as the first free clinic that he knew of in the US devoted entirely to the treatment and study of patients with congenital syphilis.[5] His practice was interrupted when he served in the US Medical Corps during World War I. He returned to the still functioning clinic in 1919 to find no shortage of patients. By the early 1930s, Public Health Service surveys of syphilis cases projected that approximately 10% of Americans were infected and 60,000 children were born annually with congenital syphilis.[6]

Multiple factors, local and national, contributed to the spread of infection. In the 1920s, Kansas City was infamous as "a wide open town" where the Pendergast political machine profited from bootleg liquor, gambling, and prostitution. Aimed at the military and public during World War I, the US War Department's Commission on Training Camp Activities anti-venereal disease campaign, also known as "Fit to Fight," had waned by the 1920s.[6] Funding for the Venereal Disease Division of the Public Health Service was cut from $4 million in 1920 to $60,000 by 1926.[6] Treatment with Salvarsan was expensive and the drug was challenging to reconstitute and administer.[3]

Prenatal care in the prevention of congenital syphilis was in its infancy (Figure 2). In 1914, obstetrician J. Whitridge Williams, MD, presented a study of 10,000 consecutive births that found syphilis was the most common cause of infant death in the US. He concluded that 40% of all infant deaths could be prevented with prenatal care that included an early prenatal visit with a physical examination and a Wassermann test.[7] Dr. Williams also cautioned that the effects of unrecognized maternal syphilis were not limited to the birth of a single affected child as the undiagnosed mother could have future pregnancies. He recommended testing for all stillborns and infant deaths.[7]

In his work in Kansas City, Dr. Dennie held clinic three times weekly for patients up to 16 years of age. Sunday was the treatment day nicknamed "Sunday School" by staff. Handwritten clinic logbooks reveal extensive use of Salvarsan and its successor Neosalvarsan. In Part VI of his memoir, "Little Known Medical History" published in the Greater Kansas City Medical Bulletin in 1970, Dr. Dennie remembered treating over 150 patients in a single day.[8]

Treatment with arsenicals required prolonged therapy, had the potential for serious side effects and was not effective against all stages of the disease. In his book, *Congenital Syphilis*, coauthored by Sidney Pakula, MD, Dr. Dennie related his experience with the use of malariotherapy and hot baths, both popular at the time, to induce high temperatures in the treatment of "certain resistant cases" especially in children with interstitial keratitis and neurological involvement.[9]

The National Campaign

In the 1930s, US Surgeon General Thomas Parran, MD, campaigned to change attitudes of moral condemnation of venereal diseases through education of syphilis as a medical condition and threat to public health. Describing syphilis as a "shadow on the land," he launched a campaign aimed at identification of individuals and contacts, testing (including premarital), treatment, prenatal testing and treatment, and education.[10] His article "The Next Great Plague to Go" graphically depicted disastrous outcome for 83% of infants born to untreated mothers[11] (Figure 3).

With the introduction of treatment with penicillin in 1944, rates of infection fell dramatically; by 1950 the Congenital Syphilis Clinic closed. By 1975 rates of congenital syphilis had decreased from 521/100,000 in 1943 (two years after the CDC began collecting national data) to 29/100,000 live births.[12] As the 20th century came to a close, rates of syphilis were still on the decline and the CDC was developing a national syphilis elimination plan.[13]

In his 1950 presidential address to the American Dermatological Association entitled The Dying

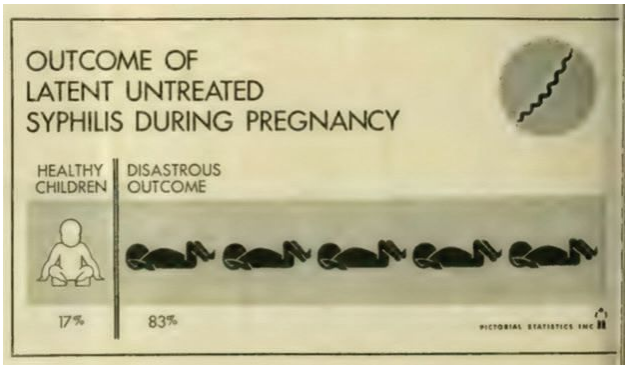


Figure 3. Graphic representation of outcome of infants born with congenital syphilis in the early 20th century, from Thomas Parran, "The Next Great Plague to Go" in Survey Graphic, July 1936.

Syphilologist, Dr. Dennie voiced disappointment that following the success of treatment with penicillin, the disease pathology wasn't being adequately taught in medical school and history and physical examination skills were lost. He concluded his speech predicting that even with the widespread use of penicillin, "It will always be a serious problem in medicine."[14]

Syphilis in the 21st Century

Seventy-five years later Dr. Dennie's prediction from The Dying Syphilologist speech is relevant. Incidence and prevalence of syphilis began climbing in the 2000s and the CDC's elimination strategic plan officially ended in December 2013.[13] As syphilis rates rose, congenital syphilis rates followed mirroring increase among women of reproductive age.[1] Coincidentally, this occurred when the CDC's total budget was cut from $7 billion in 2005 to $5.98 billion in 2013.[13] History has revealed that penicillin treatment alone, although still effective against syphilis, must be part of a comprehensive ongoing public health program.

Although Dr. Parran's legacy has been tarnished by his leadership during the Tuskegee syphilis study, the public health principles instituted by him in the 1930s remain relevant. Rather than officially end, Dr. Parran's campaign faded through budget cuts and reallocations to other programs when penicillin treatment was successful. Thus, the historical record informs that surveillance funding remains critical in preventing the silent community spread of the disease.

With the alarming increase in congenital syphilis, Dr. Williams's conclusions in 1914 on the importance of prenatal care and testing of stillborns, infant deaths, and symptomatic newborns apply today. Medical education should continue to promote the skills needed to suspect this historical "great imitator."

In 2023, the CDC termed the rise in congenital syphilis as an epidemic in babies.[15] All physicians involved in the care of women, infants, and children in the 21st century, now as much as in the past, are on the frontlines in prevention and treatment.

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Food Dating: What Does it Really Mean?



by Lauren Landfried, PhD, Jess Watson, PhD, Maggie McCoy, M.Ed & Anna Chott

Introduction

It is estimated that 9.9 million people suffer from foodborne illnesses each year.[1] Therefore, food safety is crucial in maintaining public health. Food dating is one way to keep the public informed about the food they purchase. However, except for infant formula, the date on the food product is not usually indicative of the safety of the product.[2] Instead, the dating system was developed for grocers and retailers to know when the product is of the best quality for sales purposes.[2] These dates have created much confusion for the consumer, contributing to the 133 million pounds of food waste in the United States (US) each year.[3] It is important for consumers to understand the different terminologies to not only understand food safety but also reduce overall food waste.



Defining Food Dating

The United States Department of Agriculture (USDA) Food Safety Inspection Services (FSIS) regulates that the label on the package is true and does not mislead the consumer.[2] Except for infant formula, the date on the food label is not regulated to indicate food safety.[2] Manufacturers and retailers place the label on the food to indicate the time where the food is of the best quality.[2] It is important to note that there are time periods for perishable foods, but this dating can make consumers unsure of the safety when purchasing and discarding canned and other non-perishable food items.[2]

There are two types of product dating on food labels: "Open Dating" and "Closed Dating."[2] "Open Dating" is the date on food labels referring to best quality.[2] These dates are found on most foods including protein-rich foods like meat, poultry, egg, and dairy products.[2] "Closed Dating" refers to the date and

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Table 1. Common Food Dating Terminology [2]

Terminology	Definition
"Best if Used By/Before"	This is to notify best flavor and quality of product. It is not indicative of safety or when it should be purchased
"Sell-By"	This informs stores how long before discarding. It is not indicative of safety.
"Use-By"	This is when the last peak quality is determined for the food product. It is not indicative of safety (with the exception of infant formula).
"Freeze-By"	This is when the product should be frozen if not consumed. It is not indicative of safety or when it should be purchased.
"Packing/Manufacturing"	This is for manufacturers to track the product. Not related to quality or safety

time the item was produced.[2] These are typically on shelf-stable products.[2] Table 1 includes common food dating terms that might be found on a food label. However, there are many more differently phrased labels indicating the quality dates on packaged foods. Given the lack of consistency in date labeling, it is easy for consumers to become confused about the lifespan of the food product.

Last year, the state of California took steps to simplify the food expiration dates by removing the distinction of "Sell-By" dates and either use "Use-By" or "Best if Used By" and "Freeze By" with Assembly Bill 660.[4] This law, which takes effect on July 1, 2026, aims to remove the confusion surrounding safety concerns about the food product and hopefully reduce food waste.[4] Bills have been introduced nationally to address the same issues,[5] but nothing has been passed at the national level as of yet. Additionally, some states have very strict laws restricting food donated. In March, 2025, the Zero Food Waste Coalition (ZFWC) submitted a comment to the USDA's and Food and Drug Administration's (FDA) "Request for Information on Food Date Labeling" indicating the need to create standardized food date labels.[6] The ZFWC suggests this national standardization would alleviate consumer confusion, reducing food costs for businesses and consumers, and reducing overall food waste even in the instance of strict food regulations.[6]

Food Safety

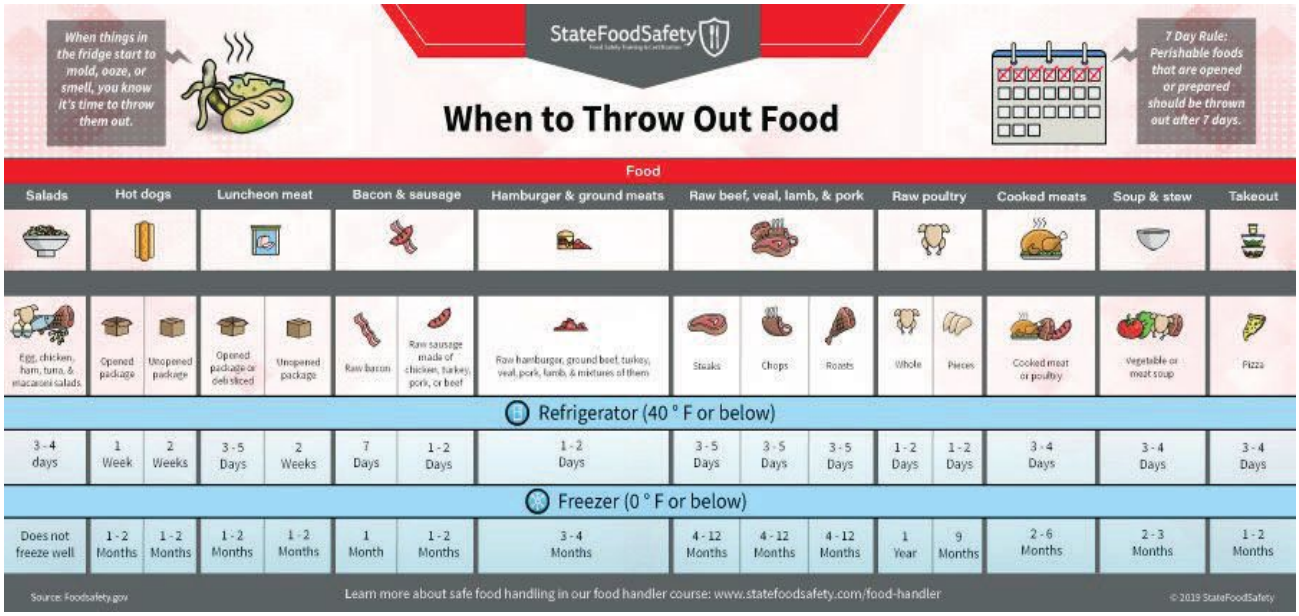
Food safety is very important. Given the millions of people suffering from foodborne illnesses each year,[1] it is important to understand when food is the safest to consume. People most susceptible to foodborne illnesses are elderly people, infants, and children, pregnant women, and people with diseases such as cancer and HIV/AIDS.[7] Many items contribute to the safety of food consumed, but the main factors can be attributed to the acronym FATTOM: food, acidity, time/temperature, oxygen presence, and moisture.[7]

Food dating on perishable foods is something to consider when assessing the safety of a food product. The FDA Food Code states that all foods that are opened and/or prepared should be thrown out within seven days.[8] Refrigerator temperatures should held be no higher than 40° F and freezer temperatures should be no higher than 0° F.[9] Some foods have a shorter length of time to be deemed safe for consumption, though. Infographic 1, created by StateFoodSafety, shows the time period for different perishable food items and leftovers to be considered safe before discarding.[10]

Food Dating's Contribution to Food Waste

While 13.5% of households in the US are deemed food insecure,[11] close to 40% of all food produced is sent to landfills,[12] costing approximately $338 billion each year.[13] It is estimated that 7% of the food waste can be attributed to food dating.[14] This is an alarming statistic given this food can still be safe for consumption.[2] The Natural Resources Defense Council (NRDC) estimates that recovering only 30% of food going to waste could meet the nutritional needs of those experiencing food insecurity in the US.[15] The USDA is working to reduce food waste and increase opportunities for food recovery efforts.[12] In particular, the "Good Samaritan Food Donation Act" was signed into law in 1996 to allow for grocers and food producers to donate items to non-profit organizations serving people in need of food.[16] However, the current food dating still adds confusion to whether the food is safe for donation. For instance, in Kentucky, all milk and dairy products are required to have a "use by"

Infographic 1. When To Throw Out Food



date on the packaging even though it is not indicative of whether the food is safe,[17] leading to further confusion on donation opportunities and possible legal implications for retailers trying to help people in need. The USDA has resources on their "Food Loss and Waste" page for producers and grocers to reduce food wasted and improve food security, economic growth, and environmental prosperity.[12] But, standardization of food labels will increase the opportunity to provide nutritious foods to the people who need it the most.

Conclusion

It would be ideal for a national standardization of terminology in diminishing confusion for safety and quality of food sold to consumers. The ZFWC suggests that there should be two different dates presented: one to indicate quality and one to indicate safety to reduce the confusion and increase food recovery opportunities.[6] In absence of the standardization, it is important that the consumer knows that food dating for all food items except for infant formula refers more to the quality of the food more so than the safety of the food.[2] Additionally, efforts to reduce food waste is important to reduce the overall waste as well as increase opportunities to serve people in need of food assistance.

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Link to state food safety website: https://www.statefoodsafety.com/Resources/Resources/when-to-throw-it-out-leftovers

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Shaping the Future: Why Physician Advocacy Matters for Patients, Physicians, and the Health System

by David O. Barbe, MD

Advocacy is medicine practiced on a broader scale—healing systems, not just symptoms.

At a Glance

- Physician advocacy is a professional and ethical imperative that improves patient care, physician practice experience, and the healthcare system.
- Engagement in policy reform helps ensure laws and regulations reflect clinical realities.
- Physician advocacy has influenced issues such as prior authorization reform, reimbursement models, workforce wellness, and public health.
- Advocacy is not extracurricular—think of it as medicine (in this case, healing a broken system) practiced on a broader scale.

The Case for Advocacy

Advocacy is not extracurricular; it is an extension of medicine's ethical duty.

The November/December issue of *Missouri Medicine* included the President's Forum, an article from MSMA's advocacy team, and the AMA report that all addressed various aspects of policy development and advocacy. It should go without saying that advocacy is critical to improving the health system for patients and physicians. Despite that, too many physicians either don't recognize the importance or just haven't found the right motivation to become involved in advocacy efforts at some level. This article is intended to address the importance of and encourage increased participation in healthcare advocacy.

Every practicing physician knows the frustration of working in a system that often impedes and impairs care. Prior authorization delays, coverage denials, and policy barriers too often define the patient and physician experience. Yet physicians hold the power to change these conditions. With that power comes an ethical duty to work to improve the system.

From expanding telehealth access during the pandemic to modernizing reimbursement policy, physician voices have been instrumental in shaping health reform that benefits both patients and physicians. Today, advocacy is not optional—it is central to the practice of medicine.



David O. Barbe, MD, MHA, is former president of the Missouri State Medical Association, the American Medical Association, and the World Medical Association. He is on the *Missouri Medicine* Editorial Board for Physician Advocacy. He practices Family Medicine at Missouri State University Care Clinic, in Springfield, Missouri, USA.



(L-R) Drs. Joe Corrado, Samer Cabbabe, David Barbe, and Edmond Cabbabe advocate for medicine during the annual Physician Advocacy Day at the Missouri Capitol.

What Physician Advocacy Means Today

Modern physician advocacy operates on multiple levels:

- Individual: Securing appropriate care for a specific patient.
- Institutional: Improving policies and practices within hospitals or practice groups.
- Health Policy-Level: Influencing legislation and regulations that define and improve health care access and experience for patients and physicians.

Because we see firsthand how laws affect care, physicians bring authenticity and data-driven credibility to policy debates. The American Medical Association defines advocacy as "the physician's duty to protect the health and rights of patients and communities."[1]

In other words, improving healthcare through advocacy is part of who we are as professionals, not an accessory to clinical work.

Engaging in Policy Is a Professional Imperative

When physicians engage, healthcare becomes more humane, equitable, and effective.

Physician advocacy stems from core medical ethics—beneficence, justice, and respect for persons. Our involvement in shaping healthcare policy helps ensure patient-centered care comes first. Healthcare, at its best, is both personal and systemic; improving one without the other is incomplete.

Policy engagement serves two overlapping missions:

- For patients: Advocating equitable access, affordability, and quality.
- For physicians: Protecting professional autonomy and building practice environments that support good medicine and economic sustainability.

Recent successes through organized advocacy on the part of physicians and our professional associations at the state and local levels underscore the importance. In the 2025 legislative session in Missouri alone, we achieved continuation of telehealth reimbursement, expanded GME funding, and additional loan repayment support.

Reforming prior authorization and reducing documentation burdens to reclaim clinical time is another area in which physician advocacy improves patient care and physician well-being.

A Powerful Case in Point

Physicians must help design the healthcare system, not merely endure it.

MSMA has successfully advanced laws limiting insurer delays in prior authorization. Physician testimony and persistent MSMA advocacy—anchored in examples of patient harm—proved decisive in persuading legislators. It demonstrates the best of advocacy: stories backed by evidence, delivered by trusted professionals. That is good for patients and good for physicians.

These outcomes occurred because informed physicians explained how real policies impact real patients. When the medical profession remains silent, those with less understanding of clinical consequence shape the rules that govern care.

Effective Advocacy is Built on Relationships

There are multiple channels for effective advocacy, but they are all based on relationships. The most direct and personal advocacy comes through developing a relationship with your state legislators. Look for or make opportunities to meet them at fundraisers and other events in your area. Legislators genuinely want to hear their constituents' opinions. Those contacts, coupled with campaign contributions, build a relationship that strengthens your impact when an important advocacy issue arises.

Relationships with your local medical society and MSMA are also important. Membership strengthens the association, making its organized advocacy efforts more effective. Contributions to the Missouri Medical Political Action Committee help support candidates and legislators that have been favorable to medicine's issues.

Barriers to Engagement—and How to Overcome Them

Even physicians who know the importance of advocacy often hesitate to participate. Common barriers include:

- Time pressure and burnout
- Limited familiarity with policy processes
- Institutional or administrative disincentives

Yet solutions exist. Joining professional associations such as the MSMA, AMA, and your specialty society (yes, you need to be members of all of them!) reduces the personal burden of engagement by leveraging organized resources and strategy. The MSMA, AMA, and some other societies now offer advocacy toolkits, policy briefings, and CME modules tailored for busy physicians.

Institutions also share responsibility. Hospitals and health systems should recognize advocacy as integral to professionalism, safeguarding time for participation and celebrating physician engagement as a sign of leadership. We need to work with relevant hospital and health system leadership to make it easier for physicians to participate in advocacy, especially on mutually beneficial policies.

Looking Forward: Building Advocacy into the Profession's Future

Sustained change requires nurturing advocacy skills in future generations. Medical schools and residency programs increasingly integrate coursework on health policy, advocacy, and leadership. Physician mentors play a crucial role in guiding students, residents, and young physicians to become involved in advocacy. Make an effort to include them in your metropolitan, county, and MSMA advocacy activities.

Meanwhile, technology is accelerating advocacy's reach. Virtual legislative visits, digital coalitions, and thoughtful use of social media allow physicians to shape debates more effectively than ever.

Ultimately, successful advocacy demands a culture shift: seeing systemic reform as an extension of patient care. When physicians bring the same rigor and compassion to policymaking that they bring to clinical medicine, the entire system improves.

Conclusion

Advocacy is medicine practiced on a broader scale—healing systems, not just symptoms.

Physicians remain the conscience of healthcare—witnesses to both its achievements and its inequities. Advocacy is the means by which that conscience acts.

Engaging in policy development and implementation protects patients, strengthens clinical practice, and ensures medicine retains its humane and evidence-based character. The choice facing the profession is simple: shape the system—or be shaped by it.

Whether by participating in MSMA/MAOPS Advocacy Day, national advocacy conferences, supporting individual candidates, or supporting legislative outreach through the MSMA, AMA, or other professional associations, every physician's involvement matters.

Your involvement matters! Be a part of shaping the change you want to see for your patients, your practice, and the health system. Advocacy is medicine practiced on a broader scale—healing systems, not just symptoms.

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Event Briefing via Zoom: Sunday, March 1 / 6:00 pm
Event: Tuesday, March 3, Millbottom Event Center, Jefferson City

WHAT'S THE AGENDA?

SUNDAY, MARCH 1

- 6:00 pm - Briefing via Zoom for Tuesday Event

TUESDAY, MARCH 3

- 7:30 am - Check-In Begins & Breakfast (Sponsored by JCMG)
- 8:00 am - Welcome & Housekeeping
- 8:05 am - Guest Speakers: Rep. Jon Patterson, MD & Rep. Gregg Bush
- 8:25 am - Group Photo at the Millbottom[#]
- 8:30 am - Shuttles to the Capitol begin
- 9:00 am - Noon - Legislative Appointments*
- Noon - 2:00 pm - Lunch with Dr. Sam Alexander at the Millbottom / Program: "Why It's Important for Physicians to Run for the Legislature"

Sam Alexander, MD, is an MSMA member and a candidate for senate district 28 (Bolivar) in 2026. A board-certified Emergency Room Physician for over 30 years, Dr. Alexander serves as a senior partner with the Emergency Physicians of Springfield, affiliated with Cox Health Systems. He earned his BA/MD from UMKC Medical School in 1982. Heavily involved in medical career outreach programs for over twenty-five years, Dr. Alexander has mentored medical students, residents, and first responders.

It is important that physicians support candidates that advocate on their behalf. Please consider a donation to Dr. Alexander's campaign. Make checks payable to "Sam Alexander for Missouri." Contributions will be collected during lunch.

[#]We realize that some will miss this due to early appointments.
**Drop in appointments: These are scheduled if the legislator was unavailable for a specific time slot. Staff can often pull the legislator off the floor during session to meet with you. If not, leave your card and leave-behind materials with staff, and offer your time if the legislator would like more information.*

HOW DO WE GET BRIEFED ON THE EVENT?

Attend the Physician Advocacy Day Briefing Session via Zoom, Sunday, March 1, at 6:00 pm, to learn about logistics and expectations for the March 3 event. Scan the QR code to register for the Briefing.

HOW DO WE FIND OUT MORE ABOUT OUR LEGISLATORS?

Who is your elected representative and senator? Is he/she a Republican or a Democrat? Does he/she serve on a key committee? What bills have they introduced? Scan the QR code to find out!

WHAT DO WE PASS OUT TO OUR LEGISLATORS?

Bring your business cards so you can write a note on the back and leave them with legislators, aides, or staff. The MSMA/MAOPS team will supply you with agendas, House and Senate rosters, Capitol maps, issues and talking points, leave-behind materials, and more!

WHERE DO WE MEET? WHERE DO WE PARK?

Physician Advocacy Day will start at the Millbottom Event Center, just down the hill from the Capitol in an all-brick building on the Missouri River side along West Main. Parking is free and on the river side of the building. Additional free parking is available across the street in the Missouri State Parking Lot. You can walk up to the Capitol or you can take the trolley. Plug address into your GPS/Maps App: 400 West Main Street, Jefferson City 65101 Or scan QR code.

NOTE: Please park in a designated parking space so the trolley can maneuver in the lot.

CONTACTS: Brian Bowles: brianb@maops.org Cheri Martin: cmartin@msma.org

MSMA advocate
Missouri State Medical Association

Effective, Advocacy Communications with Legislators

As a representative of the medical community and as a citizen, you have an opportunity to establish effective communications with your lawmakers. Your contacts can and will have an impact on the outcome of certain bills of importance to the medical profession and to your patients. While the personal visit is the single most effective lobbying technique, you can communicate with legislators also by telephone or in writing (letter, email, or text).

As a physician or physician-in-training, ***only you*** can give your federal and state legislators the most accurate picture about how the issues really affect you and your patients. Questions? Email MSMA at advocacy@msma.org.

Who is Your Representative?

Who is your elected representative? Is your representative a Republican or a Democrat? Liberal, Moderate or Conservative? Does he/she serve on a key committee?

Build a Relationship

Making contact repeatedly and being credible and reasonable every time will help build a relationship between you and your representative.

Act Locally

Every representative has a district office and most hold local meetings. Meeting with your representative and/or local staff member is a great way to communicate your concerns.

Where to Start

Start with a letter or telephone call with your elected leader before making your actual visit.

One Issue at a Time

Every communication (telephone, written, or personal visit) should stick to one issue. Do not present a laundry list of concerns. Pick the most vital and explore it in depth.

Present Your Opinion with Facts

Use background information, including statistics and studies that support your point of view.

Use Personal Anecdotes

Nothing drives home the importance of the issue like a personal story.

Offer Solutions

Don't just talk about how bad a problem is. Communicate to your representative what you'd like to see done to fix it.

Attitude Counts

Be reasonable. Don't ask the impossible. Be courteous and respectful in all communications. Be constructive.

Timing

It is better to reach lawmakers early in the debate than after they have made up their minds.

Follow Up

Be polite and persistent by following up with a thank-you letter no matter what form your communications take.

Scan code to read more about effective, advocacy communications with your lawmakers

A Crossroad for Physician-Led Care in Missouri

by Jacob Scott, MA

With the initiation of the federal Rural Health Transformation Project (RHTP) policymakers in Jefferson City face a consequential decision this legislative session that will shape the future of healthcare delivery in Missouri. They can pursue a proven, patient-centered path grounded in physician-led care, or they can follow a route that substitutes training and experience with expanded scope-of-practice for mid-level healthcare professionals, injecting unnecessary risk and uncertainty for patients and the healthcare system.

We remain optimistic that Missouri lawmakers will choose the right path when it comes to expending new federal funds for rural healthcare, but some caution is warranted. The announcement that Missouri has been awarded more than $216 million in first-year funding through the newly created RHTP is encouraging. Rural communities across the state face persistent challenges related to access, workforce shortages, and health outcomes. This investment presents a meaningful opportunity if implemented thoughtfully. MSMA appreciates the work of the Governor and his administration in securing these funds through a competitive federal process.

At the same time, optimism must be paired with realism. While the RHTP award represents a significant influx of resources, Missouri is expected to face reductions in Medicaid funding in future years. Against that backdrop, it is critical that these new dollars are used strategically to strengthen access to physician-led care, rather than being consumed by administrative growth or short-term initiatives that fail to address long-standing challenges.

Physicians are central to improving access and quality of care in rural Missouri, yet there is no guarantee that RHTP funds will be directed toward recruiting, retaining, and sustaining the physician workforce. MSMA is concerned that without intentional policy choices and meaningful physician involvement, these resources may not support the independent and community-based medical practices that form the backbone of rural healthcare delivery.

There are proven reforms Missouri can pursue to make rural practice more attractive and sustainable for physicians. These include expanding loan forgiveness and scholarship programs tied to rural service, implementing insurance reforms such as prior authorization "gold carding," creating incentive-based payment models for rural practice, and investing in telehealth infrastructure that enhances physician-led care rather than replacing it. When implemented correctly, these reforms would improve retention, access, and continuity of care for patients.

MSMA looks forward to working with the Governor, the Department of Social Services, and other stakeholders as the RHTP program moves from planning to implementation. With a deliberate focus on physician-led care and workforce sustainability, this funding can meaningfully improve access and outcomes for rural Missourians. Without that focus, however, the opportunity risks falling short of its promise at a time when rural healthcare can least afford it. **MM**



Jacob Scott, MA, is MSMA Director of Legislative Affairs.

Dr. Biggers Goes to the White House

by Brian Biggers, MD

The health of our patients is above politics.

It is remarkable how your life can change in a single week. Recently, as I was planning for a usual week, I got a phone call asking If I would be interested in going to the White House. The answer was obvious—yes, of course.

Rest assured this is not a political post. I was invited to represent Missouri in discussions on the Rural Health Transformation Program and to learn about potential new legislation aimed at reducing drug prices and improving insurance options for our patients. I gladly accepted the invitation. I did not go as a Republican or as a Democrat, but as a physician who wanted to be a voice for our state and our patients.

So, what is the Rural Health Transformation Program and how will it affect Missouri? The state of Missouri ranks tenth on the benefit of this program. This is a landmark $50 billion investment by the federal government to reshape healthcare in rural communities. Data shows health outcomes can be determined by your zip code. Missouri was awarded $216 million for the first year and projected to receive $1 billion over five years. I grew up in a small rural community and more specifically on a dairy farm. I appreciate from both personal and professional experience how this investment will improve health outcomes for our state.



Drs. George Hruza and Brian Biggers at the White House, Washington, DC.

The second part of the roundtable discussion focused on how to lower drug pricing and the cost of insurance for Americans. This seems like common sense and an improvement for American families. This issue is brought into the political discussion, but the reality is that this should be a priority regardless of political party. Recently the federal government has reached a deal with 16 pharmaceutical companies to lower drug pricing. The savings will be passed on the Medicaid program and to self-paying patients.

I went into organized medicine to be the voice of patients for the state of Missouri. An invitation to the White House is a once in a lifetime opportunity regardless of your political affiliation. A chance to be the voice for the voiceless. The health of our patients is above politics. **MM**



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

Partner in Healing: Our Lives Together in Medicine

by Kathy Perryman, MD

Thank you to everyone who touched Chris's and my lives in such profound and positive ways over the years.

John Christopher "Chris" Perryman, MD, and I met in 1976 at Saint Luke's Hospital Kansas City. Then, I was Kathy Dowell, RN. He was an internal medicine intern and I was an intensive care RN. We got to know each other at social gatherings with our medical resident and nurse friends. As we talked, our understanding of one another was augmented by our similar backgrounds. We both came from broken homes, supported ourselves financially, and persisted in pursuing our educations. Chris grew up in Wichita, Kansas and had a tumultuous childhood ultimately leading him to be placed in foster care. He was an excellent student, however, and his academic achievements gained him a full ride scholarship to Yale. He graduated from Yale with a degree in biology in 1972 and was accepted into medical school at the University of Kansas (KU). He then entered his internal medicine residency at St. Luke's Kansas City.

I grew up in a small town in Illinois and was raised by my grandparents until high school when I was moved to my mother and stepfather's home. We relocated two more times, I attended three high schools, finally graduating from Ruskin High School in south Kansas City. I wanted to go to college, but I was told that "girls don't need to go to college." I got a modest scholarship and attended the Saint Luke's Hospital School of Nursing in Kansas City. While working as an ICU nurse, I admired the skillset and medical knowledge of physicians. The idea of going to medical school myself started to seem like a real possibility, something I had never before dreamed could happen to me. However, I had a nursing school diploma, not a bachelor's degree. Advisors suggested that I could gain more skills and advance my knowledge base by becoming a nurse anesthetist. I did some research and decided to proceed.



Kathy Perryman, RN
Saint Luke's Hospital
School of Nursing in
Kansas City—Class of 1973

In 1977, just before Chris and I started dating, I was accepted to the KU Nurse Anesthesia Program. We married in 1977 during my winter semester break. I then finished my bachelor's degree at the KU Nurse Anesthesia program and accepted a job at Research Medical Center with Anesthesia Associates of Kansas City (AAKC) as a Certified Registered Nurse Anesthetist (CRNA), where I worked from 1979-1982.

In the role of CRNA, I really enjoyed caring for patients and working with a wonderful medical team. Over time, I appreciated the differences between my education and training and that of my

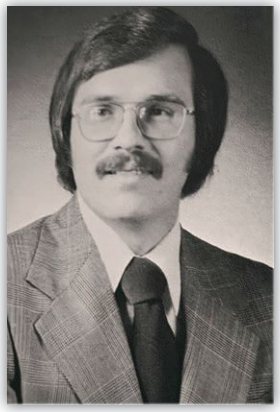




John C. "Chris" Perryman, MD, (deceased) was an Internal Medicine Specialist at Saint Luke's Hospital in Kansas City. He held many leadership positions in professional organizations and within his hospital system, including Senior Vice President and Chief Medical Officer of Saint Luke's Health System. **Kathy M. Perryman, MD**, is a retired pediatric anesthesiologist, and former department chair and President of the Medical Staff at Children's Mercy Hospital, Kansas City. She is a past-president of the Missouri Society of Anesthesiologists and served on the Editorial Board of *Missouri Medicine*.



Kathy M. Perryman, MD
University of Missouri-Kansas City School of Medicine—Class of 1986



John C. Perryman, MD
University of Kansas School of Medicine
Class of 1972

husband, my physician colleagues, anesthesiologists, and surgeons. I wanted a deeper understanding of complex physiology and disease processes so that I could diagnose and treat patients myself. I wanted to be qualified to do the most difficult cases on the sickest patients and keep them safe. I discussed this with Chris and my supervising anesthesiologists; I was encouraged to keep advancing. I applied and was accepted into the University of Missouri-Kansas City (UMKC) School of Medicine as an advanced standing student in 1982 and I graduated in 1986. I thought I would change specialties after medical school, but realized that I loved the physiology, pharmacology, anatomy, and procedures, especially advanced airway management, which are integral to anesthesiology, particularly pediatric anesthesiology. As we are all taught, children are not small adults and have unique age-related differences in their anatomy and physiology. Chris was incredibly supportive through those years of intense study and hard work. During my last two years of medical school, we started a family, adopting two lovely baby girls, nine months apart.

In medical school, I had the good fortune to be awarded the Humanitarianism in Medicine Award and the American Medical Women's Association Scholarship Award. I was also invited to join the Alpha Omega Alpha Honor Society. Then I completed my anesthesiology residency at Saint Luke's Hospital in Kansas City and my pediatric anesthesiology fellowship at Denver Children's Hospital. Our daughters lived with me in Denver and Chris, bless him, flew out to Denver every other weekend. What a year!

In 1979, Chris graduated from his internal medicine residency and joined Bill Dixon, MD's practice at St. Luke's. He also joined the teaching faculty at the University of Missouri-Kansas City School of Medicine and the Internal Medicine Residency. He became a Clinical Associate Professor at the UMKC School of Medicine and served for over 30 years on the internal medicine residency curriculum committee. He worked in his office practice and on the inpatient team. He greatly enjoyed and excelled at teaching internal medicine residents and medical students. He was a mentor to many.

Chris took his involvement in medical staff governance very seriously and became the Chair of the Department of Medicine at Saint Luke's from 1988-1992. In 1992, he joined Saint Luke's full time and became a founding member of the new Saint Luke's Primary Care-Plaza. He was on multiple committees, such as Bylaws, Credentials, Steering, Performance Improvement, Primary Care Development, and Metropolitan Ambulatory Care Development Committees. He continued his work on hospital and medical society committees, and he served as Saint Luke's Medical Staff Treasurer, Secretary, Vice-President, President-Elect, and President through the 1990s to 2000.

Chris was also an active member of many professional organizations, such as the Missouri Society of Internal Medicine, the Missouri State Medical Association, the American College of Physicians (ACP), and many others. In 1995, he was awarded the Young Internist of the Year by the Missouri Society of Internal Medicine. He was active in the ACP since his residency and earned Fellowship status in 1997. In 2010, he received the Laureate Award from the Missouri Chapter the ACP; in 2011, he was the Vice President Missouri Chapter ACP.

Chris served on the Saint Luke's Health System Board for many years and, in 2018, became the Senior Vice President and Chief Medical Officer of Saint Luke's Health System. As noted by then CEO of Saint Luke's Health System, Melinda L. Estes, MD, Chris strongly believed that being on the front lines of patient care was key to being an effective advocate on issues that affect patient care. Therefore, he accepted the CMO and Senior Vice President positions on the condition that he could maintain his clinical practice and divide his time between his practice and administrative work. Chris understood the importance of being deeply involved in his practice, the hospital,

and professional organizations and the impact they all have on patient safety and quality care.

While Chris was practicing full time and serving as Chair of the Department of Medicine, I began my pediatric anesthesiology career in 1990 when I joined the group that I had worked for previously as a CRNA. In the early 1980s, Children's Mercy Hospital asked AAKC to provide pediatric anesthesia because of the specialized training of an AAKC physician, Robert Binda, MD. When I joined AAKC in 1990, there were only six operating rooms at Children's Mercy, so I divided my work between Research Medical Center (RMC) and Children's Mercy. Children's Mercy continued to grow. Soon I was practicing there exclusively. It was during those early years that Chris and I had our twins!



Celebrating the holidays–Perryman family photo with husband, Chris, and children, Katie, Max, Mollie, and Natalie at their home in 2012.

I had so many wonderful opportunities to help grow and develop programs at Children's Mercy. I established departmental practice guidelines to initiate out of the OR anesthesia and guidelines for sedation/anesthesia in the MRI suite. I had been trained in the safety aspects of delivering anesthetics in an MRI suite in my fellowship and Children's Mercy began utilizing the MRI in the 1990s, so our department chair, Jim Glenski, MD, asked me to lead that initiative. I established departmental practice guidelines for laser safety and served as the Laser Safety Officer from 1996 until I retired. I collaborated with the operating room nursing leadership to open a Pre-Admission Testing Clinic. I participated in research projects and wrote a collaborative chapter on pediatric anesthesiology in a pediatric surgery textbook. I was active in clinical and didactic teaching of anesthesiology residents and fellows, student nurse anesthetists, and student anesthesiologist assistants. Academic appointments included Associate Professor in Pediatric Anesthesiology at UMKC and a Clinical Assistant Professor at the Department of Anesthesiology at KU. I practiced pediatric cardiac anesthesiology at Children's Mercy for 30 years. The advancement of procedures for children with congenital heart disease over those decades made my practice incredibly interesting and satisfying.

Like Chris, as I learned about department and hospital policies, I became involved in medical staff committees and attended educational meetings to learn about medical staff responsibilities. That was incredibly helpful as Chair of the Credentials Committee. I became the Anesthesiologist-in-Chief in 2001 and served two terms before becoming involved in general medical staff leadership. I had the pleasure of serving as Secretary-Treasurer, President-elect, and President of the Medical Staff at Children's Mercy Hospital from 2011-2016. In 2021, I received the Honorary Medical Staff Award.

I also became interested in professional leadership. Wonderful mentors got me involved in the Missouri Society of Anesthesiologists (MSA) and the American Society of Anesthesiologists (ASA). Barbara Bollier, MD, Sam Page, MD, Jim Gibbons, MD, and Don Arnold, MD, were among the many who encouraged me. I served as the President of MSA 2002-2003. I was also invited to serve on the *Missouri Medicine* Editorial Board as the Anesthesiology Editor in 2018. I held this honored position until my retirement. I have been serving on the Missouri State Medical Foundation Committee of MSMA for over 10 years. Throughout my career, I have been very active in these professional societies, especially in advocacy. I have testified numerous times at our state capitol since the 1990s to preserve physician-led care. In January 2025, I was a panelist at the national AMA's State Advocacy summit moderated by Rebekah Bernard, MD. The other two panelists were a Family Medicine physician and a



On October 27, 2022, a ceremony was held for the renaming of the Saint Luke's Internal Medicine Clinic to the Saint Luke's Perryman Primary Care Clinic. Family and colleagues attended. This was the clinic that Chris Perryman, MD, helped found in 1992.

nurse practitioner, who were also presenting numerous important facts to argue in favor of preserving physician-led care.

I am happy and grateful that I fulfilled my educational and career goals. My specialty of pediatric anesthesiology was challenging and required fast thinking, quick responses, and attention to detail. And it could be a lot of fun, too, especially helping children, playing with them, finding new ways to distract them and decrease their stress. What an incredible team: my anesthesiologist colleagues, surgeons, nurses, CRNAs, Certified Anesthesiologist Assistants, technicians, and other professionals working together to keep our patients safe. A life-saving championship team. I miss my teammates.

While we were pursuing so many aspects of our medical careers, we were also busy raising our family of four children: Natalie, Katie, Max, and Mollie. We took them on annual ski trips to Colorado and had the most wonderful adventures! As they each went on to their various colleges, we made a rule that when they did a study abroad semester, we had to visit them. That's how we managed to visit Switzerland, Australia, China, and Argentina. I highly recommend that rule!

In addition to having fun traveling, I decided to embrace music in my life about 10 years ago. I started taking bass guitar lessons and have been playing in a band for the past decade. I also got my old flute out and am currently playing in the Kansas City Flute Choir. I see many articles these days demonstrating the calming influence of music. Personally, I know it's true. Chris always came to these performances and embraced the joy, too!

Chris absolutely loved being a physician and caring for his patients. I still run into his patients who, when they hear the name Perryman, ask if I'm Dr. Perryman's widow. Then they go on to tell me how wonderful he was and what an impact he had on their and their family's health. He never wanted to retire, so he kept working as long as he could. Much to all our sorrow, he succumbed to amyloidosis after a short illness in 2022. We all miss him terribly. St. Luke's chose to honor his legacy by renaming the clinic that he helped found: The St. Luke's Perryman Primary Care Clinic. That was so kind and meant so much to all of his family.

Chris and I were so fortunate to have the careers and family lives that we cherished and to be married for 44 years. We were thrilled when our youngest daughter, Mollie, pursued a career in medicine. She earned her undergraduate degree at Tufts University, graduated from Kansas University School of Medicine, and has finished her residency in Otolaryngology-Head and Neck Surgery at KU. She completed a Laryngology Fellowship at the University of Alabama in Birmingham (UAB), where she has just started as faculty in the department of Otolaryngology-Head and Neck Surgery. Chris and I were so pleased with her passion for medicine and he would have been so proud to see what she has become. I know I am.

Now that I am retired from clinical practice, I plan to continue to stay active with MSA, MSMA, and ASA. I sincerely appreciate the opportunity to work with my colleagues in these organizations. I will also fill my time with making music, volunteering at non-profits, like FosterAdoptConnect, spending time with family and friends, and keeping myself active. So, I want to thank everyone who touched Chris's and my lives in such profound and positive ways over the years. You made a difference. **MM**

Correspondence

Massive Data Breech Predicted by Missouri Medicine Eventuates

Cyber attacks and the Dark Web were a featured article in the 2025 September/October *Missouri Medicine* issue (122)(5):359-365).

In October 2025, SimonMed Imaging was attacked by the Medusa ransomware group in one of the largest healthcare data breaches ever. Potentially harmful data was stolen for as many as 1.2 million patients. More than 200 GB of sensitive medical and financial data was exfiltrated.

The company quickly identified security vulnerabilities belatedly changed passwords, implemented two-factor authentication and enhanced endpoint security. This is a classic example of too little and too late. Your practice, your hospital, and you, personally, are at risk.

Review the *Missouri Medicine* article and expeditiously initiate the highest level of cyber-protection possible. As a country and as a profession we must make stopping these cyber-bandits a national imperative. It is an existential treat to Medicine, indeed all commerce.

Scan to read.

John C. Hagan III, MD
Editor Missouri Medicine
Kansas City, Missouri

Excessive Exercise Unenviable Victim of Irony

The pertinent and compelling first-person article[1] by Phillip R. Cohen, MD, in the 2025 November/December *Missouri Medicine* adds to the body of knowledge that reminds us that excessive long-distance running has the potential for unexpected consequences. We owe Dr. Cohen a debt of gratitude for his willingness to relate to us his personal account. His narrative is reminiscent of the many similarities that *Missouri Medicine*'s editor, John Hagan, MD, has revealed regarding his experiences as a long-distance runner.[2]

Dr. Cohen's narrative is an important cautionary tale. His article serves two purposes for health professionals. One purpose is to reinforce the need for physicians to be alert to the set of long-term side effects that their patients who are distance runners may be prone to. Secondly, it is a reminder to physicians who themselves are long-distance runners to take heed and avoid overdoing it (a tendency that doctors seem prone to). It is a real-world example that illustrates that when it comes to distance running, more is not necessarily better.

Regular aerobic exercise has been firmly established as a beneficial part of a healthy lifestyle. The desire to go beyond and create a "heart of titanium," that is, a marathon-capable cardiovascular system resistant to damage and enabling the runner to run for hours at a time, carries risk. Overuse exposes the distance runner to unforced and unanticipated harmful cardiovascular consequences.

An excessive pattern of exercise submits the runner to becoming the unenviable victim of irony, where the intended result, a marathon-capable cardiovascular system virtually impervious to damage, leads to the unintended result of cardiovascular impairment. It might be said that Mother Nature sometimes feels the need to remind us that our bodies are not designed to run for 26 miles straight. Dr. Cohen's reasoned plea for moderation is well-taken.

References

1. Cohen PR. Running-related silent atrial flutter presenting as a stroke: amarathoner's tale. Missouri Medicine. 2025;122(6):477-481.
2. Hagan JC III. Too much exercise? Here's the rundown. Missouri Medicine. 2024;121(3):180-183.

***Charles Lederer, MD**, Ophthalmology*
Prairie Village, Kansas

MM

In the News

Missouri Medicine Announces New Board Members

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



Joanne V. Loethen, MD, has been appointed a *Missouri Medicine* Contributing Editor and to the Publication Committee. Dr. Loethen has served as our specialty expert in Internal Medicine/Pediatrics. She is faculty at University Health in Kansas City and an Assistant Professor of Medicine at University of Missouri - Kansas City. She replaces **Amy Cabbabe, MD**, who is stepping down from the editorial board as she begins her term as President of the Missouri Society of Anesthesiologists. We thank Dr. Cabbabe for her exceptional service.



Jayaprabha LaFontaine, MD, MPH, FAPA, is the new Editorial Board member for Psychiatry. Dr. LaFontaine practices in Springfield, Missouri, and is board certified in adult, child and adolescent psychiatry. She replaces Amanda M. Kingston, MD, who moved her practice out of the state of Missouri. We thank Dr. Kingston for her service.

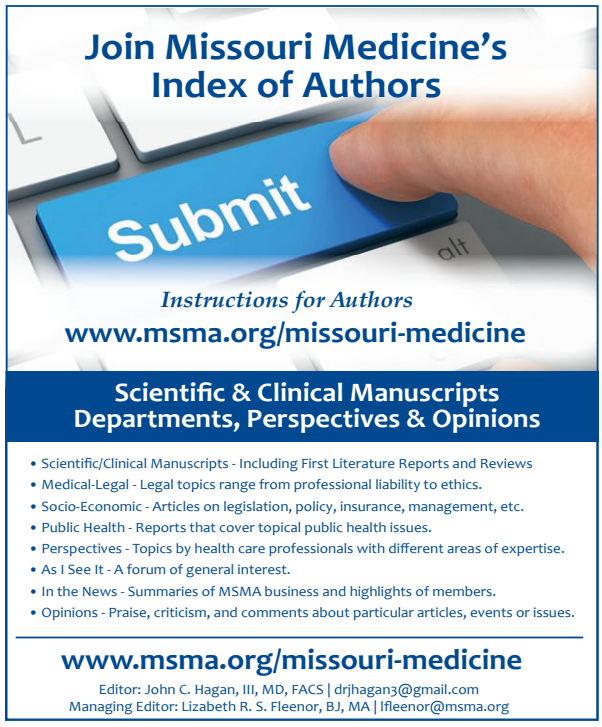


Paul Rottler, MD, FACS, is *Missouri Medicine*'s new Editorial Board member for Plastic Surgery. Dr. Rottler has over 25 years of experience in cosmetic surgery and reconstructive surgery in St. Louis, Missouri. *Missouri Medicine* thanks **Edmond Cabbabe, MD**, who served on the board for longer than any other physician.



Barbara A. White, DO, is the new Pediatrics Editorial Board member. Dr. White is a board certified pediatric physician at Hannibal Regional Hospital, Hannibal, Missouri, and sees patients in her Bowling Green, Missouri, office, as well. Dr. White replaces **April Tyus-Myles, MD**, who is stepping down as our Pediatric expert. *Missouri Medicine* thanks her for her service and for participating in our "Inspiring Lives and Careers" perspective which ran in the January/February 2024 issue of *Missouri Medicine*.

Missouri Medicine would like to thank **Katherine R. Lichtenberg, DO**, who served as Editorial Board member for Public Health for over a decade. We thank her for service and wish her well as she is moving her practice out of the state of Missouri. **MM**

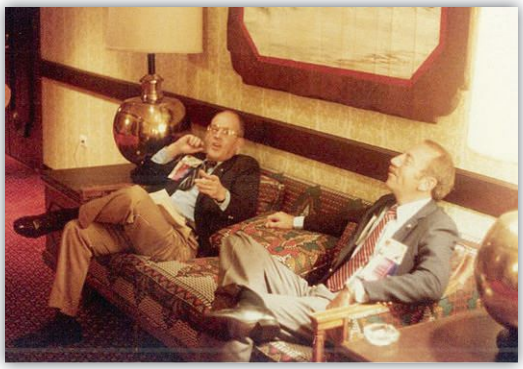


In Memoriam

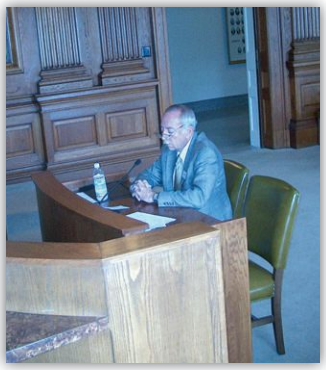
C.C. "Cork" Swarens

Former MSMA Executive Vice President August 17, 1939 - January 29, 2026









MSMA former EVP C.C. "Cork" Swarens, passed away peacefully on January 29 at age 86, surrounded by his loving family at his home in Jefferson City.

On June 1, 1972, Cork began a 38-year career at MSMA, serving first as Director of Public Relations, from 1972–1977, then as Executive Director and Chief Lobbyist, from 1977–1994. He succeeded Royal Cooper as Executive Vice President in 1995, and retired from MSMA in December 2010.

Throughout his association management career, he had worked as an MSMA administrator, communications and professional information director, as a liaison to state elected officials and state agencies. He staffed committees on legislative affairs, planning, constitution and bylaws, and public affairs.

Highlights of his executive career include the passage of the Patient Fairness Act, and Managed Care, Insurance and Tort Reform. He was also proud of the success of the Missouri State Medical Association Insurance Agency.

Cork came to the Association from the position of Managing Editor of the *Jefferson City News Tribune*. He joined that organization in 1963 as sports editor, was named city editor in 1967, and assumed his managing editorship in 1970.

A native of Jefferson City, he attended Lincoln University in Jefferson City, and received his Bachelor of Journalism degree in 1966. Our hearts and prayers go out to his wife of 68 years, Karen Swarens, who survives of the home, and their two sons, Jeff and Greg, and their families.





















MM

Washington University in St. Louis
School of Medicine

A History of Biostatistics and Data Science at Washington University School of Medicine

by Charles W. Goss, PhD & Daberru C. Rao, PhD

As we navigate the rapidly evolving landscape of biomedicine—from digital health data and artificial intelligence to precision medicine—our commitment to excellence in collaboration, innovation, and education ensures that WashU Medicine will remain at the forefront of data-driven biomedical research.

Biostatistics at Washington University School of Medicine has evolved from a modest component of pharmacology in the 1940s into a nationally recognized leader in quantitative biomedical research. In this perspective we trace the development of the biostatistics program from its early incorporation into medical education through the formal establishment of the Division of Biostatistics in 1966 and its subsequent expansion in scope and impact.

The Division's transformation into the Center for Biostatistics and Data Science (CBDS) marks a new era that integrates traditional biostatistics with modern data science, including machine learning and other advanced computational methods. Guided by three strategic pillars—team science and collaborative research, innovative methods, and education and training—CBDS continues to advance biomedical discovery through rigorous quantitative science. This historical reflection connects the early foundations to the questions and methods that define biostatistics and data science at Washington University today.

Key Words

Biostatistics, data science, clinical trials, team science, genetic epidemiology, Washington University.

Introduction

Biostatistics at Washington University School of Medicine (WashU Medicine) began as a minor component of the pharmacology program in the 1940s. It evolved into the Division of Biostatistics in 1966, ultimately becoming the internationally recognized Center for Biostatistics and Data Science (CBDS). The history and growth of CBDS exemplifies the transformation of biostatistics and data science from an afterthought to disciplines that are indispensable for advancing biomedical research.



Charles W. Goss, PhD, (pictured), and Daberru C. Rao, PhD, are at the Center for Biostatistics and Data Science, Institute for Informatics, Data Science, and Biostatistics, Washington University School of Medicine, St. Louis, Missouri, USA.

Early Foundations (1946-1966)

Before the official formation of the Division of Biostatistics, Washington University School of Medicine (WashU Medicine) saw the early development of biostatistical education within the Department of Pharmacology. Helen T. Graham, PhD, with the support of Carl F. Cori, PhD, the department's chairman, incorporated biostatistics into the medical student curriculum. In 1946, Mrs. Barbara Hixon from the Department of Mathematics joined Dr. Graham in developing and teaching biostatistics. Their innovative approach utilized students' own laboratory experiments to demonstrate statistical concepts, making the abstract principles more concrete. Oliver Lowry, PhD, succeeded Dr. Graham as Chair of the Department in 1947 and became a strong supporter of the program, helping to solidify its place in the curriculum.

The Department of Preventive Medicine and Public Health assumed responsibility for teaching biostatistics in 1948 when Robert E. Shank, MD, became head of the department. The 1950s brought about dramatic changes to the medical research landscape, marked by growing support from the National Institutes of Health (NIH) for research and training programs. This expansion created a growing need for expertise in experimental design, data analysis, and advanced biostatistical methods. The rapid advancement of computer technology during this time opened new frontiers for data design and analysis. Some departments within WashU Medicine started including their own consultants or faculty members with biostatistical and computational expertise. However, it became increasingly clear that a centralized biostatistics team was needed.

Establishment and Early Growth (1966-1979)

In 1966, with crucial support from Dean M. Kenton King and several funding agencies, the Division of Biostatistics was officially established within the Department of Preventive Medicine and Public Health. The Division established its physical home in the former Old Shriners' Children's Hospital building on South Euclid Avenue. This facility had previously served children with polio and orthopedic conditions before being acquired by Washington University for academic use.

The founding Biostatistics Director, Reimut Wette, PhD, was recruited from the University of Texas at Houston, where he served as Associate Biomathematician and Chief of the Section of Mathematical Biology. Dr. Wette brought valuable experience from his work as a biometrician at the M.D. Anderson Hospital and Tumor Institute in Houston. The nascent Division began modestly with Dr. Wette, Mrs. Barbara Hixon, a secretary, a student programmer, and a keypunch operator. Sung Choi, PhD, joined the faculty shortly after the Division's establishment, marking the beginning of its expansion.

As the first Director, Dr. Wette faced the challenge of establishing the Division's niche within the medical school community. His timing proved fortuitous, as Washington University was gaining prominence as a research-oriented institution, and federal funding increasingly required biostatistical components in research proposals. Dr. Wette's personal and professional interest in emerging computer technology led him to recruit faculty and staff with specialized skills in this area, positioning the Division at the forefront of computational statistics.

Expansion and Academic Development (1980-2000s)

In 1980, D. C. Rao, PhD, was recruited as the Division's second Director, bringing eight years of experience in population genetics and genetic epidemiology from his work with the world-renowned geneticist Dr. Newton E. Morton at the University of Hawaii in Honolulu.

Dr. Rao arrived with a mandate to develop a strong academic program. He emphasized the creation of in-house research programs and pursued the growth of clinical trials, data management, and genetic epidemiology. Growth in these areas was facilitated by the support and leadership of senior faculty members J. Philip Miller and Reimut Wette, as well as new faculty recruitment and increased NIH funding.

Under Dr. Rao's leadership, the Division established itself as a critical biostatistical resource for WashU Medicine and a center of excellence in genetic epidemiology. Biostatistical research in the division encompassed both the development of new methods for data analysis and modeling and the application of these methods to studies of complex disorders, such as coronary heart disease, obesity, hypertension, and psychiatric diseases.

Institutional Independence and Continued Growth

An important milestone occurred in 1987 when the Department of Preventive Medicine and Public Health was dissolved, and the Division of Biostatistics was granted independent status as a teaching and research division within the School of Medicine. This change reflected the Division's maturity and importance to the institution's mission.

Throughout the 1980s and 1990s, researchers in the Division secured increasing amounts of direct funding for their projects. Faculty members formed strong alliances with departments requiring biostatistical cores for their research. These biostatistical cores became integral to research projects spanning diverse areas, including AIDS, Duchenne Muscular Dystrophy, Alzheimer's Disease, cancer, cardiovascular disease, psychiatric disorders, and geriatrics. The Division's expertise also led to a number of large-scale NIH grants for coordinating multicenter studies.

Modern Era and Continued Excellence (2000s-2024)

To facilitate greater interaction with clinical research partners, the Division established a satellite location in Barnes-Jewish Hospital at the center of the Barnes-Jewish complex, enhancing collaboration with the Siteman Cancer Center and other Medical School departments.

The Division has seen remarkable growth over the years. From its founding in 1966 with seven employees, by 2006 it had expanded to more than 30 employees, including faculty with joint appointments in other departments. This growth reflected not just increased size but enhanced capability, with the Division earning international recognition for its research in biostatistics and genetic epidemiology.

Throughout the 2000s and 2010s, the Division continued to strengthen its core competencies in clinical trials, statistical methodology development, data coordinating centers, and biostatistical support services for the School of Medicine. Biostatistics faculty and staff members have been instrumental in advancing innovative statistical methods while maintaining the Division's tradition of collaborative excellence across all medical disciplines. In 2020, the Division was merged with the Institute for Informatics (I^2), forming the new Institute for Informatics, Data Science, and Biostatistics (I^2DB).

A New Chapter: Transformation to the Center for Biostatistics and Data Science (2024-2025)

In November 2024, Charles Goss, PhD, was appointed as the new Director, marking the beginning of an exciting transformation for the Division. Under his leadership, the Division has been rebranded as the Center for Biostatistics and Data Science (CBDS), reflecting both the evolving landscape of data science in medicine and the expanded scope of the unit's mission.

This rebranding signals the Center's evolution to meet the demands of modern biomedical research, where traditional biostatistics increasingly intersects with data science, machine learning, and advanced computational methods. Furthermore, as part of the I^2DB, CBDS is positioned at the nexus of Washington University's data science initiatives, strengthening its ability to drive innovation in quantitative biomedical research.

Future Directions: Three Pillars of Excellence

The Center for Biostatistics and Data Science stands at a pivotal point in its history, poised for marked growth and innovation. Our Vision is to strengthen and expand its capacity as the leading hub for biostatistical and data science research at WashU School of Medicine. As our core Mission is to provide expert biostatistical and data science research and support, we are committed to advancing biomedical research through collaboration, team science, and innovative biostatistical and data science methods.

The future of CBDS will be guided by a strategic initiative built upon three foundational pillars:

Pillar 1: Team Science and Collaborative Research

CBDS is expanding its role in strengthening biomedical research at WashU Medicine by deepening the integration of biostatistical and data science expertise into interdisciplinary research teams. We recognize that biostatistics and data science are critical to the success of biomedical research, and the most impactful advancements emerge from collaborative efforts. Building on our established collaborative foundation, we will continue to grow our impact through:

- Embedded faculty and staff within research teams across WashU Medicine, serving as integral partners from study conception through dissemination.

- Strategic partnerships with academic units and CBDS-led data and research coordination efforts to ensure rigorous design, analysis, and oversight of clinical and translational studies.
- Cross-disciplinary initiatives that bridge the full research continuum—from basic science through clinical trials to implementation in practice.
- Collaborative infrastructure development, including shared data resources and analytical platforms.
- Team-based approaches to grant development and manuscript preparation that elevate research quality and impact.

Pillar 2: Innovative Biostatistical and Data Science Methods Research

CBDS will continue to focus on methodological innovation, developing innovative biostatistical and data science approaches that address the unique challenges of modern biomedical research. To meet the evolving needs of modern biomedical research, CBDS is growing its methodological capabilities across several priority areas, including:

- Pragmatic and adaptive clinical trial designs to accelerate translation and uptake, leading to enhanced patient health outcomes.
- Causal inference methods that strengthen inferences from observational and quasi-experimental studies.
- Advanced machine learning techniques for precision medicine.
- Integration methods that combine multi-modal data (genomic, imaging, clinical, and digital health), yielding insights into disease mechanisms and outcomes.
- Artificial intelligence-driven statistical and data science methods that enhance prediction, discovery, and decision support across biomedical research.

By anchoring our methodological research in collaborative partnerships, CBDS faculty contribute statistical insights that advance both the science and practice of medicine.

Pillar 3: Education and Training

We recognize that the future of medical research depends on well-trained quantitative scientists, and CBDS is committed to comprehensive education and training initiatives:

- Our MS and PhD graduate programs in Biostatistics and Data Science prepare students to become leaders in the field, combining rigorous theoretical training with hands-on research experience.
- We offer training programs and workshops designed to enhance the analytic, programming, and data science skills both domestically and internationally.
- Through our embedded collaboration model, we provide real-time training to research teams, strengthening quantitative and analytic capacity across the institution.
- We partner with early-career investigators to provide mentorship in biostatistics, study design, and data analysis, strengthening the quality and impact of clinical research.

Moving Forward

These three pillars—Team Science and Collaboration, Innovative Methods, and Education and Training—work synergistically to realize our vision and mission, creating a feedback loop where collaborative challenges drive methodological innovation, new methods enhance our collaborative impact, and both inform our educational programs. This integrated approach positions CBDS as a research hub that accelerates discovery across the entire spectrum of biomedical research. As we navigate the rapidly evolving landscape of biomedicine—from digital health data and artificial intelligence to precision medicine—our commitment to excellence in collaboration, innovation, and education ensures that WashU Medicine will remain at the forefront of data-driven biomedical research. By maintaining rigorous statistical standards while integrating and advancing emerging quantitative methods, CBDS will continue its essential role in translating data into knowledge and knowledge into improved health outcomes well into the future.

Acknowledgments

We would like to thank Phil Miller, Bob Shank, Barbara Hixson, and Sam Guze for providing historical information regarding the inception and early history of biostatistics at WashU Medicine. Phil Miller also provided valuable insights and comments on this manuscript. **MM**

Advancing Decision Support Systems with Data, Informatics, and Learning Health Systems in a Post-Meaningful Use Era

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The confluence of three forces—the ubiquitous post-Meaningful Use clinical data, the structured rigor of the Define, Measure, Analyze, Improve, Control methodology, and the power of modern Artificial Intelligence—creates a critical opportunity.



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Abstract

The HITECH Act and Meaningful Use (MU) successfully drove widespread EHR adoption but largely missed the strategic goal of healthcare transformation. While EHRs are now ubiquitous, few institutions have transitioned to a true Learning Health System (LHS). To support achieving transformative impact, this article proposes an extension of a previously-described quality improvement life cycle model, aligning it with modern informatics and artificial intelligence (AI) capabilities. We detail how the stages of DMAIC (Define, Measure, Analyze, Improve, Control) provide the necessary structured framework for advancing decision support within a post-MU environment. We argue that by integrating AI-driven tools into each step of the DMAIC cycle, healthcare organizations can effectively leverage their vast stores of electronic clinical data. This structured approach offers a pathway to establishing agile, data-driven learning health systems necessary to fulfill the latent promise of health information technology.

Key Words

Meaningful use, learning health system, quality improvement, electronic health records, artificial intelligence.

Introduction

The passage of the Health Information Technology for Economic and Clinical Health (HITECH) Act in 2009, and its subsequent incentives under the Meaningful Use (MU) program was a significant governmental intervention in modern healthcare, especially in terms of health information technology.[1,2] Its most tangible result has been the dramatic increase in electronic health record (EHR) adoption among hospitals and eligible professionals.[3,4] Prior to MU, EHR use was fragmented; today, digital data capture is the norm. An effect of this result is the essential data infrastructure for a modern healthcare ecosystem.

However, reflecting on the full scope of MU's original legislative intent reveals a more complex picture. The program was designed not just for technology adoption, but as a mechanism to facilitate dramatic improvements in patient safety, health outcomes, and population health. The later stages of MU explicitly focused on functionalities like advanced Clinical Decision Support (CDS), patient engagement, and interoperability—with the intent that these necessary components could be used to transform care delivery. While the electronic clinical data now

exists in unprecedented volume, the use of this data for systematic, continuous quality improvement has not materialized at the scale or effectiveness envisioned.[5] The concept of a learning health system (LHS) emerged around the same time as the MU program, and fundamentally built from the expected availability of health data.[6] Research shows that while data capture is now common, other foundational LHS characteristics, such as a culture of rapid learning and aligned governance, also remain underdeveloped.[7]

The resulting gap—between data availability and data-driven transformation—is the central challenge for informatics in the post-MU era. While individual successes with data-driven improvement exist, the fundamental failure of the post-MU era is that we haven't established defined, standardized processes to convert data into dependable, bedside-applicable knowledge and ensure its regular, systemic use—a core objective of the program. This paper asserts that the conceptual foundation for closing this gap already exists, rooted in established quality improvement methodologies. By extending and modernizing the framework we have previously presented, which maps data use to a quality improvement life cycle,[8] and by integrating the emerging capabilities of Artificial Intelligence (AI), we can define a path for institutions to build effective LHSs and finally realize the transformative potential of their EHR investments.

From Optimization to Transformation: Embracing the Learning Health System

The pattern of institutional EHR adoption follows a predictable, yet insufficient, progression. Organizations first engage in Implementation, a phase characterized by configuration, data migration, and basic training to ensure go-live stability. This phase is directly coordinated with the EHR vendor, and delays due to additional configuration directly increase implementation costs. This is followed by Optimization, a necessary period where workflows are refined, efficiency is gained, and user satisfaction is incrementally improved.[9] For many institutions, the Optimization phase has become the de facto end goal, resulting in a system for charting and billing that ideally avoids physician burnout, but not necessarily for learning.[10]

This trajectory falls short of the true aims of high-value informatics and the motivations that launched the MU program. The most successful and influential healthcare systems that deployed EHRs prior to MU—often cited as models for the entire industry—did not just develop or configure systems to be useable and reduce burnout.[11] They viewed their clinical systems as fundamental tools for Transformation: fundamentally redesigning care processes, embedding best practices, and supporting continuous quality improvement initiatives. This goal of transformation is precisely the definition of a Learning Health System (LHS), as articulated by the National Academy of Medicine.[12] An LHS is not merely an EHR with data; it is a system where every patient encounter is an opportunity to generate new knowledge, and where that knowledge is rapidly and systematically incorporated back into clinical practice.[7]

The LHS concept is therefore the natural and necessary evolution beyond the compliance-driven goals of Meaningful Use. It represents a continuous feedback loop: Data to Knowledge to Practice to Data. This iterative cycle demands a structured, reproducible methodology for using clinical data that moves beyond ad-hoc querying and retrospective research. To achieve this, institutions must adopt a proven methodology for continuous improvement.

The Quality Improvement Life Cycle as the Foundation for a Learning Health System

The framework for leveraging data to support continuous improvement finds a direct analogue in established quality management methodologies, particularly Six Sigma's DMAIC cycle: Define, Measure, Analyze, Improve, Control.[13] As detailed by our previous work on clinical data warehouse architecture, this lifecycle provides a valuable and reliable blueprint for how data resources and tools should be applied as a project matures.[8]

The importance of mapping data requirements to the DMAIC steps is crucial for several reasons. Firstly, it ensures that resources—both technical and human—are appropriately deployed based on the project's maturity. Secondly, it imposes a discipline necessary for systematic improvement, preventing the premature deployment of interventions that are not well-defined or measured. Third, it recognizes the distinct stages of the improvement lifecycle, necessitating the transition to phase-specific tools, techniques, and approaches required to support them. Most importantly, the iterative nature of DMAIC perfectly aligns with the continuous, cyclic nature of a Learning Health System. Every time a project moves through the DMAIC stages, the system learns, implements change, and institutionalizes that change, ready to tackle the next opportunity for improvement.

In a post-Meaningful Use environment, where the technical challenge is no longer obtaining data but using it effectively, the DMAIC model serves as the informatics architecture for the LHS. The following sections detail

each step of the DMAIC process, examining the persistent data and informatics challenges and demonstrating how modern AI and predictive analytics can act as accelerators, helping to finally achieve the transformative goals that were only partially met by Meaningful Use.

DMAIC and the Advanced Decision Support System

The true power of the clinical data amassed through MU lies in its capacity to fuel a systematic quality improvement process. By integrating modern informatics tools, particularly AI, into the DMAIC framework, institutions can transition from simply storing data to actively learning from it.

Define: The Challenge of Data Access and Context

The Define stage is where the problem or opportunity for improvement is clearly articulated, and the relevant data and context are identified. While the move from paper records to EHRs has made data theoretically easier to query, practical limitations persist. Electronic data is a necessary but not sufficient condition for efficient querying. General purpose tools for data access (e.g., Epic's SlicerDicer)[14] are designed for broad access but often fall short when detailed, nuanced queries are needed to precisely define a clinical sub-population or an improvement opportunity. The complexity of the underlying clinical data model (CDM) remains a significant technical barrier for most front-line quality improvement staff.

A further complication is the vast amount of context-rich information locked within unstructured text—clinical notes, discharge summaries, and radiology reports. These narratives often hold the specific details necessary to establish the why and how of a problem, such as social determinants of health or the specific context of a referral, which are crucial for defining the scope of an intervention.[15]

Artificial Intelligence can revolutionize the Define stage. Large Language Models (LLMs) can be trained to help non-technical users formulate complex, precise SQL or query language statements by translating a natural language request into the correct data model logic.[16] More critically, natural language processing (NLP) tools are essential for transforming unstructured text into structured, retrievable concepts.[17] By deploying accessible data sources and robust data pipelines with NLP capabilities, institutions can move beyond simple demographic and lab data to define problems based on rich, contextual information previously only accessible through laborious chart review, thereby making the definition of the problem far more precise.

Measure: Operationalizing Metrics and Monitoring Performance

The Measure stage requires the consistent, repeated access to defined data to establish a baseline, track performance over time, and determine the success of future interventions. A key benefit of the MU program was the push for the adoption of electronic Clinical Quality Measures (eCQMs), standardizing how institutions track performance against benchmarks. However, successful quality improvement requires a greater degree of flexibility.[18] New or locally-defined metrics are often needed to monitor specific changes in a small population or a new workflow, a need that established eCQMs do not meet.

Once a metric is Defined, its regular monitoring requires a reporting infrastructure. While EHR adoption has often coincided with the adoption of tools for building reports, this frequently introduces a new technical barrier: the reporting tools themselves can be complex or run off different systems (e.g., data warehouses) than the operational EHR, creating bottlenecks and delays in generating performance reports.

AI can significantly accelerate the Measure phase by automating the conversion of defined metrics into functional, repeatable reports. AI-driven systems can automatically adapt defined query logic to different reporting environments, ensuring consistency across the various systems (EHR, data warehouse, dashboard).[19] More advanced systems can automatically detect significant shifts in performance, providing early warnings when a metric is drifting off course—a capability that moves the Measure stage from a reactive, retrospective report generation process to a proactive, real-time monitoring system. This institutional infrastructure must prioritize the development of tools that allow for the rapid development of flexible, custom reports based on the metrics identified in the Define phase.

Analyze: Deepening Understanding with Sub-Population Data

The Analyze stage is critical when initial improvement efforts fail to impact all patients equally, or when the magnitude of the improvement is less than expected. This stage focuses on understanding why the process is not working for specific groups. It usually involves deeper dives into data from specific sub-populations to identify factors—clinical, demographic, or operational—that

are contributory to poor performance.[20,21] Traditional analysis relies on manual statistical testing and domain expertise, a resource-intensive process that can limit the number of factors or sub-groups explored.

For a Learning Health System, the goal of Analyze is to turn observed variation into actionable insights that inform targeted interventions.[22] This requires identifying subtle, non-obvious factors that differentiate high and low performers, or those who benefit from an intervention versus those who do not.

The Analyze stage is an ideal stage for the application of Machine Learning (ML). ML models can rapidly and automatically analyze vast datasets to identify highly predictive factors associated with poor outcomes, that may not be apparent to analysts.[23,24] They can also be used to automatically and dynamically segment the patient population into sub-groups based on their risk profile or predicted response to an intervention. The challenge for institutions is not the availability of ML algorithms, but the creation of pipelines and platforms that allow for the rapid and ethical deployment of these models.[25] This rapid analysis capability is essential to the LHS, ensuring that feedback loops are measured in weeks or days, not months or years.

Improve: Transitioning Data into Actionable Insight

The Improve stage marks the first step where the insights derived from the data are translated into tools for clinical users. It is the transition point from purely analytical work to the creation of basic decision support. Here, the metrics and identified patient populations are integrated into workflows and presented to clinicians and care teams so that they can take action.[26] Common examples include clinical action lists, where a system displays patients overdue for a specific screening or lab test, or population health registries that identify individuals who need a proactive outreach (e.g., high-risk chronic disease patients).

AI tools can enhance the Improve stage by populating these action lists with more sophisticated intelligence. Instead of a simple rules-based query (e.g., "diabetic patients over 50"), the list can be prioritized using a predictive AI risk score from the Analyze stage (e.g., "the highest-risk diabetic patients most likely to be readmitted").[27] The key infrastructure improvement here is enabling flexibility in defining which metrics and which predictive indicators are displayed, and allowing the care team to customize the view to match their specific workflows and improvement goals.

Control: The Final Step of Integrated Clinical Decision Support

The Control stage represents the highest maturity level of decision support: the active intervention with the clinician at the point of decision-making. This is where the system intervenes to guide actions and ideally "make it easy to do the right thing" by integrating evidence-based recommendations directly into the clinical workflow.[28] As Kawamoto and others have shown, effective CDS must deliver the right information to the right person at the right time in the right format via the right channel.[29,30]

Since CDS at this stage is an active intervention, it carries the risk of alert fatigue and workflow disruption. Therefore, it is paramount that these methods undergo rigorous testing and vetting before system-wide implementation.[31] However, the rigor of the DMAIC process acts as a crucial pre-filter. A project that has successfully moved through Define, Measure, and Analyze—ensuring the problem is real, the metrics are accurate, and the targeted population is precise—is significantly less likely to produce low-value or disruptive CDS.

AI can be directly integrated into this stage to power highly contextual and non-intrusive CDS. For instance, an ML model (from the Analyze stage) predicting the risk of a complication can trigger an alert that is customized not only to the patient but also to the clinical context (e.g., a silent notification to a specialist versus a critical alert to a primary care physician). Furthermore, AI can be used to monitor the impact of the CDS intervention itself, automatically tracking clinician response and patient outcomes, and feeding that data back into the DMAIC cycle's Measure stage, thereby fully closing the LHS loop.[32] The Control stage institutionalizes the new practice and provides the final measure of whether the system is truly learning.

Conclusion

The Meaningful Use program fulfilled its mandate to digitize American healthcare, creating an electronic data infrastructure where data are consistently stored and processed in electronic form. However, this achievement has paradoxically exposed a critical gap: the chasm between data availability and systematic utility for care transformation. The widespread adoption of EHRs was merely the prerequisite for the true goal of the HITECH Act—the establishment of data-driven, continuously improving healthcare systems.

The Learning Health System (LHS) is a useful paradigm to complete this transformation. It requires organizations to move beyond the technical maturity of

implementation and optimization to embrace a process maturity model. By adopting and modernizing the DMAIC framework, healthcare institutions gain a structured, repeatable methodology for continuous quality improvement that perfectly aligns with the LHS cycle.

The confluence of three forces—the ubiquitous post-MU clinical data, the structured rigor of the DMAIC methodology, and the power of modern AI—creates a critical opportunity. AI can act as a powerful accelerator that overcomes the data access and analytical bottlenecks of each DMAIC stage. While we are not yet a nation of fully functional learning health systems, we hope that with the data, the process framework, and the technology we can achieve that vision. Applying these methods will finally allow us to create systems that are not just electronic, but transformative.

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Disclosure

No financial disclosures reported. During the preparation of this manuscript, the author used Gemini 3 Flash (Google) to assist in editing the document and conducting literature searches. Specifically, the tool was utilized to refine the clarity and structure of the prose and to identify relevant keywords and search queries for clinical and informatics databases. The author takes full responsibility for the integrity of the content generated by this tool and has verified all information, including references, to ensure accuracy and prevent the inclusion of biased or erroneous content. **MM**

Artificial Intelligence as a Catalyst for Quality, Safety, and Value in Healthcare Delivery

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When such AI solutions are integrated thoughtfully into value-based care frameworks, AI holds the promise of not only lowering costs but also improving outcomes, enhancing patient experience, and advancing the broader goals of precision health and population health management.



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Abstract

Artificial intelligence (AI) has the potential to transform healthcare by enhancing quality, improving safety, and increasing value. However, achieving these benefits requires navigating a complex interplay between data quality, interoperability, computability, workflow integration, and governance, as well as the need to create and sustain what have been described as learning health systems. The full promise of AI will only be realized through rigorous data stewardship, the design and demonstration of novel computational methods, cross-disciplinary collaboration, and a commitment to responsible and equitable technology implementation. Substantial work remains to address these challenges and capitalize on these opportunities, which can and should lead to significant improvements in human health and well-being.

Key Words

Biomedical informatics, artificial intelligence, healthcare transformation, healthcare policy, quality, safety.

Introduction

It can be argued that healthcare is entering a transformative era, where artificial intelligence (AI) is no longer a speculative idea but instead is becoming an operational reality. For this article and to contextualize the preceding statement, AI can be defined as:

"the capability of computer systems or algorithms to imitate intelligent human behavior"
(Source: Merriam-Webster Dictionary)

Across a spectrum from the use of natural language processing (NLP) to interpret unstructured clinical documentation to the use of predictive modeling of patient trajectories to the application of large language models to synthesize complex and multi-scale knowledge resources, AI offers an unprecedented opportunity to catalyze improvements in the quality, safety, and value of healthcare delivery.[1,2] Yet, these opportunities must be balanced with the need to implement AI technologies in a complex ecosystem, where fundamental questions regarding data quality, interoperability, computability, workflow integration, and governance remain. These challenges must be understood and addressed if we are to realize the

benefits of AI. To this end, in the remainder of this editorial, brief summaries of such challenges and associated opportunities for innovation and impact are provided.

Data Quality and Fitness for Use

First and foremost, AI models are only as reliable as the data on which they are trained and deployed. A recent systematic review of electronic health record (EHR) data quality assessment (DQA) methods highlights persistent variability and a lack of standardization in evaluating critical dimensions of structured clinical data quality, including completeness, correctness, plausibility, and concordance.[3] Despite decades of progress, there remains no broadly adopted DQA framework capable of addressing such concerns in a systematic and reproducible manner. As a result, we continue to see a proliferation of AI systems that amplify data imperfections or produce inaccurate results due to inadequate training or operational data. There remains a critical need for the creation and dissemination of accessible, efficient, and generalizable DQA methods that can render diverse, multi-scale clinical data "fit for use," particularly in the context of AI applications. Furthermore, the ability of such methods, if developed, to provide rigorous measures of potential sources of bias in datasets would be highly beneficial in terms of informing mitigation plans (e.g., bias cannot be mitigated if it is not first identified).

Unlocking Textual and Imaging Data

A significant proportion of the information necessary to inform clinical quality and safety improvement in healthcare resides in semi-structured or unstructured text, such as clinical notes. Similarly, high-value phenotypic data are often found in images produced by pathology, radiology, and other ancillary sources. Traditional rule-based or statistical natural language processing (NLP) pipelines have proven valuable in extracting computable features from textual assets; however, they often lack scalability and generalizability. Large language models (LLMs) are now demonstrating equivalent or superior performance when compared to more traditional NLP methods when extracting complex phenotypes from various types of clinical notes, while also requiring less time and customization to achieve such results.[4,5] Similarly, machine-learning-based approaches to image processing have been demonstrated to facilitate the extraction of computable features from various imaging modalities. However, they too suffer from concerns regarding scalability and generalizability.[4,5] Again, the use of emergent generative AI methods (GAI) is beginning to show promise in terms of enabling broader and less computationally intensive approaches to image processing and feature recognition. As these methods mature, they should help to render increasingly large amounts of unstructured and imaging data actionable in a manner that supports and enables downstream analysis, such as the use of AI. In effect, this is an example of how AI tools can facilitate the production of data that is needed for "downstream" analytical approaches (e.g., AI-enabled AI). As such techniques become more common and easy to use, they will allow the creation and use of AI tools that reason across scales of measurement and data in a manner consistent with the intrinsic complexity of human health and disease. Therefore, continued and intensive research is needed to develop, verify, and validate such methods, which are foundational to the future of AI in healthcare.

Translating Data into Evidence

The systematic conversion of "fit for use" and multi-scale clinical data into evidence that can inform care transformation is a persistent and consequential bottleneck.[6] Data streams captured across electronic health records, imaging systems, and complementary platforms, as described above, are often ambiguous, biased, or incomplete, reflecting variations in documentation practices, inconsistent coding, and gaps in longitudinal follow-up.[3,6] These limitations complicate efforts to generate reliable insights and risk amplifying existing inequities if left unaddressed. At the same time, they create opportunities for innovation. For example, AI methods can be explicitly designed to model uncertainty, reconcile

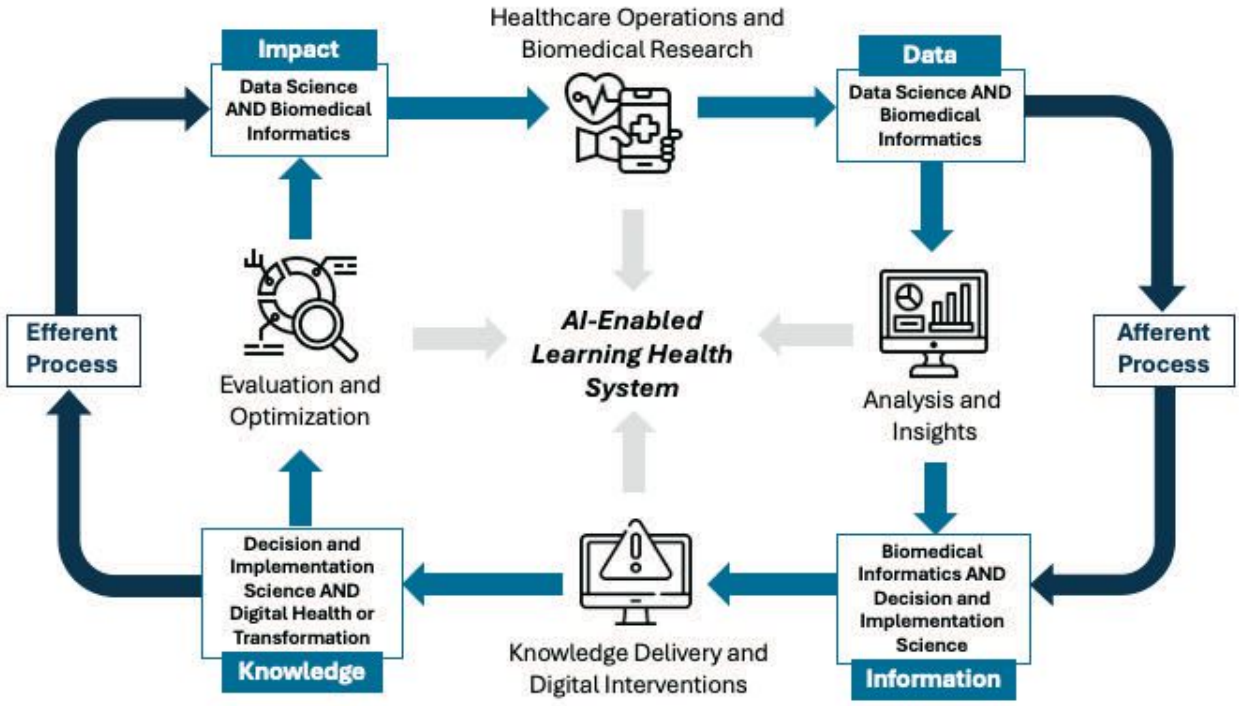


Figure 1. The role of AI and data science across the whole learning cycle, from data generation and analysis (afferent processes) to knowledge delivery, evaluation, and impact (efferent processes). This continuous feedback loop connects healthcare operations and biomedical research, ensuring that insights derived from data are transformed into digital interventions, evaluated for effectiveness, and reintegrated to optimize patient care and system performance.

discordant information, and surface patterns that are not readily apparent using more traditional methods. Similarly, computational learning techniques can quantify and mitigate biases that may exist through the analytic pipeline. At the same time, multi-modal data fusion approaches can enable cross-validation of phenotypes derived from structured, semi-structured, and unstructured sources. Further, temporal and trajectory-based data modeling can allow for the detection of subtle disease progression "trajectories" that are difficult to discern through alternative methods such as statistical modeling. These types of tools and techniques can open the door to robust real-world evidence generation, where data derived from learning health systems (as discussed shortly) is translated into evidence in a timely and efficient manner, and then disseminated via mechanisms that are responsive to diverse populations and aligned with emerging value-based care objectives. The challenge to doing so is that we must create computational solutions that can manage data quality and provenance at scale, while also developing and applying sociotechnical frameworks and constructs, such as governance, interoperability standards, and evaluation metrics, that collectively ensure AI-enabled insights are trustworthy, equitable, and actionable. This tension between data imperfection and methodological innovation may represent the most significant risk and the most significant promise for AI-enabled healthcare transformation.

AI and the Learning Health Systems

The tight coordination of AI development and deployment with healthcare IT (HIT) best practices is crucial for realizing the full transformative potential of such intelligent systems in healthcare. As health systems continue to generate unprecedented volumes and varieties of data, as introduced above, the challenge is no longer simply storing or transmitting this data, but instead converting it into models, tools, and insights that are both scientifically rigorous and operationally useful.

Three guiding axioms emerge based on these observations, namely that: 1) we should treat data as a renewable and continually enrichable resource; 2) we must ensure that the translation of algorithms and analytical products into actionable knowledge is a routine and expected outcome of the innovation enterprise; and 3) we must prioritize the rapid, responsible return of AI-driven insights to clinicians, patients, and other stakeholders.[7] These principles are part of a broader framework for building what is often referred to as a learning health system, where HIT and analytical capabilities support and enable continuous learning and improvement.[8] In this formulation, the learning health system serves as the effector arm of AI capabilities, aiming to enhance the quality, safety, and value of care, as discussed at the outset of this manuscript (Figure 1). Yet, the realization of an AI-enabled learning health system is not without intrinsic challenges. Critical and open questions remain, in addition to those noted above, such as how to align incentives across researchers, clinicians, patients, and policymakers; ensuring transparency and accountability in the design and deployment of technology; and building a workforce capable of bridging the gap between data science and healthcare delivery. However, much like the preceding examples, such challenges present powerful opportunities. By confronting them directly, we can pioneer new methods for equitable and explainable AI, design governance frameworks that balance innovation with safety, and foster collaborations that make continuous learning an operational norm rather than an aspirational goal. In this sense, building an AI-enabled learning health system is both a grand challenge and the culmination of applying AI "at scale" in the health and life science environment. It requires not only technical innovation but also cultural and organizational transformation. If these challenges are embraced as opportunities for discovery and reform, the result can and should be a resilient, adaptive healthcare ecosystem where AI continuously drives improvements in quality, safety, and value.

Discussion

Ensuring Safety and Equity in AI Deployment

Significant risks counterbalance the transformative potential of AI in healthcare. Models trained on biased, incomplete, or poorly curated data, as noted above, risk perpetuating existing inequities and even introducing new forms of harm. Insufficient transparency regarding process automation can erode clinician situational awareness, undermining trust and safety at the point of care. Furthermore, universal guidelines for evaluating the quality of AI inputs and outputs are underdeveloped, resulting in significant variability in model reliability and reporting across different healthcare systems and use cases. Equity concerns are particularly urgent; structured datasets often overrepresent advantaged populations while undercapturing the lived experiences of individuals from marginalized or underserved communities. This imbalance threatens to amplify disparities in diagnosis, treatment, and outcomes. To avoid these types of pitfalls, AI must be deliberately designed to incorporate socioeconomic, racial, and geographic diversity, with fairness and inclusivity treated as fundamental performance metrics rather than aspirational goals.[2,9]

Moving From Efficiency Gains to Care Transformation

AI's contribution to healthcare value has often been framed in terms of incremental efficiency gains, such as reducing administrative burden, optimizing scheduling, or automating routine documentation. While these improvements are essential, they represent only the beginning of AI's transformative potential. By enabling the real-time synthesis of multimodal data, as introduced here, AI can generate scalable, real-world evidence that supports both individual clinical decisions and population-level health management strategies. This capability opens

the door to care redesign, shifting from reactive treatment models to proactive approaches that anticipate disease progression, optimize resource allocation, and tailor interventions to the unique needs of individual patients. When such AI solutions are integrated thoughtfully into value-based care frameworks, AI holds the promise of not only lowering costs but also improving outcomes, enhancing patient experience, and advancing the broader goals of precision health and population health management.[1,2,4,10]

Challenges and Future Directions

Recognizing the significant benefits of AI in healthcare will necessitate addressing several inherent challenges. Standards for interoperability remain fragmented, limiting the ability to share and reuse models across health systems. Regulatory pathways for adaptive AI, tools that evolve as they encounter new data, are still in their infancy, raising challenging questions about evaluation, accountability, and approval processes. Equally pressing is the need to prepare the healthcare workforce, equipping clinicians, administrators, and data scientists with the knowledge and skills necessary to use AI responsibly and effectively. Transparency must also become a non-negotiable feature of AI systems, ensuring that models can be interrogated, explained, and trusted. Looking forward, several priorities stand out. Federated learning provides a pathway to build robust and generalizable models while maintaining data privacy. Emerging "AI assurance utilities" can provide ongoing, independent evaluation of model performance, safety, and bias. Finally, participatory design approaches, engaging clinicians, patients, and communities directly in the development process, can ensure that AI is not only technically sophisticated but also socially aligned, equitable, and sustainable.

Conclusion

In summary, the future of AI in healthcare hinges on our ability to strike a balance between innovation and responsibility, ensuring safety and equity, delivering value that extends beyond efficiency gains, and addressing the technical and sociotechnical challenges that remain. By embracing data as a renewable resource, prioritizing transparency and inclusivity, and embedding AI within a continuously learning health system, we can transform fragmented experiments into sustainable improvements in quality, safety, and value. The path forward requires not only technical breakthroughs but also governance, workforce readiness, and the active engagement of clinicians, patients, and communities. If these elements align, AI will not simply automate aspects of healthcare; it will help reimagine the way health systems learn, adapt, and deliver care for all populations, while ensuring the quality, safety, and value of that care are maintained at both the individual and community levels.

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Disclosure

No financial disclosures reported. Artificial intelligence, language models, machine learning, or similar technologies were not used in the conceptualization, study, research, preparation, or writing of this manuscript. **MM**

Trends and Determinants of Blood Pressure Control in US Hypertensive Patients: Insights from NHANES 1999–2021

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Although blood pressure control among US adults had steadily improved, recent data from the National Health and Nutrition Examination Survey suggest this positive trend has reversed.



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Abstract

This study analyzes trends and determinants of blood pressure control among hypertensive patients in the United States (US) using National Health and Nutrition Examination Survey NHANES data from 1999 to 2021. Blood pressure control rates improved through 2013 but declined thereafter. Applying machine learning methods such as XGBoost, we identify hypertension awareness and antihypertensive medication use as the strongest predictors of successful control. In contrast, resistant hypertension, chronic kidney disease, and elevated low-density lipoprotein (LDL) levels are associated with poorer control. The shift from JNC7 to JNC8 hypertension guidelines reclassified some individuals from uncontrolled to controlled, influencing observed trends. Additionally, a reduction in antihypertensive medication use among female patients may have contributed to the recent decline. These findings highlight the critical role of medication adherence and patient awareness in maintaining blood pressure control.

Key Words

Hypertension, Blood Pressure Control, Time Trend Analysis, Machine Learning.

Introduction

Controlling blood pressure is essential for reducing the risk of cardiovascular diseases (CVD), including stroke, heart attacks, and heart failure. Proper blood pressure management significantly lowers the health complications and healthcare costs related to hypertension.[1,2]

Although blood pressure (BP) control among US adults had steadily improved, recent data from the National Health and Nutrition Examination Survey (NHANES)—a nationally representative survey conducted continuously by the Centers for Disease Control and Prevention (CDC)—suggest this positive trend has reversed.[3,4] By assessing the health and nutritional status of the US population through interviews, physical examinations, and laboratory tests, NHANES provides reliable data for tracking trends in health conditions like hypertension.[4] For instance, an analysis of NHANES data by Jaeger (2023) reported that BP control among all hypertensive nonpregnant adults rose from 9.7% (1999–2000) to 25.0% (2013–2014), before declining to 21.9% (2017–2020).[3]

Earlier research using NHANES data identified several factors potentially linked to worsening BP control, including demographics, socioeconomic status, lifestyle behaviors, and medication adherence.[5,6,7] However, it remains unclear which of these factors, or potentially new ones, are specifically driving the recent trend reversal observed since 2014. This knowledge gap limits the ability to develop timely and effective public health strategies.

To address this concern, we use NHANES data from 1999–2021 to identify and quantify the factors contributing to the recent decline in blood pressure control among US adults. We aim to understand the mechanisms driving this trend to inform targeted interventions.

Methods

This study was a serial cross-sectional analysis of data from the US National Health and Nutrition Examination Survey (NHANES) spanning the survey cycles from 1999 to 2021. We accessed and processed the dataset using the R package 'cardioStatsUSA', which provides curated NHANES data suitable for cardiovascular research.[5] This package includes pre-processed data on survey design variables, demographic information, blood pressure measurements, hypertension status, and records of antihypertensive medication use and comorbidities. Detailed documentation on these variables is available at https://jhs-hwg.github.io/cardioStatsUSA/reference/nhanes_data.html.

Following the criteria of a recent key study in the field, our study population consisted of non-pregnant adults aged 18 years and older with hypertension.[5] The 2021–2023 NHANES survey cycle was not fully publicly available at the time of our analysis and was therefore excluded due to missing key variables.[8]

The primary outcome was BP control, defined as a binary variable. Participants were considered to have controlled BP if their systolic blood pressure was <130 mm Hg and their diastolic blood pressure was <80 mm Hg. Hypertension was defined according to the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines as a systolic BP ≥ 130 mm Hg, a diastolic BP ≥ 80 mm Hg, or self-reported use of antihypertensive medication. To identify a comprehensive set of potential risk factors, we merged the core dataset with NHANES laboratory data. These additional variables included lipid profiles, blood glucose levels, insulin resistance markers, kidney function tests (e.g., creatinine, albumin-to-creatinine ratio), electrolyte levels, and liver function tests.

All datasets were linked using the unique respondent sequence number provided by NHANES. A significant portion of the low-density lipoprotein (LDL) cholesterol data (~70%) was initially missing. We imputed missing LDL values for participants with triglyceride levels <400 mg/dL using the Friedewald formula, which reduced the overall missing rate for LDL to approximately 48%.[9]

All statistical analyses accounted for the complex, multistage probability sampling design of NHANES by applying the appropriate survey weights.

First, we performed descriptive analyses to characterize the demographic and clinical features of the study population. We also generated plots to visualize the temporal trends in BP control rates and the distributions of key covariates over the survey period.

Second, to robustly select a parsimonious set of important predictors from a large number of variables, we implemented an XGBoost machine learning model. The dataset was split into training (70%) and testing (30%) sets. The model was used solely as a feature selection tool based on variable importance scores ("gain importance"), rather than for its predictive performance, given the known class imbalance in the outcome (AUC = 0.87; F1 Score = 0.48). Variables with high importance scores, along with established clinical risk factors for hypertension, were selected for the subsequent regression analysis.

Finally, our primary analysis used a multivariable logistic regression model with the data pooled across all survey years. This model aimed to identify factors significantly associated with BP control and to estimate their average effect over the entire study period. To investigate the potential drivers of the observed decline in BP control over time, we subsequently examined the temporal trend plots of the key predictors identified in the regression model. This allowed us to assess how changes in the distributions of these factors may have contributed to the overall trend in BP control rates.

Results

Our analysis identified several key determinants of BP control. Feature importance analysis from the XGBoost model revealed that hypertension awareness (whether patients know of their condition), use

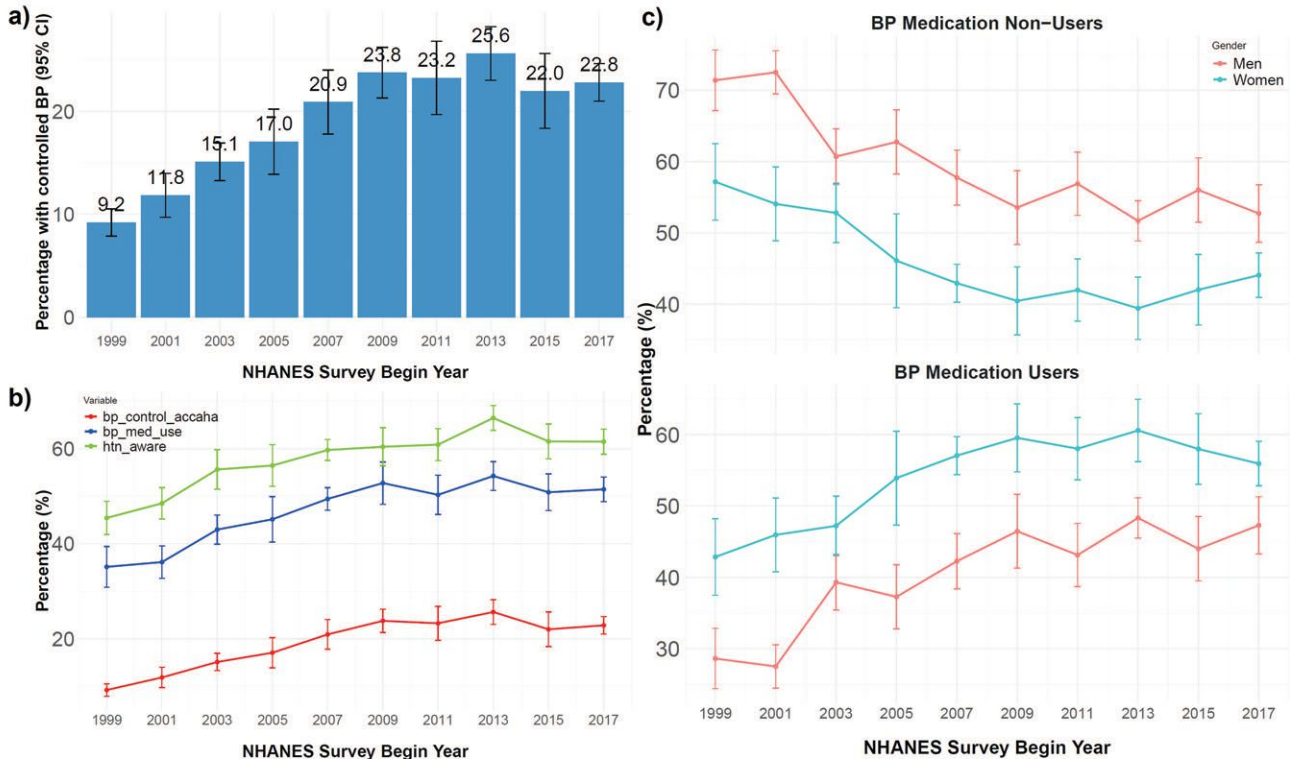


Figure 1. Represents core objective of study investigating the temporal trends in BP control.

of antihypertensive medication, and the presence of resistant hypertension were the most important predictors of BP control. Logistic regression analysis further confirmed these findings, indicating that hypertension awareness was the strongest single predictor of achieving BP control.

Several other factors also demonstrated a significant impact. Patients with resistant hypertension, chronic kidney disease (CKD), or LDL levels had significantly lower rates of BP control. Regarding demographic factors, Non-Hispanic White individuals and those from higher-income households exhibited better control rates.

In-depth analysis of specific subgroups revealed several noteworthy patterns. First, an interesting finding emerged concerning Body Mass Index (BMI). Although not a significant predictor in the overall model, stratified analysis revealed that normal-weight individuals (BMI < 25) had significantly lower hypertension awareness compared to their overweight or obese counterparts. This suggests that normal-weight individuals may constitute an underrecognized at-risk population, potentially overlooking blood pressure monitoring due to a perceived lower risk, and thus may require targeted screening and awareness interventions.

Second, we observed that older adults and patients with diabetes demonstrated better-than-anticipated BP control rates. This may be attributable to more frequent medical supervision and potentially higher treatment adherence within these groups. However, this finding should be interpreted with caution, given a baseline imbalance in hypertension awareness between diabetic and non-diabetic individuals.

The core objective of this study was to investigate the temporal trends in BP control. As shown in Figure 1a, the overall BP control rate among US adults with hypertension steadily increased from 1999, reaching a peak of approximately 25.6% around 2013. Subsequently, the BP control rate has shown a slight but persistent decline, a finding consistent with existing literature.[5]

Further analysis of the stratified trends provides critical insights into the drivers of this decline. Figure 1b clearly reveals that the overall trend is almost entirely driven by individuals who are aware of their hypertension and using antihypertensive medication, as their control rate curves closely mirror the overall

trend. In contrast, patients who remained undiagnosed or untreated had a consistently near-zero control rate throughout the entire study period. A more detailed examination of Figure 1c reveals a noteworthy shift in the gender distribution of medication users after 2013. Women made up the largest share of medication users around 2013, but this proportion fell through 2017. Conversely, among hypertensive individuals not taking medication, the proportion of women showed an increasing trend during the same period. This suggests that the post-2013 stagnation and decline in overall BP control may be disproportionately influenced by the changing medication use pattern among women. Taken together, the evidence strongly indicates that the recent decline in BP control in the US does not stem from a worsening situation among the undiagnosed, but rather from complex dynamics within the population already receiving treatment. This finding underscores that future interventions should move beyond general screening to focus on optimizing treatment effectiveness, potentially by addressing gender-specific patterns in medication adherence and persistence.

Discussion

In this comprehensive analysis of NHANES data from 1999-2021, we aimed to understand the drivers of the recent decline in BP control in the US. Our principal finding is that the decline observed after 2013 is primarily driven by changes occurring within the population of patients already aware of their hypertension and receiving treatment, rather than by a failure to diagnose new cases or a worsening among the untreated. The data consistently show that hypertension awareness and antihypertensive medication use are the most critical determinants of BP control, and the dynamics within this treated group appear central to the national trend reversal.

A compelling explanation for this trend reversal is the influence of evolving clinical guidelines, particularly the publication of the 2014 Joint National Committee (JNC) 8 guidelines. These guidelines raised the BP treatment threshold for adults aged ≥60 years to <150/90 mm Hg and relaxed targets for some patients with diabetes or chronic kidney disease.[8] This de-intensification of treatment goals may have had profound effects. For clinicians, it could have led to greater variability in prescribing practices and reduced follow-up for patients formerly considered uncontrolled.[10,11] For patients, especially older adults, the revised targets may have created a perception that their blood pressure was no longer a pressing concern, thereby reducing engagement and adherence. The temporal alignment is striking: the decline in BP control shown in our data began immediately following the widespread adoption of these more lenient standards, suggesting that they likely contributed to a reduction in both clinical vigilance and patient engagement, ultimately driving the population-level decline.

Beyond the overarching impact of guidelines, our study revealed crucial patterns within specific subgroups. Notably, we observed a significant gender-specific shift in medication use patterns post-2013. While the overall proportion of medication users remained stable, the proportion of these users who were women peaked around 2013 and subsequently declined. This suggests that the stagnation in overall BP control may be disproportionately influenced by changing medication adherence or prescribing patterns among women.

Furthermore, our analysis uncovered an "awareness paradox" among normal-weight individuals (BMI < 25), who, despite having hypertension, demonstrated significantly lower awareness rates compared to their overweight or obese counterparts. This highlights a potentially overlooked population that may require targeted screening and educational interventions precisely because they do not fit the typical risk profile.

The primary strength of this study is its use of a large, nationally representative dataset spanning over two decades, allowing for a robust analysis of population-level trends. However, our findings must be interpreted within the context of several limitations. First, the cross-sectional nature of NHANES data prevents the establishment of causality; we can only report strong associations. This is particularly relevant to our finding on gender-specific medication patterns. Because different individuals are sampled in each cycle, we cannot determine if the observed shift reflects individual women discontinuing therapy or sampling differences between survey waves. Longitudinal studies are required to confirm this trend at an individual level.

Second, despite our comprehensive analysis, there is a risk of residual confounding from unmeasured variables, such as health insurance status, lifestyle modifications, or physician attitudes. Finally, attributing population-level trends to a specific guideline change involves an element of ecological

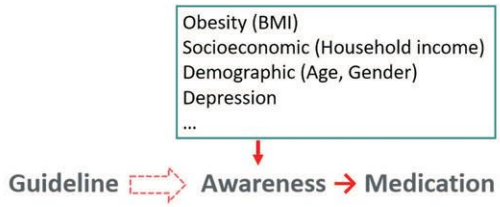


Figure 2. Schematic representation of key factors influencing BP control.

inference. While the temporal association is strong, we cannot definitively prove that the JNC 8 guidelines caused the decline in control for any single individual.

Despite these limitations, our findings have significant public health implications. The experience with the JNC 8 guidelines underscores the profound and rapid impact that clinical recommendations can have on population health outcomes. Our results suggest that reversing the decline in BP control requires a strategic shift. While broad awareness campaigns remain important, a critical focus must be placed on optimizing management within the population already under care. This includes reinforcing consistent, evidence-based treatment targets and developing strategies to address challenges like treatment inertia, medication adherence, and potential gender-specific barriers to care. Future research using longitudinal data is essential to disentangle population shifts from individual behavior changes and to design more effective, targeted interventions.

In conclusion, this study offers a new perspective on the post-2013 decline in BP control in the US. The reversal does not appear to be driven by a failure of diagnosis but rather by a complex interplay of factors affecting patients already engaged in the healthcare system. The publication of the 2014 JNC 8 guidelines likely precipitated this decline by lowering treatment intensity, with shifting medication use patterns among women potentially acting as a contributing factor. To regain momentum in the fight against hypertension, public health efforts must focus on optimizing care for the millions of Americans already diagnosed and treated.

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Acknowledgments

A presentation based on this content won the DataFest Contest at the 2025 International Biometric Society Eastern North American Region (ENAR) Conference.

Disclosure

No financial disclosures reported. Authors used ChatGPT (OpenAI; model gpt-4o-mini, version 2024-12-15) on July 31, 2025 to assist with language editing and stylistic polishing of the introduction and discussion sections. No AI tools were used for study design, data collection, statistical analysis, interpretation of results, or decision-making. **MM**

AI for Scientific Discovery in Omics Data-Driven Precision Medicine

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Abstract

In recent years, the rapid advancement of high-throughput technologies has led to the generation of vast and complex multi-omics datasets that are valuable for characterizing and understanding complex cell signaling network systems. On the other hand, large language models (LLMs), domain-specific foundation models (FMs) and AI agents, have achieved significant breakthroughs and have been revolutionizing scientific research. The convergence of these two trends is catalyzing a new era for biomedical research to augment and speed up scientific discovery and the development of precision medicine. In this study, we examine the large-scale omics datasets, emerging applications, and challenges at the intersection of massive omic datasets and related AI models and agents, highlighting how their integration is reshaping the landscape of biomedical research and precision medicine.

Key Words

Biomedical Research, Systems Biology, Multi-Omics, Precision Medicine, Signaling Network, Large Language Models, Foundation Models, Agentic AI, AI Agents.

Introduction

The recent and continued advances and breakthroughs in AI foundation models, e.g., large language models (LLMs), agentic AI and AI agents, domain-specific foundation models, are revolutionizing and transforming scientific data analysis and scientific knowledge discovery. In AI4Science, AI is not just our tool, AI is our collaborator for scientific discovery. AI models are becoming comparable with human scientists in many aspects of the scientific discovery process, such as automated data retrieval, coding for data analysis, large-scale literature search and knowledge synthesis, and hypothesis or idea generation.[1-8]

In life science, omics-data driven mechanism discovery and precision medicine studies represent the most fundamental and challenging barriers to both the theoretical and practical applications of AI, considering that there is a lack of effective or curative therapies for most diseases, and the incomplete understanding of the complex and large-scale biological and disease causal molecular signaling systems. In recent years, large-scale and massive omics datasets of diseases have been generated and publicly accessible to characterize and profile the dysfunctional biological processes in diseases from multi-

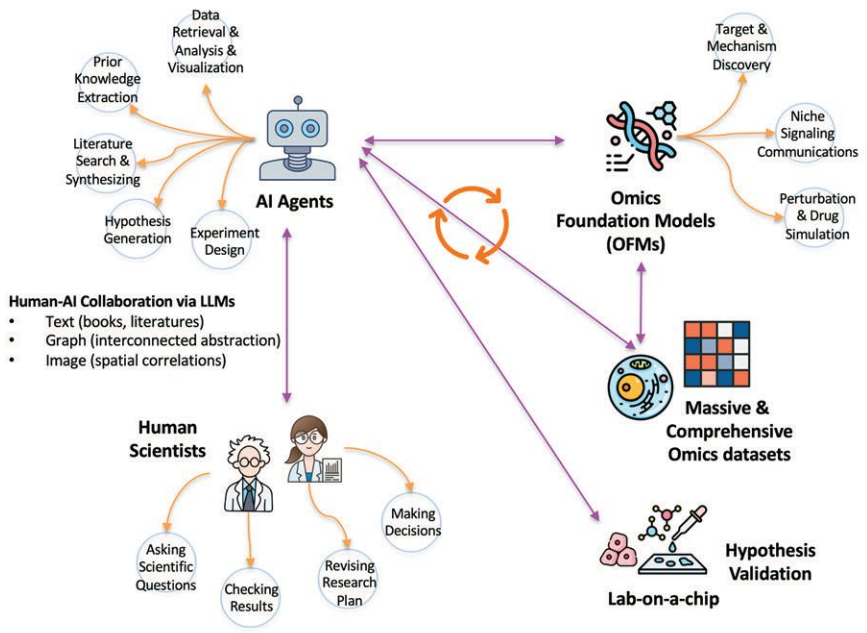


Figure 1. Human-AI collaboration for biomedical research. Human scientists chat with AI agents about the research questions. Then, the AI agents will automatically and autonomously retrieve, analyze, and synthesize omics data, literature, and prior knowledge, to generate testable hypotheses and design experiments to validate the hypotheses. AI agents will make use of FMs, which are pretrained on massive omics data can conduct the omics data analysis tasks, uncover key disease targets and pathways, and predict/simulate the perturbation targets and drugs/cocktails for disease prevention and treatment. The experiment validations using disease cell/organoids assays with crispr and compound perturbations. The AI agents will run in a closed loop, and the human scientists will check the results, revise research plans, and making the final decisions.

level views measured by using multi-omics data, like genetics, epigenetics, transcriptomics, proteomics, and metabolic datasets. Then, the meeting and convergence of LLMs, AI agents, foundation models and the massive omics datasets are speeding up scientific discovery in AI for precision medicine (AI4PM). Human scientists are using and collaborating with AI agents and foundation models in biomedical research and precision medicine studies (Figure 1), to address fundamental challenges in the field by elucidating disease pathogenesis and guiding the development of effective and curative medications and therapies.

However, AI4PM is still in its early stages. There are some fundamental challenges to make significant breakthroughs. Specifically, it remains challenging to curate, annotate, and format the massive, heterogeneous, multi-level datasets into biologically meaning and AI-ready data structures to facilitate the development of AI foundation models.[3,9] The success of LLMs is based on the transformer architectures and the civilization-level human-understandable language/text datasets. Unlike human-defined grammars for using words in a language-meaningful manner, it is unclear how to organize multi-omics data in a biologically meaningful manner (data structure) to decode the complex signaling systems of cells to diseases. Moreover, there is limited label/annotation data, e.g., disease causal mechanisms, effective therapeutic targets, effective drugs, and synergistic cocktails, associated with the multi-omics data. Therefore, it is limited to directly applying the transformer-based language or numeric models to the omics data for novel scientific discoveries in precision medicine. In other words, novel hypothesis generation or scientific discovery in precision medicine remains an open process and represents one of the most fundamental challenges in AI4PM. Though some AI models bring fundamental breakthroughs,[1-3] novel theoretic and application innovations in AI are urgently needed to solve these challenges. This study reviews the availability and resources of large-scale omics datasets, as the key foundation for developing novel AI models, and reported domain specific AI foundation models, agentic AI and AI agents, as well as the fundamental challenges.

Massive Omics Datasets Are Publicly Accessible

Along with the advancement of next generation sequencing (NGS) technology, massive omics datasets of diverse diseases have been generated and publicly accessible. These large-scale omics datasets are valuable and essential for the development of novel and transformative AI models in the field of life science and precision medicine to understand pathogenesis and mechanisms of diseases, identifying novel therapeutic targets to guide the development of effective medications in precision medicine. However, it remains a challenging task and open problem to integrate and interpret the complex and heterogeneous massive datasets to mine knowledge embedded in these datasets. Though the success of foundation models (FMs) in language and computer vision, novel and transformative AI foundation models are urgently needed for analyzing and mining these datasets to mine the key disease targets, signaling pathways and effective medications for diverse diseases.

Tissue-Level Omics Datasets

Among diseases, cancer is one of the leading causes of death worldwide. To investigate the complex pathogenesis and molecular mechanisms of cancer for the development of precision medications, large-scale omics datasets have been generated. For example, in The Cancer Genome Atlas (TCGA) project,[10,11] multi-omics, i.e., genetic, epigenetic, transcriptomic, and proteomic data of a large number of cancer samples from about 33 cancer types from different organs have been generated, which are accessible via the Genomic Data Commons Data Portal.[12] Analysis of these valuable datasets have identified numerous cancer specific targets and pathways.[10] In addition, the complete set of multi-omics data of 1,000 cancer cell lines were generated in the Cancer Cell Line Encyclopedia (CCLE) project.[13] Different from human omics data, the omics data of cancer cell lines can be paired with rich and massive perturbation data of these cancer cell lines. The integration of multi-omics data and massive perturbation data are valuable to uncover the vulnerable targets and understand the signaling pathways and molecular mechanisms of cancer cells, as well as drug response to given drugs and drug combinations, which are publicly accessible via cancer dependency map (DepMap) project.[14,15] To understand the mode of action (MoA) of drugs, the connectivity map (CMAP) project generated the gene signatures of thousands of drugs/compounds on a set of cancer cells,[16-18] which are widely used in drug prediction and repositioning. Alzheimer's disease (AD) is a progressive neurological disorder. In the United States (US), there are about 7.2 million people are living with Alzheimer's disease (AD) in US,[19] and the healthcare cost is 384 billion, which will increase to 1 trillion by 2050.[19] However, the underlying pathogenesis that leads to AD remain unclear.

To investigate the AD molecular mechanisms, multi-omics data of AD are generated, e.g., in the ROSMAP project,[20] which are publicly available via the synapse platform.[21] Compared with the AD cohorts, there is a rare cohort, who live exceptionally healthy and long life. The genomics profiles of the cohort are thus important to uncover the protective targets and mechanisms of aging and longevity. In the exceptional longevity (EL) program, like the Long-Life Family Study (LLFS) project,[22] have generated large-scale multi-omic datasets to identify protective biomarkers and pathways for aging and longevity. In addition to these disease specific datasets, as indicated in the recent study,[23] there are omics data of 6.5 million samples from over 200,000 studies, covering more than 6,000 organisms available in the Gene Expression Omnibus (GEO) database.

Single Cell-Level Omics Datasets

Compared with tissue-level omics data that measures the average signals across heterogeneous cell populations, single cell omics data is necessary to identify disease specific cell-types or cell-subtypes, cell-specific signaling system patterns, and investigate signaling communications within disease MEs.[24,25] Cells are the basic structural and functional

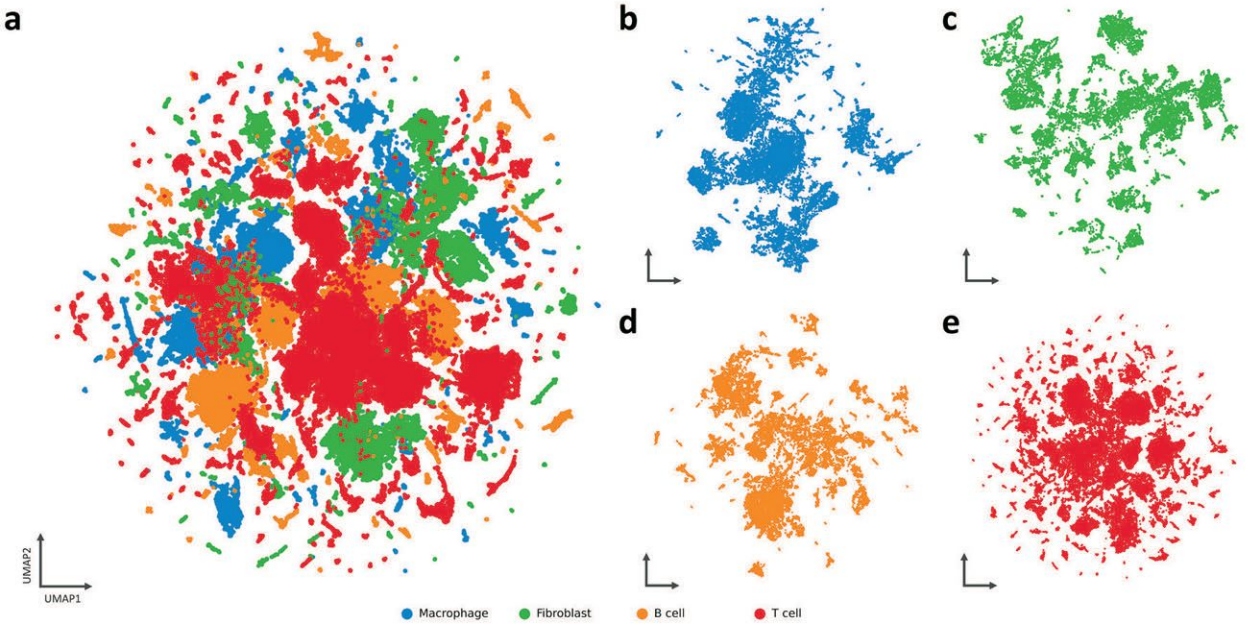


Figure 2. UMAP visualization of a sample set of immune cells. (a) Global UMAP showing macrophages, fibroblasts, B cells, and T cells. (b–e) UMAP projections of each cell type individually, illustrating distinct transcriptional clustering within macrophages, fibroblasts, B cells, and T cells.

units of the human body. Though they share the same genetic blueprint, the process of differentiation transforms them into various cell types and subtypes with distinct functions,[6] which form tissues, organs, and organ systems, creating an organized and coordinated body structure.

In diseases, the dysfunction of specific cells or subpopulations will alter the healthy body or organ cellular architectures and signaling systems. For example, the immune and inflammatory signaling processes within disease microenvironments (MEs) or niche, with the signaling communications between the activated immune cells and damaged or dysfunctional non-immune cells, play important roles in many diseases.[27] The systematic chronic inflammation (SCI) is believed as one of causal factors of 50% of all deaths.[27] It is known that intermittent activated inflammation can eliminate pathogens and promote tissue repair and recovery. Whereas, SCI (complex inflammatory disorders throughout the life cycle) might cause irreversible and lethal damages of most organs in a long and chronic process overtime, e.g., Alzheimer's disease (AD),[28,29] pancreatitis,[30-32] liver fibrosis and cirrhosis,[33,34] and diabetes.[35]

To investigate single-cell signaling patterns, many single cell omics datasets have been generated. For example, the Human Cell Atlas (HCA) is a global consortium,[24] with members from about 100 countries, and generates single-cell omics data to study every cell type in the human body. Currently, there are omics data of more than 70.5 million cells from 11.2 thousand donors. In the Human Tumor Atlas Network (HTAN),[25,36] omics profiles of single cells from approximately 20 organ-specific cancers have been generated to investigate the evolution of tumor signaling within the tumor microenvironment (TME).

The AD Knowledge Portal hosts single cell and spatial omics datasets related to Alzheimer's disease and related dementia's for public access.[37,38] The Brain Cell Atlas unifies 26.3 million single cell omics data across studies and diseases.[39] Many of the datasets were organized in the CZ CellxGene Database repository for public access.[40] In addition, numerous disease specific single-cell datasets from

the Gene Expression Omnibus (GEO) and other public repositories were incorporated.[41,42] With the combination of perturbation and single cell RNAseq technology, massive cell-specific perturbation transcriptomic profiles are being generated. For example, in the Arc institute's virtual cell atlas project, the Tahoe-100M (100 million single cell transcriptomic profiles) dataset was recently released to study and understand the transcriptomic variations caused by 1,100 small molecules across 50 cancer cell lines.[43] In another recent study, genome-scale pertub-seq (perturbing 12,748 genes) on 22 million primary human CD4+ T cells were generated to study the gene regulatory network (GRN) of CD4+ T cells, regulators of T cells and immune cytokines.[44] It is expected that more and more large-scale cell type specific perturbation profiles will be generated rapidly.

In omics-data driven scientific discovery, BioMedGraphica (BMG) synthesized human-understandable textual prior knowledge related to the entities measured in omics data,[45] which are important and should be integrated with omics data analysis for scientific discovery. Then OmniCellTOSG was reported to integrate the comprehensive textual data with a hundred million single-cell omics data using the novel Text-Numeric Graph (TNG) data structure.[7,9] Figure 2 shows a UMAP visualization of immune cells derived using the OmniCellTOSG dataset,[7,9] including macrophages, fibroblasts, B cells, and T cells, revealing their overall distribution and transcriptional separation. Figures 2b–e further show the UMAP projections of each cell type individually. These massive single cell omics datasets provide the basis for developing novel AI foundation models to understand the cell type/subtype-specific signaling patterns and uncover the complex cell components and multi-cell signaling interactions within the complex disease niches and microenvironment.

Artificial intelligence Foundation Models

There are rich computational tools and models for single-cell RNAseq (scRNAseq) data analysis, e.g., Seurat,[46,47] Scanpy,[48] cellchat,[49] to identify cell types and subtypes (cell clustering and cell type annotation based on known cell type biomarkers),[47,50,51] uncover differentially expressed genes and enriched pathways,[47,49,52] and elucidate the multi-cell signaling communications among the diverse cell subtypes within disease-MEs.[49,53,54] However, it remains an open problem to mine knowledge and generate testable hypotheses from omics data analysis, e.g., to identify key signaling targets and core dysfunctional signaling pathways to guide the development of novel therapeutic targets, drugs and drug combinations.

In recent years, there have been continued breakthroughs in AI, which have been transforming scientific research and technological development. Specifically, the breakthroughs begin with diverse and transformative AI neural network architectures, e.g., deep neural networks (DNN),[55] convolution neural networks (CNN),[56] recurrent neural networks (RNN) with attention mechanism,[57] residual neural networks (ResNet),[58] graph convolution/neural networks (GCN/GNN),[59,60] and transformer.[61] The neural network architectures introduced new computational paradigms for solving complex tasks. Based on these model architectures, AI further evolved toward large FMs, especially the LLMs, like ChatGPT, which are pretrained on "civilization-scale" datasets using self-supervised learning (SSL).[62,63] These models can be adapted to downstream tasks and exhibit significantly improved predictive performance and generalization capability. Then, AI agents and agentic AI (with multi-agents working together) further expand LLMs' capability to autonomously and automatically complete complex tasks, which use LLMs (as the brain for decision-making) and tools to perceive and interact with the data, internet and real world.[64,65]

However, in AI for biomedical science (automatic scientific discovery), there remains a lack of effective omics data AI model architectures (for representing omics and prior knowledge), and foundation models (for understanding and modeling omics data), and agentic AI/AI agents (for autonomously and automatically discovering knowledge from omics data, and generating testable

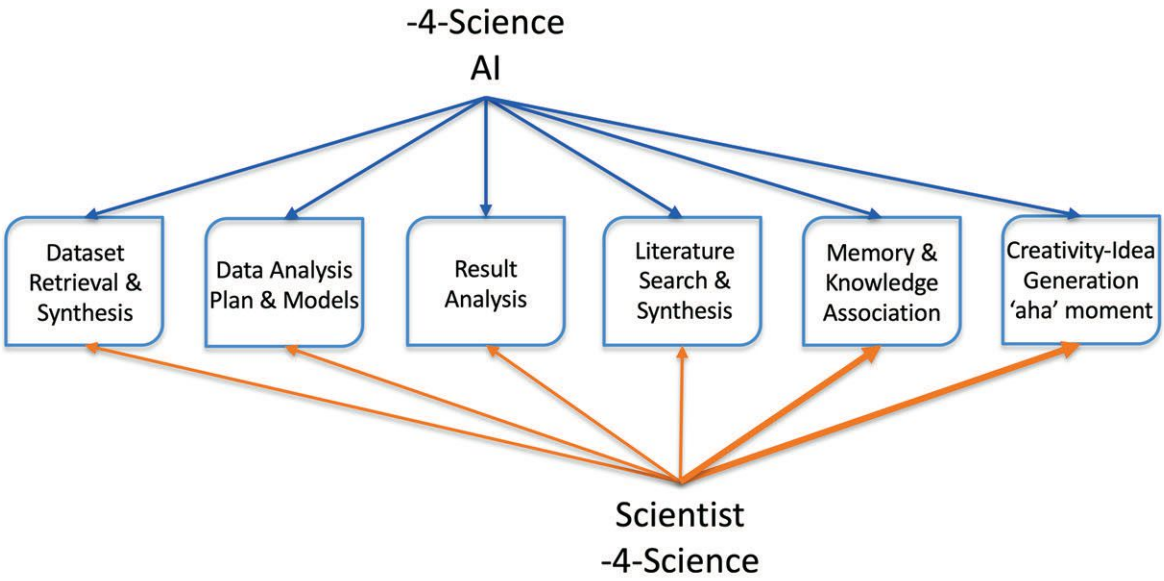


Figure 3. The key steps in the data-driven creative process of scientific discovery. Along with continued breakthroughs in AI—such as LLMs, AI agents, and domain-specific foundation models—AI now outperforms humans in many automatable steps of scientific discovery. However, AI remains limited in creative capabilities that involve associating and synthesizing prior knowledge, literature reports, and data analysis results (data-driven evidence) to generate novel hypotheses or to address unexpected challenges in pursuit of the scientific discovery goals.

hypotheses to speed up the discovery of disease mechanisms, novel therapeutic targets, and effective drugs and synergistic cocktails). In the following sections, a set of existing AI models are surveyed, which mitigate the fundamental challenges in AI for life science and precision medicine.

Foundation Models for Omics Data Analysis

One of the main aims of AI foundation models (FMs) is to understand the coding system and instructions embedded in DNA, and the complex cellular signaling systems, which can be partially measured using multi-omics data.[3] The understanding makes it possible to identify causal dysfunctional targets and signaling pathways and medications for disease prevention and treatment.

There are some sequence-based foundation models. For example, based on the amino acid sequence of proteins, AlphaFold revolutionizes protein structure prediction,[1] providing an architectural backbone for structure-informed reasoning. Yet it largely captures static conformations and remains limited in modeling molecular dynamics, complex assemblies, or post-translational modifications.[66] AlphaGenome can take up to 1Mb (1 million base) DNA sequence as input and predict 11 outputs,[2] like gene expression, ATAC, histone modification and TF binding. To learn the DNA sequence patterns in genome level, Evo was developed, which can predict mutational effects on protein,[3] activities of regulatory DNA, generate new crispr-cas molecule complexes, and generate DNA sequences at genome scale. Using EVO, novel bacteriophage genomes were generated and validated.[67]

Using single cell omics data, some foundation models have emerged pretrained on roughly 30–100 million cells to learn transferable representations for cell-type annotation, perturbation prediction, pathway activity inference, and cross-dataset integration.[24]

For example, scBERT,[68] introduced a transformer encoder trained on large-scale single-

cell data to enable cross-tissue and cross-species transfer learning. Geneformer pioneered masked-language pre-training on single-cell expression profiles,[69] learning gene–gene attention maps that capture biologically meaningful relationships. The Zero-shot benchmarking analyses revealed that,[70] while capturing biologically relevant gene–gene relationships, Geneformer underperformed on crossdataset and cross-cell-type generalization tasks. The scGPT frames single-cell learning as a generative pre-training task.[71] leveraging a transformer trained on over 30 million cells. It treated genes and cells in an analogous manner to tokens and sentences, enabling the model to learn gene and cell embeddings that enhance integration and downstream transfer. scFoundation extended the foundation-model concept to over 50 million cells,[72] employing a read-depth-aware masked reconstruction objective built on xTrimoGene.[73] This scaling enhanced model versatility but came with greater computational demands. However, recent benchmarking analyses revealed that even with large-scale pretraining, foundation models are still limited for some analysis tasks, like the post-perturbation RNA-seq prediction, showing limited generalization across perturbations and cell types as well as sensitivity to batch heterogeneity.[74] To learn the signaling interaction patterns based on the largescale signaling pathways and protein-protein interaction networks, OmniCellTOSG explores a graph foundation model using the text-omic-signaling-graph (TOSG) of massive single cells.[9]

To capture the spatial-dependence information embedded in spatial transcriptomics, large-scale spatial omics corpora have been assembled to train foundation models for spatial transcriptomics. For example, the NicheFormer is pretrained on SpatialCorpus-110M,[75] which consists of CosMx, MERFISH and Xenium platforms in the spatial part of the data. It includes spatially resolved profiles across multiple tissues and technologies.[76] Likewise, scGPT-spatial continually extends the single-cell foundation model using the SpatialHuman30M corpus,[77] which aggregates around 30 million cells/spots from Visium, Visium HD, Xenium, MERFISH, and related platforms. Complementing these token-based models, HEIST introduces a hierarchical graph foundation model trained on 22.3 million cells from 124 tissues across 15 organs,[78] jointly modeling spatial transcriptomics and proteomics as coupled cell–cell and gene-regulatory graphs.

However, the development of omics-based foundation models to decode and understand cellular signaling systems, like building AI virtual cells (AIVC) with multi-omics data,[79,80] is much more challenging than that of LLMs (foundation models) because, unlike human languages, omics data lack grammatical rules and the multi-omics datasets can only measure partial and static information or snapshots of the 3D spatial and dynamic cell signaling systems. Even for the analysis of existing omics data, it remains an open problem considering the challenges of integrating and representing multi-omics data on a multi-scale and biologically meaningful manner.[79-82] For example, the current FMs of omics data arrange the genes and cells in a random manner with a limited focus on the learning of universal embeddings/representations of individual genes and cells for prediction analysis tasks.[79] They are limited to deeply understand and decode the cellular omics signaling patterns. Cellular signaling network systems are rather complex because it consists of 3 billion base pairs long genome, about 20 thousand protein-coding genes, and tens of thousands of proteins and metabolites with millions of interactions at different biological levels. To model the large-scale and high-degree (high interactions among DNA-RNAprotein) cell signaling network systems, novel network/graph AI models are needed to mitigate the over-squashing, high frequency omics signaling (omics heterogeneity), reliability and reproducibility challenges.[83-87] Therefore, novel foundation model designs are needed to mitigate and address these fundamental challenges.

Agentic AI and AI Agents for Biomedical Research

The evolution of AI in precision medicine has progressed beyond static foundation models toward dynamic, autonomous AI agents and agentic AI systems capable of orchestrating complex multi-step workflows with minimal human intervention. In scientific discovery, Agentic AI systems can, with human comparable capabilities (Figure 2), autonomously plan, execute, and adapt their actions to achieve specified goals, leveraging multiple specialized agents that coordinate through intelligent handoff mechanisms.[64] In the context of biomedical research, the emerging multi-agent systems (Figure 1) represent a paradigm shift from tools that require expert guidance at every step to autonomous platforms that can collaborate with human scientists and independently retrieve data, integrate knowledge, perform analyses, validate findings, and generate interpretable hypotheses (Figure 2). This section reviews the landscape of agentic AI systems for omics analysis, with particular emphasis on how multiagent architectures overcome the limitations of single-agent approaches by enabling comprehensive, cross-validated, and mechanistically grounded scientific discovery.

For general-purpose biomedical research, scientific discovery is generally an iterative process that includes data retrieval and analysis, literature search, and hypothesis generation with creativity.[4-7] To augment scientific discovery process, AI co-scientist was developed,[4] which have multiple agents working on hypothesis generation, reflection, ranking, review and evolution agents, literature search. The AI co-scientist was validated in drug repositioning, novel target discovery, and mechanism explanation. Biomni is a general purpose AI agent for biomedical data analysis.[5] In addition to the literature search and reasoning agents, it includes coding agents that can write code and call a set of biomedical data analysis tools for automated data analysis. Kosmos is another general purpose AI agent,[6] which can run code, analyze omics data, and synthesize literature reports. The evaluation results showed that the agent can reproduce reported discoveries in a set of studies. The omniCellAgent is a multi-agent system for omics-data driven scientific discovery.[7] It is built based on the omniCellTOSG dataset,[9] which includes single cell transcriptomics data of diverse organs, diseases and healthy controls, and cell types. Thus, users can conduct omics-data driven studies without preparing user-specific omics datasets. By chatting with OmniCellAgent, it can automatically and autonomously retrieve and analyze cell-type specific differential analysis and enrichment analysis. The literature search and prior knowledge agents will summarize the top ranked targets and pathways, and generate possible hypotheses. CellAgent extends this capability through a hierarchical planner-executor-evaluator architecture with self-iterative optimization that autonomously refines tool selection and hyperparameters.[88] CompBioAgent democratizes access through a web interface that translates natural language queries into interactive visualizations.[89] Moving beyond predefined tasks, CellVoyager independently explores scRNA-seq datasets to generate novel biological hypotheses,[90] having identified previously unreported links such as increased transcriptional noise and brain aging. These systems collectively illustrate the evolution toward scalable, accessible, and discovery-oriented autonomous omics analysis. STAgent focuses on spatial transcriptomics with multimodal VLM+LLM agents for end-to-end analysis.[91] The SpatialAgent tackles panel design through interpretation across spatial biology tasks.[92] Recent surveys/benchmarks map this landscape and evaluate agent frameworks on dozens of single-cell tasks.[93]

Beyond chatting, recent agents for biological research can write, run, and critique analysis code end-to-end. For example, AutoBA exemplifies this trend by generating step-by-step analysis plans,[94] writing and executing code across multi-omics analysis tasks with minimal user input, supporting local deployment for privacy, and stabilizing runs via an automated code-repair loop. Systems like BIA agent autonomously conducts bioinformatics analyses from natural language instructions,[95] managing the entire analytical pipeline from data

extraction to reporting, with strength in scRNA-seq analysis. It can orchestrate data retrieval, pipeline selection, and report generation with autonomous code execution, but are vulnerable to planning errors/hallucinations and lack a dedicated coordination layer for multiagent stability. This gap is addressed in another work by Bio-Copilot, which adds agent-group management, human–agent interaction. Bio-copilot coordinates multiple LLM agents for complex workflows.[96] BioAgents emphasizes privacy preserving,[97] local multi-agent setups using small LMs plus RAG, targeting reliability and reproducibility in code generation. EpiAgent targets single-cell epigenomics by pretraining on large scATAC-seq corpora to encode chromatin accessibility and support downstream tasks (e.g., cell typing, regulatory inference),[98] illustrating an agent/foundation-model approach specialized for epigenetic layers.

Agentic AI is still in its early stage for automatic scientific discovery in biomedical research and precision medicine. While these agent systems have demonstrated the feasibility of AI-driven automation in single-cell analysis and possibly scientific discovery, they remain constrained by critical limitations, e.g., reliance on user-provided datasets, user-specific questions/prompts, incomplete integration of external knowledge sources, data resources, and the need for iterative human oversight. The recent study showed that agentic AI systems can generate reliable and impressive results in demonstration case studies by setting pre-defined and static analysis plans based on known or predicted, case-specific steps or processes.[99] However, in real-world scientific discovery processes, research questions are often open-ended and involve many unpredictable and dynamic scenarios, such as code execution failures, tool misuse, or inappropriate data analyses, new hypothesis generation and revision, which frequently require adapting goals and plans based on feedback of agents perceiving the complex environment.[99] It is critical to train AI agents with dynamic planning and human-like creativity capabilities so that they can adapt their decision-making and tool invocation to handle unexpected scenarios, like human experts.[99,100]

Conclusion

Advances in large-scale multi-omics data generation and analysis have identified numerous molecular targets and elucidated parts of the key mechanisms involved in disease pathogenesis. However, the holistic and deep understanding of complex disease cell signaling systems remains limited. Consequently, effective and curative treatments are still lacking for most complex diseases, e.g., cancers, Alzheimer's disease, systematic chronic inflammation, lysosomal storage disorder diseases. In recent years, continuous breakthroughs in generative AI and foundation models have been transforming the paradigm of data analysis and scientific research. The convergence of transformative AI models with large-scale omics data marks the beginning of a new era in biomedical research and precision medicine.

The AI for biomedical research and precision medicine (AI4PM) is still in its early stages. Unlike building LLMs and foundation models based on human understandable language and image datasets, the integration, representation, analysis, interpretation, and applications of complex multi-omics data using novel AI models represent some of the most challenging tasks in both AI and biomedical research/precision medicine. There are several fundamental challenges, e.g., problem definition and alignment (to map diverse and often vague, user-specific questions to appropriate, well-defined formulations and prompts that can effectively guide AI systems in subsequent analysis planning and task execution); analysis planning and adaptation (to handle unexpected results and feedback during iterative analysis processes); omics data retrieval and integration (to identify and integrate the right omics datasets, and analyze them with the appropriate models), knowledge search, synthesis and extraction (to synthesize and extract knowledge from large-scale literature reports and

large prior knowledge database, and associated with other data analysis results); memory and creativity (to learn from and memorize successful scientific discovery experience, and generate new testable hypotheses for new questions). There is a strong need for novel theoretical and implementation innovations in AI foundation models to mitigate these challenges, and to speed up scientific discovery in biomedical research, by decoding complex cellular signaling systems, identifying novel therapeutic targets and disease mechanisms, and developing effective and curative medications for disease prevention and treatment.

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Acknowledgment

This research was partially supported by NIA 4R33AG078799-02, NIA 1R21AG078799-01A1, NINDS 1RM1NS132962-01, NLM 1R01LM013902-01A1, NIA R56AG065352.

Disclosure

No financial disclosures reported. Use of Artificial Intelligence and Large Language Models. ChatGPT (OpenAI) was used to assist with editing and drafting portions of the manuscript text. The authors take full responsibility for the integrity and accuracy of the manuscript. **MM**

Cochlear Implants: An Overview

by Gabriella L. Boone, BA & Joshua M. Sappington, MD

Despite strong evidence supporting cochlear implantation as a safe and effective intervention, it remains underutilized.



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Abstract

Importance

Hearing loss poses a significant health burden to the Missouri population and broader United States (US). Cochlear implantation is the most effective intervention for patients with sensorineural hearing loss who do not find adequate benefit from hearing aids.

Objective

This review provides an overview on cochlear implantation including its history, mechanisms, candidacy criteria, outcomes, and continued challenges in access and utilization.

Methods

A literature review was conducted using PubMed to identify peer-reviewed articles using relevant keywords pertaining to cochlear implantation.

Findings

Cochlear implantation has evolved significantly over the past six decades, and advancements continue to be made. Extensive research has supported cochlear implantation as a highly effective intervention in both adults and children, and its indications and candidacy criteria continue to expand. However, cochlear implantation is underutilized, driven by a combination of socioeconomic, individual, and health systems related factors.

Key Words

Cochlear implants, hearing impairment, sensorineural hearing loss.

Introduction

Hearing loss affects more than 50 million Americans, and in Missouri nearly 20% of the adult population lives with some degree of hearing impairment.[1-2] The burden of hearing loss extends past communication barriers and can contribute to difficulties across many aspects of life, including lower educational attainment, reduced employment, cognitive decline, social isolation, depression, and diminished quality of life.[3]

There are three subtypes of hearing loss: sensorineural, conductive, and mixed which is a combination of the two. The most common type in adults is sensorineural hearing loss (SNHL) which results from damage to the inner ear or auditory nerve, while conductive hearing loss (CHL) arises from pathology in the external or middle ear that impairs sound transmission. Treatment options depend on the type and severity of hearing loss. For SNHL, first line management often includes hearing aids, which amplify sound and rely on residual cochlear function.[4] However,

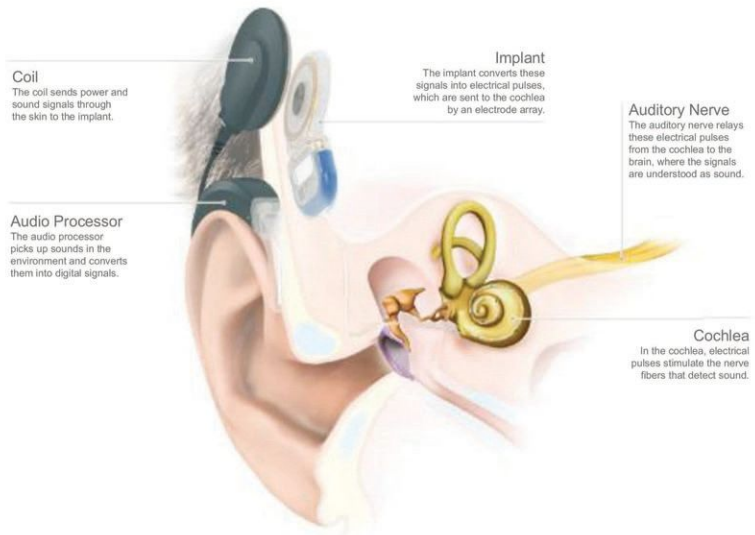


Figure 1. The basic components of a cochlear implant. The sound processor picks up sound, converts it to an electric signal, and digitally transmits it to the internal device. This internal array then directly stimulates the inner ear.

many patients with advanced SNHL experience impairment that is not adequately addressed by amplification alone.

Cochlear implantation is the most effective intervention for patients with severe to profound sensorineural hearing loss who do not find adequate benefit from hearing aids. Extensive clinical research demonstrates that cochlear implants are safe, effective, and associated with substantial gains in speech perception, cognitive performance, and overall well-being in appropriately selected candidates.[5-8] Despite its proven efficacy, utilization remains low, with only around 1 in 10 patients in the US who could benefit from implantation undergoing the procedure.[8-9] Underutilization is likely driven by a number of factors, such as limited provider awareness, referral barriers, and socioeconomic disparities.[10-12]

This review provides an overview on cochlear implantation including its history, mechanisms, candidacy criteria, outcomes, and continued challenges in access and utilization.

History of Cochlear implantation

The earliest use of cochlear implantation in the US is attributed to William House and John Doyle who performed the first procedure in Los Angeles in 1961.[13] This work was followed by Blair Simmons and Robert White at Stanford, who implanted the first multichannel electrode in 1964, which allowed for more sophisticated sound coding and improved speech perception.[14] The first patient clinical trials were performed at the University of California in the early 1970s which demonstrated that auditory sensations could be reliably reproduced in profoundly deaf patients using a single channel cochlear implant.[15] The first international cochlear implant conference was held in San Francisco in 1973, marking the introduction of this device to a worldwide audience.

Due to the limited level of success in speech discrimination with a single electrode, research shifted to the development of multichannel devices capable of stimulating distinct cochlear regions, allowing for more accurate sound encoding and improved speech perception.[16] Commercialization of the cochlear implant began in the late 1970s, where university-industry partnerships lead to the development of new devices. The US Food and Data Administration (FDA) approved the first multichannel cochlear implant for adults with profound SNHL in 1985 and for children in 1990.[17]

Today, cochlear implantation has become one of the primary treatment options for severe to profound sensorineural hearing loss in both adults and children. Modern advances include atraumatic insertion techniques, including slow electrode insertion and intraoperative monitoring, and the development of electrode arrays, which minimize cochlear trauma and are able to preserve residual hearing and structures.[18-19] Hybrid devices now allow for combined electrical and acoustic stimulation in patients with residual low frequency hearing.[8] Ongoing research continues to optimize implantation by refining device technology, surgical techniques, and patient selection.

What is a Cochlear implant?

Cochlear implants work differently from hearing aids, which amplify sound and rely on residual hair cell



Figure 2. Internal component of an Advanced Bionics implant.



Figure 3. Internal component of a MED-EL implant.



Figure 4. Internal component of a Cochlear Corporation implant.

function. Cochlear implants circumvent the natural acoustic pathway and instead provide direct neural stimulation. The basic mechanism of the cochlear implant is through direct stimulation of the auditory nerve, bypassing the damaged hair cells of the cochlea seen in SNHL (Figure 1). The implant consists of two main components: an external sound processor and an internal stimulator/receiver with an electrode array. The external sound processor is typically worn behind the ear, though an off the ear option is available. It contains a microphone that captures sound, a processor that converts sound into coded electrical signals, and a transmitter that sends signals to the internal processor by radiofrequency coupling. The internal electrode is surgically implanted into the cochlea where it receives the signal and delivers electrical stimulation along the tonotropic cochlear axis (Figures 2-4). This directly activates the spiral ganglia of the auditory nerve, allowing the brain to process the electrical signals as sound.

The different types of cochlear implants available in the US can be distinguished by manufacturer, electrode design, and clinical indication. There are three FDA-approved manufacturing companies in the US: Cochlear Americas, Advanced Bionics, and MED-EL. All offer devices with similar core components. There are two main electrode designs: lateral wall and perimodiolar. Lateral wall electrodes are often preferred for hearing preservation as they are less traumatic to cochlear structures, while perimodiolar electrodes are often chosen for improved stimulation efficiency.[20-22] The difference in long-term speech outcomes between array types is modest, and both designs are shown to be exceptionally clinically effective.[23] Traditional cochlear implant indications were for individuals with bilateral severe to profound SNHL that provide electrical-only stimulation, a configuration that is standard for patients with little to no residual hearing.[8] Hybrid electric acoustic stimulation devices are indicated for patients with residual low frequency hearing loss, and electrodes have been developed to preserve apical cochlear function and structure, allowing for both acoustic and electric stimulation.[24] Implantation can be utilized unilaterally or bilaterally depending on the pattern of hearing loss and the specific needs and goals of the individual patient.

Cochlear Implant Candidacy

Cochlear implant candidacy has evolved greatly since its initial FDA approval, where implantation was first limited to adults with bilateral profound SNHL and no benefit from hearing aids.[17] Over time clinical research demonstrated improved outcomes with earlier intervention and expansion to patients with less severe hearing loss resulted in improved speech perception, language development, and quality of life outcomes.[25] Today, adult and pediatric criteria have been expanded to include functional hearing outcomes rather than solely relying on audiometric thresholds.

Current adult candidacy criteria now include individuals with at least moderate low frequency hearing loss, as well as those with poor speech recognition despite optimized hearing aid utilization.[26] Recent consensus guidelines and studies suggest referring adults for cochlear implantation if they have a pure tone average of 60 dB HL or greater and a word recognition score of 60% or less in one or both ears ("revised 60/60 rule"), or if they demonstrate inadequate benefit from well-fitting hearing aids, even when low frequency thresholds are in the normal to mild range.[27-28] This expansion allows for candidacy consideration in adults with more residual

hearing or with aided speech scores that indicate insufficient functional benefit. Most US insurance programs currently define adult cochlear implant candidacy as scoring less than or equal to 50% in the ear to be implanted or 60% binaurally in the best aided condition on sentence recognition tests.[29-30] Candidates are typically evaluated for medical suitability for surgery, including potential contraindications such as cochlear nerve or cochlear aplasia, severe cochlear ossification or malformation, and lack of any residual cochlear function. Patients who are referred will undergo a cochlear implant evaluation with a multidisciplinary team, including audiologists and implant surgeons, who further utilize audiologic testing, verification of hearing aid optimization, medical and surgical assessment, and imaging studies to determine candidacy.

Children as young as nine months with bilateral profound SNHL, ≥2 years with severe to profound SNHL, or ≥5 years with single sided deafness or asymmetric hearing thresholds with limited word recognition may be eligible for cochlear implantation.[31] The American Cochlear Implant Alliance guidelines emphasize that children who show limited progress in speech, language, or auditory development despite appropriately fitted hearing aid use, may benefit from further evaluation regardless of their degree of hearing loss.[32] Importantly, early implantation has been associated with better language and academic outcomes.[33-34] It should also be recognized that implant utilization is nuanced within the Deaf community, and the decision to pursue implantation should arise from a partnership between the family, child, and providers.[35] This approach ensures that the family values, cultural identity, and goals are respected.

Outcomes and Quality of Life

The utilization of cochlear implants in patients with hearing loss is associated with significant benefits in speech perception, communication, social participation, independence, and overall health and well-being across all age groups. In adults with severe to profound SNHL, average word recognition improves from approximately 8% pre-implantation to 50% post implantation. These improvements are reflected across age groups, including in older adults, and can be seen in both quiet and noisy conditions, and the majority of adult recipients report achieving meaningful improvement in speech perception.[36]

In addition to measurable hearing improvements, implantation enhances communication abilities and social engagement, contributing to overall life satisfaction independent of audiometric performance.[37-38] Patient reported quality of life outcomes, such as the Health Utilities Index and Speech, Spatial, and Qualities of Hearing Scale, show significant improvement in daily functioning after implantation.[38-40] The benefits of implantation are particularly evident in older adults, where literature has shown its significant role in reducing social isolation, depression, and cognitive decline, allowing for increased autonomy and optimized mental health.[41-44]

Cochlear implantation in pediatric patients with severe to profound SNHL is associated with significant improvements in auditory skill development, speech perception, language acquisition, and academic achievement.[35,45] Children who receive implants early on and have intensive rehabilitation, especially those implanted before 18 months of age, achieve language and academic outcomes at or above the level of age matched normal hearing peers.[46] Over half of pediatric patients post-implantation are able to enter mainstream education without additional support within three years of the procedure.[47] Parent reported outcomes frequently reflect positive gains in communication, participation, and autonomy.[48-49]

Utilization and Barriers

Only an estimated 6-12% of eligible adults receive cochlear implants, highlighting a significant gap in utilization.[9,50] The cause of implant underutilization is multifactorial, involving socioeconomic, individual, and health systems related factors. Socioeconomic barriers such as lower income, inadequate insurance coverage, rural residence, long travel distance to implant centers, and non-English speaking status, are all associated with reduced likelihood of referral and eventual implantation in eligible candidates.[51-54] Individual

level barriers include fear of surgical complications, concerns of losing residual hearing, uncertainty regarding outcomes, perceived lack of benefit, apprehension surrounding post-operative recovery and rehabilitation, and lack of family or social support, all which can strongly influence decision making.[55-56] System level factors further contribute, including limited awareness among both the public and referring clinicians regarding screening, candidacy, and referral pathways.

Routine screening for hearing loss in adults and children has been proposed as an effective strategy for early identification of cochlear implant candidates. Any physician, regardless of specialty, can directly refer for implant evaluation. The American Academy of Otolaryngology–Head and Neck Surgery emphasizes that early referral and intervention is often associated with improved outcomes and decreased costs for the patient and the healthcare system.[26] Patient and family education on the benefits, safety, and outcomes of cochlear implantation may help improve awareness and acceptance. Shared decision making plays a key role in ensuring informed consent, realistic expectations, and long term engagement in post-operative rehabilitation

Conclusion

Cochlear implantation offers the ability to restore meaningful hearing and communication for adults and children with sensorineural hearing loss. Beyond auditory improvements, implantation has consistently shown to enhance cognitive, educational, and psychosocial outcomes. Despite strong evidence supporting cochlear implantation as a safe and effective intervention, it remains underutilized. Improving physician awareness, enhancing screening for hearing loss, and facilitating timely evaluation may help address the burden of untreated hearing loss in Missouri and across the US.

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Disclosures

No financial disclosures reported. Artificial Intelligence was not used in the research, preparation, or writing of the manuscript. **MM**

Digital Health Solutions for Alpha-Gal Syndrome: A Scoping Review of Telemedicine Evidence and Applications

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The distinctive clinical characteristics of AGS present challenges for disease management, positioning telemedicine as a strategically important tool.



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Abstract

Alpha-gal syndrome (AGS) is an emerging allergy initiated by tick bites that leads to delayed IgE-mediated hypersensitivity reactions to galactose-α-1,3-galactose (α-gal), a carbohydrate present in mammalian tissues. Symptoms are highly variable and include urticaria, gastrointestinal distress, and life-threatening anaphylaxis. Diagnosis relies on patient history and serological testing for α-gal-specific IgE antibodies. This scoping review, following PRISMA methodology, evaluates telemedicine for clinical management of AGS. The syndrome's characteristic delayed response pattern poses distinct challenges for standard allergy management protocols. Telehealth presents compelling solutions by enabling structured follow-up, remote data collection, and patient support, which is especially critical given that AGS is concentrated in geographic areas with limited specialist access and low provider familiarity. A case study of successful AGS desensitization using remotely monitored oral immunotherapy provides proof-of-principle for telemedicine's transformative potential. Integrating telehealth is a strategic approach to improve diagnosis, facilitate long-term management, and strengthen surveillance for this increasingly prevalent condition.

Key Words

Galactose-alpha-1,3-galactose, red meat allergy, alpha-gal syndrome, alpha-gal allergy.

Introduction

Alpha-gal syndrome (AGS) comprises an array of symptoms corresponding to immune-mediated hypersensitivity reactions to galactose-α-1,3-galactose (α-gal), a carbohydrate found in non-primate mammals including cow, goat, pig, and sheep.[1] AGS deviates substantially from conventional food allergies in several critical respects. In contrast to traditional food allergies, where allergic symptoms typically develop within minutes of consumption, allergic symptoms in AGS often begin more than two hours after consuming mammalian products.[1] Additionally, the IgE antibodies form against a carbohydrate rather than an antigenic protein, and sensitization is affiliated with ectoparasite exposure, particularly *Amblyomma americanum* (lone star tick) in the United States.[1]

Missouri represents a critical epicenter for AGS, ranking among

states with the highest prevalence of suspected cases per population.[2] Recent comprehensive analysis of 343 AGS patients diagnosed at the University of Missouri revealed distinct clinical patterns that underscore the syndrome's impact on the state's healthcare system.[3] This cohort demonstrated marked rural predominance, particularly among pediatric patients, with 64.8% of children residing in rural counties compared to 40.8% of adults. Pediatric presentations differed substantially from adults, showing significantly higher rates of gastrointestinal symptoms (35.2% vs. 19.2% for nausea/vomiting) and lower rates of anaphylaxis (2.3% vs. 6.7%), challenging conventional understanding of AGS manifestations across age groups.

The geographic distribution patterns observed in Missouri align with broader national data showing prevalence rates of alpha-gal sensitization approaching 50% within the "three corner" region of Missouri, Arkansas, and Oklahoma.[4] This concentration coincides with areas of lone star tick populations and elevated ehrlichiosis infection rates. Risk factors for AGS development include documented tick bites, residence in areas with deer populations (woodland, larger properties with vegetation), and outdoor activities.[5] Importantly, a strong association exists between alpha-gal specific IgE antibodies and tick exposure, with 98% of case patients demonstrating positive serology.[6]

Individual and familial risk factors further complicate the clinical landscape. Patients with AGS are more likely to have atopy, evidenced by other food allergies, childhood allergies, heightened cutaneous reactions to insect bites, and elevated IgE antibodies to various allergens.[6] They are also eight times as likely to have family members with AGS, suggesting genetic predisposition or shared environmental exposures. However, these familial effects could be attributed to lifestyle factors such as peridomestic exposure, outdoor activities, or enhanced AGS knowledge among affected families.[6]

The healthcare delivery challenges posed by AGS are particularly acute in Missouri's mixed urban-rural geography. The rural predominance of pediatric cases, combined with lower median alpha-gal IgE titers in this population, creates diagnostic complexity in areas with limited specialist access.[3] While allergy specialists diagnosed 75% of pediatric and 67.5% of adult cases in the Missouri cohort, primary care providers managed 13.6% and 21.2% respectively, highlighting the need for cross-specialty education given that non-allergists more frequently documented the gastrointestinal symptoms that dominate pediatric presentations.

Current management emphasizes mammalian meat and product avoidance. Even though IgE levels decrease over time, significant studies documenting AGS resolution through avoidance are lacking. For individuals interested in ending dietary restrictions, desensitization through oral immunotherapy (OIT) presents an option, though traditional protocols require considerable in-person monitoring due to safety concerns.[7]

The integration of telemedicine into allergy and immunology practice has gained considerable momentum, with support from the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI).[8] These organizations anticipate that telemedicine will enhance health outcomes, expand care access, refine resource usage, decrease costs, and elevate collaboration between patients and physicians.[8,9] For conditions like food allergy and atopic dermatitis, telemedicine proves suitable since physical examination is often nonobligatory.[10]

Individuals with AGS serve as ideal candidates for telemedicine applications, particularly given the delayed nature of reactions and the rural concentration of cases in states like Missouri. A recent case report demonstrated successful AGS desensitization using remote monitoring, where a 63-year-old woman living considerable distance from her medical practice completed OIT with telemedicine oversight.[7] This proof-of-principle case suggests broader potential for digital health solutions to address the geographic and logistical barriers that complicate AGS management in rural populations.

Given Missouri's prominent role in AGS epidemiology and the demonstrated feasibility of telemedicine approaches, a comprehensive evaluation of digital health applications for this condition is warranted to inform clinical practice and healthcare policy in the region.

Methods

This scoping review was designed and reported in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) framework, providing structured guidance for conducting reviews. This ensured transparency and consistency of the process and methodological rigor.

Eligibility Criteria

Studies were included in this review if the following criteria were met: 1) focused on patients diagnosed

with or suspected of having AGS; 2) involved the use of digital health solutions such as telemedicine, telehealth, or any form of remote monitoring or consultation as part of the diagnosis, management, or treatment; and 3) were published in English language. All study designs, including original research, case reports, case series, commentaries, and narrative reviews were considered for inclusion to ensure a comprehensive scope of the available literature on this emerging topic.

Studies were excluded if the focus was on a single specific tick-borne disease other than AGS (e.g., Lyme disease), as findings from such research may not be generalizable to AGS. However, studies on telehealth for tick-borne diseases in general, or those addressing food allergies more broadly, were included if their findings could reasonably apply to AGS management.

Information Sources and Search Strategy

A comprehensive literature search was performed in Medline Ovid, Web of Science and Google Scholar from their inception to August 2025. The search strategy was developed in consultation with two co-authors (MB and BC) and was built upon two main concepts: 1) Alpha-Gal Syndrome and 2) telemedicine. For the first concept (AGS), a wide range of subject headings and keywords were used, including: "galactose-alpha-1,3-galactose," "red meat allergy," "alpha-gal syndrome," "alpha-gal allergy," "mammalian meat allergy," and related terms. This concept also included broader terms like "food hypersensitivity," as well as terms related to "tick-borne diseases" and "tick bites," which were then combined with AGS-specific terms to capture all relevant articles. For the second concept (telemedicine), keywords included: "telemedicine," "telehealth," "remote consultation," "virtual health," "digital health," and "remote monitoring."

These two concepts were combined using the 'AND' Boolean operator to identify articles at the intersection of both topics. The search strategy was adapted for Google Scholar using key search strings such as ("alpha-gal syndrome" OR "red meat allergy") AND (telemedicine OR telehealth OR "remote monitoring"). Additionally, the reference lists of all included articles were manually screened to identify any further relevant studies. The detailed search query for Medline Ovid is documented in Appendix A.

Study Selection

The study selection process was conducted by three reviewers (AEZSA, MB, BC) independently. First, the titles and abstracts of all retrieved articles were screened against the predefined eligibility criteria. Articles that clearly did not meet the criteria were excluded. Next, the full texts of all potentially relevant articles were retrieved and assessed for eligibility by all reviewers. Any discrepancies or disagreements between the reviewers at either the screening or full-text review stage were resolved through discussion and consensus.

Data Extraction

A standardized data charting form was developed to extract relevant information from the studies included. Three reviewers independently extracted the data. The following information was collected from each study: author(s), title, year of publication, journal name, Digital Object Identifier (DOI), specific details of the telemedicine intervention, key findings related to the intervention, and the study's relevance to AGS. The extracted data was then used to generate a narrative summary of the existing literature.

Results

Study Selection

A total of 19 records were identified through database searching, with an additional 11 records identified through other sources. After removing duplicates, 29 records remained for screening. Of these, 22 records were screened and seven were excluded. The full text of 22 articles was assessed for eligibility, and one article was excluded for other reasons. Finally, 21 studies were included in the context of this scoping review (Figure 1).

Direct AGS Telehealth Evidence

The Wu et al. case study addresses a significant challenge that is particularly acute for Missouri's rural patient population.[7] The authors describe the treatment of a 63-year-old female with an initial anti-alpha-gal IgE level of 10.9 kUA/L who experienced severe anaphylactic reactions after eating meat. The patient's demanding work schedule and significant distance from the clinic made traditional, lengthy desensitization appointments impractical. To overcome this, Wu et al. implemented a novel at-home oral immunotherapy protocol using a 14-step dose escalation of cooked, 100% beef hot dogs.[7] Telehealth protocol allowed direct communication access to physicians, and the patient was equipped with epinephrine autoinjectors.

They concluded that oral desensitization for AGS can be feasible and effectively conducted using a combination of a novel desensitization protocol and

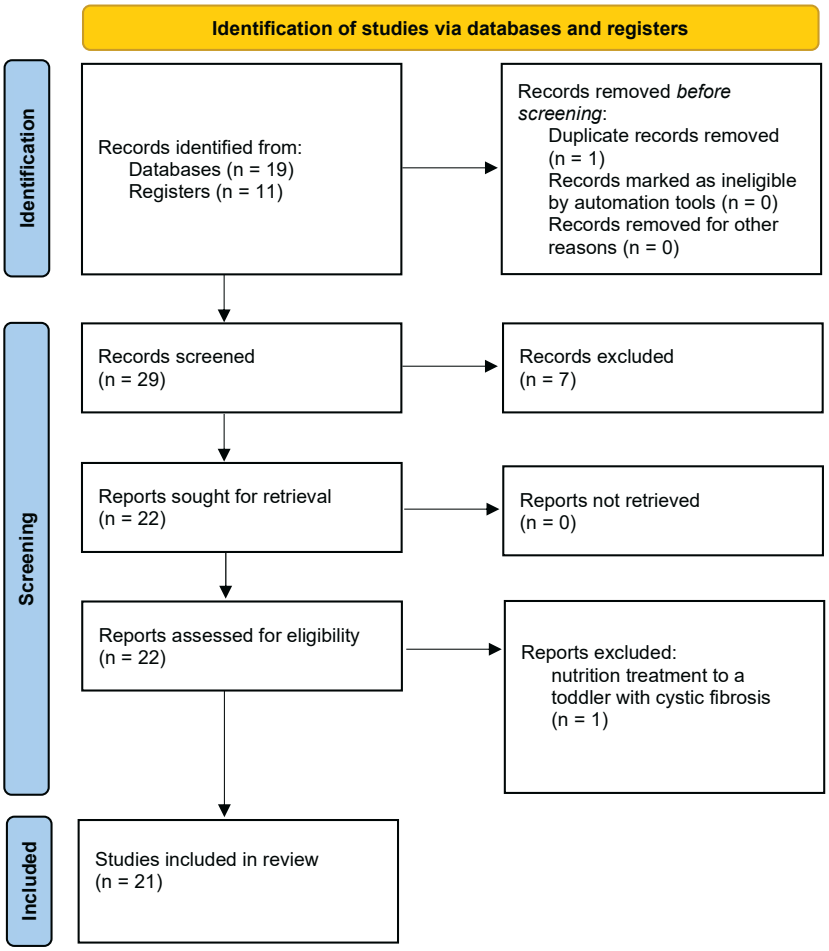


Figure 1. PRISMA flow diagram of study selection process for the scoping review.

telemedicine. This case demonstrates relevance to Missouri healthcare delivery, where many AGS patients reside in rural counties with limited specialist access.[3] The geographic barriers overcome in this case, such as significant distance from clinic and work schedule conflicts with prolonged observations, mirror challenges faced by Missouri patients seeking AGS care.

Wu et al.'s case study prompted a commentary from Richard L. Wasserman, who points out that the unique, delayed nature of AGS reactions may mean this specific protocol is not directly generalizable to other food allergies that cause more immediate reactions.[7,11] He questions the precise role of telemedicine, wondering if its purpose was for direct observation (challenging given the uncertain timing of reactions) or for patient reassurance and data collection. For other food allergies, remote observation is more straightforward, as reactions typically occur within 30 minutes, allowing a provider to advise immediately.[11]

The author raises significant safety concerns regarding patient adherence.[11] Without the regular, in person visits that serve to reinforce protocols and review sick day rules, Wasserman worries that patients might be tempted to alter their treatment plan, such as by accelerating doses, thereby increasing their risk of reaction.[11]

Further contextualizing these findings, Jutel et al. connects both AGS and telemedicine to the broader One Health framework, which integrates human, animal, and environmental health. The paper highlights AGS as a key One Health-related research topic.[12] This positions the syndrome as an exemplary condition arising from the interaction between humans and animal vectors. Concurrently, the paper advocates telemedicine as a tool to create a more sustainable and accessible healthcare system. While not a clinical study, this study provides a conceptual framework that endorses both the study of AGS and the use of telemedicine as integral components of a modern, holistic approach to allergy and immunology.[12]

Telehealth Applications from Broader Allergy Literature

Out of extracted papers, 17 did not directly address AGS. However, the findings related to telehealth in general allergy, food allergy, and immunology may be relevant and applicable to optimizing the care pathway for AGS patients. These studies provide a strong basis for incorporating virtual care into both the diagnosis and long-term management of AGS.

Applications to AGS Diagnosis

Although definitive AGS diagnosis often requires specific laboratory testing, telehealth applications can significantly refine the pre-diagnostic and initial consultation phases. Approaches from five papers demonstrated applicability to the diagnostic workflow.

Two studies demonstrated that new patient allergy consultations can be effectively conducted via synchronous telehealth, a model that could improve access to specialists for initial AGS evaluation.[13,14] An electronic multidimensional health assessment questionnaire (eMDHAQ), provides a viable method for patients to remotely document their comprehensive history, including crucial details like tick exposure and reaction timing, for a clinician's review.[15] In addition, an online tool for near-real-time reporting of allergic reactions would be invaluable for capturing the specific details of delayed anaphylaxis that are characteristic of AGS.[16] Finally, Martin et al. discussed using telehealth data and web searches for syndromic surveillance of tick-borne diseases, a method that could be applied to AGS to gain earlier public health awareness and clinical recognition.[17]

Applications to AGS Management

Managing AGS primarily centers on strict dietary avoidance and readiness for accidental exposure. Telehealth strategies outlined in the literature provide broad support across these critical areas. Strategies from 17 of the papers are applicable to the long-term management of AGS.

The efficacy of telenutrition for monitoring diet adherence can be generalizable to supporting AGS patients.[18] Mobile health (mHealth) tools offer further support; a smartphone-based Personal Allergy Assistant that helps patients track intake and scan food barcodes could be adapted to warning against mammalian ingredients, aligning with the broader potential of mHealth in disease management.[18] Given the risk of severe reactions, mobile health technology for anaphylaxis emergency preparedness could provide crucial decision support.[19]

Furthermore, the general benefits of telemedicine for routine allergy care are widely applicable to AGS management. Studies confirmed high patient satisfaction and effectiveness, showing that telehealth can increase access to specialists and be more time- and cost-effective.[8,14,20,21] These established advantages of virtual platforms underscore their value in providing continuous, long-term support for individuals living with AGS.

Discussion

The distinctive clinical characteristics of AGS present challenges for disease management, positioning telemedicine as a strategically important tool. The delayed onset of AGS reactions renders standard allergy protocols, designed for immediate responses, less applicable to this condition.[11] This temporal gap raises questions about the role of telemedicine: its function shifts from real-time observation of acute reactions to a model focused on patient reassurance, structured follow-up, and systematic data collection. The clinical urgency for such support is underscored by the findings of Binder et al., who demonstrated that 75% of AGS patients meet the criteria for anaphylaxis, with a high prevalence of severe systemic and gastrointestinal symptoms.[22]

The Wu et al. case provides a possible roadmap for addressing Missouri's documented geographic disparities in AGS care, where rural patients face both elevated disease prevalence and diminished specialist access.[7] There is a concentrated geographic burden of suspected AGS in the southern, midwestern, and mid-Atlantic United States, a pattern mirroring regional tick habitats.[3] Provider awareness presents an additional challenge. Thompson et al. reported that among surveyed providers, 42% had never heard of AGS, and 35% expressed limited confidence in their ability to diagnose or manage patients with AGS.[2] Telehealth can address these gaps by expanding specialist access, facilitating education on delayed reaction management, supporting remote follow-up for complex interventions, and strengthening public health surveillance and case reporting. Although most of the reviewed literature does not focus specifically on AGS, it consistently points to areas where telemedicine is well suited to make an impact. Telemedicine should therefore be viewed not merely as a convenience, but as a strategic approach to enhance diagnosis, sustain long-term management, and strengthen surveillance for this emerging health challenge.

For Missouri healthcare systems, the Wu et al. protocol offers a scalable model that leverages the state's academic medical centers as telemedicine hubs while serving rural populations.[7] The delayed reaction inherent to AGS makes this condition uniquely suited to remote management, distinguishing it from other food allergies and positioning Missouri to lead in AGS telemedicine implementation. Alpha-gal titers are known to decline over time in the absence of repeated tick exposures.[23] Thus, interpretation of the effectiveness of the Wu et al. protocol for desensitization is limited by the six months of time the patient was under study. Future controlled studies are needed to demonstrate its scalability.

The findings from the broader allergy literature reinforce the potential and provide a clear roadmap. To

address the diagnostic challenges of delayed reactions, telehealth platforms can be adapted to include tools like the electronic multidimensional health assessment questionnaire (eMDHAQ), allowing for detailed, remote documentation of patient history. This can be coupled with online tools for near real-time reporting of allergic reactions helping to bridge the temporal gap between consumption and symptom onset. For ongoing management, studies confirm the efficacy of telenutrition in monitoring dietary adherence, while mHealth tools like a smartphone-based Personal Allergy Assistant could be modified to help patients avoid mammalian-derived ingredients. Given the high risk of severe reactions, mobile technology for anaphylaxis emergency preparedness is also directly applicable. Importantly, multiple studies confirm that synchronous tele-allergy services for both new and follow-up visits are effective, well-received by patients, and improve access to specialists directly answering the need created by the geographic and knowledge gaps in AGS care.

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Appendix A: Search Strategy and Results from MEDLINE (Ovid)

Table 1: Alpha-gal Syndrome and Telemedicine Search Results in MEDLINE (Ovid)

#	Searches	Results
1	galactose-alpha-1,3-galactose.mp.	396
2	red meat allergy.mp. or red meat allergy/	266
3	"galactosyl-(1-3)-galactose".mp.	509
4	alpha-galactosyl epitope.mp.	263
5	GLA protein, human.mp.	228
6	alpha-galactosidase II.mp.	11
7	"O-alpha-galactopyranosyl(1-4)-O-beta-galactopyranosyl(1-4)-2-acetamido-2-deoxy-alpha-glucopyranose".mp.	1
8	alpha-gal syndrome.mp.	266
9	alpha-gal allergy.mp.	66
10	"galactose-alpha-1,3-galactose allergy".mp.	6
11	"galactose-alpha-1,3-galactose allergy".mp.	6
12	mammalian meat allergy.mp.	53
13	red meat sensitization.mp.	0
14	"alpha-gal sensitization".mp.	38
15	food hypersensitivity/ or food allergy.mp.	25,437
16	tick bites/ or tick bite.mp. or tick-borne diseases/ or tick-borne disease.mp.	7,098
17	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	26,568
18	16 and 17	174
19	telemedicine/ or telehealth.mp.	54,927
20	remote consultation.mp.	6,795
21	virtual health.mp.	1,396
22	teledermatology.mp. or teledermatology/	1,540
23	(teleallergy or tele-allergy).mp.	7
24	"Project ECHO".mp.	391
25	"Extension for Community Healthcare Outcomes".mp.	340
26	19 or 20 or 21 or 22 or 23 or 24 or 25	61,832
27	17 and 26	19
28	18 and 26	0

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Disclosure

No financial disclosures reported. Artificial intelligence, language models, machine learning, or similar technologies were not used in the conceptualization, study, research, preparation, or writing of this manuscript. **MM**

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