# Missouri Medicine

The Journal of the Missouri State Medical Association www.msma.org/missouri-medicine November/December 2020

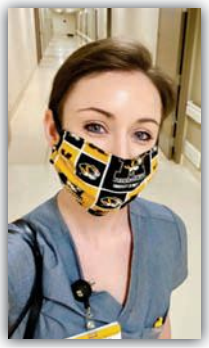





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# Missouri Medicine

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

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MSMA members representing the year 2020 and 170 years of membership.

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# Missouri Medicine

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

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### About Missouri Medicine

In publication since 1904, the peer-reviewed, award-winning, bi-monthly *Missouri Medicine: The Journal of the Missouri State Medical Association*, is indexed by Index Medicus, MEDLINE, and PubMed. Complete issues archived at PubMed Central since 2010. Content appears on EBSCO Host Research databases.

With a large and respected editorial board and regular participation by Missouri's six medical schools on eight campuses, *Missouri Medicine* is among the nation's foremost state medical journals.

Articles are frequently cited in impact factor journals and regularly featured in the national media including: *Wall Street Journal*, CSPAN-2, KevinMD, *Outside Magazine*, *Runner's World*, *NBC News*, *General Surgery News, Ophthalmology Times*, and many others. Issues of *Missouri Medicine* are printed on acid-free paper with open access to digital issues available at www.msma.org/missouri-medicine-library.

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## Missouri State Medical Association Alliance

# Holiday Sharing Card

**From the following who most generously gave to the Missouri State Medical Foundation and to the American Medical Association Foundation.**

## We bring you tidings of good cheer, & wish you a happy, healthy & peaceful New Year.

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# For 170 years, MSMA Has Been Show-Me Medicine's Most Important Advocate: All Physicians Have Benefited—All Physicians Should Belong

*by John C. Hagan, III, MD*



Since 1850, the Missouri State Medical Association (MSMA) has been the most important advocate for Show-Me State physicians and their patients. For 170 years MSMA has successfully championed the medical profession in interactions with hospitals, insurance companies, local/state/national government, regulatory agencies, and battled the junk lawsuit industry. While all physicians have benefited from MSMA efforts, the administrative costs, volunteered time and legislative burdens have been borne by its members. ***Every practicing physician in Missouri should be a MSMA member.*** 2021 would be a great time to join MSMA. We in MSMA invite you aboard. Do your part, don't be a slacker, join now.

During this terrible 2020 COVID Pandemic year, as in 169 others, MSMA has distinguished itself with its support of self-employed and employed physicians. The pages of this Journal, since 1904, have chronicled why MSMA is among the top three most effective state medical associations while having dues in the lowest five.






Look at one example: the spectacular efforts of MSMA leading a coalition to twice pass tort reform has saved physicians, hospitals, and medical schools hundreds of millions of dollars.

It is time to commit or recommit to the ideas and leadership of MSMA. Here is the time-honored formula.

## MSMA Members – Pay Your 2021 Dues

Congratulations and thanks for your membership. You are doing your part! You are the backbone of MSMA. If you have not yet paid, visit www.msma.org/JoinRenew.

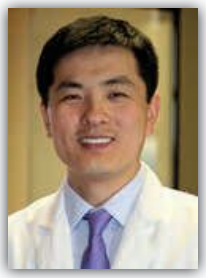
## If You Are Not an MSMA Member, JOIN NOW!

MSMA membership is especially beneficial to young and early career physicians. You have the most practice years left. MSMA, with three employed lobbyists and good relations with legislators in both political parties can do much to enhance your practice.

John C. Hagan, III, MD, FACS, FAAO, MSMA member since 1975, is a Kansas City, Missouri, ophthalmologist and *Missouri Medicine* Editor since 2000. He is a multi-year Diamond Contributor to MMPAC.

# House of Medicine Wins in General Election

MSMA would like to extend our congratulations to those physicians and spouses of physicians that have won their elections!


Dr. Patterson


Dr. Thomas

Incumbent Rep. Jon Patterson, MD ,(Lee's Summit), and first-term Rep. Lisa Thomas, MD, (Lake of the Ozarks), will represent the medical community in the House of Representatives. Spouses of physicians members that will be in Jefferson City next year include: Sen. Bill White (Joplin), Rep. Trish Gunby (Manchester), Rep. Wes Rogers (North Kansas City), and Rep. Jo Doll (Webster Groves).

MSMA member Senator Bob Onder, MD, was not up for re-election in 2020. He will continue to serve in the legislature for two more years.

MSMA looks forward to continuing our work with these legislators. Please join us in our congratulations for the members and members' spouses that will be representing physicians and their patients in the Missouri Legislature.

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MSMA is also extremely important to hospital employed physicians and academic medicine. MSMA is the most effective advocate for medical education funding and fair treatment for employed physicians. If you are a medical student, resident, or fellow, membership is free and includes an electronic copy of MSMA's award winning journal *Missouri Medicine*. Join MSMA at visit www.msma.org/JoinRenew.

## Actively Recruit New Members

MSMA members – be sure all of your practice group belong. Regular members – try to get one of your non-member hospital colleagues to join MSMA in 2021. Officers and leadership try and recruit four new members. Some physicians are just waiting to be asked. Reach out to them. Ask them to join MSMA.

## Attend MSMA's Virtual White Coat Day on March 2, 2021

MSMA's annual White Coat Day is going virtual. MSMA is currently laying the groundwork for a day of virtual lobbying and participation in the legislative process. Physician advocacy is the core mission of MSMA, so save March 2 on your calendar.

## Volunteer for Physician of the Day

If you can't make it to the Capitol on March 2, sign up to come another day and be the official volunteer physician for the entire legislature. To schedule a day visit www.msma.org/physician-of-the-day.

## Contribute to Missouri Medical Political Action Committee (MMPAC)

MMPAC supports political candidates that support physicians. As Editor, my personal recommendations are the suggested minimums: active MSMA members $150; MSMA officers and leadership $500; MMPAC Board members $1,000. To make a contribution, call MSMA's Cheri Martin at 573-691-4502.

## Read the Weekly MSMA *Legislative Report*

Respond to the "Take Action Items." Do your part, encourage others to do theirs. **MM**

Contribute at msma.org/mmpac

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Missouri Medical Political Action Committee

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# MSMA Legislative Preview 2021

*by Heidi Sutherland*

## Unprecedented Times

2020 was a year for the record books. The legislative session began in January just like any other year, but as concerning reports about COVID began to increase, we knew that we were headed toward uncharted waters. The legislature took a month and half-long hiatus in the middle of the legislative session to cut down on the risk of COVID transmission among legislators, staff, and capitol visitors. When the legislature returned at the end of April to finish the state budget, the session turned into a last-minute free-for-all as legislators created huge omnibus bills in an attempt to make up for lost time. Despite the upheaval, uncertainty, and time constraints, 2020 ended up being a very good year for medicine in the capitol.

This article includes some of our big wins from this year's legislative session and a look ahead toward 2021.



Heidi Sutherland is MSMA's Director of Government Relations.

## 2020 Wins

### *Women's Health*

The legislature has traditionally been supportive of making improvements to breast cancer screening coverage, and that trend continued in 2020. One bill expanded the catalog of equipment specifically listed as being covered under the current mandates for breast cancer screenings. That bill also expanded access to screening services for women who have an above-average risk of breast cancer, in accordance with applicable American College of Radiology guidelines.

Another piece of legislation established the Postpartum Depression Care Act, which contained a number of provisions that will improve educational resources for new mothers on the symptoms of postpartum depression. It also beefed up screening guidelines to match clinical suggestions from the American College of Obstetricians and Gynecologists. The legislation also extended the length of time new mothers are eligible for MO HealthNet benefits if they are receiving treatment for postpartum depression.

### *Credentialing*

After hearing our members' credentialing horror stories, we worked hard to promote legislation that allowed for reimbursement to physicians and other healthcare practitioners for services provided while their credentialing applications are pending with the insurance companies. The bill that passed in 2020 requires insurance companies to make a credentialing

decision within two months, rather than three. As long as the physician (or the entity they work for) has a prior relationship with the insurer, the insurance company must pay for the services provided to their members during those two months. Physicians can submit claims for reimbursement for those services once they are credentialed.

### *Punitive Damages*

The top priority for our Tort Reform Coalition this year was punitive damages reform. This legislation increased the standard for proving punitive damages to "clear and convincing" in medical malpractice cases. Healthcare providers must now perform either an intentional act or malicious misconduct in order to meet the requirements for a punitive damage award. In addition, the claim can't be made in the initial pleading, which helps keep the issue out of settlement negotiations. The final negotiations on this bill took the coalition all night to work out, but in the end the hard work paid off.

### *Medical Marijuana*

Ever since the medical marijuana program in Missouri was authorized by voters, it has been fraught with issues and complaints of fly-by-night practitioners who certify patients without first establishing a physician-patient relationship. In an attempt to add better regulation to the program, legislators proposed a slew of medical marijuana related bills in 2020. Three of those bills were successful.

The first bill requires DHSS to collaborate with the Missouri Highway Patrol to procure fingerprints and run criminal background checks for all employees, officers, managers, staff, and owners of marijuana facilities. The second prohibits the sale of medical marijuana edibles in shapes that resemble candies or would otherwise be attractive to children. The third applies the same telehealth prescribing standards to medical marijuana as are required for all other medicines. While these changes certainly won't fix the program, they will add greater accountability and patient safety measures.

## 2021 Preview

As we quickly approach the 2021 legislative session, we face many of the same questions that we did at the beginning of 2020. Will we have to contend with delays and disruption as the legislature attempts to decrease COVID risk? Will COVID shut down the legislature entirely? We can't know for sure, but we can plan ahead and stay adaptable.




Earlier this year when we were setting a date for MSMA's 2021 White Coat Day at the capitol, we hoped that COVID might be a thing of the past by March 2021. Unfortunately, this doesn't seem to be the case. With that in mind, and after Senate and House leadership asked advocacy groups to refrain from large lobby days in 2021, we'll be hosting a virtual lobby day instead. MSMA staff is currently working on logistics, but our plan is to set up virtual meetings for physicians to chat with their local legislators. Keep Tuesday, March 2, 2021 set aside in your calendar for this brand new virtual White Coat Day until you hear otherwise from us. If you have questions or suggestions for this visit day, please contact Shantel Dooling at shantel@msma.org.

### *Public Health*

Along with the bigger-ticket legislative items like PDMP, scope of practice, and insurance issues, MSMA spends time advocating for a vast array of public health items that are just as important but much less reported-on. Along with the texting while driving ban and vaccine issues included earlier in this article, we'll likely see legislation that tackles public health topics like a safe needle exchange program, gender-related treatments for minors, sunscreen in schools, access to a COVID vaccine, vapor product restriction and regulation, tanning bed ban for minors, bleeding control education, women's health, and many more. We'll also oppose decreases in public health funding or censorship of public health departments, two topics that have been suggested by legislators who are unhappy with increased COVID restrictions.

### *Medicaid Expansion*

Medicaid expansion was approved by voters in August 2020, which means that the 2021 legislative session will be dominated by discussion about the proper implementation of the program. We expect to spend a significant amount of time next year in budget hearings and department meetings as the MO HealthNet Division and the legislature make budgetary and other administrative decisions to implement this

## Receive Legislative Text Alerts Via Phone2Action App

If you would like to receive text alerts on urgent legislative developments, don't forget to sign up for the Phone2Action program. Members who have opted in to this program receive a text alert from the MSMA advocacy team when we need our members to contact their legislators quickly on an amendment or a bill. In 2020, we used the program to shore up support for a vote on the prescription drug monitoring program. If you're interested in signing up for the alerts, open your text messaging app, enter 52886 in the recipient line, enter "MOMEDICAL" in the text box, and press send. A message will then be sent to you that allows you to opt in to the program.

change and bring a new patient population into the MO HealthNet program.

### *PDMP*

The creation of a statewide prescription drug monitoring program (PDMP) has become an annual topic in the Missouri legislature. It's well-known that Missouri is the only state that has failed to pass a such a program. In 2021, we'll again try to get this important bill through the legislature. The legislation would establish a voluntary PDMP which can be used to track the dispensing of controlled substances. It would limit the ability of the state to provide that information to outside sources, contain confidentiality and privacy requirements, and otherwise create a program to assist physicians and others in the identification of potential drug misuse by their patients.

In years past, the PDMP has split Republicans into two groups. About half of them favor the PDMP as a public health tool. The other half reject it as an unnecessary intrusion into personal privacy. Democrats are traditionally in favor of the bill. We'll see which way the political winds blow in 2021. In the meantime, the St. Louis County PDMP is a fantastic resource for physicians around the state.

### *Texting While Driving Ban*

Legislation that would ban texting and driving is a frequent topic in the legislature. Currently, only two states don't have a full ban on texting and driving: Missouri and Montana. Missouri bans texting and driving by minors, but this prohibition is extremely difficult to enforce. Opponents of the bill consider the ban an infringement on their personal liberty and argue that citizens should have the ability to text and drive if they want—even if doing so endangers the safety of their fellow drivers. MSMA supports a texting and driving ban and will continue to fight for this public safety legislation.

### *Vaccines*

In 2020, we opposed a handful of bills that would have made vast changes to Missouri's compulsory immunization laws. One of those bills would have exempted parochial schools and daycares from immunization requirements, prohibited DHSS from promulgating rules for certain immunizations, and created meningococcal waivers for certain fraternities and sororities. It also contained overburdensome informed consent requirements designed to discourage immunizations. Another bill would have lowered the threshold for parents to opt out of vaccinations for religious or conscientious reasons. We expect to oppose these bills and similar anti-vaccination legislation in 2021.

### *Truth In Advertising*

This legislation seeks to reserve a number of medical specialty titles for physicians and restrict the use of the term "doctor" when used in clinical settings. In addition, healthcare professionals claiming to be "board certified" on their advertisements would need to disclose the name of their certifying board. These requirements would improve clarity for patients as they interact with both physicians and non-physician health care providers.

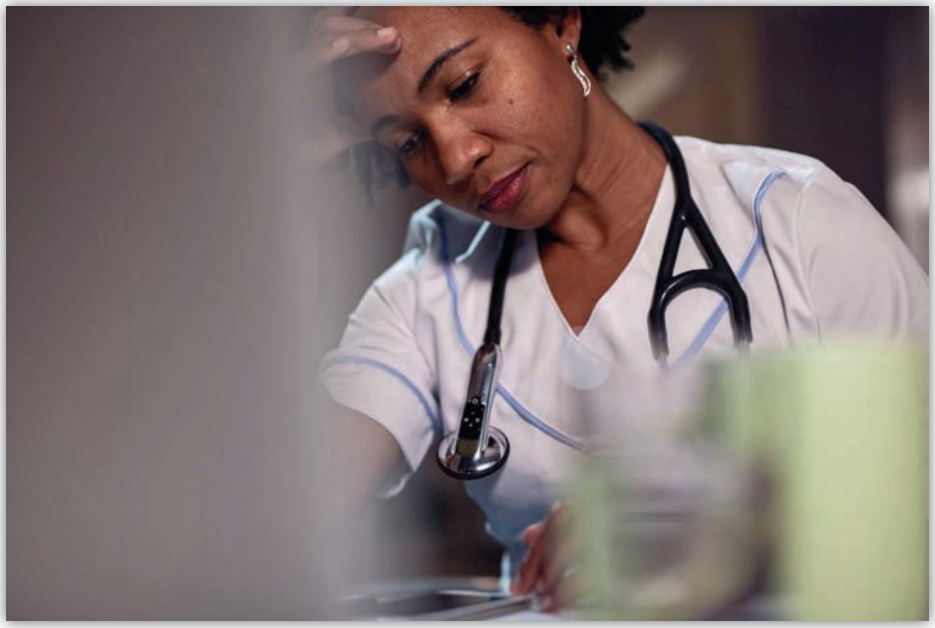
### *Scope Expansion Attempts*

2021 is sure to bring several scope of practice attempts by non-physician healthcare providers. We'll likely see the usual legislation from advanced practice registered nurses (APRNs) to chip away at collaborative practice arrangement requirements or to do away with the requirement entirely and allow APRNs to practice independently. We also expect to contend with physical therapists as they seek direct access to patients, instead of the current statute that requires a diagnosis and referral from a physician prior to physical therapy treatment. Lastly, we'll probably see a familiar bill that would create an alternative pathway to physician licensure for assistant physicians. Your MSMA advocacy team will oppose these and similar bills. **MM**

# Unintended Consequences of Prior Authorization

*by George J. Hruza, MD*

A 47-year-old mother of three presented with a basal cell carcinoma on her left nasal bridge. The spot had been there for more than a year. She was very apprehensive, having seen her grandmother lose her nose to skin cancer decades before. I proceeded with removing the skin cancer with four stages of Mohs surgery with a defect extending through the full-thickness of the nasal sidewall. I was getting ready to repair the defect with a local flap and a cartilage graft from the ear to maintain nasal valve patency. My office manager told me: "Not so fast. Her plan (the largest one in the St. Louis region) requires prior authorization (PA) for placing a cartilage graft (21235)."



The Missouri State Medical Association has been able to, through its advocacy on behalf of Missouri physicians and their patients, get S.B. 514 passed in 2019 and signed into law. This legislation requires payors to develop a standard electronic PA authorization form by 2021, provide information on PA criteria to physicians, provide 60 day notice for any PA changes, and pay for services and medications that have been approved (no retroactive denials). This legislation applies to non-ERISA plans and ACA plans.

There was no way for me to anticipate, a priori, what type of repair would be needed to get the PA before starting her surgery. What to do? Send the patient home while the PA process grinds on, which would cause unnecessary discomfort for the patient, increased risk of bleeding and infection, and additional time lost from work? Once approval has been received, the patient could come back to the office going through multiple shots again and, to add insult to injury, the charge to the patient and insurer would be twice what would have been charged on the day of Mohs surgery (no multiple surgery reduction).

I am sure that all of us have many examples of unintended consequences of prior authorization, whether for important surgical procedures or getting life-saving medications to patients. In dermatology even generic topical corticosteroids often need PA. The 2018 AMA survey of 1,000 physicians[1] found that 92% felt that PA has a negative impact on patient care. Seventy-eight percent reported that PAs led to patients abandoning the recommended care at least sometimes.



George J. Hruza, MD, MBA, FAAD, FACMS, MSMA member since 1989, is the 2020-2021 President. He practices Dermatology in St. Louis, Missouri.

Nearly a third said it takes at least three days to get a PA determination. More than one-half believe that PAs have increased significantly over the last five years. It takes almost 15 hours of staff time per physician every week to deal with PAs.[1] One can assume that a similar amount of staff time is needed by the insurer to review prior authorizations. A dermatology department in NYC has three full-time staff members just focused on doing PAs. As much as we may wish and hope, PAs will not go away as payors are convinced that PAs save them money. The data on that is not clear, especially when the costs of complying with PAs and negative impact on patient care are taken into consideration. There must be a better way!

Physicians have been at the forefront of trying to improve the PA process for the benefit of their patients. There are a number of ways that PAs could reduce burden on physicians, interfere less with patient care, save administrative costs for both sides and allow payors to focus on areas of overuse, waste and abuse of scarce healthcare resources. My wish list:

1. Electronic prior authorization with rapid turn-around time.
2. A standard form to use for PA by all payors.
3. Automated prior authorization for routine requests.
4. "Gold Card" programs that eliminate prior authorizations for a set period of time for physicians that get very high approval rates.
5. Sunset PA programs with very high approval rates as such programs do not save money and waste administrative resources.
6. Proactive information given to physicians at the point of care about when PA is required.
7. Patients with certain diagnoses and expected treatments could get proactive prior authorization for their entire expected course of treatment.
8. Development of "best practices" by physician organizations and payors working together to eliminate the need for prior authorization when such best practices are followed.[2]

The Missouri State Medical Association has been able to, through its advocacy on behalf of Missouri physicians and their patients, get S.B. 514 passed in 2019 and signed into law. This legislation requires payors to develop a standard electronic PA authorization form by 2021, provide information on PA criteria to physicians, provide 60 day notice for any PA changes, and pay for services and medications that have been approved (no retroactive denials). This legislation applies to non-ERISA plans and ACA plans. For relief with other health insurance plans, federal legislative relief is needed.

A first step at the federal level was the passage in 2018 of H.R. 6, the SUPPORT for patients and Communities Act that included streamlining of PA for Medicare Part D medications and standardized electronic PA requirement. The COVID-19 pandemic has led the Centers for Medicare and Medicaid Services to allow waivers of PAs by Medicare Advantage (MA) Plans and Medicare Part D to facilitate healthcare access for beneficiaries during the public health emergency.[3] It is not clear if the MA Plans have taken advantage of this flexibility.

Of course, there is a lot more to do. We need PA reform in ERISA plans (most employer plans) and MA Plans. The action in Congress now centers on MA Plans with H.R. 3107, Improving Seniors Timely Access to Care. The legislation would require a standardized electronic PA process and an annual report to Congress on the approval and denial rates of PA requests. In addition, any procedures arising from a procedure that has already received PA or a procedure that does not require PA would be automatically authorized and paid. H.R. 3107 has garnered a bipartisan 262 co-sponsors with all eight Missouri Representatives on the list. This legislation would certainly be a welcome change for patients, like the mother with the nasal basal cell carcinoma, to be able to have surgery completed in one session.

I am hopeful that, with the 2020 election over, Congress will consider this legislation that is very patient friendly and does not have a significant federal fiscal note. If you speak to your Congressional Representative, thank them for their sponsorship and encourage them to push their Leaders to bring this legislation to a vote. Prior authorization is here to stay, but we can make it less onerous for our practices and our patients by advocating for change. Stay engaged with Missouri State Medical Association as we advocate for you and your patients 24/7.

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**MM**

# Report of the American Medical Association Interim (Virtual) Meeting

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

The 2020 Interim Meeting of the AMA House of Delegates (HOD) was planned for San Diego, usually a great place for a meeting. But, the pandemic. So, there we were in front of our computers, all of the members of the HOD during November 13-17, 2020.

Have you ever wondered what a thousand-person Zoom call would be like? Well, wonder no longer. The AMA worked out a way for everyone to speak, so we could discuss resolutions and reports. This required a second online platform (Lumi, if you're interested), and a way of interacting with one another. It was all quite well worked out, and it was definitely a success. Nobody, however, wants to do it again.

Sue Bailey MD, AMA President, addressed the meeting. She noted that with 100,000 new cases daily, we are increasingly stressed by the COVID pandemic. A thousand health care workers have died. We have been overwhelmed by our duties and frustrated by public health responses and unmet needs for protective equipment. Now that a vaccine is on the horizon, we have an opportunity for a new start. Going forward, we should never again allow public health officials to feel pressured and intimidated into minimizing their responses to an epidemic. The AMA has advocated for vaccine development, increased testing, and has been a major national voice for response to the pandemic. We must ensure that everyone has access to health care. We must support and revitalize public health infrastructure. We must promote wellness, as well as caring for our patients

James Madara, MD, Executive Vice President, spoke as well. He feels the pandemic has confirmed the wisdom of the long-term policy of the AMA. The AMA strategy is based on equity, advocacy, and innovation, and promotes physician professional development, Response to the pandemic shows that in a crisis, both physicians and the public turn to the AMA for guidance and leadership. Moving forward, we will see a balance between telemedicine and in-person care. Inequity in the health care system has adversely affected minorities who have been disproportionately affected by the pandemic. The AMA continues to address disparities in health and health care.

The AMA Foundation supports many of the activities of the AMA. About two-thirds of its expenditures support medical education, and about one-third community health. The Foundation continues to work with the AMA Center for Health Equity As an example, the Foundation contributed $100,000 to health care on the south side of Chicago.

The HOD sessions were well attended by around 80% of the delegates. As is customary, many resolutions were considered for this meeting. However, because of the limitations of the virtual platform, there was a screening process. Resolutions were screened for urgency, and only those selected were put on the program. The HOD at this meeting was focused on urgent matters.

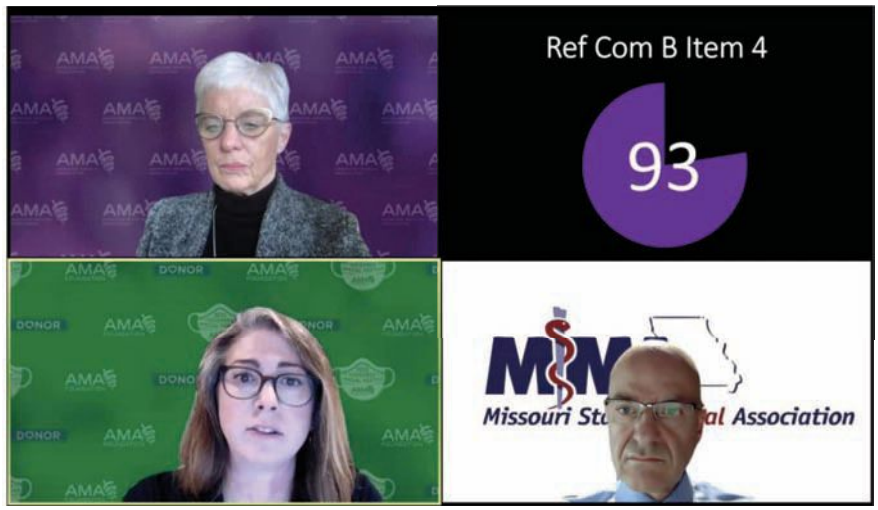
The Interim Meeting normally considers items of particular relevance to current legislation. There was considerable interest in possible health care legislation, especially after the election. A report from the Council on Medical Services (#1) recommended AMA advocacy for a public option form of medical insurance, with a



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list of requirements that must be met. The report was a "middle of the road" approach, which allows AMA support, but provides significant reservations. It was adopted only after a lot of debate. Related to this, another CMS report (#4) continued AMA support for Medicaid expansion, calling for continued federal funding and reimbursement for physicians at 100% of Medicare.

A Council on Science and Public Health report (#4) discussed the public health effects of legalization of cannabis use. This also produced extensive discussion. The AMA has long advocated against legalization. Some delegates argued that this policy should be reversed, the reasoning being that cannabis use is being legalized across the country, and the AMA should comply with the will of the people. Nonetheless, the policy continues. However, the AMA continues to advocate for more research to better understand the effects of cannabis, measures to limit youth use, and attention to adverse effects on public health as outlined in the report.




MSMA President George Hruza, MD (bottom right), testifies in the AMA's Reference Committee B on Saturday, November 14, 2020.




MSMA member Nathan Nolan, MD (bottom center), testifies in Reference Committee E on behalf of the Infectious Disease Society of America.

The thorny issue of continuing board certification was addressed by the Council on Medical Education (#01). The American Board of Medical Specialties and its member organizations have set up a Vision for the Future Commission. It is hoped that this Commission, whose report is due later this year, will provide some long-term direction. The AMA supports this Commission. In medical education, there was (again) a call for the National Board of Medical Examiners to retire the Step 2 Clinical Skills examination, which has proved to be an expensive and pointless burden on medical students, especially during the pandemic.

Current political issues were brought up, in particular the police and racism. A resolution (#409) supported restrictions on police use of chemical agents and rubber bullets. This was referred for further study, basically asking the AMA to develop ways of controlling protest movements without causing injuries. A second (#410) presented a long list of proposed reforms to police departments. Several of these were referred for further study, the HOD adopted part of this resolution which states that "police brutality is a manifestation of structural racism." A resolution (#005) identified racism as a public health threat included language that "the primary drivers of racial health inequity are systemic and structural racism." All of these were obviously influenced by current political rhetoric and by positions taken in recent political campaigns. What these policies will mean past the

# First Missouri Physician Installed as World Medical Association President



WORLD MEDICAL ASSOCIATION

David O. Barbe, MD, MHA, a board-certified family physician from Mountain Grove, Missouri, and past MSMA President and AMA President, is the first Missouri physician to be installed as the World Medical Association President. He was installed via videoconference on October 30, 2020. Dr. Barbe was a member of the World Medical Association Council from 2016-2019, and represented the AMA at international medical meetings. He has presented on behalf of the AMA and WMA at meetings in Taiwan, China, Iceland, Israel and Japan on topics ranging from medical education and augmented intelligence to shaping the future of the physician practice environment and expanding universal health coverage.

The WMA is an international organization representing physicians and was founded in September 1947, when physicians from 27 different countries met at the First General Assembly of the WMA in Paris. The organization was created to ensure the independence of physicians, and to work for the highest possible standards of ethical behaviour and care by physicians, at all times.

Visit www.msma.org to watch his virtual installation on YouTube.

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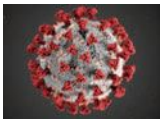
heat of the moment is an open question. The hope is that the AMA will work towards eliminating racism in health care and in society.

The AMA has created a Private Practice Physician Section. That there is a need to have such a section is a testimony to the increasingly fragile place of independent practice. Resolution #602 called for a global non-discrimination policy to be adopted by the AMA. While the AMA has long been against discrimination, and has many individual policies, this resolution advocates a global policy. The resolution was widely supported in principle, and was referred to the BOT for a report, which will presumably be available by June, 2021.

Other resolutions supported changes in practice, many related to the pandemic. Not surprisingly, a resolution (#406) recommended the AMA strongly support the wearing of masks, and other related measures. Telemedicine has been greatly expanded during the pandemic. Resolutions (#203, 205, 218) supported retaining this expansion, anticipating that telemedicine will become a permanent part of medical practice. Opioid use has actually expanded during the pandemic. A Board of Trustees report (#16) recommend facilitating treatment of opioid use disorder in primary care practices. Another (#14) called for better regulation of outpatient addiction treatment facilities.

Several physicians from Missouri served in leadership roles. David Barbe, MD, represents the AMA on the world stage as President of the World Medical Association. Edmond Cabbabe, MD, serves on the Council for Long Range Planning and Development. Elie Azrak, MD, serves on the board of the AMA Political Action Committee. Jerry Kennett, MD, serves on the AMA Foundation Board. Marc Mendelsohn,MD, is chair-elect of the Young Physicians Section. Sue Ann Greco is the AMA Alliance President. Charles Van Way III, MD, is on the Steering Committee of OSMAP, the Organization of State Medical Association Presidents.

Your AMA delegation would very much like to hear from AMA members throughout Missouri about all of the issues discussed at the meeting. For further information, the business of the meeting is available on the AMA website. Highlights from the meeting are at https://www.ama-assn.org/house-delegates/special-meeting/highlights-november-2020-ama-special-meeting. Details are at https://www.ama-assn.org/house-delegates/special-meeting/business-november-2020-special-meeting-ama-house-delegates . The Annual Meeting of the HOD is scheduled to take place in Chicago, June 12-16, 2021. We all hope that it will take place as planned. **MM**



COVID-19 REPORT

# The Danger of Misinformation in the COVID-19 Crisis

*by Taylor Nelson, DO, Nicole Kagan, BS, Claire Critchlow, EdS, Alan Hillard, MD & Albert Hsu, MD*




The SARS-CoV-2 pandemic is the first of its kind during this modern age of technology. Past pandemics have similarly affected millions, but constant media coverage regarding COVID-19 has placed this crisis at the forefront of our hearts and minds. The pandemic has become the backdrop for a political battle, with leaders clashing over public policy as well as interpretations of medicine. Providers are overwhelmed by an onslaught of medical literature, along with pressure from the media and the community to navigate the unknown with precision. Likewise, the public is bombarded with information from often unreliable sources. Misinformation is a powerfully destructive force in this era of global communication, when one false idea can spread instantly to many vulnerable ears.

## Threats to the Individual

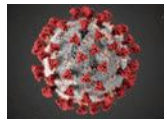
Mental health professionals have noticed trends in coping mechanisms during the pandemic, even without the compounding issue of misinformation. Some patients feel a sense of foreshortened future, a common symptom after trauma. Many have experienced symptoms of depression and grief. Additionally, while the pandemic has been a shared global experience, there is an increasing sense of isolation and loneliness.

Misinformation further aggravates an already complex emotional situation. Healthcare providers are not immune to these effects. A recent study evaluated mental health effects of COVID-19 in over 1,200 Chinese healthcare workers. Over 70% reported psychological distress, with symptoms including anxiety, depression, and insomnia.[1] These traumatic emotional effects are heightened by conflict, confusion, and conspiracy theories circulating in the news media and online.

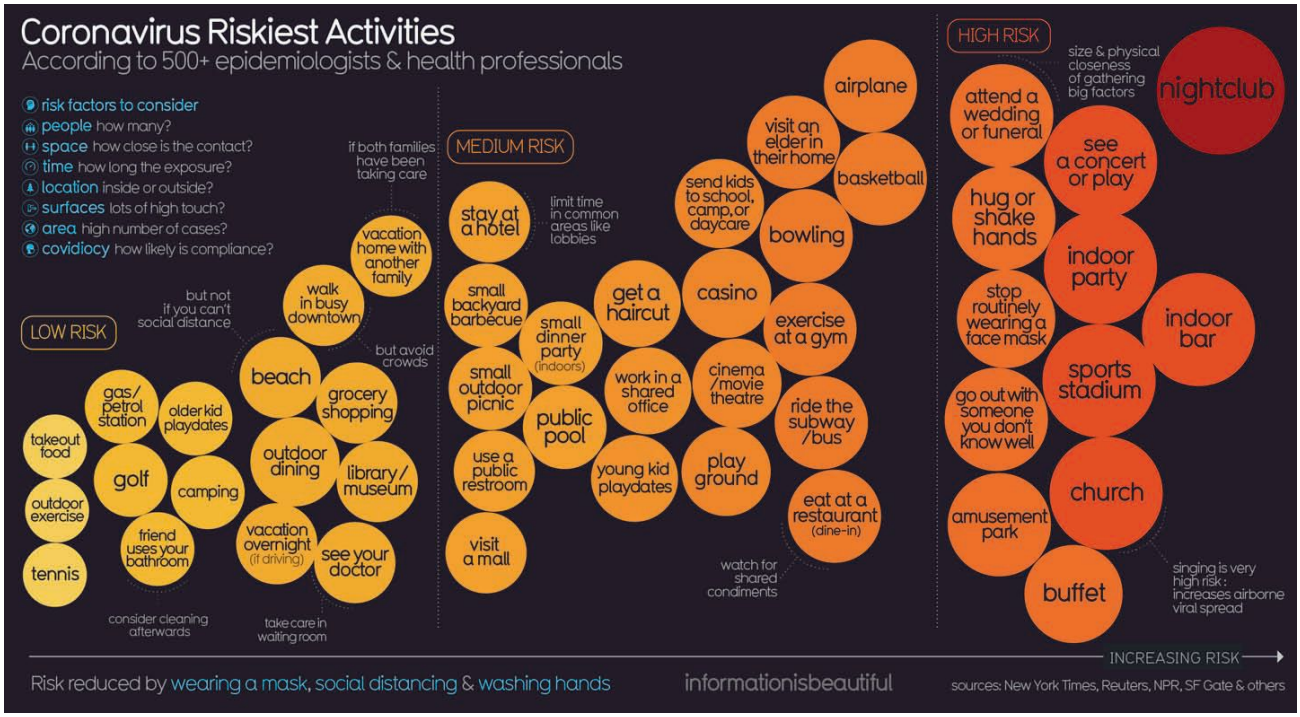
Several well-publicized incidents have demonstrated the negative impact of false information. As an example, early during the pandemic, questions were raised regarding the possible use of disinfectants administered internally to patients with COVID-19. On June 5, the Centers for Disease Control (CDC) reported a steep increase in calls to poison centers regarding exposure to household disinfectants.[2] A CDC survey of 502 adults in the United States found that 39% of responders engaged in dangerous practices including washing food products with bleach, applying household



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**ONE PICTURE = 1,000 WORDS**




cleaners directly to skin, and intentionally inhaling or ingesting disinfectants with the goal of preventing COVID-19 infection.[2] Another troubling issue secondary to heightened anxiety is the substantial decline in visits for chronic conditions, preventative care, and non-COVID associated medical emergencies which was especially prominent early on during this pandemic. The fallout from delayed care may extend well beyond the current global crisis.

Beyond the physical and psychological consequences of misinformation, confusion can trigger actions based on fear. Fear has been a palpable sensation throughout this pandemic, and is often amplified when trusted authorities promote inconsistent opinions. Chloroquine and hydroxychloroquine were initially have been proposed as potential therapies for SARS-CoV-2 infection. A small trial in France suggested hydroxychloroquine plus azithromycin may be beneficial for treatment of COVID-19.[3] Other researchers have investigated these drugs, with variable results, prior to robust research displyaing lack of benefit. One study from Brazil assessed safety of low- versus high-dose chloroquine in patients with COVID-19. Early unfavorable results showed deaths in both groups,[4] prompting the son of the Brazilian president to accuse the authors of conflicting political motivations on Twitter. Consequently, the principal investigator received multiple death treats necessitating police protection.[5]

## Threats to the Medical Literature

The hydroxychloroquine debate in the spring has also highlighted the issue of misinformation in medical literature. A recent publication in *The Lancet* associated use of hydroxychloroquine or chloroquine with several harmful outcomes.[6] Three days after publication, the World Health Organization (WHO) abruptly halted hydroxychloroquine use in its Solidarity trial, based primarily on data from this observational study. However, the study methods and reliability of data were quickly brought into question by many external experts. After numerous inconsistencies were identified, *The Lancet* study was retracted.[7] The WHO subsequently resumed

hydroxychloroquine trials for a time. During a global health crisis, research is of utmost importance. The need for rapid research has led to relaxation of normally rigorous academic evaluation, with pre-prints often published before peer review. Peer review is crucial in academic scholarship, and the standards of publication must be maintained even when data is desperately needed.

Physicians may fall prey to misinformation in this way. As new data is published hourly and guidelines are ever-changing, there is potential for doubt in the validity of manuscripts from previously trusted journals. Uncertainty can be stressful while caring for COVID-19 patients, but may also increase general stress as a trusted healthcare professional during these unprecedented times. When we are unsure how to educate ourselves and our patients amid questionable literature, this can affect the mental wellbeing and confidence needed to perform at our best.

## Social Media Amplifies Misinformation

A unique feature of the COVID-19 pandemic is the effect of social media. Researchers from Stanford University have developed a model to understand the spread of misinformation in social media, ironically, like a virus.[8] It evaluates individuals' "susceptibility" to false information, and their likelihood to spread it to others. The elderly, youths, those active on social media, and those with fewer years of formal education appear to be the most susceptible to misinformation. Repeated exposures may increase susceptibility. Individuals at political extremes are also more likely to believe information that confirms pre-existing biases. This effect is of particular concern when the information comes from a trusted source.[8]

Many organizations are attempting to counter false information and raise awareness of this issue.[9] It is difficult to keep pace with the instantaneous communication provided by social media, and falsehoods continue to spread. With time, some individuals have become desensitized to the dangers of SARS-CoV-2 and are increasingly disregarding public health guidance. Controversial opinions from medical professionals are frequently widespread in the media. The circulation of misinformation is not the root of all problems, but shifting the focus from fiction to fact will positively impact all involved.

## Conclusion

As healthcare providers, we must acknowledge the problem of misinformation and its potential consequences. We have a duty to be transparent, and to educate ourselves with a critical eye. As we look ahead to the development of further treatments and vaccination for SARS-CoV-2, careful testing and peer-reviewed study will be essential. Physicians are trusted by many, and before sharing our ideas and opinions, we should be informed by the highest quality data available. This responsibility to disseminate reliable information extends to public health officials, social influencers, and civic leaders whose words may reach the ears of many.

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MM

# New Study Confirms Physicians Are Scapegoats for High Healthcare Costs

*by Arthur Gale, MD*

**The U.S. is the only country in the free world where patients do not have freedom of choice of physicians.**

A new study shows that American physicians' practice patterns are similar to the practice patterns of physicians in countries with much lower health care costs. The new study was published in a book titled, "Which Country has the World's Best Care?" by Ezekiel Emanuel, MD, professor and chair of the Department of Medical Ethics and Health Policy at the University of Pennsylvania. Health care systems in eleven countries were studied: United States, Canada, United Kingdom, Norway, France, Germany, Netherlands, Switzerland, Australia, Taiwan, and China.[1]

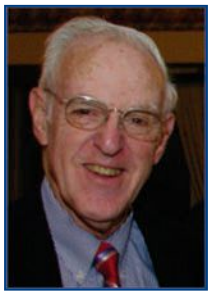
There was no one country with the best overall health care system. In respect to quality of care the United States comes out somewhere in the middle of the pack–better in some categories and worse in others. This review will focus on only two categories: cost of health care and freedom of choice of physicians. The United States ranks dead last in both of these categories.

It comes as no surprise that the U.S. has by far the highest health care costs of any country in the study. This dubious honor has been previous published in studies comparing the U.S. to other developed countries. The author writes that the U.S. "has a strange combination of being lean–with fewer physicians, hospital admissions, and other services than almost every other country-while having bloated costs."… "Surprisingly the United States does not use more of the most expensive services than other OECD (Organization of Economic Cooperation and Development) countries do such as hospitalizations or visits to a doctor"… "In general, the substantial differences between the United States and European countries on cost do not exist exclusively because other countries provide care more efficiently or have lower use of services; quite the contrary. Many have greater use of hospitals and drugs: many experts believe these countries have substantial rates of unnecessary care."… "The big reason for the higher expenditures in the United States is the *higher prices* (italics added) paid for health services."

This conclusion has clear cut implications for the U.S. If the U.S. wants to cut health care costs it should focus not on physician practice patterns but on the prices charged by hospitals, insurance companies, and drug companies. Doctors are convenient scapegoats.

A few egregious examples that are notorious for causing physician frustration and burnout are: insurance companies requiring prior authorization before a doctor can order tests or procedures, hospitals' requiring physicians to see patients on an assembly line basis, and demanding rapid throughput of hospitalized patients. These failed strategies have been in effect for years now and they have had no significant effect on lowering overall health care costs, and they never will. One definition of insanity is doing the same thing over and over again and expecting different results.

The crucial role that high prices have in causing high health care costs is in agreement with experts such as the late Princeton University economist Uve Reinhardt, PhD,[2] and Ashish Jha, MD,[3] of the Harvard School of Public Health. I have reviewed the studies of both of these authors previously in articles that have appeared in *Missouri Medicine*.[4]



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That the new study confirms that the U.S. has the highest health care costs of any nation came as no surprise. What did come as a big surprise is that the U.S, along with China, has the least freedom of choice by patients in selecting a physician of any of the eleven countries that were studied. Emanuel writes, "The choice of physician is much more limited in the United States than most other countries–not by the government but by private insurers. (Medicare has excellent choice but private insurers have constantly changing networks.)"

It is shocking to learn that the U.S. has the least freedom of choice of physician of any country other than China–the only authoritarian country in the study which severely restricts the freedom and rights of its citizens.

Not having freedom of choice is distinctly un-American. Most citizens of the U.S. have been taught that they have the most freedom of any country in the world. Freedom was the rallying cry during the American Revolution and nearly every war the U.S. has been involved in since that time.

The concepts of freedom have been mentioned in the country's most cherished and important documents-the Constitution, the Declaration of Independence and the Gettysburg Address. Freedom is mentioned four times in the first amendment of the Bill of Rights and is mentioned in each of the refrains of the four stanzas of the National Anthem. Government leaders frequently declare that the U.S. is the leader of the free world.

In the U.S. insurance plans have severely restricted patients' freedom of choice of doctors through limited networks where doctors assume financial risk. These limited networks are prevalent in the pre-Medicare population. They are also prevalent in Medicare Advantage plans to which thirty to forty percent of Medicare patients belong.[5] To date these limited networks have not had a significant effect in lowering overall health care costs.

Probably the most telling criticism of limitation of freedom of choice of doctors comes from Milton Friedman, PhD, the conservative Nobel Prize winning economist. His theories on free market competition inspired the academics, MBAs and attorneys who created managed care. Before he died Friedman wrote a famous op-ed in the *Wall Street Journal* where he denounced managed care comparing it to Soviet style health care because it limited freedom of choice of doctor and because under both systems physicians work on behalf of the system not the patient.[6]

Somewhat surprisingly, Emanuel makes no recommendations in his book on how to address out of control health care costs. He does not recommend expanding Medicare. Nor does he mention how to increase freedom of choice.

I was in private practice for almost three decades before managed care really took hold of medical practice in the 1990s. Contrary to the accepted wisdom disseminated by advocates of managed care health care costs at that time were low, patients were generally satisfied and physicians had high morale. It is only since the managed care takeover of medicine that health care costs have skyrocketed, patients are frustrated and physicians are burned out and have low morale.

That's not what the managed care advocates back in the 1990s told the public would happen. Managed care was explained as necessary to control high health care costs when ironically at the time health care costs In the U.S. were no higher than in other OECD countries. Charting health care costs over the past three decades clearly shows that U.S. health care costs only began to rise after managed care's takeover of the American health care system in the in the 1980s and 1990s.[7]

Whether intentionally or not the advocates of managed care misled the American people and the medical profession. Now the U.S. has by far the highest health care costs of any nation. And, it is the only country in the free world which does not allow patients to have freedom of choice of physician.

Sad.

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MM

# Our Language Creates Our Future

*by Philip G. Boysen, MD & Ly Zhang, MD*

The language of business has invaded and supplanted the language of medicine diminishing our professional profiles. The ethical and moral foundation of our profession, which recognizes service above reward, is in jeopardy. Being relegated to a commodity threatens patient safety and quality of care.

## Language of Medicine

The commercialization of health care is undermining and eroding the ethical and moral foundation of medicine as a profession. For centuries the medical profession has valued service above reward. Until recently, the doctor-patient relationship (a relationship between two human beings) has been sacred and inviolable. In a fast-moving market driven environment that merely counts numbers and relative value units "physician autonomy at times appears to be more aligned with ... increasing physician revenue (such that) social justice may be decreased."[1] The recently developed Charter on Medical Professionalism is being challenged on a daily basis.[2] Along with Big Pharma the rise of Big Medicine is meteoric.

Basic to the dilemma is the medical profession allowing the language of business to invade the language of medicine, thus facilitating the very phenomenon we must avoid. Language develops the social and cultural world we live in as physicians.



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It is a critical exploitable resource that can be used against us if we do not guard against it. Language includes body language, headset, posture, vocal tone, and facial expression.

Language is constitutive. Language identifies the specific nature of what it refers to. For example, a desk has little meaning until it is "languaged" even though it exists as an object. With language it becomes brown, three feet tall with drawers, existing in an office, giving it the "how of its effectiveness."[3] Language creates our world.[4]

Language leads to sensemaking, and with it the power not only to communicate but also the power to think, to imagine, and to plan for possible future actions.[5] Guarding the language of our profession is a complex adaptive challenge as opposed to the simpler challenge of the mechanical and straightforward issues. Lucey and Souba opine that reinforcing rules, e.g. compliance with a series of rules, rewarding "right" behavior, punishing by expulsion are common techniques but inadequate tactics.[5]

It isn't just medical language that has been corrupted. In an era of email tainted by shortcuts, messaging, and tweeting, it is no longer necessary to complete a sentence, spell correctly, or punctuate. Language interrupters dominate our speech. Molly Worthen, an academic at the University of North Carolina at Chapel Hill published an essay in the *New York Times* on April 20, 2016, titled "Stop Saying I Feel Like", wherein she writes, "the phrase is an absolute trump card – it halts an argument in its tracks." Unlike saying, "I think", or "I believe", saying "I feel like" avoids having an opinion or taking a stand, which is the basis of rational argument or persuasion. No one can argue with your linguistic hedging in your effort NOT to express an opinion.[6]

Quoting George Orwell: "If thought corrupts language, language can also corrupt thought." Orwell formed his opinion during his Spanish Civil War experience; the totalitarian government of the



Language includes body language, headset, posture, vocal tone, and facial expression.

dictator Franco used language to oppress citizens and exert absolute control. His thinking culminated in his book 1984, a book with profound influence popularizing the term Big Brother, and describing totalitarian tactics as "Orwellian."[7]

The language challenge is eloquently supported by Parse when she stresses that words like delivery system, consumer, provider, compliance, and cost-effectiveness are indicative of a business model context:

To call healthcare pathways a delivery system is a language that conjures up an image of an assembly line model of efficiently moving products to a consumer…These words with the images, sounds, and suggestions, are so imbedded in the healthcare language that they not only reflect but continue to foster the idea that humans are objects who must fit into a standard system where uniqueness is ignored and personal meaning is not honored.[8]

The federal government has taken the provider language one step further in assigning National Provider Identification numbers, the NPI, We are no longer professionals in this designation, but now are also nameless. Being numbered is dehumanizing and strips away our professionalism. Our recognition as professionals has been attacked on multiple fronts. The Goldfarb Supreme Court decision reduced medicine (physicians) and law (attorneys) from a profession to a business and as "ordinary purveyors of commerce" no different from any other business. It resulted in complete control of medicine and its practice by the Federal Trade Commission.[9] The FTC attempted further totalitarian control by suing the American Medical Association to nullify professional standards, deemed by the FTC to be a restraint of trade.

Imagine an anesthesia group in a corporate practice covering an active outpatient gastroenterology suite examining 60 – 80 patients per day. Intravenous general anesthesia (unconscious patient, not intubated) is administered for these patients with a staff of two anesthesiologists and eight Certified Nurse Anesthetists (CRNAs). This system was based on an analysis of patient preparation and flow through the facility and minimizing recovery time in post-procedural area. The ratio of 4:1 CRNA/anesthesiologist is in compliance with CMS regulations to code and process charges as medical

direction. The physician examines all patients preoperatively, monitors intra-procedural care, and releases patients from the post-anesthesia care unit when "street ready," entering signed notes into the record for all phases of care.

A unilateral and upper level corporate decision was made to trial "alternative methods of care," changing the assignment to an 8:1 ratio of CRNAs/physician, thus changing the CMS code to supervision rather medical direction. The anesthesiologist does not perform pre-procedural examinations, nor examine patients for discharge, and does not sign the anesthetic record even though his/her name is recorded in the computer. Payment to the hospital remains the same, monies billed in the name of the CRNA flow to the hospital. Physician compensation drops precipitously despite liability. The managed care organizational focus is to provide the least qualified and credentialed person to deliver care without reduction in cash flow to the organization, and with no regard for patient safety.

The point to recognize is that since both the CRNA and physicians are called "providers," they fall under the same umbrella and changes can be made at will by corporate decision. To continue the scenario, the organization soon launches a five/day, eight hour/day course to "certify" sedationists, i.e. a new provider, neither nurse nor physician. From the start the unspoken but clearly defined corporate goal was to replace both the physicians and the CRNAs.

We don't have to imagine this scenario. We have experienced it in a large corporate practice.

Paying attention to experts who impact our profession suggests an alternative. James Reason, an expert on human error (developer of the Swiss cheese model of error trajectory) recently published a book dealing with organizational error. He makes a distinction between the people involved in direct patient care – whom he designates as the front line professional – and the organizational hierarchy who do not practice. He maintains that the front line professionals are change-makers, creative and resilient, and recognizes the friction with the hierarchy that often develops.[10] Being a front line professional is consistent with our desired image and function as physicians.

Don Berwick, MD, founder and former CEO of the Institute for Healthcare Improvement (IHI) has changed the way in which patient safety, quality of care, and process improvement are viewed and implemented in healthcare. The initial certification by IHI is based solely on an online learning process with 11 modules, and is an example of online learning at its best. Further learning and expertise can be demonstrated by self-study and an online closed book examination at a learning center. If successful, the individual is certified ty IHI as Certified Professional in Patient Safety, or CPPS.[11] Dr. Berwick does not use the word "provider." The two "Ps" in the certification stand for Patient and Professional, as it should be!

As authors of this article, we are a generation apart, and differ in gender and ethnicity. We experienced our medical education at a different time during a different century. However, neither of us started our journey in medicine intent on becoming a provider. We both set out on an educational journey to become a physician. We expected to join in a social contract with our patients as individuals, and in so doing adhere to the principles of service and altruism. It is our sworn duty to maintain our profile as professionals which will emphasize patient safety and quality of care as the core of our practice.

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**MM**




# In Praise of Veterans

*by Charles W. Van Way, III, MD*

Veterans Day is a time to reflect on those who have been lost in our country's wars, and on just how much we owe them. And we also honor those who served and came home, and those who still serve. Military veterans have a special place in the American heart. It has always been thus, from the early days of the Republic. As the quote above from Henry V shows, respect for those who fight a country's battles goes back much farther. Ancient texts from Rome, Sparta, and Athens show the same pattern. There have been times and places where military veterans have been scorned, but these have been isolated. The default attitude is respect, even veneration. The author Robert Heinlein, himself a Naval Academy graduate, wrote a novel about a society rebuilt from devastating wars in which the only people allowed to be full citizens, and to vote, were military veterans. Of course, that was science fiction.




The military virtues of honor, courage, and self-sacrifice have always inspired soldiers and civilians alike. Much of our regard for veterans comes from the perception that they embody these virtues. Individuals are imperfect, but the veteran as an ideal is built into our culture.

Simple gratitude explains some of our regard for veterans. We owe much to our veterans. Our nation was born in revolution, and has survived in war the practice of slavery plagued us for 80 years, and was settled in our Civil War. We fought in both of the World Wars. Even Korea and Vietnam, as unpopular as they were, played a major role in our winning of the Cold War. Today, our military forces are fighting for our interests around the world. Perhaps too many places around the world, but that's a topic for another time. We live in a time of cynicism, but still, our debt to those who have served remains visible.



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Confession time. I am, myself, a veteran. I've served during two wars, although not at the sharp and pointy end of either. Like many, I'm often bemused by people's attitudes. Today, it's pretty positive. Back in the 1970s, things were a little more dicey. That was one of the "times and places" where a lot of folks didn't like soldiers or veterans. That attitude died out in a few years. Today, people come up to me and saying, "Thank you for your service." I don't always know quite how to respond, but I always appreciate it. Usually, I just smile and say, "Thank you."

Some years ago, I began to realize that many people simply wish they had served. After Vietnam, nobody was drafted. A fair number of people began to realize that their father's and grandfathers had served, and their older colleagues, but they hadn't. Perhaps some of them felt guilty about that. But I think the majority simply felt that they had failed to have a significant experience in their lives. And they were correct. Because military service, even in a time of relative peace, changes a person.

The essence of military service is this: you turn your life over to your country for a period of time. Literally, because your country may send you someplace where you might die. It does make you think about priorities. You realize that your own personal life is at risk. We value things in direct proportion to how much we have paid for them. Making a commitment to your country that may cost your life is a very high price. You think a lot before you pay it. Once you have done it, it alters your value system, how you see yourself. It affects how others see you, as well.

We come back around to Veterans' Day. Originally Armistice Day marked the end of World War 1. Now, we remember all veterans, most especially commemorating those who died in our wars. It's a solemn holiday, as it should be.

This is a difficult time in our nation's history. After a very divisive election, we remain at odds with one another. The COVID pandemic continues to spread. Economic times are hard for many of us. Yet our nation will endure. Veterans' Day is a good time to reflect on just why it has, and why it will continue to do so despite our adversities and our current challenges.

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- Radiation Oncology
- Radiology
- Rheumatology
- Sleep Medicine
- Telemedicine
- Trauma Surgery
- Urgent Care
- Urology
- Vascular Surgery

# "The Fed Med" 90 years in Springfield, Missouri




*by Michael S. Clarke, MD*

The official name of the hospital facility pictured above is the United States Medical Center for Federal Prisoners. Turn back the clock to October of 1929. Springfield, a small town of approximately 25,000 in the Missouri Ozarks, had proffered a bid for a proposed new federal Medical Center. On "Black Tuesday," October 29, the very day the biggest percentage drop in the history of the Stock Exchange took place, Springfield received word its formal bid had been received and was being considered.

The roaring '20s had been kind to Springfield, and it was a growing, dynamic town and a major hub for the Frisco Railway. The acquisition of the federal Medical Center would stabilize its economy for the soon to come depression of the '30s. The bid for the Medical Center came just ten years after the Spanish flu of 1918 and 1919 that devastated the United States. This flu, however, like today's coronavirus, had little adverse impact in the Ozarks. Fifty million people worldwide had died, and there had been 675,000 deaths in the United States out of a population of 103,000,000 in 1918. But only a few deaths occurred in the Ozarks. Also, World War I had only recently ended on November 11 at 11:00 a.m. in 1918. The "war to end all wars" was still vividly on the minds of Ozark citizens. Under the direction of an aggressive Chamber of Commerce, Springfield persevered with its bid despite the unsettled times. Eleven other communities throughout the U.S. had put forth bids. How many withdrew due to the stock market collapse is unknown.

Four months later on February 1, 1930, Springfield's post-crash economy was bolstered by the announcement in the *News-Leader* of the winning bid. The hospital would employ more than 1,000 personnel with high wages and benefits. Construction of this three million dollar facility began in March 1930 and completion was March 1933, the day after President



A retired U.S. Army Colonel, Michael S. Clarke, MD,a is a Springfield orthopedic surgeon and the *Missouri Medicine* Editorial Board member for Military Medicine. He has written for the *Greene County Medical Society Journal* for over 30 years. He has been a member of MSMA since 1976.

Franklin Delano Roosevelt with his "New Deal" took the oath of office for his first term.

Springfieldians rejoiced at having the handsome new hospital structure, then the largest general hospital in Missouri. There had been no resistance from the public. A prominent banker Lewis Meyer, president of the Exchange National Bank, had sold to the city for a nominal sum a 620-acre plot of land on the Springfield plateau approximately two miles south and west of the city limits. This land was offered as part of the bid. It may well have been the deciding factor in Springfield's success. For many years inmates farmed the excess land producing a significant source of revenue for the prison hospital. Additionally, inmates sold handicrafts once a week to the outside public. For legal reasons in the early '50s farming was discontinued, and the sale of handmade crafts was also abandoned a few years later. A good deal of excess land surrounding the prison sight was returned to the city of Springfield and subsequently purchased by Missouri State University for agricultural research.



Many prominent celebrity criminals have been imprisoned in Springfield among them are John Gotti, and Joseph Bonanno, mafia kings; Robert Stroud, the Birdman of Alcatraz; and Larry Flynt, publisher of Hustler Magazine.

During construction, a large Indian burial ground was encountered. The city had not mentioned this known burial ground to the government, and it was feared that knowledge would be an item of contention and possibly curtail construction. However, construction continued unabated. Bones from the Kickapoo and Osage Indian tribes that inhabited Southwest Missouri were found in addition to many buffalo skeletons. Also, on the acreage were the banker's beautiful home and a natural lake. The home was used for several years as the warden's residence, and the area about the lake became a poorly kept park. As lake levels fluctuated a small island would appear in the center. Children swimming to the island would often return with bones. The bones were identified as buffalo and human femora and tibiae used by children as bats in their ball games. These "bats" were eventually dated at between 1700 and 1830.

Through the years, the facility came to be known as the "Fed Med" by the locals who did not care for the long acronym USMCFP. The "Fed Med" also acquired a second name, "The Country Club" of the federal prison system. Many convicted criminals actually requested assignment to Springfield upon sentencing. "Trustees" were allowed a good deal of freedom. Medical staff living on campus were provided houseboys and yard maintenance crews. The "Fed Med" fielded a competitive baseball team. Area city league teams were invited to compete on the sports fields in the courtyard of the prison. The new hospital immediately became quite active with medical transfers received from throughout the federal prison system consisting of 240,000 prisoners. The bed census blossomed to over 1,000. The city of Springfield also quickly grew out toward the Medical Center, and soon affluent residential areas arose surrounding the prison property.

In the '30s, the most common medical diagnosis was tuberculosis. Today heart disease, diabetes, renal and prostate conditions are prevalent. The entire federal prison system refers patients to the "Fed Med" which receives those with more serious medical problems. The "Fed Med" throughout its 90-year history has been fortunate in having very few uprisings or attempted escapes. Three escape attempts occurred in 1940, 1944, and 1959. Small riots were associated but brought under control with tear gas. The 1944 uprising was alerted by sirens, and a group of nearby picnicking American Legionnaires quickly mobilized and assisted guards in squelching the attempt. The escape attempt of 1959 led to two inmates being shot by one of their own. These were the only casualties in the history of the Medical Center. Several hunger strikes have

spontaneously subsided. The hospital capacity has remained at 1,070, approximately a third of which are psychiatric patients, and a fourth are geriatric patients. One of the most active dialysis units in the nation treats around 300 renal patients regularly.

Although the Medical Center is considered a general hospital, there has been a tendency for surgical procedures to be referred to local hospitals, especially Mercy Hospital in Springfield. Attempts to establish an open heart surgery program in the 1990s were unsuccessful. There are no other federal prisons in Missouri. The "Fed Med" holds accreditation from the American Correctional Association, the Hospital Joint Commission, the College of American Pathology, and the American Psychological Association. Many patients are transferred from throughout the federal judicial system by air or land for mental competency determinations. The present medical staff consists of 18 full-time physicians, three of which are psychiatrists, plus three dentists, approximately 130 nurses and therapists. Full laboratory and x-ray services are available in-house. The warden was formerly required to be a physician (MD or DO) from the public health service. Today, a hospital administrator serves as warden. The U.S. Public Health Service formerly supplied the medical staff. This also has changed. Now the Bureau of Prisons hires the medical staff. Approximately 18 consultant specialists from Springfield are also on staff. The entire staff numbers approximately 1,100, slightly over a one to one staff to patient ratio. The annual budget is about twenty million dollars.

Many prominent celebrity criminals have been imprisoned in Springfield among them are John Gotti, and Joseph Bonanno, mafia kings; Robert Stroud, the Birdman of Alcatraz; and Larry Flynt, publisher of Hustler Magazine. Mr. Flynt's wife, Althea Flynt, was the center of attention and in the news a good deal during the time Flynt was an inmate in Springfield. She generated a great deal of controversy in Springfield by ripping a metal detector from the walls of the hospital entry and inflicting additional damages to the building, plus verbally abusing the warden. Springfieldians followed her antics with interest. There were several demonstrations in her favor in front of the hospital. Her dress was usually pink tights and a metal-studded jacket with a harness and magenta-colored hair in a rooster comb hairstyle. Nine months after Larry Flynt was transferred from Springfield to another facility his wife was convicted of drug charges. Another famous inmate was terrorist Omar Abdul Rahman, also known as the "Blind Sheik." He spent a great deal of time in the Medical Center and died there. For several years, the prison hospital held over 100 transfers from Guantanamo, Cuba. The "Fed Med" is only for male prisoners. Narcotic addicts are treated in Springfield if they have a concomitant major medical problem. If not, they are treated in Leavenworth, Kansas. Certain complex medical patients can be transferred to the federal Medical Center in Rochester, Minnesota. This facility is staffed by Mayo Clinic physicians.

The death rate is 35-40 yearly. Unclaimed corpses are handled by contract with a local mortuary. Autopsies are performed on-site. If requested, bodies can be shipped to the deceased's home and burial provided.

The federal Medical Center affords many opportunities for physicians with a military or civil service or other government service background. For instance, those physicians who are Vietnam or Gulf War veterans may attain their 20 years of service by working at the Medical Center for their needed years. This applies to National Guard and military reservists (Army, Navy, Air Force, Coast Guard, and Merchant Marines). Certain age requirements apply, but waivers are available on occasion. One's rank or pay grade may be promoted adding to the physician's retirement. More information can be obtained by calling: 417-862-7041 or writing to: 1900 W. Sunshine St., Springfield, MO, 65807.

The "Fed Med" will soon be celebrating 90 years in Springfield. It continues to be the nation's largest, oldest, and the best-known federal prison hospital and a major resource to the Ozarks. It is one of three 1,000-plus bed hospitals in Springfield.

Through the years, especially after World War II and the Korean War, public health physicians on the staff of the Medical Center have opted to join the Springfield medical community. Most were in line for transfer, and the lure of Springfield's pleasant climate and geography plus good private hospital facilities caused them to remain and practice in the Ozarks. Many present-day prominent physicians in the Ozarks have roots at the "Fed Med."

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- Springfield *News-Leader* archives


**MM**

# Greene County Medical Society Tackles COVID-19 Challenges

*by Jim Blaine, MD*

The Greene County Medical Society began our year with the installation of our new President Kayce Morton, DO, and set sail with our wonderful Managing Director Cathy Leiboult and a great Executive Council on a promise of an exciting year. It certainly has been exciting, but not what anybody expected.

The GCMS Alliance under the leadership of co-presidents Barbara Hover and Jana Wolfe began the year hosting our third annual Physician Family Night at the Museum. This popular well-attended event is held at Springfield's Discovery Center after hours to allow our families to enjoy time with children and grandchildren. Additional social activities including Physician Family Day at the Zoo had to be cancelled due to COVID-19 restrictions. Committee meetings and the GCMS Alliance Book Club continued to meet throughout the year via Zoom and conference calls.

Dr. Morton is the ultimate over achiever. She was the Pediatric Section Chair at Cox Health System and a Pediatric Hospitalist, and is now the Pediatric Medical Director at Jordan Valley Community Health Center. She is on numerous boards, and committees and has received many well-deserved accolades. She is also wife to Brandon, and mother to two wonderful children.

We have had, over the years, many GCMS Summer Family Trips, and have fond memories of Rocky Mountain Medicine in Colorado and CME by the Sea in Destin Florida. This year we had reservations for multiple GCMS families at Crystal Beach in Destin, but, of course, it was not to be due to concerns for the coronavirus pandemic.

We began our 2020 projects by sponsoring a Medical Marijuana Symposium that was hosted by our friend David Claborn, DrPH, Director of the Masters of Public Health at Missouri State University, and in collaboration with the Springfield-Greene County Health Department. Speakers included Director of Health Clay Goddard, Lyndall Fraker, Director of Missouri's Section for Medical Marijuana Regulation, and his Deputy Director and Counsel Amy Moore.

The GCMS Community Health Advisory Committee (CHAC) with new chair Nancy Yoon, MD, kicked off a memorable meeting addressing proposed management of COVID-19 in our city and county. Nancy is also the Chief Medical Officer of the Springfield-Greene County Health Department. Presenters included, in addition to Nancy, Health Department Director Clay Goddard, David Barbe, MD, President Elect of the World Health Association, Greene County Commissioner and former Health Director Harold Bengsch, Springfield Mayor Ken McClure, Mark Griesemer, DO, Director of Mercy Emergency Department, Howard Jarvis, MD, Director of Cox Emergency Department, Bala Allam, MD, Director, Mercy Hospitalists, Tom Lewis, MD, Medical Director, Mercy EMS, Larry Woods, Greene County Emergency Management Director, Jean Grabeel, Nursing Director, R-12 Schools, Mark Alexander, Director, Cox EMS, and Bob Patterson, Director, Mercy EMS.

The MSMA and GCMS both wrote letters to the governor to encourage him to "shelter in place", and he did. Unfortunately, like most of the country, we came out of a successful shelter a little too early, and, without a national plan, our cases quickly began to climb.



Jim Blaine, MD, MSMA member since 1984, is Co-Editor of the *Greene County Medical Society Journal.*
*Co-Published with the GCMS Journal.*

May spawned many heroes. Cox Health President, and National Top COVID-19 Hospital Administrator Steve Edwards was the first to encourage the governor to follow the science. Steve wrote a poignant and positive Op-Ed for the GCMS Journal and continues to lead by encouraging mandating masking and distancing in Springfield and the area. Robin Trotman, DO, is a Cox Infectious Disease specialist and is leading a group of University of Missouri Medical Students as they discover a different educational experience than they were anticipating. Health Department Director Clay Goddard, and Medical Director Dr. Nancy Yoon are doing a fantastic job coordinating local testing, and contact tracing. And, while our heroic Springfield City Council unanimously passed a mandated masking ordinance for the city to keep our numbers in check, our surrounding rural counties have not. Without a statewide or local masking mandate, their communities are surging and filling our hospitals with COVID victims.



2020 GCMS Executive Council.



Medical Student's with Dr. Trotman: Trotman's Team - smart and tough! Steve Edwards, President and CEO, CoxHealth.

Several GCMS physicians participated in a "White Coats for Black Lives" demonstration in the front of Cox Hospital in June. We published the GCMS Statement on Racism in our May/June Journal. Many GCMS members, and especially Dr. Kayce Morton, actively supported the Medicaid Expansion ballot issue by collecting signatures, doing interviews, and statewide PSAs. GCMS and MSMA member, and former AMA President David Barbe, MD, was inaugurated as World Medical Association (WMA) President on October 30. Originally scheduled to be in Spain, the WMA meeting was virtual. We are very proud of him.

Jordan Valley Community Health Center in collaboration with the GCMS, and the Springfield-Greene County Health Department is developing a Mobile Vaccination Unit (MVU). The MVU is financed by a grant provided by the CARES committee. Jordan Valley Health Center Medical Director Matt Stinson, MD, long time GCMS Flu Committee Chair Jim Rogers, MD, and GCMS President Kayce Morton are leading the effort to prepare for our eventual COVID conquest by developing an innovative method to deliver COVID vaccines in a rapid and efficient fashion.

Finally, we will bid farewell to our GCMS Journal Co-Editor Victor Pace, MD, who has moved to St. Louis but will continue serving on our Editorial Committee. Minh Thu Le, MD, has agreed to fill Dr. Pace's position as Co-Editor beginning in January. **MM**

# A Volatile Year for Investors: What to Expect Next

*by Michael T. Carpenter, JD, CPA*

**After such a whirlwind of a year, it is prudent for investors to revisit asset allocation and confirm its alignment with long-term goals and objectives.**

The year 2020 has undoubtedly been a memorable one for many people. For those who enjoy traveling, it was a year of cancelled vacation and travel plans after the worldwide pandemic took hold in February. For sports fans, there was a period of a few months void of athletic competitions. For investors, the memories will be marred with historic investment volatility produced by an economic recession early in the year and a contentious election late in the year.

For almost anyone with exposure to equity investments, the first three quarters of the year served as a gut check and reminded investors that investments don't always go up at all times. After a tumultuous year like this one, it is often a good opportunity for investors to revisit the asset allocation of his/her portfolio and ensure alignment with long-term goals and objectives. But the potential impact for investment markets of the ongoing pandemic and results of the U.S. election should also be considered.

The onset of the worldwide pandemic earlier this year upended equity markets, the sharpest decline in history with corporate earnings plummeting in many industries. The likely cause: uncertainty around business closures and population lockdowns, and the opacity around when corporate earnings might recover.



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Governments across the globe acted swiftly with unprecedented fiscal and monetary policy support and corporate earnings have significantly recovered since March, all which have served as tailwinds for equity investments pushing many sectors of the market to new highs. Consensus earnings estimates for 2021 now match or even surpass levels seen in 2019, and the outlook for the following year is even brighter (Figure 1).

On the other hand, interest rates dropped precipitously during the pandemic and bond yields fell near record-low levels (Figure 2). Despite record levels of government debt, inflation does not appear to be on the horizon – at least not yet. And recently, the Federal Reserve shifted its inflation target and will, in the future, allow interest rates to remain low even if inflation does eventually flare up, further supporting that the current "easy money" policies are here to stay. In sum, interest rates seem likely to remain low for at least the next few years; consequently, fixed-income investors should have low expectations for bonds, Certificates of Deposit, and other fixed-income investments for the foreseeable future.

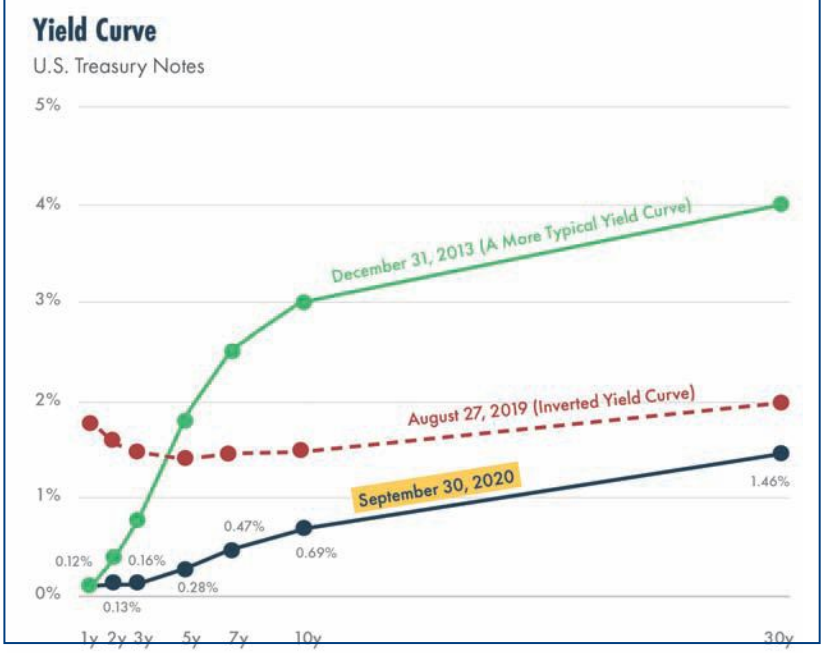
Political party affiliation aside, there has been much trepidation surrounding the election. The rhetoric from both sides of the aisle can best be characterized as strident. The divisiveness feels like it is at peak levels. Add to that the ongoing social debate, and it's clear that anxiety and unrest in this country have been high. Consequently, a record number of U.S. voters showed up November 3 and cast their ballots. At the time of this writing, the election results remain uncertified, but, unofficially, Joe Biden is the President-elect.

A significant issue for investors is whether the election cycle matters to the stock market. Refer to Figure 3. There is no easy answer, and the impact to the markets is highly dependent on numerous factors.

Figure 1. S & P 500 Earnings




Figure 2. Yield Curve - U.S. Treasury Notes



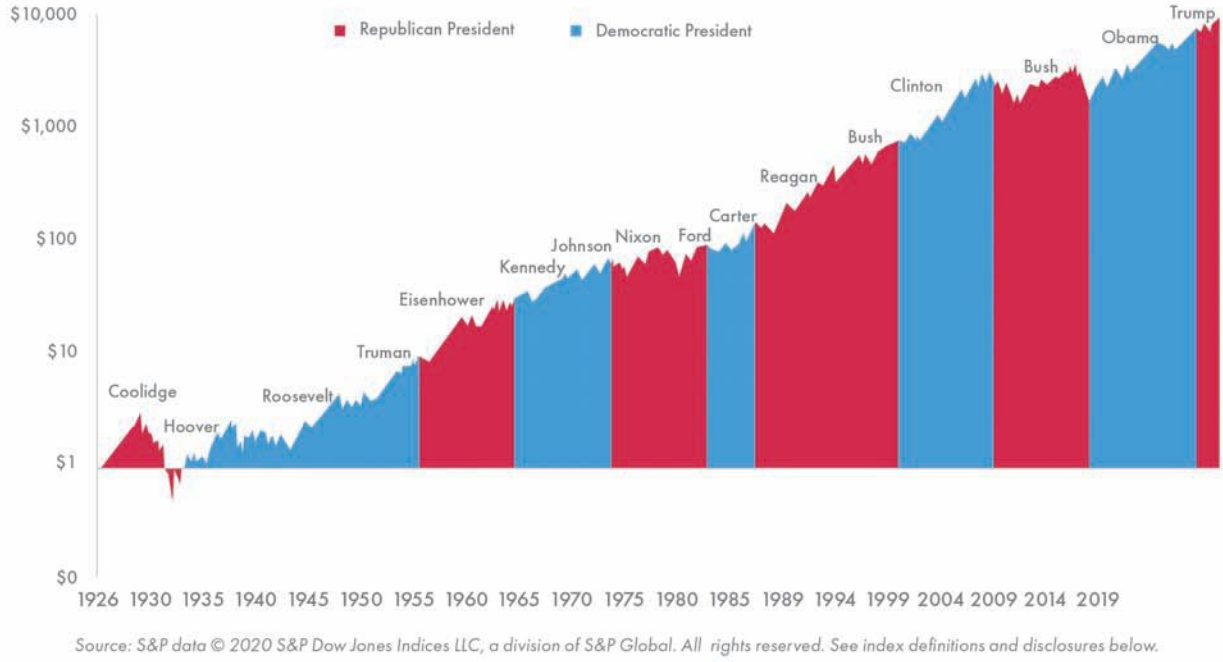

Many market participants are surprised to learn that, since 1976, the average annualized return under Democratic presidents has been 14.3% against 10.8% under Republicans. A continuously-held Democratic portfolio (Carter-Clinton-Obama) outperformed a continuously-held Republican portfolio (Reagan-Bush, Sr.-Bush, Jr.-Trump) 14.9% to 4.9%. However, when looking further, one can see that it is a small sample size and heavily influenced by the second Bush's presidency, which was book-ended by the 9/11 tragedy and the "Tech Wreck" on the front-end, and the Global Financial Crisis in the latter stages. In other words, many events that influence the markets are beyond the control of the president.

There has been a significant amount of research conducted on both election year performance and the performance under various scenarios (one party sweep; Democratic president, Republican Congress; etc.). While most of the sample sizes are relatively small, a few patterns and thoughts emerge:

- There is a relatively consistent "Presidential Cycle" to the market's performance that shows the first two years of a presidential term tend to have below average returns, while the second two years tend to have a higher return. This could be attributed to a variety of reasons, such as the influence of mid-term elections and a president's thoughts and policies turning towards reelection in the last half of the term.
- In the short-term, fear and hope around a president's proposed policies can influence the markets, but it is the impact of those policies on the economy and corporate earnings that matters over the longer term.

Over the long-term, the economy matters more than the person in the White House. Growth, inflation, earnings, interest rates, and independent monetary policy all are the most influential forces in driving long-term returns. The economy and the markets, while influenced by politics, want to grow and are more significant than which way the political winds

Figure 3. Presidential Terms and the S & P 500




are blowing. It is also very important to remember that the mid-term elections provide the opportunity for course changes if the public is unhappy with the health of the economy and the markets.

Undoubtedly, the election is an important milestone that will have a modest amount of influence on the markets in the short-term. However, in the intermediate term, the fiscal and monetary stimulus being provided are a larger factor to the markets and unlikely to change regardless of the election outcome. Those extraordinary policies – low interest rates, enhanced benefits and stimulus checks – have created something of a safety net for the broader economy and to-date, a powerful tailwind for the stock market.

What does all this mean for investors? Most importantly, after such a whirlwind of a year, it is prudent for an investor to revisit his/her asset allocation and to confirm its alignment with his/her long-term goals and objectives. Studies have shown that, by far, the most impactful variable on a portfolio's long-term returns is the asset allocation decision. As such, a prudent long-term investor should place his/her focus there, rather than worrying about the impact of events that might not come to fruition. Secondarily, an investor should confirm the underlying investments in his/her portfolio align with that long-term asset allocation. An experience like this year reminds us of one thing – while we do not know with certainty when the next bout of market drawdown will occur, the best time to prepare is *before* the next storm.

## Disclosure

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**MM**

# Correspondence

## Medical Marijuana: First Do No Harm

All physicians take the oath to "first do no harm." As a pediatrician and emergency medicine physician, I feel it is necessary to address the daily harms I see as a result of cannabis use/misuse by both patients and physicians. Without a doubt, since legalization of cannabis in Colorado, drug use has gone up in all age groups. The most recent Healthy Kids Colorado Survey[1] indicates a marked increase in the number of school aged children using cannabis. Not only are they using younger, they tend to start with the high potency products–dab, wax, shatter, THC concentrates. Recently, I had two children, both under the age of 14, obtain a cannabis infused candy that contained 500 mg of THC (remember, marijuana joints of the '90s had about 3 mg THC). They each ate half of the candy and ended up in our emergency room. Young people and children have figured out how to get marijuana via social networks, such as snap chat. I would like to say this is an aberrancy, but we are seeing this on an increasingly frequent basis.

Since Colorado has legalized "medical' marijuana, Cannabinoid Hyperemesis Syndrome (CHS) has become a daily problem in our emergency room (ED). Cost for a single visit for CHS symptoms in our ED, including IV medications, nursing time, radiographic studies, physician evaluation is estimated (on the low side) to be about five to six thousand dollars. A study done by David Zimmer, et al.[2] showed that due to recurrent visits and chronicity of presentation, the eventual cost to ultimate diagnosis per patient with diagnosis of CHS is $76,920.92. Over a total year the costs just one Emergency Department for CHS exceeded $1.8 million, much of this is unreimbursed. Costs estimated here does not include endoscopy or inpatient stays.

No other "medicine" in the United States was determined by vote. No other medication has the directions: consume/use as much as you want. There are interactions and major medical and psychological primary and secondary consequences of high potency THC use including death (e.g. automobile deaths driving under the influence of THC). To ignore these harms is to do an injustice to the public. As physicians, before we start encouraging the public to use cannabis, we have the duty to study the consequences/harms and inform them of these.

Thank you to *Missouri Medicine* for having the courage to provide peer-reviewed literature with regards to the consequences of legalization. I wish our medical organizations and publications had done so here in Colorado. Finally, I extend an invitation to Missouri physicians to come and spend a day in our emergency department; you will see for yourself the catastrophe of easy and wide-spread cannabis use.

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## Medical Marijana: Physicians Need Science

There is much confusion as to whether or not marijuana is beneficial. There is evidence there may be medical benefits in well studied components of the marijuana plant. For instance, there is one FDA-approved natural cannabidiol (CBD) which has met the muster of scientific rigor for a narrow spectrum of pediatric seizures. Liver impairment, suicidal behavior, and sedation are known side effects of that medication.

Since Colorado has had medical marijuana starting in 2001, more than 90% of medical marijuana has been recommended for pain. Despite that, Colorado had a record number of opioid overdose deaths in 2019, and preliminary data only through the third quarter of 2020 the drug deaths have already outstripped the 2019 numbers. Marijuana is not helping the opioid epidemic and may be contributing to it.

Expansion of marijuana programs, particularly in Colorado, is negatively impacting our youth. As an example, marijuana is the most prevalent substance found in completed teen suicide in Colorado. That trend coincided with legalization, and reversed years of data showing that alcohol was previously most often found. The link between marijuana use and depression has been well demonstrated. Recent data in Colorado has shown our youth has seen a dramatic

increase in vaping marijuana and dabbing high potency pot. Remember, we were in the middle of a vaping epidemic pre-COVID, where Vitamin E acetate and tetrahydocannabinol (THC) were associated with more than 80% of the EVALI deaths. There has been recent, national data, showing that our youth are using substances significantly less, with the exception of marijuana, which is on the rise. It also has showed that the number one risk factor for adolescent opioid misuse is having ever used marijuana. Recent publications have shown that the risk of developing cannabis dependency is 33% in adolescents who use weekly or daily. There has been an increase emergency department presentations of adolescents since marijuana expansion in Colorado with nearly 70% related to psychiatric illness.

Health care utilization has increased related to marijuana related illnesses, including mental health, serious gastrointestinal effects such as cannabinoid hyperemesis syndrome (CHS), among many other health impacts. CHS can have fatal consequences. Even the American Heart Association released a position statement that there are risks of heart attack, sudden death, arrhythmia, and stroke related to marijuana use. Marijuana-related driving fatalities have increased in states with expanded marijuana programs. There are a significant number of drug interactions between cannabinoids and commonly prescribed medications most providers have no idea about. Some of these interactions may have lethal consequences.

It is critical to differentiate between what is cannabis-based medications and medical cannabis. Cannabis-based medications have met the muster of scientific research and are dosing guidelines are available to the medical community. Medical cannabis bypassed the pathway of required research and study to be proven effective. Recently, there was a recall of marijuana products contaminated with aresenic. The Oregon Secretary of State issued an audit report noting that only 3% of stores and 1/3 of growers had a compliance inspection and could not guarantee that test results were reliable or products were safe for human consumption, despite having robust medical and recreational marijuana programs for years.

The public health and safety concerns regarding use of marijuana for medical purposes already far outstrip any real or perceived benefit. Missouri Medicine needs to be commended for bringing to light the concerns medical providers need to know and holding physicians to a higher standard. There is a mountain of evidence of harm related to marijuana use and a paucity of evidence of benefit, particularly with medical cannabis. Colorado has seen this first hand and it would be a shame to see the state of Missouri go down the same unfortunate path. The medical community should support FDA drug development protocols and provide providers with cannabis-based medications we can use safely for our patients. Physicians should be pro-science and public policy should be driven by that, not public opinion.

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*Colorado Governor's Task Force on Amendment 64, which legalized marijuana for recreational use*
*Editor of Cannabis in Medicine: An Evidence-Based Approach*

## MSMA Should Embrace Scientific Cannabis Education

Medical cannabis is currently legal in Missouri and over 33 US states.

The current editor has promoted his personal agenda against "Big Weed" using our Journal, *Missouri Medicine*, publishing articles solicited to support his position.

*Missouri Medicine* belongs to all MSMA members and should provide diverse viewpoints and medically factual information on cannabis use to guide Missouri physicians.

The question remains for Missouri physicians- "What do we tell our patients about medical marijuana?"

MSMA should provide balanced views and education for Missouri physicians on medical marijuana. We expect our society to facilitate education on issues like medical marijuana including medical, legal, and drug interactions. I understand the official position of the AMA and MSMA on cannabis, but by taking the head in the sand approach to this issue, MSMA opens the door for patients to receive advice from unqualified non-medical cannabis purveyors and marginalized physicians.

Physicians are not educated about cannabis in medical school or postgraduate training. They struggle to provide factual and scientifically valid advice to their patients on cannabis use. Patients trust their physicians to provide sound advice.

*Missouri Medicine* should step up to the plate to educate physicians on cannabis, including potential

side effects, contraindications, and risks vs. benefits of its use for approved medical conditions.

Medical cannabis is seen as a legitimate medical therapy by many Missouri physicians and is here to stay. Labeling physicians who advocate medical cannabis as "unethical" is a disservice to reputable Missouri physicians and to current MSMA members who see a benefit of medical cannabis use in their patients. The MSMA should be an inclusive organization and embrace scientific cannabis education for its members and readers of *Missouri Medicine*.

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*MSMA Member since 1979*
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## Cannabis and Pregnancy Don't Mix

In the September/October 2020 *Missouri Medicine*, Polocaro and Vettraino raise the important issue of the transgenerational effects of prenatal cannabinoid exposure (PCE) on subsequent generations.[1] The implications of multigenerational toxicity of cannabinoids is very far-reaching with major policy implications.

The picture presented by Polcaro and Vettraino relating to the mental health implications of PCE is correct if too conservative. As they observe the subject is deeply confounded with multiple other factors impacting post-natal neurological development. For these reasons the significant concordance between reports from five longitudinal studies of childhood development relating to impaired indices of concentration, startle, excitability, poor visuospatial processing and executive functioning including ADHD-like and autism-like features are of particular concern.[2-6] Under a legalization paradigm the state effectively condones unlimited all day every day exposure to extremely high concentrations of THC, other cannabinoids and cannabis tars. What is especially concerning about this is that many of the neurotoxic and neurodevelopmental toxicities of cannabis exhibit threshold dose effects above which severe damage becomes commonplace.[7] In the context of an increasingly solid consensus relating to the harmful impacts of adult and adolescent cannabis exposure[8] the implications of PCE-neurotoxicity have not been carefully considered. It has been shown that nationwide autism rates are undergoing an exponential rise and indeed New Jersey has been shown to have 4.5% of 8-year-old boys who carry an autism spectrum disorder diagnosis.[9,10] Our space-time and causal inference studies demonstrate that indeed cannabinoid exposure to THC and cannabigerol amongst other fractions of cannabis, is a principal driver of this nationwide epidemic (manuscript submitted).[9,10]

A very concerning consensus is now emerging relating to cannabis-induced teratogenesis, embryotoxicity and fetotoxicity. A 2007 Hawaiian study found that 21 birth defects including many cardiovascular defects, Downs syndrome, orofacial clefts, gastroschisis and arm and hand defects were elevated in offspring of women exposed only to cannabis gestationally with odds ratios up to 40-fold and upper confidence intervals to 123-fold.[11] A report on Canada found that total congenital defects were three times more common in the northern territories where cannabis is smoked about three times as much.[12,13] In October 2018 Colorado Health reported an excess of 20,152 total birth defects beyond their baseline expected 67,620 defects 2000-2013 across the period of cannabis legalization when the use of other drugs was falling, representing an elevation of 29.8% above background rates.[14] In a high cannabis use area of Australia 13 defects were found to be elevated compared to Queensland, which for methodological reasons is a conservative estimate.[15] Concerningly elevated rates of Downs syndrome in Colorado, Hawaii, Australia and Canada clearly indicate that heritable cannabis genotoxicity can occur at the hundred megabase chromosomal scale.[11,12,14,15] A close association of atrial septal defect (secundum type) with rising patterns of cannabis use across space and time in the US was recently reported, suggesting that the list of known teratological associations of prenatal cannabis exposure is as yet incomplete.[16] This epidemiological literature is closely concordant with studies in experimental animals.[17-19] Again an abrupt rise in genotoxicity with increasing cannabinoid exposure has been demonstrated for many cannabinoids and is of particular concern.[20-23]

Links between cannabis and several paediatric cancers including acute lymphoid leukaemia (ALL), acute myeloid leukaemia, rhabdomyosarcoma and neuroblastoma suggest further implications of cannabinoid genotoxicity.[24-28] Since these tumours together encompass the common tumours of childhood, it is at least possible that cannabis is

responsible for the 43% elevation in total childhood cancer across US 1975-2017.[29] Indeed Downs syndrome is well known to be associated with a 2,000-fold elevated risk of childhood ALL from 2/100,000 to around 5/100.[30,31]

This diverse assemblage of highly congruent evidence of severe cannabis-related neurotoxicity and genotoxicity from varied locations can only be described as extremely concerning indeed. In view of its well described epigenetic and chromoanagenetic effects[32-34] and its clearly transgenerational-multigenerational impacts one can only conclude that if the evidence base is not admitted to the cannabis debate and access to fetotoxic and embryotoxic cannabinoids is not immediately restricted the community will inevitably pay a heinous price in terms of avoidable paediatric neurotoxicity, congenital birth defects, heritable cancerogenesis and multigenerational epigenotoxicity.

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## Medical Marijuana and Professional Ethics

In your recent *Missouri Medicine* journal article you called on physicians to, ". . . oppose any petition or referendum aimed at making high THC marijuana legal for recreational use." I question whether physicians doing so would not only be hypocritical, but also unethical.

From the excellent science-based information that you and our journal have provided, it seems that marijuana's potential for adverse public health and societal impact is very similar to alcohol. Is it not then hypocritical for us to oppose legalization of recreational marijuana when we are not also calling for the reinstitution of the Eighteenth Amendment (and Volstead Act)? Is it not quite awkward that we serve/offer alcohol at our medical association and local medical society meetings?

Putting the issue of hypocrisy aside, your request sounds reasonable on its face. However, is it fully consistent with our professional ethics? Fighting to preserve the current marijuana laws presents is ethically problematic for physicians because these laws clearly still include the penalty of incarceration (albeit enforcement has become considerably more lax). Is it ethical to support laws that threaten incarceration for recreational marijuana use? Is harming some individuals with imprisonment for breaking these laws an ethically acceptable means for physicians to use in a well-intentioned effort to safeguard the health of the majority; especially when other options are available? While I am not an ethicist, Iwould say that though it is a risk/benefit calculation society may choose to make, for physicians to support the legal status quo here doesn't pass the ethics smell test. It likely violates the principal of non-malfeasance and the maxim "primum, non nocere?"

Though I share your discontent with "Big Weed," blocking entrepreneurs from profiting, no matter how unscrupulous they are, is not worth compromising our ethics. Perhaps physicians should care more about "Big Prison," the for-profit prison system, than "Big Weed." The human toll–the severe, indelible mental and physical harm–that resulted from decades of racially biased incarceration for minor drug offenses should never be forgotten when we consider our public health effort on this issue. In your article you dismissed the idea that ongoing efforts to legalize pot had anything to do with decriminalization by pointing out that "Big Weed" cares only about self-enrichment and that "Missouri's law enforcement and judicial systems are no longer prosecuting small amounts of pot for personal use; those incarcerated for the same are being released and their criminal records expunged." However, I believe that the current law you are asking us to protect still retains the threat of incarceration for marijuana possession–up to a year in prison even for small amounts without intention to distribute/sell. If you are found to be in possession of more than 30 grams, up to 7 years in prison–(https://norml.org/laws/missouri-penalties-2/).

In summary, marijuana, alcohol, and incarceration are each associated with significant adverse public health risks and consequences. If we wish to avoid hypocrisy, remain ethical, and minimize the health impacts of marijuana, we should fight to change marijuana law, not preserve it. The lesson learned from Prohibition of the 1920s was that making a popular recreational drug illegal is a recipe for disaster. Why not legalize marijuana to the same extent as alcohol? With marijuana, as with alcohol, society will probably accomplish an imperfect, but more desirable outcome if it pursues the path of legalization, regulation, and (with our help) public education.

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## Calling Marijuana "Medical" Makes It Safe? No Way!

I want to commend *Missouri Medicine* and the editorial staff for helping to get the word out regarding the down sides of marijuana. I am an addiction psychiatrist and have been treating people with addiction and mental health issues for the last 30 years. When we first legalized medical marijuana in Colorado in 2000, I was not that worried about

it. At the time I thought it would not have a significant impact on the people I see. However, the highest concentration of THC in the plant at that time was 5% and there were no concentrates. Over the last 20 years, without any governmental regulation, the industry has been allowed to dramatically increase the concentration of THC to where the average in the plant is now 18.8% and 69.4% in the concentrates, such as wax, shatter, dab, vape oil, with some up to 95% THC.

While there is evidence that marijuana can be beneficial for some medical conditions, the research supporting this has been done with THC concentrations less than 10% in the smoked plant.[1] There is no legitimate research on the concentrates as a medical treatment and there is no research on 18 – 95% THC indicating it is efficacious for anything medical or safe for anyone. On the other hand, there are multiple studies from around the world showing serious problems with high potency THC including addiction, psychosis, depression, anxiety, sleep problems, suicide, and violence. Based on their experience, Dutch researchers have stated anything higher than 15% THC should be considered a hard drug, comparable to cocaine and ecstacy.[2]

Despite this lack of research on concentrates, the 2019 Colorado Regulated Marijuana Market Update[3] demonstrates an increasing amount of concentrates in both the medical and recreational market with a higher percentage in the medical market (34% versus 32%). This means that a physician may recommend a medical marijuana card for a patient and may even make recommendations about using something that is low in THC and higher in CBD, but there is no "prescription" with product type, amount, method of delivery, etc. So, the patient goes to the dispensary and purchases concentrates because of the belief "more potent is more efficacious". This is the travesty of our current "medical marijuana"; people are dabbing with a blow torch to get their "medicine."

Sadly, the fact that we call this "medical" makes people believe it is safe. Kids are increasingly using concentrates. The 2019 Health Kids Colorado Survey reported 10.2% of high school students using marijuana are using dab[4] compared to 3.7% of adults who use dab[5] (nearly three times higher rate). More kids and adults are ending up in the emergency room with psychotic symptoms, panic attacks, suicidal ideation, or cannabis hyperemesis syndrome because of using high potency THC.[6]

According to the 2019 Market Update,[3] Colorado has a much higher share of "heavy" marijuana consumers compared to the national average. Daily or near daily users constitute 6.1% of marijuana users in Colorado and they purchase 75.7% of the product. This is truly an industry profiting from addiction.

Before even considering adding recreational marijuana, Missouri should do better than we have in Colorado and first regulate your medical marijuana by following the science. Potency should be limited to less than 10 % THC. Concentrates, such as wax, shatter, dab have no place in medical dispensaries as there is no research demonstrating they are safe and effective for any medical condition. Medical marijuana should be on the Prescription Drug Monitoring Program. Prescribers should be fully educated regarding the down sides of marijuana and working within their scope of practice when making recommendations.

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## Cybersecurity Update: Recent Ransomware Attacks Against Healthcare Providers

On October 28, 2020, the Cybersecurity and Infrastructure Security Agency (CISA), the Federal Bureau of Investigation (FBI), and the United States Department of Health and Human Services (HHS) issued Alert AA20-302A (Alert) which describes recent

ransomware attacks by criminal groups exploiting healthcare institutions and the distractions caused by the current pandemic and election cycle.

Of particular note is that healthcare providers across four different states have already fallen victim and that 400 more are reportedly on a list of targets circulating among criminal organizations. When ransomware penetrates a provider's network, it often encrypts data and deletes backups before the ransom request is issued. While it is debatable whether the ransom should be paid, most government agencies advise against doing so as such payments (1) incentivize the criminal activity and (2) do not guarantee recovery of data or the end of the ordeal. Cybercriminals are typically not good on their word and, even if they are, once PHI is encrypted by ransomware it is presumed compromised from a HIPAA perspective and triggers breach notifications obligations.

To help mitigate risk exposure: (1) healthcare providers must assume that ransomware is already within their networks; (2) executives must be ready to activate business continuity plans; and (3) IT departments must patch software, inspect audit logs and implement multifactor authentication across their systems. Additionally, providers should consider joining a healthcare Information Sharing and Analysis Center/Organization (ISAC/ISAO), which offers the opportunity to receive critical information and services to help manage the risks of ransomware. Providers should also adopt the "*3-2-1 Rule*" for backing up data which calls for *three* copies of all critical data sets, stored on at least *two* different types of media, and with at least *one* of the media formats stored offline.

*Erik Dullea, JD*
*Husch Blackwell Denver, Colorado*
*Chris Budke, JD & Pete Enko, JD*
*Husch Blackwell Kansas City, Missouri*




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## Letters to the Editor

Submissions reflect readers' opinions and may be edited for length. Use in subject line: "For Publication"

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# MSMA Members in the News

Did you make the news? Submit your success story and photo to lfleenor@msma.org.

## New Editorial Board Members

Jessica A. Gold, MD, MS, has been named the *Missouri Medicine* Editorial Board member for Physician Wellness. Dr. Gold, MSMA member since 2020, is an Assistant Professor Psychiatry at Washington University School of Medicine in St. Louis and a Scholar at the WU Institute for Public Health. Her research interests are in physician wellness and college and women's mental health.



Jonathan M.T. Bath, MD, is the new *Missouri Medicine* Editorial Board member for Vascular Surgery. An MSMA member since 2020, he is an Assistant Professor Surgery where his interests are aneurysm, carotid, peripheral arterial diseases, and vascular surgery. He replaces W. Kirt Nichols, MD, whom the Journal thanks for his service on the Board since 1988. Dr. Nichols has been honored with the *Missouri Medicine* Distinguished Service Award.



## Thank You Non-Editorial Board Contributors

*Missouri Medicine* would like to publicly thank the following invited non-Editorial Board experts who have done peer-review of submitted manuscripts in 2020: Muhammad Farhan, MD, Mala Goyal, MD, Junaid Siddiqui, MD, Joel Shenker, MD, David McKinsey, MD, Armin Krvavac, MD, Elizabeth Reznikov, DO, PhD, Fariha Shafi, MD, and Arpit Aggarwal, MD.

## Missouri Medicine Editor Completes 20 Years of Service

John C. Hagan, III, MD, FACS, FAAO, an ophthalmologist at Discover Vision Centers in Kansas City, Missouri, has served two decades as Editor of *Missouri Medicine*. His first Journal editorial was November/December 2000. That issue, which he did not produce, was 41 pages and had one scientific article. Over the past 20 years the Journal has improved dramatically in quality, reputation, and excellence of content. Presently each Journal issue publishes 10 to 14 scientific articles and has an average size of 78 pages or when necessary, such as COVID-19, more than 100 pages. Medical articles are up-to-date reviews and original research including more than a dozen first-literature reports. Medical, legal, opinion, perspectives, and MSMA matters are also important content. *Missouri Medicine* is considered one of the top three state medical journals in the United States. Besides being indexed at PubMed, the Journal is now archived at PubMed Central and has a national footprint. More details of the Journal's 116-year history are found at www.msma.org/missouri-medicine-library.

Dr. Hagan, an MSMA member since 1975, has authored more than 200 scientific articles, contributed to or edited five medical textbooks, and is actively involved in clinical research. He writes and lectures on the international level. He has won several awards for his writings. Dr. Hagan has served in leadership for many organizations including President of Clay-Platte County Medical Society, Kansas City Metropolitan Medical Society, the Missouri Society of Eye Physicians & Surgeons, and has been honored by many of these organizations including the American Academy of Ophthalmology. He and his wife Becky, both from Mexico, Missouri, have been married 53 years. They have two adult daughters and two grandsons.

## *Missouri Medicine*'s Near Death Experiences Book Published in Brazil

*The Science of Near Death Experiences* (Missouri University Press, 2017) a medical textbook based on a series of peer-reviewed articles appearing in *Missouri Medicine,* continues to be an in-category best seller. Editor, John C. Hagan III, MD was interviewed recently by a Brazilian publisher that has purchased the rights to distribute a Portuguese language edition in paper-back and audiobook. Profits from sales go to MSMA for medical student grants.




MU Press also recently reported that *The Science of Near Death Experiences* is listed among their six best sellers. **MM**

DIETS & HEALTH MINISERIES

# Obesity and the Western Diet: How We Got Here

*by Varundeep Rakhra, DO, Suguni Loku Galappaththy, MD, Sheetal Bulchandani, MD & Peminda K. Cabandugama, MD*

**By avoiding certain foods that are popular in the American diet and including healthier options such as those recommended by the USDA, we can significantly reduce the rate of obesity and its long-term complications.**

## Introduction

Through the course of the last several decades, the rate of obesity has progressively increased and is now one of the leading causes of death worldwide. The World Health Organization reports 1.9 billion adults were overweight in 2016 and 650 million were considered obese.[1] According to the Center for Disease Control, the prevalence of obesity in the United States was 30.5% in 1999. This increased to 42.4% by 2017.[2] In conjunction with this, chronic illnesses associated with obesity such as diabetes and cardiovascular disease are now among the top causes of death in the United States.[3] In 2008, the medical cost for obesity was $147 billion. This was $1,429 higher than the cost for non-obese patients.[2]

Several factors have been attributed to this epidemic with the western diet considered to be a major contributor to the growing rate of obesity in the United States. Although current lifestyle trends emphasize the importance of eating healthy, we continue to see foods high in fat and sugar as major components of the Western diet which has corresponded to the steady rise in obesity. The management of obesity is therefore an important discussion with many now acknowledging that diet modification would have the greatest impact on this growing epidemic.



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## What We Should Eat

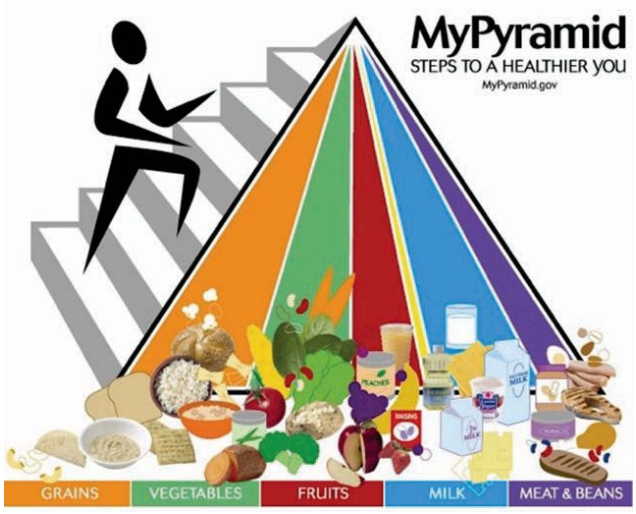
The recommended daily caloric intake depends on an individual's age, gender, and level of physical activity.[3] Weight gain occurs when more calories are consumed than expended. Healthy weight loss can be achieved with a daily caloric intake of 1,200-1,500 for women and 1,500-1,800 for men.[4] The U.S. Departments of Health and Human Services (DHHS) and Agriculture (USDA) have released the Dietary Guidelines for 2015 to 2020.[4] This plan encourages a diet rich in nutrients while limiting calories from added sugars, saturated and trans fats, and sodium.[5] Added sugars and saturated fats should each contribute less than 10% of the daily caloric intake.[5] The American Heart Association recommends that women consume less than 6 teaspoons of sugar daily and men consume less than 9 teaspoons of sugar daily.[3] Finally, the recommended daily sodium intake should be less than 2,300 mg.[5]

A healthy diet should include foods such as fruits, vegetables, whole grains, and fat-free or low-fat dairy (Figure 1).[4] A 2,000 calorie diet should consist of 2.5 cups of vegetables and 2 cups of fruit daily. Protein can be obtained from seafood, lean meat, chicken, legumes, and nuts. Whole grains such as brown rice, quinoa, and oats are also suggested. The USDA dietary guidelines recommend adults consume three cups of non-fat or low-fat dairy per day.[4] Eating a

healthy diet not only results in weight loss, it can decrease the risk of cardiovascular disease.

The DASH diet is a well-known diet that encourages more fruits and vegetables.[6] It avoids foods high in sodium, fats, and sugars. In fact, the Dietary Approaches to Stop Hypertension study found that a diet low in fat and rich in fruits, vegetables, and low-fat dairy resulted in lower systolic and diastolic blood pressures when compared to a standard western diet.[6]

Figure 1. USDA My Pyramid




*2005: MyPyramid Food Guidance System; U.S. Department of Agriculture. ChooseMyPlate https://www.choosemyplate.gov/eathealthy/brief-history-usda-food-guides*

## What is the Western "American" Diet?

The typical Western (American) diet is low in fruits and vegetables, and high in fat and sodium. Moreover, this diet consists of large portions, high calories, and excess sugar.[3] This excess sugar accounts for more than 13% of the daily caloric intake with beverages constituting 47% of these added sugars.[4] Other sources include cookies, cakes, and candy.

Although fruits and vegetables contain natural sugars, they provide nutrients such as vitamins, minerals, and antioxidants while added sugars only contribute calories.[3] The western diet is also noted to be high in saturated and trans fats. These fats not only contribute more calories; they increase low-density lipoproteins leading to atherosclerosis.

There has recently been increasing interest in the effect of dietary patterns on the immune system. One study compared mice that were fed a western diet to mice that were fed a standard fiber-rich diet.[7] The western diet consisted of foods high in fats and sugars and low in fiber. These mice were found to have higher levels of inflammation and sepsis resulting in worse outcomes.[7]

## The True Cost of Obesity and the Western Diet

Individuals who are obese or overweight are at a higher risk of developing chronic illnesses such as type 2 diabetes, cardiovascular disease, hypertension, hyperlipidemia, sleep apnea, or cancer. In fact, half of all Americans have a preventable chronic illness.[3] According to the American Heart Association, 81 million American adults have cardiovascular disease which includes coronary artery disease or cerebrovascular disease. One-third of American adults have hypertension and more than 85% of patients with type 2 diabetes are considered overweight.[3]

Type 2 diabetes mellitus, once a disease primarily seen in adults, now presents in younger generations as a result of increasing childhood and adolescent obesity. According to the CDC, 13.7 million children and adolescents are considered obese in the United States.[8]

Multiple studies have also shown that obesity during midlife increases the risk of developing dementia. With fifty million people affected by dementia worldwide, there has been great interest in identifying preventable risk factors.[9] A recent study evaluated the effect of diet modification and weight loss in elderly obese patients with mild cognitive impairment. These patients reduced their caloric intake and consumed more fruits, vegetables, fibers, and whole grains. The findings proved that weight reduction through diet modification improves cognition with these individuals showing improvements in verbal memory, verbal fluency, executive function and global cognition.[9]

Reproductive studies have reported that the increase in obesity rate has had a significant effect on fertility as well. More than 20% of reproductive-age women in the United States are considered obese.[10] Pathophysiology of the infertility processes have shown that obesity affects the hypothalamic-pituitary-ovarian axis by suppressing gonadotropin release. This leads to anovulation and infertility.[10]

Polycystic Ovarian Syndrome, another common endocrine condition which increases a woman's risk for

infertility, is also associated with obesity. Studies have shown that modifying diets to include healthy and nutritious foods results in improved fertility.[10]

Interestingly, there have been reviews describing the benefit of healthy eating patterns on male fertility as well.[11] Studies from several countries have shown that diets consisting of fruits, vegetables, seafood, chicken, and whole grains are associated with better semen quality while consumption of high amounts of trans and saturated fats were linked to poor semen quality.[11]

## The Current Crisis: COVID-19 and Obesity

With the current COVID-19 pandemic, there are multiple studies showing associations between illness severity and obesity. A study done in New York City found patients with a BMI of 30-34 were 1.8 times more likely to be admitted to an intensive care unit.[12] Those with a BMI greater than 35 were 3.6 times more likely to be admitted to an ICU. A corresponding report from France found that the use of mechanical ventilation was seven-fold higher for patients with a BMI greater than 35 compared to patients with a BMI of less than 25.[12]

Hypotheses to explain these findings include a link between obesity and hypoventilation syndrome and obstructive sleep apnea. Prior studies have also shown higher levels of inflammatory markers in obese patients. Moreover, COVID-19 has been associated with venous thrombosis. There is now grave concern for obese patients affected by this virus given the increased risk of thrombosis already seen in these patients.[12]

The new healthcare crisis with the COVID-19 pandemic has changed the way of living for many Americans. Most people are now working from home, and unfortunately many others are now unemployed. This has also appeared to have a significant effect on dietary patterns as well. Healthcare providers are now observing that patients are consuming more than they did prior to the lockdown. This, combined with limited physical activity due to stay-at-home orders is resulting in weight gain. With many individuals now unemployed, the issue of food insecurity has also been brought to the forefront. With limited access to healthy foods already a challenge for a large proportion of the United States' population, the current economic and health crisis is expected to unfortunately increase the prevalence of obesity.

## Conclusion

The western diet has been a significant contributor to the growing rate of obesity over the last several decades. Individuals who are overweight or obese have a higher chance of developing comorbidities such as diabetes, cardiovascular disease, and cancer. Although obesity is a significant risk factor, it is preventable and can be improved with changes in diet. We now see a link between obesity and COVID-19 illness severity which again emphasizes the importance of such interventions during the time of the pandemic. There are various types of diets that all promise weight loss. However, by avoiding certain foods that are popular in the American diet and including healthier options such as those recommended by the USDA, we can significantly reduce the rate of obesity and its long-term complications.

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## Disclosure

None reported.

MM

# The Importance of Maintaining a Low Omega-6/Omega-3 Ratio for Reducing the Risk of Inflammatory Cytokine Storms

*by James J. DiNicolantonio, PharmD & James O'Keefe, MD*

**A higher omega-6/3 ratio is associated with lower immune cell function, which may result in lower immunity.**





James J. DiNicolantonio, PharmD, (left), and James H. O'Keefe, MD, (right), MSMA member since 2003, are at Saint Luke's Mid America Heart Institute, Kansas City, Missouri.

## Abstract

**Inflammatory cytokine storms in the lungs are a potential consequence of RNA viruses. One issue that may increase the risk of developing inflammatory cytokine storms in the lungs during viral infections is an imbalance in the dietary omega-6/3 ratio. Indeed, over the past 100 years the omega-6/3 ratio in the Western world has increased from approximately 4:1 to 20:1. This has increased the production of pro-inflammatory metabolites from omega-6 and reduced the anti-inflammatory metabolites from omega-3s. A high dietary omega-6/3 ratio may promote excessive inflammation, which may be contributing to inflammatory cytokine storms in the lungs during viral infections.**

## Introduction: The Omega-6/3 Ratio and Inflammation

Inflammation is important in treating infections and wounds as it promotes tissue healing and the killing of pathogens. The omega-6 fat linoleic acid, and arachidonic acid (AA) formed from it, are important in responses such as redness, swelling, heat, and pain.[1] However, acute inflammatory responses are meant to be quickly suppressed by resolvins formed from the long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Thus, a balance in the dietary omega-6/3 ratio may be important for ensuring that an excessive and prolonged inflammatory response does not occur, which could lead to tissue damage and potentially to autoimmune disease.

Up until about 100 years ago, the omega-6/3 ratio had been around 4:1 or less.[2] However, the typical Western diet now provides an omega-6/3 ratio approximately 20-fold higher in favor of omega-6.[2] While foods such as nuts, seeds, and eggs are high in omega-6, the increase in the omega-6/3 ratio is primarily due to an increase in the intake of industrial seed oils (soybean, corn, safflower, cottonseed, and canola). Additionally, there has been a reduction in the intake of long-chain omega-3s, which can primarily be found in fatty fish and shellfish. A high omega-6/3 ratio predisposes

to supraphysiologic inflammatory responses and perpetuates chronic low-grade inflammation.[3] The overconsumption of linoleic acid, mainly from industrial omega-6 seed oils, and the lack of EPA and DHA, has been proposed to put the population in a pro-inflammatory and pro-thrombotic state.[3, 4]

## The Immune System

One of the functions of our immune system is to fight against pathogenic viruses, fungi, bacteria, and parasites.[5] The immune system does this by releasing inflammatory cytokines during infections to defend against these pathogens. If our immune system, and especially our gastrointestinal system is healthy, then there is a lower risk of autoimmunity.[5]

There are two main types of immunity: Innate (natural immunity) and acquired (adaptive immunity).[5] Immune cells concentrate in lymphoid organs (lymph nodes, thymus, spleen and gastrointestinal lymphoid tissue) and in the circulation as well as other parts of the body. The innate immune system is a first line of defense against infection. It functions to prevent and eliminate infectious pathogens. Examples of the innate immune system include complement, skin, phagocytic cells (neutrophils, eosinophils, basophils), monocytes, and macrophages.

The acquired immune system has "memory" (unlike the innate immune system), whereby prior exposure to pathogens improves its response. Although the acquired immune system is slower to respond than our innate immune system, once it becomes effective it has a lasting effect. Acquired immunity involves antibodies, which help bind to and neutralize pathogens as well as activate complement proteins, which promotes phagocyte activation and pathogen elimination. Once an invading pathogen is inside a host cell it has escaped antibody defense, otherwise known as humoral immunity. However, T lymphocytes can eliminate these pathogens in conjunction with helper T lymphocytes (indicated by the presence of CD4 protein on their surface). Type 1 helper T cells activate macrophages, cytotoxic T lymphocytes (CD8+) and natural killer cells, whereas Type 2 helper T cells activate mast cells and basophils. Regulatory T cells are involved with suppression of inflammation and cell-mediated immunity via production of IL-10.[5]

## The Importance of Omega-3s for Suppressing an Overactive Immune System and Reducing the Risk of Inflammatory Cytokine Storms

There is a need for an effective immune system to prevent and eliminate infectious agents. However, the immune system can become over activated leading to self-attack. This can start by the immune system mounting a response to dietary or environmental allergens. Arachidonic acid is the main fatty acid in immune cell membrane phospholipids and mainly forms the inflammatory 2,4-series eicosanoids, whereas incorporation of EPA/DHA will decrease AA-derived eicosanoids and increase the anti-inflammatory 3/5-series eicosanoids, docosanoids and resolvins/protectins, leading to an overall anti-inflammatory state.[5] Consuming a typical Western diet leads to immune cells (neutrophils, lymphocytes and monocytes) that contain ~20% of fatty acids as arachidonic acid with just 1% EPA and 2.0-2.5% DHA.[5] However, supplementing the diet with 3.2 grams of EPA/DHA for 12 weeks has been shown to increase phospholipid long-chain omega-3 fatty acids to around 3.5% EPA and 3.5% DHA.[5] Thus, a dietary increase in omega-3 PUFAs will lower the omega-6/3 ratio in immune cells.

Animal models have demonstrated that omega-3 polyunsaturated fatty acids (PUFAs) have immunomodulatory effects and are useful in inflammatory disorders.[6] Infections can also increase arachidonic acid and decrease the anti-inflammatory omega-3 PUFA DHA.[7] Dietary, or supplemental omega-3 PUFAs, can incorporate into the cellular membranes of all immune cells investigated to date.[8] Numerous clinical studies in humans have found that supplementing with EPA/DHA (reducing the omega-6/3 ratio) lowers inflammation in humans, whereas oxidized linoleic acid metabolites (OXLAMs) activate nuclear factor kappa-beta (NF-kB), which increases proinflammatory cytokines.[3] Importantly, cytokine storms and lung injury in persons infected with coronaviruses, such as severe acute respiratory syndrome (SARS-CoV) or middle east respiratory syndrome (MERS), are usually the result of NF-kB activation.[9, 10] Studies show that inhibiting NF-kB-mediated inflammation increases survival in animal models of SARS-CoV.[11] Considering that SARS-

Table 1. **Potential mechanisms of omega-3s for reducing cytokine storm in the lungs**

| |
|---|
| Decrease AA-derived eicosanoids and increase the anti-inflammatory 3/5-series eicosanoids, docosanoids and resolvins/protectins/maresins/lipoxins.[5] |
| Lower omega-6/3 ratio in immune cells.[5] |
| Inhibiting NF-kB activation.[3] |
| Resolving inflammation and potentially improving survival in sepsis.[12-14] |
| Suppression of arachidonic acid-derived eicosanoids and leukotrienes produced from immune cells as well as inflammatory interleukins and cytokines.[15-21] |
| Increase in neutrophil and monocyte phagocytic activity.[25] |

CoV and SARS-CoV2 are both coronaviruses, and that the latter can lead to COVID-19, inhibiting NF-kB activation by increasing omega-3 intake and reducing processed omega-6 seed oil intake,[3] may be an important strategy in combating inflammatory cytokine storms in the lungs and acute respiratory distress in patients infected with RNA viruses such as influenza and coronaviruses. Moreover, considering that the dietary intake of omega-6/3 is now ~ 20:1 or higher, compared to an ancestral intake of ~ 4:1 or less, this may predispose to inflammatory cytokine storms and chronic inflammatory conditions.[2, 3] Omega-3 PUFAs are important for resolving inflammation and may improve survival in sepsis and acute respiratory distress syndrome (ARDS).[12-14]

EPA/DHA not only reduces AA-metabolites by competition in the cellular membrane phospholipids, but they also inhibit AA metabolism via inhibition of cyclooxygenase and lipoxygenase. Inhibiting the metabolism of arachidonic acid to proinflammatory metabolites is likely more consequential in preventing a supraphysiological inflammatory response than reducing the phospholipid content of arachidonic acid. Many studies have shown that fish oil (between 2.4 and 14.4 grams of EPA/DHA/day) suppresses the arachidonic acid-derived eicosanoids and leukotrienes produced from immune cells as well as inflammatory interleukins and cytokines.[15-21] Moreover, the metabolites from EPA/DHA are considered less inflammatory compared to those from arachidonic acid.[5, 22, 23]

A higher omega-6/3 ratio is also associated with lower immune cell function, which may result in lower immunity.[24] DHA-rich fish oil (3 grams per day, 26% EPA, 54% DHA) has been shown to increase neutrophil and monocyte phagocytic activity by 62% and 145%, respectively,[25] whereas changes in neutrophil and monocyte phagocytic activity was not found with EPA-rich fish oil.[26] In other words, DHA may strengthen the immune system while at the same time suppressing its overactivation.

Long-chain omega-3s can also inhibit inflammatory cytokine production from monocytes, macrophages, and endothelial cells. Many of the benefits of long-chain omega-3s are due to their ability to reduce gene expression for producing inflammatory cytokines partly by reducing the activation of NF-kB.[1] Thus, supplementing with long-chain omega-3s not only reduces inflammatory eicosanoids derived from arachidonic acid but also increases the anti-inflammatory eicosanoids and resolvins/protectins/maresins/lipoxins derived from EPA/DHA, thereby reducing inflammatory cytokine production from NF-kB. Table 1 summarizes the potential mechanisms of omega-3s for reducing cytokine storm in the lungs.

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## Disclosure

JD is Director of Scientific Affairs for Advanced Ingredients for Dietary Products (AIDP). JOK is an owner of a nutraceutical company.

**MM**

# Evolution of Diagnostic and Treatment Patterns of Cardiac Sarcoidosis

*by Anna Grodzinsky, MD, Timothy J. Fendler, MD, Gregory Howell, MD, Sanjaya Gupta, MD, Stephanie Lawhorn, MD, Bhaskar Bhardwaj, MD, Akshit Sharma, MD, Siva Sagar Taduru, MD, Brett Sperry, MD & Ibrahim M. Saeed, MD*

**It is important to identify the presence of cardiac involvement given the potential for alternate treatment approaches.**



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## Abstract

**Cardiac sarcoidosis (CS) may impart substantial morbidity and mortality, and novel imaging modalities are now available to aid in early diagnosis of this clinically silent disease. A better understanding of the clinical experience with CS is important.**

**Twenty-eight patients were diagnosed with the aid of multimodality imaging techniques and were treated by a multidisciplinary team. Demographics, symptomatology, imaging, and therapeutic interventions were compiled from our referral center.**

**In patients with CS, nuclear and MR techniques were often the first studies performed. Echocardiographic findings differed widely. Immunosuppressive therapy and cardiac devices were frequently used. Importantly, isolated CS was not an infrequent finding.**

## Background

Traditional teaching suggests that cardiac involvement in patients with sarcoidosis remains relatively rare, but cardiac manifestations of sarcoidosis are responsible for substantial morbidity and mortality. Clinically silent cardiac sarcoidosis (CS) has been estimated to affect up to a quarter of patients with pulmonary or systemic sarcoidosis. The principal manifestations of CS are conduction abnormalities, ventricular arrhythmias, and heart failure.[1]

It is important to identify the presence of cardiac involvement given the potential for alternate treatment approaches. Contemporary data support cardiac magnetic resonance imaging (MRI) and cardiac positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose (FDG-PET) imaging in the diagnosis of CS. Though controversial, immunosuppression remains the mainstay for the treatment of clinically manifest CS, and prognosis is poor if patients are untreated or undertreated, particularly those with severely reduced left ventricular function.[2] Cardiac implanted electronic device therapy, primarily with implantable cardioverter-defibrillators (ICDs), is recommended for patients with clinically manifest disease.[3] Despite the increasing recognition of CS, several key diagnostic and therapeutic questions remain unanswered, such as how to optimally manage immunosuppression and what modality is best for evaluation of response to therapy. Further

complicating the diagnosis is that endomyocardial biopsy (the gold standard) is historically only confirmatory in less than a third of patients.[2, 4]

In this case series, we describe the diagnostic and treatment patterns of 28 patients with confirmed CS, including several patient with diagnostic dilemmas in the setting of overlapping diagnostic criteria for CS and other conditions (such as myocarditis and arrhythmogenic right ventricular dysplasia). This experience highlights the diagnostic difficulty and presents a platform for optimal recognition and management of patients with cardiac sarcoidosis.

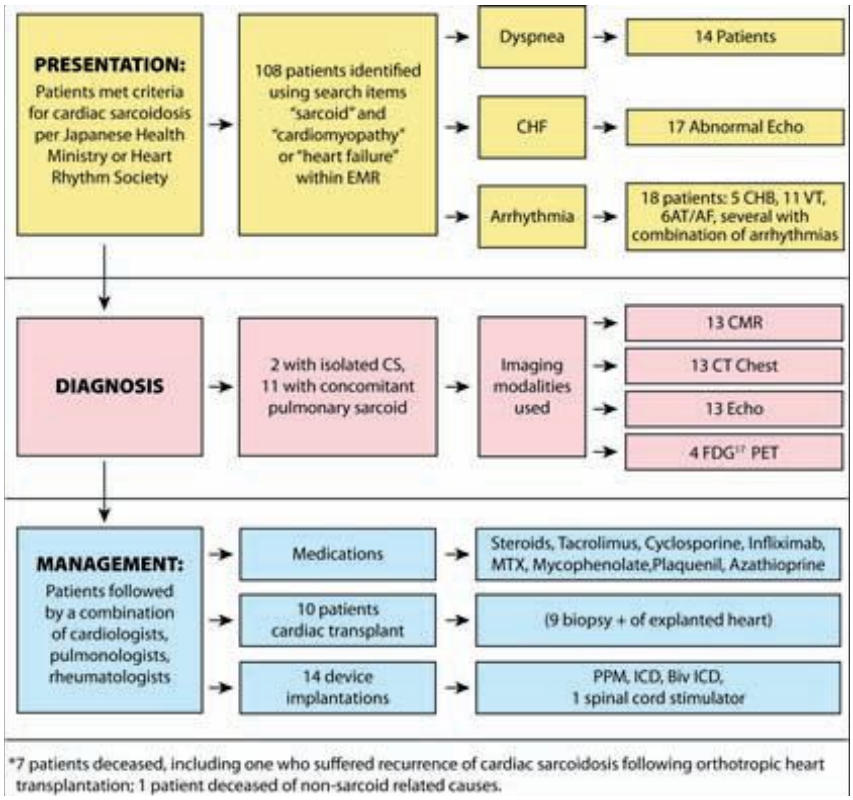



Figure 1. Presentation, diagnosis, and treatment characteristics of analytic cohort

## Methods

We initially screened patients using the search terms "sarcoid," "sarcoidosis," "cardiomyopathy," "heart failure," and "congestive heart failure" in our institution's electronic medical record. We investigated each patient's cardiac, pulmonary, rheumatologic documentation and reviewed imaging modalities including echocardiography, cardiac MRI, FDG-PET, and pathology reports of pulmonary or endomyocardial biopsy results when applicable. We then identified patients with (1) biopsy-confirmed cardiac or (2) biopsy-confirmed extra-cardiac sarcoidosis with cardiovascular imaging findings consistent with CS. In addition, we included several patients with a probable diagnosis of cardiac sarcoidosis based on either the Heart Rhythm Society Criteria or Japanese Ministry of Health criteria,[3, 5] yet those patients were initially diagnosed with cardiomyopathies related to viral or eosinophilic myocarditis, or arrhythmogenic right ventricular cardiomyopathy.

We describe patient characteristics including age, presenting symptoms, echocardiographic findings, diagnostic modality, treatment regimen (including type of immunosuppressive and cardiac device therapy) and follow up visit information. We received approval from the St. Luke's Hospital Institutional Review Board to perform this analysis.

## Results

Of the 108 patients screened using the institution's electronic medical record, we identified 28 patients with biopsy-confirmed cardiac or biopsy-confirmed extra-cardiac sarcoidosis with cardiovascular imaging findings consistent with CS (Figure 1). Of these 28, 17 patients were found to have biopsy-confirmed CS. Four of these patients initially had isolated CS.

Of the 28 patients included in our cohort, age at diagnosis ranged from 28-69 years, the diagnostic modalities included autopsy of explanted heart, cardiac MRI in combination with mediastinal lymph node biopsy, endomyocardial biopsy, and cardiac PET. Presentation was most commonly with dyspnea and heart failure, but included palpitations and atrial and ventricular arrhythmias. Of our cohort, 11 patients had concomitant pulmonary sarcoidosis. Follow up duration has ranged between 1 and 12 years.

### *Dyspnea and Heart Failure Evaluation*

- Approximately a third (9) were African American
- 14/28 patients presented with dyspnea

- Most patients presented with NYHA class I or II symptoms.
- Over a third had preserved left ventricular systolic function (10), In the 18 without global hypokinesis, discrete wall motion in 6 (4 inferior, 4 apical, 3 septal, 2 inferolateral).
- Five had an abnormal right ventricle (2 without LV dysfunction. One presented with constrictive pericarditis. Of the 13 that had abnormal Cardiac MRIs, 7 had PETs, 2 were confirmatory, and 5 were normal.

### *Arrhythmias*

- Approximately 25% had documented arrhythmias, including ventricular tachycardia, complete heart block, and atrial fibrillation.
- 5 patients presented with Mobitz II atrioventricular block or higher, and tended to be younger (44-59)
- Those with atrial and ventricular tachycardia had a wider age range and tended to be older (38-73)
- Approximately half of the patients underwent ICD implantation.

### *Management*

- Nine patients proceeded to cardiac transplantation, four of which were discovered on examination of the explanted heart and found to have isolated cardiac sarcoid. Two patients are deceased, including one patient who suffered recurrence of cardiac sarcoidosis following orthotropic heart transplantation.
- Steroids were the most common immunosuppressive and were the initial treatment in 10 patients.
- Many transitioned to other regimens, including 5 on methotrexate, as well as others including infliximab, hydroxychlorouine, mycophenolate, leflunomide, and azathioprine.
- Those on steroids for arrhythmias often still received PM/ICDs.
- One patient with continued thoracic pain received a spinal cord stimulator.
- Of this initial cohort, 20 are still alive at the time of the document. Of these, they have a stable burden of heart failure, few arrhythmias on current stepwise regimen of antiarrhythmics and immunosuppressive, and renal disease.

Causes of death were VT storm, multi-organ failure (renal disease followed by sepsis), or during the peri-transplant evaluation.

## Discussion

In this single quaternary center case series, we describe the evolution of the approach to recognizing and diagnosing patients with clinically manifest cardiac sarcoidosis. The most common imaging modalities used to support the diagnosis of CS were cardiac MR and FDG-PET. This practice pattern supports the message published by Vita et al. regarding the complementary use of CMR and PET. [6]

Though endomyocardial biopsy diagnosis remains the diagnostic gold standard, it is not as often performed because of the concerns of its low yield coupled with the invasive nature of the study. Cardiac devices were commonly implanted for primary and secondary prevention of sudden cardiac death or for symptomatic or high-grade conduction system block. Our site's practice patterns support and extend current guideline recommended management of CS, yet the heterogeneity of cardiac manifestations in this group contributes to the challenge of diagnosing and treating patients with CS.

There continue to be significant differences in presentation. In our series, although many presented with NYHA class I/II symptoms and/or arrhythmias, one patient presented with constrictive pericarditis. We show a lower incidence of pulmonary sarcoidosis than others have reported.[7] Another was initially diagnosed with ARVC (arrhythmogenic right ventricular cardiomyopathy) by non-contrast MR only to be diagnosed with extensive RV involvement of CS that mimicked ARVC during transplantation. Over the last decade, cardiac sarcoidosis diagnosed after heart transplantation has transitioned to earlier diagnosis before transplantation, likely with increased awareness of isolated CS and with improvement in imaging modalities beyond traditional echocardiography and gallium scan. Furthermore, it is now more common to have MR imaging in the presence of non-conditional devices that were previously felt to be contraindicated. In addition, there is increased rigor in the dietary preparation for FDG-PET scans. There remains a large overlap between imaging studies consistent with CS and the diagnosis of myocarditis, thus emphasizing the need for either endomyocardial biopsy or imaging of other organs for opportunities for biopsy to

unequivocally establish the correct diagnosis. While immunosuppressive therapy may be an option for both myocarditis and CS, the latter diagnosis is important in the decision tree when considering transplantation. It remains unclear if, after transplantation, recurrence of CS has been delayed by transplant-related immunosuppressive therapy or that the primary insult had already quiesced.

The use of nuclear imaging with fluorodeoxyglucose[18] (FDG) positron emission tomography (PET) to guide treatment has become more common, but lacks rigorous data from larger cohorts. Whether an improvement in inflammatory burden as assessed by FDG-PET is correlated with clinical outcomes is yet unproven.[8]

Regarding cardiac implanted electronic device therapy, in a 2015 retrospective analysis of 235 patients with CS and implantable cardioverter-defibrillator over a mean of four years, nine of 13 patients with isolated CS received appropriate ICD therapy, including anti-tachycardia pacing (ATP) and/or shock.[9] Further, the University of Colorado retrospectively analyzed 112 CS patients from three sites, identifying that 32% received appropriate therapies for ventricular tachyarrhythmias (VT) over a mean follow-up period of 29 months. VT storm (>3 episodes in 24 hours) occurred in 14% of CS subjects. Inappropriate therapies occurred in 13 CS subjects or 12%.[9,10] Based on our experience, device therapy with implantable-cardioverter defibrillators should be considered in all cardiac sarcoidosis patients for either primary or secondary prevention of ventricular arrhythmias and cardiac death.

In previous descriptions of patterns of immunosuppression use in the treatment of CS, a 2013 Canadian systematic review of outcomes after initiation of corticosteroid therapy from 10 publications suggests that early initiation of steroids [was] associated with prevention of left ventricular function decline and remodeling.[11] The best data reported relate to AV conduction recovery and corticosteroids appear to be beneficial for these patients.[12,13]

Therapy pre-transplantation focuses on immunosuppression, most commonly with glucocorticoids. Immunosuppressant medications may be prescribed for either cardiac or extra cardiac symptoms such as dyspnea or arthritis. Treatments for arrhythmias, whether medications for atrial or ventricular arrhythmias, pacemakers for heart block, or ICDs for VT (primary or secondary prevention), were often used. One patient received pericardial stripping for constriction. Another patient received a spinal cord stimulator for intractable angina-like symptoms. However, the presentation of angina was exceedingly rare in our cohort.

Several of our patients were treated with immunomodulators aside from steroids. Previous studies of weekly methotrexate therapy with daily small doses of corticosteroids revealed that the ejection fraction and NT-proBNP levels in the serum stabilized without eliciting adverse effects longitudinally.[14] Our experience includes 18 patients prescribed immunosuppressant therapy in combination with, or following a patient's non-response to, steroid therapy. While one patient on combinations of mycophenolate, hydroxychloroquine, and infliximab had a rather favorable course with CS remission, several other patients on similar therapeutic combinations required either diuretic escalation, died of cardiogenic shock, or required home inotropes for persistent ambulatory NYHA class III symptoms. As mentioned, immunosuppressive regimen was of course guided by pre- and post- cardiac transplant course, where applicable. Given the diagnostic difficulty of CS, we hope that our experience in the diagnosis, management, and outcomes of patients with CS and potential CS adds to the body of literature and highlights the need for complementary diagnostic modalities to guide diagnosis. Especially poignant is that we treated several patients who met criteria for CS yet were initially (or later) determined to have alternative diagnoses, such as eosinophilic myocarditis or arrhythmogenic right ventricular dysplasia. Several important questions remain unanswered, such as whether patients with systemic sarcoidosis and diastolic heart failure should be considered to have cardiac involvement, and the role of advanced imaging in diagnosing of such cardiac involvement. Clearly, the diagnosis and treatment of CS remains a challenge, yet our experience supports that newer imaging modalities (cardiac MRI[15] and FDG-PET) are sensitive instruments to detect CS and also to follow therapeutic response. Based on our cohort and others, it is not uncommon that standard echocardiography will be normal. The use of strain in the setting of a normal echocardiogram may enhance this in the future. Adherence to the FDG-PET preparation protocol has been well-documented by others.

Further, terms that stratify CMR by likelihood of the presence of CS should be considered, particularly in the setting of non-traditional patterns of late gadolinium enhancement, such as involvement of the right ventricular insertion points or pericardium. In addition, imaging after non-MR-conditional cardiac implantable electrical device is placed may provide further information in the setting of a non-ischemic cardiomyopathy. Given the significant overlap with myocarditis, ultimately, a biopsy is most helpful, and there are continued efforts at targeted assessment of potential site of pathology.

While there is heightened awareness of the diagnosis of cardiac sarcoid, particularly in the setting of arrhythmias and heart failure, this consideration is also important even in the absence of extra-cardiac sarcoid. We certainly acknowledge that by design, we selected cases that may have systematically underrepresented patients with isolated cardiac sarcoidosis. Previous work by Okada et al. suggested isolated cardiac sarcoidosis occurs in approximately 25% of cases.[16]

There has been improved adeptness at the recognition of cardiac sarcoid over the past decade, and this should promote a more comprehensive approach to identifying other organ involvement. Extended efforts to document historical lung imaging findings or biopsy results, or those performed elsewhere is similarly important.

## Conclusions

In this single center case series of 28 patients with cardiac sarcoidosis, we describe patient patterns that vary depending on the initial presenting symptoms, ranging from arrhythmia, dyspnea, or NYHA II-IV CHFs. Attempts at diagnosis also vary, most commonly undergoing cardiac MR and FDG-PET imaging to support the diagnosis of CS. This diagnosis must be considered, even in the absence of pulmonary sarcoidosis, as the incidence of pulmonary involvement in our population was far lower than previously reported. Although tissue diagnosis remains the standard, it also varies considerably, ranging from an outside historical report, to extra cardiac or cardiac samples, and not uncommonly of the explanted heart after transplantation in isolation. Immunosuppressive therapy and cardiac implantable electronic devices are frequently used, and further follow up data would be helpful in describing outcomes related to these therapies. The evolution of treatment beyond steroid therapy alone is particularly notable. Given the variations of quaternary care center described here, this cohort can not only provide support for individual clinicians in their attempt to diagnose and treat patients, but should also prompt larger registries that document diagnostic and therapeutic modalities in this complex, often multi-organ disease process.

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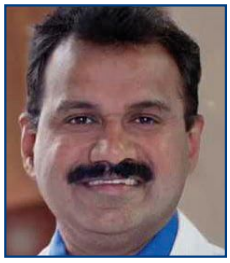
## Disclosure

None reported. **MM**

# Review of Rapid Advances in Cystic Fibrosis

*by Stephanie L. Link, DO & Ravi P. Nayak, MD*

**Previously cystic fibrosis was primarily a focus of study in pediatrics; however, due to medical advancements and an increase in life expectancy, internists must acquire further understanding of the disease to maintain optimum health outcomes for patients.**



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## Abstract

**Cystic fibrosis (CF) is an autosomal recessive disease that was previously a fatal pediatric disease with no treatment; however, due to scientific advancements, the median age of survival for the CF population born in 2018 has increased from 29 in 1989 to 47.4 in 2018. This is an innovative era for the treatment of CF as advanced research continues to evolve and novel treatments for the disease and related illnesses are discovered.**

## Introduction

According to the Cystic Fibrosis Foundation Patient Registry Annual Data Report 2018, there were 30,775 individuals with CF in the United States and 70,000 people worldwide. The adult CF population composed of 54.6% adults compared to 29.4% in 1988.[1] In Missouri there are approximately 747 CF patients in the registry. Previously CF was primarily a focus of study in pediatrics; however, due to medical advancements and an increase in life expectancy, internists must acquire further understanding of the disease to maintain optimum health outcomes for patients.

## Pathophysiology

CF is a genetic disorder that is inherited in an autosomal recessive manner. The cystic fibrosis transmembrane conductance regulator (CFTR) gene is located on chromosome 7 and codes for the CFTR protein which is either abnormal or absent in individuals suffering from CF. CFTR is a chloride channel that is dependent on phosphorylation. The CFTR protein is composed of 1480 amino acids. The protein contains five specific domains: two transmembrane domains (TMD), two nucleotide-binding domains (NBD), and a regulatory (R) domain (Figure 1).[2] The CFTR protein regulates the transportation of chloride ions into and out of epithelial cells which in turn regulates salt, fluid absorption, and secretion. Due to the abundance of epithelial cells in the body, CF affects the respiratory, gastrointestinal, and reproductive tracts.[3]

## Diagnosis

Throughout the United States, all newborns undergo a newborn screening test (NBS) which screens for a variety of health conditions including CF. This test involves pricking the newborn's heel and collecting the blood on a Guthrie card. This

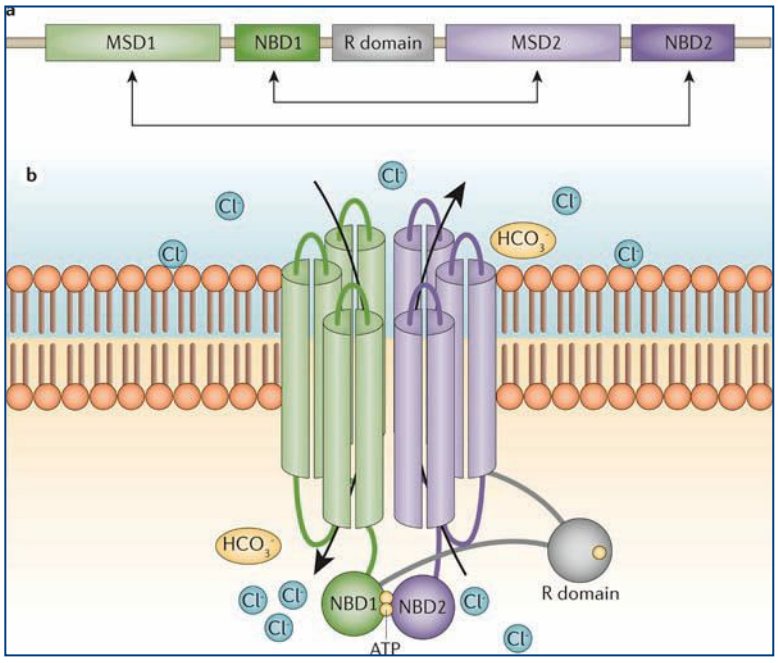



Figure 1. Structure of CFTR. The cystic fibrosis transmembrane conductance regulator (CFTR) protein is comprised of two, six span membrane-bound regions each connected to a nuclear binding domain (NBD1 and NBD2), which bind ATP, as well as a regulatory (R) domain that is comprised of many charged amino acids. The channel opens when its R-domain is phosphorylated by protein kinase A and ATP is bound at the NBDs.[2]

card is then sent to a laboratory which identifies the level of immunoreactive trypsinogen (IRT). IRT is a chemical produced by the pancreas that is typically low in a healthy individual. In patients with CF, the pancreatic duct is blocked causing an increased amount of IRT in the blood. If the newborn screen is positive, then the patient will undergo a sweat test which is considered the gold standard for CF diagnosis. A test is considered positive if the sweat chloride concentration is greater than or equal to 60 mmol/L. If the chloride concentration is less than or equal to 29 mmol/L, then CF is unlikely. The test is indeterminate, if the chloride concentration is between 30-59 mmol/L. If a test is indeterminate then CFTR genetic analysis is the next step. After CF is diagnosed, genetic testing is required to identify the CFTR gene mutation in order to choose the appropriate treatments. According to the 2017 Consensus Guidelines from the Cystic Fibrosis Foundation, a diagnosis of CF-related metabolic syndrome (CRMS) also known as CF Screen Positive Inconclusive Diagnosis (CFSPID) is made when an infant has a positive NBS test and either of the following: a sweat chloride test less than 30 mmol/L and 2 CFTR mutations, at least one of which has unclear phenotypic consequences or an intermediate sweat chloride value between 30-59 mmol/L and zero or one CF-causing mutations.[4]

## Cystic Fibrosis Effects

Patients with CF experience a wide variety of symptoms that affect multiple organ systems including the pulmonary, gastrointestinal, and reproductive system.

### *Sinopulmonary System*

The most serious manifestations are related to the respiratory tract. Sinusitis occurs when thick mucus accumulates in the sinuses impairing appropriate clearance of particles which can be a site for infection. This results in obstructed airways which can be a reservoir for infection and ultimately lead to respiratory failure. Lung disease is the leading cause of morbidity and mortality in patients with CF. CF patients experience frequent pulmonary exacerbations which can present with cough, chest congestion, increased sputum production, wheezing, shortness of breath, and dyspnea on exertion. In 2018, the most common respiratory pathogens were *Staphylococcus aureus* 70%, Pseudomonas aeruginosa 44.4%, mycobacterial species 13.6%, Stenotrophomonas maltophilia 12.3%, and Burkholderia cepacia 2.6%. Overall, the percentage of patients with positive Pseudomonas aeruginosa has declined over time likely due to the current therapies preventing the acquisition.[1] Overtime as patients experience worsening lung disease, inflammation increases in the airways leading to tissue destruction. There are several morphological changes that occur in the CF lung. The earliest sign of airway disease in CF patients is bronchiectasis which is found in about 29.3% of CF patients by three months of age and 61.5% at three years of age.[5] Due to the accumulation of thick mucus, CF patients often experience mucus plugging in the airways. Lung disease is monitored with various

tests and imaging modalities including pulmonary function testing, chest x-ray (CXR), computed tomography (CT), and magnetic resonance imaging (MRI). Specifically, forced expiratory volume in one second (FEV1) is measured to determine disease progression and response to treatment.

### *Gastrointestinal System*

Several organs in the gastrointestinal tract are affected by CF including the pancreas, gallbladder, liver, and intestines. In CF, pancreatic dysfunction ranges in severity. Patients are labeled as pancreatic sufficient (PS) and pancreatic insufficient (PI). This is determined based on the amount of exocrine pancreatic function.[6] Studies revealed that approximately 85% of patients with CF are PI, and patients who are PS can develop PI throughout their lives.[7] Patients with exocrine pancreatic insufficiency can experience gas, bloating, weight loss, dyspepsia, and steatorrhea. Children will often present with failure to thrive. Intestinal manifestations of CF are common; the earliest presentation is meconium ileus in a newborn. As CF patients age, this same phenomenon can occur in adults and is called Distal Intestinal Obstructive Syndrome (DIOS) which results in partial or complete bowel obstruction that must be treated with laxatives and/or enemas. In the small intestine the harsh stomach acid is not neutralized by pancreatic enzymes leading to small intestinal bacterial overgrowth (SIBO); this can cause diarrhea, abdominal pain, and weight loss.

### *Endocrine System*

Pancreatic endocrine insufficiency leads to Cystic Fibrosis Related Diabetes (CFRD) which is present in 2% of children, 19% of adolescents, and 40-50% of adults. Studies have also shown that patients with CFRD that are treated with insulin show improvement in BMI and respiratory function.[8] Insulin is the standard of treatment for CFRD.

### *Reproductive System*

CF affects the reproductive system of both males and females. In males, the vas deferens may be absent, or if present thick mucus causes obstruction. Regardless, this results in semen that does not contain sperm leaving males infertile. In females, cervical mucus is too thick and may impair fertilization.

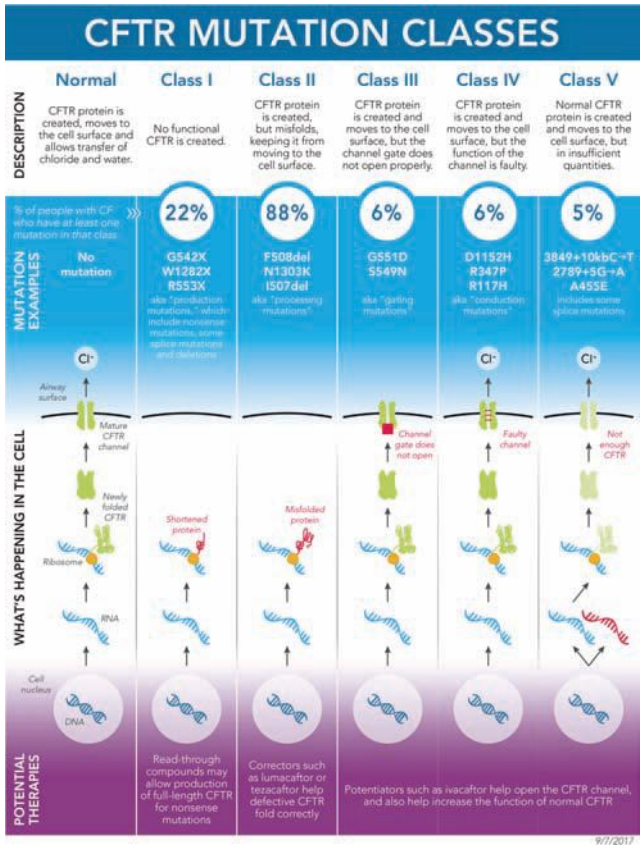



Figure 2. CFTR mutations. Description of types of CFTR mutation classes.[10]

### *Skeletal System*

Due to the nutritional deficits mentioned earlier, patients with CF are at higher risk of lower bone mineral density. A study in 2010 revealed that approximately 23.5% and 38% of CF patients had osteoporosis and osteopenia respectively.[9] For this reason it is recommended to monitor bone density with dual-energy X-ray absorptiometry (DXA) scans every five years.

## Targeted Gene Therapy

### *Mutations*

Currently there are over 2,000 mutations that have been identified in the CFTR gene, and there are new mutations being identified to this day (Figure 2).[10] It is critical to understand these mutations in order to develop effective

treatments. The mutations have been classified into six different groups: class I – protein production mutations, class II – protein processing mutations, class III – gating mutations, class IV – conduction mutations, class V – insufficient protein mutations, and class VI – reduced amount of protein.[11]

### *Drug Modulators*

Over the past two decades scientific advancements have made it possible to determine a CF patient's specific mutations, and drug modulators have been developed to target the specific CFTR mutations. There are five types of modulators: read-through agents, correctors, potentiators, stabilizers, and amplifiers.[12]

The first CFTR modulator approved by the FDA was ivacaftor (IVA). Ivacaftor is a potentiator that works on gating mutations by keeping the ion channel of the CFTR protein open. Ivacaftor works on patients with CF who have a G551D CFTR mutation which is approximately 5% of patients with CF.[13] Trials revealed a 10.6% increase in FEV1 from baseline through 24 weeks in patients treated with ivacaftor compared to placebo. Through 48 weeks of treatment with ivacaftor vs placebo, patients were 55% less likely to have pulmonary exacerbations, gained an average of 2.7 kg of weight, and a decrease of 48.1 mmol per liter of sweat chloride.[14] These studies proved ivacaftor to be the benchmark for all future treatments. As of today, ivacaftor is FDA approved to treat patients age six months and older with one of 38 mutations that are responsive to Ivacaftor potentiation based on clinical and/or in vitro assay data.[15] Ivacaftor has a relatively safe drug profile, and common side effects include cataracts, elevation in transaminases, and interactions with CYP3A inducers which can reduce the effectiveness of ivacaftor.

Further studies revealed that ivacaftor treatment alone was ineffective for patients homozygous for the F508del mutation. This became a large area of interest because the most common mutation in CF patients is the F508del mutation with about 50% of the CF population being homozygous for this mutation.[16] Correctors were the next type of modulator discovered. When correctors are paired with a potentiator, it improves cellular processing and trafficking of the CFTR protein allowing it to reach the cell surface and function appropriately.

The first corrector discovered was lumacaftor. Lumacaftor showed significant benefits when combined with ivacaftor. Lumacaftor/ivacaftor was approved in 2015 and is indicated for patients two years and older who are homozygous for F508del.[17] Trials where patients were treated with lumacaftor/ivacaftor revealed a 2.6 – 4.0% improvement in FEV1 and a 30 - 39% reduction in pulmonary exacerbations compared to placebo.[18] Trials also showed a decrease in sweat chloride and increase in BMI. Lumacaftor/ivacaftor has more side effects than ivacaftor alone. Reported side effects include hypertension, worsening liver function in patients with advanced liver disease, and drug interactions due to lumacaftor being a CYP3A inducer. During initiation of the drug, it was noted that patients had increased occurrences of respiratory events defined as chest discomfort, dyspnea, and abnormal respirations.[19]

The next modulator aimed to have the efficacy of lumacaftor/ivacaftor without the significant respiratory symptoms on initiation of drug therapy and drug interactions; this drug is tezacaftor/ivacaftor. Tezacaftor/ivacaftor was approved in 2018 and is indicated for CF patients ages 6 years and older who are homozygous for the F508del mutation, or who have at least one mutation in the CFTR gene responsive to the drug in in vitro data and/or clinical evidence.[20] In the first trial, EVOLVE tested tezacaftor/ivacaftor on patients homozygous for F508del mutation which revealed 4.0% improvement in FEV1 and a 35% reduction in pulmonary exacerbations vs placebo. The second trial, EXPAND, focused on individuals heterozygous for F508del and revealed a 6.8% improvement in FEV1 vs placebo.[21, 22]

With the advent of drug modulator combinations, the next area of research shifted to minimal function (MF) mutations. MF mutations are defined as gene mutations that leave the CFTR protein minimally functional or unable to function at all. Unfortunately, patients with a minimal function mutation and heterozygous for F508del account for approximately 30%

of patients with CF. These patients were not responsive to ivacaftor, or the combination of tezacaftor/ivacaftor, or lumacaftor/ivacaftor.[23] Trials began combining a third corrector to the already existing texacaftor/ivacaftor.[22] Trials on patients who were F508del/MF genotypes were treated with elexacaftor/tezacaftor/ivacaftor and through 24 weeks had 14.3% increase in FEV1 compared to placebo and 63% lower annual rate of pulmonary exacerbations compared to placebo. There was also significant decrease in sweat chloride production and increase in BMI.[23] In 2019 the FDA approved elexacaftor/tezacaftor/ivacaftor for CF patients ages 12 and older with at least one copy of the F508del mutation regardless of the second mutation. [24] This was a huge advancement for CF patients as now over 90% of CF patients are eligible for drug modulator therapy.[25]

There are several other drug modulators that are undergoing research. Amplifiers increase the amount of CFTR being made. Read-through agents work on class I (protein production) mutations by preventing the results of the splice and nonsense mutations which in turn will allow the production of a functioning protein. Stabilizers work on class VI (reduced amount of protein) mutations and allow the CFTR channel to stay at the cell surface and prevent degradation. This is a very exciting time for the treatment of CF as drug modulators are becoming the new standard of care for treatment. Researchers around the world are developing various trials to enhance CF treatment and provide the best care.

## Treatments

### *Chronic Medications*

In 2007, the CF Foundation established the Pulmonary Clinical Practice Guidelines Committee to help guide providers in the use of chronic medications for CF; these guidelines were reviewed and updated in 2013. It was deemed that beta-two agonists and anticholinergics had insufficient evidence to recommend for or against use. It was recommended to use inhaled tobramycin and aztreonam for mild and moderate to severe lung disease. It was recommended against using anti-staphylococcus aureus agents for prophylactic use, and there was insufficient data to recommend using anti-staphylococcus aureus and anti-pseudomonas aeruginosa agents for or against chronic use. It was recommended to use dornase alfa for mild and moderate to severe lung disease. All lung disease regardless of severity were recommended to use hypertonic saline. Hypertonic saline is a sterile saline solution that comes in three different concentrations (3 percent, 3.5 percent, 7 percent). This essentially adds a salt solution into the airways which attracts water and in turn results in thinned secretions allowing a CF patient to expectorate. Patients with chronic pseudomonas aeruginosa infections were recommended to use chronic azithromycin.[26]

### *Airway Clearance Therapies (ACT)*

Airway clearance therapies (ACT) are a vital component of treatment for CF patients. It is imperative that ACT is performed by patients in order to help clear the airways of secretions in order to maintain healthy airways and prevent inflammation and infection. In 2009, the CF foundation reviewed all the therapies that exist in order to compare their effectiveness and guide providers. The review focused on the following categories: percussion and postural drainage (P&PD), positive expiratory pressure (PEP) devices, active cycle of breathing techniques (ACBT), autogenic drainage (AD), oscillatory PEP devices (OPEP), high-frequency chest compression (HFCC) devices, and exercise (Figure 3). It was determined that there was no form of ACT that was found to be superior to other forms.[27]

### *Pulmonary Exacerbations*

The goal in CF patients is to reduce the amount of pulmonary exacerbations. There is no universal definition of a pulmonary exacerbation, but it is generally defined as a worsening in respiratory symptoms and decrease in lung function. Exacerbations can be triggered by viral and/or bacterial infections, medication non-adherence, or stress. In 2009, the CF Foundation's Pulmonary Therapies Committee met to define a set of recommendations for the treatment of pulmonary exacerbations and found that there was insufficient evidence to make official



Figure 3. Airway clearance therapies. Chest physical therapy, high-frequency chest wall oscillating vest, positive expiratory pressure, airway oscillating device.

recommendations. Overall, it was agreed that during an exacerbation, chronic medications be continued, airway clearance therapies continued, IV antibiotics should be delivered only in a healthcare setting rather than in the home. There was insufficient evidence to recommend specific antibiotics or a duration of antibiotic treatment.[28] The STOP: Standardized Treatment of Pulmonary Exacerbations Pilot Study trial was an observational study conducted from 2014 – 2015 that evaluated the treatment used and the response to treatment in CF individuals experiencing pulmonary exacerbations. The data revealed that the average time of antibiotic treatment was 15.7 days and there was a large variation of the type of antibiotic prescribed.[29] This data was the framework for the ongoing STOP 2: Treatment of pulmonary exacerbations in people with CF that is currently attempting to evaluate the safety and effectiveness of different length of IV antibiotic treatment for pulmonary exacerbations. [30] At present the recommended antibiotic therapy is two antipseudomonal drugs because pseudomonas aeruginosa is the most commonly isolated pathogen in CF patients.[28]

### *Nutritional Considerations*

Dieticians are crucial to the care team for CF patients. Dieticians educate patients and their families on the appropriate nutrition and supplementations. At this time the standard diet is a high-calorie, high-fat diet with pancreatic enzyme replacement therapy (PERT).[31] PERT dosing is based on body weight or based on the fat content of a meal. Fat soluble vitamin supplementation should also be given with PERT.

### *Lung Transplantation*

Lung transplantation remains an option for CF patients with end-stage lung disease. As patients with CF age, lung disease becomes more advanced which can lead to reduced airway clearance, frequent exacerbations, hypoxemia, pulmonary hypertension, hypercapnia, and respiratory failure. The International Society of Heart and Lung Transplantation recommend evaluation for lung transplantation if a patient has any of the following: FEV1 is less than 30% predicted or rapidly declining lung function, frequent exacerbations requiring antimicrobial therapy, recent exacerbation

requiring mechanical ventilation, increasing oxygen requirements, recurrent hemoptysis despite embolization procedures, refractory or recurrent pneumothorax, baseline hypercapnia (PCO2 > 50 mmHg), pulmonary hypertension, or ongoing weight loss despite aggressive nutritional supplementation.[32] Transplantation is indicated for CF patients that are clinically declining, have a two-year predicted survival of less than 50%, and who have functional limitations. The median survival from lung transplantation in the international registry for patients with CF is 8.3 years.[33] The CF Foundation works with multiple organizations to increase the number of organ donors and decrease lung transplantation waiting time.[34]

## Conclusion

Advancements in the treatment of CF have resulted in overwhelming findings within the past two decades. Much of this had to do with the progression in genetic sequencing allowing scientists to target specific mutations. Though CF remains a disease with no cure, the lifespan of those affected with CF is drastically improving. Currently, there are several drugs in the pipeline to treat mutations not affected by existing treatments. As research continues to flourish, optimism remains that future treatment regimens can target a patient's specific gene mutations, and the potential for cure is on the horizon.

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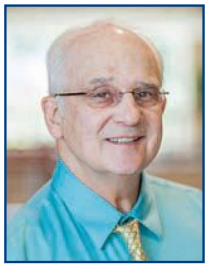
## Disclosure

None reported. **MM**

# Esophageal Dilation for Strictures: A 36-Year Prospective Experience in Private Practice Setting

*by Leslie E. Tucker, MD*

**This prospective study over 36 years on 3,112 patients undergoing 5,960 dilations with an adverse event rate of 0.05% and no mortality, shows that dilation of esophageal strictures can be done safely in a private practice setting. It also demonstrates the decline of Maloney dilation with increased usage of balloon dilators, and the emergence of eosinophilic esophagitis as a cause of stricture.**



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## Abstract

**The author dilated 3,112 patients with esophageal strictures over 36 years. Most strictures were peptic, esophageal rings, cervical webs or eosinophilic. Strictures were assessed for presence of hiatal hernia, hernia size, stricture diameter, and type and size of dilator used. Complex strictures were present in 19.7% of patients. Re-dilation was needed in 30% of patients within five years. Three adverse reactions occurred, one perforation and two bleeds in 3,112 patients (0.1%) and 5,960 dilations (0.05%).**

## Introduction

Esophageal strictures are a common occurrence in the private practice of gastroenterology. Patients usually present with solid food dysphagia, such as to meat, and bread. It is thought that 50% of esophageal circumference must be narrowed to result in dysphagia. Patients with solid food dysphagia have luminal diameters less than 14 mm wide. Most strictures in community practice are peptic in origin. In the last several decades, there has been an increasing frequency of strictures attributed to eosinophilic esophagitis.[1] Less common stricture causes include malignancy, post-surgical, lye ingestion, radiation, and post endoscopic strictures due to Mucosal Resections and Radiofrequency Ablation.[1,2] I report on 3,112 patients seen prospectively from September 1982 to November 2018.

These results will be contrasted from a prior report of 300 patients reported by this author in 1982.[3]

## Patients and Methods

Three thousand, one hundred and twelve patients, (1,468 men and 1,644) women, with dysphagia for solids, were dilated for esophageal strictures over a 36-year period. Dilatations started at 1 mm above estimated stricture diameter based on scope diameter used, usually 9.5 mm. Dilations were done once or every 3-14 days until the desired lumen was achieved. The "rule of 3" dilator method was used, never dilating beyond 3 mm per session.[4,5,6] Maloney and wire-guided dilations were all done using fluoroscopy. Wire-guided dilators were used for more complicated strictures (diameter less than 10 mm, tortuous esophagus, stricture length over 2 cm, and inability to pass a Maloney dilator despite fluoroscopy). Complex

strictures accounted for 1,139 dilations (19.7 % of dilations). Peptic strictures were defined by distal esophageal erosions or ulcerations, usually with concomitant hiatal hernia. Typical mucosal changes of eosinophilic esophagitis were absent. All peptic strictures were serially dilated to 18 mm, 20 mm if no relief of dysphagia or no disruption of stricture seen. Disruption was evidenced by a notable tear or widening of the stricture on immediate post dilation endoscopy. Lower Esophageal Rings were all dilated to 20 mm, and all four quadrants were disrupted with large biopsy forceps. Radiation and eosinophilic strictures were dilated initially to 15 mm, then to 16.5 mm if no relief of symptoms or disruption seen. Eosinophilic strictures presented with typical endoscopic appearance and 15% eosinophils on biopsies of mid and distal esophagus. If stricture was not visibly evident, pull through technique was used to identify strictures. A 15 mm balloon was pulled slowly from EG Junction through the esophagus to assess resistance and possible strictures. Patients with no initial response to dilation all underwent barium swallow using a 14 mm sugar pill. If no stricture was seen and the patient was still symptomatic, they were than empirically dilated with Savary dilators using fluoroscopy. Patients with peptic and eosinophilic esophagitis related strictures were offered treatment with proton pump therapy. Conscious sedation was used on 2,340 cases predominantly until July 2009. Only 32 cases were done with General or Monitored Anesthesia Care (MAC) during this time. Since July 2009, all cases were done with MAC, 740 cases.

## Results

Types of strictures present were peptic 2,317; lower esophageal rings 313; eosinophilic 93; post- Nissen fundoplication 75; post-surgical 45; malignant 39; radiation 34; other 27; and lye 4. There were 165 cervical webs. Only 4 strictures (4.3 %) due to eosinophilic esophagitis were seen prior to the year 2000. See Table 1.

Hiatal hernias were present in 2,318 patients, 74.5%. Sizes of hiatal hernias are shown in Table 2.

One thousand five hundred thirty-two dilation episodes were re-dilations on patients with prior strictures, 49.2% of patients. Patients needing re-dilation were dilated within five years after the first dilation in 79% of cases. Re-dilation within five years occurred in 30 % of all patients.

Dilators used were "through the scope" balloons 3,188 (53.5 %); wire-guided 886 (14.9%); and Maloney 1,886 (31.6%). All Maloney dilations done after 1983 were done using fluoroscopy. Three covered stents were used for refractory strictures. Steroid injections were also done in three cases.

Types of Dilators and sizes used are depicted in Table 3.

Table 1. Types of Esophageal Strictures

| Stricture Type | Number | Percentage |
|---|---|---|
| Peptic | 2317 | 74.5 % |
| Lower Esophageal Ring | 313 | 10.1 % |
| Cervical Web | 165 | 5.3 % |
| Eosinophilic | 93 | 3.0 % |
| Post Fundoplication | 75 | 2.4 % |
| Post-Surgical | 45 | 1.4 % |
| Malignancy | 39 | 1.2 % |
| Radiation | 34 | 1.1 % |
| Other | 27 | 0.9 % |
| Lye | 4 | 0.1 % |

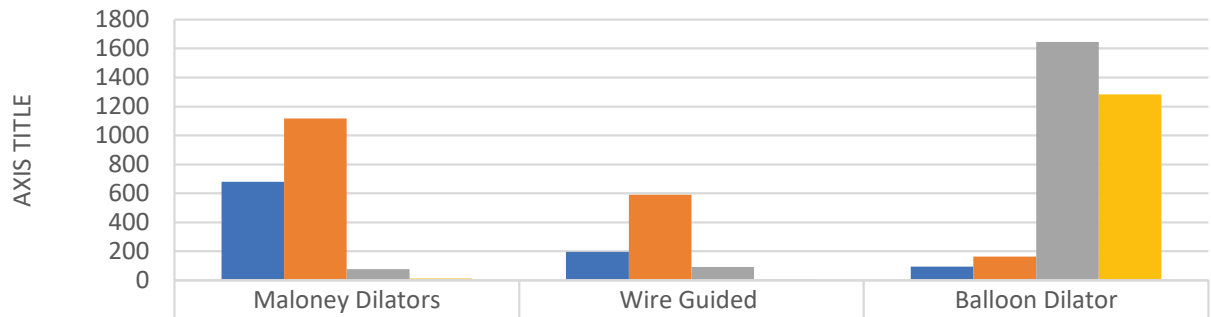
Table 2. Sizes of Hiatal Hernia

| Hernias | Size of Hernia | 1-3 cm | 4-6 cm | 7-10 cm | ➢ 10 cm |
|---|---|---|---|---|---|
| 2318 (74.5%) | | 1335 (57.6 %) | 726 (31.3 %) | 247 (10.7 %) | 10 (4.3 %) |

Table 3. Types of Esophageal Dilators Used

| Size dilator In mm | 7-10 mm (3.8 %) | 10.3-13,3 mm (10.4%) | 13.7-16.7 mm (26.9%) | 17-20 mm (58.8%) | Total Number Dilators Used |
|---|---|---|---|---|---|
| Balloon | 112 | 250 | 781 | 2045 | 3188 (53.5 %) |
| Wire Guided | 109 | 217 | 240 | 320 | 886 (14.9 %) |
| Maloney | 8 | 153 | 586 | 1139 | 1886 (31.7 %) |

Graph 1.




| | Maloney Dilators | Wire Guided | Balloon Dilator |
|---|---|---|---|
| 1982-1990 | 679 | 195 | 94 |
| 1990-2000 | 1117 | 591 | 163 |
| 2000-2010 | 77 | 93 | 1647 |
| 2010-2018 | 13 | 7 | 1284 |

The majority of Maloney and wire-guided dilations were done from 1982 through 2000, with balloon dilation dominating after year 2000. See Graph 1.

There were three complications in 3,112 patients (0.1%), and 5,960 dilations (0.05%). One patient had a cervical perforation with 18.6 mm Maloney dilator, treated successfully with surgical drainage. After this complication, all Maloney dilations were done using fluoroscopy. Two Mallory Weiss tears occurring after balloon dilation resulted in bleeding and hospitalization. There were no deaths.

## Discussion

Perforations have been reported in 0.1% to 2.6% of all dilations, with associated 1% mortality.[3,7 8,9,10,11,12] Perforation rates are not thought to be increased for dilation of strictures due to eosinophilic esophagitis.[13] A recent metanalysis reported a perforation rate of 0.03% since 2009 for eosinophilic esophagitis.[14] Perforation risk has been reported to be higher for complex strictures which are longer, angulated, severely narrow, often requiring multiple sessions for dilation.[15]

This series is the largest reported for stricture dilations in a community practice setting. Hagel et al. reported a retrospective review of 368 patients undergoing 1,497 dilations over a 10-year period in a tertiary care center.[16] He reported 8 perforations (0.53% per procedure) and 1 death (0.08% per procedure). Complications were in complex strictures, with no perforations in benign strictures. They did use the "rule of three."

Two retrospective studies involving 297 and 751 patients recently questioned the validity of the "rule of three" for dilation of strictures.[17,18] The perforation rates were 0.5 % (2,216 dilations) and 0.4 % (5,453 dilations). In contrast to our study where strictures were mostly simple peptic, rings or eosinophilic, their strictures were predominantly post-endotherapy, radiation, malignant, anastomotic, and complex peptic strictures. Dilations were also done by multiple endoscopists. Neither study found nonadherence to the "rule of three" to be a risk factor for adverse events.

Strictures associated with eosinophilic esophagitis were rare prior to the year 2000, with 95% occurring after that date. I observed no perforations in 93 patients. Diagnosis of eosinophilic esophagitis has become more commonplace in recent decades due to

increased awareness, high definition endoscopes, and increasing disease prevalence.

Proton pump therapy has been demonstrated to decrease the need for dilation.[19,20] Despite recommending proton pump therapy, need for re-dilation of strictures was common, occurring in 30% of all patients within five years

## Conclusion

This study is the largest and unusual in the setting of community private practice. Use of Maloney and wire-guided dilators are now much less common, since the advent of balloon dilators and current lack of ready access to fluoroscopy. Balloon dilators accounted for 9.7% of usage in the first decade, but 98.5% in the last decade of my practice. I observed no difference in perforation rate with different dilators, or with stricture type. Techniques included use of "rule of 3" method and fluoroscopy for passage of Maloney and wire-guided dilators in complex strictures. This prospective study over 36 years on 3,112 patients undergoing 5,960 dilations with an adverse event rate of 0.05% and no mortality, shows that dilatation of esophageal strictures can be done safely a in a private practice setting. It also demonstrates the decline of Maloney dilation with increased usage of balloon dilators, and the emergence of eosinophilic esophagitis as a cause of stricture.

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## Disclosure

None reported. **MM**

# Thunderbeat™ Integrated Bipolar and Ultrasonic Forceps in the Whipple Procedure: A Prospective Randomized Trial

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**Thunderbeat™ appears to be safe to use in pancreatic surgery and further trials with larger cohorts are needed to address the device's learning curve to ensure its optimal application in the operating room.**



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## Abstract

**Thunderbeat™ is a device that uses both ultrasonic and advanced bipolar energies to achieve hemostasis. It has been evaluated in a variety of clinical contexts, but no literature exists regarding its application to pancreatic surgery. Using a prospective, randomized controlled trial, we evaluated its safety and efficacy in the Whipple procedure. Thirty-two participants were enrolled in the study. The Thunderbeat™ device during the Whipple procedure showed similar safety profile compared to standard of care.**

## Introduction

A new type of surgical scissors that deliver ultrasonically generated frictional heat energy and electrically generated bipolar energy simultaneously, known as the Thunderbeat™ (Olympus, Japan), is now an available alternative for dissection and hemostasis.[1,2] Thunderbeat™ obtained United States Food and Drug Administration (FDA) clearance in March 2012 for use in open, laparoscopic, and endoscopic surgery, or in any procedure in which cutting, vessel ligation (sealing and cutting), coagulation, grasping, and dissection is performed. The Thunderbeat™ device provides the first integration of both bipolar and ultrasonic energies delivered simultaneously from a single multi-functional instrument. This integration provides the surgeon the ability to rapidly cut tissue with ultrasonic energy and to create reliable vessel seals with bipolar energy without having to change devices.

In animal models, Thunderbeat™ has been shown to provide superior cutting speed and versatility compared to other commercially available electrosurgical devices (Harmonic ACE, Ligasure V, and EnSeal).[1,2] It has been applied to a variety of clinical settings including gynecologic, colorectal, hepatic, and thyroid surgery.[3-12] Review of these experiences show the Thunderbeat™ to be equally safe and effective, possibly associated with decreased operative times and decreased postoperative pain, as well as having a similar cost profile when compared to conventional instruments.

However, there are no clinical studies to date evaluating Thunderbeat™ in pancreatic surgery. The Whipple procedure, first

described by Allessandro Codivilla in 1898,[13] is the standard therapy for cancerous tumors, inflammation, and stenosis near the head of the pancreas. The Whipple procedure is a technically complex operation, involving extensive peripancreatic dissection. Safe dissection around the pancreas is dependent on efficient as well as durable hemostasis. The goal of our study is to test the safety and efficacy of the Thunderbeat™ in pancreatic surgery. As such, we present the first prospective, randomized trial to evaluate the use of Thunderbeat™ during the Whipple procedure.

## Methods

This single-institution, prospective, randomized clinical trial was performed from January 2015 to August 2017 by the Hepatobiliary Surgery Service at Barnes-Jewish Hospital in St. Louis, Missouri, (ClinicalTrials.gov ID: NCT02204124). Approval was obtained from the Washington University Institutional Review Board. Inclusion criteria were patients scheduled to undergo an elective Whipple procedure, at least 22 years of age, Karnofsky performance status greater than or equal to 80%. Patients were randomized in a 1:1 ratio and assigned to the Thunderbeat™ group or standard electrosurgery instruments. In the Thunderbeat™ group, dissection and hemostasis of vessels was performed using the Thunderbeat™ device. In the control group, LigaSure (Covidien, USA), scissors, ligatures, clips, and sutures were used for dissection and hemostasis as necessary based on attending surgeon preference. In order to minimize measurement bias, patients were blinded to the assigned operating technique. Surgeon blinding was not possible due to the nature of the study. Exclusion criteria were patients who were pregnant or breastfeeding, and patients who, in the surgeon's opinion at the time of dissection, would have their well-being compromised (e.g., bleeding or other independent acute health problems).

All patients were prospectively followed for 90 days postoperatively in our complications database. Patient demographic, perioperative, and pathologic data were also collected. All complications were identified and graded prospectively using the Modified Accordion Grading System (MAGS)[14] at a weekly conference, by clinical staff using methods and definitions we have previously published.[16] Patients were diagnosed with postoperative pancreatic fistula if there was any measurable drain output of fluid on or after postoperative day 3, with amylase content greater than three times the serum amylase activity in accordance with the International Study Group of Pancreatic Fistula (ISGPF) guidelines.[15] Data on gland texture and duct size were not uniformly available for all patients. Estimated blood loss (EBL) was obtained from the intraoperative anesthesia notes where it is recorded during each surgical procedure and reflects the consensus of anesthesia and the primary surgeon. Time points for data collection were at screening, day of surgery, hospital discharge, 30-day post-op visit, and at 90 days as part of standard care.

Univariate analysis was performed to evaluate for any differences between the Thunderbeat™ and conventional groups. The student t-test, Mann-Whitney test, and Chi-Square tests were performed when indicated. Statistical analysis was performed using SPSS (SPSS Inc., version 23, Chicago, IL), probability values were considered statistically significant at less than 0.05.

## Results

Forty-four patients were enrolled to the study. Twelve were enrolled but not randomized to an arm and did not start the study due to reasons such as ineligibility, physician discretion, and because Thunderbeat™ was not in the operating room. Therefore, 32 patients were available for analysis. Of these, 19 patients were in the Thunderbeat™ arm and 13 were in the standard electrosurgery arm. Median age was 64 years, 65% of patients were male. Preoperative characteristics are summarized in Table 1. Patients were well matched between groups with no significant differences regarding to age, smoking status, Body Mass Index (BMI) and rates of neoadjuvant therapy.

Indications for Whipple were malignancy in 75% of patients and similar between groups. Tumor characteristics are were also similar between groups including tumor size, percentage of cases requiring vascular resection, lymphovascular invasion and positive margin percentage (Table 1). Average tumor size was 2.8 cm (SD of 0.95 cm), vascular resections were performed in 31% of cases, and half of cases had documented lymphovascular invasion. Margins were microscopically positive in 28% of cases. With the exception of one patient in the Thunderbeat™ group, surgeries were performed to grossly negative margins with frozen sections taken intraoperatively at the discretion of the attending surgeon. There was one patient in the Thunderbeat™ group in whom intraoperative frozen section revealed positive pancreatic margin but additional pancreas was not resected based on preoperative discussions with the patient.

As seen in Table 2, there were no significant differences noted in perioperative complication rates.

Table 1.
BMI = body mass index; SES = Standard Electrosurgery; Tobacco use defined as documented evidence of current or former use;
*as noted on pathology report
**microscopically positive margin as noted on pathology report, 31/32 operations were performed with grossly negative margins

**Table 1** – Patient Characteristics

| Variables | Overall (n = 32) | Thunderbeat ™ (n = 19) | SES (n = 13) | P-value |
|---|---|---|---|---|
| | *Patient Demographics* | | | |
| Race (Caucasian) | 29 (90.6%) | 18 (94.7%) | 11(84.6%) | 0.335 |
| Ethnicity (Non-Hispanic) | 32 (100%) | 19 (100%) | 13 (100%) | - |
| Gender (Maleness) | 21 (65.6%) | 14 (73.7%) | 7 (53.8) | 0.246 |
| Age | 64.7 (11.4) | 64.8 (11.3) | 64.6 (11.9) | 0.980 |
| BMI (SD) | 27.1 (5.2) | 28.6 (5.3) | 25 (4.4) | 0.055 |
| Tobacco Use* | 23 (71.9%) | 13 (68.4%) | 10 (76.9%) | 0.599 |
| Neoadjuvant Therapy | 8 (25%) | 5 (26.3%) | 3 (23.1%) | 0.835 |
| | *Tumor Characteristics* | | | |
| Indication (Malignant %) | 24 (75%) | 15 78.9%) | 9 (69.2%) | 0.533 |
| Tumor Size (cm) (SD) | 2.8 (.95) | 2.6 (.8) | 3.1 (1.1) | 0.208 |
| Vascular Resection | 10 (31.2%) | 5 (26.3%) | 5 (38.4%) | 0.246 |
| Lymph-Vascular Invasion* | 16 (50%) | 9 (47.3%) | 7 (53.8%) | 0.719 |
| Positive Margin Percentage** | 9 (28.1%) | 6 (31.6%) | 3 (23.1%) | 0.626 |

There was a significant difference in mean estimated operative blood loss in Thunderbeat™ versus standard electrosurgery (480.2 mL versus 263.5 mL, p = 0.032). The mean operative time differed significantly between groups as well (282.6 minutes for the Thunderbeat™ group versus 225.6 minutes for standard electrosurgery, p = 0.034).

There was no observed 90-day mortality in either group. Postoperative morbidity was similar between groups for all complications observed, with delayed gastric emptying (DGE) being the most commonly observed complication (15.6% of patients) in each group. There was one patient in the Thunderbeat™ group who suffered a superficial wound infection that was treated by bedside drainage. One patient in the Thunderbeat™ group had a postoperative pancreatic fistula requiring depot octreotide. One patient in the standard electrosurgery group had a postoperative intra-abdominal fluid collection that required image-guided percutaneous drainage. No patients required reoperation. The mean postoperative length of stay was 7.2 days (range 4 – 23) in the overall group without significant differences between groups.

## Discussion

Since its first reported use in 1928, electrosurgical energy use has quickly established itself as the standard of care in the majority of operations.[17] Over the last decade significant advances have been made in the field, increasing efficiency and versatility in the operating room. A wide range of options currently exist ranging from monopolar or conventional bipolar for smaller vessels to advanced bipolar or ultrasonic devices for the safe dissection of medium-sized vessels. In 2012, bipolar and ultrasonic capabilities were uniquely combined in a single device to create the Thunderbeat™. In animal models Thunderbeat™ demonstrated similar safety profile compared to existing devices, with possibly increased versatility and faster dissection speed. When the device was expanded to a variety of clinical settings it achieved similar results. Thunderbeat™ appears to be a safe and efficient alternative to conventional bipolar devices in laparoscopic gynecologic procedures, colorectal procedures, hepatic resections, and thyroid surgery.

This is the first randomized clinical trial to examine the safety of Thunderbeat™ in pancreatic surgery. We found Whipples performed with Thunderbeat™ had no differences in mortality, postoperative morbidity, or length of stay compared to those performed with standard electrosurgical devices. However, our data also shows that Thunderbeat™ cases were associated with increased mean EBL and longer mean operative time compared to standard electrosurgery instruments.

However, there are several important limitations to our study that impact our ability to generalize the findings.

Firstly, there is a learning curve when introducing a new surgical device into the operating room. Study enrollment was halted early which resulted in a smaller cohort than we had planned for (32 actual versus 60 planned). The increased operative time may simply reflect that we did not get past the device's learning curve with our small subset of patients. Additionally, while it did not reach significance (p = 0.055), the mean BMI in the Thunderbeat™ group was higher. Although there is debate regarding effects of increased BMI on long-term surgical outcomes, it does appear to be associated with increased intraoperative blood loss as

Table 2 – Legend
SES = standard electrosurgery; EBL = estimated blood loss; DGE = delayed gastric emptying; pRBC = packed Red Blood Cells

**Table 2** - Outcomes

| Parameter | Overall | Thunderbeat (n = 19) | SES (n = 13) | P-value |
|---|---|---|---|---|
| | *Perioperative* | | | |
| EBL (mL) (SD) | 392.2 (279.5) | 480.2 (300.5) | 263.5 (190) | **0.032** |
| Intraoperative Blood Transfusion | 2 (6.3%) | 2 (10.5%) | 0 | 0.227 |
| Operative time (min) (SD) | 258.7 (75) | 282.6 (82.7) | 225.6 (48.5) | **0.034** |
| Perioperative Complication | 3 (9.4%) | 3 (15.8%) | 0 | 0.132 |
| | *Postoperative* | | | |
| Mortality (90-day) | 0 | - | - | - |
| Morbidity | 15 (46.9%) | 8 (42.1%) | 7 (53.8%) | 0.513 |
| *Wound Infection* | 1 (3.1%) | 1 (5.3%) | 0 | 0.401 |
| *DGE* | 5 (15.6%) | 3 (15.8%) | 2 (15.4%) | 0.975 |
| *Pancreatic Fistula* | 1 (3.1%) | 1 (5.3%) | 0 | 0.401 |
| *Intraabdominal abscess* | 1 (3.1%) | 0 | 1 (7.7%) | 0.219 |
| *pRBC Transfusion* | 1 (3.1%) | 0 | 1 (7.7%) | 0.219 |
| *Reoperation* | 0 | - | - | - |
| *Readmission* | 5 (15.6%) | 3 (15.8%) | 2 (15.4%) | 0.975 |
| Length of Stay (days) | 7.2 (3.8) | 6.7 (3.0) | 7.9 (4.7) | 0.408 |

well as operation time.[18] It is possible that this difference in BMI contributes to the difference in EBL between the two arms.

## Conclusion

Although the findings of increased EBL and operative time achieved statistically significant values in this study, this did not translate into any difference in postoperative outcomes. Thunderbeat™ appears to be safe to use in pancreatic surgery and further trials with larger cohorts are needed to address the device's learning curve to ensure its optimal application in the operating room.

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# Are We Prescribing Enough HIV Pre-Exposure Prophylaxis in Missouri?

## *A Cross-Sectional Study at University of Missouri Health Care*

*by Suha Abu-Khalaf, MD, James Dent, MD, Michelle Teti, DrPH & Dima Dandachi, MD*

**Within Missouri, increasing testing rates to identify undiagnosed people with HIV, providing targeted pre-exposure prophylaxis education for both healthcare providers and patients, and utilizing new routes of healthcare delivery to expand access to rural areas all represent specific interventions with the greatest potential to affect rates of new HIV infection.**



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## Abstract

**Despite the proven efficacy and safety of HIV pre-exposure prophylaxis (PrEP), it remains underutilized. PrEP use among Missouri providers has increased as the rate of new HIV infections grows statewide, but remains lower than the Midwest and United States (U.S.) averages. Because the Centers for Disease Control and Prevention (CDC) identify Missouri as at-risk for an HIV outbreak, we seek to characterize HIV testing practices and PrEP knowledge and use among Missouri healthcare providers.**

## Introduction

In the United States (U.S.), the Centers for Disease Control and Prevention (CDC) estimates that more than 1.1 million people, aged 13 and older, have HIV. From 2013 to 2017, the number of new HIV infections remained stable.[1] In 2018, around 40,000 people were newly infected with HIV.[2] As people with HIV (PWH) are living longer and new infections continue to occur, more people are living with HIV than before.[3] However, HIV remains a leading cause of death for those ages 24 to 44.[4] The impact of the HIV epidemic is not uniformly distributed, disproportionately affecting the South, racial and ethnic minorities, and men who have sex with men (MSM).[2] The U.S. Department of Health and Human Services (HHS) has launched plans to end the HIV epidemic and reduce the number of new HIV infections by 90% by 2030.[5] In the absence of an effective vaccine, this ambitious goal requires expanded HIV testing, treating PWH to reach sustained viral suppression, and preventing new HIV transmission through behavioral counseling, pre-exposure prophylaxis (PrEP), and syringe services programs.[5]

In Missouri, the number of new HIV diagnoses per year is trending upward, increasing by 11% from 2013 to 2016.[10] The CDC has identified Missouri as at-risk for a significant injection drug use (IDU)-associated HIV outbreak at the state level based on measures of IDU prevalence and access to healthcare. Additionally, 13 counties were specifically identified as being among the top 5% of counties in the U.S. that are most vulnerable to HIV outbreak.[11,12]

PrEP, in the form of daily emtricitabine/tenofovir disoproxil fumarate (FTC/TDF), has been approved by the U.S. Food and Drug Administration (FDA) since 2012 for people who are at risk of acquiring HIV.[6] In 2019, the FDA also approved

emtricitabine and tenofovir alafenamide (FTC/TAF) for PrEP use among MSM who have bone or renal contraindications to FTC/TDF. PrEP is highly effective and safe. When taken daily, it reduces HIV sexual transmission by 99% and HIV acquisition through injection drug use by 74%.[7] However, despite strong evidence supporting the use of PrEP for HIV prevention, its implementation remains limited. The CDC estimates that in 2018, only 18% of 1.2 million persons with an indication for PrEP received it.[1] Additionally, significant geographic and demographic disparities in PrEP prescribing practices exist. Men and white individuals are more likely to be prescribed PrEP than women, black, or Hispanic individuals.[8] Studies among physicians in the U.S showed a gap in PrEP awareness and uptake, especially among generalists.[9]

Differences in training, familiarity with, and clinical practices of prescribing PrEP could be based on the demographics of a county, with proximity to urban or metropolitan areas resulting in increased provider exposure to PWH and comfort with prescribing PrEP. However, to our knowledge, there are no studies looking at PrEP awareness and adoption among healthcare providers, particularly in Missouri.

This study aims to evaluate PrEP-related knowledge, attitudes, and common practices of Missouri healthcare providers in order to identify causes of their lower rates of PrEP use, inform strategies to increase use of PrEP, thereby curbing Missouri's increasing rates of new HIV infection and reducing risk of outbreak. In addition, we sought to analyze data from the Behavioral Risk Factor Surveillance System (BRFSS)[13] and AIDSVu in order to compare HIV testing, viral suppression, and PrEP use in Missouri relative to the Midwest and the U.S. overall. AIDSVu is a free resource for visualizing the HIV epidemic in the US and accessing HIV surveillance data at enhanced geographic levels.[14]

## Materials and methods

This is a cross-sectional study, consisting of a one-time self-administered anonymous survey distributed manually to healthcare providers from different specialties at two different hospitals in Columbia, Missouri, University Hospital (UH) and Women's and Children's Hospital (WCH), in 2019.

The study has been approved by the University of Missouri Institutional review board.

### *Survey Development*

The survey was adapted from previously used surveys[15,16] and designed to collect information about potential PrEP providers, including: characteristics of the responders (age, gender, specialty, position, and number of years in practice), assessment of their knowledge about PrEP (indications, contraindications, the correct antiretroviral medications, and appropriate follow-up for patients on PrEP), attitudes toward prescribing PrEP, comfort level evaluating risk factors, and initiating PrEP.

### *Statistical Analysis*

Descriptive statistics were used to summarize patient data. Frequency and percentage were used to report categorical variables. Median and interquartile range were used to report continuous variables. Statistical analysis was performed using the SPSS software program (version 24; IBM Corporation, Armonk, NY).

### *AIDSVu's Data*

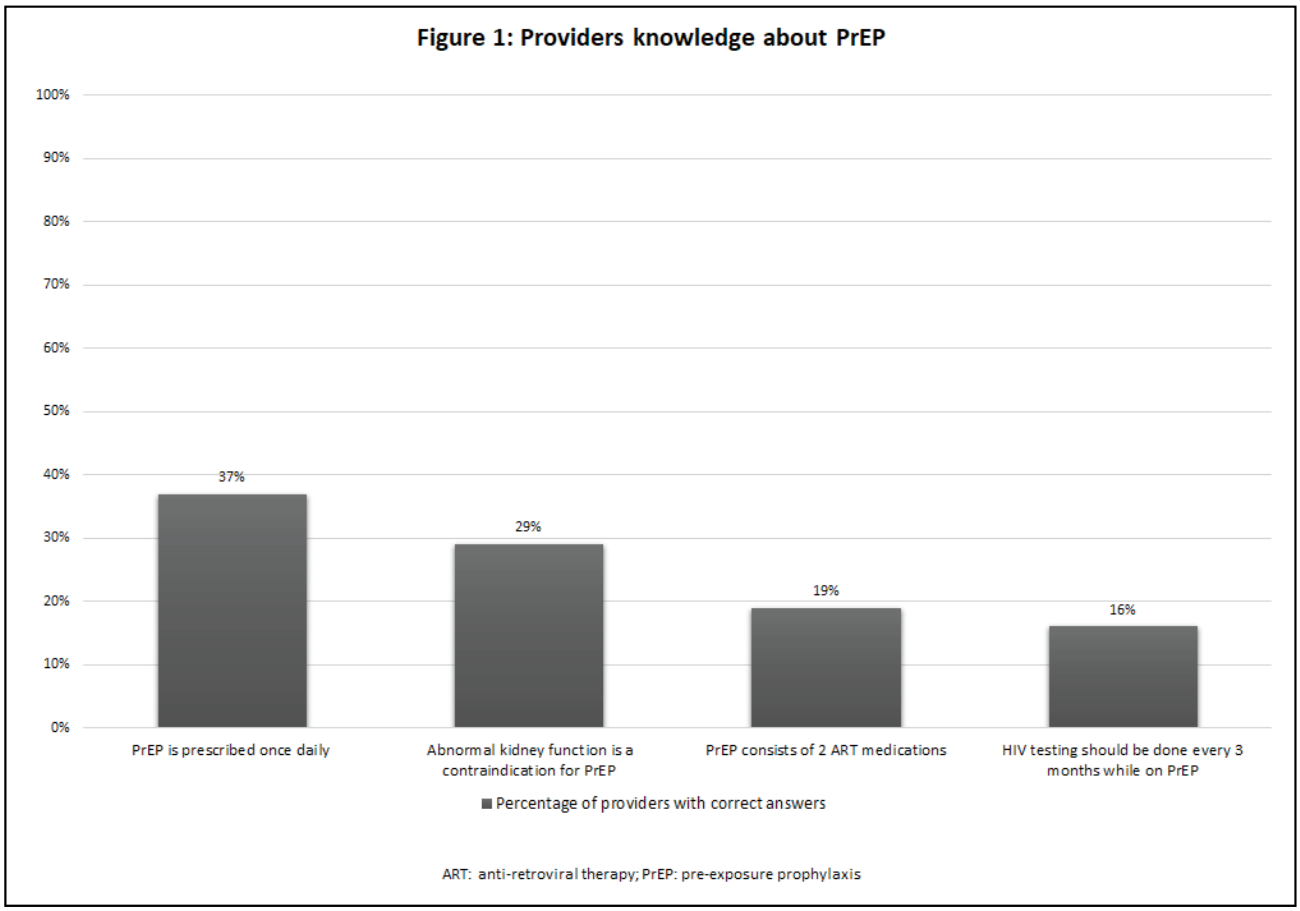
AIDSVu is presented by Emory University's Rollins School of Public Health in partnership with Gilead Sciences, Inc. and the Center for AIDS Research at Emory University. This data is collected by state and local health departments and processed by the CDC to meet data quality standards for comparability and reliability. AIDSVu maps HIV new diagnoses by gender, race/ethnicity, transmission category, and PrEP use data at the national and state level.

AIDSVu's PrEP data represents the number of people who were prescribed TDF/FTC for PrEP in a calendar year, referred to as "PrEP users" in each state in the U.S. by year. Rate of PrEP use is calculated as the number of PrEP users per 100,000 population. The PrEP-to-Need Ratio (PnR) is the ratio of the number of PrEP users in a given year to the number of people newly diagnosed with HIV that same year. PnR serves as a measurement for whether PrEP use appropriately reflects the need for HIV prevention. A lower PnR indicates more unmet need.

## Results

### *Survey Results*

Sixty-two respondents completed the survey at the two hospitals UH and WCH in 2019, with the following characteristics: median age of 30.5 years (Interquartile range (IQR) 25.7 – 37.0); 42% females and 58% males; 40% residents and fellows,




26% faculty or practicing physicians, and 34% mid-level providers/other; specialties consisting of 41% in primary care (internal medicine and family medicine), 36% in obstetrics and gynecology, and 23% in medicine subspecialties including infectious diseases (ID); and median number of 3.5 years spent in practice (IQR 2.0 – 14.0).

When asked about PrEP, only 37% knew it is prescribed once daily, 19% knew that PrEP consists of two active antiretroviral medications, 29% recognized that abnormal kidney function would be a contraindication to PrEP (note that the survey was taken prior of FDA approval for TAF/FTC), and only 16% knew that HIV testing should be done every three months when a patient is on PrEP (Figure 1). However, the majority felt comfortable (comfortable or very comfortable) discussing sexual orientation with patients (79%) and sexual practices (69%), assessing HIV risk factors (64%), and providing HIV risk reduction counseling (56%). Moreover, 79% of participants agreed (agree or strongly agree) that PrEP is a cost-effective tool for HIV risk reduction, and 68% disagreed (disagreed or strongly disagreed) that people will engage in high-risk sexual behavior as a result of being prescribed PrEP. Respondents were split (50% disagreed) on whether widespread use of PrEP will lead to increase in HIV resistance in the community.

Only a minority of providers felt comfortable (comfortable and very comfortable) determining if PrEP is indicated (39%), discussing PrEP with a patient (37%), prescribing PrEP (37%), determining if the patient has a contraindication to PrEP (26%), discussing PrEP side effects (31%), and providing ongoing management for patients on PrEP (32%). The vast majority of participants (87%) had never prescribed PrEP for any patient. Only five participants had prescribed PrEP to more than two patients, and four out of these five participants were ID physicians.

### *Comparative Data Results*

Based on responses from the BRFSS 2018 survey, only 34.1% of 1,522 Missourians reported ever

**Table 1.** HIV testing, diagnosis and PreP use comparative data between Missouri State, Midwest, and the U.S.

| | Missouri | Midwest | U.S. |
|---|---|---|---|
| 2018 prevalence of HIV testing based on responses to BRFSS survey question, "Have you ever been tested for HIV?" | 34.1% | -- | 37.8% |
| Rate of PrEP users per 100,000 population, 2018 | 51 | 56 | 68 |
| Percent of PrEP users, by Sex, 2018 | | | |
| Male | 94.5% | 93.1% | 94.1% |
| Female | 4.9% | 6.9% | 6.3% |
| PnR, 2018 | 5.20 | 6.42 | 4.89 |
| PnR, by Sex, 2018 | | | |
| Male | 6.24 | 7.48 | 5.69 |
| Female | 1.23 | 2.18 | 1.62 |
| Number of new HIV diagnosis in 2017, | 504 | 5,015 | 38,627 |
| Trend of new HIV cases from 2015-2017 | 9.33% increase ⬆ | 3.87% decrease ⬇ | 5.04% decrease ⬇ |
| Percent of people newly diagnosed with HIV, by sex | | | |
| Male | 79.2% | 81.2% | 80.8% |
| Female | 20.8% | 18.8% | 19.2% |
| Percent of people newly diagnosed with HIV, by Race/Ethnicity | | | |
| Black | 51.2% | 48.0% | 43.1% |
| Hispanic/Latinx | 7.3% | 12.1% | 24.4% |
| White | 38.1% | 34.6% | 26.0% |
| People Newly Diagnosed with HIV, by transmission category | | | |
| Female Heterosexual Contact | 90.5% | 59.6% | 85.7% |
| Female Injection Drug Use | 9.5% | 38.1% | 13.7% |
| Male-to-Male Sexual Contact | 84.2% | 84.8% | 82.4% |
| Male Heterosexual Contact | 6.5% | 6.5% | 9.1% |
| Male Injection Drug Use | 3.3% | 4.1% | 4.4% |
| Male-to-Male Sexual Contact & Injection Drug Use | 5.8% | 4.4% | 4.0% |
| AIDS diagnoses within 3 months of initial HIV diagnosis, 2016 | 23.7% | 22.7% | 21.3% |

Behavioral Risk Factor Surveillance System (BRFSS)
The 2018 PrEP-to-Need Ratio (PnR) is the ratio of the number of PrEP users in 2018 to the number of people newly diagnosed with HIV in 2017. PnR serves as a measurement for whether PrEP use appropriately reflects the need for HIV prevention. A lower PnR indicates more unmet need.
As defined by the U.S. Census Bureau, the Midwest region includes Iowa, Illinois, Indiana, Kansas, Michigan, Missouri, Minnesota, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin.

having been tested for HIV (Confidence Interval: 32.3-35.9), compared with 37.8% of the U.S. overall. While new HIV diagnoses decreased both regionally and nationally from 2015 to 2017, Missouri experienced a 9.3% increase in new diagnoses. Data from 2016 also showed that Missouri has a higher rate of people being diagnosed with AIDS within three months of initial HIV diagnosis than the Midwest or U.S. averages (Table 1).

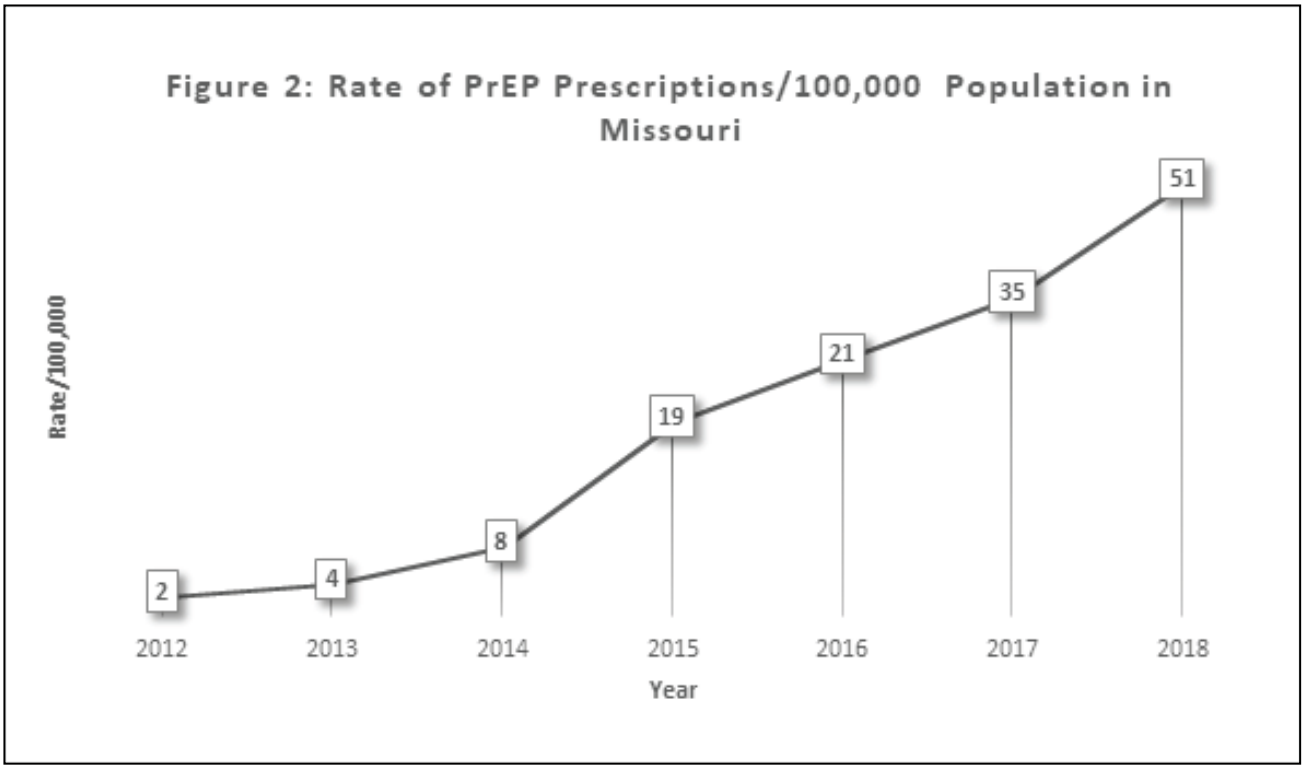
The Midwest has the lowest PrEP use of any region in the U.S., with a rate of only 56 per 100,000 persons. By comparison, the Northeast, the region with the highest use, has nearly double the rate of PrEP use, at 106 per 100,000 persons.[8,17] Despite Missouri's steady increase in PrEP use since 2012 (Figure 2), it continues to have lower than the average PrEP use among Midwest states. Looking at the 2018 PnR data comparing PrEP users to the number of people newly diagnosed with HIV, Missouri has lower PnR than the Midwest average, indicating greater unmet need than surrounding states. Nationally, women had much lower PnR than men (1.62 vs 5.69), indicating significant inequity of PrEP use among women relative to their need.[18] Missouri women specifically had nearly double the rate of unmet need for PrEP compared the Midwest overall (PnR 1.23 vs. 2.18).

## Discussion

The HHS's initiative to end the HIV epidemic in the U.S. focuses on diagnosing those living with HIV and preventing new HIV transmission. Although the rate of new HIV cases in the U.S. decreased in recent years, rates in Missouri continued to increase. Several reasons may explain these increases.

Missourians receive HIV testing significantly less frequently than the national average, likely resulting in more PWH going undiagnosed and contributing to the higher-than-average number of Missourians who are diagnosed with AIDS within three months of initial HIV diagnosis. Additionally, 40% of HIV transmissions are attributed to undiagnosed PWH.[19] Increasing Missouri's rate of routine HIV screening, including repeat screening for those at high risk, is critical to identifying these patients and allowing implementation of treatment as prevention (TasP) initiatives.

HIV prevention through PrEP use, as estimated by the prescribing rate of healthcare providers, remains very low in the Midwest and Missouri. There are also ongoing disparities in PrEP uptake among women and African-Americans.[24] Multiple barriers contribute to the slow uptake of PrEP, including individual patient factors, healthcare system barriers, and barriers related




to healthcare providers. Multiple cross-sectional studies were conducted to assess medical providers' awareness of HIV PrEP.[15,25-34] In these studies, the majority of healthcare providers supported the idea of using PrEP for HIV prevention, yet they did not feel comfortable prescribing PrEP. Some of the barriers listed and discussed include lack of knowledge and awareness[35] and concerns about the efficacy, safety, and cost of PrEP.[15,34] Although our survey is limited to two hospitals in Columbia, Missouri, it clearly shows that providers have a positive attitude toward PrEP. However, their lack of knowledge appears to cause associated unease with PrEP and avoidance of assessing indications, prescribing, and following patients on PrEP.

On June 11, 2019, the U.S. Preventative Services Task Force (USPSTF) made offering PrEP a Grade A recommendation.[37] Notably, our survey population likely does not accurately represent the average Missouri provider as it consisted of mainly of newer providers and providers currently in training, with currently practicing respondents having a median practice duration of only 3.5 years and 40% of respondents being current residents or fellows. All respondents also worked in an academic setting at the time of the survey. If these providers feel largely unfamiliar with PrEP, we suspect that many other Missouri providers, who are likely further out from training and do not practice in academic settings, would have even less familiarity with PrEP prescribing and monitoring. Our findings indicate that both primary medical training and continuing education programs should do more to highlight PrEP as a safe, effective method to prevent disease.

Missouri also suffers from the same significant disparities in urban vs. rural access to HIV care identified in other states, resulting in lower rates of HIV testing, PrEP, and TasP, even in situations where providers do feel comfortable with managing PrEP and PWH.[20,21] Many Missourians live in rural areas, sometimes driving four hours or more round-trip for a clinic visit. The U.S. Census Bureau's Census-defined Metropolitan Statistical Area defines 14 Missouri counties as urban.[36] The remaining 101 counties were defined as rural (based on a population density of less than 150 persons per square mile), including all 13 counties identified as at-risk for IDU-associated HIV outbreak. Designing outreach services in underserved areas, strengthening the HIV workforce,[22] and implementing statewide telehealth systems could increase delivery of HIV care to many of the most vulnerable Missourians.[23]

Based on our investigation, we conclude that, within Missouri, increasing testing rates to identify undiagnosed PWH, providing targeted PrEP education for both healthcare providers and patients, and utilizing new routes of healthcare delivery to expand access to rural areas all represent specific interventions with the greatest potential to affect rates of new HIV infection. By focusing on these three areas, we can better equip our providers to identify and assist those Missourians most at-risk and maximize the impact of efforts to reverse Missouri's trend of increasing new HIV infections. Studies exploring the attitude and practice of PrEP prescription and ways to increase the use of PrEP on a state level are needed.

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## Disclosure

None reported. **MM**

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