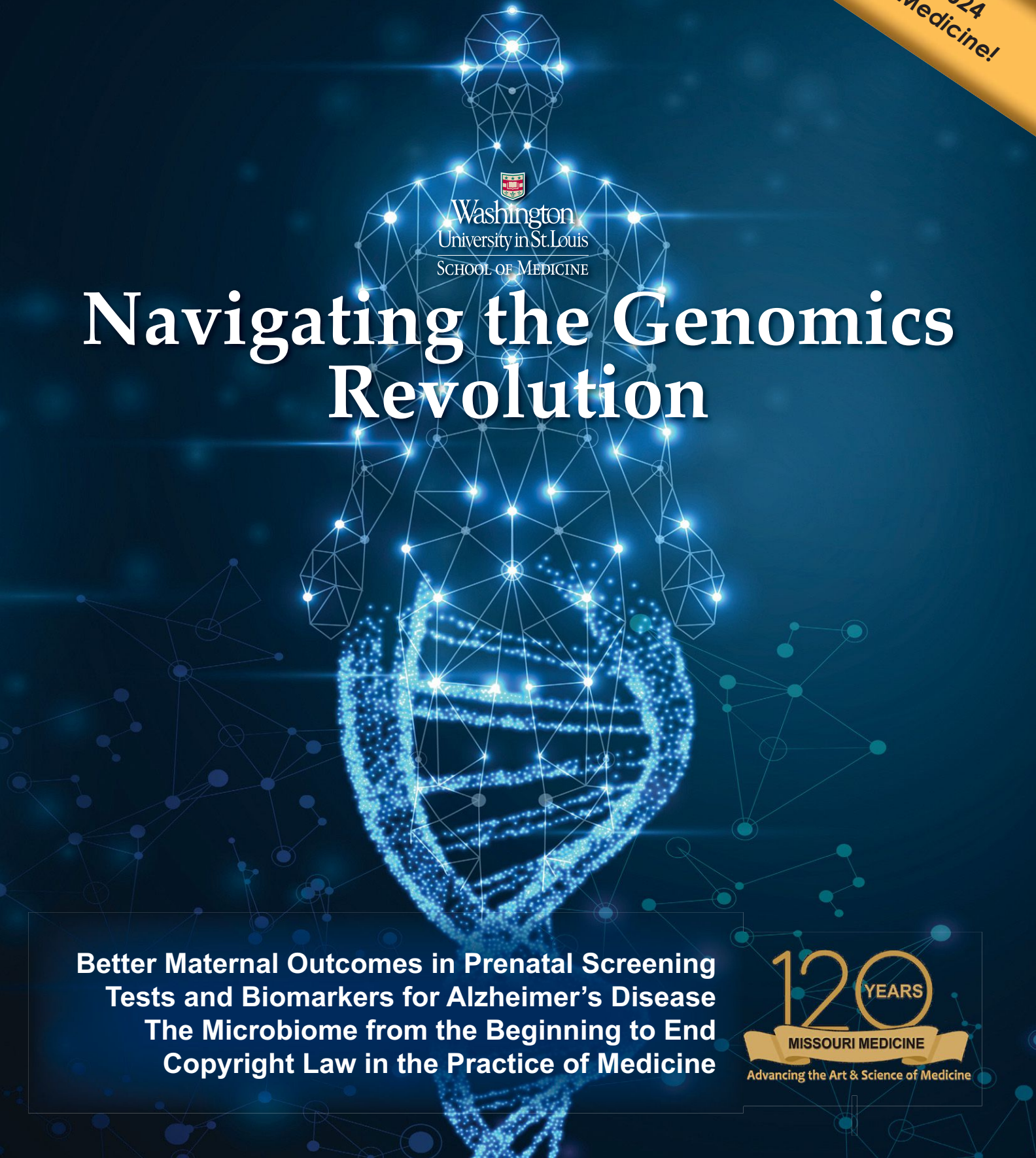
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Missouri Medicine

The Journal of the Missouri State Medical Association www.msma.org/missouri-medicine July/August 2024



Navigating the Genomics Revolution

Better Maternal Outcomes in Prenatal Screening
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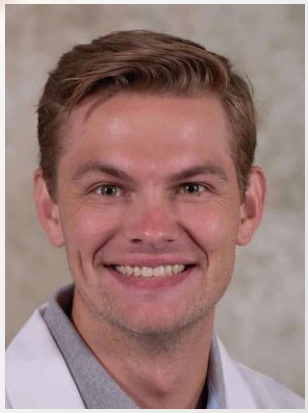
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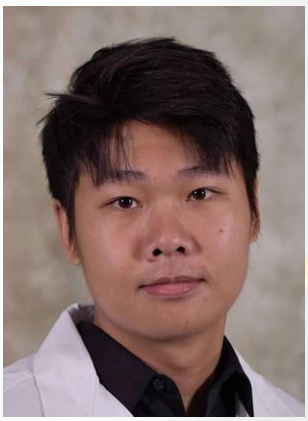
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Missouri Medicine

The Journal of the Missouri State Medical Association – Since 1904

Volume 121 | Number 4 | July/August 2024 **www.msma.org/missouri–medicine**

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

Missouri Medicine

The Journal of the Missouri State Medical Association – Since 1904

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About Missouri Medicine

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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 national media. Manuscripts are submitted from many countries. 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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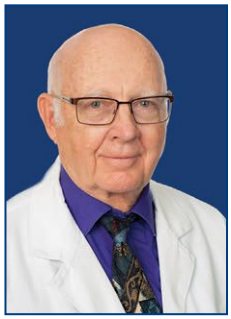


Like a Fine Wine, *Missouri Medicine* Continues to Improve with Age

by John C. Hagan, III, MD

Missouri Medicine is now regarded as among the top five state medical journals in the United States.

What was notable about 1904? The Russo-Japanese War began, the United States started construction of the Panama Canal, for the first time a steam locomotive exceeded 100 miles per hour, the New York subway opened (no one was mugged or murdered that year; it has been all downhill since then), and the automotive tire chain was patented.



John C. Hagan III, MD, is a retired ophthalmologist, and editor of *Missouri Medicine* since 2000.

A notable singularity in the Midwest was the Missouri State Medical Association (MSMA) in July 1904 published Volume 1, Number 1 of its newly conceived journal, popularly known now as *Missouri Medicine*. This July 2024, MSMA's journal celebrates 120 years of continuous publication. Only a handful of medical journals have such a long pedigree. As depicted in our new call-out logo, for 120 years *Missouri Medicine* has been advancing the art and science of Medicine.

The chronicle of *Missouri Medicine* was extensively memorialized in our May/June 2004 Centennial issue and makes for an interesting read in the Special Theme Issue section at www.msma.org/Missouri-Medicine-Library. I hope you will take the time to learn of our first century of achievement. I shall herein highlight the achievements in the twenty years since our centennial.

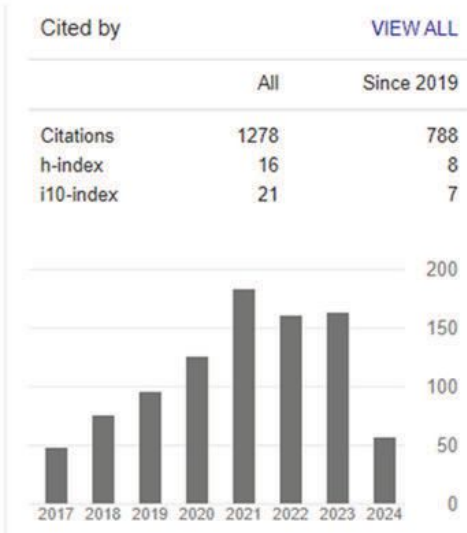
For the past century, in a remarkable partnership, *Missouri Medicine*, in print and now electronic copy, has been published by Ovid Bell Press, now doing business as Walsworth Publishing Company. It has been a symbiotic relationship and both our journal and the publishing company have prospered. Please see page 246 for comments from our century long publisher.

The foremost metric of quality in scientific publishing is inclusion in the world's leading data banks, indexing and abstracting services. Several years ago, *Missouri Medicine* went through an exhaustive and rigorous recertification process for PubMed, archiving at PubMed Central, MEDLINE, and the National Library of Medicine. The recertification process evaluated content, timeliness of publication, and how often articles in our journal are cited elsewhere (very often). With considerable assistance from Liz Fleenor, our Managing Editor, and Contributing Editor David Fleming, MD, we were recertified. Later we were solicited by Scopus, the indexing service of Elsevier, to allow them to assess our content. Scopus now indexes our journal as well as ProQuest and EBSCO Research Databases. Our journal is highly desirable for authors knowing their manuscripts will have world-wide dissemination through comprehensive indexing. Accordingly, the journal regularly receives manuscripts from countries around the world. For unsolicited manuscripts our acceptance rate is about 15%.

For several years, the Missouri Association of Publications gave their Ranly Award for Outstanding Journalism. *Missouri Medicine* received several of these including: Best Single Issue, Best Writing, and Best Article. *Missouri Medicine* was also chosen for affiliation with MedHelp.org a leading internet health website. Our journal also helped several other state journals obtain certification for PubMed and other indexing services.

Missouri is fortunate to have six outstanding medical schools, four allopathic and two osteopathic on eight campuses. For almost a quarter century, on a rotating basis, the strongest departments at these schools have produced theme issues. There is keen competition for the honor of a theme issue; typically, we are subscribed for a year and a half in advance. Based on material published in *Missouri Medicine*, two medical textbooks have been published: *Care of the Dying Patient* edited by David Fleming, MD, and myself (Missouri University Press 2010, available on Amazon, reader rated 5 out of 5 stars), and T*he Science of Near-Death Experiences* edited by myself (Missouri University Press, 2017, available on Amazon, rated 4.5 out of 5 stars and translated into several foreign languages). ProQuest and other indexing services report that our articles are among the highest cited for state medical journals. For example, see a recent Citation search for your editor (Figure 1).

Figure 1. **Google Scholar Citations John C. Hagan III, MD**



Missouri Medicine has annually regularly published world first literature reports. *Missouri Medicine* has been in the international vanguard of reporting the health dangers of hyper-exercising (Figure 2, March/April 2014). These articles drew the ire of marathon runners, the running industry, and endurance exercise-addicted physicians. Over the last decade, our research and conclusions

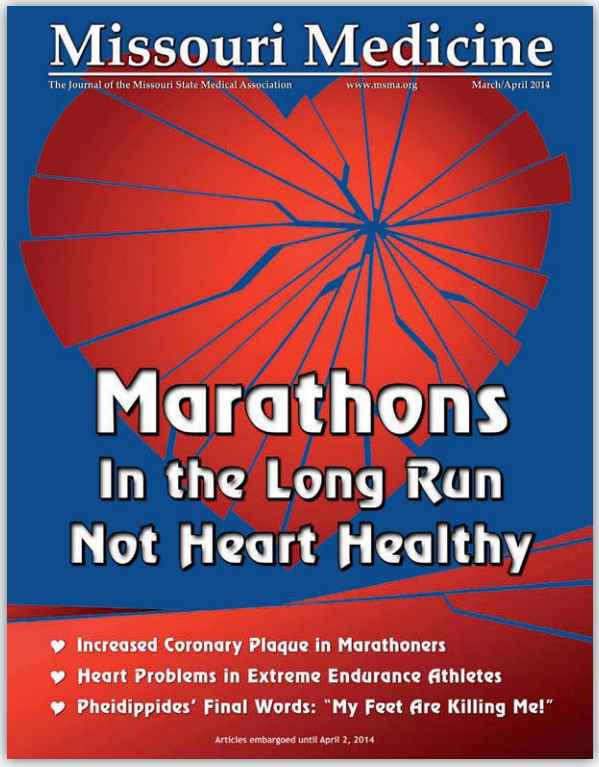


Figure 2. *Missouri Medicine* has been in the international vanguard of reporting the health dangers of hyper-exercising.



Figure 3. The world's first literature report of timolol 0.5% solution delivered nasally for the successful treatment was presented in *Missouri Medicine*.

have been substantiated again and again. Prolonged, endurance exercise, e.g. marathons, especially after age 40, is no longer recommended.

In an innovative series of articles starting with July/August 2014 "Beta Blocker Eye Drops for Acute Migraine" by Carl V. Migliazzo, MD, and myself, for the first-time beta blockers were used to successfully treat acute migraine. Subsequently our small case series success was confirmed with prospective, placebo-controlled studies by Gratton et al. in *JAMA* Neurology (2018), and Kurian et al. in *JAMA* Ophthalmology (2020). In our January/February 2024 issue (Figure 3), Steve C. Kosa, MD, and I authored the world's first literature report of timolol 0.5% solution delivered nasally for the successful treatment 9 out of 16 (62.5%) refractory referred acute migraine patients. A university department of neurology is seeking a grant for a large prospective, placebo-controlled study of nasal timolol spray that could establish a new paradigm in acute migraine treatment.

Our journal is not without challenges. Advertising revenue, like for other medical journals, has fallen to inconsequential levels. Exacerbated by unprecedented inflation, the costs of production and postage of our journal have become challenging. Accommodations have included down-sizing the maximum page count of each issue and optionally digitally delivering more subscriptions to dues paying active members and all subscriptions to medical students and residents who incredibly pay no dues.

I began my editorship in 2000. I had sent the then Executive Director of MSMA, Cork Swarens, a long list of perceived shortcomings of *Missouri Medicine* and gave a still longer list of ways the journal could be improved. Shortly after that critique, the editorship was vacated. Cork called me and said: "If you think you can do a better job and improve the journal then the editorship is yours." Game on!

When I on-boarded, our Journal was produced monthly. That is not enough time to produce a highest quality medical journal. We went to bi-monthly. Producing six issues per year gives us twice the time to make each unique and of the highest quality. Initially, I worked with a different managing editor long enough to appreciate what a gem Lizabeth R. S. Fleenor, BJ, MA (Liz) is and what a crucial role she plays in the art and



Figure 4. Contributing Editor Charles W. Van Way, III, MD, presents the *Missouri Medicine* Distinguished Service Award to Managing Editor Lizabeth R. S. Fleenor, BJ, MA.

science of putting out a visually appealing and content rich journal. In 2024 the *Missouri Medicine* Publication Committee and Contributing Editors unanimously bestowed on Liz our journal's highest honor the Distinguished Editorial Service Award (Figure 4).

For all its accomplishments and excellence, *Missouri Medicine*, at the power-train level, is really a two-person operation: myself as editor and Liz as managing editor. That isn't hubris or pride, it's just the way it is and has been for over 20 years. From its inception in 1904, *Missouri Medicine* has published 232 issues; the Hagan-Fleenor team has created more than a quarter of them. Liz has multiple other jobs and responsibilities for MSMA. When I accepted the editorship of *Missouri Medicine* in 2000, I was working seven days/week, doing surgery twice per week, regularly covering three emergency rooms and professionally engaged about 60 hours per week. I felt like Houdini trying to find time to be an editor. As our journal's editor I receive no salary or expense account. I personally pay full membership dues. At present, to maintain the quality of the journal takes about eight to ten hours of my time per week. I triage and monitor all peer-review, recruit outstanding departments for theme issues, and keep a steady stream of high-quality request articles in various stages of development; of these only about three of four promised papers are completed.

Elsewhere being a medical journal editor, at least at the national level is a pretty good gig. The *JAMA* editor, like many AMA executives, allegedly makes over seven figures in salary and benefits. Like the government and other bureaucracies, if money is available, and the AMA has plenty, higher salaries, more benefits and more staff follow closely behind. The average salary for various types of medical editors (national journals often have quite a few) is about $89,000 per year. State medical associations, with few exceptions, do not have that kind of money. Nevertheless, some states are starting to pay their medical editors. I have not been able to research this exhaustively, but the states I know about annually pay their medical editor between $5,000 and $15,000.

I'm not asking for compensation. However, there is often a thin line between an honor and a burden. To do a good job, the next editor may want compensation. Regression to the mean is the modus of most things. Our journal excellence will not brook incompetence or indifference. When the time comes, a great deal of thought and effort should be invested in finding the right follow-on editor for our journal. A full time academic does not guarantee success. Being an editor of a peer-reviewed medical journal looks great on a CV; spending the time and effort to maintain and increase excellence are likely more time and effort consuming than many academics or busy private physicians are willing or able to invest. A highly qualified semi-retired or retired physician may be the best option available. I would hate for this fine journal to regress into mediocracy.

In October 2023, after 59 years in medicine, I retired from clinical practice. At age 80, I am still actively involved in clinical research, I'm a contributing editor to other publications and write and publish frequently. For my age, my health is robust. My plan is to remain as *Missouri Medicine* editor as long as my physical and mental health are good, my editing and writing skills intact, and I continue to enjoy the position. Heck, Mick Jagger and Keith Richards of the Rolling Stones, both older than me, just played a fab concert at Thunder Ridge Arena in Ridgedale, Missouri. Rock on!

Happy 120th Birthday *Missouri Medicine.* Best wishes for the next 120 years!

Disclosure

Artificial intelligence was not used in preparing this paper, only native, non-artificial intelligence. **MM**



A Long-Standing Partnership: Walsworth Celebrates 100 Years with Missouri State Medical Association

by Will Lubaroff, Walsworth

Customers like the Missouri State Medical Association define our role as a printing company, and we would not be where we are today if not for their century of service to the state of Missouri.

Here at Walsworth, we're honored to celebrate our enduring partnership with the Missouri State Medical Association (MSMA). This remarkable journey began in 1924 when a different name graced our doors: The Ovid Bell Press. Though we've grown and evolved significantly since then, our commitment to quality and service has remained constant.

The Early Days: Setting the Stage for Success

In those early years, the printing industry, as well as the world, operated at a much slower pace. At that time, The Ovid Bell Press relied on Linotype machines for typesetting, hand-fed letterpresses for printing, and manual processes for binding and mailing. Yet, even then, They were dedicated to providing the MSMA with exceptional service.

The decades that followed were marked by a continuous embrace of innovation. The 1950s saw the introduction of automatic feeders, significantly increasing production speed. The arrival of offset presses in 1970 revolutionized their capabilities, offering a 275% increase in production speed, thanks to their capabilities to perform double-sided printing in a single pass.

The installation of phototypesetting equipment in 1977 further accelerated their workflow, allowing them to quickly scale up the speed of their production by a factor of hundreds. Soon, they ceased tracking their production in lines per minute and began counting in pages.

The dawn of the 21st century ushered in computer-to-plate technology, streamlining the process further and enabling online collaboration with clients. These developments significantly enhanced the proofing process, allowing The Ovid Bell Press to change and update projects in real time.

These days, the plant boasts a 2010 Goss M600 press which, once fully operational, has the capability to run 60-70,000 impressions per hour; almost 150 times faster compared to those early days. The

quality is exceptional and products come out with amazing, vibrant colors. Our latest saddle-stitching equipment can average up to 12,000 copies per hour and our Perfect Binder can now run up to a 288-page book in one pass.

Mailing has enjoyed even more dramatic changes. We have significantly upgraded our mailing inkjet heads and tables to virtually eliminate downtime, increase efficiencies and give exceptional quality of addressing. With these upgrades, all of our bind production equipment can mail in line in one pass.



Ovid Bell

Bill, Ed, and Don Walsworth

A Family Tradition of Dedication

The Walsworth story is deeply intertwined with the MSMA partnership. In 1924, it was Ovid Bell, founder of The Ovid Bell Press, who made the initial proposal, pledging his personal attention to the project. This commitment to service became a family tradition. His son, Ovid H. Bell, joined the business in 1945 and oversaw significant growth during his leadership. Finally, after having worked in the press since the age of 14, his son, John Bell, began working full-time in 1973 – the third generation of Bells to work in the press.

John Bell wrote in his 2004 article celebrating 80 years of printing for MSMA: *"We are very pleased to have served the MSMA for the last 80 years. It is rare in this day and age that any firm can tout continued service for that time span. We are extremely proud of our relationship and pledge ourselves to continued service, we hope for at least another 80 years. My only regret is that my grandfather didn't call on you sooner."*

Thirteen years after the MSMA began its relationship with The Ovid Bell Press and about a hundred miles away from where those first journals were printed, Don Walsworth began printing playbills on a borrowed typewriter in Marceline, Missouri. It was difficult to find work during the Great Depression, but nonetheless, his product line soon expanded to include cookbooks and, following World War II, memorial books to honor those who had served their country.

Don Walsworth's company flourished throughout the rest of the 20th century, switching its focus to scholastic yearbooks in 1947 and launching its commercial printing division in 1970. Fast forward to 2012 when Walsworth reached an agreement to purchase The Ovid Bell Press, and along with it came a history of excellence and quality service that we are steadfast in upholding.

Today, Walsworth is the 29th largest printer in the United States and Canada, the number three magazine and book printer, and, above all, still a family-owned company.

Looking Forward: A Continued Partnership

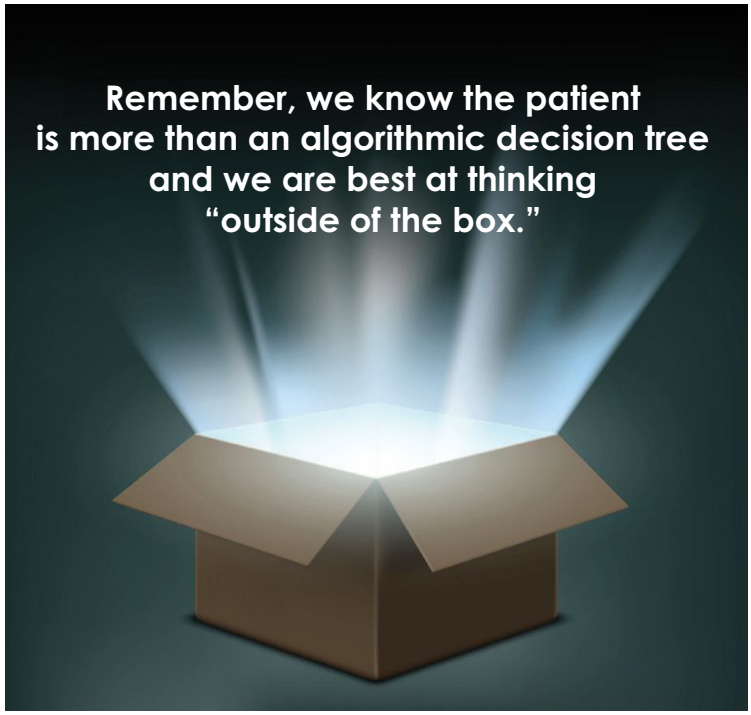
We at Walsworth are incredibly proud of this 100-year partnership with the MSMA and its journal, *Missouri Medicine*. It's a testament to The Ovid Bell Press and Walsworth's combined, unwavering dedication to quality, innovation and exceeding expectations.

Customers like the Missouri State Medical Association define our role as a printing company, and we would not be where we are today if not for their century of service to the state of Missouri.

We look forward to serving them for at least another hundred years, building upon this legacy of trust and collaboration. **MM**

Back to the Basics

by David L. Pohl, MD



It will be the end of Medicine as we know it.

Are we talking about Artificial Intelligence (AI)? No, that was the AMA in June of 1965 taking out advertisements in opposition to the official beginnings of Medicare and Medicaid stating it would be the "beginning of socialized medicine." Every so often we need to do some introspective thinking and look at where we have come from, how we have changed, and what we can do to improve our current situation.

Many physicians entered medicine because they want to help people. That laudable goal has been inhibited by the ongoing corporatization of medicine by wreaking changes that are damaging the art and practice of medicine in the pursuit of profit. To the corporate businessmen they think they are simply "squeezing the fat" and taking the profits while making Medicine "more efficient." They are wrong—medicine is about caring for our patients since the essential dyad of medicine has been, is, and should be the relationship of the physician and patient.

Many people today see the advent of AI as the beginning of the end of the highly personal relationship between us and our patients. But that does not need to be the case. We need to remember that AI is a tool, and like any tool, it can be used for good, or not so good, purposes.

One thing I hear from many people, once they find out that I am a physician, is the lament "My doctors don't listen to me because they are always typing at the computer." Artificial Intelligence can help us return to listening. During my training, I was often told to listen to the patient because they want to tell you what is wrong, and in many cases, will tell you the diagnosis (though maybe not in the same words you or I would use). I remember one patient in the clinic, when I asked: "What brings you in?" He said: "I need to get my aneurysm fixed." Needless to say, my chief resident sort of rolled his eyes and asked: "How do you know you have an aneurysm?" The patient related the story of talking to his neighbor about how his aneurysm was found and its subsequent repair. Our patient felt his abdomen, "discovered" his aneurysm,



David L. Pohl, MD, is a Radiologist from St. Louis, Missouri, and the 2024-2025 MSMA President.

and came to the clinic to get it fixed. To make the long story short, after all the examinations, testing and imaging, we scheduled the patient for repair of his abdominal aortic aneurysm.

During a recent visit with my own physician, we let AI listen. We had a good discussion about many topics, the vast majority of which had nothing to do with the appointment. At the end we looked at the AI-generated summary. What I found interesting was not just the relatively accurate summary of the medical discussion, but instead the lack of recording of the non-relevant side-discussions of our sometimes-meandering conversation. AI presented a relatively accurate summary of our interaction, which could then be edited without requiring the physician to try to "remember" everything in order to write the note later, and, more importantly, allowed for the intense interaction between the physician and the patient without having to type at the computer in real-time. In one sense, this is even better than having a scribe present since the presence of an additional person in the room can inhibit the interaction of the patient with their physician, whereas many patients may forget that AI is listening.

Next, as physicians, we need to re-emphasize thinking. In the current EMR, there is a lot of clicking on items that supposedly help guide our thought processes to become more efficient and not overlook details. What often happens is that we are led down the algorithmic limbs without realizing what happened along the way that sent us to our final conclusions. Remember, we know the patient is more than an algorithmic decision tree and we are best at thinking "outside of the box."

Our ultimate responsibility to the patient is to be caring. That means not always adhering blindly to what an algorithm suggests, but rather to consider what is best for the patient and their desires. Not all treatments achieve that result. Caring means not adopting a paternalistic "here's what needs to be done" attitude. Sometimes no treatment is what is needed and/or wanted; the patient just wants someone to listen without judgement. Many of the best physicians I know explain options, give the advantages and disadvantages of those options, and help the patient decide what can be done and, importantly, with what they will be compliant.

Listening. Thinking. Caring. Back to the Basics.

MM

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Report of the American Medical Association Annual Meeting

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

The 2024 Annual Meeting of the American Medical Association (AMA) House of Delegates (HOD) was held in Chicago, June 7-12, 2024. The HOD is the policy-making body of the AMA, so the Annual Meeting considers many issues. These include new policies to promote public health, reports on previous concerns, calls for new legislation, and initiatives for regulatory issues. The meeting also included inauguration of the new President and elections for President-Elect, Board of Trustees (BOT), several Councils, and the Speaker and Vice-Speaker. Bobby Mukkamala, MD, was elected to be President-Elect of the AMA. Lisa Egbert, MD, was re-elected as Speaker. John Armstrong, MD, was re-elected as Vice-Speaker.

Highlights

Outgoing President, Jesse Ehrenfeld, MD, spoke at length, both at Organization of State Medical Association Presidents (OSMAP) and at the opening session of the HOD.

"There is privilege and great responsibility that comes with being a physician. There is a responsibility to be an advocate, speak out against injustices, stand up for science, and give voice to the real-world challenges facing physicians. But being an advocate comes with personal costs. Why should any of us fight for change?" Dr. Ehrenfeld said that he kept coming back to the same answer. "This moment in health care demands the attention of all of us. It is our fight." Furthermore, "We fight for what we know is right. A better health care system. A more accessible health care system. A more equitable health care system. A more financially sustainable health care system. The future of our profession and our nation's health cannot be left to chance. This is why we fight."

James Madara, MD, Executive Director, highlighted the 175-year history of the AMA. The AMA's position as the physicians' powerful ally in patient care "has never been more secure—nor more evident." The AMA has achieved "outstanding financial stability." Membership has "climbed to levels not seen for decades." Dr. Madara took over as the AMA's CEO in 2011, succeeding Michael Maves, MD, who he credited for stabilizing the AMA's finances and operations. This stability allowed Dr. Madara to concentrate on developing a policy-driven strategic plan with focus and impact, which has allowed the AMA to flourish. Dr. Madara announced that he will leave his post in June 2025. His focus will be to ensure that there is a productive and trouble-free transition to the next Executive Director.

Racheal Kunesh, President of the AMA Alliance, spoke of the Alliance as a catalyst for change. Its role is to advocate, educate, and connect on behalf of physicians. She outlined current initiatives of the Alliance.

How the AMA Works

Turning to the business of the AMA, the HOD guides the AMA, setting policy, and recommending action to be taken. This is done in one of two ways. Resolutions are submitted to the HOD by delegates, proposing policy changes, or action. The HOD may accept, reject, or modify them. Also, the BOT or one of the Councils may submit a report which contains recommendations for policy or actions. These recommendations are discussed by the HOD, and may be adopted, modified, or rejected.



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

Summary of Issues

An ongoing issue is reform of the Medicare physician payment system. See the website: https://fixmedicarenow.org. Virtually all speakers referred to the need to reverse the payment cuts, which have totaled 30% over the last 25 years. The BOT Reports 6 and 12 outlined current efforts and policy on Medicare payment reform, recommending among other things that the AMA should appeal to the public at large to mobilize support. Resolution 427 called for continuing payment for telemedicine as was allowed during the pandemic.



MSMA members represented Missouri to the American Medical Association's Annual Meeting, advocating, testifying, and collaborating. Thank you to Drs. Ed Cabbabe, George Hruza, Charles Van Way, III, Ravi Johar, Elie Azrak, Peggy Barjenbruch, Albert Hsu, Joe Corrado, Kelly Schmidt, and medical students Charlie Adams and Sham Manoranjithan for representing Missouri physicians and patients.

There was continuing concern that physicians are losing control over their work environment. This issue was mentioned in several presentations. It isn't a policy issue since the AMA has strong policy support for physician autonomy. But this concern was evident throughout the meeting. The BOT Report 24 dealt specifically with preservation of independent practice for physicians.

Medical education is always a concern of the AMA. Passage to graduate medical education (GME) continues to be problematic for some graduates, with six to eight percent of seniors in American MD and DO schools being unable to find further training through the match system. American graduates of foreign schools have a much higher rate of not matching. Resolution 302 called for the AMA to consider alternatives to the present match system. Certainly, aspects of the system could be adjusted. For example, excluding international applicants is discriminatory. Resolution 315 condemned this practice. But the basic issue is the lack of GME positions. Resolution 312 proposed to create training opportunities in the Indian Health Service, like the Veterans Administration Health Care System. This would provide new training slots, especially in primary care, and would improve health care for a neglected segment of our population. It would require major upgrade to the IHS, which may be difficult to get through Congress. There were no other initiatives to increase residency positions. That said, the number of first year positions continues to increase, reaching 30,000 in 2023. But the numbers of applicants, including qualified international graduates, continues to increase as well, as does the shortage of practicing physicians.

Missouri Resolutions

Two Missouri resolutions were of particular interest. Resolution 306 called for studying alternatives for unmatched medical school graduates, such as Missouri's Assistant Physician law. This was referred to the BOT for further study, which accomplished the purpose of the resolution. Resolution 006, asking for revisions to the current code of ethics to allow physicians to treat friends and family members, where appropriate, met with general approval. But it was felt to be included under existing policy.





Drs. Kelly Schmidt and Albert Hsu testify at Reference Committees.

Equity in Health Systems

Equity in the health system was a recurring theme in the meeting. There were three lecture sessions during the meeting on aspects of equity, considering barriers to patient care within the health system for disabled patients, members of minority groups, and barriers within the insurance system. The BOT Report 10 was an annual report on health equity. Several resolutions advocated for various aspects of equity. Resolution 416 called for furthering environmental justice and equity by supporting occupation-based screening programs. Resolution 220 called for "restorative justice" in treating substance use disorders. Resolution 224 called for antidiscrimination protection for LGBTQ+ youths in foster care. There was particular concern for American Indian and Alaskan Native (AI/AN) care. Resolution 242 addressed cancer care in Indian Health Service facilities. Resolution 215 called for improvements in elder care within AI/AN communities.

Other Issues: Employed Physicians, Scope Creep, Technology & Augmented Intelligence

As part of the ongoing effort to ensure all physicians have access to the AMA, a decision was made to charge the Organized Medical Staff Section (OMSS) with representing employed physicians. This represents a logical extension of the OMSS, which already represents many employed doctors. In another decision (Council on Long Range Planning and Development, Report 1), the Lesbian, Gay, Bisexual, Transvestite, Queer Section (LGBTQ+) was created. Sections represent major subgroups within the AMA and are provided with staff and financial support.

There was discussion of "scope creep." Non-physician groups are constantly trying to gain privileges formerly reserved for physicians. The AMA funds opposition to such actions, which are most commonly at the level of state legislatures. Resolution 201 called for research into political misinformation about scope of practice. There is continued concern over the role of non-physician providers. Scope of practice issues and conflicts between training of physicians and training of non-physician providers were discussed. Finally, movement of non-physician providers between specialties can interfere with physician practices, because of the time and effort invested in training such providers.

There is a concern that emergency departments, often in rural areas, are often not staffed by physicians. Resolution 204 called for federal legislation to mandate physician supervision of emergency departments. While there may be a "carve-out" for rural hospitals in actual legislation, there should be a clear statement from the AMA.

There was action taken in response to the increasing role of computer technology in health care.





In the House of Delegates, from left, Drs. Kelly Schmidt, Peggy Barjenbruch, Edmond Cabbabe, Elie Azrak, Charles Van Way, III, and Joe Corrado.

Resolution 606 called for establishing a task force on computers and technology, with the intent of moving towards a permanent Council on Technology. This will be a significant increase in the ability of the AMA to deal with the rapidly-changing environment in technology.

Of particular concern is AI. The AMA defines AI as "augmented intelligence" rather than the more commonly-used "artificial intelligence." It's an AMA thing. In any case, an extensive BOT Report 15 dealt with augmented intelligence in health care. Resolution 202 dealt with use of AI and advanced technology to deny insurance claims. Resolution 246 dealt with AI in health care. Together, these contained several pages worth of recommendations and new policies. The HOD sent the whole question back to the BOT for more study, and the issue will be considered again at the AMA Interim Meeting in November.

War, Drugs, Gun Violence & Nutrition

Resolutions 603 (with 610) called for a cease fire in the "Israel-Palestine" war. After considerable discussion, the original resolution was voted down. A compromise resolution passed, urging "peace in Israel and Palestine in order to protect civilian lives and healthcare personnel."

The drug epidemic continues unabated. Resolution 507 called for opposition to companies being in both medical and recreational cannabis sales. Resolution 503 called for regulation of hemp-derived cannabis-like agents, which are presently not regulated by the FDA because of a loophole in the farm legislation. The farm bill ("Agriculture Improvement Act") is currently before Congress and will last for the next five years. The resolution was referred, with the expectation that the AMA will support closing the loophole in the current farm bill. Resolution 508 called for regulation of cannabis products appealing to children, such as "gummies," and was also considered to be covered by current policy. There was emotional debate in favor of the resolution. When the HOD reaffirms a policy, the policy will be extended for 10 years before being reconsidered under the "sunset" regulation. In a related action, Resolution 510 called for improved regulation by the FDA of false and misleading claims made by companies selling OTC vitamins. This also was a reaffirmation of existing policy. Resolution 517 asked for FDA regulation of nicotine analogue products. Such products, notably 6-hydroxy nicotine, are currently being marketed for vaping.

There has been a policy shift over the past several years towards decriminalization of drug possession for personal use and towards harm reduction as a general approach. The BOT Report 16 called for support for mental health courts, to include substance use. The BOT Report 17 summarized AMA policy on drug policy reform, recommending abolition of penalties for drug possession for personal use. While the recent failure of legalization in Oregon was cited, advocates



Missouri Delegate Charles Van Way, III, MD, listens to testimony as part of the Reference Committee E that heard issues on science and public health reports.

held that the failure of the Oregon experience is not relevant. The BOT Report 18 supported promotion of harm reduction initiatives, rehabilitation, and treatment for drug use. Resolution 229 called initially for opposition to legalization of psilocybin. It was amended to call for decriminalization of possession of psychedelics, entactogens (psilocybin), and related substances, very much in line with the policy shift.

The AMA has long been concerned about gun violence. The Council on Science and Public Health (CSPH) Report 11 studied the public health impact of "stand your ground" laws, concluding that the AMA should oppose such laws. Resolution 405 called for restrictions on firearm sales and for safe storage laws.

Nutrition as an aspect of public health is a continuing concern of the AMA. The CSPH Report 3 assessed the use of Body Mass Index (BMI). The report recognized the simplicity and widespread use of BMI, but also recognized its inaccuracies. BMI should be used with other measures of body composition to better define obesity and malnutrition. While the Council did not recommend abandoning the use of BMI, it recommended that BMI be used in conjunction with other measures of body habitus.

The meeting of OSMAP, the Organization of State Medical Association Presidents, takes place at the AMA meeting. As noted earlier, Jesse Ehrenfeld, MD, AMA President, spoke at length. Russell Libby, MD, gave an update on the activity of the Physicians' Foundation. Raymond Tu, MD, from the DC Medical Society, spoke of their successful opposition to a piece of legislation which would have opened much of medical practice to non-physicians. There was further discussion of the issue of financial solvency of local and state medical societies, a crucial issue for organized medicine at the local level. Melina Davis from Virginia spoke on their SafeHaven program, which has done a great deal to help physicians who require mental health services, or who are struggling with addictions.

On June 11, Bruce Scott, MD, was inaugurated as the 179th President of the AMA. In his inaugural address, he focused on family, on the role of physicians to change and improve the lives of their patients. He said the AMA must be an ally for physicians, fighting for reducing barriers to physician practice, against barriers to patients, and for reform of the health system. He concluded that "we will be defined by what we fight for."

Physicians from Missouri continue to serve in leadership roles. David Barbe, MD, is Past President of the AMA. Edmond Cabbabe, MD, serves on the Council for Long Range Planning and Development, and is past Chair. Elie Azrak, MD, serves on the Board of AMPAC, the AMA Political Action Committee. Jerry Kennett, MD, serves on the Board of the AMA Foundation. Deepu Sudhakaran, MD, is on the Governing Council of the International Medical Graduate Section. Marc Mendelsohn, MD, serves on the Council on Science and Public Health. Charles Van Way, III, MD, is Vice President of OSMAP, the Organization of State Medical Association Presidents. Jeff Howell, JD, our Executive Director, was elected to the Board of Directors for ASMAC, the American Society for Medical Association Counsel.

This meeting considered over 230 reports and resolutions. This is only a summary of activities. The proceedings of the meeting, as well as summaries of addresses by Drs. Ehrenfeld, Madara, Scott, and others, are available on the AMA website. Highlights from the meeting can be found at https://www.ama-assn.org/house-delegates/annual-meeting/highlights-2024-ama-annual-meeting. Details of the AMA Recovery Plan for American Physicians can be found https://www.ama-assn.org/amaone/ama-recovery-plan-america-s-physicians. The Interim Meeting of the HOD is scheduled to take place in Orlando, Florida, November 9-13, 2024. **MM**

Not All Heroes Wear Capes! Sometimes They Just Donate

by Jacob Scott, MA

As another legislative session has drawn to a close here in Jefferson City, your advocacy team has gathered some valuable insight on how MSMA is viewed by members of the legislature. Work is already underway to improve our standing prior to the 2025 legislative session.

There's an old adage in association management that says 30% of an organization does 70% of the work. This is generally true for organizations, but it is also analogous to the way the House of Medicine is organized and functions in Jefferson City. Your in-house lobbying team does 70% of the work to defend and advance the practice of medicine, while the specialty societies complement and supplement that work the rest of the way. This dynamic, while perhaps not unique to physician advocacy, does create needs that must be met by MSMA physicians in order to fortify our defenses and sharpen our knives.

We must organize and give generously today so that we may be prepared for whatever the future brings. In many cases, specialty societies' contracted lobbyists are simply too busy with other clients or lack the institutional support that they need. Thus, they rely on us (or better put, rely on you) to meet those needs.



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

This spring, we were able to successfully rally opposition to beat back a hostile amendment on the Senate floor that would have granted an expanded scope-of-practice to certain nurses, essentially allowing them to function as physicians. It wasn't a guarantee that our efforts would be successful. It was a humble reminder that a physician's place as the leader of patient's healthcare is just a few votes away from being eliminated.

Our team often has to justify the physician's leadership role in healthcare, a task that might have been unnecessary or unthinkable in years past. Instead, MSMA faces a constant barrage of misinformation, false promises, and weak ideas to "improve" healthcare delivery. In a term-limited legislative environment that is significantly underrepresented by physicians and manifests power in special interests (insurance companies, hospitals, trial attorneys, etc.), we face many challenges getting the truth to elected representatives.

In this last session alone, we saw numerous scope-of-practice bills receive positive votes in either a House committee or a Senate committee. This includes removing collaborative practice, allowing optometrists to do eye surgery, and the licensing of naturopathic "physicians." Another bill which received consideration would have allowed CRNAs to administer anesthesia without physician supervision. In addition, we had hospitals working against our emergency department staffing bill and our truth-in-advertising bill. We made

significant progress on our prior authorization bill to then watch it languish in the Senate insurance committee.

We mustn't despair; instead, let's prepare.

In my opinion, the solution is two-fold: we must recruit and retain membership and we must strengthen our political arm, the Missouri Medical Political Action Committee (MMPAC). If we are to be successful at the Capitol in the coming years, we have to grow our membership. This adds significantly to our voice in Jefferson City. Medical students and residents are taught to join their specialty society, but these societies lack the united front that MSMA has to offer. You must take every opportunity to share the important work MSMA does in Jefferson City with your colleagues. "Free ride" physicians must be encouraged to join the association. We're all in this together.

MSMA is encouraging more members to donate more to your Medical Political Action Committee (MMPAC). Campaign contributions are very necessary for getting elected to public office—especially medicine- and physician- friendly candidates. MMPAC's goal is to improve its position among similar healthcare association-based PACs. We know that politicians keep tabs on who has a political war chest and what their issues are. Having a sizable PAC balance is key to maintaining influence in the legislative process. Gone are the days when you can just rely on the reputation of the profession (or the lobbyists) alone. We must play the game as it is now, not as it once was. If given the chance, we believe you will answer the call and not only meet expectations, but exceed them.

1850 SOCIETY
Missouri Medical Political Action Committee

$1,850
1850 Society

$1,200
Rotunda Club

$200
MMPAC Ambassador

$50
MMPAC Member

We have so many things to be proud of here at the MSMA and often reflect on how big of a risk it must have been in the year 1850, for MSMA's founders to decide to band together in the pursuit of advancing and protecting medicine in this state. Just as then, we now have to take a risk to improve our stature at the legislature.

Coinciding with the 2025 MSMA dues year and MSMA's 175th Anniversary, MMPAC is rolling out some exciting new tiers designed to encourage and stimulate more donations. The new benefits kick in with just as little as $200 per year, but only get better with the more that you contribute. In fact, our top level of giving will provide an opportunity for weekly exclusive access to our legislative team, who will give you an insider's political peek into what's going on during the legislative session.

To answer this call, beginning in September, MMPAC will establish our new set of tiered giving, the highest level of which called the 1850 Society. Please consider throwing your financial weight behind this new effort by joining MMPAC as an 1850 Society member today.

Also, make it your mission to not only renew your MSMA membership, but to call a physician friend who is not a member today, and ask them to join. Together we will remain strong and advance the house of medicine.

For more information, visit www.msma.org/MMPAC or scan code.

The "Rights" Prescription: Navigating Copyright Law in Practice of Medicine

by Kris Kappel, JD, Lisa M. Luetkemeyer, JD & Maggie Mannebach, JD

Introduction

When considering the legal risks of practicing medicine, copyright infringement may not be top of mind. Nonetheless, in this digital era with seemingly infinite resources at our fingertips, respecting and adhering to intellectual property rights is essential to mitigate legal and financial risk for both practitioners and organizations. The legal use of creative works for business and professional purposes requires more than simply attributing credit to the artist. And for any business—including medical practices—the risk of copyright infringement can be costly. The recently settled case of *Verch v. Alpha and Omega Vision Center* in the Georgia Southern District Court provides a classic example of the potential liability at stake.[1]

Plaintiff, Marco Verch, filed a claim in November 2023 against Alpha and Omega Vision Eye Center, a full-service eye and vision care provider, alleging that Alpha and Omega violated his copyright rights by copying a photo from his Flickr page and using it to advertise, market, and promote Alpha and Omega's business on its Facebook page. While Verch's work was freely available to the public through a Creative Commons license, Alpha and Omega copied the photo and displayed it without abiding by any of the license terms, including giving appropriate credit to Verch, providing a link to the license, and including a statement of whether any changes were made to the photo. After months of costly litigation, the parties reached a confidential settlement in March 2024. Had it merely abided by the terms of Verch's license, Alpha and Omega could have used Verch's photo as intended and avoided expending valuable time and resources on litigation. Copyright infringement liability is a risk that every practitioner and practice should consider in their business practices to avoid exposure to the same circumstances as Alpha and Omega.



Kris Kappel, JD, Intellectual Property Partner, Lisa M. Luetkemeyer, JD, Healthcare Regulatory and Compliance Senior Counsel, and Maggie Mannebach, JD, Intellectual Property Associate of Husch Blackwell, LLP, co-wrote this article. Husch Blackwell represents a full spectrum of healthcare providers and other businesses in developing compliance strategies, preliminary enforcement measures, employment concerns, and litigation matters. The information contained in this article should not be construed as legal advice or a legal opinion on any specific facts or circumstances. The contents are intended for general information purposes only, and readers are encouraged to consult their attorney concerning specific situations and specific legal questions.

You Received a Demand Letter—Now What?

Let's play out a hypothetical scenario. You own a practice that creates a website for patient education. The site houses a variety of materials for patients to view, access, and read. Employees have been pulling articles from various sources across the web, and uploading portions of some articles, and in some cases, the entire article, onto the site. You assume that this use of the articles is okay because they are freely available online and the website accurately cites the author and source.

This website has been well-received, and you believe it has been a major contributor to an increase in new patients. However, you receive a letter from a law firm with the subject headline: "Notice of Copyright Infringement." To your surprise, the author

of an article posted on your website has sent your practice a demand letter for copyright infringement. The letter alleges that your practice copied over 70% of the author's article (which the author wrote after performing their own independent research) without permission, and therefore, violated the author's copyright ownership rights. The author demands that your organization pay for the right to use the article and retroactively pay for the time the article has been available on the webpage. The letter also states that if you do not comply, the author may pursue other legal remedies, such as litigation.

How do you verify whether these allegations are legitimate? Before responding to the letter, you reach out to your attorney and provide them with the background surrounding your use of the article. You want to know if your use is legal, and if not, what your next steps should be.

Copyright Law, Generally

Under federal law, copyright owners have the exclusive right to reproduce, distribute, perform, display, and prepare derivative works of their creations.[2] Copyright law protects a variety of creative works so long as they are original, fixed in a tangible medium, and created by a human author. Copyright generally covers art, books, articles, periodicals, manuscripts, photographs, music, websites, and other types of creative expressions.

However, just because something was conceived and created by a human author does not mean it is protected. Many creations do not qualify for copyright protection, including titles, names, short phrases, slogans, or familiar symbols. Similarly, facts, ideas, procedures, methods, processes, concepts, principles, discoveries, clichés, and materials in the public domain are also excluded.

Copyright Ownership

Your attorney lets you know that the article itself does qualify as a copyrightable work and that the author likely has valid and enforceable copyright ownership rights because, except under limited circumstances, ownership of copyrighted works typically belongs to the author. This prompts the question—is it possible that any ownership exceptions apply? Your attorney responds that there are two common exceptions—work made for hire and an ownership transfer via written agreement.

The first exception—the work made for hire doctrine – establishes that the employer owns works created by an employee within the scope of employment.[3] Here, the author wrote the article using their own independent research—free of an employment obligation. Therefore, the work was not made for hire and the exception likely does not apply.

That said, the second most common exception is that one can also obtain copyright ownership in a work through a contractual agreement, such as an assignment. Here, this exception does not apply because there was no agreement between the author and the practice for use of the article.

Defenses

Because an exception does not apply, your attorney investigates potential legal defenses, including permission to use the article and the "fair use" doctrine.

Permission to use the article is one defense and the process is rather simple. No specialized forms or agreements are required. However, because your practice did not reach out to the author before using the article, this defense does not apply. So, what about a potential defense under the "fair use" doctrine?

The "fair use" doctrine permits use of copyrighted material under certain conditions without the copyright owner's consent.[4] Fair use functions as an affirmative defense—where the infringer says, "Yes, I used your copyrighted work without your permission, but for these cited reasons my use of your work is legal." Uses that may be fair use include criticism, commentary, teaching, scholarship, and research. There are no bright line rules to determine whether a use is "fair use;" instead, it entails a nuanced legal analysis of four key factors. All factors must be considered in the analysis of fair use as a valid defense to copyright infringement (Table 1).

Considering the factors outlined above, your attorney informs you that the author likely has a legitimate claim for copyright infringement. Given that you copied the article to drive traffic to the practice's website, did not obtain the author's permission, and copied a substantial portion of the article, any defense of fair use would be weak.

Table 1.

Factor	More Likely To Be Fair Use	Less Likely To Be Fair Use
Purpose and character of the use, such as whether the use is for commercial purposes vs. nonprofit education purposes	Using excerpts from a medical textbook for a single, non-public, nonprofit educational presentation provided to a limited number of people	Using artwork found online in marketing materials being distributed to patients
The nature of the copyrighted work, such as the degree to which the work relates to copyright's purpose of encouraging creative expression	Copying a small amount of information that is completely factual in nature from a medical journal	Copying an original artistic design to use on your webpage in slightly different colors
The amount of the work used	Quoting a small portion of a medical journal article in a research paper with proper attribution	Copying most of a written work that essentially amounts to copying the "heart of the work"
The effect the use has on the market	Reproducing medical illustrations for educational handouts may not necessarily impact the market for original illustrations	Copying an article from a scholarly website with a pay wall and freely distributing it on your organization's website

If the copyright owner files a claim for copyright infringement, they must only prove two elements: (1) that they have a valid copyright; and (2) that you copied constituent integral elements of the work that are original.[1] They may have remedies so long as they demonstrate that they either suffered damages from the practice's infringement or that the practice profited from the infringement. One important caveat, however, is that a copyright owner may not file a lawsuit for copyright infringement until they obtain a copyright registration (or receive a denial of registration) for the work in question from the U.S. Copyright Office.[2]

Remedies

A court would determine whether the practice's use of the article qualifies as fair use by reviewing the specific circumstances based on the four factors outlined above. If a court found that you did infringe on the copyright without a fair use defense, then the remedies available to the author could include: (1) damages for losses suffered by the author due to the infringement; (2) recovery of any profits obtained by the practice for the infringing use of the copyrighted work; (3) statutory damages of up to $150,000 per infringing work;[3] and/or (4) attorney fees.

Due to the potential damages, copyright infringement poses significant legal and financial risk for the practice. Consequently, your attorney advises you to: (1) promptly remove the disputed content; and (2) try to negotiate an amicable resolution with the author, rather than risk escalating to litigation. Removing the content demonstrates good faith and a willingness to cooperate with the copyright owner's concerns, and taking swift action to cease the infringing activity can mitigate potential damages. Negotiations may involve discussions on licensing agreements, settlement terms, or other options to resolve the dispute. Your attorney can develop a negotiation strategy to achieve the best possible outcome while minimizing legal risks and potential damages.

In the meantime, a thorough assessment of the claim's validity and potential defenses may take place, with your attorney conducting a comprehensive analysis of the situation, gathering evidence, and evaluating the strength of your position. The assessment will inform both a negotiation strategy and legal defense, ensuring your rights are protected throughout the process.

Given the potential liability involved, and the time-consuming nature of dealing with a potential infringement claim, your practice should be aware of the importance of avoiding copyright infringement altogether. Dealing with the legal matter and having to rework materials (e.g., deleting social media posts,

revising the website, redoing marketing materials, etc.) can be costly for an organization. To mitigate the risk of infringement and avoid potential liability, your practice may consider instituting common best practices.

Best Practices

Implementing best practices makes good business sense given the popularity and ease of creating online content and promotional and educational materials. Below are some key guidelines to promote compliance.

Online Content: Blogs, Websites, Social Media, Marketing Materials, etc.

- **Obtain Proper Licenses**

Copying an image from an online source and using it on your website or in any social media or marketing materials without obtaining permission, likely infringes on another person's copyright. Therefore, we recommend always obtaining written permission from the owner. A permission request generally includes details such as the title, the specific parts of the work that will be used, the number of copies that will be made and distributed, and the purpose of the use. Best practice involves obtaining a license, ensuring that the license aligns with your specific needs in terms of duration, geographical limits, and scope of use. Commercial entities like Shutterstock often offer inexpensive licenses to purchase. Additionally, you may have access to certain sites like Creative Commons, Wikimedia Commons, Flickr Commons, among others, which allow for a perpetual, paid up license. Your attorney can assist with drafting or reviewing the terms of a license agreement.

- **Do Your Due Diligence**

Before posting any content online that you did not independently create, conduct your own research to determine whether the content is protected by copyright. Avoid relying solely on materials from "sharing" sites like Pinterest, as usage rights may differ for individual and commercial users.

- **Check Terms of Use**

Always review the terms of use from any online source of text, images, videos, or music, even if it is

Copyright Q&A

Must copyrights be registered to receive protection?
No. While registration is generally voluntary, it offers several advantages. Registration is a prerequisite for filing an infringement action and is necessary to obtain statutory damages and attorney fees in connection with such actions.

The Public Domain—What is it? How do I know if something is in it?
Copyright protection has a limited term and may be used without restriction after the protection expires and the work enters the public domain. The public domain comprises creative works that are not protected by copyright and are therefore available for unrestricted use by the public. Determining if something is in the public domain can be complex and depends on factors such as copyright expiration, lack of copyright protection, or voluntary dedication by the creator.

The author has been dead for over 100 years. Can I copy their work?
The amount of time one has rights in a copyrighted work varies depending on the circumstances. By default, copyright lasts for the life of the author plus 70 years. For works created prior to 1987, the duration may vary. For anonymous, pseudonymous, or works made for hire, copyright lasts for 95 years from the first publication or 120 years from creation, whichever is shorter.

Can I copy other renditions of an author's works?
New interpretations or adaptations of a deceased author's works may still be protected by copyright, particularly if they involve original creative elements.

If something does not include the © symbol, then is it not copyrighted?
Not necessarily. Effective March 1, 1989, the copyright symbol is optional for works, unpublished works, and foreign works. For works published before 1989, the copyright owner was required to place notice on all publicly distributed copies. That said, it is still recommended to provide proper notice to third parties that the work is protected by copyright. Proper notice includes the copyright symbol, the year of first publication or registration, and the name of the copyright owner.

from a "free" stock photo or clip art site to ensure that your use falls within the guidelines.

Work Product, Patient Materials, and Clinical Education Materials

- **Consider Fair Use**

It is crucial to note that fair use does not imply a blanket acceptance of copying for educational or noncommercial purposes. For educational and noncommercial purposes, consider the purpose, nature, amount, and effect on the potential market of your use of the copyrighted work. Giving proper attribution and citing your source may not always be sufficient. While attribution is essential and always a good practice, it does not negate the need for permission if the usage does not fall under fair use. Given the nuances of the fair use doctrine, consider getting legal advice on its application to a particular scenario.

- **Understand Works Made For Hire**

Be aware of the distinction between works created by employees within the scope of their employment and those by independent contractors. Ensure that written agreements are in place for any transfer of intellectual property rights, especially for independent contractors.

Organizational Practices

- **Vendor Management**

Obtain intellectual property assignments or licenses from vendors to document ownership and usage rights.

- **Maintain Documentation**

Maintain a database of works created by employees and vendors, along with contracts and copyright registrations.

- **Prioritize Independent Creation**

Prioritize independent in-house creation of materials to minimize the risk of copyright infringement.

- **IP Policy**

Develop policies and procedures surrounding your organization's use of intellectual property.

- **Education**

Educate your employees – particularly those who develop marketing and education materials and those with control over your practice's social media and website – on the use of materials created by third parties and the practice's intellectual property policies and procedures.

- **Maintain Insurance**

Purchase cyber liability insurance for your organization which includes media liability defense.

- **Contractual Indemnification**

Have vendors indemnify your organization from the vendor's infringement of intellectual property.

Conclusion

Physicians' and physician practices' use of copyrighted works in publications, social media and websites, and patient education and marketing materials can pose a risk of copyright infringement, especially if safeguards aren't put in place to monitor use of third-party materials. Understanding the legal elements of copyright infringement and its potential consequences can help practitioners and organizations alike mitigate this risk. However, intellectual property law is complex and constantly evolving, and each case may have different circumstances and implications. Therefore, it is always wise to consult an attorney who specializes in this area before taking any actions.

References

1. Verch v. Alpha and Omega Vision Center, LLC et al, 1:23CV00167.
2. 17 U.S.C.A. § 106. Under certain narrow circumstances, works by independent contractors may also fall within the work made for hire doctrine. More typically, ownership of works created by independent contractors, outside agencies, and freelancers is transferred by a written agreement that expressly states the assignment and transfer of all ownership rights.
3. 17 U.S.C.A. § 201.
4. 17 U.S.C.A. § 107.
5. Feldman v. Twentieth Century Fox Film Corp., 723 F. Supp. 2d 357 (D. Mass. 2010).
6. 17 U.S.C.A. § 411; Fourth Est. Pub. Benefit Corp. v. Wall-Street.com, LLC, 139 S. Ct. 881, 203 L. Ed. 2d 147 (2019).
7. To be eligible for statutory damages, the copyright owner must register the copyright within three months of first publication or before the infringement occurs.

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A Path Chosen Long Ago and Where It Went

by Louis P. Dehner, MD

The same question that was posed to me over 60 years ago and remains relevant for young pathologists today: "Is there a place for a surgical pathologist or the subspecies of a subspecialty anatomic pathologist in academic medicine?"

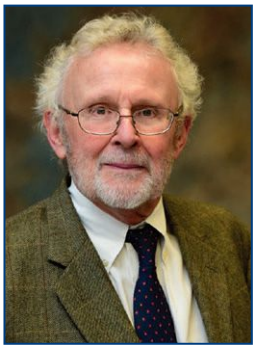
When I thought that I had an answer to that question many years ago, I was fortunate to have had as a mentor one of the foremost advocates that surgical pathology was indeed something more than simply signing out one case after another, but the case material for the systematic analysis of morphologic detail with clinical outcome to correlate those pathologic findings with prognostic significance. It was on the basis of these clinicopathologic studies that the foundation was established for the formulation of the AJCC Cancer Staging Manual and the College of American Pathologists synoptic reports.[1,2]

During the past 60 years, several important techniques and methods emerged from the bench to the bedside. Once the basic ultrastructure of the cell was established,[3] its application to the diagnosis of "undifferentiated tumors" through the identification of characteristic substructures such as intercellular junctions, identification of cell specific organelles such as neurosecretory granules and cytoplasmic filaments. The limitations of standard histologic "special stains" in terms of their specificity and sensitivity were no longer a barrier to the ability to differentiate a poorly differentiated carcinoma from a melanoma or Ewing sarcoma from rhabdomyosarcoma, identification of viruses and immune complex diseases of the kidney.[4-7] It was the antigen-antibody reaction and a secondary antibody to horseradish peroxidase that served as the next advance in diagnostic pathology through immunohistochemistry which emerged in the later 1970s and early 1980s with polyclonal and later monoclonal antibodies.[8-10] Like electron microscopy before it, immunohistochemistry expanded beyond a few specialized centers into the general practice of pathology in the community.

We have now moved beyond the identification of nuclear, cytoplasmic, and membranous epitopes to reveal the phenotype of a neoplasm through molecular genetics with the identification of non-random fusion transcripts, loss of heterozygosity, methylation profiles and actionable mutations.[11,12] These molecular aberrations are now the targets for an ever-expanding menu of pathway inhibitors.[13] What has been summarized highlights the major advances in diagnostic pathology over the past almost 60 years.

Where and How It Began

But how did I come to the decision to pursue pathology, in particular anatomic pathology, with its disease-associated gross and microscopic manifestations at autopsy and surgical specimens? My first encounter with a pathologist occurred in the course of working at St. Mary's Hospital in the laboratory in my hometown of East St. Louis, Illinois, while an undergraduate at Washington University in St. Louis (WUSTL). I saw firsthand what Joe Campos, MD, did and with him saw my first autopsy. That small flicker became a larger, brighter flame during the second year pathology course at WUSTL School of Medicine with my introduction into the basic pathologic processes and specific diseases across the spectrum of organ systems, age groups and genders. The soon to follow clinical rotations fortified my decision about pathology since it would provide me with the opportunity to encounter these many diseases without the circumscription of a clinical specialty. In the current subspecialty world of anatomic-surgical pathology, I have tried to remain true to the role of general surgical pathologist.



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Vietnam in 1967 – 1968

It was between the completion of my PGY-1 year in pathology at Barnes Hospital in St. Louis and the Armed Forces Institute of Pathology (AFIP) that I served the hybrid role of general medical and laboratory officer at the Station Hospital, U.S. Naval Support Activity (NSA), Da Nang, Republic of Vietnam (RVN).[14] Shortly before I left to report to the Field Medical Service School at Camp Pendleton, California, on July 3, 1967, Lauren V. Ackerman, MD, Director of Surgical Pathology, Barnes Hospital-WU Medical Center called me into his office to wish me well. Although I had only completed my first year, he asked me to return to St. Louis upon completion of my tour as one of his five surgical pathology fellows beginning in July, 1970. At least one individual in the world was more hopeful than myself that I would return from RVN. I was leaving behind a pregnant wife with a daughter on the way in October, 1967 and three sons, six-, five-, and four-years old.



Dr. Dehner.

I joined the US Navy's Ensign 1915 program so that I could support my family while in medical school.[15] One of the conditions of the contract was active duty after my PGY-1 year. It was difficult to know what the Navy expected of me having completed all of one year of pathology residency. The Senior Medical Officer, Harry Paul Mahin, CAPT, MC, USN, to whom I reported in RVN asked me: "Dehner, what am I going to do with you?" After this dubious "welcome aboard," my next stop was the administrative officer, Daniel A. Brandan, LCDR, MSC, USN, who informed me that my duties were those of an ad hoc general medical officer (GMO) with scheduled assignments to Receiving One ("the pit") where Marine casualties arrived directly from the field.[16] My primary duty was that of "laboratory officer" whereupon I was introduced to the senior enlisted, Chief Petty Officer (E-8) Leslie. The laboratory was part of a labyrinth of Quonset huts, on an expansive sandy beach extending to the South China Sea. I was the first medical officer to be assigned to the laboratory. It happened that an earlier inspection in 1966 of military hospital laboratories in RVN by Joe M. Blumberg, BG, MC, USA, the senior pathologist in the American military, critiqued the Navy's Bureau of Medicine and Surgery (BuMed) about the absence of a pathologist at the largest medical facility in RVN.[17] After all, each of the two hospital ships, the USS Sanctuary and USS Repose, each had a board certified pathologist and together the ships had fewer beds than the Station Hospital. I suppose that it could be argued that the Navy still did not have a pathologist at the Station Hospital.

The hospital was located on the Tien Sha peninsula and was separated from the city of Da Nang by the Da Nang River which had been used as a Viet Cong (VC) assault route into the city. Immediately across the road from the hospital was Marine Air Group-16 (MAG-16) on the South China Sea side of the peninsula. MAG-16 was the largest base for the Huey gunships (Bell UH-1) and other aerial assets in the I Corps (five northern provinces to the DMZ). Needless to say MAG-16 was target-rich for rocket and mortar attacks and the hospital was a not infrequent recipient of putative short rounds; those occasions brought us to our bunkers in the middle of the night after a combination of sirens and explosions.

Through the efforts of an excellent crew of 20-25 Navy corpsmen-laboratory technicians, we expanded the clinical laboratory including the blood bank and set up surgical and autopsy pathology with histology. Prior to my arrival, it was necessary to send requested autopsies to one of the hospital ships or Saigon. Once we were set up, hospital deaths, killed in action with

no obvious cause of death from an external inspection at graves registration, and a lesser number of forensic cases were the general categories of autopsies. Among the hospital deaths which accounted for ~50% of our autopsies, we had the opportunity to see some of the first cases of so-called Da Nang lung or as it is known today, adult respiratory distress syndrome, with its hyaline membranes, all too familiar to me from those first year autopsies on premature infants. Other notable autopsy cases during that year included cerebral malaria, Japanese B encephalitis, melioidosis, and rabies.[18,19] One case that was particularly challenging was a young Marine who had multiple admissions to the San Diego Navy Hospital for bouts of recurrent lower lobe pneumonia. He made his appearance at the 1st Medical Battalion on Hill 327 with mid-upper abdominal pain, which was thought to be due to an ulcer, but none was found at surgery and unfortunately he became an intraoperative death. At autopsy a right atrial myxoma was found which had been embolizing to his lungs to account for the past episodes of "pneumonia" and had an intraoperative pulmonary embolus. We had no echocardiogram, CT, or MRI 56 years ago.

Surgical specimens were largely discarded before my arrival. Traumatic injury to the lung, gastrointestinal tract, liver, spleen, kidney, and amputations accounted for the hundreds of specimens. There had been an unfulfilled need to document these resections for the medical record. Additionally, we received specimens from the civilian hospitals which were interesting and challenging.

Every war that the United States has fought in since the First World War has seen advances in the care and survival of casualties and the Vietnam War was no exception.[20] The surgical research team under Larry Carey, LCDR, MC, USNR, studied and later reported on aggressive resuscitation, if possible before, and certainly upon arrival from the field via helicopter. These and other studies in the midst of the war demonstrated that rapid volume expansion with Ringer's lactate in the presence of severe life-threatening trauma significantly improved survival.[21,22] Despite these efforts and excellent care, some of these young Marines ended up on the stainless steel table.

The nautical phrase, all hands on deck, became more than a metaphor during malarial season when we were inundated with dozens upon dozens of thick and thin smears for the detection of Plasmodium vivax or falciparum or both in rare cases. Despite the weekly mefloquine, not every Marine took the big white tablet.

All hands on deck acquired a more comprehensive and immediate response beyond the laboratory with the Tet holiday (Lunar New Year) when a massive, coordinated country-wide offensive by the North Vietnamese army and VC began on the night of 29-30 January 1968; the tactical situation in the Da Nang area was characterized as precarious.[23] As facilities to the north of us in the I Corps were forced to evacuate their casualties, we quickly became the medical facility of last resort for a steady stream of wounded from the field and transfers from the medical battalions. Our own perimeter was not secure, as it became necessary for the Huey gunships from MAG-16 to take their runs from the South China Sea over the hospital to diminish the threat of being overrun from the river by the VC. As part of the Tet offensive, Hue, the old imperial capitol to the north, became the site of protracted urban warfare with 147 killed and 857 wounded Marines representing almost 50% total force casualties.[23] The latter cases arrived on our landing pad or the hospital ships during this campaign.

During my tour (July 1967 to July 1968), we received more than 30,000 admissions, both surgical and medical from the field, and the hospital had expanded to 700 beds, including facilities for POWs. It was an honor to serve with this most dedicated group of physicians, nurses, and corpsmen.[24] We were there for the Marines, sailors, allied military forces, Vietnamese civilians, American contract workers, and those who even tried to take our lives. All received equal care as patients.

The Tet offensive was one of a succession of events which had cast shadows over the world as we referred to the continental United States (CONUS): the riots and incineration of major cities to protest the war and civil rights, the assassination of Martin Luther King, Jr, Lyndon Johnson announcing that he would not run for another presidential term, and the killing of Robert F. Kennedy as he campaigned for the presidency. What were we returning home to? I received an answer to that question upon my arrival to CONUS after one year of my life which was summarily judged as a waste by a young man who confronted me in the San Francisco International Airport on my way home to St. Louis to join my family so that we could report to my next duty station.

Armed Forces Institute of Pathology

My two-year tour at the Armed Forces Institute of Pathology (AFIP) was an important next step on the pathway. But before I could take that next step, I was fortunate that Bruce H. Smith, CAPT, MC, USN, was Director of the AFIP. Captain Smith was willing to accept me despite a succession of rebuffs for an assignment to the AFIP by the same BuMed that sent me to Da Nang as a pathologist of sorts. They were unwilling to send me, a mere GMO, to one of the sought after billets at the AFIP which were reserved for real pathologists. I served as Captain Smith's research assistant and during those two years I had the opportunity to conduct several studies with him and other senior pathologists including Kamal Ishak, MD, PhD, Herbert Taylor, MD, Jason Norris, MD, and Franz Enzinger, MD. One of the studies with Captain Smith was awarded the Wellcome Medal and Prize in 1969 for our paper on fatal motorcycle injuries in military personnel;[25] this study among others was cited to support helmet laws for motorcyclists. During this same period, one of my first papers on pyogenic hepatic abscesses in children was published with my beloved mentor and friend, the late John M. Kissane, MD, one of the preeminent pediatric pathologists.[26] I discovered the reprint of that paper in the Smith (Bruce H.) Collection with my inscription to Captain Smith in July, 1969, "For the benefit of your knowledge and rich experience in pathology, the freedom of your laboratory and direction to pursue those areas of interest to me. To you, a profound debt of gratitude for accepting me at the Armed Forces Institute of Pathology."[27] As I learned then and have continued to learn throughout this journey of life, a word and a hand of encouragement at moments of doubt and discouragement continue to remind me of the many opportunities afforded to me.

Finishing the Training and Pursuing the Path

Another of those opportunities was the fellowship in surgical pathology that Dr. Ackerman had offered me before I left for RVN. It was an intense year (1970-1971) with the four other fellows (Bruce L. Webber, MB, BS, David Judge, MD, J. Bradley Arthaud, MD, and Kavous Khodadust, MD); we were responsible for frozen sections, gross examinations (no pathology assistants in those days), case sign-out, conferences and completion of a research project. During the fellowship year, I was offered my first faculty position by Dr. Ackerman as an Instructor in Surgical Pathology for the coming academic year, 1971-72. At that time, we had the benefit of 50% off-service time to start and complete projects for presentation and publication and preparation of lectures and laboratory sessions for medical students.

As I had made the decision to pursue an academic career, it was important to have a vision and plan if it was to have any hope for success (whatever that was to be). The plans began with the materials which were the surgical pediatric cases as they came into the gross room. Gross specimens with interesting and characteristic features were taken to Medical Illustration; in those days, both gross and photomicrographs were captured in black and white images, by the master medical photographer Cramer Lewis. Once the invoices began arriving, I was summoned to Dr. Ackerman's office to render an accounting of my activities and for what purpose. I discussed with him my plan to write a book on pediatric surgical pathology with a format similar to his *Surgical Pathology* and a companion in a sense to Kissane and Smith's *Pathology of Infancy and Childhood*.[28,29] I asked him to approach his publisher with my proposal which he did and in 1975, the first edition of *Pediatric Surgical Pathology* appeared.[30]

It had become apparent to me during the fellowship year that pediatric surgical pathology was a tabula rasa as we were called upon by Jessie Ternberg, MD, PhD, and her colleague, Richard Bower, MD, to examine pediatric specimens in the operating room or to perform a frozen section to confirm the diagnosis of Wilms tumor as one example so that dactinomycin could be started in the operating room. Ternberg became the first Director of the Division of Pediatric Surgery in 1972. The director of the Division of Pediatric Hematology-Oncology, Teresa Vietti, MD, was already regarded as the "mother of multimodality cancer treatment" in children; she had co-authored *Clinical Pediatric Oncology*, the first major reference in pediatric oncology and first chair of the Pediatric Oncology Group.[31] The third pediatric specialist was William H. McAlister, MD, the first director of pediatric radiology. Was there possibly a niche for pediatric surgical pathology?

During this same period, I organized a short course entitled: Surgical Pathology of Infants and Children, which was offered at the annual meeting of the United States-Canadian Academy of Pathology. There were also presentations at the meeting of the Pediatric Pathology

Club, later the Society for Pediatric Pathology. Dr. Ackerman's unqualified support in the years between 1971 and 1973 set me on a firm, purposeful path.

Minnesota and "Golden Gopher" Years

The transition occurred for many of us in surgical pathology at Barnes and St. Louis Children's Hospitals in 1973 when Dr. Ackerman retired and moved to the State University of New York, Stonybrook. One of my colleagues, Juan Rosai, MD, who was now a co-author of *Ackerman's Surgical Pathology,*[28] was ready to take the next step in his career when he accepted the position of Director of Anatomic Pathology at the University of Minnesota Medical School, Twin Cities. He asked me to join him and we were together from 1974 to 1985. We often referred to those years together as our golden years. The move to Minnesota gave me the opportunity to begin our studies on a newly recognized childhood pulmonary neoplasm, pleuropulmonary blastoma (PPB), together with my colleague and friend, John R. Priest, MD, pediatric oncologist. A Registry (International PPB/DICER1 and Ovarian and Testicular Sex Cord Stromal Tumor Registries) to study these tumors was established in 1990. All cases entered into the Registry allowed us to define the natural history and pathology as our understanding of this tumor evolved from a purely cystic lesion thought to represent a benign congenital lung cyst to a high grade primitive, multipatterned sarcoma.[32] An important observation to emerge from these studies was the occurrence of PPB and other childhood tumors within families. As these families were identified and willing to participate in molecular genetic studies, a former resident, fellow and now colleague, D. Ashley Hill, MD, identified the germline heterozygous variant in DICER1. The PPB tumor predisposition syndrome (OMIM 601200, 606241) was defined during the Minnesota years.[32,33]



Ta-Chiang Liu, MD, PhD, Associate Professor in Pathology and Immunology at Washington University, and Dr. Dehner.
Photo courtesy of Washington University Record.

While in Minnesota, my friend J. Thomas Stocker, MD, well-known pediatric pathologist, suggested a book project on pediatric pathology but in broader terms beyond pediatric surgical pathology; the fruits of that endeavor, *Pediatric Pathology* appeared in 1992 and the fifth edition, *Stocker* and *Dehner's Pediatric Pathology* was published in 2021.[34] We are currently gearing up for the sixth edition.

Return to Washington University in St. Louis

The return home to St. Louis took place in 1989 when Emil R. Unanue, MD, Chair of the Department of Pathology and Immunology, offered me the position of Director of Anatomic Pathology at the WU Medical Center which I regarded as an honor since it was the same position that Dr. Ackerman held from 1948 to 1973. However, there were many challenges and expectations upon my arrival, but Emil stood by my side and gave me the opportunity (that word again) to rebuild the division with his unconditional support. There was invaluable assistance of my colleagues, Mark R. Wick, MD, Paul Swanson, MD, Deborah Gersell, MD, Michael Kyriakos, MD, Mary Zutter, MD, Cheryl Coffin, MD, Peter Humphrey, MD, PhD, and Frances White MD; the goal of a successful division with their support and loyalty was largely accomplished during the 17 years in that position.

Finding a mentor is a complex endeavor, but it should be an individual that you wish to emulate. I was fortunate to have several mentors along the way. When I began my academic career, time was made available to me to think about and create projects and bring them to fruition. If one is only signing out one case after another while trying to establish a career path, the energy can be siphoned off so that creativity loses its vigor. A plan, purpose, persistence and a goal are words

that only attain meaning in action and the time to overcome the initial inertia.

Post Facto

As for some final thoughts and reflections on this traveled path: I served in one of the most unpopular wars in US history during which the social and political fabric of my country began to unravel and it continues to reverberate even to this day. I am a proud graduate of WU where I received my undergraduate and medical education, my post-graduate education in pathology, my first faculty appointment, and ultimate current faculty position as professor. This institution has been the home for much of my professional life where the foundation was laid on which any aspirations and any accomplishments were nurtured and facilitated by the likes of Hamburger, Levi-Montalcini, and Moog in my undergraduate years and Trotter, Ackerman, Kissane, Moore, Moyer, Vietti, and Ternberg in my medical school years.[35] Each of these individuals instilled in me some part of themselves allowing me to become the person that I am today; the aspiration was to be like them in some manner.

Whether one likes it or not, especially for those of us who have been blessed with a long life, change is inevitable over the course of the journey along the path. We all experience change from our individual perspective in terms of our reaction and how it affects us. With the exception of a few institutions, medical education as it existed in the late 19th and early 20th century in this country consisted of numerous store-front proprietary schools operated by private practitioners who awarded certificates after a few months. The successor four-year medical schools were university-based with laboratories that supplemented lectures where the latest developments in anatomy, biochemistry, physiology, bacteriology, and pathology provided the basis for understanding disease processes. The revolution in American medical education and its template was initiated by the report of Abraham Flexner who judged the quality of medical schools in the United States and Canada including Washington University's "medical department;"[36] after a two-day evaluation, he concluded that "the school is little better than worst I had seen elsewhere, but absolutely inadequate in every essential respect."[37]

One aspect of the current curriculum is the loss of the general and organ system pathology course as an entre into the human disease process. Pathology today is at its best a vignette and this would appear to be the case for many of the other basic sciences that served as the foundation of medicine as a science. It has now become a rush to the bedside to follow clinicians as an apprentice with a truncated period of preparations.

Something has been lost in medical education in my opinion with its shift from a meritocracy to a holistic admission process, the elimination of academic standards of performance, abandonment of board scores, and election to Alpha Omega Alpha as an acknowledgement of academic excellence. Medical education and the practice of medicine have become incorporated into the current social-political ideology with its agenda. Aaron Rothstein, MD, a neurologist, and others have opined that "doctors as doctors are not responsible for poverty, gun violence, racism, climate change, or social injustice;" he further pointed out that in the examination room the physician's only allegiance is to that patient and his/her health.[38] The realist may say to me, "It is no longer your worry Dehner, so enjoy your twilight years." But it is my concern and my deep respect for this noble profession which still remains for me a "calling."

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Correspondence

Full Practice Authority by NPs

I am writing in response to Dr. Gary Gaddis's articles regarding nurse practitioner issues. He has given an excellent review of the issue with a deep dive into the financial implications of "full practice authority." Let's be very clear with our definitions —"full practice authority" by NPs is actually the "unsupervised practice of medicine." NPs are not trained in medicine, they are trained in "nursing" and do not have the depth of education to practice medicine at the level of a physician. The American College of Emergency Physicians passed a resolution in council last year regarding the terminology to correct the "FPA" definition to "UPM" (unsupervised practice of medicine). Dr. Gaddis also provides great visual aids with the Missouri maps of practitioner density from 2013 and 2018. These maps are available from the AMA from every state, which contradict what they tell legislators that they will provide rural areas improved access to care. They don't go rural any more than physicians do, and these maps are proof of that fact. The rural shortages continue even in states that have allowed the unsupervised practice of medicine by non-physicians. We do need to find better answers, but "trophy legislation without education" is not helpful for patients. The safest thing for all patients is still physician-led medical care.

Debbie Fletcher, MD, FACEP, FAAEM
President, Louisiana Physicians for Patients

Errata

In the September/October 2022 issue of *Missouri Medicine,* the name of one of the authors of the article "Monkeypox, A New Public Health Threat" on page 424-425 was misspelled. The correct spelling should be: Nongnooch Poowanawittayakom. **MM**

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Beta Blocker Nasal Spray News

Steven C. Kosa, MD, presented a scientific poster on the use of nasal spray timolol 0.5% for successful treatment of acute migraine at the June 2024 Annual Meeting of the American Headache Society meeting in San Diego, Calif. This was original research first published in *Missouri Medicine*.

This same study, presented as the first world literature report on using timolol 0.5% by nasal spray for the successful treatment of a series of refractory patients referred to a headache clinic (January/February 2024 **Steven C. Kosa, MD**, and **John C. Hagan III, MD**) has now been featured on KevinMD.com, social media's leading physician voice titled: Big Pharma Ignores Low-Cost Migraine Solution.



Dr. Hagan was interviewed by Kevin Pho, MD, on a featured podcast. Recorded in July, the 18-minute podcast can be viewed at https://www.kevinmd.com/2024/07/revolutionizing-migraine-treatment-the-untold-story-of-beta-blocker-nasal-sprays-podcast.html. The subject is the promising use of liquid beta blockers for acute migraine and the failure of pharma to pursue development.

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Current Screening Tests/Biomarkers for Alzheimer's Disease: Implications for Clinicians

by Vimita Patel, MD & George Grossberg, MD

Alzheimer's disease (AD), a neurodegenerative disease, afflicts approximately seven million people in the United States as of 2024 (Figure 1).[1] This chronic, progressive disorder can only be definitively diagnosed on autopsy by directly observing characteristic atrophy in the cerebral cortex as well as amyloid-beta (Aβ) plaques and neurofibrillary tangles via microscopy. Without an autopsy, Alzheimer's disease can be suspected based on clinical findings. Other conditions that can present similarly must be ruled out and features are identified via an accurate history, physical exam, bloodwork and neuroimaging in clinical settings, often primary care being the first point of contact. Additionally, cognitive tests and supportive imaging/lab testing require a clinical indication to perform them in the first place: oftentimes the emergence of symptoms or family history. Cognitive tests such as the Saint Louis University Mental Status (SLUMS) exam, the Mini Mental Status Exam (MMSE) and Montreal Cognitive Assessment (MoCA) are efficient and widely used tools to screen for cognitive impairment however are limited by language, education, and lower sensitivity for mild cognitive impairment (MCI).

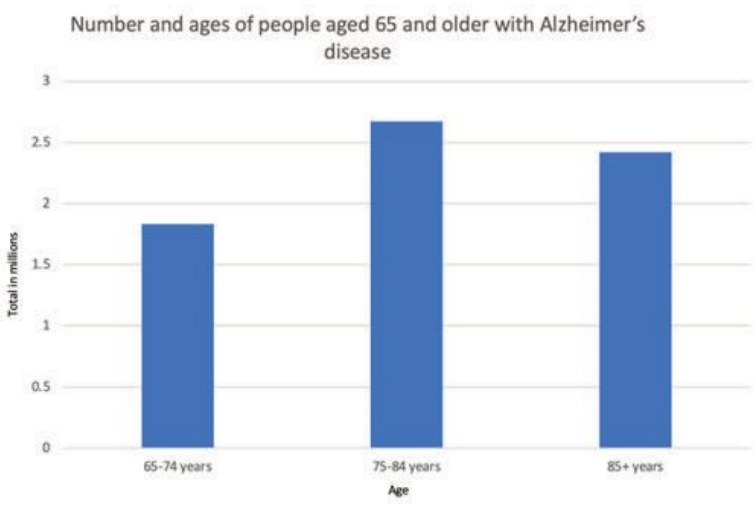


Vimita Patel, MD, (pictured), is a Resident in the Department of Psychiatry and Behavioral Neuroscience, and George Grossberg, MD, is the Henry and Amelia Nasrallah Professor, and Director, Division of Geriatric Psychiatry, Department of Psychiatry and Behavioral Neuroscience, Saint Louis University School of Medicine, St. Louis, Missouri.

Current Federally Approved Supportive Modalities for Alzheimer's Disease Diagnosis

Imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) are frequently utilized and validated to aid a probable diagnosis. 18F fluoro-deoxy-glucose (FDG)-PET imaging, which measures cerebral glucose metabolism, has shown vbenefit in distinguishing mild cognitive impairment as it relates to AD from other neurodegenerative diseases and healthy controls. However, FDG-PET imaging has limitations in accuracy when it comes to older patients with late-onset AD. This led to the development of amyloid precursors for PET imaging as the more specific biomarkers for AD. Radiopharmaceuticals such as ^{11}C-labeled Pittsburgh Compound-B (used in the first amyloid human amyloid PET study, but limited by a short half-life), [^{18}F]Florbetapir and [^{18}F]Florbetaben enable the quantification of cortical Aβ plaque burden and have a high specificity for the detection of AD pathophysiology.[2] The newer radiotracers are taken up rapidly through the blood brain barrier and quickly washed out from areas that do not contain Aβ, allowing a clear contrast for cerebral amyloid burden. A limitation of the well-studied [^{18}F]Florbetapir scans is that amyloid burden may be detected even in cognitively intact older individuals,[3] especially those who have uncontrolled hypertension or who are carriers of the APOE4 gene (genetic variant known for risk of developing AD). Tau misfolding (a hallmark of Alzheimer's pathology) can also be detected via PET imaging, for example via the United States Food and Drug Administration (FDA) approved radiotracer Flortaucipir.[4] However, it is posited that this agent is a better diagnostic tool in people with more advanced stages of dementia rather than mild cognitive impairment. The utility of brain PET in general is limited by cost and availability to the patient.

Figure 1. Prevalence of Alzheimer's disease in 2024 by age.



The standard of care relative to the use of biomarkers to support a diagnosis of mild cognitive impairment due to AD includes amyloid PET or cerebrospinal fluid (CSF) examination. CSF biomarkers, specifically reduced amyloid-beta 42, elevated total tau and elevated phosphorylated tau, have been recognized since 2010s as important supporting evidence for early detection of AD. However, obtaining these samples still involves an invasive procedure (the lumbar puncture). This led to a growing need to discover blood/plasma-based biomarkers that may similarly aid diagnoses but are easier to obtain in primary care settings and can be used as preliminary screens to see if more expensive/invasive testing is indicated.

Developments in Blood-Based Biomarker Testing

In August 2019, a cohort study published in *Neurology* concluded the utility of plasma amyloid-beta 42/40 ratio in predicting current and future amyloidosis.[5] The authors used an immunoprecipitation and liquid chromatography-mass spectrometry assay to measure this ratio in both plasma and CSF samples from 158 cognitively intact individuals. They compared the ratio to each person's amyloid PET scan, which was the reference standard for current amyloidosis. They found high, statistically significant correspondence between plasma ratio and amyloid burden; in addition, they found that individuals with a positive amyloid-beta 42/40 ratio, but a negative amyloid PET scan, were at a 15-fold risk to convert to amyloid PET positive. Given this, the functional prospects of measuring a serum amyloid-beta 42/40 ratio to predict amyloid burden and in turn the development of AD were promising. The study also concluded that APOE4 status and age can improve the accuracy of utilizing this test. However, it is worth noting that an important limitation in the study was that the correspondence between the plasma amyloid-beta 42/40 ratio and cognitive impairment was not studied. In other words, the idea that this test will accurately predict a transition to cognitive impairment has not been studied.

Quest Diagnostics released the AD-Detect™ Test on July 31, 2023, a direct-to-consumer plasma-based biomarker test for AD that measures amyloid-beta 42 and amyloid-beta 40 in blood to provide an amyloid-beta 42/40 ratio.[6] It was marketed for people aged 18 and older who may have mild cognitive impairment or a family history of AD. It could be purchased directly from the Quest website followed by scheduling an appointment at Quest labs. A telehealth physician would then review the purchase for medical necessity per the website, however it was not clear what the exact criteria to determine this necessity were. The results would then be made available online. Should the test be positive, a physician would contact the individual to talk about further steps. Broadly, Quest reported that the goal was to create an accessible, patient-initiated test that may be able to predict the risk for Alzheimer's disease in patients with only mild symptoms. However, this test has not been approved by the FDA.

According to the Quest website, the AD-Detect™ Test was set to cost $399. It was not reimbursed by insurance. The results were to be provided in a numeric fashion along with distinct categories of low, medium, and high risk of amyloid presence in the brain. In addition, the website stated a report would be provided to patients of their current and past 5 amyloid-beta 42/40 ratios for patients to trend their risk. Per the Quest press release[7] on July 31, 2023, a licensed physician would be reviewing website orders for the test to determine "appropriateness," however the exact criteria for appropriateness and the specialty of the physician were not made clear. In addition, the press

release also mentioned the option for individuals to discuss their results with a licensed physician, however the specifics of results interpretation and discussion were not made clear.

Due to the lack of long term, large scale clinical trials that can support the use of the AD-Detect™ test to conclusively guide assessment and treatment, it is not recommended for routine use in clinical settings. In addition, the Alzheimer's Association did not endorse the use of the AD-Detect™ test by consumers given the lack of rigorous data and FDA approval.[8] No peer-reviewed research validating the AD-Detect™ test had been published except an abstract of a poster presented at the Alzheimer's Association International Conference; however, Quest then noted some of the data presented was incorrect and that the assay had a specificity of 71% for detecting PET-positivity.[9] Experts then raised the concern that this number was not reassuring enough given the downstream impact of false positives attached to a test such as this.

The consequences of asymptomatic people accessing direct-to-consumer blood-based biomarker tests need to be considered carefully. Given this test is not currently considered evidence-based medicine, interpreting results can be confusing both for the patient as well as their physician. In addition, if an asymptomatic individual screened positive on the test, they may still not be eligible for current, FDA-approved AD treatments. Lifestyle modification may be the only advice that can be made to an asymptomatic individual who is deemed "intermediate" or "high" risk for amyloid burden, however it can be argued that these recommendations should be followed by all individuals anyway (better diets, exercise, controlling cardiovascular risk factors, keeping the mind active, etc). It is also worth noting that the presence of cerebral amyloid deposition does not always correlate with the development of cognitive impairment and may be related to normal aging and APOE genotype.[10] Ethically, given the cost of this test and limited insurance coverage, the accessibility of this test may already be limited to individuals of certain financial means. The question also arises of how an individual who has been categorized as "intermediate" or "high" risk is supposed to use that information in their day-to-day functioning—should the individual be cognizant of their risk if they are working a high-stress, highly intellectualized job? Should they feel compelled to let family, friends, and employers know about their risk even if they have not manifested any symptoms? And what role should their clinicians, who did not directly recommend or administer the test, be playing for their patients? Dementia is still a highly stigmatized illness; the psychological ramifications of utilizing direct-to-consumer tests are not yet fully understood.

On July 19 2023, the University of Michigan published the results of a poll of people aged 65-80 and their thoughts relative to various tests to screen for cognitive impairment/disorders.[11] Specifically for blood-based biomarkers, only 17% said they were familiar with such tests and 80% of older adults stated that they look to their health care providers for cognitive screening or blood-based biomarker tests if they feel they are appropriate. A majority of older individuals (74%) felt that a positive blood biomarker test result would make them believe they were likely to develop Alzheimer's disease. Remarkably, the poll also found that 60% of older adults, women more than men, would experience significant distress in response to a positive result on either cognitive screening tests or blood tests. The responsibility of diagnosing a progressive illness such as AD should weigh heavily on clinicians determining the need to administer these tests; but for a direct-to-consumer test, these numbers highlight the potential for misunderstanding results if not guided carefully.

As of March 2024, AD-Detect™ is no longer being marketed on the Quest website for unclear reasons. It is also unclear if this withdrawal is temporary.

Another leading candidate for blood-based biomarker testing is phosphorylated tau 217 (p-tau217). A systematic review published in 2022 utilizing 676 publications showed that p-tau217 is a sensitive marker of manifestation and progression of AD and is specific to AD alone as it does not predict these changes in other neurodegenerative diseases.[12] Previous studies have shown 100-400% increase in phosphorylated tau in patients with Alzheimer's disease;[13] this specific biomarker also correlates the most to an amyloid burden. Another study[14] showed that plasma p-tau217 and phosphorylated tau 231 (p-tau231) had the strongest association with Aβ PET retention in early accumulating regions in preclinical Alzheimer's disease. The PrecivityAD2, marketed by Washington University startup C2N Diagnostics, is a promising algorithm that combines plasma measures of percent p-tau217 with amyloid-beta 42/40 ratio. In a recent study[15] involving 583 individuals with suspected AD, PrecivityAD2 yielded 88% agreement with amyloid PET and showed strong clinical validity across two independent cohorts. This test, like most

other blood-based biomarker tests, is expensive and not reimbursed by insurance. At the time of this writing, there are no FDA-approved blood-based biomarkers.

Towards a New Definition of Alzheimer's Disease?

The standard of care at this time for diagnosing AD is clinical; with the advent of blood-based biomarkers, there has been discussion about how this may change the very definition of AD diagnosis. A currently active National Institute on Aging and Alzheimer's Association (NIA-AA) working group posits revising criteria for AD diagnosis from a clinical one to one strictly characterized by the objective presence of biomarkers.[16] Per Dr. Clifford R. Jack Jr., the chair of this group, as quoted in a recent New York Times article, the definition of AD should be changed to mean "someone who has biomarker evidence of amyloid in the brain has the disease, whether they're symptomatic or not".[17] This group does not recommend utilizing biomarkers for someone who does not have cognitive decline. However, this is likely to happen inadvertently and inevitably (especially given direct-to-consumer biomarker tests being marketed) and may lead to a diagnosis of AD without any associated clinical signs or symptoms. There are strong ethical concerns regarding asymptomatic individuals being diagnosed with AD and how they are expected to use this information—as mentioned earlier, should they be restricted from certain jobs, inform their friends and family, and suffer the significant distress of being diagnosed with AD when there is no absolute certainty that they will develop cognitive decline? Per the article, the American Geriatrics Society has already called the proposed idea "premature" and pointed out potential conflicts of interest due to several of the involved panel members having ties to pharmaceutical/biomarker companies.

Treatment Based on Biomarker Testing

Discussion regarding the drive to develop blood-based biomarker testing to detect cognitive impairment due to AD would be incomplete without mentioning the role of newer AD treatments. The argument has been made by proponents of using biomarker testing as the gold standard for AD diagnosis that clinicians can then start treatment with medications indicated for MCI due to AD and early stages of AD dementia. Specifically, aducanumab and lecanemab—these monoclonal antibodies administered via IV infusion target Aβ plaques. Aducanumab received accelerated FDA approval (not full FDA approval) but not without intense controversy. Lecanemab has received full FDA approval. Both drugs are indicated for mild cognitive impairment due to AD and mild AD. Biogen has since abandoned aducanumab.

In a phase III trial of lecanemab with 1,795 patients aged 50-90 years with MCI due to AD or early AD dementia AD, lecanemab slowed the rate of clinical decline by 27% after 18 months of treatment compared to placebo, leading to the authors concluding that "lecanemab reduced markers of amyloid in early Alzheimer's disease and resulted in moderately less decline on measures of cognition and function than placebo at 18 months but was associated with adverse events."[18] One major potential side effect of these monoclonal antibodies is amyloid-related imaging abnormalities (ARIA), which most commonly presents as temporary swelling of the brain and may be accompanied by small areas of hemorrhage in or on the surface of the brain. It is often asymptomatic, but some people may have symptoms such as headache, confusion, and even seizures.[19] These are not insignificant risks and need to be weighed versus potential clinical benefits.

Currently, a major four-year phase III clinical trial is underway called the AHEAD study which investigates whether administering lecanemab to amyloid-positive people who have no symptoms can prevent cognitive decline.[20] Healthy adults aged 55-80 and without a prior diagnosis of AD are eligible for the study and individuals are divided to two separate sister trials depending on their baseline amyloid PET burden. Both trials utilize PET, plasma biomarker testing including PrecivityAD2, and CSF biomarker testing for outcome measures. Primary outcome measure for one of the two sister trials is cognitive testing and the other is amyloid PET.

Retinal Scans as Screening Tools

Emerging research is targeting other potential screening tools for Alzheimer's disease including retinal scans. According to recent studies,[21] optical coherence tomography angiography (OCTA) scans can be used to detect reduced capillary density and other retinal changes in APOE4 carriers. It was also discovered by the team that the capillary abnormalities were independent of amyloid pathology as suggested by prior PET scans. APOE4 variant has long been known to increase the risk of developing AD however new research just published[22] has shown APOE4 homozygosity may be a

true genetic cause of AD. The study, conducted in over 500 people with APOE4 homozygosity, showed by age 55, over 95% of them had AD related brain changes and by age 65, most of them had abnormal amyloid plaque accumulation. Detecting abnormalities that may be specific to APOE4 carriers in a non-invasive way may be very useful. However, it is important to note that the risk of ARIA with amyloid targeting drugs such as lecanemab is significantly elevated in individuals with two copies of APOE4, to the extent that some experts do not recommend this treatment for APOE4 homozygous individuals. The challenge remains—even if non-invasive tests can reasonably suggest the presence of APOE4, would the benefits of early treatment in those with mild cognitive impairment or no symptoms at all outweigh the risks?

Conclusion

Alzheimer's disease screening and diagnosis remains an evolving field and is only set to become more complex. Robust evidence is still needed to justify routine use of emerging biomarkers, and in particular blood-based biomarkers, safely and effectively in the office setting. Thorough counseling, keeping in mind what is in the patient's best interest, will be ever more important in selecting/utilizing biomarker testing for patients with cognitive impairment or at-risk for cognitive impairment due to conditions such as Alzheimer's disease.

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Disclosure

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Genetics is Scary

by Patricia I. Dickson, MD

Does genetics scare you? While the practice of medical genetics has been around since the 1940s,[1] studies repeatedly show that both health care professionals and their patients feel that they do not have sufficient understanding of genetics.[2,3] For patients, this lack of understanding leads to low uptake of genetic testing, lack of follow-through with referrals, and misunderstanding of genetic testing results. Health care professionals often feel unprepared to help and may communicate outdated information about the practice of medical genetics. It is easy to understand how the health care team might fall behind this vast and rapidly evolving field. For example, at the present time, there are an estimated ~7,000 genetic diseases, with that number increasing at a rate of 50-60 new diseases each year.[4]

Due perhaps to a shortage of medical genetics practitioners and the complexity of our practice, many of our colleagues do not know who we are—and internet searches rarely help. Clinical geneticists are medical doctors who are boarded by the American Board of Medical Genetics and Genomics (ABMGG). Many, but not all, completed residency training in pediatrics prior to a second residency in medical genetics, but the ABMGG is not a sub-board of pediatrics. Medical geneticists are trained in the practice of adult genetics too, including cancer and prenatal genetics, so that we can see adults as well as children. Medical laboratory geneticists have MD, DO, or PhD degrees and are boarded by the ABMGG to oversee and interpret genetic testing in diagnostic laboratories. Some clinical and medical laboratory geneticists are biochemical geneticists, who work in the subfield of inborn errors of metabolism (for example, phenylketonuria). Medical geneticists (clinical and laboratory) often work with metabolic dietitians and genetic counselors. Genetic counselors are trained in dedicated master's degree programs and boarded by the American Board of Genetic Counselors. Metabolic dietitians specialize in the careful dietary management of patients with inborn errors of metabolism. The ACMG is a good source for explanations of the genetics workforce, as well as clinical guidelines, continuing medical education, and other resources.[5]

The purpose of this issue is to bridge the gap between medical genetics services and the broader healthcare community. We hope to communicate some of the recent developments in medical genetics diagnostics, including the availability of clinical exome and genome sequencing and nuances in interpreting these and other genetic test results. Genetics will always be a little scary, because it is not possible to be fully knowledgeable about all genetic conditions and their myriad presentations. However, we hope to arm you with some practical knowledge to help you better recognize and care for patients with genetic disorders.



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Disclosure

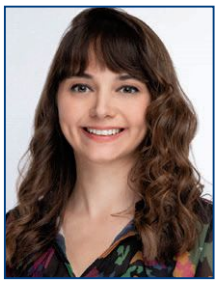
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Genetics and Primary Care: Raising Awareness and Enhancing Cooperation

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The rapid expansion of interest in genetics and the availability of genetic testing has led to increased need for genetics services.



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Abstract

The rapid evolution of the field of genetics in the past several years has opened new opportunities for diagnosis of treatment of genetic disorders. However, the limited availability of medical geneticists has led to difficulty in meeting this evolving need. Integrating awareness of genetic disorders and genetic screening into primary care may facilitate early diagnosis, while strategic support and cooperative care between primary care physicians and geneticists can improve long term management.

Introduction

The expansion of genetics and genomics in medicine has resulted in an increased role for primary care physicians (PCP) to integrate genetics and genomics into their practice, including assessing and educating patients about genetic risks and management of some genetic disorders. PCPs serve as a point of first contact for patients within the health care system, emphasizing their role in identifying patients with genetic conditions, and potentially providing further evaluation and management as guidelines become more available for patients with a genetic disorder. Even though medical geneticists have the primary role in diagnosing and managing genetic conditions, access to specialists may be limited, and the importance of early diagnosis and management has advanced over the last decade with the evolution of genetics and genomics medicine. Providing the appropriate education and resource tools to the PCPs will help to improve their daily practice with engagement of genetics care and broad access to evidence-based genetic testing for their patients. In some cases, surveillance and management may be shared between the PCP and the geneticist, while in others, the PCP may take over surveillance entirely, with support from the geneticist available as needed. Finally, the longitudinal relationship built between the PCP and the family is essential in understanding the familial dynamics and psychosocial issues which can be raised by diagnosis of a genetic disorder.

The Pediatrician's Role in Newborn Screening Follow-up

One of the primary care pediatricians' essential roles is management of newborn screening. Newborn screening is essential for the diagnosis of potentially fatal or disabling conditions so that treatment

can be initiated as early as possible. The newborn metabolic screen is designed to have a high sensitivity and low false negative rate, so that all true cases of the disease are identified and none are missed. While some of these screening tests are highly specific with a low false positive rate, others may have a higher false positive rate or higher number of infants that need rescreening. Because of this goal to identify all affected infants accurately, specific diagnostic tests are still necessary to confirm or refute a diagnosis.

All infants born in a medical setting should have a newborn screen performed prior to discharge. If newborn screening was not obtained due to circumstances such as home birth, emergency birth, hospital transfers, international adoptions, or parents' refusal, the pediatrician should arrange the specimen collection during the first newborn visit. In the case of parental refusal, the pediatrician should educate the parents regarding the benefits of newborn screening. Educational resources appropriate for the lay person can be provided, such as Baby's First Test https://www.babysfirsttest.org), or the American Academy of Pediatrics' website for families (https://www.healthychildren.org). The lack of screening should then be added to the patient's chart to prompt an evaluation if there is a concern in the child's growth or development, vomiting, seizures, developmental delay, lethargy, or poor feeding.

The pediatrician should also monitor for results of the initial newborn screen. Some of the conditions on the newborn screen can be fatal if immediate action is not taken. The timeframe for follow-up and referral varies depending on the abnormal screening results. For some disorders, for example maple syrup disease, congenital adrenal hyperplasia, and methylmalonic aciduria, immediate treatment and follow-up would be necessary. In other cases, the newborn screen may only need to be repeated, such as if the initial screen was not sufficient or had a borderline or low risk result. PCPs may also be able to order confirmatory testing as necessary for an abnormal newborn screen, collaborating with genetics teams at the newborn screening referral sites.[1]

If more information is desired, the American College of Medical Genetics (ACMG) has developed web-based resources called action (ACT) sheets to guide physicians through preliminary responses to newborn screening results. ACT sheets are located at ACMG's website (www.acmg.net) and provide focused algorithms to summarize the possible diagnoses, description of the conditions, actions that need to be taken for diagnostic evaluation, and reporting requirements. ACT sheets also give state-specific information for the referral resources. More information about the newborn screening program specific to Missouri can be found on the Missouri Department of Health's website (https://health.mo.gov).

Most importantly, PCPs are typically the initial point of contact with families about positive newborn screen results. The longitudinal and trusting relationship between the family and primary pediatrician is an asset when discussing newborn screening results, which can cause anxiety in new parents. The pediatrician can educate the family about the need for additional testing to confirm or refute a diagnosis. Providing some basic resources to families about the disorder, such as referring them to the newborn screening informational resources as above, can relieve parental anxiety while confirmatory testing is ongoing.

If a genetic diagnosis is confirmed after a positive newborn screen, the infant will have ongoing management with a geneticist. Since most of the possible conditions in newborn screening are hereditary, genetic counseling will also be beneficial for the family: carrier testing studies can be offered for the parents to determine recurrence risk in siblings, and testing may be available for the siblings and potentially other relatives as well.

Primary Care Physician's Role in Identifying Patients at Risk for a Genetic Disorder

One of the pediatrician's primary roles is to ensure that each child's health and development is proceeding as expected. Because of this, pediatricians are experts in identifying what is normal versus what is atypical or out of the ordinary. Pediatricians should be aware of potential clues or red flags that could indicate an underlying genetic disorder (Table 1).

Similarly, primary care physicians for adults are trained in the typical progression of diseases seen in adults. With respect to genetic disorders, the single most important role for the PCP is to consider the possibility of an underlying genetic diagnosis. A patient with a genetic disorder may present with an

Table 1. Symptoms which could indicate a genetic diagnosis.

Congenital anomalies	Family history	Neurological symptoms
• Dysmorphic features • Birth defects • Congenital heart disease • Hearing loss	• Multiple miscarriages • Early childhood deaths • Stillbirths • Hearing loss • Early onsey cancer/heart condition	• Seizures • Hypotonia • Developmental delay • Intellectual disability • Sensorineural hearing loss
Growth anomalies	**Extreme presentation of common conditions**	**Abnormal lab results**
• Growth failure • Asymmetry/Overgrowth • Tall stature	• Severe viral/bacterial illnesses • Recurrent infections • Unexpected fractures • Abnomral bleeding pattern	• Metabolic acidosis • Hyperbilirubinemia • Abnormal cholesterol levels • Abnormal iron profile

unusual symptom, multiple unusual symptoms in the same person, lack of response to treatment, or a more severe progression than typical for a specific problem. For example, the presence of an LDL-C >190 mg/dL and a first degree relative with premature coronary artery disease indicates a diagnosis of familial hypercholesterolemia.[2] Or, a young adult who presents with an unusual combination of distal weakness, fatigue, cataracts, cardiac arrhythmia, and dysphagia may have myotonic dystrophy type 1. However, in some cases, the signs of a genetic disorder may be more subtle. An individual with fatigue, joint pain, and liver function abnormalities may have typical aging and possibly a fatty liver; or, they could have a genetic condition like hemochromatosis, which requires targeted treatment of iron overload. Screening tests with iron studies could differentiate the scenarios, but the physician must be aware of the possibility in order to consider screening.

Given the significant workload placed on primary care physicians, ways to improve screening for genetic conditions without placing additional time burdens on the PCP are under investigation, such as system level screening for common conditions. In one study, a case-finding tool for familial hypercholesterolemia (FH) was applied to the electronic medical record to identify adults at increased risk. Individuals identified by the tool completed a questionnaire and if still screen positive were offered genetic testing for FH.[3] This tool identified many affected individuals which allowed specific treatment for their disorder. Another study, a randomized controlled trial called BRIDGE (Broadening the Reach, Impact, and Delivery of Genetics Services) is comparing uptake of genetic counseling, update of genetic testing, and patient adherence to management recommendations when identified by an automated algorithm analyzing family history data in the electronic medical record versus standard of care delivery models.[4]

Family history is also a necessary component of the primary care evaluation. Detailed family history can be essential to identify the risks of genetic conditions that might be prevented and need close monitoring or referral.[5,6] Obtaining a multigenerational pedigree or family tree would be the most informative in assessing risk of a genetic disorder, although such an extensive history may not be practical in the typical primary care practice. The minimum family history should include documentation of what diagnoses are present in the family, the ages of the condition onset, and the relationship of the family members (parent, cousin, grandparent, etc.). If a pattern is noticeable such as multiple affected family members with the same condition, early age of onset of cancer, ethnic background associated with certain conditions (i.e., breast cancer risk in those of Ashkenazi ancestry), or multiple affected family members with neurodevelopmental delay or intellectual disability, then the family should be referred for genetic evaluation.

One important reason for adequate family history is cancer risk assessment. For example, the United States Preventative Services Task Force (USPSTF) recommends that women with a family history associated with increased risk for BRCA1 or BRCA2 be referred for genetic counseling and possible testing.[7] In 2013, the USPSTF clarified that PCPs should conduct the proactive risk assessment for breast and ovarian cancers. However, one study by Linfield in 2022 showed that only 22% of high-risk patients in their large integrated health system in Cleveland were appropriately referred for genetic

Table 2. Educational resources available for physicians.

The American Medical Association - Educational Hub for Genetics and Genomics
• Short learninng modules - 0.5 CME/each
• https://edhub.ama-assn.org/collections/5664/genetics-and-genomics
The American College of Medical Genetics and Genomics
• Genetics101 for Healthcare Providers - 5 CME
• https://www.acmgeducation.net/Public/Catalog/Main.aspx
The Heartland Regional Genetics Network (HGRN)
• Provides education about the process of genetic testing, including pre-test counseling, evaluation, post-test counseling, follow up
• https://www.heartlandcollaborative.org/resource-center/
Other resources
• Genetic Testing Registry - database of available tests: https://www.ncbi.nlm.nih.gov/gtr/
• The US Preventive Services Task Force - screening recommendations: https://www.uspreventiveservicestaskforce.org/uspstf/
• The Centers for Disease Control and Prevention's Office of Public Health Genomics - precision health https://www.cdc.gov/genomics/default.htm

counseling.[8] These results are similar to a National Health Interview Survey, which found that 24% of patients met criteria for genetic testing but only 9% were referred.[9] Given the burdens placed on PCPs, screening tools have been created to assist PCPs with risk assessment and some EHRs may include an integrated Hereditary Breast and Ovarian Cancer (HBOC) risk calculator, although these tools may not capture all relevant cases or all information necessary to monitor utilization when considering health disparities.[10,11] Adding another layer of complexity is that guidelines for screening for cancer syndromes change over time, making it necessary for the PCP to maintain awareness of the current recommendations. Additional research is still needed to optimize integration of cancer risk assessment and simplify the screening process to improve uptake.

Primary Care Physician's Role in Evaluation and Diagnosis

Ideally, once a patient is identified with a symptom concerning for a genetic disorder, the patient would be referred to a genetic specialist. However, the increasing awareness of genetic conditions in the general population and the rapid expansion of available genetic testing has led to increased demand for genetic evaluation. In some areas, access to a geneticist may be difficult due to distance and lack of ability to travel, or the wait time for an appointment with a geneticist may be long. Incorporating genetic testing into primary care practice could shorten the time to diagnosis and benefit the patient, while also decreasing healthcare costs by avoiding specialist visits and travel.

However, the process of choosing the most appropriate genetic test and navigating insurance is complex, as outlined by Lee et al. in the July/Aug 2022 issue of *Missouri Medicine*.[12] For example, as recently as 2010, the American Society for Human Genetics recommended chromosomal microarray as the first line genetic test for individuals with global developmental delay, intellectual disability, and multiple congenital anomalies with a diagnostic yield of 15-21%.[13-15] However, with the evolution in genetic testing techniques and methods, the number of identifiable genetic conditions has significantly expanded. As of 2021, the American College of Medical Genetics published

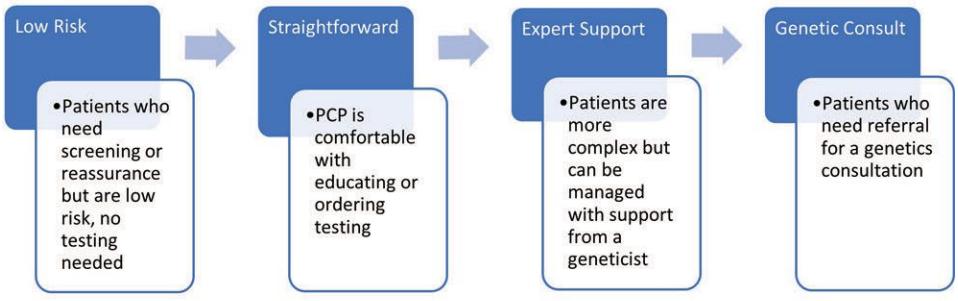


Figure 1. Proposed progressive model of care with escalating support from medical geneticists.
Adapted from Harding et al. BMC Medical Education (2019) 19:195.

Table 3. Common indications for genetic testing and the recommended first line test for the indication.

Indications	Recommended First Line Genetic Test
Global developmental delay or Intellectual disability	Exome or genome sequencing
Multiple congenital anomalies	Exome or genome sequencing
Autism spectrum disorder	Chromosomal microarray and Fragile X for males
One specific gene or suspected disorder, or family history of a known gene variant	Targeted testing
Single symptom (ie, epilepsy)	Gene panel for that symptom
Down syndrome, Turner syndrome, or concern for a translocation or structural anomaly	Karyotype

guidelines recommending WES/WGS as the first or second line test for the same indications, based on new data that broad based testing with exome or genome sequencing has an increased diagnostic yield of 38%.[16-17] While it is uncommon for a PCP to utilize WES/WGS in their clinics due to its complexity, the evolving recommendations for appropriate testing illustrate the challenge a PCP may face in staying up to date in genetics.

Studies exploring barriers for PCPs ordering genetic testing have shown perceived barriers of lack of education and confidence, and lack of access to formal and informal consultation with specialists.[18] Many physicians in practice completed their medical training prior to clinical availability of tests like CMA and exome sequencing, creating a knowledge gap. If a PCP would like to incorporate genetic testing into their practice, educational resources have been developed by several organizations to increase their knowledge about ordering genetic testing and results interpretation (Table 2).

A progressive model for care has also been proposed (Figure 1), where PCPs could monitor their patients for symptoms that could suggest a genetic disorder. If they felt comfortable in doing so, they could order testing for the condition independently (Table 3). If needed, support could be provided to the PCP by the specialist for simple questions. More complex patients would be referred directly to the geneticist for consultation.[18] Research is still ongoing to determine the utility and the most effective way to structure such arrangements. For example, at Washington University in St. Louis and St. Louis Children's Hospital, we provide support to PCPs through phone consultation with genetics specialists and accept referrals for both adult and pediatric patients.

Investigation is also ongoing regarding other potential tools to expand genetics services. A pilot "eConsultation" service was trialed in Canada, where PCPs utilized an asynchronous web-based application to submit clinical questions to a geneticist. The geneticist was then able to provide recommendations, including requesting additional information or referral for genetic evaluation. This service allowed the PCP to obtain necessary information and avoid referral in 47% of cases where a referral had initially been considered. Post consult surveys showed that the PCPs reported this service to be of high value for both the PCP and the patient.[19]

In addition to choosing the correct test, a primary care physician who orders genetic testing also has a legal and ethical duty to provide adequate informed consent, especially for broad tests such as exome and genome sequencing. Informed consent should include a discussion of: the risks, benefits, and limitations of testing; the possibility of uncovering information which is incidental to the reason for testing or that alters familial relationships such as non-paternity; implications of test results for other family members; cost; and other possible consequences such as anxiety or the possibility of genetic discrimination.[20-21,23] The Genetic Information Nondiscrimination Act (GINA) prevents discrimination in health insurance and most employment, but patients should be made aware that there are exceptions to this protection. If a patient

has a positive test for a genetic disease, they may become ineligible for life, long-term care, or disability insurance. Another important exception to GINA is that it does not apply to the members of the United States military or those who receive medical insurance through the federal government, such as through the Veterans Administration.[22]

For the PCP who may want to order genetic testing, choosing the correct test and completing the ordering process is only the first step. The interpretation of genetic test results is also complex: the physician must understand whether a variant identified on a test is pathogenic or causative of disease, versus a benign variant, or potentially a variant of uncertain significance. Variants of uncertain significance are frequently identified on sequencing panels, but do not automatically provide a diagnosis and in most circumstances are not medically actionable without additional information and analysis. As discussed by Green and Toll in the July/August 2022 issue of *Missouri Medicine*, physicians have the legal and ethical responsibility to accurately communicate to the patient all results of genetic testing and the implications of the results for the patient's future health, since this information could affect the patient's ability to make informed decisions about their medical care.[12,23] Ultimately, it is the responsibility of the physician to ensure they have adequate training in determining the appropriate test to order and to interpret and counsel the patient or family about the results.

Primary Care Physician's Role in Management of Genetic Disorders

Primary care pediatricians play a significant role in managing confirmed genetic conditions by monitoring symptoms and applying health maintenance recommendations specific to the condition. Any child with a significant medical condition or diagnosis including a genetic disorder should have a medical home with a primary pediatrician.[24] A child with special health care needs or a chronic disorder will likely need diagnosis-related subspecialty visits, written care plans, appropriate patient and family educations, and regular comprehensive follow up visits. Longitudinal follow-up appointments, referrals, and surveillance could all be managed by pediatricians if they are comfortable in doing so.

The American Academy of Pediatrics and the American College of Medical Genetics have published medical management guidelines for several common genetic conditions to empower PCPs to manage longitudinal care for these patients. For example, medical management guidelines exist for achondroplasia, Down Syndrome, Turner Syndrome, Fragile X, Noonan Syndrome, and others.[25-30] These management guidelines provide information about the clinical presentation of the disorder, natural history, possible complications, and specific outlines for the recommended monitoring and surveillance tests to perform over time. Management of this surveillance by the PCP may allow for more frequent monitoring and earlier recognition of complications. The close longitudinal care can also build the relationship with the PCP and improve these patients' quality of life.

Similarly, primary care physicians for adults can also manage a cohort of their patients with common genetic disorders. For example, individuals who are homozygous for a common variant causing hemochromatosis, HFE C282Y, may never show evidence of iron overload, but should have routine monitoring of iron studies.[31] Individuals with familial hypercholesterolemia could initially be managed by the PCP, including pharmacotherapy with statins, reducing CAD risk factors such as cessation of smoking and healthy diet, and treatment of hypertension.[32] If cholesterol levels are not sufficiently reduced with standard therapies, referral to a lipid specialist with expertise in FH would be indicated.

Conclusion

The rapid expansion of interest in genetics and the availability of genetic testing has led to increased need for genetics services. Given their longitudinal relationships with patients and their ability to recognize unusual symptoms, the primary care physician is optimally placed to recognize when a genetic disorder could be present and to initiate an evaluation. While barriers to extensive genetic testing in the primary care setting certainly exist, such as time and insurance difficulties, educational resources and cooperative models of care with geneticists may expand opportunities and facilitate earlier diagnosis and treatment.

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Medical Genetics for the Undiagnosed and Rare Patient: "Chasing Zebras"

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This collaborative effort aims to improve diagnosis and treatment options for individuals facing rare and undiagnosed diseases, particularly those who may lack resources or live in underprivileged communities.



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Abstract

The world of genetic testing continues to evolve as new technologies provide insight into previously unchartered territories. Access to genetic testing, especially for complex medical patients, could potentially improve the lives of thousands of individuals with undiagnosed conditions. Barriers to testing include financial and physical limitations, along with the emotional and social fortitude that is at times needed for vulnerable populations to agree to testing and participation in research. As healthcare providers, it is imperative that we adopt a wholistic approach to care so that we can arm our patients with the necessary resources to navigate their medical journey.

Introduction

Washington University in St. Louis is part of two national programs that provide a regional resource in Missouri designed to aid in diagnosing and managing patients with undiagnosed and rare conditions. The National Organization for Rare Disorders (NORD) Center for Excellence brings together leading clinicians, researchers, and educators with a dedication to rare diseases, while the Undiagnosed Diseases Network (UDN) fosters innovative approaches in genomics and diagnostics. Together, they form an invaluable partnership that has the potential to transform the lives of countless individuals and families grappling with undiagnosed and rare conditions.

The Undiagnosed Diseases Network

The UDN is a national research study funded in part by the National Institutes of Health with the purpose of solving complex medical mysteries. The UDN connects a variety of clinical experts with the latest research technologies to aid in diagnosing patients. Since its initiation in 2014, the program has evaluated complex patients through collaboration with different medical specialties, and with different clinical and research sites across the country.[1] Patients are referred from their primary care provider or subspecialist and have an extensive medical record review prior to acceptance. Patients accepted into the program are offered a multi-disciplinary evaluation along with extensive genetic testing utilizing the most progressive technologies. Patients

Figure 1. WashU/BJC is part of an innovative network seeking to expand access and the advancement of care, treatment, and research for those affected by rare disease.



receive comprehensive neurocognitive testing and developmental assessments. Genetic data is analyzed in our research lab and offers the use of cutting-edge technologies such as RNA sequencing, long read sequencing and the identification of structural variants and deep intronic variants. Candidate genes are further explored through the UDN model organism screening center (MOSC) for potential functional studies. Collaboration among healthcare professionals from different specialties, including physicians, surgeons, radiologists, and geneticists, is essential for collecting diverse perspectives and expertise. This interdisciplinary teamwork enables a comprehensive evaluation of the patient's condition, enhances diagnostic accuracy, and fosters effective treatment planning.

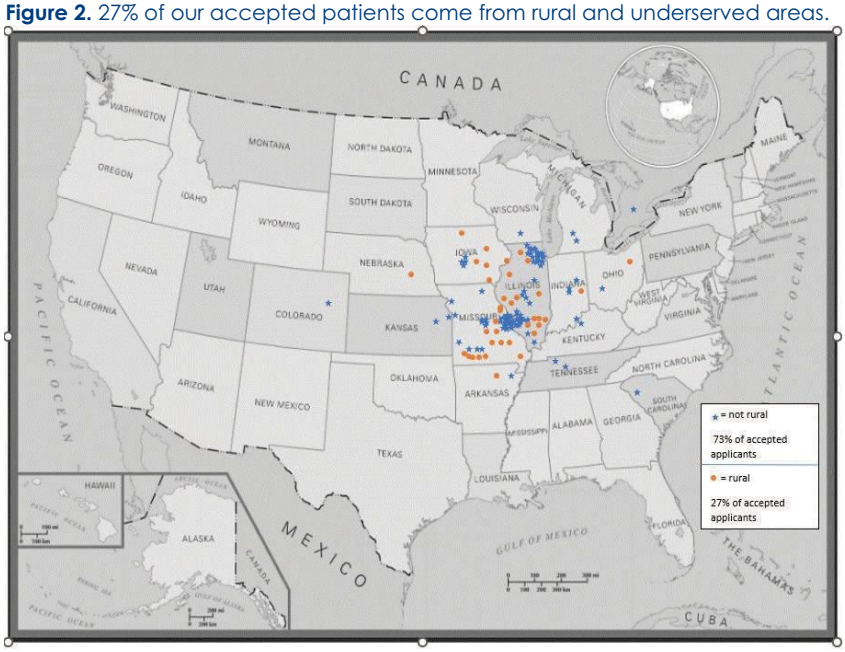
Washington University: A Rare Disease Center of Excellence

The United States considers a disease rare if it affects fewer than 200,000 individuals and based on current reports, there may be well over 10,000 rare diseases.[2] Rare disease patients face many challenges, including diagnostic delay, misdiagnosis, and lack of therapies.[3] The difficulty in determining a timely diagnosis is often referred to as the diagnostic odyssey.

In November 2021, Missouri was recognized nationally when Washington University (WashU) and Barnes-Jewish Christian (BJC) Hospital received the distinction of being one of the first 31 Rare Disease Centers of Excellence (CoE) from the NORD. Attaining this distinction required a rigorous application process outlining our commitment to the rare disease population's quality of life. Key parameters assessed include research, access to studies, and care collaboration with multiple medical disciplines. Providing an extensive array of experts covering multiple medical specialties required to diagnose and treat a broad range of rare diseases for children and adults is paramount in selecting a CoE. The CoE network demonstrates a strong commitment to supporting all stages of rare disease research, with the goal of increasing knowledge of the cause of the disease, identifying pathways within the body that lead to disease symptoms, and improving diagnostic techniques while developing rare disease treatments and cures. As a CoE, we remain committed to mentoring the next generation of rare disease clinicians and researchers.

Our designation by NORD with like-minded institutions advances the diagnosis, treatment, and care of patients with rare disorders, thereby improving and shortening the diagnostic odyssey. As one of the

Figure 2. 27% of our accepted patients come from rural and underserved areas.



now forty designated CoE's nationwide, WashU/BJC is part of an innovative network seeking to expand access and the advancement of care, treatment, and research for those affected by rare disease. NORD acts as a conduit in assisting and leading the centers through the establishment of 13 working groups. These groups tackle challenging subjects such as diagnostic approaches, testing access, diversity, equity and inclusion, newborn screening, and the education of medical professionals and patients. By leveraging real-world data-based solutions, the working groups address the key unmet needs of the rare disease population.

Collaboration across a nationwide network is no small feat. As seen in Figure 1, sites are spread geographically, and depending on location, it can be difficult for patients to access a CoE. The program's vision aims to connect patients and families so they can receive expert care and participate in research. Therefore, a knowledge-sharing platform on a shared intranet named NORDCentral was created. In 2024 the portal expanded access to include scientific networking among all members of the healthcare team who work in the rare disease field at a CoE. Networking items include best practices, diagnostic criteria, and access to experts in ultra rare disorders. NORDCental aims to increase clinical and research collaborations among centers by making it easier for clinicians and researchers to find each other. It will also reduce provider burden by minimizing the time it takes to research information about the diagnosis and management of rare disease. Similarly, educational opportunities and clinical management tools can be shared quickly across all sites. NORDCentral is essentially a space where providers within the network can act as, or access, rare disease experts who contribute to best practices, standards of care, and treatment plans, collaborate in research studies, and either host or attend educational sessions for a potpourri of rare diagnoses.

Moreover, NORD benefits the rare disease patient population directly through its advocacy in policy, education, and resources. Their website has a rare disease database that provides general education and links to patient advocacy groups and studies. Another tool allows patients and caregivers to access assistance funds that help cover healthcare costs from transportation to, labs, testing, medical formula, and co-pays. Each fund has specific criteria for allocating monies to qualified applicants.

Providing Local Access to Rare Disease Support: WashU/BJC's Role

Since its inception as a CoE, the Department of Genetics and Genomic Medicine has sought to be a hub for rare diseases within WashU/BJC and the region. Our goal is to minimize the silos found in complex and multidisciplinary medicine. Far too often, patients are lost to follow-up care only to return when in crisis. We aim to establish rapport within the community by connecting with Missouri patient advocacy groups and expanding our website as a resource for rare care inquiries and research information in an effort to promote outreach that makes services more accessible to both providers and patients.

One example of our efforts is hosting a Rare Disease Day Symposium on the last day of February. Rare Disease Day is observed worldwide to bring awareness and community support to those affected by such diseases. The event brings together medical professionals, researchers, scientists, patients, families, patient advocacy groups, and other stakeholders who

have an interest in rare disorders. The symposium offers insight into the many struggles and triumphs of patients and families affected by rare diseases while inspiring hope. Attendees are educated on the frontiers of treatment, research and emerging science. Over the last two years, WashU hosted four keynote speakers, received more than 140 abstract submissions, and in 2024 held its first patient and family-led Meet and Greet. This year a second Rare Disease Day event was held at St. Louis Children's Hospital with hand painting, giveaways, and interactions with a zebra mascot (an animal adopted to symbolize rare disease) resulting in a successful event mixing fun, with rare disease education and awareness for the pediatric population. Participating in a Rare Disease Day event can lessen the isolation and stigma of those who have or who are caretakers of those with rare disorders.

UDN and NORD CoE in Action

WashU joined the UDN in 2019. Since that time, we have received 226 applications, accepted 157 patients, and have completed 116 evaluations. We have completed clinical whole genome sequencing and full sequencing reanalysis on 91 of these cases and have solved or likely solved 28 of these, with 24 additional cases with candidate genes to further investigate. On a national level, the UDN as a whole has established a diagnosis in 35% of the evaluated patients, as described in this article by Splinter, et al.[4]

WashU supports the Midwest region of the country for this study. We have evaluated patients from Missouri, Illinois, Arkansas, Nebraska, Colorado, Kentucky, Tennessee, Ohio, Indiana, Wisconsin, Iowa, Michigan, and Canada.

We have established a collaborative relationship with NORD, and are able to utilize available resources to support our UDN program. Once accepted, our families are enrolled in NORD, and to date, 39% of our patients and families have received monetary support from NORD.

The UDN is committed to increasing the representation of participants from underserved communities. Underserved populations, including low-income individuals, ethnic minorities, rural communities, and marginalized groups, often experience disproportionately higher rates of illness, limited healthcare resources, and barriers to affordable treatments. These underserved populations are also hesitant to participate in research, as highlighted by McConkie-Rosell, et al.[5]

In order to address these barriers, our site is establishing community partnerships to reach those individuals and families who may not otherwise have access to research opportunities and advanced genetic testing. To date, 27% of our accepted patients come from rural and underserved areas, as shown in Figure 2.

Missouri is a predominantly rural state comprised of 115 counties in which 16 are classified as urban and 99 are classified as rural.[6] Fifty-two percent of referrals made to the rare disease nurse navigator come from rural areas in Missouri and half of these rural populations are in a region with a greater propensity for unmet healthcare needs according to the Human Resource Services Association.[6] Traveling to and from appointments for testing and procedures, along with meeting multiple specialists located hours away, can lead to missed work and school days.

Coordination of care plays a crucial role in addressing these challenges. By facilitating communication and collaboration between healthcare providers, coordination of care can help minimize the need for multiple distant appointments, reducing the amount of time and resources spent on travel. This can help individuals to better manage their work and school commitments while still receiving the necessary medical care.

In addition to retaining employment and promotion of school attendance, coordination of care can ensure necessary follow-up care is attended to promptly, helping individuals manage their health conditions effectively and prevent complications. This can lead to improved overall health outcomes and a reduced financial burden on both individuals and the healthcare system.

It is important to consider the socio-economic impact of living with a rare disorder that can contribute to social stigma, the inability to participate fully in everyday activities often coupled with an increased economic burden.[3] The rare disorder nurse navigator role seeks to lessen the burden of healthcare access for the rare

disease diagnosed adult and pediatric population by receiving referrals sent from genetics and genomics providers for assistance with coverage of medically necessary medications and formula, school advocacy, and coordination of care for follow-up testing and appointments.

Through our websites, patients and primary care providers can find a direct route to the UDN and rare diagnostic services offered at WashU with our diagnosis referral link or by contacting the nurse navigator. Last year 18% of patients requesting services were self- referred.

Conclusion

Living with an undiagnosed health condition can be a challenging and frustrating experience. Patients may struggle with mysterious symptoms, delayed treatment, and a lack of understanding from the healthcare system. It is imperative that we reach out to those undiagnosed patients, especially in underserved areas where deficits in resources are more pronounced. These patients may not be given the opportunity to participate in research that is vital to solving medical mysteries and advancing therapeutic strategies. Dealing with a complex medical condition without a diagnosis can have profound psychological implications for patients and their families. Empathy, compassion, and effective communication become fundamental components of patient-centered care. Undiagnosed patients face arduous journeys in search of answers. Research offers hope and promise for improving the lives of these patients and their families through advancing medical knowledge and facilitating interdisciplinary collaboration. Investing in research and supporting initiatives that prioritize the underserved populations will empower and transform healthcare for the better.

Research efforts heavily contribute to the identification and characterization of rare genetic disorders that might otherwise go undiagnosed. Genetic studies and collaborations across institutions worldwide enable the gathering and analysis of comprehensive datasets, ultimately leading to improved recognition and diagnosis of these rare conditions. Accurate diagnosis is instrumental in providing appropriate medical care to affected individuals and their families.

WashU, in collaboration with NORD and the UDN, is committed to bridging the gap in healthcare disparities by providing research and access to genetic testing for underserved populations. This collaborative effort aims to improve diagnosis and treatment options for individuals facing rare and undiagnosed diseases, particularly those who may lack resources or live in underprivileged communities. By combining the expertise and resources of WashU, NORD, and UDN, we strive to empower and support underserved populations in their journey towards better health outcomes and personalized care.

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Hypermobile Ehlers Danlos for the Primary Care Provider

by Laura White, NP & Sara S. Procknow, MD, PhD

Primary care providers can effectively assess hypermobility and manage most patients with hypermobile spectrum disorder/ Ehlers Danlos Syndrome. Physical therapy, occupational therapy, and pain management specialists are an integral part of the care team.



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Abstract

Joint hypermobility is very common in the general population as is arthralgia. Increased awareness of hypermobility and hypermobile Ehlers Danlos Syndrome (hEDS) among patients and providers has led to a surge in demand for evaluation. Many patients with hypermobility meet clinical criteria for a diagnosis of hypermobile spectrum disorder (HSD) or hEDS, but monogenic connective tissue diseases (CTD) are rare. Genetic testing is not recommended for patients with HSD/hEDS unless another underlying CTD is suspected. Given the high prevalence of HSD/hEDS in the general population, primary care providers should be familiar with HSD/hEDS evaluation, management, and indication for referral to a CTD specialist.

Introduction

Approximately 10-30% of the population has some degree of joint hypermobility (JH), but only 1:500 patients meet diagnostic criteria for hypermobility spectrum disorder (HSD) or hypermobile Ehlers Danlos Syndrome (hEDS).[1-3] The cause of HSD and hEDS is unknown.[4] There is no genetic test for HSD or hEDS. Joint hypermobility can also be seen in rare disorders such as other forms of Ehlers Danlos Syndrome, Marfan Syndrome, and Loeys-Dietz Syndrome but these are readily clinically recognizable with distinctive features not found in HSD/hEDS. Genetic testing is only recommended when another connective tissue disorder (CTD) is suspected.[5] Regardless of the cause, management of JH is symptomatic and follows general good practice for joint health. The goal of this article is to empower general practitioners to evaluate JH and recognize signs and symptoms that suggest an alternative diagnosis that should prompt referral to a specialty center.

Assessing Joint Hypermobility

Joint hypermobility occurs when a joint can be being actively or passively moved "beyond normal limits along physiological axes."[6] It may be caused by an inherent laxity of the connective tissue, as in heritable CTD, but it can also be a manifestation of an acquired condition of the muscles, joints, or bones such as past trauma, age-related joint degeneration, hypotonia, or other neuromuscular conditions.

The Beighton score (BS) is used to diagnose HSD, hEDS, and pediatric hypermobility.[7-9] There are other tools available for the assessment of JH but these have

Table 1: Beighton Score

Maneuver	
1.	 **5th fingers: Passive dorsiflexion of the 5th metacarpophalangeal joint ≥90°** With the palm and forearm on flat surface, have the patient use their opposite hand to extend their 5th finger. The distal interphalangeal joint is not included in this assessment **Assign 1 point for each pinky that extends to 90° or greater at the MCP.** Right: __ /1 point Left: __ /1 point
2.	 **Thumbs: Opposition of the thumb to the volar aspect of the forearm** With arms straight, palms down, have the patient use their opposite hand to touch their thumb to the volar aspect of the forearm. **Assign 1 point for each thumb that touches the forearm** Right: __ /1 point Left: __ /1 point
3.	 **Elbows: Hyperextension of the elbows >10°** Have the patient extend their arms, palms facing upwards. **Assign 1 point for each elbow that extends >10°** Right: __ /1 point Left: __ /1 point
4.	 **Knees: Hyperextension of the knees >10°** Have the patient stand with knees locked. **Assign 1 point for each knee that extends >10°** Right: __ /1 point Left: __ /1 point
5.	 **Spine: Ability to place hands flat on the floor with knees fully extended** Have the patient bend forward with feet together and knees fully extended. **Assign 1 point if the palms of the hands can be placed flat on the floor** __ /1 point
	Total = __ / 9 points

5 point questionnaire
☐ Can you now (or could you ever) place your hands flat on the floor without bending your knees?
☐ Can you now (or could you ever) bend your thumb to touch your forearm?
☐ As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
☐ As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
☐ Do you consider yourself "double jointed?"
☐ Can you now (or could you ever) place your hands flat on the floor without bending your knees?
__ Positive
Add 1 point to the Beighton Score if 2 or more questions are answered in the affirmative
Final Score: __ / 9

not been validated for diagnosis of hEDS or pediatric hypermobility.[7,9]

The Beighton score (BS) is a quick, easy tool to assess JH in adults and children ≥5 years.[7] It is the recommended tool for diagnosing HSD, hEDS, and pediatric hypermobility.[7-9] The BS incorporates of five maneuvers, with a score of 1 given for each positive maneuver, yielding a possible score of 0-9 (Table 1). The BS is not reliable in children under 5.[9,10] A score of 6 or more should be used for pediatric patients age 5 to 17 or skeletal maturity. Skeletal maturity is defined as a growth velocity <1cm/yr using two measurements at least three months apart or a mature bone age on X-ray studies. A score of 5 or more is required from age 18 to 50 and 4 or more for patients older than 50. For adults within 1 point of the age-specific cutoff, a 5 point questionnaire can be administered - one additional point can be added to the score if the patient answers "yes" to at least two questions (Table 1).[11]

Diagnosis

Adults

For adults and adolescents who have reached skeletal maturity, hEDS should be diagnosed based on the 2017 criteria.[7,12]

HSD is currently described as any generalized, peripheral, localized, or historic JH in the absence of an underlying etiology.[12] While no strict or consistent definition exists in the literature, HSD is generally considered an appropriate diagnosis in patients with a BS that meets age-specific cut-offs but does not meet the systemic criteria required for hEDS. HSD is not an appropriate diagnosis if there is an alternative explanation for JH (past trauma, age-related joint degeneration, hypotonia, and other neuromuscular conditions).

Diagnosis of hEDS requires a positive age adjusted BS, and two of the following: A) chronic musculoskeletal pain or recurrent joint dislocations; B) five systemic symptoms (Table 2); or C) a family history of a first degree relative (parent, child, or sibling) who meets 2017 diagnostic criteria.[7] The final diagnostic criteria is exclusion of alternate diagnoses. Most alternate diagnosis can be excluded based on

Table 2: Systemic Criteria for Hypermobile Ehlers Danlos

1.	Unusually soft or velvety skin This should be assessed on the volar aspect of the forearm. Skin softness and texture is subjective but is marked in patients with hEDS. A high threshold for positivity is recommended
2.	Mild skin hyperextensibility Skin extensibility can be affected by location and extrinsic factors such as sun exposure and weight fluctuations. This should be measured in the middle of the volar surface of the non-dominant forearm. Skin should stretch >1.5cm to be considered positive. Stretch >2cm should prompt consideration for alternative diagnosis such as classic EDS or classic-like EDS
3.	Unexplained striae **in adolescents, men, or prepubertal women without a history of significant gain or loss of body fat or weight**
4.	Bilateral piezogenic papules of the heel
5.	Recurrent or multiple abdominal hernia(s) (e.g., umbilical, inguinal, crural) Congenital umbilical hernias are common particularly in preterm infants and are generally not counted towards this criterion unless they recur
6.	Atrophic scarring involving at least two sites without papyraceous or hemosideric scars Atrophic scars are typically wide and sunken due to impaired wound healing and subsequent dermal atrophy. Linear scars are more reliable than elliptical scars (such as from shave biopsies) which are more difficult to assess without knowing the size of the original wound. **Scars that result from multiple incisions, wound infections, or inflammatory conditions should not be considered.**
7.	Pelvic floor, rectal, and/or uterine prolapse in children, men or **nulliparous women without a history of morbid obesity or other known predisposing medical conditions** Pregnancy, morbid obesity, and other conditions such as chronic constipation predispose patients to pelvic organ prolapse. This criterion should be considered positive in the absence of those predisposing conditions.
8.	Dental crowding **and** high or narrow palate This is a subjective measure but history of extensive orthodontia, tooth extractions, or palate expansion suggest the presence of significant crowding
9.	Arachnodactyly, as defined by a bilateral positive wrist (Steinberg) sign and/or bilateral positive thumb (Walker) sign. Wrist sign is only considered positive if the tip of the thumb overlaps the **entire nail** of the pinky. Thumb sign is only considered positive if the **entire distal phalanx** of the adducted thumb extends beyond the ulnar border of the **palm**.
10.	Arm span-to-height ≥1.05
11.	Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria
12.	Aortic root dilatation with Z-score > +2

history and exam. Symptoms of an alternate diagnosis that should prompt referral to a CTD specialist are discussed in more detail below.

The history and exam should also evaluate for acquired connective tissue disorders such as autoimmune disorders, age-related degeneration, instability caused by trauma, hypotonia, and neuromuscular disorders. While patients with autoimmune disorders may have underlying JH, they also typically have joint pain due to their autoimmune disorder, so the criterion regarding pain is not considered in diagnosis of hEDS. Because the pain criterion is not considered in diagnosis, patients with a coexisting acquired connective tissue disorder, such as lupus or rheumatoid arthritis, can only be diagnosed with hEDS if there is a positive family history of hEDS in a first degree assessed by the 2017 criteria. A first degree relative with HSD or a subjective report of hypermobility does not fulfill this criteria. If symptoms of an autoimmune disorder are present (morning stiffness lasting >30 min, pain that improves with activity, joint swelling in the absence of trauma) this should prompt a rheumatologic evaluation. Adult patients should also be evaluated for a history of joint trauma and age related joint degeneration.

A convenient hEDS diagnosis checklist can be found on the Ehlers Danlos Society website at https://www.ehlers-danlos.com/.

Pediatric Patients

JH is naturally prevalent in young children and adolescents and typically declines with age.[10,13] Infants and toddlers have insufficient skeletal maturity to meaningfully assess ligamentous laxity, therefore, JH cannot be accurately assessed in children <5 years of age.[10] Tone should be assessed in infants and children with apparent hypermobility as hypotonia may give the appearance of an intrinsic connective tissue abnormality.

In 2023, pediatric-specific guidelines were released for patients ages 5-17 years old or until skeletal maturity is established as described above.[9] In accordance with the 2017 hEDS diagnostic criteria, the 2023 pediatric guidelines recommend a minimum BS of 6 for diagnosis and classify patients as either pediatric generalized JH (in the absence of musculoskeletal complications) or pediatric hypermobile spectrum disorder (in the presence of musculoskeletal complications). These are further subdivided into patients with skin and soft tissue abnormalities and core comorbidities (Table 3).

Table 3: Pediatric Diagnosis

	Skin and Soft Tissue Abnormalities	Musculoskeletal Complications	Core Comorbidities
Asymptomatic			
pGJH	Absent	Absent	Absent
pGHJ with skin involvement	Present	Absent	Absent
Symptomatic			
pGHJ with core comorbidities	Absent	Absent	Present
pGJH with core comorbidities and skin involvement	Present	Absent	Present
pHSD, Musculoskeletal subtype	Absent	Present	Absent
pHSD Musculoskeletal subtype with skin involvement	Present	Present	Absent
pHSD: systemic subtype	Absent	Present	Present
pHSD: Systemic subtype with skin involvement	Present	Present	Present

pGJH – Pediatric Generalized Joint Hypermobility
pHSD – Pediatric Hypermobility Spectrum Disorder

A convenient Pediatric Hypermobility diagnosis checklist can be found on the Ehlers Danlos Society website at https://www.ehlers-danlos.com.

This diagnostic framework "provides the foundation for appropriate current treatment and support, but not a lifelong diagnosis which may result in over medicalization and potential harms."[9] It also allows for diagnostic flexibility, so patients can be reclassified as their musculoskeletal system matures and symptoms change.

A convenient hEDS diagnosis checklist can be found on the Ehlers Danlos Society website (https://www.ehlers-danlos.com/).

Genetic Testing

Currently, there is no genetic testing for diagnosis HSD/hEDS. Hypermobility and hEDS have a clear autosomal dominant pattern of inheritance but despite years of work, no genetic cause has been identified. The genetic etiology is likely heterogeneous and hypothesized to be due multiple benign rare or common variants within connective tissue genes. Genetic testing is not recommended for patients with HSD or hEDS unless there are signs/symptoms of a distinct connective tissue disorder.[5]

At the Connective Tissue Disorder Center at Washington University in St. Louis, we evaluate hundreds of patients for concerns for possible connective tissue disorder annually. Genetic testing is only recommended for a small proportion of individuals with HSD/hEDS and atypical symptoms. However, genetic counseling is provided to patients with HSD/hEDS and some elect to undergo genetic evaluation. In review of our testing over the last year, of the 102 tests sent on patients without clinical suspicion of a specific disorder, none were diagnostic: half were negative and the other half had variants of uncertain significance (VUS) that were not felt to suggest an alternate diagnosis. Of those patients, a change in clinical management was only recommended in three patients who had variants of uncertain significance in FBN1 or FBN2 without a clinical diagnosis of Marfan or Congenital Contractural Arachnodactyly. While an adverse vascular event was considered unlikely, those periodic screening with echocardiograms were recommended in those patients.

Genetic counseling should be provided to all patients undergoing genetic testing. While genetic testing is generally thought to be low risk, it can have lasting implications on the individual's health care, life and long-term disability insurance, military service, and for family members. Importantly, genetic testing can never rule out a genetic condition. All genetic testing has lab and test specific limitations that should be understood by ordering providers in order to assess risk of an underlying genetic disorder not evaluated by any given test. These risks and limitations should be discussed with patients prior to genetic testing to obtain informed consent.

Additionally, identification of variants of uncertain significance can cause high anxiety in any population.[14-16] Increased anxiety is seen in patients with HSD/hEDS.[17,18] In our experience, many

Table 4: Symptoms of other Connective Tissue Disorders

Symptom	Considerations
Skin hyperextensiblity[1]	cEDS, Classical-like EDS
Skin tearing with minor trauma[2]	cEDS
Papyraceous or hemosideric scaring	cEDS
Skin tears at birth	Dermatosparaxis EDS
Uterine or bowel rupture	vEDS
Aortic dilation, aneurysm, dissections[3]	vEDS, Marfan Syndrome, Loey Dietz
Tall Stature, marfanoid habitus	Marfan Syndrome, Loeys-Dietz Syndrome
Hindfoot deformity[4]	Marfan Syndrome, Loeys-Dietz Symdrome
Cleft palate/bifid uvula, craniosynostosis	Loeys-Dietz Syndrome
Pneumothorax	Marfan Syndrome, Loeys-Dietz, Birt-Hogg-Dubé[5]
Lens dislocation	Marfan Syndrome, Loeys-Dietz Synrome, Homocystinuria, non-syndromic ectopia lentis
Corneal rupture	Brittle cornea syndrome
Atraumatic retinal detachment <30y	Stickler Syndrome
Short stature	Spondylodysplastic EDS, Skeletal Dysplasia
Atraumatic fractures or fractures that do not heal	Osteogensis Imperfecta, Skeletal Dysplasia
Hearing loss	Stickler Syndrome
Hypotonia	Myopathic EDS, Spondylodysplastic EDS, Neuromuscular disorders
Congenital hip dislocations	Arthrochalasia type EDS
Congenital contractures	Myopathic or Muculocontractural EDS, Congenital Contractural Arachnodactyly
Severe, early periodontal disease, tooth loss	Periodontal EDS, Hypophosphatasia
Severe progressive cardiovalvular disease	Cardiovalvular EDS
Congenital heart disease	Noonan Syndrome, Kabuki Syndrome
Seizures	FLNA
Dysmorphic features	Multiple
Birth defects	Multiple
Intellectual disability	Multiple

1. >2cm on the volar surface of the non-dominant wrist
2. Does not include delayed wound healing from trauma expected to break the surface of the skin
3. Patients with a first degree with TAAD should be screened by echocardiogram. Screening for abdominal aortic aneurysms is based on multiple risk factors [PMID: 37389507]
4. Distinguished from simple pes planus with pronation by the presence of forefoot abduction
5. When accompanied by associated skin manifestations. This is not included on most CTD panels

patients with HSD/hEDS experience significant anxiety related to VUS despite extensive pre- and post-test genetic counseling. Identification of a VUS can also lead to medically unnecessary testing due to patients' and/or providers' perception of the risk associated with VUS.

Rare Connective Tissue Diseases

Diagnosis of HSD and hEDS requires the reasonable exclusion of other heritable disorders of connective tissue.[7] HSD and hEDS are clinically distinct from other rare forms of EDS and other CTD such as Marfan Syndrome and Loeys-Dietz Syndrome. Reasonable exclusion of other heritable CTD can usually be made based on history and exam, with referral to a CTD specialist made if there are any concerning signs or symptoms for an alternate diagnosis.

The most common concern among the patients we see and their referring providers is regarding vascular Ehlers Danlos Syndrome (vEDS). Patients with vEDS rarely have generalized hypermobility or significant arthralgia. Hypermobility in patients with vEDS is typically limited to the distal extremities and is rarely, if ever, the presenting symptom for patients with vEDS. Patients with vEDS also typically have exceptionally thin, translucent skin with pronounced visible vasculature. Visible veins are also common in hEDS particularly in patients with fair skin and the skin is often soft, velvety, and doughy but these characteristics are much more pronounced in patients with vEDS. We recommend evaluation for vEDS in patients with a personal history or first degree relative with an unprovoked, spontaneous arterial rupture at a young age (<40y), carotid-cavernous sinus fistula, hollow organ rupture, or a family history of vEDS.

Symptoms of Classic Ehlers Danlos Syndrome (cEDS) can overlap with hEDS including generalized JH. However, cEDS can easily be distinguished from hEDS by severe skin hyperextensibility and fragility: Skin hyperextensibility >2cm at the volar surface of the non-dominant wrist is suggestive of cEDS. Patients with cEDS also demonstrate extreme skin fragility with tearing of the skin with minor trauma not expected to break the skin. Patients develop

papyraceous (tissue paper) or hemosideric scaring, frequently on the shins, forehead, chin, knees, and elbows. Patients with severe skin hyperextensibility, skin tearing, or papyraceous or hemosideric scaring should be referred to a CTD specialist for evaluation.

Marfan syndrome can be evaluated using the 2010 Ghent criteria.[19] Key characteristics that differentiate Marfan Syndrome from HSD/hEDS include arachnodactyly, pectus or chest asymmetry, hindfoot deformity, spontaneous pneumothorax, and ectopia lentis. Arachnodactyly can be assessed by the wrist and thumb sign. The thumb sign is considered positive when the entire distal phalanx extends beyond the ulnar border of the palm and the wrist sign is positive when the tip of the thumb covers the entire fingernail of the fifth finger. These should be present bilaterally to count towards the systemic criteria. Hindfoot deformity is distinguished from pes planus with pronation by the presence abduction of the forefoot. A systemic score of 7 or higher is indicative of a diagnosis of Marfan Syndrome and necessitates genetic testing and evaluation of the aortic root and ascending aorta. Patients with aortic root dilation (Z = >2) or ectopia lentis should be referred to a CTD specialist for evaluation.

The presentation of Loeys-Dietz Syndrome (LDS) has more overlap with hEDS but typically includes features of Marfan Syndrome and may include additional symptoms such as craniosynostosis, cleft palate or bifid uvula, and arterial tortuosity. Musculoskeletal and craniofacial manifestations of LDS are variable. Patients with a personal or family history of arterial tortuosity or aneurysms or dissections should be referred for evaluation.

Severe musculoskeletal manifestations other than hypermobility may also prompt referral to a CTD specialist. Tall stature is often familial even in the absence of a CTD but may raise suspicion for Marfan Syndrome or Loeys-Dietz Syndrome as would a marfanoid habitus. Musculoskeletal features that may prompt consideration for an alternate diagnosis include severe or early onset (prior to puberty) scoliosis, pectus carinatum, pectus excavatum, and multiple or recurrent hernias. Flat feet with or without pronation is common in HSD/hEDS and in the absence of other concerning findings is not indicative of an alternate diagnosis. However, patients with a true hindfoot deformity (pes planus with pronation and forefoot abduction) warrant additional evaluation. Ligamentous tears in pediatric patients with hypermobility or multiple ligamentous tears in adults are not uncommon in patients with HSD/hEDS. Adults with ligamentous tears should also have an evaluation for joint pathology as some common ligamentous tears in adults are more strongly associated with age related degeneration. With the exception of vascular manifestations, most signs and symptoms of an alternate diagnosis are readily identifiable on clinical exam and are typically much more pronounced in patients with other CTD. A thorough family history may suggest vascular manifestations of a CTD and a one time screening echocardiogram is recommended in adults with hEDS which would identify aortic pathology. See Table 4 for additional symptoms that may suggest an alternative diagnosis.

Management

HSD an hEDS are lifelong conditions. Patients require ongoing management of joint pain and associated symptoms, but these can often be managed effectively by primary care providers. There are many detailed papers that describe the management of hypermobility associated symptoms including an excellent overview in the American Family Physician.[20] Here we hope to provide you with a basic overview.

Many patients with hypermobility have joint pain. Pain due to hypermobility typically begins in childhood with acute injuries (sprains, subluxations) and progresses to chronic pain in late adolescence or early adulthood.[21,22] Pain is typically worse with activity. Joint pain starting in adulthood is not typical of HSD/hEDS and other causes of joint pain should be evaluated. Swelling in the absence of trauma, morning joint pain, or other markers of rheumatologic conditions is not indicative of pain due to hypermobility.

The pain in HSD/hEDS is multifactorial and incompletely understood.[23] Pain does not always correlate with degree of hypermobility.[24] Management of pain associated with hypermobility is symptomatic and follows the same general principles for treatment of any musculoskeletal pain. Physical activity is strongly encouraged. Kinesiophobia is common but inactivity will exacerbate joint pain.

Some patients with chronic pain require referral to pain management. Pain management referrals should be multidisciplinary and include, at a minimum, physical therapy and psychology. Expectations for therapeutic goals should also be discussed in patients with chronic pain. Complete resolution of pain is unlikely. Instead, treatment should focus on reduction of pain to manageable levels.

Physical therapy is a mainstay of treatment. Therapy should include evaluation of any acute injuries and overall balancing the joints and musculature. The approach should be comprehensive rather than focusing on a single joint whenever possible as pain and injuries in one location often lead to biomechanical stress on other parts of the body, muscular imbalance, and pain at remote sites.

Short-term bracing and taping may be used with the guidance of physical therapy while working to strengthen and stabilize the joint. Manual physical therapy can be helpful for patients with severe pain or comorbidities that limit activity such as postural tachycardia syndrome (POTS). Massage, acupuncture, and myofascial release can also be beneficial in some patients but may cause worsening of pain for 24-48 hour following treatments.

There are no specific recommendations for medications to treat musculoskeletal pain in patients with hypermobility. Over the counter analgesics (acetaminophen) and NSAIDS are first-line but use should be monitored and patients counseled on side effects and effects of medication over-use. Topical analgesics are well tolerated and have limited systemic effects. Muscle tension often develops as a result of joint stability and many patients benefit from use of muscle relaxers. Patients with neuropathic pain may benefit from medications such as SNRIs, TCAs, or gabapentin. Opiates are not recommended and should be used with extreme caution only when necessary.

Mitral valve prolapse and aortic dilation is seen more commonly in patients with hEDS and slightly more common in patients with HSD.[25] A screening echocardiogram is recommended during late childhood and in adulthood. Serial echocardiograms are not recommended unless there are abnormalities identified on screening echocardiogram. True aortic aneurysms and arterial dissections are rare and should prompt consideration of an alternate diagnosis.[25]

POTS and orthostatic intolerance are common in patients with HSD/hEDS. Many patients experience symptom relief by increasing water intake to 2-3L per day, compression stockings, or increasing salt intake to 3-5g/d when there are no medical contraindications. Those with severe symptoms may require referral to a POTS specialist.

There is connective tissue throughout the body and abnormal connective tissue affects nearly every system. Easy bruising and slow wound healing may improve with vitamin C supplementation. Headaches and are common.[26] Patients with severe headaches should be referred to a neurologist with low threshold for imaging to evaluate for Chiari malformation which is common in patients with HSD/hEDS. GI symptoms are very common. Many patients have functional GI disorders but there is also an increased incidence of gastroparesis and diverticulosis.[27,28] Mental health disorders, particularly anxiety and depression, are also very common in patients with HSD/hEDS and concurrent mental health treatment is recommended in all patients.[29,30]

Conclusion

Joint hypermobility is common in the population and frequently associated with both musculoskeletal and systemic symptoms. A subset of patients with hypermobility meet clinical diagnostic

criteria for HSD or hEDS. HSD/hEDS is a clinical diagnosis and genetic testing should not routinely be recommended. Patients with symptoms of other connective tissue disorders should be referred to a CTD specialist for evaluation. Primary care providers can effectively assess hypermobility and manage most patients with HSD/hEDS. Physical therapy, occupational therapy, and pain management specialists are an integral part of the care team.

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Metabolic Bone Disease: An Overview

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Metabolic bone diseases, although rare, have spurned the creation of sophisticated new drugs that target disease at its molecular level.



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Abstract

Metabolic bone diseases are a heterogenous group of conditions that all result in aberrant bone mineral homeostasis with resulting skeletal disease. The underlying causes are variable, ranging from nutritional deficiencies to pathogenic variants in skeletal genes. To properly diagnose and treat these conditions, a clinician needs to understand bone metabolism as well as recognize the signs of disease in a patient. This review will focus on three relatively common metabolic bone diseases (osteogenesis imperfecta, hypophosphatasia, and X-linked hypophosphatemic rickets) that are caused by genetic variants, not by nutritional deficiency. As molecular DNA sequencing has improved, the scientific community has been able to better understand the genetic basis of these conditions and create sophisticated medical treatments based on the genetic deficiency.

Introduction

Bone is a living tissue which provides protection, shape, and support to several organ systems as well as the environment for blood cell production.

Bone is a composite material composed of both inorganic and organic elements; The inorganic component is primarily crystalline hydroxyapatite, [Ca3(PO4)2]3Ca(OH)2, while the organic component of bone comprises more than 30 proteins. Type I collagen is the most abundant of these proteins and exists as a triple-helical molecule of three polypeptide chains, each of approximately 1,000 amino acids in length. Two of these three polypeptide chains are identical α1(I) chains and the third one is a structurally similar α2(I) chain.[1] Non-collagenous proteins, such as glycoproteins and gamma-carboxyglutamic acid-containing proteins are thought to play roles in cell attachment, cell differentiation, and the regulation of hydroxyapatite minerals deposition.[2]

Bone is a metabolically active tissue which underoges modeling in the developing child and cycles of remodeling in adults to develop normal contours and maintain strength and mass, heal fractures, and function properly. Through this process, old bone is resorbed by osteoclasts and is replaced by new bone formed by osteoblasts.[1] Fibroblast growth factors, bone morphogenetic proteins, induction of the Wnt signaling pathway, osteoblast-specific transcription factor osterix (OSX), and receptor activator of the nuclear factor kappa-β ligand (RANKL) are all involved in pathways which affect this process. These pathways

are regulated by hormones, cytokines and growth factors such as the parathyroid hormone, vitamin D, osteoprotegerin, sex hormones, fibroblast growth factor-23 (FGF23), and sclerostin.[3] Osteocytes are additional bone cells which are responsible for regulating biomineralization, both by controlling osteoblast/osteoclast activity and by playing a role in phosphate metabolism.[4] FGF23 is mainly produced by osteocytes and plays a critical role in human mineral ion homeostasis.[5] Bone is the principal store for calcium and phosphate within the human body and is one of the main regulators of mineral metabolism.

During the last two decades remarkable therapies have been developed for rare metabolic bone disorders including hypophophatasia, and X-linked hypophosphatemia (also known as X-linked hypophosphatemic rickets in children). Other previously FDA-approved drugs for adults have been used off-label in pediatrics to great effect, especially in osteogenesis imperfecta and steroid induced osteopenia/osteoporosis.[6] Additionally, newer drugs are in the pharmaceutical companies' pipelines that may expand the metabolic bone therapy armamentarium and improve outcomes with safer therapies and fewer adverse side effects.

Osteogenesis Imperfecta

Case Report

A 15-year-old teenage boy was referred to genetics clinic due to a personal and family history of fracturing. Family reported at least two fractures per year recently, which was a decreased fracture incidence from when he was younger. His fractures have healed without deformity. He had to have hardware placed only once at age 13 years after an elbow fracture. The patient's sister, mother, and maternal grandfather all have a history of recurrent fractures. No genetic testing has been done. Physical exam showed multiple surgical scars, but no bony deformities. Sclerae were blue grey. Dentition was normal.

DXA revealed osteopenia with Z-scores of –2.5 in spine and –2.8 in hip (normal +2.0 to-2.0). Initial laboratory workup included CMP, Mg, Phos, 25-OH vitamin D, PTH, osteocalcin, C-telopeptides (CTX), Procollagen type 1 Intact N-Terminal Propeptide (P1NP). Significant lab findings included alkaline phophatase activity of 395 U/L (reference range 70-260) and Osteocalcin of 213 ng/mL (reference range 19-159). Both these elevations indicate increased bone turnover.

Molecular genetic testing revealed a pathogenic variant in COL1A1. This is consistent with a diagnosis of osteogenesis imperfecta.

History of Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) or "brittle bone disease" was identified in the partially mummified remains of an infant from 1,000 BCE Egypt and stories of Ivar the Boneless, a Viking leader who invaded Anglo-Saxon England in the 800s CE allude to possible OI.[7] Other reports of brittle bones coupled with hearing loss appear in publications since the 1600s, though it was not until the mid-1800s when Vrolik described OI as a disease of congenital bone fragility separate from rickets. Later, associated reports of blue sclerae and deafness were connected to the condition.[8]

Description

Osteogenesis imperfecta (OI) is caused by pathogenic (disease causing) genetic variants in Type 1 collagen (approximately 85-90% of cases) and proteins that interact with Type 1 collagen (approximately 10-15% of cases)[9]. Type 1 collagen is one of the major support proteins of bone. Pathogenic variants in the genes for Type 1 collagen, COL1A1 and COL1A2, lead to a spectrum of phenotypes characterized by bone fragility with varying degrees of recurrent low impact fractures, tooth involvement called Dentinogenesis Imperfecta (DI), hearing loss, scoliosis, and short stature. OI is most commonly autosomal dominant when caused by pathogenic variants in the Type1 collagen genes (Figure 1). However, disease from variants in the collagen support genes can be recessive or X-linked (Figure 2). OI affects 1:10,000-20,000 and is pan-ethnic.[10]

There are a few ways to classify OI, with the Sillence Criteria being the classic model (Type I-Type IV) However, this has recently been revised to accommodate our improved understanding of the genetic causes of OI. With the advent of DNA sequencing, molecular/biochemical classification criteria have also been described. Transitioning to a mild, moderate and severe classification system with associated molecular information has been more clinically useful in recent years.[11]

There is significant phenotypic heterogeneity among patients. Patients with mild OI may be diagnosed in childhood or adolescence, when their increased fracture burden becomes suspicious for an underlying pathology. DI, blue sclera, hearing loss and other minor features

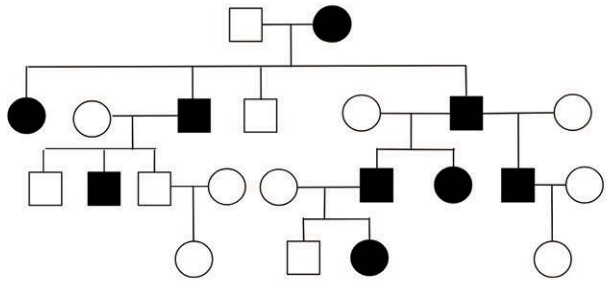


Figure 1. Autosomal Dominant Pedigree (Most OI/Some HPP)
Key: Shaded Affected; Unshaded Unaffected

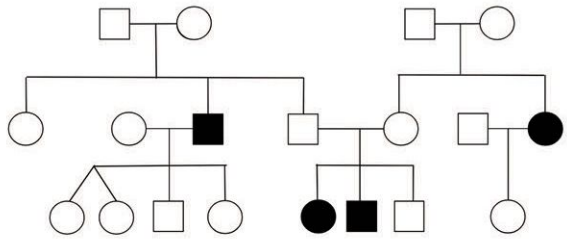


Figure 2. Autosomal Recessive Pedigree (some OI/some HPP)
Key: Shaded Affected; Unshaded Unaffected

Table 1. Summary of Pertinent Findings

	Lab Abnormalities	Imaging	Inheritance	Exam Findings
OI	Elevated Alkaline Phosphatase if acute fracture	Hypomineralization, often multiple fractures in different states of healing	AD(autosomal dominant) rare AR (autosomal recessive) and X-linked	Blue sclerae, dentinogenesis imperfecta, long bone deformities
HPP	Low serum Alkaline Phosphatase High serum B6 High Urine PEA (phosphoethanolamine)	Perinatal/Infantile: severe hypomineralization, rickets, and long bone bowing Childhood: hypomineralization with radiolucent tongues Adult: Hypomineralization and Pseudofractures	AD or AR	Short stature, premature tooth loss with root intact, rickets, bowed legs, hypotonia, motor delay
XLH	Low serum phosphate Inappropriately normal or low calcitriol levels High serum FGF23	Wide physes and metaphyseal flaring of long bones, lower leg deformity	X-linked dominant	Short stature, wide joints, lower leg deformities, dental abscesses

increase clinical suspicion. Severe patients often present prenatally with in-utero fractures and deformations. These patients will have progressive deformity with fractures and severely compromised bone growth. Their exam findings are striking and their clinical courses are notable for multiple orthopedic procedures and signficant growth impairment. Morbidity and sometimes mortality is due to respiratory distress. Over time, progressive scoliosis can worsen respiatory compromise and lead to stress on the cardiopulmonary system (Table 1).

An elevated alkaline phosphatase may occur in the setting of a recent fracture. Calcium, phosphorus, magnesium and vitamin D should all be normal.

Imaging findings vary depending on the phenotype. Mild OI patients may only have slight osteopenia and slender bones. Wormian bones, bony islands in the sutures of skull bones, can be seen in all severities of OI. Severe patients will also have osteopenia, bony deformities, thin ribs, poorly mineralized metaphases, and scoliosis. DXA scans demonstrate low bone mineral denisty.[12,13]

Medical Treatment

Presently bisphoponates remainthe mainstay of medical treatment in children. Zoledronate and pamidronate are the most common IV bisphosphonates and alendronate is the most common oral bisphosphonate used in U.S.. Bisphophonates decrease osteoclast activity, so that osteoblast activity is unopposed. In OI patients, this leads to net positive cortical bone formation with improved bone density, but bone quality remains poor.[13] Patients on bisphosphonate therapy will still fracture, although there is evidence that fewer vertebral compression fractures occur. Bone pain is usually improved with bisphophonate treatment, which can lead to patients becoming more active. Pediatric patients are usually medically treated until their growth plates close. Some adults with a significant fractures may require continued treatment. However, the persistent rate of long bone fractures leaves patients and providers dissatisfied and with hope for research on emerging novel therapies.[14,15]

Anabolic therapies (drugs that stimulate bone formation), teriparatide and abaloparatide have been used off-label in clinical settings. Milder variants of OI have responded to teriparatide therapy but more severe variants did not.[16] Two anti-sclerostin antibody therapies are presently undergoing formal clinical trials to determine if they will be helpful.[17] Additionally, therapy with an anti-TGF-beta antibody is in clinical trials to treat OI.[14,15]

Hypophosphatasia

Case Report

A two-week-old full term male infant was seen in skeletal dysplasia clinic with a history of an in-utero femur fracture. He was 7 pounds and 19 inches at birth. He did not require NICU care and went home with his mother from the newborn nursery. In clinic, his exam was was normal with no deformities of extremities.Alkaline phosphatase activity was remarkably low at 30 U/L (reference range 110-320), 25-OH vitamin D was 15 ng/mL (reference range 20-100), and vitamin B_6 was 437 mcg/liter (reference range 5-50). Skeletal survey showed osteopenia, healing femur fracture, and metaphyseal cupping and splaying. Molecular genetic testing showed biallelic pathogenic variants in ALPL. This is consistent with a diagnosis of infantile hypophosphatasia.

History of HPP

Hypophosphatasia (HPP) is the inborn error of metabolism caused by a low tissue-nonspecific alkaline phosphatase (TNSALP) activity resulting from deleterious variants in ALPL.[18] Alkaline phosphatase was discovered in 1923 and is probably the most frequently tested human enzyme.[19] HPP was first reported in 1948 by Dr. J.C. Rathbun in a 3-week-old patient noted to have wrist deformities and bowing of the femora, marked decalcification throughout the skeleton, and reduced serum alkaline phosphatase (ALP) activity. [20] In 1953, premature tooth loss was attributed to the condition.[21] In 1988, pathogenic variants in ALPL were attributed as the underlying etiology.[22] There was no targeted treatment for this condition until 2015, when recombinant asfotase alpha obtained FDA approval under the brand name Strensiq.[23]

Description of HPP

Impaired TNSALP activity leads to accumulation of it's substrates in the body. One of these is inorganic pyrophosphate (PPi), which inhibits bone minrealization. High levels of PPi lead to the rachitic skeletal phenotype in HPP.[21]

HPP has a very wide phenotypic spectrum, ranging from life threatening bone demineralization in the fetus to isolated dental problems. The classic disease categories are perinatal severe, perinatal benign, infantile, severe childhood, mild childhood, adult and odonto.[18,24] The wide range of phenotypes correlates with different pathogenic gene variants. Over 400 pathogenic variants in ALPL are known.[24] Severe, early onset cases tend to have biallelic loss of function ALPL variants (autosomal recessive disease) and milder patients are more likely to have a single dominant negative ALPL variant (autosomal dominant disease) (Figures 1, 2). Perinatal cases are often identified via prenatal ultrasound due to polyhydramnios, bone demineralization, shortening of long bones, in-utero fractures, and pulmonary hypoplasia. These cases can be indistinguishable from severe OI in utero and were uniformly fatal prior to targeted therapy.[23] Vitamin B_6 associated seizures may occur in the most severe surviving patients.[18,24] Infantile and severe childhood HPP presents with obvious rickets, craniosynostosis, and faltering growth. Mild childhood to adult-onset cases are not always diagnosed due to the often subtle phenotype. Signs such as early tooth loss, low bone mineral density, increased fracture frequency, mild rachitic changes on radiographs along with poor exercise tolerance may not be noticed without a thorough diagnostic evaluation. All forms of HPP have early onset tooth loss, often with the root intact. Odontohypophosphatasia is limited to dental disease with generalized skeletal changes absent.[25]

Significantly low alkaline phosphatase activity is the hallmark of the disease, often in single digits in perinatal and infantile cases. Vitamin B_6 levels will be elevated if the patient is not B_6 deficient, as B_6 is a substrate for TNSALP. [26] Another substrate for TNSALP , phosphoethanolamine (PEA) may be elevated on urine amino acids, but is not as specific as vitamin B_6.[27]

Imaging findings vary based on severity. Radiographs often show significant demineralization, splayed cranial sutures (undermineralized, but possibly still be fused), a rachitic rosary, flared metaphyses and long bone bowing. Many patients will develop characteristic "tongues of radiolucency" in the long bone metaphyses. Most patients have low bone mineral

density.[12] Pseudofractures become common amongst adult patients[24] (Table 1).

Medical Treatment

Trials of a recombinant TNSALP- IgG molecule, asfotase alfa, started in 2008 in severe HPP patients with initial results published in 2012. The initial trial showed significant improvement in bone mineralization and motor skill acquisition with significant decreases in respiratory support and healing of rickets.[23] Asfotase alfa obtained FDA approval in 2015 for perinatal, infantile and childhood HPP as Strensiq. Asfotase alfa is given daily or every other day by subcutaneous injection. Treatment is life-long. Patients often have rapid gains in muscle strength and motor skills. Over time, rickets heal, joint deformities improve and mineralization normalizes. Side effects can be mild but most patients have injection site skin reactions and some may develop disfiguring skin atrophy and lipohypertrophy at injection sites.[28]

X-linked Hypophosphatemic Rickets

Case Report

An 8 year-old girl was referred by an orthopedic surgeon to genetics clinic for genu varum. Mother first noted bowing when she started walking around age 1 year. She was initially diagnosed with multiple epiphyseal dysplasia at another hospital, but recently sought a second opinion from orthopedic surgery because of recurring knee pain. The orthopedic surgeon suspected a form of hereditary rickets. The patient's mother had short stature, lower extremity bowing and joint pain. Exam revealed wide wrists and knees and tibial bowing. Laboratory evaulation was notable for serum phosphate of 3.3 mg/dL (reference range 3.5-6.8) and alkaline phosphatase of 346 U/L (reference range 110-320) Imaging studies included radiographs, which demonstrated metaphyseal cupping and fraying and DXA showed a normal bone density (Z score +2 in hip and spine). Molecular genetic testing identified a pathogenic variant in PHEX. The patient was started on burosumab therapy with consistent improvement in her rickets and hypophosphatemia.

History of X-Linked Hypophosphatemic

X-linked hypophosphatemic (XLH) rickets is the most common heritable form of rickets; XLH has an incidence of 1:20,000 live births and accounts for more than 80% of familial hypophosphatemic rickets.[29] In the late 1930s, Albright et al. reported a case of vitamin D resistant rickets. In the early 1970s, Bianchine et al. reported investigations of the rare phosphate-wasting disorder, autosomal dominant hypophosphatemic rickets (ADHR), which is phenotypically similar to XLH, elucidating the importance of FGF23 in ADHR. Later increased levels of FGF23 were found in many, but not all patients, with XLH.[30] Reports of [pathogenic] variants on the X chromosome's PHEX gene in the mid-late 1990s provided additional insight into the pathophysiology of XLH.[31]

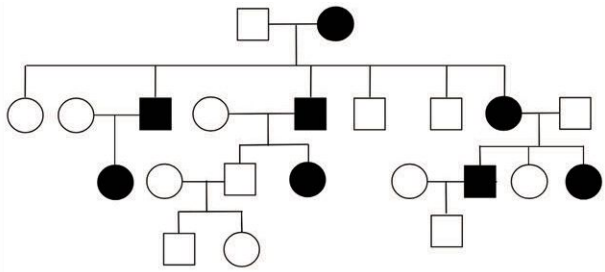


Figure 3. X-linked Dominant Pedigree (XLH)
Key: Shaded Affected; Unshaded Unaffected

Description

XLH is caused by pathogenic variants in the PHEX gene and leads to high levels of the phosphatonin FGF23 in the blood. FGF23 functions to suppress phosphate reabsorption and alters Vitamin D synthesis, leading to renal phosphate wasting and inappropriately low Vitamin D[32]. Hypophosphatemia results in impaired apoptosis of the chondrocytes at the growth plate, leading to disorganization and impaired imeralization.[35] It has an incidence of between 1:20,000 and 1:60,000. Somewhat atypically for an X-linked condition, males and females are affected equally (Figure 3). Without treatment, XLH is progressively deforming. Patients develop lower leg deformities (genu valgum, genu varum, and windswept deformity are all seen), weakness, short stature, musculoskeletal pain and an abnormal gait. Dental abscesses, hearing loss and craniosynostosis can also complicate the disease course. Symptoms generally start in the toddler years, with leg bowing worsening when the child becomes weight bearing.[12,33] Laboratory evaluation will show low serum phosphate (best seen on fasting sample) and renal phosphate wasting on urine studies[34] (Table 1).

Medical Treatment

The landscape of medical treatment has enitrely changed in the last decade. XLH was traditionally treated with calcitriol (active vitamin D) and supplemental phosphate. This lessened the disease burden, but it was not curative. Treatment was burdensome as supplements needed to be given three to five times per day. Calcitriol and phosphate must be administered as a combined therapy or severe hyperparathyroidism can occur. A side effect of this treatment is nephrocalcinosis from higher serum and urine calciums levels. Many patients found frequent dosing challenging which limited the pharmacological response.[35,36]

Burosumab is a monoclonal antibody to FGF23. Burosumab binds serum FGF23, leading to increased renal phosphate absorption. Therapy leads to normalization of serum phosphate, improved growth, improvment of rachitic skeletal abnormalties, less bone pain and improved gait.[36] In 2018, burosumab was FDA- approved therapy for all XLH patients over 6 months-old under the brand name Crysvita. Treatment consists of one subcutaneous injection every two weeks in pediatric patients and every four weeks in adult patients. However, some adult patients report better symptom control with an injection every two weeks. As with asfotase alfa, treatment is life-long. Burosumab is well tolerated by most patients. Common adverse effects include mild injection site reactions and restless leg syndrome. Hyperphosphatemia is rare.[36] Dental absecesses often remain a problem, despite treatment. . A mild variant of XLH has been described and accounts for about 10% of all XLH patients in the U.S. and lower doses of burosumab normalize serum phosphate and heal the rickets.[37]

Multidisciplinary Treatment in Metabolic Bone Disease

All patients with metabolic bone disease benefit from multidisciplinary care. A metabolic bone team often includes genetics, endocrinology, nephrology, orthopedic surgery, neurosurgery, physical medicine and rehabilitation, therapy services and dentistry.[38] Geneticists serve as rare disease experts, facilitate and interpret genetic testing, and may prescribe medical treatment. Due to the large role of hormones in bone and mineral homeostatsis, endocrinologists often follow these patients and may also prescribe medical treatment. Nephrologists often follow patients with a renal component of their disease such as renal phosphate wasting in XLH and those at risk for nephrocalcinosis. Orthopedic surgeons should follow patients at risk for fracture or those with deformtiies that may require surgical intervention. Neurosurgeons often follows patients with spinal involvement or with potential CNS complications such as basilar invagination in OI. Physical medicine and rehabilitation doctors help with non-operative modalities like bracing and injections, prescribing and fitting medical devices, and managing pain medication. Physical therapy and occupational therapy sees most patients with a metabolic bone disease to help with motor skills and for rehabilitation after injury or surgery. Dental services are needed for patients with metabolic bone disease as the teeth are often affected and patients may need significant dental interventions.

Conclusion

Metabolic bone diseases, although rare, have spurned the creation of sophisticated new drugs that target disease at its molecular level. Due to bone's constant remodeling, medications are able to alter impaired pathways to improve or correct bone metabolism. This is significant area of new drug development and there are multiple ongoing clinical trials. This will result in a new armament of medications that will improve the lives of patients with a wide variety of bone diseases.

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Disclosure

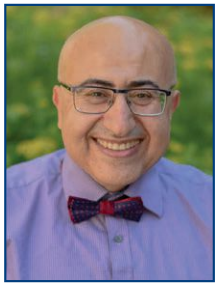
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The DESSH Clinic: A New Multidisciplinary Clinic to Address the Complex Needs of Individuals with a Rare Genetic Disorder

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This highlights the utility of a multidisciplinary approach to evaluating individuals with rare genetic diseases and the value of collaborating with family support groups to establish multidisciplinary clinics for these disorders, and provides guidance for future clinic planning.



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Abstract

DeSanto-Shinawi (DESSH) syndrome is a rare autosomal dominant condition caused by pathogenic variants in the WAC gene. DESSH syndrome was first identified in 2015 in six patients, but has since been diagnosed in more than 200 individuals worldwide. Patients exhibit a variable degree of developmental delay (DD), intellectual disability (ID), hypotonia, gastrointestinal and eye abnormalities, epilepsy, behavioral difficulties, and recognizable facial features. In order to educate families and address the complex medical needs of the increasing number of patients with DESSH syndrome, we established a new multidisciplinary clinic at Washington University in St. Louis. The first clinic was held in September 2022 and attended by 15 patients and their families. Herein, we report the structure of the clinic and present the main clinical findings of these patients. This pilot experience highlights the utility of a multidisciplinary approach to evaluating individuals with rare genetic diseases and the value of collaborating with family support groups to establish multidisciplinary clinics for these disorders, and provides guidance for future clinic planning.

Introduction

In 2015, six individuals with heterozygous loss-of-function pathogenic variants in the WW domain containing adaptor coiled coil (WAC) gene were identified by whole exome sequencing.[1] The individuals in the initial cohort exhibited developmental delay, hypotonia, behavioral problems, eye abnormalities, GI problems including constipation and feeding difficulties, seizures, and sleep problems.[1] Characteristic facial features such as broad/prominent forehead, synophrys and/or bushy eyebrows, depressed nasal bridge and bulbous nasal tip were also observed among all individuals. The recognizable facial gestalt and the constellation of findings associated with pathogenic variants in WAC highly suggested a new syndromic intellectual disability condition

which later was named DeSanto-Shinawi (DESSH) syndrome (OMIM #616708) or WAC-related intellectual disability.[2]

Since DESSH syndrome was first reported,[1] 39 additional individuals have been reported.[3–13] However, it is estimated that more than 200 individuals worldwide have been diagnosed with this condition. Additional reports describing DESSH syndrome have allowed for further characterization of individuals with this condition. It became clear that children with DESSH syndrome exhibit varying degrees of developmental delay and intellectual disability. Although almost all children display speech or motor delay and the majority of individuals have intellectual disability, affected individuals may have low normal range cognitive abilities.[1,5] Children often have a variety of behavioral difficulties including anxiety, ADHD, and aggression. Autism and autistic features are also common features in affected individuals. Epilepsy has been reported in individuals with DESSH syndrome;[10,14] the seizures often occur during sleep and may be associated with focal epileptiform discharges and continuous spike-wave on EEG.[4,6,7] Structural brain anomalies (e.g., hydrocephalus, corpus callosum hypoplasia, pineal cyst and Chiari malformation type 1, etc.) have been reported.[4] Eye problems including myopia, hyperopia and strabismus have also been reported.[1,8] Frequent respiratory infections, skin infections, and hypogammaglobulinemia have been detected in DESSH individuals.[5,8,9]

The WAC gene (OMIM *615049) maps to the 10p12.1 region and encodes 647 amino acid protein called WW domain-containing adapter protein with coiled-coil.[15,16] Most disease-causing variants in WAC are predicted to cause loss of function and haploinsufficiency; however, a missense variant has been reported in one individual with DESSH syndrome.[3] There are individuals with microdeletions encompassing the short arm of chromosome 10 at 10p12p11 who also exhibit similar manifestations to individuals with DESSH syndrome secondary to single nucleotide variants, though larger deletions are typically associated with more severe clinical and developmental findings. [6,8,17]

The WAC protein is mainly located in the nucleus but also found in Golgi[18] and is involved in several cellular functions and pathways. It is expressed in all adult and fetal tissues but highest expression is found in the cerebellum. It regulates transcription elongation through histone H2B monoubiquitination and in vitro studies showed that loss of WAC function results in decreased H2B ubiquitination and subsequently inhibition of gene transcription.[19] WAC also regulates p53-dependent cell-cycle checkpoint activation after DNA damage. While, this may implicate DESSH patients are at a higher risk of malignancy, this has not been reported.[2,3] In addition, WAC is involved in microtubule generation, Golgi apparatus reformation, autophagy regulation, autophagosome formation, and mTOR signaling pathway.[20,21] Given the multiple roles of the WAC protein and its ubiquitous expression in the body, it is not surprising that dysfunction of WAC results in disease affecting several organ systems.

Here, we describe our experience building a multidisciplinary clinic for individuals with DESSH syndrome and present a detailed clinical characterization of 15 individuals with this condition who attended our inaugural clinic in 2022.

Methods

To address the complex medical needs of patients with DESSH syndrome and to further explore the DESSH phenotype, in September 2022, Washington University School of Medicine (WUSM) and St. Louis Children's Hospital in collaboration with the DESSH Foundation (https://www.dessh.org/) hosted the first DESSH clinic in St. Louis, Missouri. A multidisciplinary team including genetics, neurology, ophthalmology, and neuropsychology evaluated each individual. Of the 15 individuals who traveled to the clinic, 13 patients came from USA, one from Germany, and one from Australia. The guardians of the individuals signed consents form to participate in research approved by Washington University Institutional Review Board. Biospecimens were obtained for research purposes. At the conclusion of the clinic, families were invited to stay for an additional day where

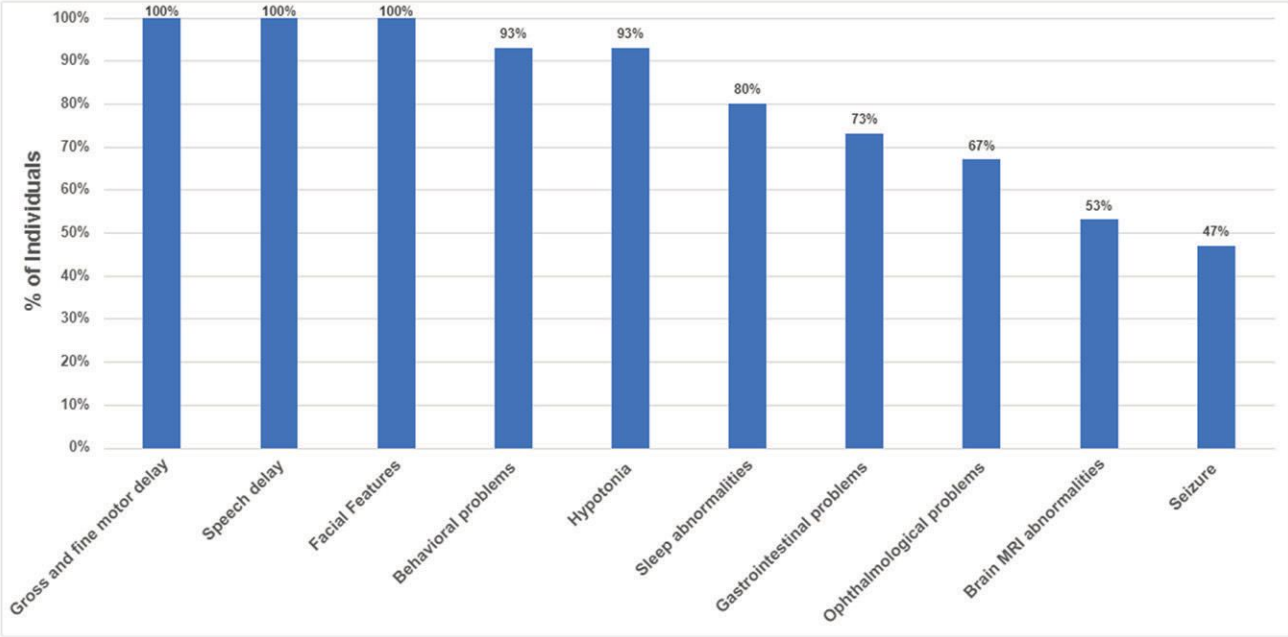


Figure 1. Frequency of most common clinical findings among individuals with DESSH syndrome.

the DESSH Foundation hosted the DESSH Family Conference at WUSM, where experts presented educational materials and discussed the condition with families and answered their questions. Demographic, clinical and neurological data were pulled from each of the specialty note visits to determine the prevalence of various aspects of the DESSH phenotype.

Results

Each individual was examined and assessed by all four specialty teams. The duration of each specialty visit ranged from 20 to 60 minutes, and the clinic lasted for 2 days. The genetics team counseled the parents about the genetic results, recurrence risk, and the phenotypes associated with DESSH syndrome. Other specialty teams discussed their recommendations with families and issued clinic notes to be shared with each individual's local providers. The mean age of individuals who attended the clinic was 9.27 +/- 4.26 years (Range 3 y 1 month, 18 y 4 months). Eight of the individuals were females and seven were males. All individuals were previously diagnosed by their medical teams with DESSH syndrome at a mean age of 5 y 7 mo (range 3mo-16 yo) based on clinical exome sequencing (n=13), neurodevelopmental expanded panel (n=1), and chromosomal microarray analysis (CMA) (n=1). For 12 individuals, parental testing has been completed; the pathogenic variant was *de novo* in 11 and maternally inherited in one individual. All patients had heterozygous loss of function pathogenic variants in WAC. Eight of these variants were frameshift, four nonsense, and two splicing. In addition, one female individual had a 715 Kb deletion encompassing the WAC gene on 10p12.1 (28,637,557-29,352,961; hg19).

All patients experienced gross motor, fine motor, and speech delay (15/15) (Figure 1) as well as characteristic facial features (Figure 2). Nine patients had formal cognitive testing based on which they displayed mild to moderate intellectual disability (mean Intelligence Quotient=66; range:51-81; n=7; 2 additional patients diagnosed with moderate ID using other tools). Expressive language delay, within the realm of a speech apraxia, in early childhood and fine motor delays were particularly common. Hypotonia was also a common finding in infancy and early childhood, occurring in 14 out of the 15 patients in this cohort. Ninety-three percent of patients experienced behavioral problems (Figure 3) including obsessive compulsive disorder (OCD)



Figure 2 A, B, C. Physical findings in individuals with DESSH syndrome. A. A 16-year-old boy with facial differences that are typical for DESSH syndrome including broad forehead, squared face, deep set eyes, and think and straight eyebrow. B. Hirsutism is a common feature in DESSH syndrome as illustrated here on the back of a 6-year-old girl. C. Foot and toe anomalies are being increasingly recognized as a common finding; show her hallus valgus deformity and 2-3 toe syndactyly.

(67%), attention deficit hyperactivity disorder (ADHD) (60%), autism or autistic traits (40%), anxiety, aggressive behaviors and impulsivity. Eighty percent of children in this cohort experienced sleep disturbances including difficulty falling asleep, multiple awakenings, and sleep apnea. Gastrointestinal problems were reported in 73% of the patients including constipation, gastroesophageal reflux, and feeding difficulties. Eye findings were also common and detected in 67% of patients and included strabismus (53%), astigmatism (13%), and cortical visual impairment (13%). Forty-seven percent of individuals experienced seizures and seven out of the 13 individuals who underwent brain imaging (53%) had nonspecific MRI findings. Interestingly, five out of the seven individuals with epilepsy had brain abnormalities; this correlation may suggest a higher seizure risk among individuals with structural brain abnormalities.

All patients displayed recognizable facial and physical features. Common findings included

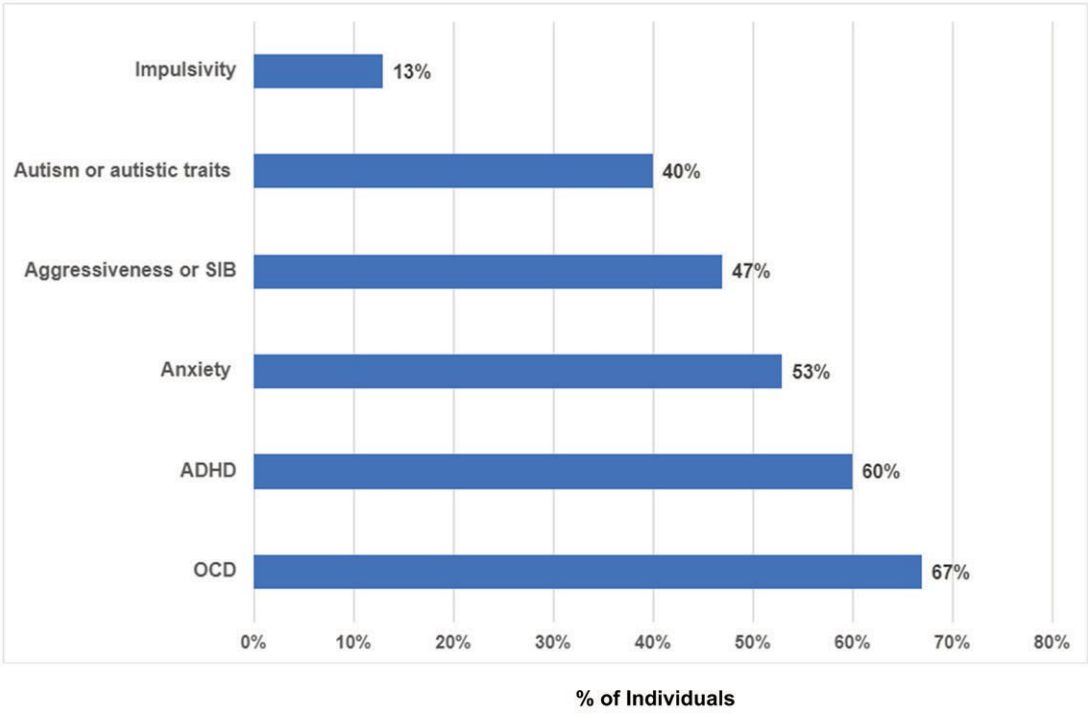


Figure 3. Prevalence of behavioral problems in individuals with DESSH syndrome. ADHD- attention deficit hyperactivity disorder; OCD-obsessive compulsive disorder; SIB- self injurious behavior.



Figure 4. Dr. Margaret Reynolds presented a talk at the DESSH Family Conference about the ophthalmological findings in individuals with DESSH syndrome.

deep set eyes (100%), hirsutism and/or low hairline (100%), thickened eyebrows (80%), broad forehead (60%), depressed nasal bridge (53%), synophrys (53%), wide mouth and dental anomalies (47% each).

At the conclusion of the multidisciplinary clinic, families were invited to stay for the DESSH Family Conference hosted by the DESSH Foundation. Expert speakers gave talks to families attending the event regarding the genetic aspects of DESSH syndrome, ongoing molecular research utilizing animal and *in vitro* models, and the neurological manifestations, ophthalmological findings, and psychiatric/psychological difficulties associated with this syndrome (Figure 4). This conference provided families with the opportunity to speak with experts and ask questions about interventions and management options, and it enabled experts to engage with each other to discuss research opportunities to advance the molecular understanding of this disorder. Overall, feedback from families indicated the success of this multidisciplinary model.

Discussion

DESSH syndrome is a rare autosomal dominant syndromic intellectual disability condition caused by pathogenic variants in the WAC gene resulting in characteristic facial features, variable degrees of developmental delay/intellectual disability, hypotonia, and behavioral problems. We also show high prevalence in our cohort of gastrointestinal problems, ophthalmological findings, nonspecific brain MRI abnormalities and epilepsy.

We show that the complex problems and needs of individuals with DESSH syndrome can be evaluated successfully in a multidisciplinary setting. Such multidisciplinary clinics for rare diseases will help pave the way for medical professionals to develop expertise in rare conditions. In addition, this pilot experience highlights the value of collaborating with family support groups and provides guidance for future DESSH clinic planning. Furthermore, the collection of biospecimens will serve as a platform for the establishment of a sizeable repository that will benefit researchers looking into this condition.

The limitations of this study included a relatively small sample size, which limited the power of our statistical analysis. Although all individuals had a uniform assessment by same medical professional, a formal cognitive assessment has not been conducted due to time constrains in the clinic. There may have been a bias in the selection of individuals attending the clinic based on the severity of their condition or epilepsy.

We plan to study larger cohorts of individuals with DESSH syndrome in subsequent clinics to understand the full spectrum of manifestations and investigate potential genotype phenotype correlation. In the future, questionnaires distributed to parents will be used to assess utility of this clinic from the viewpoint of the families. Formal neuropsychological evaluation, either as part of the multidisciplinary clinic or through an evaluation collaborative, can help to further characterize the cognitive phenotype beyond diagnoses of intellectual disability, as well as better delineating the specific behavioral phenotype of DESSH syndrome, as has been the case for other intellectual disability syndromes.[22, 23] It is important also to evaluate adult individuals with DESSH syndrome to understand the natural history of this condition focusing on signs or symptoms of developmental regression or

neurodegeneration. There is a great need to study the effect of early therapeutic interventions on ameliorating the neurobehavioral abnormalities and medical treatments (e.g., medications for ADHD and anxiety) on improving neurocognitive outcomes. To accomplish these objectives, it is crucial to research in depth the functions of WAC and the pathophysiology of DESSH syndrome in model organisms and *in vitro* systems. We anticipate that the utilization of available resources, including the DESSH clinic, and opportunities in science, which will be enhanced by the biorepository collection, will advance our efforts toward the long-term goal to find a cure for DESSH syndrome.

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The Microbiome: From the Beginning to the End

by Rajeev Aurora, PhD & Thomas Sanford, MD

All data strongly suggest that the microbiota have a significant impact early in life on neural/cognitive development, and on metabolism setting the health trajectory to develop, for instance obesity, cardiovascular disease, and other comorbidities of aging.



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Abstract

The human microbiota, a community of microorganisms in our bodies, is crucial for our health. This paper explores its development from birth through old age, highlighting some of the unique roles at key life stages—infancy, adulthood, and in the elderly years. Understanding the significant health impacts and consequences of changes in the microbiota offers insights for both the public and clinicians.

Introduction

The human microbiome has been intensely studied over the last two decades, leading to some surprising findings. We have previously written on the topic summarizing known mechanisms by which microbes influence health in this journal.[1] Here, we highlight recent findings which show that at each age, the microbiota contributes uniquely to our health. Our bodies are protected by barriers such as the skin, as well as mucosa that lines the mouth, airway, and the intestinal tracts. Each anatomical site has a defined community of bacterial and fungal species. The collection of ("omes") genomes that are encoded by the microbiota is called the microbiome. The gut microbiome is the largest by mass, most diverse, and most well studied. The gut microbiome is affected by age, sex, and geography. In addition, it is influenced by diet, whether we live in urban or rural setting, ethnicity, socioeconomic status, and other aspects including medications and presence of household pets.[2-5] Rather than focusing on the variation across populations, here we summarize recent data that reveals how the microbiome develops and effects our health (Figure 1). We provide examples of functions encoded by the bacterial genomes and how gain or loss of these functions impacts health.

Bacterial Nomenclature

A short paragraph on nomenclature may be helpful here. In the context of microbiology and clinical sciences, taxon refers to the groups or categories into which organisms are classified based on shared characteristics and genetic similarities. This classification system, known as taxonomy, is fundamental in understanding the diversity and relationships among different organisms, including bacteria, viruses, fungi, and other microorganisms commonly encountered in clinical settings. Taxa are arranged hierarchically, ranging from broad categories like kingdoms and phyla to more

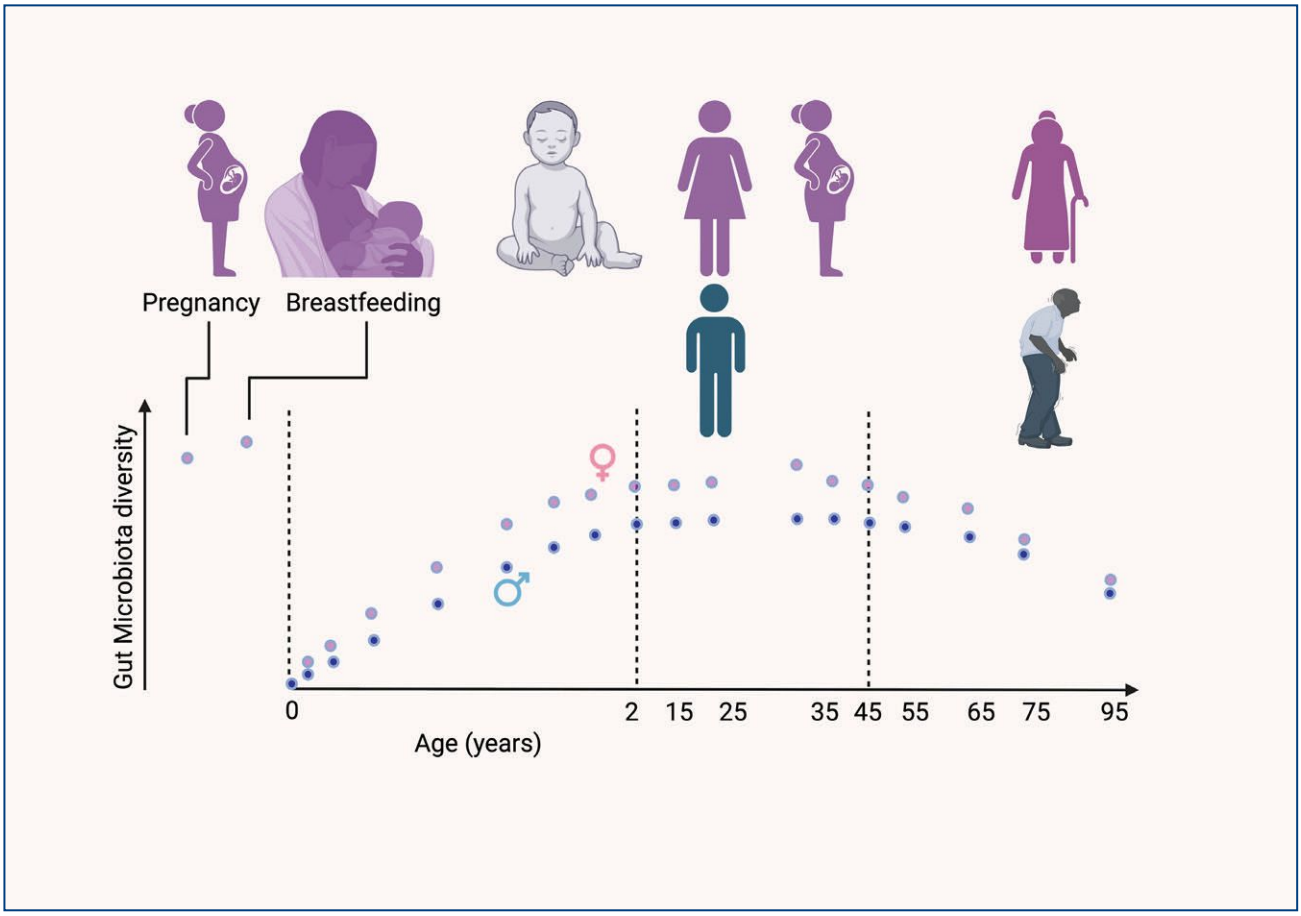


Figure 1. Changes in gut microbiome diversity across age: Multiple recent studies show that the gut microbiome is established by age of two years. A majority of the gut microbiota is inherited from the mother via breastmilk, that remains stable into adulthood. The diversity and abundance of the taxa vary with sex, geography, pets, hygiene, and urban vs. rural environments. Antibiotic use also has a significant impact. As individuals age, the microbiota starts to change, coinciding with reproductive senescence (menopause and loss of testosterone). Diet, medications, and lifestyle influences the rate of change that impacts human physiology. The microbiota has both a negative and positive influence of risk diseases, strongly suggesting that early events may set the health trajectory during aging.
Source: This Figure was produced using Biorender.

specific ones such as genus and species. For example, in the human microbiome, identifying taxa at various levels provides an understanding of the composition and functions of the communities present in different parts of the body. While clinically, bacterial classification uses gram staining positivity and growth in selective media (e.g., Bergey's classification), molecular techniques such as 16S ribosomal RNA sequencing has given rise to classification based on class, order, family, and genus. Sequencing of amplicons identifies orthogonal taxonomic units (OTU) that correspond approximately to species level of taxonomy. In this review, we use taxa to specify organisms, typically at the genus level.

Microbiota Effect on Traits

A central tenet of biology is that all traits or phenotypes (P) arise from the interaction between the genetic material (G) inherited from the parents, and the environment (E), often written in shorthand as P = G x E. The microbiome is inherited and is also a consequence of the environment. As it is inherited the microbiome has been referred to as the second genome. Further, as it is both inherited and influenced by environment, the microbiome has a strong influence on development in early life. It has been shown to impact metabolism, education of the immune system, and cognitive development.[6,7] One reason to focus on early events is because they set the

foundation and determine the trajectory, or arc, of health and disease risk with age.

Maternal Microbiomes Seed the Infant's Gut Microbiome at Birth

At birth, the infant's gut microbiome is primarily seeded by the maternal microbiome. During the passage through the birth canal, the baby is exposed to a diverse array of bacteria, marking the first significant microbial contact.[8] In the third trimester of pregnancy, the vaginal microbiome undergoes a transformation, increasing in microbial diversity and becoming rich in *Lactobacilli* species. These species are known to lower vaginal pH and enhance vaginal secretions, contributing to vaginal health. Concurrently, changes also occur in the maternal gut microbiome during pregnancy.

Infants born vaginally typically inherit a microbiome that reflects the maternal vaginal flora. This flora is abundant in *Lactobacillus*, *Prevotella*, and *Sneathia* species, which are instrumental in early gut colonization. These taxa are needed to digest and extract nutrient from milk. In contrast, infants delivered via Cesarean section are more likely to be colonized by skin and environmental microbes. This initial difference in microbial exposure can have enduring effects on the infant's health, potentially influencing their susceptibility to various conditions and diseases.[9] For instance, in premature infants admitted to neonatal intensive care units, prolonged exposure to antibiotics results in gut dysbiosis has been associated with adverse neonatal outcomes e.g., necrotizing enterocolitis a condition that is associated with high mortality and life-long morbidity in survivors.[10,11]

Interestingly, the composition of the vaginal microbiome varies based on factors such as ethnicity, maternal age, and parity.[12,13] Alterations from the normal vaginal microbiota, known as dysbiosis, have been linked with pregnancy complications, with preterm labor being the most extensively studied condition.[9] Thus, the mother's microbiome, encompassing vaginal, gut, and skin microbiota, serves as a critical source for the newborn's initial microbial colonization, setting the foundation for the development of the infant's own microbiome.

Breastfeeding and Microbiome of the Infant

Exclusive human milk feeding for the first six months of life, with continued breastfeeding for one to two years of life or longer, remains the normative standard and is recommended by the American Academy of Pediatrics for infant feeding.[14,15] Mother's own milk is uniquely suited to infants, both in its nutritional composition and in the non-nutritive bioactive factors that promote survival and healthy development.[16] Milk is not only a nutrient source for the infant, but also contains oligosaccharides and lipids that promote growth of specific gut microbiota (prebiotics).[17-21] There are roughly 4,000 different species of (~10^{14} cells) bacteria that inhabit the gut. Remarkably, mothers sense their baby's health and development and alter the composition of the milk within hours.[22] Saliva during suckling is allowed to flow back into the breast, and the interaction between the saliva and the milk is sensed to alter the breastmilk composition.[23-25]

Recent studies on breastmilk microbiome have shown that various bacterial species contain genes for bile salt hydrolases (BSHs).[26] The existence of BSHs in these bacteria is noteworthy. These enzymes split the peptide bond in bile acids, separating the amino acid group from the steroid core.[27] Human milk, with a fat content of 5%, requires bile salts for fat solubilization. These salts are synthesized by the infant's liver and are stored in the gall bladder. Normally, bile acids are effectively recycled through a process called enterohepatic recirculation. Both conjugated and unconjugated bile acids are absorbed throughout the gut passively and actively in the terminal ileum. BSH-produced bile acids and their metabolites act as ligands for the farnesoid X receptor (FXR), found in the liver. The metabolic derivatives of these reactions have diverse effects on human health.[28] Some lead to weight gain, fatty liver disease, and other metabolic disorders.[29] Other derivatives are implicated in cognitive and inflammatory diseases.[30,31]

The infant's gut microbiota is colonized from both breastmilk and the skin. As the communities that colonize the skin are distinct from those in breastmilk, the infant's fecal microbiome shows

that about 70% is derived from breastmilk and remainder comes from the areole.[32,33]

Next, we summarize evidence that the microbiome can have a positive and negative influence in commonly observed pathologies like atherosclerosis, metabolic diseases, and bone fracture healing in adults.

Changes in the Microbiome From Two Years Old to Adulthood

Puberty is a critical milestone that is associated with multiple physiological changes driven by sex hormones during the transition towards adulthood. Therefore, this dynamic period could have significant impact on the gut microbiota. Several studies have examined the dynamics of the microbiome between the ages of two and 15 years of age. These studies show that by the age of five years there are clear differences in the microbiome between boys and girls. Surprisingly, puberty (i.e., sex hormones) does not appear to have a significant impact on the gut or oral microbiome.[34-36] The overwhelming conclusion from these studies is that by age two years the microbiome is established and then remains stable over time.[37-39]

As the microbiota is being established at this early age, broad-spectrum antibiotics can have a lasting impact on the disease risk in the infant and into adulthood. In addition to having concerns for developing drug resistance, the benefits of antibiotics should be carefully balanced against the risks on the infants' health. Probiotics are live bacteria that provide benefits. The use of appropriate probiotics should be considered post-antibiotic therapy, but clinical trials are needed to determine the use of standardized probiotics.

Impact of the Adult Microbiome on Disease Risk

The adult human microbiome is a complex ecosystem, comprised of approximately 5,000 bacterial species. A meta-analysis representing 545 microbiomes collected from around the world showed that B*acteroides, Ruminococcus, Blautia, Clostridium*, and *Coprococcus* are prevalent in all human populations studied.[40] This research underscored the crucial role of the microbiome in maintaining systemic homeostasis, influencing a range of physiological processes including metabolism, epithelial barrier integrity, immune and inflammatory responses, neuroendocrine functions, and hematopoiesis. The gut microbiome functions akin to an autonomous organ within the host, orchestrating a bidirectional communication network with various body systems through neural, endocrine, immune, and metabolic pathways. While stable from the age of two years, the adult microbiome's composition can be modulated by dietary habits, cultural factors, use of prebiotics, probiotics, medications like proton pump inhibitors (PPIs) and antibiotics. Alterations leading to a detrimental imbalance in the microbiome, termed dysbiosis, have been implicated in various disease states.[41,42]

Interplay Between Gut Microbiota and the Immune System

The gut microbiota has a complex relationship with the immune system that is multifaceted and impacts host physiology. The gastrointestinal tract, beyond its roles in digestion and nutrient absorption, harbors a diverse microbial community that engages in a symbiotic relationship with the host. Many gut bacteria, such as commensal *Escherichia coli* providing essential nutrients derived from metabolic byproducts in exchange for a habitat and steady nutrient supply. The immune system, particularly within the gut mucosa, is instrumental in distinguishing pathogenic microbes from commensals, maintaining a balance between immune tolerance and activation. Interestingly, the same *E. coli* strain can elicit distinct immune responses depending on their location within the body. T cells, for instance, demonstrate both tolerance to commensal *E. coli* in the gut and robust inflammatory responses to these bacteria in other tissues, such as the bladder via a contaminated catheter, or lungs post intubation. This suggests a sophisticated level of immune education by the microbiome that is both microbial species and tissue specific. This implies that the gut microbiome is pivotal in shaping the resident T cell memory population.[43-45]

Gut-Bone Crosstalk in Osteoimmunology

Recent advancements in osteoimmunology have elucidated the intricate relationship between the gut microbiome and bone health. Notably, research in murine models has identified key pathways linking the microbiome to bone physiology, encompassing the immune system, metabolic byproducts, endocrine signals, and extracellular vesicles. The microbiome's influence on T cell differentiation, particularly in the context of bone healing, has garnered attention. The work of Dar et al. highlights the microbiome's role in bone repair processes.[46] They observed that gut microbiota influences the production of T_H17 cells in the intestines. Post-fracture, sphingosine-1-phosphate, a signal molecule released by bone tissue, attracts these T_H17 cells from the gut. These cells are crucial in promoting bone healing. Colonization of segmented filamentous bacteria (SFB) increased T_H17 cell populations in the gastrointestinal tract, correlated with increased T_H17 presence at fracture sites in the mouse model. This was further confirmed using a UV reporter mouse strain to track the migration of T_H17 cells from the gut to the healing bones, underscoring the gut microbiome's impact on bone healing. These findings suggest the gut microbiome's potential as a therapeutic target, especially considering how disruptions like antibiotic use could impact bone healing.[46,47]

The gut microbiome has also been shown to contribute to osteoporosis. Das et al. analyzed the fecal microbiomes from 181 men and women over the age of 55 with either normal bone mineral density (BMD), osteopenia, or osteoporosis.[48,49] They corrected for several confounding factors such as dietary habits, prescribed drugs, leisure time, and physical activity using statistical models to partition the taxa and assign them to each of these factors. They identified six genera that were significantly altered in abundance in the osteoporosis or osteopenic groups compared with age- and gender-matched controls. Despite controlling for biological confounders like BMI, health status, diet, and medication, which explained 15-17% of the variance within the microbiota dataset, these taxa remained significantly associated with bone mineral density. The cohort with osteoporosis had lowest microbial diversity with lowest levels of these taxa. Unexpectedly, the cohort with osteopenia had the highest diversity and higher abundance the six taxa relative to the cohort with normal BMD. Consistent with prior studies, the study finds that proton pump inhibitors (PPI) had a large impact on reducing the diversity of microbiome taxa, presumably because it alters the gut pH and reduction of these taxa also affected BMD. Together, these studies indicate that either an increase or decrease in diversity impacts the immune response and bone health.

Changes with Aging

Aging has been an area of intense study over the last five decades in hopes of understanding the biology and regulation of the process. Recently scientists have proposed twelve hallmarks of aging. Broadly, these hallmarks are interconnected among each other and include dysbiosis of the host microbiome. It is now recognized that aging is influenced by the interaction of the host and the gut microbiome. The microbiome itself has mechanistic pathways that have been associated with aging.

Recent research of individuals 65 years and older has revealed important connections between the composition of the gut microbiome and various health indicators, such as physical fitness, frailty, and dietary habits.[50] This research builds on earlier findings that demonstrated a change in the microbiome from adulthood into older age. This change is characterized by a decrease in microbiome diversity, lower levels of *Bifidobacterium*, and increased populations of bacteria such as *Clostridium, Lactobacillus, Enterobacteriaceae*, and *Enterococcus*. A significant 2021 study, examining the gut microbiomes and metabolic products of 9,000 people across three cohorts, found that microbiome diversity increases with age.[51] Despite the variations in microbiome composition, metabolic functions remained relatively consistent. The study highlighted two metabolites—tryptophan-derived indole and phenylacetylglutamine—which are linked to longer lifespans in mice and found in high concentrations in human centenarians. Notably,

this unique microbiome evolution was mainly seen in healthy individuals aged 80 and above, while it was less evident in their less healthy peers. These insights suggest an ongoing development and specialization of the gut microbiome in the context of healthy aging.[52-54]

Is it possible to slow aging by altering the gut microbiome? Metformin, a diabetes treatment used for over 60 years, offers an interesting case.[55] Not only does metformin extend life expectancy in humans and animals, but it also influences various aging-related factors, including the gut microbiome.[56] Its concentration in the gut is significantly higher than in the blood.[57] Metformin's impact on the gut microbiome includes inhibiting the growth of pathogenic bacteria in older individuals. This action helps reduce inflammation and counteract the immune system weakening caused by dysbiosis.[58,59]

Conclusion

Summarizing, the gut microbiome changes dynamically in the first two years of life and then is highly stable until age 40 (Figure 1). The microbiome is inherited primarily from the mother in these first years. After the age of 45 years, the microbiome changes, which coincides with reproductive senescence. In infants the gut microbiomes vary by sex, ethnicity, and geography. All data strongly suggest that the microbiota have a significant impact early in life on neural/cognitive development, and on metabolism setting the health trajectory to develop, for instance obesity, cardiovascular disease, and other comorbidities of aging.

A great achievement of modern medicine has been to increase lifespans. Recognizing the key contributions of microbiome starting at infancy and its relationship to the hallmarks of aging may allow us to develop new interventions that reduce the comorbidities of aging.

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Improved Assessment: The Path to Better Maternal Outcomes in Missouri

by Daniel Quay, MA, Ashlie Otto, RN, George Hubbell, MD, Karen Harbert, MPH & Crystal Schollmeyer, RN

Improvements to assessment, specifically at the provider, facility, and system levels, could have potentially prevented the tragic loss of maternal life.



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Abstract

Maternal Mortality Review Committees are one of the methods employed to measure and address the problem of pregnancy-related death. Reviewing Missouri cases from 2017-2020, 79% of the cases where failure to screen or provide an adequate risk assessment by a health care provider were identified in a pregnancy-related death were determined to be preventable. Recommendations for improvement most commonly addressed issues with assessment of mental health conditions, substance use disorder (SUD), intimate partner violence (IPV), and cardiovascular disease. Although limited, these findings indicate an opportunity for providers to lower the state of Missouri's pregnancy-related mortality ratio.

Introduction

In the United States, 1,205 women died of maternal causes in 2021. Comparatively, there were 861 such deaths in 2020 and 754 in 2019.[1] On average, there are roughly 70 women who die during or within one year of pregnancy in Missouri. Pregnancy-associated deaths were spread across the state of Missouri (Figure 1). However, as shown in Figure 2, pregnancy-related deaths have the highest ratio among metropolitan residents. Additionally, every year, roughly 60,000 women had a serious complication or severe maternal morbidity event,[2] while Missouri averages 956 severe maternal morbidity events annually. To address the underlying issues contributing to these adverse outcomes, the Missouri Pregnancy-Associated Mortality Review (PAMR) board, the state's Maternal Mortality Review Committee, has completed reviews of maternal deaths from 2017-2020.[3]

Methodology

The board reviews all cases of pregnancy-associated death when a Missouri resident dies while pregnant, during delivery, or within one year postpartum, regardless of the cause. Cases are identified using the pregnancy checkbox from the death certificate, ICD-10 coding indicating pregnancy, and a birth-death linkage, which matches death certificates to birth certificates and fetal death reports. After identification, the PAMR nurse abstractor requests medical

Figure 1: Count of Pregnancy-Associated Deaths by County, Missouri 2017-2020

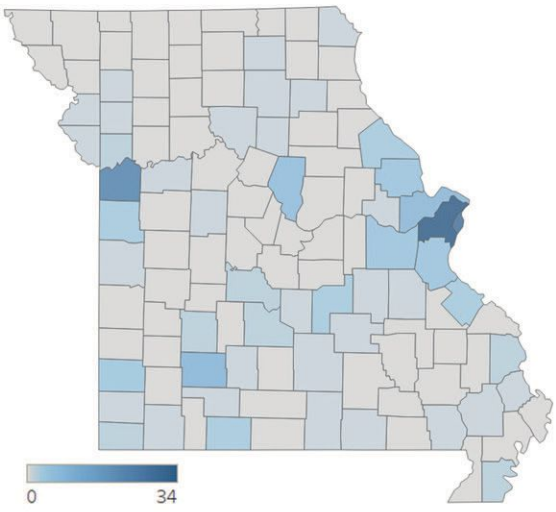
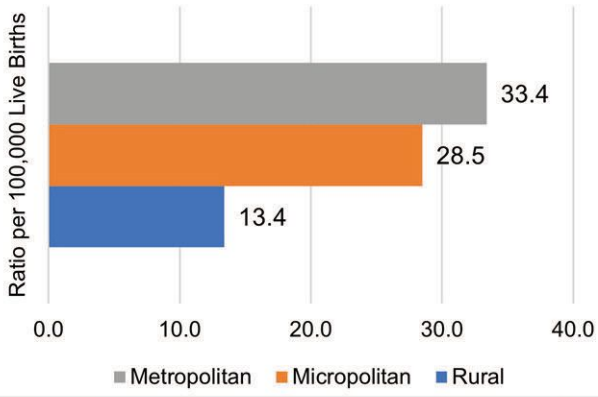


Figure 2: Ratio of Pregnancy-Related Death by Residential Area



Metropolitan: area that contains an urban core of 50,000 people or more
Micropolitan: area that contains an urban cluster of at least 10,000 people but fewer than 50,000 people.
Rural: counties that are not metropolitan or micropolitan
Based on county of residence at time of death

records, autopsy reports, and police records when applicable. The abstractor merges these records with social media histories and other data to create a de-identified case summary that is then presented to the board. Using the most complete data obtainable, the board then evaluates each case and determines if it is pregnancy-related.[4] A pregnancy-related death is defined as a death attributable to a pregnancy complication, a chain of events initiated by pregnancy, or the aggravation of an unrelated condition by the physiological effects of pregnancy. The board's determinations and other findings are recorded using a standardized committee decisions form[5] generated by the Centers for Disease Control and Prevention (Appendix A) and used in reports to provide data-driven guidance to those working to end maternal mortality.

Several distinctions exist between the PAMR process and other maternal mortality surveillance systems. For example, the committee can review and disagree with the cause of death listed on the death certificate.[6] Perhaps chief among these systemic differences is that the board seeks to determine if a death was preventable, meaning that after reviewing the circumstances surrounding a death, they found that there was at least some chance one or more reasonable changes could have prevented the death. The board then makes recommendations to ensure similar situations may have a different outcome in the future. These recommendations address specific factors that contributed to a death, such as delays in treatment, violence, and lack of knowledge.

Analysis

After aggregating data from 2017-2020 reviews, one contributing factor emerged as the most common factor that could have altered the outcome if addressed. For pregnancy-related deaths, the most commonly identified contributing factor was assessment (Table 1). Assessment was identified as a contributing factor when the board determined that failure to screen or inadequate screening of risk factors placed the pregnant individual at increased risk for a poor clinical outcome, and/or they were not transferred to receive timely, appropriate care.

The majority (79%) of pregnancy-related deaths where the board determined that inadequate provider assessment occurred were determined to be preventable. A provider is defined as an individual with training, expertise, certification, and licensure to provide care, treatment, and/or medical advice.

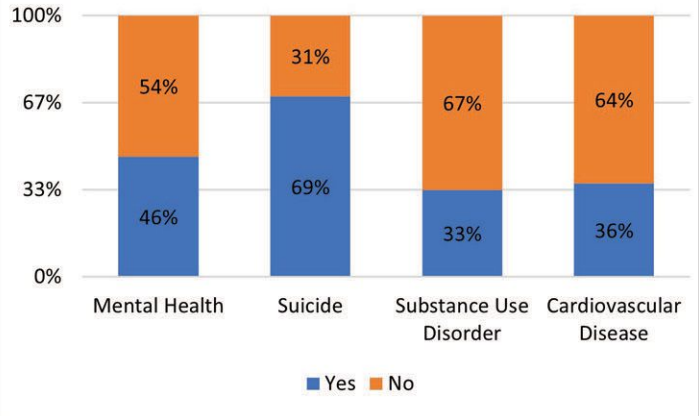
Table 1: Percentage of Contributing Factors for Pregnancy-Related Deaths

Factor	Percentage	Factor	Percentage
Assessment	13.2	Clinical Skill	4.3
Mental Health Conditions	9.8	Delay	4.0
Knowledge	9.2	Chronic Disease	3.7
Substance Use Disorder	8.3	Referral	3.7
Other	7.0	Discrimination	3.4
Access/Financial	6.7	Social Support	3.4
Adherence	5.8	Policies/Procedures	3.1
Continuity of Care	5.8	Unstable Housing	2.5
Violence	4.6	Communication	1.8

Figure 3: Leading Recommendation When Contributing Factor is Assessment.

All providers should perform validated Mental Health/SUD/IPV screenings at multiple intervals throughout pregnancy and the postpartum period, making referrals and providing resources as needed.

Figure 4: Assessment Issues Identified in Pregnancy-Related Deaths



Instances where the board determined that assessment was a contributing factor were linked, on a case-by-case basis, to recommendations to improve health outcomes. These recommendations most commonly resembled Figure 3. While the majority (88%) of recommendations for enhanced assessment occurred at the provider level, hospital or health system-level changes would also result in enhanced assessment. Improved systematic assessment through screening can result in early intervention, potentially reducing the impact of major complications, and decreasing maternal morbidity and mortality.

Further, 12% of assessment recommendations were explicitly directed at facility or health system improvements. Often, these recommendations focused on utilizing standard practices and procedures using evidence-based programs such as the Alliance for Innovation on Maternal Health (AIM), which provides the adoption of patient safety bundles—specifically those that will improve the identification and treatment of issues in the perinatal period. The majority of these recommendations were specific to the AIM bundles: Care for Pregnant and Postpartum People with Substance Use Disorder, Severe Hypertension in Pregnancy, and Cardiac Conditions in Obstetric Care.

From 2017-2020, assessment was identified as a contributing factor for 46% of cases where the board determined that mental health conditions other than SUD contributed to the death. This explains why nearly one in four (24%) assessment recommendations addressed perinatal mental health. Further, assessment issues were identified in 69% of pregnancy-related suicide deaths, which were all determined to be preventable and all attributed to mental health conditions as the underlying cause of death (Figure 4).

Additionally, assessment was identified as a contributing factor in 33% of cases where the board determined that SUD contributed to the death. These recommendations for systematic assessment focused on standardizing care to assess for SUD, utilizing validated screenings performed at multiple intervals throughout the pregnancy and postpartum period rather than relying on urine drug screens alone.

Cardiovascular disease is the second most common cause of pregnancy-related death after mental health conditions. More than one-third (36%) of these deaths had a recommendation for improved assessment. Special attention was given to screening for cardiomyopathy and both chronic and gestational hypertensive disorders of pregnancy (HDP). This included recommendations for expanded training regarding HDP for all providers, especially emergency medicine physicians and primary care physicians, where patients often present for general health care. The board recommended that patients with a personal history of HDP or a family history of cardiovascular disease should have a baseline Blood Urea Nitrogen level, an echocardiogram, and an electrocardiogram if indicated.

Discussion

Based upon this analysis, the board determined the most immediate way to impact pregnancy-related deaths in Missouri is to improve patient assessment through maternal screenings, beginning with the initial obstetrician's assessment and expanding to emergency department providers, pediatricians, intake nurses, nurse practitioners, family physicians, and health care systems in alignment with 2023 American College of Obstetricians and Gynecologists (ACOG) guidelines.[7] In Missouri, the board has a 60/40 ratio of clinical to nonclinical members representing various disciplines, geographic regions, and organizations for quality case reviews. As such, this data may be skewed toward provider solutions as the board may be better able to identify issues at the provider level than at other levels. However, this also means that they are intimately aware of what is necessary for providers and their institutions to potentially impact maternal morbidity and mortality in Missouri.

Three themes that emerged as most prominent from these recommendations focused on improvements to assessment and provider knowledge regarding how to treat and refer patients using a warm handoff based on screening results when indicated. A warm handoff is a transition conducted in person, between two health care team members, in front of the patient (and family if present).[8,9,10] The PAMR board recommended that all perinatal patients be screened for mental health conditions using validated tools (e.g., the Edinburgh Postnatal Depression Scale or the Patient Health Questionnaire).[11,12] Screening for substance use using validated tools available through the National Institutes of Health's National Institute on Drug Abuse[13] was also suggested.[14,15]

Intimate partner violence (IPV) screening was recommended; however, there were concerns about a patient's ability to safely communicate this information without putting themselves at risk of harm, whether actual or perceived. Creating safe, nonjudgmental, and non-stigmatized health care settings is a critical step providers, and systems can take to increase trust and patient-provider communication. Screening for risk factors for these issues may require providers to innovate ways of communicating with patients, such as motivational interviewing to empower a patient to make behavioral changes in the case of substance use or providing a way to communicate that cannot be overheard or intercepted regarding IPV. The Safety Card for Reproductive Health, an evidence-based screening and intervention tool, is available.[16]

A provider's knowledge of cardiovascular disorders associated with pregnancy (i.e., cardiomyopathy, hypertension, etc.) should include properly assessing, treating, referring, and educating patients on their diagnosis and risks.[17] The board recommended that practices and procedures be standardized across both obstetric and nonobstetric providers, including emergency medicine physicians and primary care providers.[18] While the utilization of specific AIM bundles was recommended,

the need for other practices such as screening for current or recent pregnancies to determine optimum treatment pathways was also identified as nearly 45% of pregnancy-related deaths occurred between 43 and 365 days postpartum.

Conclusion

Maternal mortality both in the US and Missouri is unacceptably high, and the board's findings underscore the significance of systematic assessment of obstetric patients by Missouri providers and health systems. The PAMR boards' determination that improvements to assessment, specifically at the provider, facility, and system levels, could have potentially prevented the tragic loss of maternal life warrants further study. This study's findings suggest an area for improvement where health care providers and their systems may directly and immediately begin working to significantly decrease pregnancy-related mortality and morbidity within the state of Missouri.

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For More Information

For more information on the CDC Maternal Mortality Prevention, visit https://www.cdc.gov/maternal-mortality/php/mmrc/decisions-form.html.

Disclosure

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