# RRNMF Neuromuscular Journal

vol. 2:1 January 2021

## FACILITATORS



**Cover Image:** "Woman in Shock" (2007) by David Bates. From the Katrina paintings series.

# CONTENTS

# What's In This Issue?

## Letter from the founding facilitator for Volume 2, issue 1

This is the first issue of Volume 2 and the first issue of 2021. Overall it is our sixth issue as we published five in 2020, our inaugural year. I think we had a very successful year in launching this new and unique journal.

For this issue, in the "what's on your mind section" we have several submissions. Once again, Josh Freeman, our good friend and family medicine doctor who has great insight into the nature of our health care system, has allowed us to publish one of his outstanding essays that he puts on his blog site. This one focuses on how we as a nation are struggling to respond to the COVID-19 pandemic and our "get out the vaccine" effort. Raghav Govindarajan has written two very empathetic pieces. One is about celebrating humanism in medicine and the other is about his experience with a patient with ALS. William Pridmore has submitted two articles from Tasmania, Australia. The first is an optimistic essay about ALS, and suggesting that we may be closing in on cracking "the code". Dr Pridmore became close to ALS when his mother was diagnosed with the disease. This then stimulated him to find out more about the disease and he has written a very nice review article in the "Looking Past/ Looking Forward" section on some of the off-label and over the counter new potential therapies for ALS.

In the last issue I published "Rick's North America Museum Ranking List". In this issue I am joined by a number of colleagues to publish our recommended "Books to read before you graduate high school". In the piece I relate the tale of how so many of my friends helped collect this list for the children of friends and relatives of mine who were going through a Bar or Bat- Mitzvah and I was trying to give them a unique gift. Read this piece to learn how it turned out! And send in comments to "what on your mind" to let us know if you agree or not on our selections. Remember, I also have lists for "books to read while you are in college", and "books to read before you are 30", etc. for each decade. So, if your book isn't on this list, it may be on forthcoming lists I will send in.

Also in the "What's on Your Mind" section is a piece I just wrote for my EVC of Health Affairs messages at the University of Missouri in honor of Black History Month about Vivien Thomas, a pioneer in open heart surgery.

In the "New Stuff" category we have Laura Herbelin and the University of Kansas Neuromuscular group presenting our new PADL-ALS scale, which is a modification of the traditional ALSFRS by our ALS patients. Our group was fortunate to be part of a PCORI network project called the Greater Plains Collaborative that chose ALS to be the rare disease of focus. We asked patients seen in ALS clinics throughout the GPC to consider modifying the ALS-FRS to make the language more patient friendly and also to suggest any other parameters they thought we should be assessing. They said we should add pain, easy crying or laughing, and spirituality questions, and they created the language. This paper is the first publication of these efforts and the data obtained in having ALS patients in the GPC complete the PADL-ALS.

We have a number of interesting cases in the "clinic stuff" category. Dr. Govindan and the anesthesiology pain group at the University of Kansas Medical Center report using pulsed radiofrequency ablation for entrapment of the anterior cutaneous nerve which they report can be a cause of chronic abdominal wall pain. Dr. Rim and colleagues at the Cleveland Clinic report a case of extraocular muscle metastasis of breast cancer producing the presenting symptoms of the cancer. Dr. Dhasakeerthi and colleagues at the University of Tennessee and University of Arkansas present a great case of a Marcus Gunn jaw "winking" phenomenon in a teenager with videos. In "visual stuff", Dr. Inan and colleagues in Turkey (Hacettepe University Faculty of Medicine) show an MRI picture of an enlarged, swollen sciatic nerve which they term the "cane sign" because the image looked like a cane!

Finally, for the first five issues of the journal I have used the art of Rembrandt for the cover. It seemed that was a good place to start. The art I chose was found on search. creativecommons.org and is available to show without getting permission. For this issue, I wanted to honor Black History Month and I chose a painting by the Black artist David Bates. I own this painting so I do not need permission to publish the image. He painted a series of the faces of people in New Orleans post-Katrina. They are haunting. I think the one called "Woman in Shock" is particularly heart wrenching.

Rick

# Black History Month: The Pioneering Work of Vivien Thomas

Richard J. Barohn, MD
University of Missouri

**Below is a message from the EVC of Health Affairs office I recently sent out in honor of Black History Month.**

There are so many ways one can contemplate the significance of Black History Month. I am a history of medicine buff and have been thinking about Black medical scientists who have had a remarkable impact in the medical field. Let me briefly retell the story of one of these pioneers you may have heard of. In the next EVC message later this month, I will tell you about another hero of mine I suspect will be a new story to you.

The hero you may have heard of is Vivien Thomas. A movie was made about his inspiring life called "Something the Lord Made." Vivien was born in Louisiana in 1910 and grew up in Tennessee. He graduated from high school on the cusp of the Great Depression. His father was a carpenter and taught Vivien carpentry skills, but Vivien wanted to be a doctor. He began working in the medical research laboratory as a technician for Dr. Alfred Blalock, a cardiothoracic surgeon at Vanderbilt University, in 1930.

He enjoyed the work but was paid very little. He soon learned why: his official job description was a janitor because he was Black. When he told Dr. Blalock he would have to leave due to his pay, Dr. Blalock obtained him a pay raise equal to white research lab employees. He became an indispensable member of Dr. Blalock's team because of his technical proficiency in the animal research laboratory and his work ethic.

Vivien and his wife and children moved with Dr. Blalock to Johns Hopkins Hospital in 1941 when he became the chief of surgery at that eminent institution. Shortly after arriving, Dr. Helen Taussig, a pediatric cardiologist, asked Dr. Blalock to think about how to do open-heart surgery on "blue babies" with fatal congenital heart abnormalities (the medical name for the anomaly is tetralogy of Fallot).

Open-heart surgery had never been performed on these patients before. Dr. Blalock put Vivien on the problem and he began thinking creatively about how to correct the abnormality. In dogs, he devised a way to suture an artery coming from the heart to an artery going to the lungs while the dog was anesthetized and while the heart was still beating. The surgeries on the dogs were successful. (The first dog was called Anna and her portrait can be found in books retelling this story.) Vivien also designed very small needles that could be used in the tiny chests of infants and surgical clamps to help stop bleeding in a very small space.

On Nov. 29, 1944, they were ready to try this procedure on a blue baby patient of Dr. Taussig's. All of the dog surgeries were performed by Vivien, not Dr. Blalock. Therefore, Dr. Blalock had Vivien stand directly behind him in the OR. They conversed quietly during the 90-minute operation as Vivien instructed Dr. Blalock on the proper techniques to use. Viewers wondered: Who was the Black man giving Dr. Blalock instructions?

The baby survived and over the next two weeks, her lips and body turned from blue to pink. This heralded a new era in open-heart surgery and in the treatment of congenital heart abnormalities. Dr. Blalock did many more procedures and Vivien stood behind him coaching him as he did in the initial operation. The news of the miraculous procedure went international, however, all of the attention and credit went to Drs. Blalock and Taussig. Vivien was not even invited to a celebration party about the new procedure. In fact, when he walked through the halls of Johns Hopkins wearing a white coat, he was often looked at with suspicion because a Black man in the hospital was expected to wear a janitor's uniform, not a white medical coat.

After Dr. Blalock's death in 1964, Vivien would continue to operate the medical research laboratory for 15 more years and trained hundreds of surgeons to do open-heart surgery. He finally began getting the recognition he deserved late in his career. In 1971, the Old Hands Club, a group of doctors who trained under Vivien, commissioned a formal portrait of him that was displayed in the hospital across from Dr. Blalock's portrait. In 1976, Vivien was awarded an honorary degree by Johns Hopkins University and he was officially appointed an instructor in surgery. He retired in 1979 and died in 1985.

Vivien Thomas was never able to make it into college or medical school. He and his family endured segregation in Tennessee and Maryland throughout their lives. Nevertheless, he used his talents in an amazing way to advance medicine. About 40,000 babies are born each year with heart problems. Because of the creative thinking, surgical skills and tenacity of Vivien Thomas, many of these children now have a chance to live.

Sincerely,

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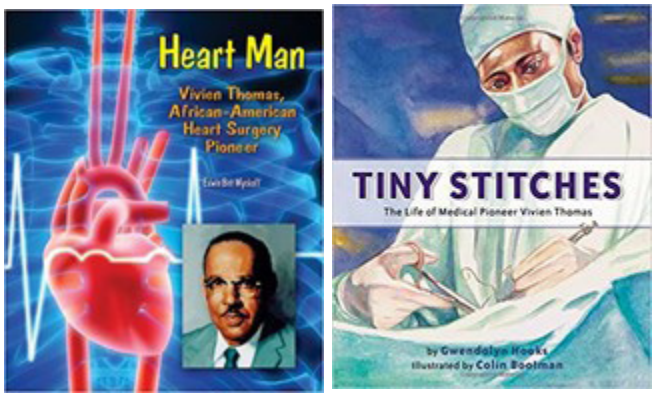
P.S.: For deeper reading on Vivien Thomas, read his posthumously published autobiography: "Pioneering Research in Surgical Shock and Cardiovascular Surgery: Vivien T. Thomas and His Work With Alfred Blalock."

Also, there are two wonderful children's books about Vivien. One is called "Heart Man: Vivien Thomas, African-American Heart Surgery Pioneer" by Edwin Brit Wyckoff. The other book is "Tiny Stitches: The Life of Medical Pioneer Vivien Thomas" by Gwendolyn Hooks and illustrated by Colin Bootman. I recommend you get these children's books for your kids 12 and younger. You can watch the movie on HBO!

Finally, there is an interesting audio recording of an interview with Vivien Thomas. He describes his working relationship with Dr. Alfred Blalock at Vanderbilt University and Johns Hopkins. You can access the interview at this link: https://soundcloud.com/hopkins-medical-archives/interview-with-vivien-thomas-1976




Covers of "Heart Man: Vivien Thomas, African-American Heart Surgery Pioneer" by Edwin Brit Wyckoff, left, and "Tiny Stitches: The Life of Medical Pioneer Vivien Thomas" by Gwendolyn Hooks.

# Protecting the community: Essential workers, nursing homes, and the incarcerated

Joshua Freeman, MD

Originally published in the *Medicine and Social Justice* blog, https://medicinesocialjustice.blogspot.com/2020/12/protecting-community-essential-workers.html

The COVID-19 pandemic continues, resurging across the US and in many other places. Different strategies have been adopted in different places, with varying degrees of success in slowing the spread of infection and death. This should provide us with information on what works well, and what strategies we should be adopting. For one example, family medicine colleagues in São Paulo, Brazil, report on their experience in nursing homes in the Royal Australian Journal of General Practice. They used public health management techniques including no visitors, rigid use of testing, recommended PPE and isolation, and others, as well as medical management and psychosocial management working with families and patients to help them through this process. They have had only 4 cases in the last 90 days (as of the November publication date), no people in isolation, and a low death rate.

In Arizona, as in the US, case rates and mortality continue to rise. We have more cases than ever, and fewer hospital and ICU beds. The state has chosen to address this issue by lifting restrictions on businesses, opening restaurants, bars, salons and gyms. Based on all evidence from everywhere, this is likely to further increase infections and deaths ("Health chief changes benchmarks so no Arizona business will be shuttered in pandemic".) It was clearly done in response to business owners concerned about their livelihoods and the probability that they will even survive, a real problem for them, and for us, in the horrific economic downturn that has accompanied the pandemic for most people (for major investors, however, the stock market has done well). Pima County, where Tucson is, has taken a more aggressive and restrictive approach; after more than 320 cases reported among county employees, including the chief health officer, it has furloughed 20% of the work force for 3 weeks. Obviously, this will be an economic hardship for those people's families.


| | TOTAL REPORTED | ON DEC. 21 | 14-DAY CHANGE |
|---|---|---|---|
| Cases | 18 million+ | 201,723 | +7% → |
| Deaths | 319,763 | 1,963 | +19% → |
| Hospitalized | | 115,351 | +13% → |

Thus we have the situation where we know what to do to prevent increased infections and deaths, but have to also address the serious financial impact on regular people who lose their jobs and businesses and incomes. Sadly, efforts to reopen have been almost linearly associated with increased infection rates and deaths. The efforts taken by our Brazilian colleagues were effective in an important and high-risk, but ultimately limited, venue, that of nursing homes. The fact that the increased infection and death rate in our communities will take its greatest toll on the elderly and those with chronic disease, not those whose exposure to others in workplaces, schools, and meetings (although they are also at risk, and not immune) makes it even more complicated. The leadership at the federal level, sometimes inaccurately described as "lack of leadership" when in fact it is actively leading us in entirely the wrong direction, is making things much worse, and creating and exacerbating an incorrect understanding of the disease among many people.

Those who work in high-risk occupations who cannot "phone (or Zoom) it in" but rather have to be present, most often among the lowest paid, those who live in multi-generational and multi-family households, are paying the highest price. These people are not only members of racial and ethnic minority groups, but those groups are far over-represented in their numbers. A recent article in the New York Times again makes the point that Black and Latinx people are hardest hit, not because of any genetic or biologic reason but because of their social and economic situation resulting from centuries of structural racism. Race, it is clear but requires repeating, is a social, not a biological, construct. The negative impacts on health, income, longevity, education, and everything else is not from "race" but from "racism"; indeed, the only significance of "race" is that it is the basis for racism.

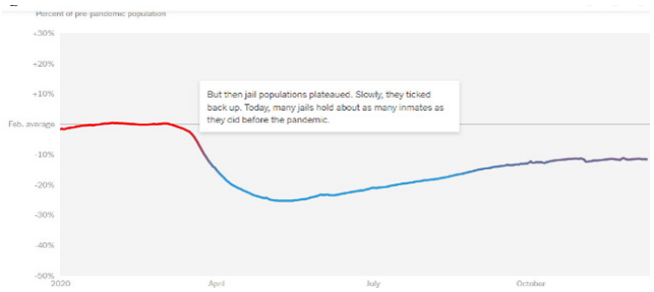
Now there is a vaccine (actually, two, and probably soon three, vaccines) and administration of them is rolling out, especially in the wealthy countries that have acquired most of the doses (of course, in the US the Trump administration jeopardized this by passing on an opportunity to acquire

more doses of the Pfizer vaccine, and this was certainly not to help out the poor parts of the world!) The debate now moves to who should get it first and in what order. In most places in the US, priority is going to health care workers and nursing home patients, which makes sense. They are, respectively, the most likely to contract and transmit the infection and the most likely to die from it. And then? Who? Those with the highest risk or those with the best connections? In many hospitals we hear reports of the C-suite executives (the "front office") being at the front of the line for vaccine, despite the fact that they do no health care. Nice of them to want to "model" behavior, but the vaccine should go first to those who see patients. The priority should be those who not only interact with the public, but who cannot do their jobs if they don't actually show up for work, and among those, people who would be the worst off if they lost their jobs (and those who have already been laid off but might be able to come back and begin working again). The last would be those who can continue to work from home, or are retired without major health risks, and can continue to isolate themselves.

Another major group that is finally getting so media attention, even if it is unlikely to get much vaccine, is the incarcerated population. The AP reports that "1 in 5 prisoners in the US has had COVID-19, 1,700 have died". This could be predicted; it is a group crowded together, unable to isolate, often with pre-existing conditions, and essentially without agency – they have to do what they are told. There are, broadly, two reasons for immunizing them. The first is human – they are human, and they are at very high risk, and they are already being punished; they should not be further punished by getting this disease. The second is practical; prisoners are not, actually, entirely separate from the rest of the population. In addition to guards and others who move between the inside and the outside, many prisoners are released; this is most especially true for jails, where the length of stay is short (usually awaiting a court appearance for those who cannot post bond), and thus is really part of the community from which inmates come – and go back to. Nathaniel Lash makes this case convincingly in the New York Times Sunday Review, "The coronavirus has found a safe harbor". For example,

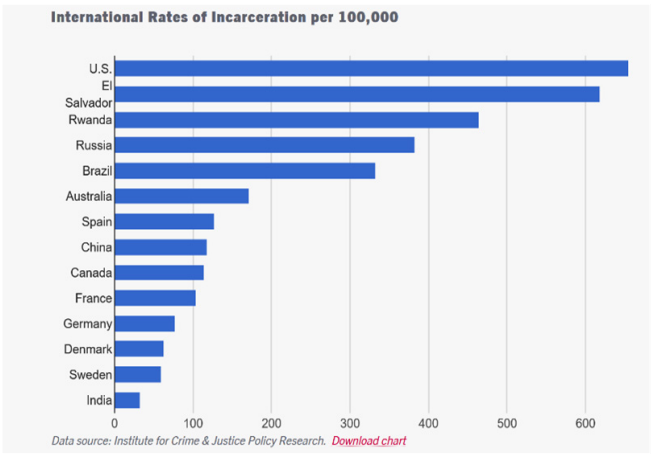
> *Cook County Jail was the site of the largest detected outbreak in the country early in the pandemic. In recent weeks, it has exceeded that — there were 340 active cases among inmates on Dec. 16. The population, meanwhile, has returned to levels typical before the pandemic, about 5,500 people.*

We should have fewer people in jail. It is outrageous that people are incarcerated because they cannot pay bond, overt discrimination against the poor, and cannot afford to support the very politically powerful bail-bond industry. This was true before COVID, and is more true now. ""There's no question with a new peak in infections that we have to be decarcerating now," said Dr. Emily Wang, the director of Yale School of Medicine's Health Justice Lab. "If we don't have larger-scale decarceration efforts, we won't control Covid."' The answer is bail reform that corrects these inequities – vicious inequities with frequently fatal outcomes. But the opposition continues to cloak itself in the mantle of morality rather than greed, public safety rather than racism. '"We're seeing the extent of the opposition to bail reform: They so strongly oppose it they will do it in the face of a pandemic," said Andre Segura, legal director for the American Civil Liberties Union in Texas.'




The US incarcerates more people than anywhere in the world, a lot for relatively minor drug offenses. This does not prevent crime, especially violent crime, and it continues to rise even as crime rates decrease. In 2020 it is out of control, it is inhumane, and it is a significant cause of the spread of COVID.

We need to get the vaccine out there soon, especially to those at highest risk of both dying and transmitting it to others. Clearly, the incarcerated population must be included.



# It is Time to Celebrate Humanism in Medicine!

Raghav Govindarajan, MD
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Last week, the school of medicine celebrated its second annual Gold Humanism Honor Society induction where 15 third year medical students who had displayed exemplary humanistic care throughout their clerkship were inducted into the honor society. The Gold Humanism Honor Society (GHHS) members are peer nominated and are the ones that others say they want taking care of their own family.

Unlike the traditional honor societies membership in GHHS signifies the students are specifically committed to the highest level of compassionate patient/family centered care and more importantly the creation of a GHHS chapter signifies that an institution places high value on the 'interpersonal skills and attitudes that are essential for the highest level of patient care'.

As the GHHS chapter advisor, I am thrilled to see humanistic patient centered care getting its due under the sun and being celebrated by the school of medicine. As I saw those 15 bright students recite the oath and don the pin, I was reminded of my own experience with doctors.

My aunt who was in her 30s had developed chest pain while teaching at the school. She was evaluated by the school nurse who thought the chest pain was due to acid reflux and gave her some antacids. The chest pain continued all night and got worse the next day. She was evaluated by her primary care physician who immediately recognized she was having a heart attack (myocardial infarction) and she was taken to the 'big hospital' in the town. We were all anxious and I distinctly remember my mother (her sister) crying. We were scared, confused and lost coming to the big hospital not knowing what to expect and whom to speak with.

My mother tried to talk with one of the doctors taking care of my aunt. He was in his mid-thirties moderately built with a husky voice. As my mother started talking to him, he seemed disinterested, had no eye contact, didn't refer to my aunt by her name and kept addressing her as 'case number' and even seemed annoyed that we were asking questions.

Our anxieties only got worse after this and although none of us had slept for more than day, we could not close our eyes. Then as the shift changed, a new doctor came in to take care of her. He was mild mannered but quickly built a rapport with us, held my mother's hand and spent more than an hour answering all our questions. Most importantly, he had a calm reassuring voice.

We were finally able to close our eyes and sleep. My aunt recovered from there on and was back to teaching in a month and continues teaching (it's been more than 15 years).

Medical schools have come a long way from days of labeling patients as cases. Providing patient centered, humanistic care has slowly but surely become a part of the medical school syllabus. Yet the stratosphere of physicians is occupied by physicians with large grants, physicians with administrative background, physicians with encyclopedic medical knowledge and so on. Research, diagnostic acumen and even administration are all very essential but there is enough space in the stratosphere to include those physicians who have been recognized as providing exemplary humanistic care by patients, medical staff and colleagues alike. These physicians should be honored and celebrated and made into role models for students to emulate. Both Sherlock Holmes and Dr. Watson need to be celebrated. For Dr. House fans, both Dr. House and Dr. Wilson need to be celebrated!

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# The Smile Gone

Raghav Govindarajan, MD
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Julie was a woman in her 40s who loved her job as a beautician. She had saved up enough money to open her own business along with her husband who had recently retired. She always took pride in her work and had clients from all over the town. A few months later she started noticing that her hand grip was weak and she could no longer hold onto her eye liner or mascara brush.

Worried that she might lose her clients, she decided to seek an opinion from a plastic surgeon who recommended a wrist brace for carpal tunnel syndrome. She wore it for a couple of months but the weakness continued to get worse. It was then that I saw her in my clinic for the hand weakness.

What struck me the most about Julie was her smile! Despite putting her through multiple tests including electric shocks, spinal taps, and needle pokes, she always had her angelic smile. Even on the day I gave her the diagnosis of ALS the smile never vanished. As months passed by, the torrid disease took over her body and the weakness worsened, but she always had her smile. Even when she was completely wheel chair bound and had to depend on her husband for everything she still had her smile on.

Our ALS association clinic is a tough place to be as a physician. You helplessly watch as the disease takes over the lives of our patients and their loved ones and yet Julie's smile was the bright spot in that dark place. Despite her breathing muscles becoming weak and being hooked onto the breathing machine she managed to keep her smile.

Throughout this time she developed multiple complications including pneumonia, blood clots, and heart problems and through it all she managed to keep her smile. During one of these hospital admissions Julie stopped smiling. The pearly white teeth that I was so accustomed to seeing were not visible any more.

It's always hard for physicians to let go of their patients especially after taking care of them for a long time and having gone through the disease with them. But I realized Julie's time had come. She no longer enjoyed her life and was in constant pain. Her biggest fear she told me was that she was going to die.

After a long discussion we decided to hospice care at home. A couple of days ago I received a call that Julie had peacefully passed away at her home. I am saddened by her loss but the memory of her smile will forever be with me. More importantly it will keep my spirits up while taking care of my other ALS patients.

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# Keeping Our Eyes on the Stars

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**Keywords:** *Motor neurone disease, humanities, hope.*

The real problem is time.

She was finding it a bit harder to lift her foot. It was irritating, and she found she was limping. She made passing comments to her husband and son of some "electrical shocks" in her legs, which she thought were due to anxiety. That combination worried me, but I didn't tell her. It couldn't be.

A "foot drop" is a symptom in which the muscles that lift the toes towards the head lose this ability. There are many causes for such a presentation, and determining the culprit is challenging. Things didn't improve, and so she underwent a series of investigations. The neurologists who administered the nerve conduction studies were kind, but she noticed they exchanged serious looks throughout the test. She'd have to wait for the full report.

The full report was not good.

When the diagnosis of motor neurone disease is made in a family member, the world changes. It darkens around the edges, and loses some of its lustre. One can deal with the impending physical challenges as they arise. But it's the time that gets you. For most patients, lifespan is between two and five years from diagnosis. Nothing stops the march towards oblivion. We know how this story goes.

Massachusetts native Dr Stanley Appel is one of the rock stars of this condition. At 87, he valiantly continues the research and clinical work he began as a young doctor. He calls MND "nice guys' disease", based on his observations that MND patients are typically driven, empathetic, generous, and otherwise healthy. Scientific studies, comparing patients with a healthy control population, confirm his notion [1]. MND patients are card-carrying nice guys – that's part of the injustice.

Research into MND has been frustratingly slow since the condition was first described by French neurologist Jean-Martin Charcot in the 1860s. Degeneration and death of motor neurones (nerve cells that control muscle movement) in the brain and spinal cord leads to progressive paralysis of voluntary muscles. The causes have remained elusive, and the biological processes that go astray are highly complex.

Most cases occur at random, but a minority run in families. When the first known genetic contributor was identified in the 1990s, it inspired the first animal model of MND, using laboratory mice. Such mouse models of MND have provided important insights about the injury of motor neurones, and have offered a useful way to test for the beneficial effects of various drugs. Unfortunately, these models have failed to bear much fruit. Contributing factors include poor experiment design, incompatibilities between mouse and human disease, and inadequate understanding to allow for informed therapeutic proposals [2].

But something is shifting.

Decades of work by devoted researchers has discovered much of what leads to MND. There is more optimism than ever before. Slowly but steadily, scientists are developing a working knowledge of motor neurone death. In the same way MND insidiously takes over a body, research is progressively uncovering its secrets – and will eventually banish it. Several drugs and treatments show early promise.

2020 has seen the launch of three MND "platform trials": one in the UK, one in the USA, and one in Europe. Regularly used in cancer research, platform trials allow several drug candidates to be compared to a single placebo (fake drug) group at the same time. Contrasted with traditional clinical trials, platform trials may cut testing time in half, and expense by a third. The arrangement also means fewer patients who participate in trials will receive placebo. For a platform trial to be viable, there must be enough medications in development. For a drug company to develop a medication, it must know enough about a particular condition to identify a likely therapeutic target. Drug company interest in MND has increased out of sight over the last five years [3].

University of Michigan linguist John M. Lawler offers the term "railroad time". It describes how, when science and technology is sufficiently advanced, it is natural for several people to make a discovery concurrently. Railroads were invented when it was "time for the railroads". I guess it is "railroad time" for MND platform trials.

Key discoveries hint that laboratory tests to reliably diagnose and monitor nerve damage may soon be available [4]. "Biomarkers" like these are desperately lacking. Implementation of such tests would revolutionise drug development, as researchers could tell quite quickly whether their medication was having an effect.

The code is being cracked. You can hear the pins falling into place.

For now, we have learned to celebrate the small things, and seek joy. A new orthotic has stabilised her walking. Her arms are still strong – suddenly her love for kayaking is amplified. Her painting studio, always a special place, is now her salvation.

It is clear that MND is increasing in prevalence [5]. Despite its dramatic effects, the condition remains relatively underfunded. The Fight MND Foundation, championed by Australian Football League great Neale Daniher, has brought needed attention to our plight – and other excellent organisations around the world continue to raise funds.

More is needed, and needed quickly. Two Australians are diagnosed with, and die from, MND every day. The battle against this condition has felt like Sisyphus eternally pushing his boulder up a hill, only for it to roll back down when it nears the top. But now there is a difference. With renewed awareness and financial support, we may actually, finally, reach the summit.

And hopefully Mum will be standing with us, waving the flag of victory.

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# Books to Read Before You Graduate High School

Richard J. Barohn MD, Joshua Freeman MD, John Kissel MD, Marc Wallis, Jonathan Katz MD, Todd Levine MD, Dave Saperstein MD, Omar Jawdat MD, Joel Barohn MS, Erik R Ensrud MD, Kenneth Gorson MD, Laura Herbelin, Russel Swerdlow MD, Jeff Burns MD, Gretchen Ayer, Karen Easton, Carlayne Jackson MD, Richard Dubinsky MD, Sonya Fabricius, Aziz Shaibani MD, Tahseen Mozafar MD, Gil Wolfe, Walter Anderson, Ted Burns MD, Jeffery Statland MD, Mamatha Pasnoor MD, Mazen Dimachkie MD, Anthony Amato MD

In 2016 when two close friends and one of my cousins all had children ready to be Bar or Bat mitzvahed, I had to think of gifts. Bar Mitzvah is for boys and Bat Mitzvah is for girls. Rather than a typical gift (check, cash) I decided to come up with a list of books they should consider reading before they graduated high school, and I was also planning to give them a book bag containing most or all of them on the list. The original goal was to come up with 13 books to correspond to the age 13 at which Jewish boys at least go through the Bar Mitzvah ceremony. Girls go through the rite of passage at age 12 or 13, depending on their tradition. I began to email many of my friends to try to get some consensus on such a list. That was not as easy as I thought- many different views on this! My starting point was that we would not have a book on the list that they probably would've been assigned to read as required reading during junior high and high school. This also was not as easy as I thought as all my friends had graduated high school either 20 to 40 years ago and what we were required to read then has changed, or so it seems. I had my son Joel, as the closest to high school, weigh in as well to give us a current reality base. So, over a period of weeks and many email exchanges we came up with "the list of books you should read before you graduate high school." I was able to get the first thirteen in paperback for each Bar or Bat Mitzvah and I can say that each teenager that we gave the book bag to thought it was a great and unique gift and so did their parents. The book bag included both lists of 13 books, so they had the list of the next 13 to try to find as well. How many of these they read, I don't know. But one of the dads would tell me he would see all the books laying around in different places and it looked like they were reading them...maybe.

Flush with this success, the original group of book list contributors decided to send in a short letter to the editor of the New York Times with a few lines of introduction and then the list of the 13 books. We saw it was received by the NYT but we never got a response. So it goes.

In 2019 another set of teenagers were up for Bar and Bat Mitzvah-same parents (prolific parents). I took out the original lists we did and they just did not look right even after all of the back and forth we went through at the time. I thought some of the books were too advanced for our current 13-year olds, and some may have in fact been on the edge of being a bit too explicit sexually. I was worried perhaps we were crossing the line in the eyes of some of the parents. One that comes to mind is Phillip Roth's *Goodbye Columbus.* Should we really be telling kids to read this in high school and would their parents approve? Or is this more of a book for college reading? And *Sophie's Choice* by William Styron was in the second 13 to read list. Again, should this have been a college book?

So, in May 2019 I resent the list to my colleagues and said I wanted to revise the list. Also, when we put together the first 13 books, they were mainly male authors. We did ultimately include several female authors (Eudora Welty, Virginia Wolfe, Flannery O'Connor, Sandra Cisneros) but we thought we should add more female authors. We also had very little diversity. What we ended up developing was a list of 20 male authors for fiction and 20 female authors for fiction: total of 40 fiction books. Then we also added 13 nonfiction books; 5 poetry books and a Shakespeare play. Then there was a lot of discussion on including foreign language (non-English) authors in translation- should we or shouldn't we? In the end I think we did limit the lists to authors writing in English. One exception is the nonfiction list in that we kept "The Way of Life" according to Laotzu, translated by Witter Bynner, an amazing translation of an essential book that is accessible to teenagers. All of these were supposed to be in addition to whatever books they were required to read in high school and we renamed the list as: Books to read before finishing high school from 13 to 17: The Bar/ Bat Mitzvah/ Sweet 16/ Quinceanera/ Confirmation reading list. Since the number of books had expanded, I gave each Bar/ Bat Mitzvah a book bag of about 6 books as well as the list of all the other books.

The following is the letter to the editor to the NYT we sent on October 27th, 2016 and the two lists of 13 (Table 1,2). It was in response to an article in the NYT on October 25th, 2016 that was titled "12 Books to Read in your 20s."

Letter to the Editor:

RE: *12 Books to Read in your 20s*, appearing on 111.nytimes.com on October 25th, 2016

Attachments: Letter to the Editor, Book list participants.

Must read book lists seem to be growing in popularity. I am frequently invited to Bar/Bat Mitzvahs, and instead of the usual gifts, I came up with an idea of presenting each young teenager with the 13 books they should read before high school graduation. They generated many suggestions with some cautions. We stayed away from children's books and those that are commonly read in college courses. We aimed for diversity and inclusion and chose the books we believed sill had "legs," providing a lasting impression in our adult years. A list is attached.

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List of Participants who created the 13 Books to Read Before Graduating High School and the next 13 Books to Read before Graduating High School:

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**Table 1.** 13 Sept 2016 Bar, Bat & B'nai Mitzvah Book List

13 Books to Read
Before Graduating High School That Are Not on the Required Reading Lists

(To be read in recommended order between ages 13-18)
According to Rick Barohn and Friends

1. *Siddhartha*
   Hermann Hesse
2. *The World's Religions*
   Houston Smith
3. *Franny and Zooey*
   J.D. Salinger
4. *Cat's Cradle*
   Kurt Vonnegut
5. *The House on Mango Street*
   Sandra Cisneros
6. *The Caine Mutiny*
   Herman Wouk
7. *Goodbye, Columbus: And Five Short Stories*
   Philip Roth
8. *A Good Man is Hard to Find: And Other Stories*
   Flannery O'Connor
9. *Thirteen Stories*
   Eudora Welty
10. *A Room of One's Own*
    Virginia Woolf
11. *The Great Gatsby*
    F. Scott Fitzgerald
12. *The Way of Life, According to Laotzu*
    Witter Bynner
13. *A Portrait of the Artist as a Young Man*
    James Joyce

**Table 2.** 13 Sept 2016 Bar, Bat & B'nai Mitzvah Book List

The Next 13 Books to Read
Before Graduating High School That Are Not on the Required Reading Lists
(To be read in recommended order)
According to Rick Barohn and Friends

1. *A Separate Peace*
   John Knowles
2. *The World According to Garp*
   John Irving
3. *Sophie's Choice*
   William Styron
4. *The Maltese Falcon*
   Dashiell Hammett
5. *The Big Sleep*
   Raymond Chandler
6. *The Bell Jar*
   Sylvia Plath
7. *Raise High the Roof Beam, Carpenters and Seymour: An Introduction*
   J. D. Salinger
8. *Walden Two*
   B. F. Skinner
9. *Dubliners*
   James Joyce
10. *The Story of Philosophy: The Lives and Opinions of the World's Greatest Philosophers*
    Will Durant
11. *The Hero with A Thousand Faces*
    Joseph Campbell
12. *On the Road*
    Jack Kerouac
13. *The Sun Also Rises*
    Ernest Hemingway

When we revised the list in May 2019 I enlisted additional input. All the individuals above participated and we added input from the following participants:

Aziz Shaibani MD, Tahseen Mozafar MD, Gil Wolfe, Walter Anderson, Ted Burns MD, Jeffery Statland MD, Mamatha Pasnoor MD, Mazen Dimachkie MD, Anthony Amato MD.

The following is the revised list:

**Table 3.** Fiction Books to Read Before Finishing High School Age 13-17: The Bar/ Bat Mitzvah/ Sweet 16/ Quinceanera/ Confirmation Reading List.

**Female Authors**

1. Muriel Spark- The Prime of Miss Jean Brodie
2. Virginia Woolf- Mrs. Dalloway
3. Sandy Cisneros- The House on Mango Street
4. Eudora Welty- Thirteen Stories
5. Flannery O' Connor- A Good Man is Hard to Find
6. Charlotte Bronte- Wuthering Heights
7. Emily Bronte- Jane Eyre
8. Jane Austen- Sense and Sensibility
9. George Eliot- The Mill on the Floss
10. JK Rowling- All Harry Potter if not read by age 13
11. Anna Sewell- Black Beauty
12. Daphne Du Maurier- Rebecca
13. Ursula K. Le Guin- The Left Hand of Darkness
14. Laura Esquivel- Like Water for Chocolate
15. Carson McCullers- The Member of the Wedding
16. Laura Ingalls Wilder- Little House on the Prairie series
17. Sylvia Plath- The Bell Jar
18. Toni Morrison- The Bluest Eye
19. Betty Smith- A Tree Grows in Brooklyn
20. Louisa May Alcott- Little Women

**Table 4.** Fiction Books to Read Before Finishing High School Age 13-17: The Bar/ Bat Mitzvah/ Sweet 16/ Quinceanera/ Confirmation Reading List.

**Male Authors**

1. CS Forester- Captain Horatio Hornblower trilogy
2. Charles Dickens- Pickwick Papers (assuming Great Expectations was required)
3. Mark Twain- Connecticut Yankee in King Arthur's Court (assuming Tom Sawyer and Huck Finn were required)
4. James Baldwin- Go Tell it On the Mountain
5. Kurt Vonnegut- Cat's Cradle and Slaughterhouse Five
6. J.D. Salinger- Franny and Zoey and The Catcher in the Rye
7. J.R.R. Tolkien- The Hobbit
8. Jack Kerouac- On the Road
9. Daniel Quinn- Ishmael
10. Aldous Huxley- Brave New World

11. George Orwell- 1984
12. Ernest Hemingway- The Short Stories of Ernest Hemingway or In Our Time (short stories)
13. Hermann Hesse- Siddhartha
14. Franz Kafka- The Metamorphosis
15. John Knowles- A Separate Peace
16. John Steinbeck- Of Mice and Men
17. RL Stevenson- Treasure Island
18. Ray Bradbury- Fahrenheit 451
19. AC Doyle- Begin reading all Holmes...start w/ A Study in Scarlet and The Red Headed League
20. Dashiel Hamlett- The Maltese Falcon

**Table 5. Nonfiction: The Bar 13**

1. Anne Frank- The Diary of A Young Girl
2. Hellen Keller- The Story of My Life
3. Virginia Woolf- A Room of One's Own
4. Houston Smith- The World's Religions
5. The Way of Life, According to Laotzu translated by Witter Bynner
6. Will Durant- Story of Philosophy
7. Henry David Thoreau- Walden
8. James Baldwin- Notes of a Native Son
9. Maya Angelou- I Know Why the Caged Bird Sings
10. Malcolm X- The Autobiography of Malcolm X
11. Elie Wiesel- Night
12. John F. Kennedy- Profiles in Courage
13. Barack Obama- Dreams from My Father: A Story of Race and Inheritance

**Table 6. Poetry**

1. T.S. Eliot- The Love Song of J. Alfred Prufrock
2. Emily Dickinson- Start reading all poems
3. Maya Angelou- On the Pulse of the Morning (read at Bill Clinton's inauguration)
4. John Keats- Ode to a Nightingale; Ode on a Grecian Urn
5. Robert Frost- A Boy's Will

**Table 7. Plays**

1. Shakespeare-Henry IV Part 1 (presuming Julius Caesar, Romeo and Juliet and Hamlet were required reading.)

After creating the above lists, I began making other lists:

- Books you need to read between the ages 8 to 12
- Books you need to read before graduating college (approximately 18 to 22)
- Books you need to read before 30
- Books you need to read before 40
- Books you need to read before 50
- Books you need to read before 60
- Books you need to read before 70
- Books you need to read before 80
- Books you need to read before 90

The largest list is in books to read before college and before 30. Here is when I began to insert all of the non-English writing authors that had come up in the teenage list. With each successive decade, I have fewer and fewer books in each category. The books to read by 90 is a bit short!

But over the last decade there have been a number of books called "books to read before you die" or some similar titles. Two of my favorites are: 1001 Books You Must Read Before You Die, written by more than 100 international critics, General Editor Peter Boxall, Universe Publishing, New York, NY 2015; and 1000 Books to Read Before you Die, A Life-Changing List by James Mustich, Workman Publishing Co, New York, NY, 2018. But I thought I would hone down a bit by going decade by decade and I did not refer to either of these published books as I made my lists.

In future "what's on your mind" columns I will provide some of these lists.

Rick and fellow list creators

# A Patient Activities of Daily Living Scale for Amyotrophic Lateral Sclerosis

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**Keywords:** *Amyotrophic Lateral Sclerosis, ALS, Activities of Daily Living, ADL, Scale, Neuromuscular, Outcome measures, Patient Reported Outcome, Pragmatic research*

## ABSTRACT

Background: Motor neuron disorders are rare, progressive neurodegenerative diseases which affect multiple domains of motor function. The ability to assess function from home using an electronic medical record (EMR) would facilitate pragmatic studies.

Objective: To develop a Patient Activity of Daily Living scale for Amyotrophic Lateral Sclerosis and other motor neuron disorders (PADL-ALS) to support large pragmatic trials.

Methods: The Greater Plains Collaborative Clinical Data Research Network (GPC) developed and tested the feasibility of using the PADL-ALS. We convened patient and caregiver focus groups and in-person meetings to recommend changes to the ALS Functional Rating Scale-Revised (ALSFRS-R), which clarified language and added questions about pseudobulbar affect, pain, and faith. Feasibility was determined by conducting a survey of participants identified using EMR-computable phenotypes and returned via patient-preferred modalities.

Results: Surveys were distributed to 1079 participants at nine GPC health systems. The survey response rate was 44.4% (range 12.9-57.66%): male to female ratio 1.56; 84% self-identified as a patient with ALS. Patient respondents used computers or tablets more frequently than caregivers responding on their behalf. The PADL-ALS correlated to clinic-performed ALSFRS-R within 4 weeks of survey completion (n=33, rho=0.93, Kansas only). The pseudobulbar affect question correlated to functional motor burden. Over 80% agreed to be contacted for future research opportunities.

Conclusion: We demonstrated the feasibility of determining functional burden with the PADL-ALS using an EMR-computable phenotype. Future directions include implementing the PADL-ALS to answer pragmatic questions about ALS care.

## Introduction

Amyotrophic Lateral Sclerosis (ALS) is the most common progressive motor neuron disease with an estimated US prevalence of 1:20,000 or 16,000 affected individuals in the US.(1) It is characterized by loss of motor function, including strength, swallowing, speech and breathing.(2) Median survival is approximately 2 years with early death or slowly progressive with survival > 5 years. (2) Other motor neuron diseases demonstrate variable progression and include: primary lateral sclerosis (PLS), a pure upper motor neuron variant, and progressive muscular atrophy (PMA), a pure lower motor neuron variant. The ability to gain real-world information on the effectiveness for medications for ALS is limited. This creates a standard of care gap, with unclear information about who will


Figure 1. the GPC Network is comprised of 12 midwestern academic institutions with the EMR connected. Children's Mercy was excluded as ALS patients are not seen there. Indiana University and University of Missouri joined the network after the survey was completed.

best benefit, and no information about utility for PLS or PMA. There is a validated patient reported functional measure used in clinical trials, the ALS Functional Rating Scale – Revised (ALSFRS-R) that was developed largely without patient input.(3,4) A patient-centric functional disease measure could improve existing disease altering or symptomatic therapies for motor neuron disorders.

The Greater Plains Collaborative (GPC) is a PCORI-funded Clinical Data Research Network (PCORnet) comprised of 12 midwestern health systems. (Figure 1).(5,6) The GPC used this opportunity to develop and test the feasibility of deploying a Patient Reported Activity of Daily Living Scale (PADL-ALS) for patients with motor neuron disease (ALS,PLS and PMA), created with patient input, and tested by identifying likely patients using EMR-computable phenotypes, and multiple modalities for completion.

## Methods

We used a multi-step process to create and test the feasibility of the PADL-ALS. We conducted virtual and in-person patient focus groups and meetings with key stakeholders during the development phase followed by a prospective de-identified patient survey in the feasibility phase conducted at nine US sites from 02/02/2015 through 01/10/2017. The survey study protocol was reviewed by the University of Kansas Medical Center Central IRB, and consent or assent was obtained from all survey participants.

PADL-ALS development. We convened a patient and caregiver focus group (5 patients, and 2 caregivers) via telephone; interviews were facilitated by the KUMC GPC community engagement officer; and she wrote a summative report. The facilitator and KUMC research team explained that the goal was to create afunctional outcome measure deemed valuable from both the clinician and patient/care giver perspectives to be used in future comparative effectiveness studies in ALS. During this first meeting, patients stated their desire for a simple method to communicate their health functional status and areas of concern to their health care providers. The ALSFRS-R is widely used in both ALS Association and Muscular Dystrophy Association multidisciplinary ALS care clinics, so patients and their caregivers were familiar with the ALSFRS-R. Participants in the focus group believed that the ALSFRS-R was a good starting point. They expressed interest in a form that they could fill out on their own, from home, preferably on a tablet, and send to their health care provider. They offered that it would be beneficial if they could complete the survey and provide a functional status update either prior to their next appointment, or to complete over time so that they could track their condition from home. They recommended several changes to the current ALSFRS-R. First, patients requested clarification and simplification of medical terminology in the existing ALSFRS-R. Patients suggested the addition of questions on pain and concerning bouts of laughter or crying (pseudobulbar affect). The focus group recommendations were incorporated into the existing ALSFRS-R, and two additional questions were added following the ALSFRS-R question template, where 4=unaffected, and 0=severe impairment interfering with daily function (Table 1 and Figure 2).

Following the focus group, an in-person meeting was held at the annual GPC meeting in Kansas City, KS in August 2014, and included healthcare providers representing each GPC site, a group of patients and caregivers not previously

Table 1. Changes to the ALSFRS-R.

| |
|---|
| Modify the instructions |
| •ALSFRS-R – 'We are comparing how you are today to before the start of the disease' |
| TO |
| •PADL-ALS – ' Please think about how your are doing on an average day over the past month or so (and this includes your routine use of therapies, devices, medications, etc.) when answering these questions. Please choose only 1 answer. |
| Changed the wording/more information on some questions |
| •Handwriting – added (with the hand you normally write with) |
| •Added (can include zipper pulls, button fasteners, sitting instead of standing) to the intermittent assistance or substitute methods in Dressing & Hygiene |
| •Adjusting sheets instead of bedclothes |
| Discussed whether to complete online or paper |
| •Most of the group wanted to complete online |

Figure 2. Additional questions.

**13. Pain**
4 No pain
3 Some pain, but does not limit my activities
2 Pain that minimally limits my activities
1 Pain that moderately limits my activities
0 Severe pain that limits what I can do

**14. Crying or laughing uncontrollably**
4 No problems
3 Sometimes, but it doesn't interfere with my daily activities
2 Yes, and this causes some minor limits on my activities outside of my home
1 Yes, and this moderately limits my activities outside of my home
0 Yes and I am unable to control it and it severely limits my activities outside of my home

**15. For some people, their religious or spiritual beliefs act as a source of comfort and strength in dealing with life's ups and downs; is this true for you?**
4 This is very true for me
3 This is usually true for me
2 It depends – sometimes this is true and sometimes not
1 This is usually not true for me
0 This is not at all true for me

engaged in the study, and patient advocacy representatives. At that meeting, the revised version of the ALSFRS-R with additional questions was reviewed, and additional recommendations were made. The GPC meeting group endorsed the focus group recommended changes, and requested adding three additional domains of interest that include a non-denominational question regarding faith, questions about participating in future research, and possible future research directions to the survey. The final survey, now called the PADL-ALS to reflect the patient input in its design, also includes questions about demographics, about type of motor neuron disease, and disease characteristics (i.e. symptom onset, diagnosis, current medications). (Appendix 1)

PADL-ALS survey. Survey participants were identified using a multi-step process which included identification of patient lists using an EMR-computable phenotype; followed by local ALS study team review of patient lists. The EMR computable phenotype included the following searchable parameters: 1) motor neuron disease diagnostic codes (ICD9 codes: 335.20, 335.29, and 335.24), 2) living, 3) >1 encounter with the motor neuron disease diagnostic code; and 4) seen within the last 2 years. Motor neuron disorders have the benefit of specific ICD9 or ICD10 codes, and the fact virtually all patients are followed in multi-disciplinary clinics due to the nature of the disease. A search of the nine connected EMRs was performed using i2b2 queries. (7,8) Each site received an electronic list with the names and address of the patients that met those criteria which could be edited using a REDCap(9) database. The initial number per site identified using the EMR-computable phenotype, and the number retained after local review is presented in Table 2. The survey was distributed using a variety of techniques depending on site capabilities which included: invitation letters sent through EMR patient portals; invitations sent via the US postal service mail; and in-person recruitment during ALS clinic visits. Six weeks after the initial survey distribution, individuals who had not responded were contacted with a second invitation, and 2 weeks later with a phone call by their care site.

Statistical considerations. A goal of the GPC network survey was to provide proof of concept that the network can accurately identify and recruit patients; therefore, response rate to the survey was the primary study outcome. The PCORI defined goal for survey response was 50%. Response rate was determined as: 100 X (Number replied either yes or no to complete the survey) / (Number sent – Number deceased or "other"). "Other" included participants who could not be contacted (moved, disconnected phone, etc). Descriptive statistics were used to describe the overall ALS clinic cohort including demographics (age, sex, race, ethnicity, living situation, occupation, years of education) and functional burden as identified by survey response (clinical diagnosis, and functional status). Responders as a group (GPC overall) and by participating site were compared to published regional and national ALS demographics to identify any differences in GPC responder characteristics. (1) The PADL-ALS questions 1-12 overlap by content to the ALSFRS-R, so were used to assess functional burden. Comparison between the PADL-ALS Q1-12 and in-person clinic performed ALSFRS-R between research staff at the University of Kansas Medical Center ALS clinic and patient within 4 weeks of survey response was done using Spearman correlation. All statistical testing was two-sided, and 0.05 was the cut off for level of significance. Analysis was performed using SAS 9.3 (Greensboro, NC).

## Results

The initial EMR-computable phenotype identified 1800 possible motor neuron disease participants seen in the last 2 years across the GPC network of sites (Table 2).

After review by local ALS clinic site personnel, 1079 were determined to be active motor neuron participants seen in clinic, or 61% (range 19-100%). The total number sent out was then adjusted based on whether the participant was still living, and maintained an active contact information in the EMR to 972 (or 90.1%). The response rate for the survey was 44.4% overall, and varied by site (19-58%, Table 3).

The majority of participants self-identified as ALS (83%), and the median age of responders was 66.5 years (25% quartile [Q1] 53, 75% quartile [Q3] 73, Table 3). When comparing survey respondents to demographics in the CDC ALS registry, our respondents were on average older, and more frequently non-Hispanic white. The median symptom duration was consistent with other large

Table 2. Number of participants identified using the EMR computable phenotype, and the % retained after local ALS clinic staff review.

| Site | # identified | % retained after site review | # sent out |
|---|---|---|---|
| KUMC | 361 | 72 | 260 |
| Iowa | 88 | 82 | 72 |
| MCW | 163 | 100 | 163 |
| UMN | 237 | 24 | 57 |
| UTHSCSA | 267 | 63 | 168 |
| UNMC | 78 | 89 | 69 |
| UTSWMC | 271 | 80 | 217 |
| Marshfield | 89 | 29 | 26 |
| Wisconsin | 246 | 19 | 47 |
| Total | 1800 | 62 | 1079 |

Table 3. Response rate by site.

| Site | Num sent | Numerator* | Completed | Refused | Denominator* | Deceased | Other | Response Rate (%)* |
|---|---|---|---|---|---|---|---|---|
| KUMC | 265 | 128 | 106 | 22 | 222 | 22 | 21 | 57.66 |
| Iowa | 72 | 8 | 6 | 2 | 62 | 7 | 3 | 12.90 |
| MCW | 163 | 87 | 74 | 13 | 153 | 10 | 0 | 56.86 |
| UMN | 58 | 26 | 26 | - | 58 | - | - | 44.83 |
| UNMC | 69 | 35 | 32 | 3 | 69 | 0 | 0 | 50.72 |
| UTHSCSA | 167 | 73 | 71 | 2 | 132 | 3 | 32 | 55.30 |
| UTSWMC | 213 | 58 | 51 | 7 | 210 | 3 | 0 | 27.62 |
| Marshfield | 26 | 9 | 8 | 1 | 24 | 1 | 1 | 37.50 |
| Wisconsin | 46 | 8 | 8 | - | 42 | 4 | - | 19.05 |
| TOTAL | 1079 | 432 | 382 | 50 | 972 | 50 | 57 | 44.44 |

*Response rate = numerator (number responded + number refused)/denominator (number sent – [deceased+other]). KUMC = Kansas University Medical Center; MCW = Medical College of Num = number; Wisconsin; UMN = University of Minnesota; UNMC = University of Nebraska Medical Center; UTHSCSA = University of Texas Health Center – San Antonio; UTSWMC = University of Texas Southwestern Medical Center.

motor neuron disease cohorts, with ALS around 2 years, and PLS 8 years. Figure 4 shows how the questionnaire was completed, and the method used: 68.3% of surveys were completed by patients who typically used a computer or tablet more frequently (49% of the time) compared to surveys completed by caregivers on behalf of the patients, who preferred paper (64% of the time, Figure 3).

Evaluating the PADL-ALS questions that correspond to the ALSFRS-R (PADL-ALS Q1-12, Table 4) one can see a breakdown of functional burden that matches the motor neuron disease subtype, with ALS most severely affected (PADL-ALS Q1-12 median 29) and with a broader range (Q1, Q3 21, 38), than PLS or PMA. For a subgroup of respondents at the University of Kansas Medical Center we compared the PADL-ALS Q1-12 to in-person clinic evaluator assessed ALSFRS-R obtained within 4 weeks of the survey response date: and the PADL-ALS and ALSFRS-R questions were correlated (n=33, Spearman's rho=0.93, Figure 4).

Pain did not show any correlation to the PADL-ALS Q1-12, even though > 50% of respondents reported pain, and 23.8% reported pain impacting their daily life (Table 5).

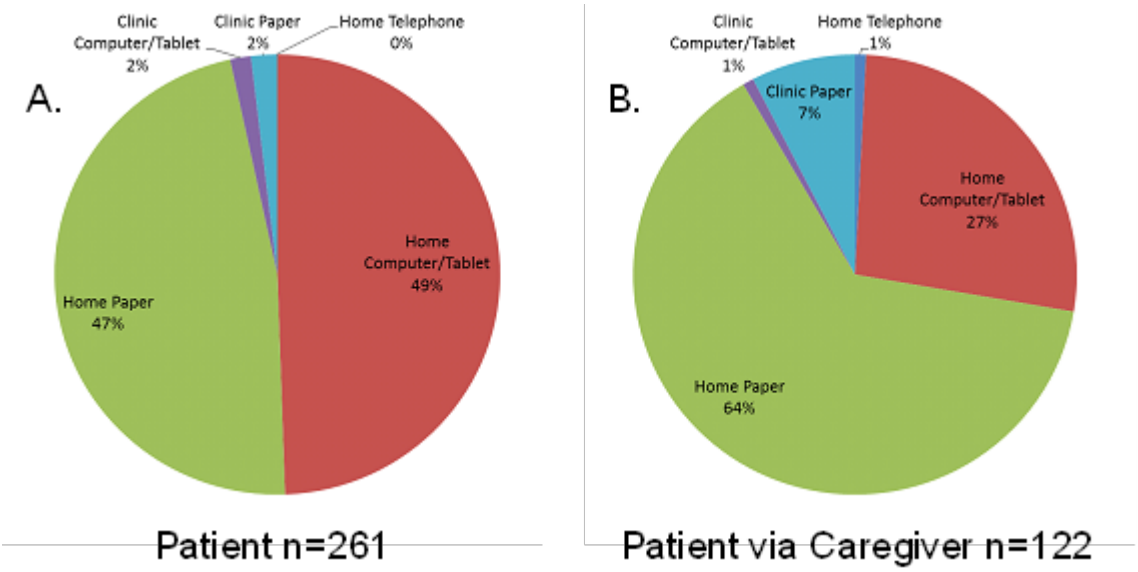



Figure 3. Preferred modality for completing survey for patient completed surveys (A), and for surveys completed with the assistance of a caregiver (B). Patients were more likely to use a home computer or tablet.

Table 3. Survey respondent characteristics.

| | ALS | PLS | PMA | Other | Total | CDC ALS Registry |
|---|---|---|---|---|---|---|
| **n** | 317 | 40 | 7 | 18 | 382 | 12187 |
| **M:F** | 1.6 | 1.5 | 1.3 | 0.9 | 1.5 | 1.45 |
| **Age (%)** | | | | | | |
| **18-39** | 6 (1.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (1.6) | 186 (9.7) |
| **40-49** | 22 (6.9) | 1 (2.5) | 0 (0.0) | 0 (0.0) | 23 (6.0) | 396 (20.6) |
| **50-59** | 66 (20.8) | 9 (22.5) | 0 (0.0) | 4 (22.2) | 79 (20.7) | 616 (32.0) |
| **60-69** | 109 (34.4) | 13 (32.5) | 3 (42.9) | 1 (5.6) | 126 (33.0) | 457 (23.7) |
| **70-79** | 94 (29.7) | 13 (32.5) | 3 (42.9) | 8 (44.4) | 118 (30.9) | 152 (7.9) |
| **>80** | 20 (6.3) | 4 (10.0) | 1 (14.3) | 3 (16.7) | 28 (7.3) | 27 (1.4) |
| **Median Sx Dur (Q1, Q3)** | 2 (1,5) | 8 (5, 13) | 4 (0, 6) | 3 (1, 15) | 3 (1, 6) | - |
| **Median PADL-ALS Q1-12 (Q1, Q3)** | 29 (21, 38) | 37 (30, 40) | 27 (25, 35) | 35 (27, 39) | 30 (22, 38) | |
| **Race (%)** | | | | | | |
| **White** | 284 (89.6) | 32 (80.0) | 6 (85.7) | 16 (88.9) | 338 (88.5) | 9638 (79.1) |
| **Black** | 7 (2.2) | 3 (7.5) | 0 (0.0) | 0 (0.0) | 10 (2.6) | 798 (6.5) |
| **Other** | 6 (1.9) | 2 (5.0) | 0 (0.0) | 0 (0.0) | 8 (2.1) | 535 (4.4) |
| **Unknown** | 20 (6.3) | 3 (7.5) | 1 (14.3) | 2 (11.1) | 26 (6.8) | 1216 (10.0) |

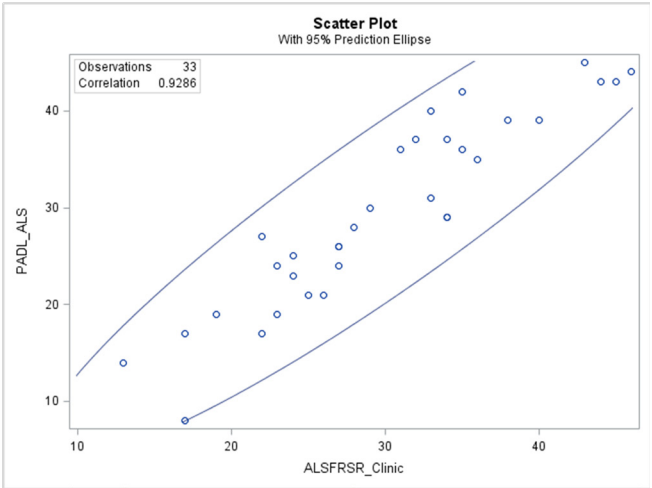
ALS = amyotrophic lateral sclerosis; PLS = primary lateral sclerosis; PMA = progressive muscular atrophy; CDC = Center for Diseases Control; n = number; M = male; F = female; Sx = symptom; Dur = duration;

Fewer patients reported crying or laughing uncontrollably, but this symptom showed a moderate correlation to the PADL-ALS Q1-12 (Spearman's rho=0.35, $p<0.001$). For the non-denominational question about faith, over 50% of respondents indicated that religion or spiritual beliefs act as a source of comfort, however responses were not correlated to functional burden as measured in the PADL-ALS Q1-12.

Survey respondents were asked how interested they would be in participating in future research, and eight in ten (82%) indicated interest in hearing about future research. To prepare for possible pragmatic studies in ALS, we asked what direction they would like to see research take beyond the testing of investigational drugs. The highest percentage of respondents indicated interest in studies that address diet (49.2%) or use of vitamins or supplements (61.8%, Supplemental table e-2).

## Discussion

We used a multi-step process to develop a patient-oriented activity of daily living scale for pragmatic studies in ALS. We developed a survey to demonstrate the feasibility of using EMR-computable phenotypes to identify patients, and ease of using those identified to conduct a survey on patient-preferred content and response modalities. After review, 61% of the EMR-computable phenotype identified candidates were confirmed as ALS patients and considered appropriate to receive the survey. The survey response rate was 44%, just below the PCORI-identified target, but ranged from 19-58% among the nine sites involved in the study. Patient respondents were more likely to use and prefer electronic response format. This study shows that




Supplemental Figure e-2. Relationship of PADL-ALS Q1-12 to clinic performed ALSFRS-R.

Table 5: Additional symptom and research questions.

| Question | Freq (%) |
|---|---|
| **Pain** | |
| No pain | 166 (43.8%) |
| Some pain, but does not limit my activities | 123 (32.5%) |
| Pain that minimally limits my activities | 45 (11.9%) |
| Pain that moderately limits my activities | 33 (8.7%) |
| Severe pain that limits what I can do | 12 (3.2%) |
| **Crying or laughing uncontrollably** | |
| No problems | 242 (63.9%) |
| Sometimes, but it doesn't interfere with my daily activities | 107 (28.2%) |
| Yes, and this causes some minor limits on my activities outside of my home | 20 (5.3%) |
| Yes, and this moderately limits my activities outside of my home | 8 (2.1%) |
| Yes and I am unable to control it and it severely limits my activities outside of my home | 2 (0.5%) |
| **For some people, their religious or spiritual beliefs act as a source of comfort or strength in dealing with life's ups and downs; is this true for you?** | |
| This is very true for me | 172 (45.3%) |
| This is usually true for me | 76 (20%) |
| It depends - sometimes this is true and sometimes not | 63 (16.6%) |
| This is usually not true for me | 31 (8.2%) |
| This is not at all true for me | 38 (10%) |
| **Would you be willing to be contacted about opportunities to take part in our ALS Specialty Clinics medical research?** | |
| Yes! Please count me in! | 192 (51.4%) |
| Please ask me about a specific research project, and then I'll decide | 114 (30.6%) |
| No, I'm not able to at this time | 67 (18%) |
| **In addition to brand new experimental treatments for ALS, it is also important that we study how to best use currently available treatments. Which of the following clinical research questions would you be interested in knowing the answer to? (check all that apply)** | |
| Is there a benefit to combining drug therapies in ALS? | 170 (40.5%) |
| Are there vitamin combinations/herbal supplements which can slow down ALS? | 236 (61.8%) |
| Does starting BiPAP earlier provide any benefit in ALS? | 101 (26.4%) |
| Do special diets have any role in treatment of ALS? | 188 (49.2%) |
| What is the best way to treat throat spasms that lead to choking or coughing? | 129 (33.8%) |

using a computable phenotype and remote or "low touch" strategies to recruit survey participants with ALS can yield substantial engagement. Furthermore, respondents shared enthusiasm for being contacted about future research opportunities (82%).

This was the first attempt to utilize the Greater Plains Collaborative network of connected EMRs to and REDCap to store data, and to try to utilize this network to identify and carry out an ALS research study.(8, 9) The EMR identified 1800 potential subjects that met the criteria for the survey, and 1079 individuals were deemed eligible to receive a survey (range 19 -100%). There are many considerations when using an EMR-computable phenotype for recruitment in ALS studies. While lists can be filtered using Social Security death index,(10) there will still be individuals who may be deceased on the captured lists. Patients need to have up-to-date contact information or they cannot be contacted effectively. Different EMRs may have different mechanisms for tying encounters to diagnosis codes, and individual clinics may have different customs for using the diagnosis codes for ALS and related disorders. This variability introduces challenges to making sure all eligible individuals who meet the computable phenotype are recognized. While the broad implementation of EMRs was supposed to reduce the rate of misdiagnosis in medical records, this remains an important problem especially when electronically approaching patients regarding a terminal illness such as ALS.(11) Some of the names on the computable phenotype list were not known to the physician and since this disease usually requires specialized care, the physician did not feel comfortable sending out the survey to unknown individuals. Furthermore, the physician and/or nurse may make the decision to not involve the patient if they believe that the patient is too ill or that it would be too difficult for the patients to respond. Despite these reservations, EMR-developed lists have a real possibility to mechanize and simplify the recruitment process, as additional search terms could be added, including age, gender, lab values, etc. to further refine the resulting registry.

The study participant population was older than comparable demographics from the CDC ALS registry. (1) This likely reflects issues related to our Midwestern locations, and a type of survival bias in clinic, where approximately 50% or patients will be dying within 2 years, leaving older survivors over-represented in clinics. Additional issues related to EMR data is similar to issues when evaluating registries: data is limited to what is collected at the time of the clinical visits; data quality suffers from incomplete or missing data; and there may be referral bias regarding who is referred to the academic medical centers. (12) Our population was more racially homogeneous than populations in the CDC ALS registry, again likely due to regional differences, but also may reflect the same bias that is seen in referrals to clinical trials where patients from underrepresented populations are less likely to be referred to clinical trials.(13)

The response rate was just below the PCORI set target of 50%, and did not appear to depend on the method of survey distribution. All but one site mailed out the questionnaire to their patients. One site used the EMR patient portal to communicate with their patients, and that site had a 28% response. The sites that had the better responses used a more personal approach, including mail and phone calls. We did have problems with consenting patients at one site, where survey response did not automatically get tied to the electronic consent. This reduced their response rate to 12% (University of Iowa). During the initial patient meetings, patients wanted the ability to answer surveys online. While indeed computer or tablets were the most frequent patient-preferred response modality, still less than 50% of the patients answered online.

The PADL-ALS had high correlation to in-person administered ALSFRS-R for the overlapping questions, similar to reports for self-administered versions of the ALSFRS-R,(14) and could distinguish between motor neuron disease subtypes based on functional burden. Of the added questions, the pseudobulbar affect question had the strongest correlation to the PADL-ALS questions 1-12, or the functional burden questions, and raises the possibility that by adding it we may increase the sensitivity of the PADL-ALS to disease progression. Pain likely represents an important question to follow in interventional studies, but it is disconnected from disease progression, and represents multi-factorial causes. The non-denominational question about faith does not strictly track with disease progression – for example it does not appear true that progression of motor neuron disease favors either gain or loss of faith. This question more likely would have utility at the individual respondent level, where a change in answer may trigger questions about the patient's well-being.

Limitations to the study include the Midwestern locations and the possible referral bias of the academic centers. ALS and motor neuron disorders more than other diseases tend to be followed in accredited multi-disciplinary clinics, making it more likely a patient will be seen at least once in these clinics. However, the nature of the disease to progress can limit respondents to those less severely affected or individuals with slower progression. The search criteria itself is limited by the physician properly coding the patient with a diagnosis in the EMR. Our search criteria limiting to the last two years might have excluded patients who either lived in a more rural location, so could not make

frequent clinic visits, or patients who came to the academic center for diagnosis, but then were followed at local clinics.

Here we show the first effort to use the PCORI-funded GPC Research Network to use EMR-computable phenotypes to identify patients with ALS and other motor neuron disorders, then reach out to them with a survey. We show the feasibility of using a patient-informed revision of the ALSFRS-R, called the PADL-ALS, to track patient function, and query about future research directions. The responses to the survey set the stage for pragmatic studies exploring the patient-identified topics of interest, including the effects of diet or use of supplements on disease progression in ALS and other motor neuron disorders.

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Appendix 1: PADL-ALS Survey.

| | |
|---|---|
| Today's Date: (day/month/year) _ _ / _ _ / _ _ _ _ | |
| How did you complete this survey?<br>Please check one box | ☐ In clinic using a paper form<br>☐ At home using a paper form<br>☐ In clinic using a computer or tablet<br>☐ At home using a computer or tablet<br>☐ At home by telephone (administered by clinic staff) |
| Who is completing the survey?<br>Please check one box | ☐ Patient<br>☐ Patient via Caregiver |

| | |
|---|---|
| What diagnosis did your doctor tell you that you have? | ☐ ALS (Amyotrophic Lateral Sclerosis)<br>☐ PLS (Primary Lateral Sclerosis)<br>☐ PMA (Progressive Muscular Atrophy)<br>☐ I do not know my diagnosis<br>☐ Other (please enter):<br>_____ |
| Would you be willing to be contacted about opportunities to take part in our ALS Specialty Clinics medical research? We are not keeping your name at this time, we are just asking the number of possible future participants. | ☐ Yes! Please count me in!<br>☐ No, I'm not able to at this time<br>☐ Please ask me about a specific research project, and then I'll decide |
| When were you given your diagnosis, if known? (month and year) | _ _ / _ _ _ _ |
| When did your symptoms / weakness start? (month and year; we understand that this might be a "best guess" or estimate) | _ _ / _ _ _ _ |

In what region(s) of your body did the **first** symptoms of ALS begin? (please be as specific as possible)

| Area | Right Side | Left Side |
|---|---|---|
| Hand | ☐ | ☐ |
| Foot | ☐ | ☐ |
| Arm | ☐ | ☐ |
| Leg | ☐ | ☐ |
| Swallowing ☐ | | |
| Speech ☐ | | |
| Breathing ☐ | | |
| Other? (please write in): _____ | | |

Appendix 1: PADL-ALS Survey.

**DIRECTIONS for the following questions:**
Please think about how you are doing *on an average day* over the past month or so (and this includes your routine use of therapies, devices, medications, etc.) when answering these questions. Total score at end.

**1. Speech**

☐ 4 Normal speech processes
☐ 3 Detectable speech with disturbances
☐ 2 Intelligible with repeating
☐ 1 Speech combined with non-vocal communication
☐ 0 Loss of useful speech

**2. Salivation**

☐ 4 Normal
☐ 3 Slight, but definite excess of saliva in mouth; may have nighttime drooling
☐ 2 Moderately excessive saliva; may have minimal drooling
☐ 1 Marked excess of saliva with some drooling
☐ 0 Marked drooling; requires constant tissue or handkerchief

**3. Swallowing**

☐ 4 Normal eating habits
☐ 3 Early eating problems – occasional choking
☐ 2 Dietary consistency changes
☐ 1 Needs supplemental tube feeding
☐ 0 Feeding tube only

**4. Handwriting (with the hand you normally write with)**

☐ 4 Normal
☐ 3 Slow or sloppy; all words are legible
☐ 2 Not all words are legible
☐ 1 Able to grip pen but unable to write
☐ 0 Unable to grip pen

5. Please answer question 5a if you do not have a feeding tube or if you require the use of a feeding tube for 50% or LESS of your nutritional needs.

**5a. Cutting food and handling utensils**

☐ 4 Normal
☐ 3 Somewhat slow and clumsy, but no help needed
☐ 2 Can cut most foods, although clumsy and slow; some help needed
☐ 1 Food must be cut by someone, but can still feed slowly
☐ 0 Needs to be fed

 

Appendix 1: PADL-ALS Survey.

Please answer question 5b if you always use a feeding tube OR if you have a feeding tube and use it MORE than 50% of the time for your nutritional needs.

**5b. Cutting food and/or handling feeding tube closures, cans or utensils**

☐ 4 Normal
☐ 3 Clumsy, but able to perform all manipulations independently
☐ 2 Some help needed with closures and fasteners
☐ 1 Provides minimal assistance to caregivers
☐ 0 Unable to perform any aspect of task

**6. Dressing and hygiene**

☐ 4 Normal function
☐ 3 Independent and complete self-care with effort or decreased efficiency
☐ 2 Intermittent assistance or substitute methods (can include zipper pulls, button fasteners, sitting instead of standing)
☐ 1 Need attendant for self-care
☐ 0 Total dependence

**7. Turning in bed and adjusting sheets**

☐ 4 Normal
☐ 3 Somewhat slow and clumsy, but no help needed
☐ 2 Can turn alone or adjust sheets, but with great difficulty
☐ 1 Can initiate, but not turn or adjust sheets alone
☐ 0 Helpless

**8. Walking**

☐ 4 Normal
☐ 3 Early ambulation difficulties
☐ 2 Walks with assistance (includes holding on to someone's arm)
☐ 1 Non-ambulatory functional movement only
☐ 0 No purposeful leg movement

**9. Climbing stairs**

☐ 4 Normal
☐ 3 Slow
☐ 2 Mild unsteadiness or fatigue
☐ 1 Needs assistance
☐ 0 Cannot do

 

Appendix 1: PADL-ALS Survey.

**10. Shortness of breath (Dyspnea)**

☐ 4 None
☐ 3 Occurs when walking
☐ 2 Occurs with one or more of the following: eating, bathing, dressing
☐ 1 Occurs at rest, difficulty breathing when either sitting or lying
☐ 0 Significant difficulty, considering using mechanical respiratory support

**11. Trouble breathing while lying down (Orthopnea)**

☐ 4 None
☐ 3 Some difficulty sleeping at night due to shortness of breath; does not routinely use extra pillow(s)
☐ 2 Need extra pillow(s) in order to sleep (at least one pillow more than usual)
☐ 1 Can only sleep sitting up
☐ 0 Unable to sleep

**12. Breathing Assistance/Respiratory Insufficiency** (Note: A BiPAP is a machine that changes the pressure as per the breathing pattern; a CPAP is a machine that delivers air pressure at a single level. Both machines make it easier to breathe.)

☐ 4 None
☐ 3 Intermittent use of BiPAP or CPAP
☐ 2 Continuous use of BiPAP or CPAP during the night
☐ 1 Continuous use of BiPAP or CPAP during the night and day
☐ 0 Invasive mechanical ventilation by intubation or tracheostomy or noninvasive mechanical ventilation

**13. Pain**

☐ 4 No pain
☐ 3 Some pain, but does not limit my activities
☐ 2 Pain that minimally limits my activities
☐ 1 Pain that moderately limits my activities
☐ 0 Severe pain that limits what I can do

**14. Crying or laughing uncontrollably**

☐ 4 No problems
☐ 3 Sometimes, but it doesn't interfere with my daily activities
☐ 2 Yes, and this causes some minor limits on my activities outside of my home
☐ 1 Yes, and this moderately limits my activities outside of my home
☐ 0 Yes and I am unable to control it and it severely limits my activities outside of my home

**15. For some people, their religious or spiritual beliefs act as a source of comfort and strength in dealing with life's ups and downs; is this true for you?**

☐ 4 This is very true for me
☐ 3 This is usually true for me
☐ 2 It depends – sometimes this is true and sometimes not
☐ 1 This is usually not true for me
☐ 0 This is not at all true for me

**16. In addition to brand new experimental treatments for ALS, it is also important that we study how to *best use currently available* treatments. Which of the following clinical research questions would you be interested in knowing the answer to? (check all that apply)**

☐ Is there a benefit to combining drug therapies in ALS? (For example, testing if combining two currently available drugs with riluzole benefits patients)
☐ Are there vitamin combinations/herbal supplements which can slow down ALS?
☐ Does starting BiPAP earlier provide any benefit in ALS?
☐ Do special diets have any role in treatment of ALS?
☐ What is the best way to treat throat spasms that lead to choking or coughing?
☐ Do you have an idea for research that you would like to share? Please write in below

_____

_____

**17. Is there something you'd like to share that we have not asked about? Please use this space to tell us! Please do not enter any information in this area that we would be able to identify you. This includes name, date of birth, location.**

_____

_____

_____

_____

**THANK YOU VERY MUCH FOR COMPLETING THE SURVEY!**

**Total Score for Items 1- 15 above: _____**

Appendix 2: Co-investigators, collaborators and co-authors*

| Name | Location | Role | Contribution |
|---|---|---|---|
| Tiffany Robinson | University of Kansas Medical Center, Kansas | Regulatory Project Manager | IRB submissions, gather regulatory documents |
| Tamara McMahon | University of Kansas Medical Center, Kansas | Honest Broker | Designed the database |
| Carlayne Jackson, MD | University of Texas Health Science Center, San Antonio | Site Investigator | Role in the acquisition of data |
| Pam Kittrell, RN | University of Texas Health Science Center, San Antonio | Study Coordinator | Role in the acquisition of data |
| Alfredo Tirado-Ramos, PhD | University of Texas Health Science Center, San Antonio | GPC PI | Supported this study through their GPC |
| Angela Bos | University of Texas Health Science Center, San Antonio | Honest Broker | Ran queries to recruit patients |
| Jaya Trivedi, MD | University of Texas Southwestern Medical Center, Dallas | Site Investigator | Role in the acquisition of data |
| Sharon Nations, MD | University of Texas Southwestern Medical Center, Dallas | Co-Investigator | Role in the acquisition of data |
| Lindsay Cowell, PhD – GPC PI | University of Texas Southwestern Medical Center, Dallas | GPC PI | Supported this study through their GPC |
| J. Americo Fernandes, MD | University of Nebraska Medical Center, Omaha | Site Investigator | Role in the acquisition of data |
| Jim McClay, MD | University of Nebraska Medical Center, Omaha | GPC PI/Honest Broker | Supported this study through their GPC; Ran queries to recruit patients |
| Deborah Heimes | University of Nebraska Medical Center, Omaha | Study Coordinator | Role in acquisition of data |
| Lisa Houdesheldt | University of Nebraska Medical Center, Omaha | Study Coordinator | Role in acquisition of data |
| Andrea Swenson, MD | University of Iowa Hospitals & Clinics, Iowa City | Site Investigator | Role in acquisition of data |
| Gary Rosenthal, MD | University of Iowa Hospitals & Clinics, Iowa City | GPC PI | Supported this study through their GPC |
| Jeri Sieren | University of Iowa Hospitals & Clinics, Iowa City | Study Coordinator | Role in acquisition of data |
| Prakash Nadkarni | University of Iowa Hospitals & Clinics, Iowa City | Honest Broker | Ran queries to recruit patients |
| David Walk, MD | University of Minnesota, Minneapolis | Site Investigator | Role in acquisition of data |
| Connie Delaney, PhD | University of Minnesota, Minneapolis | GPC PI | Supported this study through their GPC |
| Michelle Coady | University of Minnesota, Minneapolis | GPC Study Coordinator | Supported the site coordinator |
| Deborah Schiltz | University of Minnesota, Minneapolis | Study Coordinator | Role in acquisition of data |
| Supreet Kathpalia, MS | University of Minnesota, Minneapolis | Honest Broker | Ran queries to recruit patients |
| Andrew Waclawik, MD | University of Wisconsin, Madison | Site Investigator | Role in acquisition of data |
| Marc Drezner, MD | University of Wisconsin, Madison | GPC PI | Supported this study through their GPC |
| Andrea Maser, MS | University of Wisconsin, Madison | Study Coordinator | Role in acquisition of data |
| Eneida Mendonca, MD, PhD | University of Wisconsin, Madison | Primary Honest Broker | Ran queries to recruit patients |
| Tom Mish, BCG/SMPH | University of Wisconsin, Madison | Secondary Honest Broker | Ran queries to recruit patients |
| Paul Barkhaus, MD | Medical College of Wisconsin, Milwaukee | Site Investigator | Role in acquisition of data |
| Bradley Taylor, PhD | Medical College of Wisconsin, Milwaukee | GPC PI | Supported this study through their GPC |
| Jo Berghotle | Medical College of Wisconsin, Milwaukee | Study Coordinator | Role in acquisition of data |
| Lynn Wheeler | Medical College of Wisconsin, Milwaukee | Study Coordinator | Role in acquisition of data |

Appendix 1: Co-investigators, collaborators, and co-authors*

| Name | Location | Role | Contribution |
|---|---|---|---|
| Sabrina Uppal | Medical College of Wisconsin, Milwaukee | Study Coordinator | Role in acquisition of data |
| Glenn Bushee | Medical College of Wisconsin, Milwaukee | Honest Broker | Ran queries to recruit patients |
| Kathy Williams | Medical College of Wisconsin, Milwaukee | Honest Broker | Ran queries to recruit patients |
| Jamie Boero, MD | Marshfield Clinic, Marshfield | Site Investigator | Role in acquisition of data |
| Robert Greenlee, MD | Marshfield Clinic, Marshfield | GPC PI | Supported this study through their GPC |
| Deb Multerer | Marshfield Clinic, Marshfield | Study Coordinator | Role in acquisition of data |
| Laurel Verhagen | Marshfield Clinic, Marshfield | Honest Broker | Ran queries to recruit patients |

# Diplopia and Extraocular Muscle Enlargement as an Initial Presentation of Breast Cancer

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**Keywords:** *diplopia, exophthalmos, extraocular muscle, orbital metastasis, breast cancer, invasive lobular carcinoma.*

## Introduction

Diffuse extraocular muscle enlargement is a rare condition that can be encountered by neurologists or neuromuscular specialists. Thyroid ophthalmopathy is the leading cause, but many other etiologies may account for such a presentation.[1-4] Here we describe a patient presenting with diffuse extraocular muscle enlargement on imaging who was later found to have metastatic breast cancer through further workup.

## Case description

A 28-year-old female presented with progressive diplopia, asymmetrical proptosis left being worse than right, right sided headache, and right facial numbness for three months. Her past medical history was notable for intracranial hemorrhage secondary to a ruptured left posterior communicating artery aneurysm having occurred four years prior to presentation, and tobacco use. On physical examination, she was alert and oriented, without aphasia or dysarthria. Her visual fields were full, and her visual acuity was 20/200 OD and 20/70 OS. Pupils were sluggishly reactive to light, without afferent pupillary defect. Extraocular movement of both eyes was severely restricted to no movement in all directions. Bilateral exophthalmos was present with significant conjunctival injection on the left side. Facial sensation to pinprick was reduced in the territories of the second and third branches of the right trigeminal nerve. The remaining neurological examination was unremarkable. A non-contrast brain CT revealed marked thickening of all extraocular muscles bilaterally.

Initial differential diagnoses included thyroid ophthalmopathy, neurosarcoidosis, idiopathic orbital inflammatory disease, immunoglobulin G4 (IgG4) related disease, granulomatosis with polyangiitis, and orbital lymphoma or metastasis. Her serum complete blood count, complete metabolic panel and thyroid function tests were unremarkable. Serum thyroid stimulating immunoglobulin was undetectable. Serum angiotensin converting enzyme, soluble interleukin-2 receptor was and IgG4 were all normal. Cerebrospinal fluid (CSF) studies revealed the following finding: white blood cells 3 cells/µl, protein 150 mg/dl (normal range: 15 to 45 mg/dl) and glucose 47 mg/dl (normal range: 40 to 70 mg/dl). The CSF cytological examination revealed clusters of atypical cells with plasmacytoid to epithelioid morphology.

Cerebral arterial angiogram showed the presence of a 3 mm right middle cerebral artery aneurysm without evidence of cavernous carotid fistula or cavernous sinus thrombosis. Subsequent brain MRI exhibited diffuse enlargement of all extraocular muscles in both eyes with uniform contrast enhancement (Figure). MRI also revealed an infiltrative process affecting the retro-orbital fat and extending into the right cavernous sinus. Chest CT showed a 1.3 cm nodular density in the left breast, as well as enlarged bilateral axillary lymph nodes. Subsequent positron emission tomography-computed tomography confirmed hypermetabolic lesions in both breasts with asymmetric cutaneous thickening of the left breast, diffuse hypermetabolic lymphadenopathy, and hypermetabolic lesions in the axial and appendicular skeleton. Exam revealed peau d'orange appearance on the skin of the left breast and a punch biopsy showed invasive lobular carcinoma. The previously noted atypical cells found in her CSF matched the breast carcinoma morphologically. Her orbital lesions were thought to represent metastasis from the breast carcinoma. She underwent palliative whole brain and orbit radiotherapy while hospitalized with significant improvement in her visual symptoms and radiographic appearance of the extraocular muscles. (Figure). One month following discharge, her diplopia and headache had entirely resolved. Hormonal therapy was planned on discharge.

## Discussion

The differential diagnosis for diffuse extraocular muscle enlargement is wide. Non-neoplastic etiologies include thyroid ophthalmopathy, idiopathic orbital inflammatory disease, IgG-4 related disease, sarcoidosis, granulomatosis with polyangiitis and others.[1-4] Solid tumor metastasis is a rare but well recognized cause of extraocular muscle enlargement. Our patient's presenting symptoms of progressive and asymmetrical proptosis, blurred vision, and diplopia by themselves could not reliably differentiate between these etiologies. Breast exam, breast biopsy

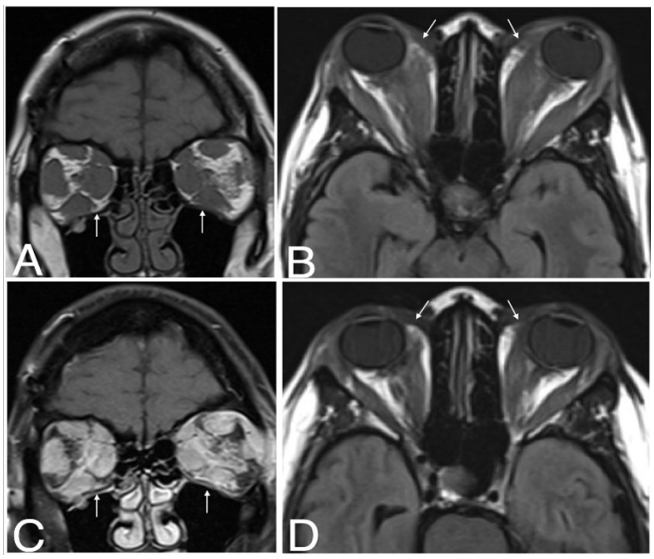


Figure. Diffuse enlargement of extraocular muscles on magnetic resonance imaging. Enlargement of extraocular muscles, proptosis and soft tissue enlargement (arrows) is seen on coronal T1 pre-contrast (A) and axial T2 FLAIR (B) images. Diffuse enhancement involving retro-orbital fat (arrows) is seen on coronal post contrast T1 image (C). Follow-up MRI (D) one month later shows marked improvement in proptosis and extraocular muscle infiltration (arrows).

and CSF cytology were instrumental in establishing the final diagnosis of metastatic breast cancer to the orbits. Metastases to the trigeminal nerve and the CSF signaled meningeal involvement (meningeal carcinomatosis) in addition to the orbital metastasis.

Breast cancer is the most frequent primary tumor to metastasize to the orbit, representing 29 to 48% of metastatic cases. Metastasis from prostate, melanoma, lung and renal cell carcinoma occurs less frequently.[5-7] In addition to the extraocular muscles, other sites of orbital metastasis included intraocular structures such as the uveal tract, retina, lacrimal glands or surrounding fat. Orbit metastasis from breast cancer is often a late-stage finding, and the average duration from diagnosis of breast cancer to presentation with orbital disease is 4 to 8.5 years.[5,8-10] While rare, extraocular metastasis as the initial presentation of breast cancer similar to our patient have been previously described.[11-13] Bilateral orbital metastasis is often less frequent than unilateral disease, representing 6 to 25% of cases.[2,8-9] However, bilateral orbit involvement tends to occur more frequently in breast cancer.[14]

In this report we have shown than metastatic disease should be considered in the evaluation of diffuse, bilateral extraocular muscle infiltration causing proptosis and diplopia, even in a patient without prior known history of malignancy. A timely diagnosis is needed as patients may respond well to palliative radiotherapy. Radiotherapy with or without chemotherapy is the preferred therapy for diffuse orbital metastasis and may improve vision.[14-15]

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# Pulsed Radiofrequency Ablation for Anterior Cutaneous Nerve Entrapment Syndrome: A Case Report

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## ABSTRACT

Anterior Cutaneous Nerve Entrapment Syndrome (ACNES) is a cause of chronic abdominal pain in which nerves become pathologically entrapped and irritated, leading to pain. The prevalence of the syndrome is 15 to 30 percent, and many treatment approaches begin with pharmacologic therapy. If pharmacologic therapy fails, trigger point injections, nerve blocks, and neurectomy are subsequent therapeutic options. We present the case of a 50-year-old female with chronic abdominal pain and steroid allergy who presented to the pain clinic after failed mainstay therapy including gabapentin, amitriptyline, nortriptyline, duloxetine, NSAID, and acetaminophen. She was diagnosed with Anterior Cutaneous Nerve Entrapment Syndrome (ACNES). A primary intervention of Bilateral Transversus Abdominis Plane (TAP) Block with local anesthetic provided 80% pain relief. Following successful primary intervention, a secondary intervention of Pulsed Radiofrequency Ablation (PRF) provided pain relief for 2 months.

**Glossary of Terms:**

ACNES – Anterior Cutaneous Nerve Entrapment Syndrome
TAP – Transversus Abdominis Plane
PRF – Pulsed Radiofrequency Ablation
RFA – Radiofrequency Ablation

**Keywords:** *Nerve Entrapment, Abdominal Pain.*

## Introduction

Abdominal pain and associated gastrointestinal diseases utilize a significant portion of healthcare resources in the United States. It is estimated that abdominal pain accounts for 5 to 10% of all chief complaints in the emergency department, and that healthcare expenditures nationwide can exceed $10 billion annually.[1,2] Therefore, adequately diagnosing and treating abdominal pain can have a dramatic impact in overall public health. Many etiologies behind abdominal pain exist, including hepatobiliary, cardiac, gastric, pancreatic, colonic, and genitourinary pathologies. Moreover, characterization of the pain itself can provide insight into causation. For example, visceral nerve fibers that innervate organs can cause poorly-localized, achy pain. In contrast, somatic fibers that innervate the peritoneum may cause sharp, well-localized pain.[1]

Another factor important to the appropriate treatment of abdominal pain is the chronicity of the problem. The approach to chronic undiagnosed abdominal pain starts with an appropriate history and physical exam. Further clues to diagnosis can be found in location of pain, particularly the difference in etiologies behind localized and diffuse abdominal pain. Diffuse abdominal pain can be pathologically derived from disorders such as centrally mediated abdominal pain syndrome (CAPS), endometriosis, narcotic bowel syndrome, Ehlers Danlos Syndrome, mast cell activation syndrome, and chronic mesenteric ischemia. On the other hand, localized pain can be further differentiated using the Carnett's Sign. Localized abdominal pain with a negative Carnett's Sign can be indicative of functional dyspepsia or irritable bowel syndrome, while a positive Carnett's Sign can point to chronic abdominal wall pain.[3]

Chronic abdominal wall pain, also known as Anterior Cutaneous Nerve Entrapment Syndrome (ACNES), is a cause of abdominal pain in which thoracic intercostal nerves are trapped and irritated by abdominal pressure or postoperative scar tissue formation. Anatomically, as thoracic intercostal nerves exit the spinal neuroforamina, subcostal nerves can become trapped between the internal oblique and transversus abdominis, while lateral cutaneous nerves can become trapped between subcutaneous tissue and the external oblique.[4] The prevalence of the syndrome ranges between 15 and 30 percent, with the most common age group affected being those between 30 and 50 years of age.[5] It is the underlying diagnosis in 2% of patients presenting to the emergency department with abdominal pain, and 10% of chronic abdominal pain cases in the outpatient setting.[6] Patients with ACNES traditionally present with well-localized pain, with an increase in tenderness to palpation during muscle tensing. Right upper quadrant pain is the presentation in 40% of patients.[6] Furthermore, patients often present with a positive Carnett's sign. To test this sign, a patient lies supine while the provider places a finger on the painful site. The patient raises both legs off of the table, or solely their head off of the table, contracting abdominal muscles. This maneuver can worsen ACNES symptoms, leading to a positive Carnett's sign.[7] Along with a positive Carnett's sign, the diagnostic criteria for ACNES include well-localized abdominal pain and a response to trigger point injection of local anesthetic. Recent retrospective studies have shown

that pseudovisceral symptoms, including a change in defecation habits, appetite suppression, nausea, and bloating can be associated with ACNES.[8] Current treatment options include pharmacologic therapy, trigger point injections, ultrasound-guided nerve blocks, chemical neurolysis, and surgical neurectomy.[5]

We present a case of a 50-year-old female with chronic abdominal pain who was diagnosed with ACNES. After failed mainstay pharmacologic therapy, and with consideration to the patient's allergy to corticosteroids, a bilateral Transversus Abdominis Plane (TAP) Block followed by Pulsed Radiofrequency Ablation (PRF) were performed. The patient had 2 months of pain relief following this intervention. The manuscript adheres to the applicable EQUATOR guideline. HIPAA authorization was obtained from the patient to publish this case report.

*Case Report*

A 50-year-old female with a past medical history of deep vein thrombosis, pulmonary embolism, hypertension, hypothyroidism, gastroesophageal reflux disease, and depression presented to the pain clinic in 2019 with a chief complaint of chronic abdominal pain, recurrent since 2003. Her only surgery was a cholecystectomy in 1996. She had a syncopal allergy to steroids, further complicating her clinical course due to intolerance of steroid-based therapies. She presented with right upper quadrant abdominal pain, worse with eating, that lasted five to six hours with each episode. Along with her symptoms, she also noted weight loss and intermittent vomiting since the pain started. Her history was significant for multiple visits to gastrointestinal specialists since 2003, resulting in upper and lower endoscopies, ERCP, and a gastric emptying study. She underwent laparoscopy for lysis of adhesions in 2003 and 2011, which provided minimal relief. All CT scans and endoscopies were negative for pathology. One gastrointestinal specialist noted right rib tenderness on physical exam, and leading differentials included musculoskeletal pain, mesenteric ischemia, functional bowel disorder, and radiculopathy. Barium esophagram, endoscopic ultrasound, and mesenteric dopplers came back negative. A lower esophageal injection of botox for possible achalasia provided no relief. Moreover, laboratory workup, including enzymatic analysis during an episode of pain, were negative. The patient tried a variety of pharmacologic therapies such as acetaminophen, non-steroidal anti-inflammatory drugs, gabapentin, amitriptyline, nortriptyline, and duloxetine. The only medication that provided relief to the patient was cyclobenzaprine, and the relief was minimal. Exercise and physical therapy also proved to be ineffective.

Physical exam at the time of presentation to the chronic pain clinic showed epigastric and right upper quadrant tenderness, guarding, and a positive Carnett's sign. Due to the minimal effect of pharmacologic therapy alone, and with her pain approaching midline, the team opted for a primary intervention with a bilateral TAP Block using a 1:1 solution of 2% lidocaine and 0.5% bupivacaine. Using ultrasound guidance in an anterolateral plane, a 22-guage, 3.5 inch spinal needle was advanced to the border between the internal oblique and transversus abdominis muscle. After negative aspiration, the solution was injected. The patient had 80% pain relief for thirty hours following the procedure.

After a successful primary intervention for short-term pain relief, the patient opted to pursue an additional therapy with the goal of long-term pain relief. After discussion with the patient, the team performed a secondary intervention with PRF, using 10mL of 0.5% bupivacaine and 2mL of 1% lidocaine prior to ablation. Using ultrasound, 2 needles were inserted at different locations in the fascial plane, between the internal oblique and transversus abdominis (Figure 1). Following injection of bupivacaine, PRF was performed using an Interventional Spine RF Generator System, 1MHz, at 42 °C for 120 seconds. A 100 MM curved, 10 MM, 18 gauge radiofrequency cannula was used to perform the ablation. The patient had pain relief for the following two months after the procedure.

## Discussion

ACNES has both non-invasive and invasive treatment modalities. Although previous literature has indicated up to 42% of patients having complete pain remission after injection of local anesthetic into the abdominal wall alone, patients with persistent pain are forced to search for alternative methods of pain relief.[9,10] The addition of adjuvants to local anesthetic has been attempted for longer duration of pain relief. One such adjuvant, dexamethasone, has been shown to prolong the effect of long-acting anesthetics up to 1,306 minutes.[11,12] If pain continues after local anesthetic and adjuvant injection, neurectomy use has been shown to provide pain relief in up to 90% of patients.[13] However, the lasting nerve damage associated with neurectomy has led to the search for less destructive methods of pain management. One such method with recent utilization is PRF for ACNES.

PRF uses high-frequency intermittent current with tissue temperatures below 42 °C to stun nerves and prevent long-term neuronal damage.[14,15] In terms of efficacy, a clinical

trial recently showed PRF to be a minimally invasive treatment alternative to neurectomy in patients with ACNES.[16] In the case presented, the patient had a notable allergy to corticosteroids, resulting in the search alternative treatment options. Before attempting PRF for long-lasting pain relief, a treatment of shorter duration was used to determine the location of nerve irritation and efficacy of nerve disruption. After the patient received substantial short-term pain relief following TAP Block, a long-acting therapy was initiated. The alternative option of neurolysis was considered for intervention, but the concern of post-procedure neuritis and Deafferentation Pain Syndrome supported the choice of PRF. Moreover, the patient's allergy to steroids would have made the prophylaxis and treatment of neurolysis-associated complications difficult to address.

In regards to hydrodissection prior to PRF, it is unlikely that the local anesthetic provided prolonged pain relief. Previous studies have even shown that hydrodissection with saline or local anesthetic is safe and effective in reducing surrounding tissue damage when combined with RFA.[17] Additional studies have implicated that pre-ablation local anesthetic injection may improve pain scores in the early post-operative period, justifying clinical usage.[18] Therefore, attributing this episode of sustained pain relief solely to pre-RFA local anesthetic is not supported by clinical evidence. Unfortunately, the patient's pain returned following two months of relief. Currently, a more permanent treatment approach is being explored, with the possibility of future peripheral nerve stimulator implantation.

## Appendix

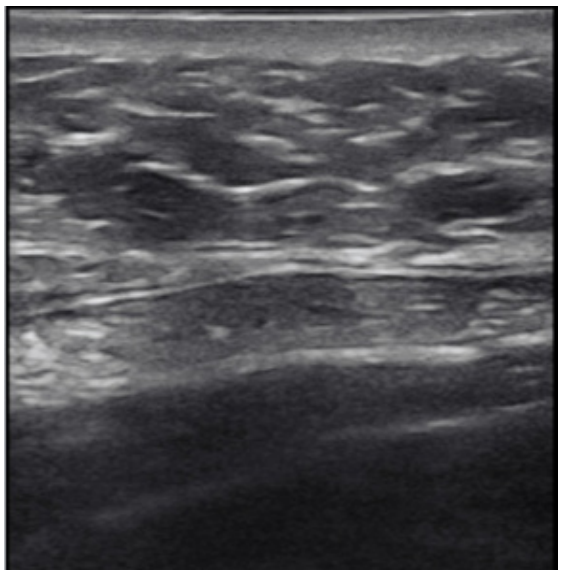

Figure 1: Ultrasound capturing PRF between the internal oblique and transversus abdominis.

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# Updates from the fray: rational off-label and over-the-counter prescribing in amyotrophic lateral sclerosis

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**Keywords:** *Amyotrophic lateral sclerosis, clinical trials, review, off-label prescribing*

## ABSTRACT

Background: Amyotrophic lateral sclerosis (ALS) is a terminal condition, which is increasing in incidence. Therapeutic interventions have enjoyed limited success. However, research is progressing, with some promising drug candidates emerging. Patients cannot always wait for the results of large trials. The general practitioner has a central role in management of ALS.

Objective: To review and summarise available evidence evaluating the disease-modifying and life-extending potential of approved medications available off-label or over the counter. To inform doctors and patients of updates in the field and assist their decision-making.

Method: A literature search was conducted of PubMed, UpToDate and Google Scholar from 1st January 2010 until 1st July 2020. Search terms were "amyotrophic lateral sclerosis", "motor neuron(e) disease", "clinical trial", and "treatment", with review articles and clinical trial results evaluated by the author for safety and efficacy. Only literature investigating medications already approved for use in Australia was included.

Discussion: Four experimental candidates were deemed to have a reasonable likelihood of efficacy, and doses/routes of administration were clarified. Possibilities for novel therapies were outlined, and the importance of research support was highlighted.

## Introduction

A 65-year-old woman presented to her general practitioner (GP) with foot drop. Neurological examination and neurophysiological studies confirmed sporadic amyotrophic lateral sclerosis (ALS), a terminal condition. Two Australian patients receive this diagnosis daily (1). She was offered standard treatment, including riluzole and medications to relieve symptoms. She sought further therapeutic options in concert with her treating team, but found no clear source of research updates.

## Aim

Advances in ALS have been limited. There is some optimism at present, which has not been widely reported. This article presents news of current research into potentially useful disease-modifying and life-extending treatments for this condition, to inform GPs and patients. In particular, evidence for off-label prescribing of approved medications, and over-the-counter medications/supplements, is examined. While robust randomised controlled trials with hundreds of participants provide the strongest evidence of efficacy, ALS patients often cannot wait for these results. There is therefore more freedom applied to the therapies discussed, following demonstration of an adequate safety profile. However, medications are still assessed with reference to available evidence. This article does not outline ongoing clinical trials, as these are changing rapidly. Also, it does not focus on standard treatment, which is covered elsewhere (2).

The treatments discussed in this paper are experimental. This information must be handled with caution and used only in consultation with a neurologist. No assurance is offered that use of these medications for this condition is safe or appropriate for any particular patient. Off-label prescribing remains the responsibility of the prescriber, and treatments should be added in a stepwise fashion to allow observation of benefit and/or side effects. Clinicians should be aware of the limitations of trials with small patient numbers (for example, Phase II trials), even if they show a statistically significant effect. [Lithium (3) and dexpramipexole (4), though initially promising in ALS, were shown to be ineffective in trials with larger patient numbers.]

## Method

A literature search was conducted of PubMed, UpToDate and Google Scholar from 1st January 2010 until 1st July 2020. Search terms were "amyotrophic lateral sclerosis", "motor neuron(e) disease", "clinical trial", and "treatment", with review articles and clinical trial results filtered out for closer assessment. Patient-oriented ALS news websites and social media were also consulted to locate relevant sources. All literature was reviewed by the author, with interventions evaluated for safety and efficacy. Only literature investigating medications already approved for use in Australia was included. Pertinent findings were summarised.

**Results**

- Abacavir/dolutegravir/lamivudine (The Lighthouse Trial)

The role of retroviruses in the pathogenesis of ALS was first suspected following reports of Human Immunodeficiency Virus (HIV) patients presenting with ALS-like symptoms, as well as research demonstrating increased levels of the reverse transcriptase enzyme in ALS patients' serum (5). A search for the causal agent has led to human endogenous retroviruses (HERVs), whose genetic sequences are believed to have become incorporated into the human genome over millions of years (6). One virus, HERV-K, may be responsible for the increased enzyme activity (7).

Abacavir 600mg/dolutegravir 50mg/lamivudine 300mg (marketed as "Triumeq") is a medication used to treat HIV patients. It is highly effective against HERV-K, and easily penetrates the blood-brain barrier. An HLA-B*5701 blood test must be negative prior to administration of any medicine containing abacavir. A 24-week, open-label, Phase IIA trial of Triumeq was commenced in Australia in late 2016 (8). This trial found a decrease in the slope of clinical progression based on the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) of around 30%, as well as an effect on biomarkers. The lack of blinding and placebo control were mitigated in part by a 10-week, pre-treatment observation period against which to compare clinical decline.

The trial dose was 1 tablet daily, with no safety concerns or interactions with co-administered riluzole noted. The Lighthouse Trial has now progressed to Phase III.

- Curcumin (ALSUntangled)

Professor Richard Bedlack and the Duke ALS Clinic have made great contributions to this field. Among their projects is "ALSUntangled", which analyses possible alternative and off-label treatments based on several criteria, creating a comprehensive review for each candidate (9). Many treatments examined by the group have received equivocal assessments. One of the more promising is curcumin. Researchers deduced four plausible mechanisms of action involving neuroinflammation, protein aggregation, oxidative stress and the faecal microbiome.

They also identified some positive case reports, as well as three pre-clinical and two clinical studies showing a beneficial effect. All five studies have limitations and are difficult to interpret (10). In this setting, planning for a trial of Integrative Therapeutics' "Theracurmin HP" formulation, at 90mg oral twice daily, is underway at Duke University. This product was chosen on the basis of previous encouraging research in neurodegeneration (11).

Among other proposed treatments, the group posits some value from carnitine supplements. This is again based on feasible mechanisms, laboratory evidence, and a limited clinical trial showing a positive effect. They suggest a theoretical benefit of 1g three times daily of oral acetyl-L-carnitine (12). Some common alternative therapies for ALS (vitamin E, coQ10 and creatine) have poor evidence and might better be avoided (9).

Another project, "ALS Reversals", aims to document and understand rare cases of patients who experience disease remission (13). It has produced intriguing work relating to potential treatments, but has not yet achieved a significant victory.

- Sodium phenylbutyrate/tauroursodeoxycholic acid (The CENTAUR Trial)

Sodium phenylbutyrate was initially approved for use in urea cycle disorders, based on its activity as an ammonia scavenger (14). It is approved in Australia for this indication, as granules for oral administration – however it does not appear readily available. Other mechanisms of sodium phenylbutyrate include ameliorating endoplasmic reticulum stress from misfolded protein accumulation by acting as a chemical chaperone (15), and promoting appropriate transcription by inhibiting histone deacetylase (16). These processes are of interest in neurodegeneration, and the molecule shows some pre-clinical efficacy (16, 17).

Tauroursodeoxycholic acid is a bile acid which has a demonstrated role in some cholestatic liver diseases. It has antiapoptotic actions, likely related to reduced mitochondrial dysfunction. Various studies have documented the role of bile acids in neuroprotection (18). One randomised controlled trial in ALS showed mixed effects (19), and another demonstrated statistically significant slowing of the ALSFRS-R slope (20).

A proprietary combination of these two compounds has been marketed as "AMX0035" by Amylyx Pharmaceuticals Inc. They recruited 137 patients and completed a 24-week Phase II randomised controlled trial in 2019. Results demonstrate statistically significant slowing of disease progression measured by the ALSFRS-R (21). Secondary outcomes included muscle strength, slow vital capacity, and survival. Secondary outcomes were not statistically

significant between groups – although they generally favoured AMX0035. All-cause mortality was evaluated at 35 months, indicating a survival benefit of 6.5 months among participants in the active group (22).

The trial dose was oral sodium phenylbutyrate 3g and tauroursodeoxycholic acid 1g, both twice daily. The researchers plan to move towards regulatory approval.

- Methylcobalamin

Methylcobalamin is an active form of vitamin $B_{12}$ which has demonstrated neuroprotective effects in vitro and in vivo (23, 24). The importance of vitamin $B_{12}$ for neural function is clear, and deficiency can manifest as central or peripheral nervous system pathology. Methylcobalamin reduces homocysteine levels, inhibiting neuronal degeneration (25).

Interest in high-dose methylcobalamin gained momentum in 1998 with the publishing of the first human trial, which demonstrated a statistically significant increase in compound muscle action potential amplitudes among the treated group over 28 days (25). Subsequent trials have yielded some positive results, the most significant of which was a Phase II/III randomised controlled trial of 373 patients over 3 years (26).

Population-wide results of this trial were negative. Among participants who were diagnosed within 12 months of symptom onset, ALSFRS-R decline was reduced and time to death or full ventilatory support was prolonged in post-hoc analysis. The greatest effect was seen with intramuscular methylcobalamin 50mg twice a week. Investigators have sought to confirm these results in a subsequent trial (27).

- Other possibilities

Mild functional benefits were observed in a Phase II trial of tamoxifen 40mg oral daily (28), and a Phase I trial using trimetazidine to modulate ALS hypermetabolism is planned (29). Masitinib, which is approved for treatment of mast cell tumours in dogs, showed a positive effect on ALS progression at 4.5mg/kg oral daily in a Phase II/III trial (30).

Outside the realm of off-label and over-the-counter therapeutics, encouraging clinical trial results for novel compounds and biological interventions have been published. These include mesenchymal stem cell-neurotrophic factor cells (31), autologous regulatory T-lymphocyte infusions (32), CuATSM (33 p. 280), reldesemtiv (34), and others. These (and any) preliminary findings should be interpreted with appropriate caution. To find clinical trials recruiting volunteers, patients should ask their neurologist or Motor Neurone Disease Australia.

## Conclusion

This article hopes to provide some direction for the compassionate and inquisitive GP. Patients often have more access to GPs than specialists, and they are an integral source of information and support. GPs may also have the important role of reducing the diagnostic delay (35). As a co-ordinator of care for ALS patients, GP awareness of ongoing scientific inquiry is invaluable. This patient group needs the best chance of asserting control over their disease process.

Historically, many ALS clinical trials protocols have faced design flaws. Some features, including poor outcome measures, lack of blinding and inadequate statistical power, persist in many trials (36). This is clear from the current review. However, recent paradigm shifts have begun to align modern trials with best practice. Watertight clinical trial design is crucial, as it allows for more reliable conclusions to be drawn from earlier data – thereby enabling faster transmission of information to patients (36). A new focus on patient-centered trials is welcome – but validity of results must remain the priority.

Whether current experimental prescribing is ultimately demonstrated to be efficacious in large trials remains to be seen. Regardless, patients may attend appointments equipped with knowledge of research, seeking clarification and guidance. ALS patient groups are increasingly engaged with research, perhaps aided by desperation (37). The informed GP will be familiar with the field, and able to discuss options and temper expectations.

The prognosis and morbidity of ALS necessitate urgent and zealous support of research, and the hastening of approval processes. Drug candidates are frequently stuck in clinical trials for a decade or more, which is highly regrettable. As the incidence increases (38), so does the importance of taking up arms against what the Fight MND Foundation calls “The Beast”.

## Acknowledgements

Professor Saxby Pridmore, for his suggestions. Clinical researchers, including Professor Julian Gold, Professor Richard Bedlack, Professor Stanley Appel, and Assistant Professor Sabrina Paganoni, for their kindness and contributions. Dr Mary Pridmore, for her joie de vivre.

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# Cane sign: Sciatic Neuropathy Appearance in Magnetic Resonance Imaging

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An-eighteen-year-old male patient presented with slowly progressive foot drop on the left for two years. He was also suffering from a sharp pain radiating down the left posterolateral limb. There was no history of trauma. Neurological examination revealed weakness in knee flexion, foot eversion and inversion (4/5 according to the Medical Research Council (MRC) motor scale), foot dorsiflexion (1/5, according to the MRC), and hypoesthesia in the lateral aspect of the leg, dorsum and lateral part of the foot on the left. Left Achilles reflex was also absent.

Magnetic resonance imaging revealed diffuse thickening and intense contrast enhancement of the left sciatic nerve, starting from the lumbar and sacral nerve roots, extending 10 cm distal to the popliteal fossa. This enlarged appearance of the sciatic nerve looks like a "cane"; thus, we decided to use the term "cane sign." Sciatic neuropathy, perineuroma, schwannoma, and malignant peripheral nerve sheath tumors were considered in the radiological differential diagnosis. Perineuroma and schwannoma were unlikely because the involved segment was too long. Similarly, long segment and cylindrical involvement were atypical features for a neurofibroma. Moreover, since it must have already invaded the surrounding soft tissues within two years, the diagnosis of malignant nerve sheath tumor was also avoided (Figure 1). Electroneuromyography showed a proximal lesion between the popliteal fossa and lumbosacral plexus in all branches of the left sciatic nerve, characterized by severe and chronic axonal loss. Laboratory work-up including autoimmune and infectious markers were unremarkable. With these findings, we suggested that idiopathic sciatic neuropathy was the most likely diagnosis. Five days of 1000 mg intravenous methylprednisolone followed by a tapering course of oral methylprednisolone were started. As the patient did not benefit from this treatment, 3 months later, a trial of intravenous immunoglobulin (IVIg) 0.4 g/kg/day for 5 days followed by monthly infusions was given. Unfortunately, improvement of muscle strength was insignificant, but his pain was relieved by gabapentinoids. Follow-up electrophysiological study depicted severe and chronic axonal loss of all branches of left sciatic nerve with minimal regeneration / reinnervation findings.

Sciatic neuropathy is the second most common neuropathy of the lower limbs and a frequent cause of foot drop.[1] Drop-foot may be associated with many clinical syndromes, so electrophysiological examinations

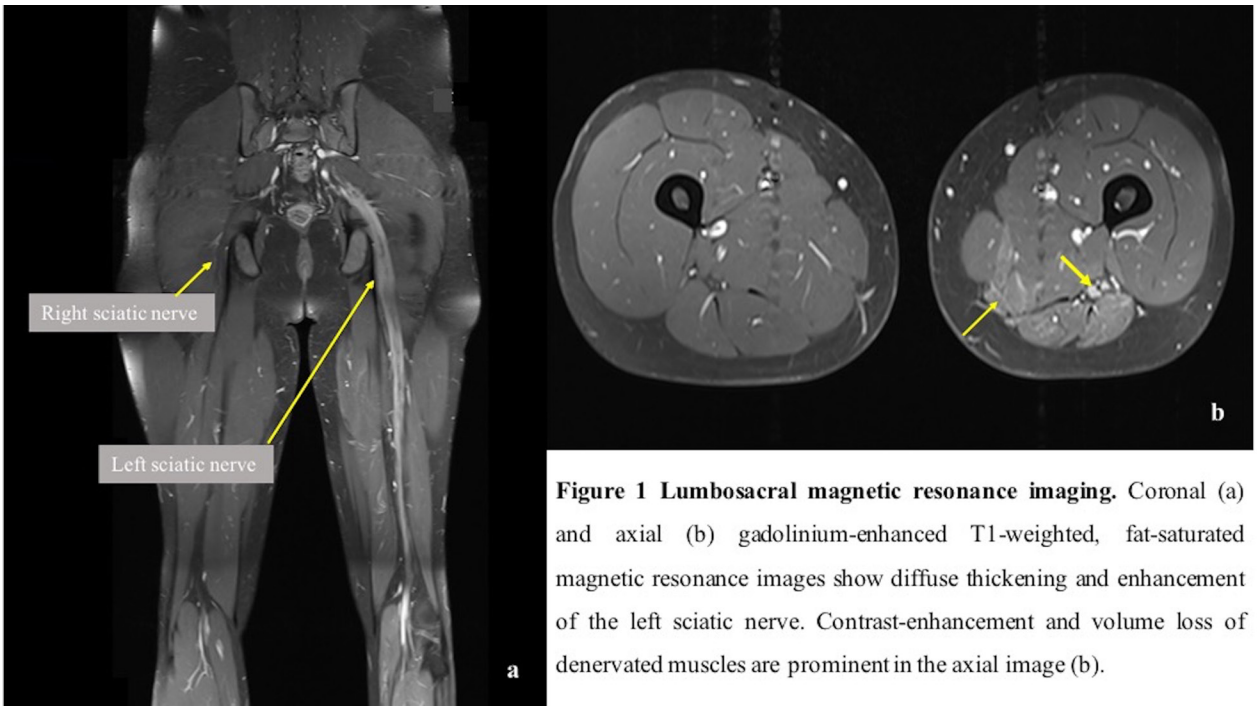


**Figure 1 Lumbosacral magnetic resonance imaging.** Coronal (a) and axial (b) gadolinium-enhanced T1-weighted, fat-saturated magnetic resonance images show diffuse thickening and enhancement of the left sciatic nerve. Contrast-enhancement and volume loss of denervated muscles are prominent in the axial image (b).

and imaging studies, as well as clinical and neurological examination findings, are essential in the differential diagnosis.[1, 2] Trauma, surgery, injections, infections, inflammation, vascular events, or tumors can cause sciatic neuropathy and up to 16% of cases, it can be idiopathic.[1, 3] If any, treatment of the underlying cause, immunosuppressive and supportive treatments, and physical therapy applications can be beneficial.[1] Unfortunately, in our case, who was presented with demonstrative magnetic resonance imaging findings, delayed medical treatment initiation caused an insufficient clinical response.

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# A rare neuro-ophthalmological phenomenon: Marcus Gunn jaw winking ptosis

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Patient is a 13 year old girl with right upper eyelid ptosis since birth and elevation of her right upper eyelid with mouth opening, lateral jaw movements, and tongue protrusion. Marcus Gunn jaw winking ptosis is extremely rare occurring in 2-13% of patients with congenital ptosis. It is due to aberrant neuronal connection between motor fibers of trigeminal nerve and superior division of oculomotor nerve that innervates levator palpebrae superioris[1]. Acquired forms may develop after eye surgery, trauma, syphilis, and pontine tumors. It is mostly sporadic but can be associated with amblyopia, strabismus, and anisometropia[2].

Video 1

Video 2

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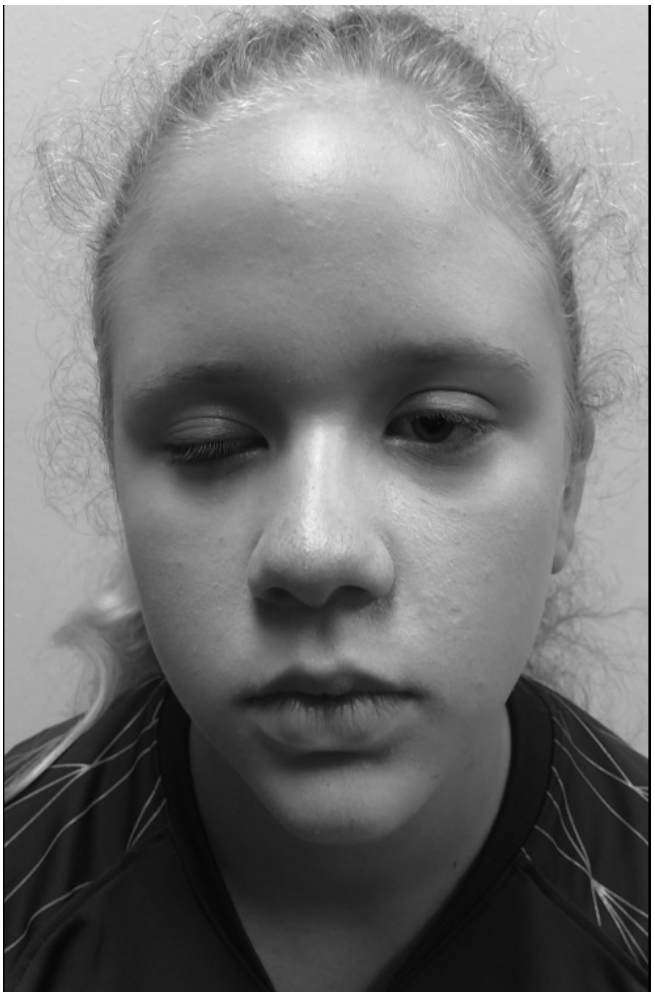

Figure. Still from video of 13 year old girl with Marcus Gunn jaw winking ptosis right upper eyelid. Elevation of right upper eyelid noted with mouth opening and lateral jaw movements (video 1) and tongue protrusion (video 2).

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