“Reengineering Clinical Trials - The Promising Pathway Act” (Al Musella) [#90]

Brad Power
March 27, 2024

“In my opinion, it's impossible to run a valid phase 3 trial in the United States right now.” – Al Musella

“Insanity is doing the same thing over and over again and expecting different results.” – Albert Einstein

“The difference is, instead of doing a phase 3 trial, you're letting anybody participate in this virtual trial. So it's basically just a different way of doing the phase 3 trial.” – Al Musella

“For the first time in history, we'll know how a treatment performs in the real world as every patient is tracked in a learning system.” – Al Musella

Meeting Summary

Advanced cancer patients and their caregivers, especially those diagnosed with an aggressive cancer with few treatment options, face a number of challenges:

- There may be many promising new therapies, but you can’t access a lot of them in a combination. You have to pick and choose which ones you're going to pursue.
- If a treatment doesn't work and your disease is very aggressive, you have to pivot quickly to the next one.
- The current drug development process is too slow and costly for rare diseases, yielding few new treatments.
- Only a very select few, about 5% of the population, can access clinical trials, which can offer many advantages over standard treatments.

One of the ways to address the regulatory hurdles to accessing treatments and accelerate treatment development is through policy and regulatory changes. A key initiative to drive these changes is “The Promising Pathway Act”, pending legislation which will create a conditional approval pathway for the FDA. After you see that a drug is safe, and it has the effect you want it to have (Phases 1 and 2 of the three-phase regulatory approval process), it would get a conditional approval. Any doctor could prescribe it, and insurance would handle it like any other approved drug. Any patients who use these drugs would be followed as if they're in a clinical trial. We would learn from every patient. We would continue the research. The only difference from the standard pathway is that it's more flexible, where you can do combinations if you like, and any patient could get access.

Al Musella is uniquely qualified to describe the issues behind the need for "The Promising Pathway Act" and what the changes might mean to patients and caregivers. He founded the Musella Foundation, which offers comprehensive resources including videos, written information, discussion forums, patient navigation services, and advocating for change in the

system. They have been conducting a study on brain tumor patients since 1993, focusing on the treatments received and the outcomes, with the aim of identifying more effective treatment combinations. Al was personally motivated by his family's experience with brain cancer and has been instrumental in creating an online database of clinical trials. The foundation also encourages participation in their brain tumor Virtual Trial, which tracks patient outcomes, and seeks support through updates on treatment options, spreading the word, advocating for change and donations to sustain these vital projects.

What are the problems with the current FDA approval process, especially phase 3 trials?

- **Access**: Access to the drugs is limited to the small population able to qualify and get to a site, and getting access is expensive. It's very hard to get into the best trials right now. You may not get access because you don’t meet the eligibility criteria which favor relatively healthy patients.
- **Unrepresentative**: The patients selected for clinical trials are not representative of the patient population. They may publish some research on a select group of patients, but you won’t get published results on a typical patient.
- **Slow**: Clinical trials take a long time (typically five to ten years).
- **Expensive**: Clinical trials are expensive to run, and those costs are incorporated into drug prices to repay the research and development costs. A drug company can pay $1 million per patient to a hospital for a phase 3 clinical trial.
- **Unreliable**: The results are often not trusted by the research or provider communities.

What about getting access through newer alternative pathways (“Right to Try” and “Expanded Access”)?

These two pathways help, but they are not enough. The average patient is not going to get a drug through these alternative pathways. They are also not going to increase the number of drugs available to patients.

- Drugs are expensive. Insurance can't pay for it, and nobody's going to give it for free. Only the rich people get it.
- Drug companies are a little bit afraid to go outside of the FDA. They are also afraid to publish their actual costs.
- It takes too much time for the doctor.

How does the Promising Pathway Act solve the problems with the current process?

The difference is, instead of doing a phase 3 trial, you're letting anybody participate in this virtual trial. It's just a different way of doing the phase 3 trial. The benefits include:

- **Access**: Improves patients’ access to treatments, especially experimental treatments for rare and aggressive cancers.
- **Information**: Improves transparency and enables data analysis through a database of medical records, yielding much more data on each drug and on how to use it, including

exploration of drug repurposing using real-world evidence and how drug combinations work.
- **Engagement**: Engages patients and caregivers in accelerating cancer research through clear consents.
- **Cost reduction**: Reduces drug costs, passing on the reduced research and development costs. After approval in the relatively small phase 2 trial, the drug company can start making money. Phase 3 trials, the largest and most expensive phase, will be minimized, and cut out the phase where the most time and money is spent.
- **Drug discovery**: Increases new drugs in the research pipeline.
- **Learning**: Speeds up the pace of learning from visibility into more real-world experiences – if something is working or isn't working everybody can find out about it, opening up treatment options and avoiding repeating the same mistakes.
- **Incentives**: Releases the liability of the doctor and the drug company if things go badly.

What can you do to promote the Promising Pathway Act?

Patients and caregivers need to be the cheerleaders for this. Pharmaceutical companies will be able to discover more drugs, but it will lower the bar to competition.

You should contact your senators and representatives. An easy way is to send an email using the form on the Musella Foundation website. You put in your name and address, and it only takes a couple of clicks to send a message to your senators and representatives.

“Reengineering Clinical Trials - The Promising Pathway Act” (Al Musella) [#90]

Meeting Notes

KEYWORDS

drug, patients, people, trial, brain tumor, treatment, clinical trials, doctor, approval, phase, good, pathway, years, fda, glioblastoma, data, access, tumor, progression free survival, give

SPEAKERS

Al Musella (82%), Chris Apfel (5%), Richard Anders (4%), Roger Royse (4%), Amit Gattani (2%), Brad Power (1%), Vanessa Hugo (1%), Jeff Waldron (0%), Dan Moynehan (0%)

OUTLINE

1. Promising new legislation to transform the FDA drug approval process. (0:02)
2. Glioblastoma diagnosis and treatment in 1992. (1:03)
3. Cancer treatment and advocacy efforts. (2:56)
4. A drug that helps brain cancer patients with limited access. (8:03)
5. Drug development and access restrictions. (13:31)
6. Drug approval pathways and their challenges. (16:39)
7. Clinical trials and FDA approval for cancer treatments. (22:45)
8. Clinical trials for glioblastoma treatment. (27:27)
9. Accelerating drug development for glioblastoma. (29:34)
10. Improving cancer treatment through data analysis and patient consent. (35:48)
11. Accelerating drug development for rare and aggressive cancers. (41:28)
12. Brain tumor advocacy and legislation. (46:47)
13. Using a database to improve cancer treatment outcomes. (51:55)
14. Using real-world evidence for drug repurposing. (57:58)

SUMMARY

Promising new legislation to transform the FDA drug approval process.

- Roger Royce introduces Al Musella, president of the Musella Foundation for Brain Tumor Research and Information, to discuss the Promising Pathway Bill.

Glioblastoma diagnosis and treatment in 1992.

- Al Musella shares his personal story of losing his sister-in-law to glioblastoma in 1992, despite doctors telling them there were no more treatment options available.

Cancer treatment and advocacy efforts.

- Al Musella shares his personal experience with cancer treatment and the challenges he faced in finding clinical trials and affordable treatments.
- He created the first online support group and database of clinical trials, which helped revolutionize the way clinical trials are reported and managed.
- He has dedicated his career to advocating for brain tumor patients, including creating the first online registry of brain tumors and navigating over 25,000 patients through the healthcare system.

“Reengineering Clinical Trials - The Promising Pathway Act” (Al Musella) [#90]

- Despite his efforts, Musella believes that most brain tumor patients are not receiving adequate care and are dying or suffering due to a lack of progress in the field.

A drug that helps brain cancer patients with limited access.

- Dr. Musella suggests an experimental drug for a patient with glioblastoma, despite the patient's poor prognosis and lack of access to clinical trials.
- The patient experiences improvement in symptoms after receiving the drug through an expanded access program.
- Al Musella shares his experience with a drug that has helped a child with a rare disease, but the FDA has denied expanded access and requires a randomized trial to prove its effectiveness.
- The FDA's denial has left hundreds of other people without access to the drug, despite published reports showing it more than doubles average survival for this disease.

Drug development and access restrictions.

- Al Musella discusses the challenges of accessing experimental treatments, including high costs and restrictions on expanded access programs.
- He believes the Privacy Pathway Act could provide a solution by allowing nonprofits to raise money for drug development and providing more affordable access to treatments.

Drug approval pathways and their challenges.

- Al Musella discusses the limitations of the accelerated approval pathway for drugs, including the lack of impact on overall survival despite positive progression-free survival and response rates.
- The FDA has been critical of using progression-free survival and response rate as endpoints in drug trials, as they do not directly impact overall survival.
- He discusses challenges with accelerated approval for brain tumor drugs, including lack of good data and limitations in expanded access.
- He explains the Conditional Approval Pathway for drugs, where the FDA grants provisional approval for up to 8 years, with the possibility of full approval after presenting additional data.
- The drug must demonstrate substantial evidence of safety and early evidence of a positive therapeutic outcome in at least a phase 1 trial, with the level of risk being the same as a phase 3 trial.

Clinical trials and FDA approval for cancer treatments.

- Al Musella argues that pathway X is more effective than traditional phase 3 trials.
- He discusses the challenges of getting FDA approval for a new cancer treatment, including the rejection of a phase 3 trial due to issues with the blinded design.
- He highlights the case of Optune, a treatment that was approved despite similar concerns about the blinded design, demonstrating the inconsistency in FDA decision-making.

Clinical trials for glioblastoma treatment.

- Al Musella discusses issues with clinical trials for DCVax and Optune, including problems with endpoint analysis and patient response.

Accelerating drug development for glioblastoma.

- Al Musella argues that phase 3 clinical trials for glioblastoma are useless due to selection bias and inadequate representation of the target population.

“Reengineering Clinical Trials - The Promising Pathway Act” (Al Musella) [#90]

- He proposes a virtual trial as a better alternative, citing potential benefits of increased sample size and more accurate data representation.
- He believes the 21st Century Cures Act will improve cancer treatment by allowing for more clinical trials and access to new drugs.
- He expects the act to lead to better drug combinations and lower prices, as well as more data on how to use drugs effectively.
- He also notes that the current system makes it difficult for patients to access the best clinical trials, and that the act will provide more options for patients and doctors to make informed decisions.

Improving cancer treatment through data analysis and patient consent.

- Al Musella emphasizes the need for transparency in tracking patient outcomes to speed up the pace of cancer research and find a cure.
- Roger Royse agrees and adds that there is resistance from doctors themselves, and the FDA and insurance companies are also significant barriers.
- Al Musella explains that the biggest obstacle to using new cancer drugs is the risk aversion of doctors, who are hesitant to prescribe them due to liability concerns.
- He also notes that the current system is not designed to be a moneymaker for hospitals, and that the promising pathway act could potentially incentivize doctors to prescribe new drugs by reducing liability concerns.

Accelerating drug development for rare and aggressive cancers.

- Richard Anders and Al Musella discuss the complexity of excluding patients in clinical trials, with Al Musella suggesting that drug companies may propose specific criteria for inclusion and exclusion in their trials.
- Richard Anders raises concerns about the potential for subjective exclusions based on non-scientific factors, while Al Musella emphasizes the importance of scientifically-driven exclusions.
- Al Musella proposes a new law to reduce the cost of drug development by eliminating phase 3 trials for serious diseases with no effective treatment, such as ALS, brain tumors, and pancreatic cancer.
- Amit Gattani asks about the number of drugs that have gone through this process so far, and if it's focused primarily on brain cancer or open to other types of cancers.

Brain tumor advocacy and legislation.

- Al Musella and Amit Gattani discuss the importance of contacting congresspeople to support a bill that would provide access to experimental treatments for brain tumor patients.
- Al Musella emphasizes the need for people to contact their representatives and push for support, as congressmen rely on public pressure to make decisions.
- Al Musella and Vanessa Hugo discuss the Promising Pathways Act, a bill that aims to provide funding for cancer research and treatment, particularly for rare and aggressive forms of cancer.
- They mention the Cancer Moonshot program and how it could be a catalyst for the bill's passage, and they plan to rally support in the House of Representatives.

Using a database to improve cancer treatment outcomes.

“Reengineering Clinical Trials - The Promising Pathway Act” (Al Musella) [#90]

- Al Musella discusses a bipartisan effort to create a database of medical records, with patients having access to their own data and the ability to verify its accuracy.
- He suggests creating a database to store and analyze patient data, including treatment outcomes, to help doctors and researchers identify effective treatments for brain cancer.
- Richard Anders agrees, noting that such a system could be a goldmine of potentially useful semi-anecdotal information, and could be useful for drug companies to populate the database with required test results.
- Al Musella presents a peer-reviewed paper on using Prosek in brain tumor patients, showing that taking the drug decreases the chance of living.

Using real-world evidence for drug repurposing.

- Dr. Chris Apfel discusses potential benefits and risks of repurposed drugs for cancer treatment, advocating for offline discussion and tissue testing to confirm results.
- Al Musella and Chris Apfel discuss the potential of real-world evidence to support the Promising Pathway Act.

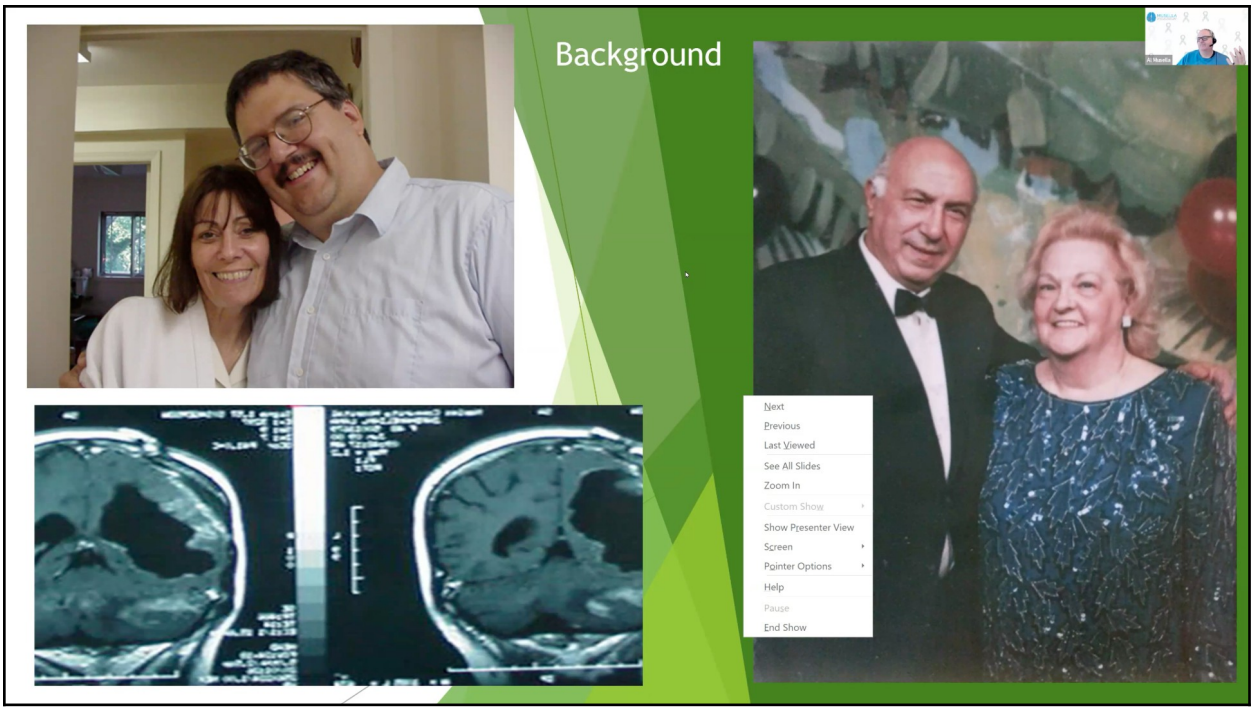
“Reengineering Clinical Trials - The Promising Pathway Act” (Al Musella) [#90]

Meeting Transcript

Roger Royse
Welcome to this week's presentation by the Cancer Patient Lab. We're a group of, I guess you'd call us patients, that are very interested in going beyond standard of care and exploring what's out there in terms of cancer treatment. This week we have a speaker who is going to take us in a little bit of a different direction, and talk about something that's very important, and of interest to all of us.

Al Musella is the president of the Musella Foundation for Brain Tumor Research and Information. Al is going to talk to us about the Promising Pathway Bill. It's a promising new legislation that could transform the FDA’s drug approval process. I think everybody here has experienced some frustration with the FDA and getting drugs and getting treatments, as well as costs.

“Reengineering Clinical Trials - The Promising Pathway Act” (Al Musella) [#90]



Al Musella 1:02
First, a little bit of a bit of background because this is a really strange concept. At first, you're going to say, “You're crazy. You can't do that.” I want to let you know the background of why I'm doing this, so that you understand the process. You have to pay attention when we get to the part about the bill and see that all the little nuances come together to create something that's really, really impressive.

I was a podiatrist in private practice doing very well. I was very happy. Then in 1992, my sister-in-law Alanna was diagnosed with glioblastoma. She had four little kids at the time. This was her MRI. Pretty soon afterwards, she had a part of the tumor removed, but this is all tumor. There's all this stuff in here that is all tumor. It doesn't look good. This is one of the most horrible diseases a person could have. Because aside from all the normal cancer stuff, it affects your brain and your actual person, your personality, everything else. The doctors at Sloan Kettering told her there was absolutely nothing else to try. This is a few months after she was diagnosed. They actually said, “You're not going to make it to Christmas. Just make your plans.”

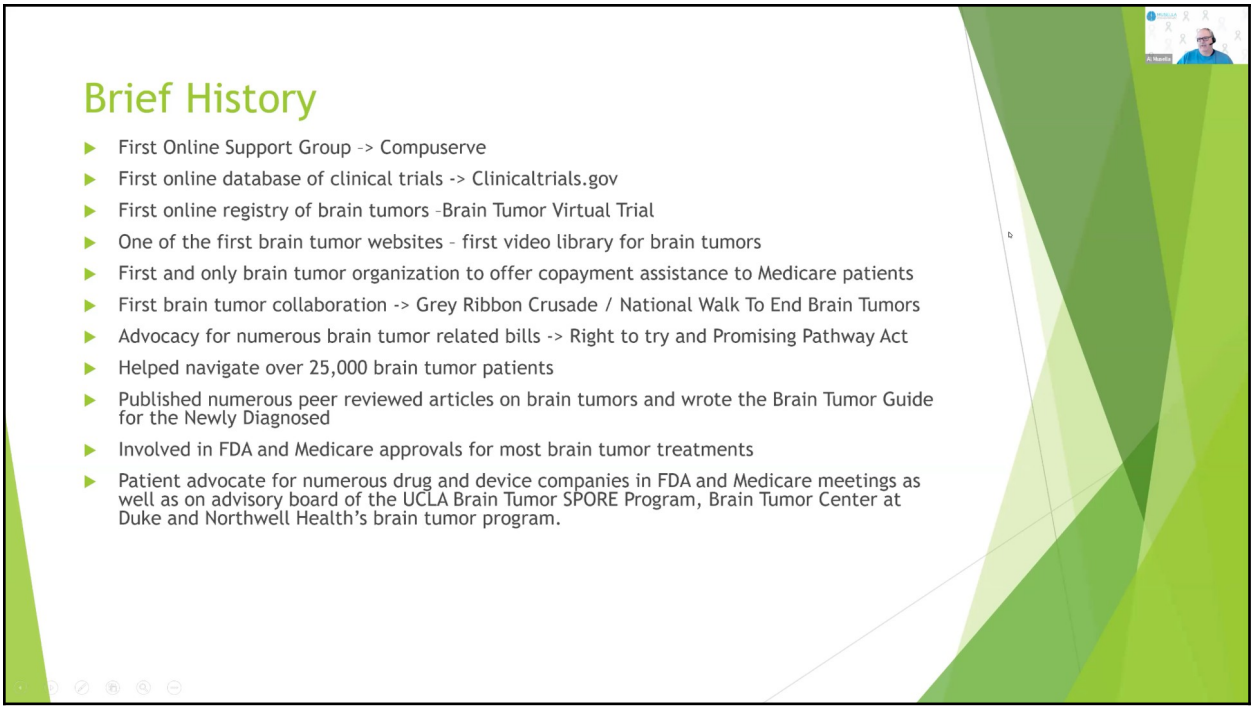
At the time, there were no internet resources because the internet was basically discovered that year. That was the year that Netscape came out. When you called the National Cancer Institute and asked for a list of clinical trials, they only had a small list of trials that they sponsored. They didn't know anything about investigator-sponsored trials or drug company-sponsored trials. They didn't have the technology to even fax it or email it to you. You had to wait for the mail, and it would take like three weeks. It was useless.

After I started the foundation in 1998, my dad was diagnosed in 1989. He didn't do too well.

“Reengineering Clinical Trials - The Promising Pathway Act” (Al Musella) [#90]

To go back to my sister-in-law. We found a clinical trial that would take her that Sloan Kettering didn't know about, and it was just like three miles away. I found an off-label drug that had a little study and publication. We used that on her. She actually lived eight-and-a-half years after being told it was over at the beginning. Strangely, her insurance ran out. It hit its lifetime maximum, which was a million dollars. So she stopped taking the drug about five years after starting it. Then she had a recurrence, and she died soon thereafter. So I blame the insurance company for her death. If she was still on the drug, it might have kept her going.

My dad was diagnosed the same month that temozolomide (a chemotherapy which is used to treat brain cancer) came out. To show you how different life was back in the 1990s, his insurance had a $500 per year maximum on drugs. How far would that go today? When he went to the drugstore to get it, there was like a $1,500 co-payment. He had the money, but he didn't want to leave his wife penniless. So he refused to take it. My sister and I got together and bought it. I just told him we got free samples of it. Otherwise he wouldn't take it. It didn't really help, and he died a few months later. But I also blamed the insurance delay in getting him started with it. Which is why I started the co-payment assistance program years later. I'll get to that later.



A brief history of me.

The only reason I'm telling you all this stuff is not to gloat, but so you understand that I'm not just a crackpot saying, “Let's try this new thing.” I have experience in this.

- I started the first online support group back on CompuServe.
- I created the first online database of clinical trials. With our support group, the first thing I did is I got all the members together, and we did a survey of every hospital in the United

States to see what treatments they were doing. Because there was no master list at that point. So I created that master list. The National Institutes of Health came to me, and they modeled clinical trials.gov off of me. My big contribution to that was to tell them to write a law that said, “Everybody doing clinical trials or human research had to report to clinical trials.gov what they were doing.” That revolutionized the whole thing. It meant that everybody had a list of all the clinical trials going on.

- I did the first online registry of brain tumors. We collected the treatments that people were doing and the outcomes. That was the brain tumor virtual trial.
- I created one of the first brain tumor websites and had the first video library for brain tumor information.
- I was the first and only brain tumor organization to offer co-payment assistance to Medicare patients. Medicare's funny, you can't just give money to them to help them pay for drugs. That's why coupons don't work on Medicare patients usually. There are kickback rules. So I had to get special permission from the United States government to do this. I did it a certain way. We've given out over $12.5 million to patients to help pay for drugs so far.
- I created the first brain tumor collaboration, which was the Grey Ribbon Crusade, and turned it into the national Walk to End Brain Tumors, which fell apart because of friction between the large groups and the small groups. Right now I'm involved in four other collaborations. They’re going relatively well, but there's still a lot of friction between larger and smaller groups.
- I did a lot of advocacy for numerous brain-tumor-related bills, such as the Right to Try and now the Promising Pathway Act.
- I helped navigate over 25,000 brain tumor patients. I go through this with a lot of people every single day. I'm starting to see that there are a few people that do well, but so many people are dying and suffering. It's the suffering that gets me. I just can't take it anymore. I know a better way to approach this. I think it's time to try it. Because over the last 30 years, we've really made no difference at all. We delayed it a little bit. But it's still a horrible, horrible disease.
- I also published numerous peer-reviewed articles on brain tumors. I wrote a brain tumor guide for the newly diagnosed. I'm just putting the finishing touches on a new book about low grade brain tumors.
- I was involved in the FDA Medicare approvals for most of the brain tumor treatments we have right now. I was a patient advocate for numerous drug and device companies for FDA and Medicare meetings. I’m on the advisory board of the UCLA Brain Tumor SPORE program, the Brain Tumor Center at Duke and Northwell Health's Brain Tumor Program.

So I'm not just like this crazy person. Let's keep that in mind.

“Reengineering Clinical Trials - The Promising Pathway Act” (Al Musella) [#90]

First: can early access really help patients?

I got permission from the parents of this kid to use his picture and his name. He was diagnosed with DMG (Diffuse Midline Gliomas, a fast-growing brain tumor) about May 2018. He tried two different clinical trials, radiation, and standard treatment. There's no standard treatment for this, but he tried the standard treatment for glioblastoma (another brain cancer), which is temozolomide (a chemotherapy). He failed everything. He was doing really miserably. He was on a downward spiral.

“Reengineering Clinical Trials - The Promising Pathway Act” (Al Musella) [#90]

He was bedridden, had vision problems, had trouble talking, had weakness in half of his body, severe nausea, in general, not really good. The family came to me for help. They wanted to do one last ditch effort to try something, anything. I suggested the drug Onc-201 (an oral, well-tolerated experimental drug used to treat serious rare pediatric and young adult brain tumors). I was familiar with Onc-201 because I gave these researchers their first grant to get the drug started. In general, to get drugs through this pipeline, you need early data to show some proof that it's worth something. What my organization does is we give those early grants to things that sound different and wild, that theoretically have a small chance of working, but it gets them enough data to get to bigger government grants, so that they could bring it to the pipeline. I know these people.

At the time it was a small company. There were only three employees at the time. They said they couldn't do an expanded access program because they didn't have the resources. They didn't have the people. They couldn't even answer the phones or answer email because they were just overwhelmed. I told them a lot of people want this drug. They couldn't get access to the clinical trials because of the very narrow entry criteria, and there were very few geographical locations. So I said we needed to get an expanded access program started. I said, “I'll help you run it, and I'll help fund it.” They agreed. We gave them $750,000 to get it started.

For this kid, I told them about this drug. We sent them to MD Anderson to get into the clinical trial. MD Anderson said, “He is too far gone, progressing too fast, nothing's going to help this kid. There's no treatment for him. No need to bother with any kind of treatment. Go home on hospice and just die.” That was it. Strangely, they charged like $50,000 for that one day visit and an MRI. He didn't have insurance at the time. So they paid $50,000, which I felt terrible about. They wanted to get on expanded access. We were just starting up the expanded access

program at that time. He was actually the second person to ever get into the expanded access program. We got him the drug. Right from the beginning, he started feeling better. He's been using it every day since then. It's been five years. I just heard from the family last week. It was the five year mark on the drug.

This kid is back in school. He's riding a bicycle. He's playing soccer. He's a happy, normal kid right now. It made a huge difference in this kid's life.

In our experience, it helps about half the people a little bit. And about a third of people a lot; not as much as him, he's our best person. About a third of people go on for a much longer time, at least two or three times what would be expected. Some of them are still going strong too.

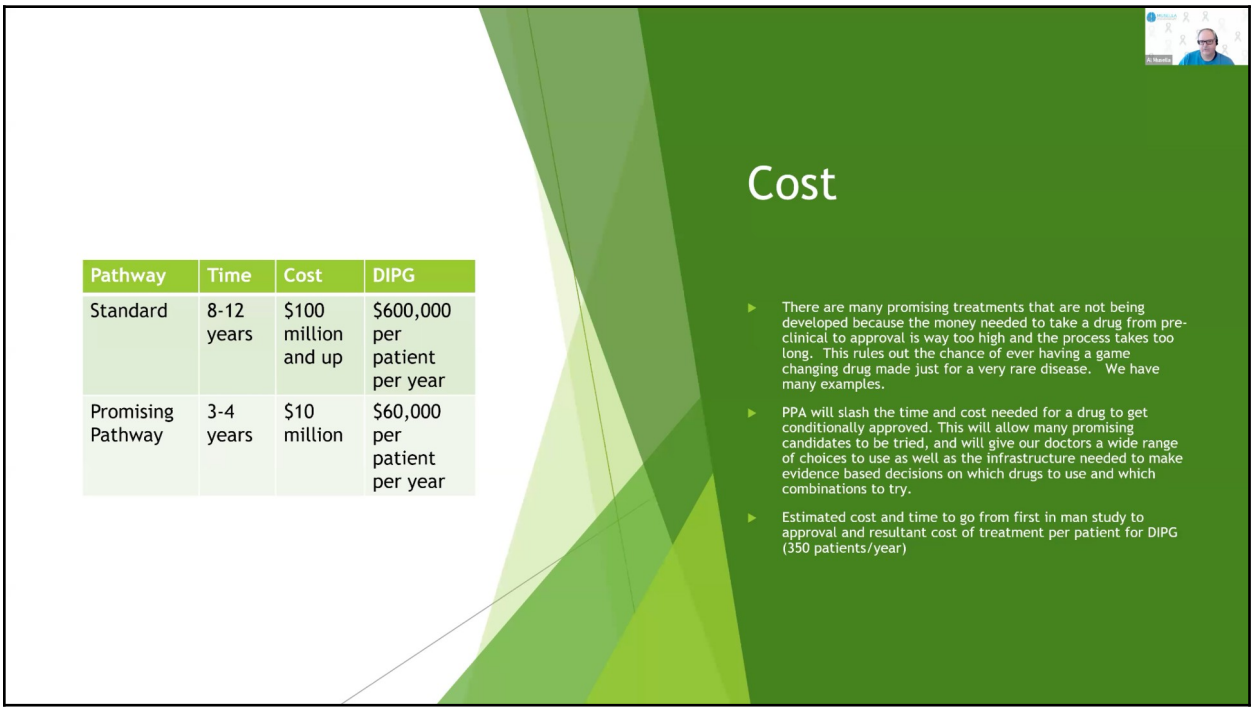
It sounds like expanded access worked perfectly. The trouble is, about 200 people contacted me asking for the drug, whom I couldn't get onto expanded access. It still had regulation. It still had requirements. They also were not allowed to do combinations in the expanded access program. It ran out after 133 patients.

We went to the FDA, there was an ODAC (Oncologic Drugs Advisory Committee) meeting, where the drug company presented all the data on the drug. I presented our experiences with it. We asked for permission to apply for accelerated approval. They said, “No.” They wanted a randomized trial to prove that this actually works. They were shown many cases where those responses on MRIs, and kids were doing well. I brought two kids with me who were doing very, very well at the time on it. They testified. I also testified. The FDA said, ”No. We want a randomized trial.” The problem is: no drug has ever been shown to help this disease. So there's nothing to randomize it against. So they decided to use an actual sugar pill placebo. Right now

the clinical trial is two-thirds of people get the drug, and 1/3 of the people get a sugar pill placebo, which is horrendous to me. I couldn't imagine being a parent, where they came to a trial where they may get a sugar pill to treat a disease like this, when you know there's a drug that works. Published reports say this more than doubles average survival. So there's no reason that the FDA can't just give this an emergency approval right now. But they just won't. They don't understand our needs. It's very, very upsetting.

It worked in this one case. But there are so many hundreds of other people who wanted access and just couldn't get it. Expanded access is not meant for a large number of people to get access. It's for a very small, select group of individuals. Because people who have bad insurance or no money, will go to a Medicaid doctor, and they don't have the time. It takes a doctor probably 12 hours of paperwork to do an expanded access program like this. They can't get paid for it. How many doctors are not going to waste that much time on a patient when they're not getting paid for it? It's just not practical.

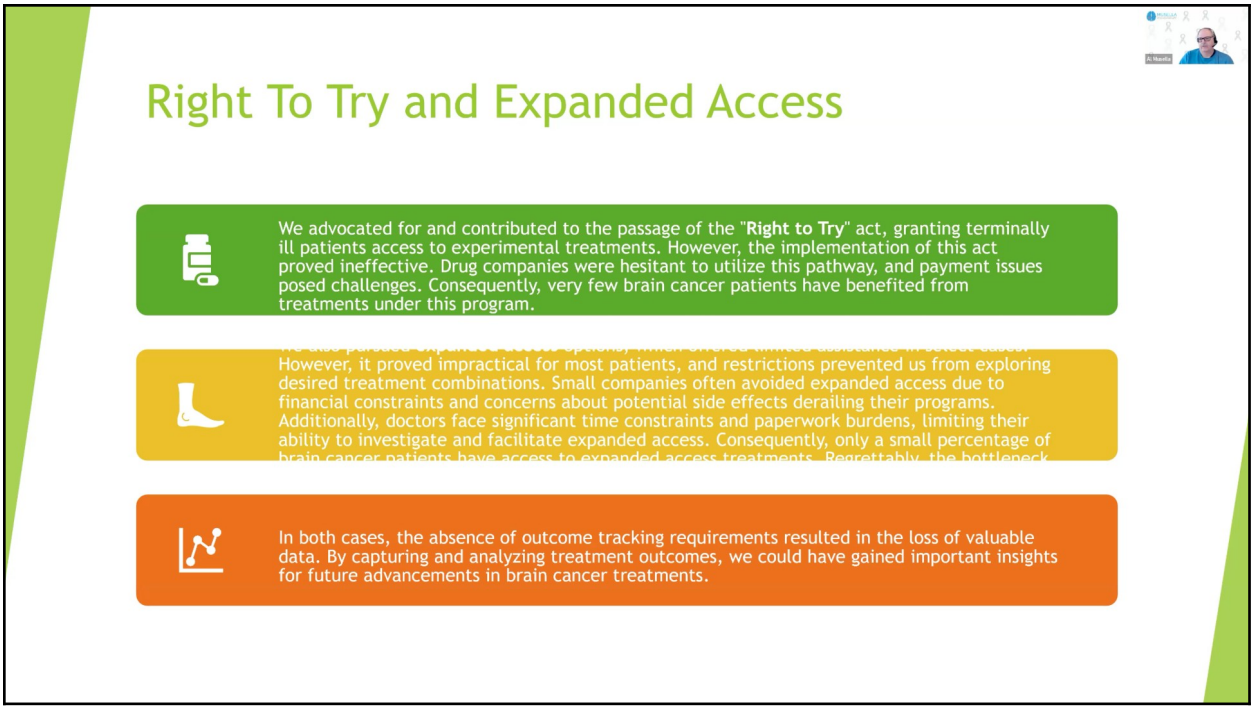
We need a solution where any patient who wants these drugs can get access to them.



Then there is the issue of cost. Under the standard pathway, a drug for DIPG (Diffuse Intrinsic Pontine Glioma, an aggressive childhood cancer in the brainstem) has to cost at a minimum $600,000 per patient per year just to repay the cost of the development, not including the cost of the actual treatment itself. Under the Promising Pathway Act, we could cut that down to these numbers. A drug could be like $60,000 per patient per year. If you keep in mind that we're thinking it's going to be a three- or four-drug combination, you have to quadruple these numbers. So for the standard pathway you're talking about a $2.5 million treatment per year per patient. That's really not practical. It gets way too expensive, whereas it's possible under the

“Reengineering Clinical Trials - The Promising Pathway Act” (Al Musella) [#90]

Promising Pathway Act. The important thing is: I know of so many different drug candidates in preclinical research that can't make the jump into human trials because they can't think of raising money like this. Under the Promising Pathway Act, they can. As a matter of fact, we get a few of the nonprofits together and get three or four new drugs into the pipeline every year. We try them in a phase 1 trial, and of the ones that have passed, we'll put them through this pathway. And we'll get a few drugs every year going into a pathway where eventually we're going to hit a homerun. But you can't do that in the normal pathway, because it's just too expensive.



The other alternatives are the “Right to Try” and “Expand Access”. I thought Right to Try was going to be the big one. I spent so much time and energy on this. We got it passed, but it didn't work. In brain tumors, probably a handful of people ever got a treatment through Right to Try. The biggest problem is cost. Insurance can't pay for it, and nobody's going to give it for free. For example, there's an experimental vaccine available on the Right to Try right now. Only like three to five people got it so far. It was really expensive. Their initial estimates were about $30,000 per month, which was insane for most normal people. Only the rich people get it. It makes it look bad that only rich people can get these treatments. Drug companies were a little bit afraid to go outside of the FDA, thinking that the FDA would hold that against them. Everybody's afraid of the FDA, which was really not right either.

With expanded access, there are still too many restrictions. It takes too much time from the doctor. Not enough people are getting access to these drugs. It's just not a solution for a large number of patients. It's good for a select few people. But still, this problem of price where a drug company is allowed to charge their actual cost. Very few would actually do it. They wind up giving it for free, because they don't want that situation of making it look bad to have only rich

people getting access. They also don't want the government to know how much it costs, because if they're going to charge, you have to go through an audit with the FDA to see exactly how much the drug costs. Once they get approval, how do they explain that a drug that costs $10,000 is now $100,000.

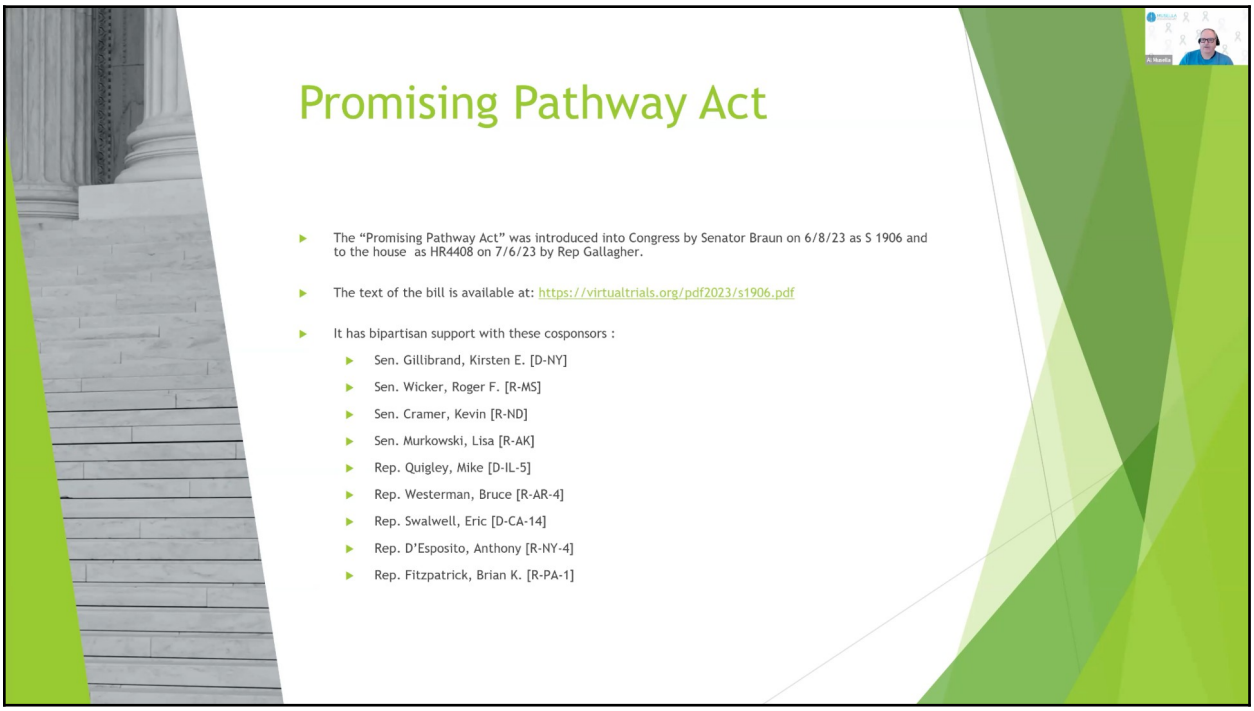
These two pathways, although they do help, they are not enough. The average patient is not going to get a drug from this. It's also not going to increase the number of drugs available to patients.

Accelerated approval was a great start. This is a modification of standard approval where you use a surrogate endpoint instead of a clinical endpoint. Instead of overall survival, you would use progression-free survival. But that broke down recently, with the Avastin trials for glioblastoma. Avastin in glioblastoma makes the MRI look great, even the next day because it tightens up the blood-brain-barrier a little bit, and it doesn't let the gadolinium (the contrast agents used with MRIs) get through. So it makes the MRIs look much better. One of the surrogate endpoints was response. Like 100% of patients had a response. It looked fantastic.

The second one was progression-free survival. Because it makes the MRIs look good, it hit the progression endpoint. Even though people were progressing, their MRI still looked good. It made the progression-free survival look good, even though it wasn’t helping. But then the overall survival did not change at all. So the FDA looks at this, and they say, “You had a major increase in progression-free survival, but no change in overall survival, which means progression-free survival has no impact on overall survival.” They said they don't really like this as an endpoint. So they didn't like progression-free survival, and they didn't like response rate, which doesn't leave that much. We have a problem with accelerated approval. I don't know how

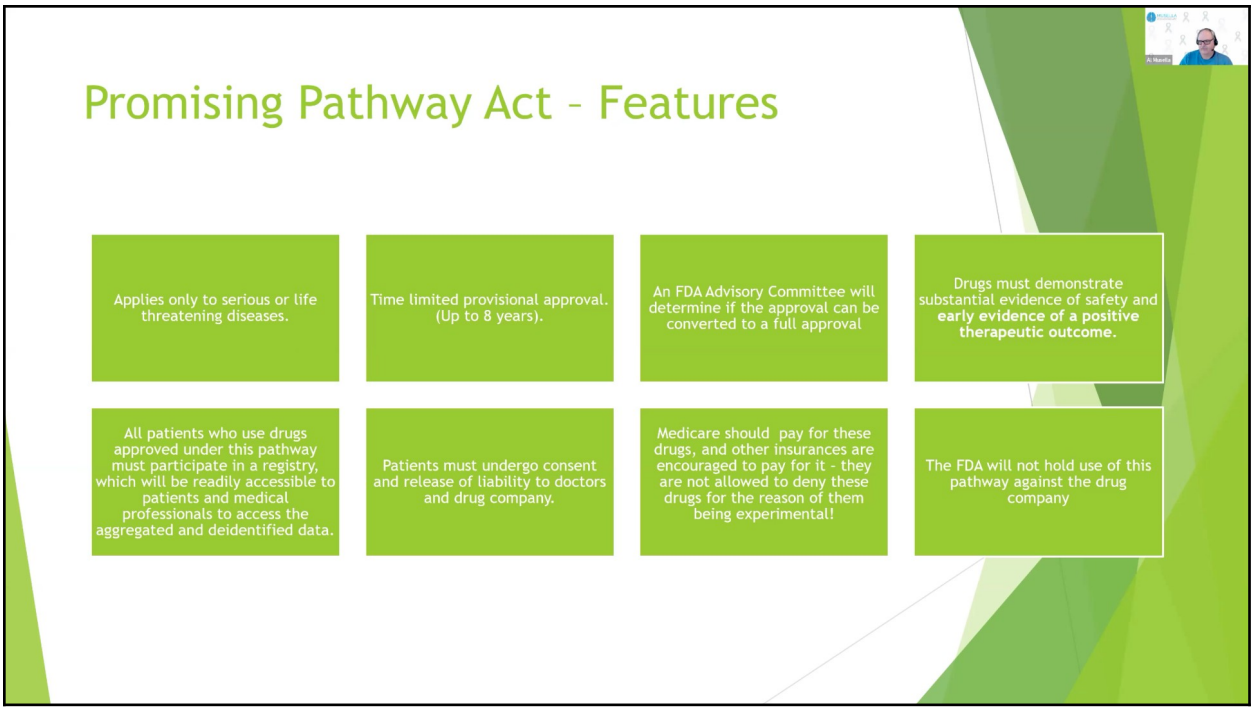
it is with all these other cancers. But in brain tumors it is not good. We asked for accelerated approval of Onc-201, but, as I said, they rejected it.

Accelerated approval drugs have to be good enough on their own to get approval. Like Onc-201 is the best drug we have for these diseases. But by itself, it might not hit the standard of being good enough to get approved. But it doubles overall survival. Thinking that that might not be good enough for some reason? I have no idea. But we know that combinations of it will be much better. You can't do the combinations under accelerated approval. Under Right to Try you can. It's just a matter of money. But under expanded access, you can't. Usually there's a protocol in place that says you can only do exactly whatever the protocol says.



Al Musella 19:49
That brings us to the Promising Pathway Act. It was introduced into Congress. We have bipartisan support with all these different senators, but there was some pushback on it. So we went back to the drawing board, and we modified it. We came out with Promising Pathway Act 2.0, which is going to be introduced into Congress in the next week or two. Congress has been really busy with other stuff, which is why it's taking so much time. I hate all the delays that we get on things like this and all the time it takes, but that's how life is.

“Reengineering Clinical Trials - The Promising Pathway Act” (Al Musella) [#90]



Here are the features of the Promising Pathway Act. It applies only to serious life-threatening diseases. So obviously, the current pathways for a blood pressure drug are fine: you want to make sure something is very, very safe and effective before you approve a drug that 10 million people are going to take for a disease, where if that drug wasn't available, there are many other options. We're talking about diseases where there are no other options.

It's time limited, provisional approval for up to eight years. An FDA Advisory Committee determines if the conditional approval can be converted to a full approval. So you're going to get two chances. You could ask for a FDA advisory committee meeting at any time to present the data that shows that it's good enough, or at the end of the eight years, there's an automatic meeting where the FDA advisory committee looks at all the data and says whether you can get full approval, or not. If you don't get full approval, you lose your conditional approval and have to go back to the original pathway. At that meeting, the level of proof is the same as under the standard pathway. So it has to be good enough to stand on its own.

Or if you have enough proof of a combination that works, you can get the combination approved. This gives us the time – those eight years – to work on combinations. Hopefully, we'll get enough data that shows something works.

To get into this pathway a drug must demonstrate substantial evidence of safety and early evidence of a positive therapeutic outcome. What that means is: it has to go through at least a phase 1 trial in pediatrics and in adults a phase 2 trial. There's a little bit of a lower bar for pediatrics.

“Reengineering Clinical Trials - The Promising Pathway Act” (Al Musella) [#90]

Early evidence of positive therapeutic outcome could be a biomarker, like if it's an EGFR inhibitor, if it lowers EGFR, that's a good enough positive therapeutic outcome. It doesn't have to be overall survival at this point because you don't have the time to get to that much proof. It'll just be enough to get into the conditional approval pathway. The way I look at it is, if the drug is deemed good enough to go into a phase 3 trial, it's good enough to go into the conditional approval pathway. So the level of risk is the same as if you're going to a phase 3 trial. Actually, it's less of a risk, because you don't have the risk of getting a placebo. The Promising Pathway Act removes all placebos.

It's just a different way of doing research. Instead of a phase 3 trial where you take a select group of people, and have to be very rigid in how they're treated, you take any patient who is willing to take it, and it's optional, you have to be willing to take this, you're not forced to take this. We'll see how it does for every single patient. We get much, much more evidence on how effective the drug is. Because you’re not only tracking the experimental drug, you're also tracking all the other treatments that they are taking. You are looking at the combinations.

In my opinion, it's impossible to run a valid phase 3 trial in the United States right now. A perfect example is that Onc-201 trial. There's a counterfeit version of Onc-201 floating around. It's made in Germany. Probably 200 families in the United States are using this illegal drug from Germany. And most of those kids who are taking it are also in a different phase 3 clinical trial where they don't know that the kids are taking Onc-201. So you have these clinical trials. But people are taking a pretty effective drug and not telling their doctors. It destroys all the other clinical trials. It's crazy. There are many cases. I would say the vast majority of people in a phase 3 trial are taking something in addition to the trial drug. For example, they might be taking CBD oil, some other supplements, or some other off-label treatments, and not telling their doctors. These other treatments might have more of an effect than the trial drug. So I think it's better to look at a large number of patients, find out all the treatments they're doing, and analyze it, instead of the charade of a regular phase 3 trial. There were three successful phase 3 trials in brain tumors. In all three of them nobody believed the outcomes. It was insane. They all got picked apart completely to the point where they were useless.

In one of them there was a drug called “Gliolan”. (Gliolan helps surgeons to see the tumor more clearly during an operation to remove it from the brain.) It was used in Europe for about 25,000 patients as a standard of care all over Europe and Asia. But the FDA refused to give an approval. One of my friends was developing this drug. The FDA said they wanted one more phase 3 randomized trial before they would give approval in the United States, even though it was 100% completely safe and showed a remarkable effect, and it was used in 25,000 patients. So they ran this big phase 3 trial that took about five years, and something like $30 million. When we got to the FDA meeting, going for FDA approval, they picked apart the trial and said they didn't like the way that it was blinded. They just picked apart the design, and they approved the design in the beginning, which makes no sense. You would think that once they approved the design, how could they pick apart the design? They didn't like the way it was blinded. They said the way it was blinded, half the patients got the dye. This is a dye that is used during surgery, and lights up the tumor, so the surgeon knows where the tumor is, so you get a more

complete resection. The way they blinded it is before the surgery, they would get a piece of paper that said either “yes”, you use the drug, or “no”, you don't use the drug. So the ones who used the drug, they got the dye, they were able to use the special light in surgery and remove most of the tumor. There was a much bigger number of people who had complete removal of the tumor in that group. The people that didn't get the dye just went on to the normal surgeries. The FDA said, “No. That's not the right way to do it. The right way to do it is everybody gets the dye.” And then at the time the surgeon thinks he's done under the normal surgery, he gets a slip of paper saying “yes” or “no” whether he could turn on the light that makes the tumor glow. Which is crazy. Because they said it induces bias because the surgeon knows whether they're able to use a dye or not before the surgery, they could do things differently. They basically said it was a completely invalid trial. However, based on all the other research that's already been done in Europe, and all these other places, we're going to give you approval anyway. The bottom line was they wasted five years and all those millions of dollars, when they should have really gotten approval right at the beginning.

Then Optune comes along. Optune is one of my favorite treatments. These are these electrodes that are on top of the skull. People said they didn't like that. It was a randomized trial with half the people using the device, and half the people didn't use the device. They said the device should have had a mock control, where you have to wear these arrays, but it doesn't turn on the energy. It's a very big hassle to use. It makes no sense at all to make people undergo this. And they were using overall survival as the endpoint anyway. So you don't have a placebo effect with overall survival. And if you did, it wouldn't matter. Because if the placebo effect was that big, people would want it anyway. So they disregarded most of that trial and half the doctors in the country still don't use it because of that.

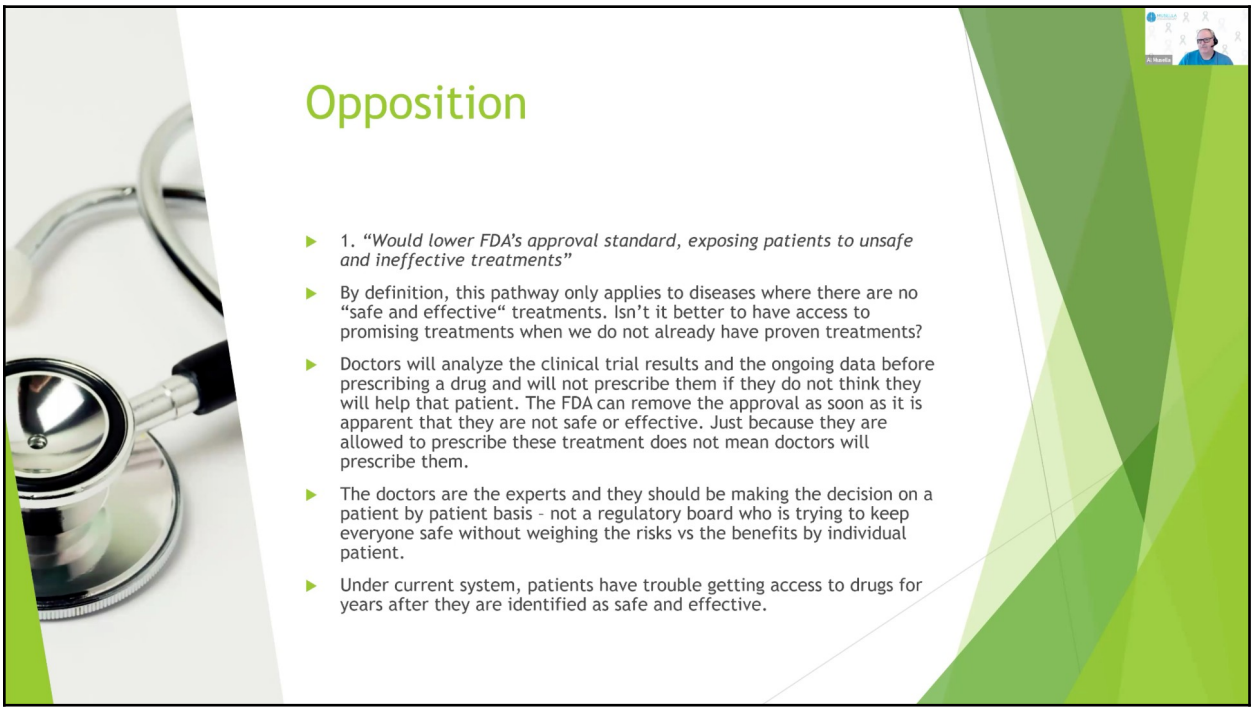
The other one is DCVax. It's a vaccine. It did great in clinical trials – the best results for recurrent glioblastoma of anything we've ever seen. But there were a few problems with the trials, such as they changed the trial around so that there was a crossover because patients really wanted a crossover. The endpoint was overall survival. And if you do a crossover where people who progress go on to the drug, now you're comparing people who use a drug against people who use the drug, which makes it hard to analyze. They also found that patients who used the drug and had a good response to it got pseudoprogression. The scans looked worse because the vaccine was working. It made it look like the progression free survival was shorter, even though it wasn't. These people lived a long time. It just made the MRIs look bad. So they removed the progression free survival endpoint. And people are criticizing and saying, “Once you change the endpoints, you have to change the trial around.” And they used an external control group, instead of a randomized control group, because of that crossover. So it gets criticized so much. I don't think half the doctors in the country believe it right now anyway.

If you're not going to trust these phase 3 trials that are so expensive, and you're not going to use their information, why bother with them? There's a better way where we could study it. The data you get in a virtual trial like this is not as theoretically clean as data you get in a clinical trial. But if you're using 10 times as many patients, I think that sort of evens out, and you could

get better data from a large group of people with no other information, rather than a small select group of patients who are not even similar to the target population anyway.

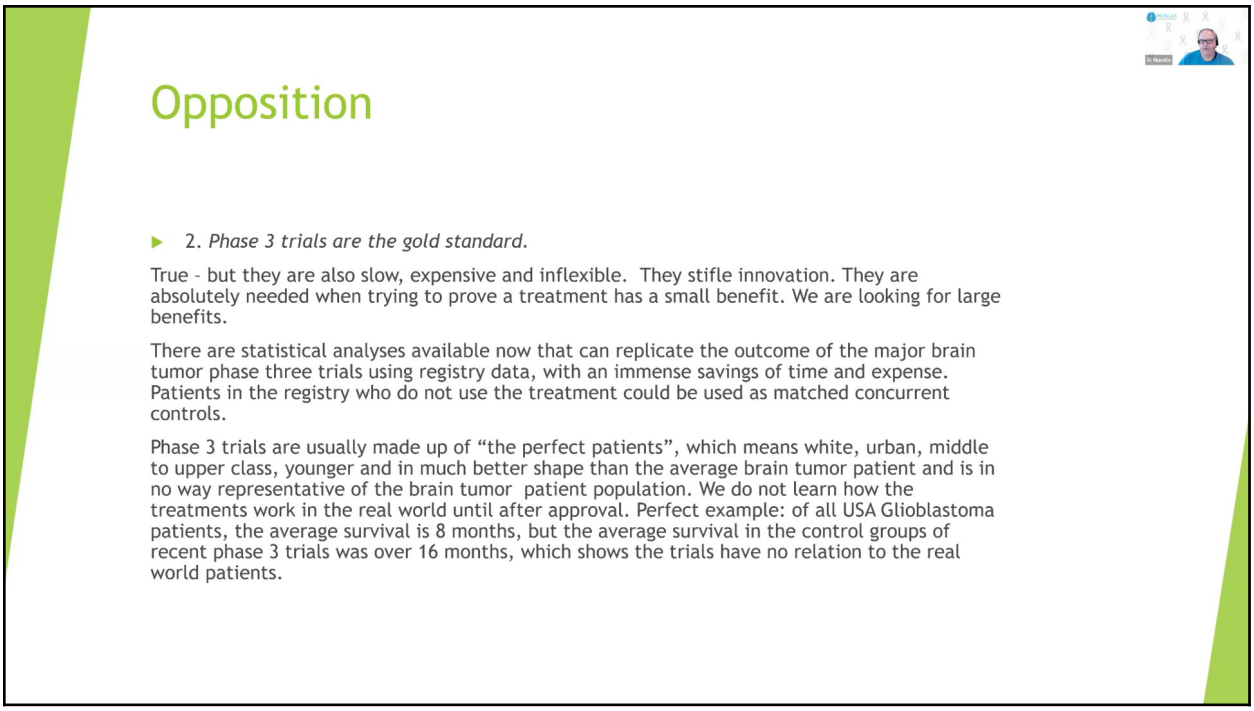
In the United States, the average survival for glioblastoma is only eight months. But in clinical trials, the control groups’ average survival is about 16 months. So just getting into the clinical trial, you would say, on a control group, doubles your survival. But that's not really true. What's happening is there are such selected patients that they're in a better prognosis group, and they don't represent the average patient in the country.

These phase 3 trials that they're running are useless. This is a much better way.

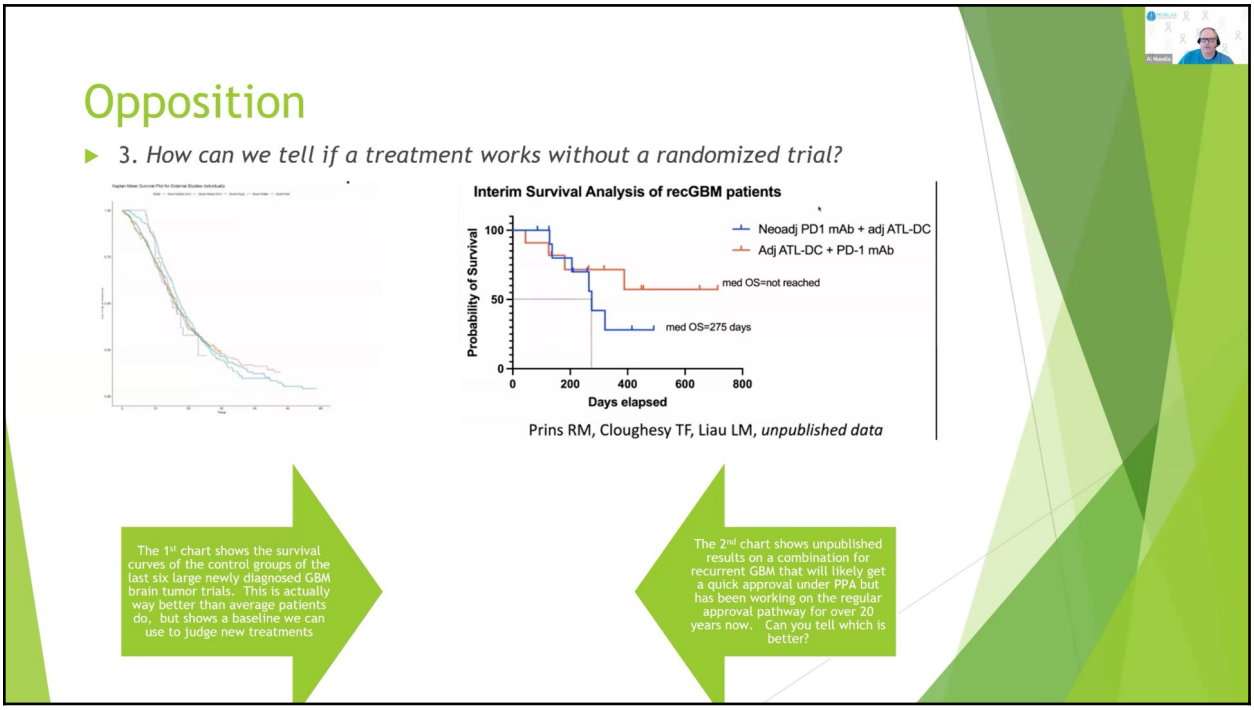


There's some opposition to it. One of the biggest things they say is that this will lower the FDA approval standard, exposing patients to unsafe and ineffective treatments. These people don't understand. It's basically the same approval standard. Once they get full approval, it's the same standards. The difference is, instead of doing a phase 3 trial, you're letting anybody participate in this virtual trial. So it's basically just a different way of doing the phase 3 trial.

“Reengineering Clinical Trials - The Promising Pathway Act” (Al Musella) [#90]



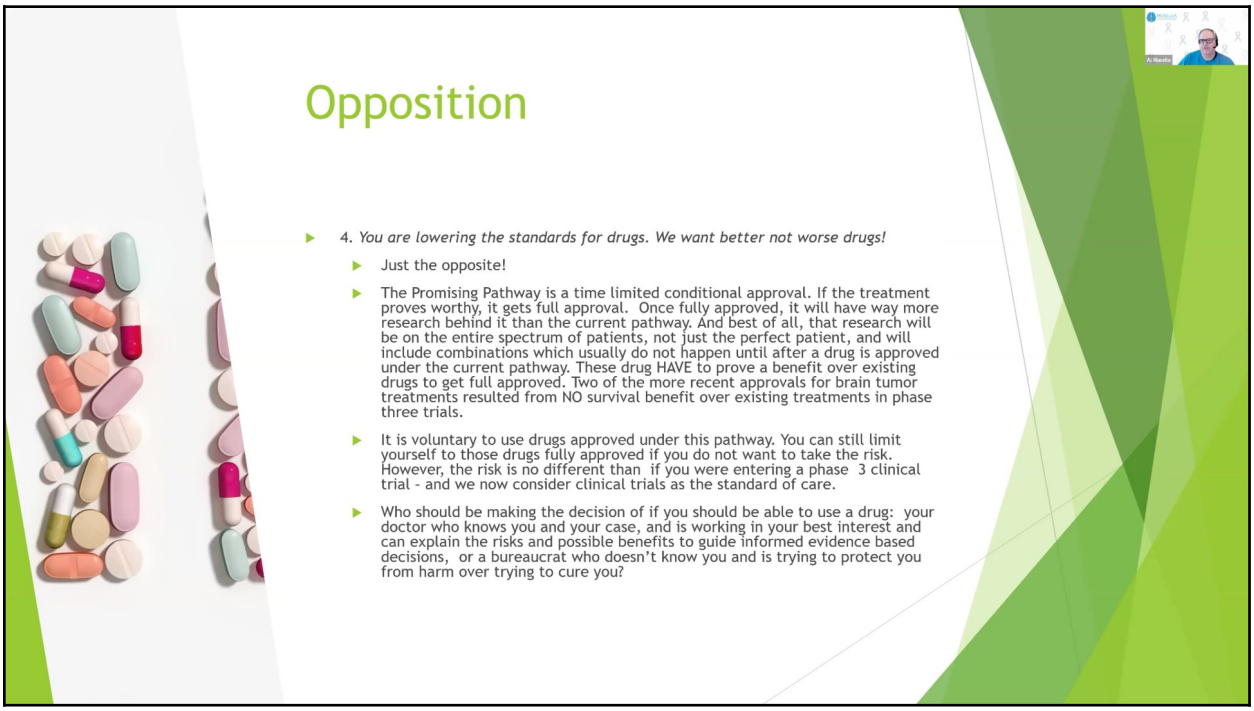
They say phase 3 trials are the gold standard, but I just explained why there are so many problems.



How can we tell if a treatment works without a randomized trial? This graph on the left, although it's hard to read, you can’t see the numbers, but that's the last six large clinical trials for newly diagnosed glioblastoma. This is a control group. All these treatments are exactly the same. All

these patients did exactly the same. You know what a patient is going to do with glioblastoma if the treatment doesn't work. This is the standard treatment. For the people who take the standard treatment, that's how bad it looks.

I mentioned DCVax. This is an offshoot of DCVax. This is DCVax plus a checkpoint inhibitor. They did it two different ways. Even the worst way is tremendously improved over this. The best way, you're talking about a major difference. All you have to do is look at the shape of the curve. If you could convert a curve like this into a curve like this, I would try it no matter what the statistics said. Statistically, this is going to wind up looking good. I don't need the phase 3 trial to confirm that this is working. If I saw a graph like this, I would take this drug.



They say you are lowering standards. We want better drugs, not worse drugs. It's just the opposite. This will allow us to get many new drugs into the pipeline. You'll get much more data on each drug on how to use it. And we'll get to see how the combinations work, which you don't see on the regular pathways. We'll see much better drugs and much better combinations than you can now.

“Reengineering Clinical Trials - The Promising Pathway Act” (Al Musella) [#90]

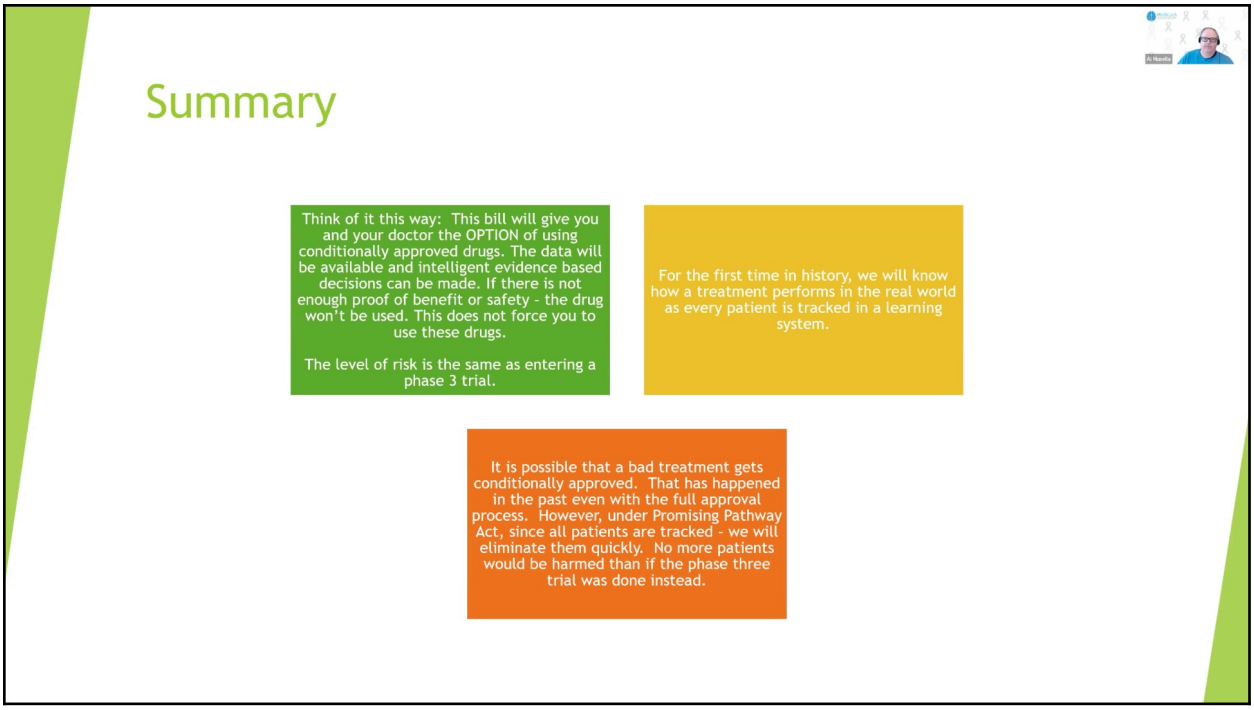
We expect a few brain tumor drugs to get approved quickly after the act is approved, then a few more each year. We have a patient navigation program that has been creating combinations of these drugs. We just couldn't get access to them. But it's a perfect learning system to use to figure out which combinations are best.

Doctors will finally be able to use their brains and think up these combinations, instead of just going through this little checklist of saying, “Well, for sure do a clinical trial. If you can't do a clinical trial, try A, B and C.” They never vary from this, especially at the major centers.

We also think that drug prices will eventually drop, or at least remain stable as you get much more competition and the cost of development plummets. Without the PPA, the new drugs are going to have to skyrocket in price to the point where we're not going to be able to afford them. There was just a drug approved recently that was about $4 million a dose. That's insane.

We will dramatically speed up the search for the cure. The amount of research on each drug will dramatically increase. From the point of view of a new patient, for example, if a new patient comes to us and they say, “What do you think would be the best treatment?” I know that there are three or four treatments that I would want to take if it was me. We went through this on a different webinar. But the trouble is you can't get access to it. For example, if you want a vaccine. Right now, it's really hard to get a vaccine, especially the better vaccines. There are a few vaccines out there that already showed at least doubling survival and long term survivors. In general, they say the five year survival rate is about 5%. Each of these different vaccines had about a 20 to 25% increase in five year survival. You combine a few of those, and we will be able to have a shot. But in this current system we just can't get access to it and it's so terrible. We tell people to get into clinical trials. For my two or three favorite clinical trials, I would send

20 patients to the trial, and we're lucky if one of them gets in. It's so hard to get into the best trials right now. Let alone that it's hard geographically. For example, the best trial might be in Los Angeles, and people aren't going to be able to travel from New York to Los Angeles for a clinical trial. It's just not fair. We need these drugs approved now, so that we can just get easy access to them.



In summary, think of it this way. This will give you and your doctor the option of using these conditionally-approved drugs, the data will be available, and intelligent evidence-based decisions can be made. Under the current system, you don't get details about how a treatment has done. You'll never get it. They might publish some research on a select group of patients. But you'll never get published results on a typical patient.

If there's not a proof of benefit of safety, the drug just won't be used. Just because they're available doesn't mean anybody's going to use these things. Your doctor has to be ready to try these. In the beginning, when there's very little evidence, it might be tough. Although you always get people who are in a difficult situation willing to try anything. They'll try it first. And then when the first few people do well on it, then other people will start using it.

For the first time in history, we'll know how a treatment performs in the real world as every patient is tracked in a learning system. That's one of the keys. That's why we need to speed up the pace of this research. We need to know how every person is doing with every doctor in the country. Many doctors around the country try different combinations, once they get rid of the standards. But nobody's tracking it. If they happen to come upon something that's working, nobody benefits from it. And worse, if they find a combination that definitely doesn't work, they never publish it. Nobody knows about it. Other doctors keep repeating the same mistake over

and over and over. I think we need to track every single patient in the system so we don't make those mistakes. It's possible that a treatment gets conditionally approved. That's happened in the past, even with a full approval process. Why? Because we're tracking these people in a learning system. We will eliminate those quickly. No more patients would be harmed than if the phase 3 trial was done instead.

There are some alternative treatments out there that have been used for over 30 years. We have no idea how well they work. People keep falling for this. These are very expensive treatments. We think that they're worse than the standard of care, if that's possible. But because nobody's tracking it, we can't say 100% that it's not working. We know what's not working, because if it was working, we would have a lot of survivors. There are only about two or three long term survivors from this. But those two or three long term survivors are all over the internet, getting new people into this. We're not even sure if it's true because there's no transparency. With this, there's transparency, and we see how every patient does.

Insanity is doing the same thing over and over again and expecting different results. And that's what we've been doing. And I want to change the system so that in my lifetime, we see a cure.

Roger Royse 38:09
What I've found, and I think a lot of us have found, is a lot of resistance from the doctors themselves. We know the FDA is a problem. We know the insurance companies are a huge problem. But oddly enough, once you get past all those hurdles, then you have to find a doctor that's willing to take the risk.

Does this legislation provide any sort of incentive there for that to happen?

Al Musella 38:45
One of the incentives is the patient has to consent to it and release the liability of the doctor and the drug company. The biggest worry most doctors have is, “If I try a new drug like this, and it doesn't work, the family is going to sue me.” They don't have to worry about that. That's really the big one.

Roger Royse 39:06
Is there enough money in this to make it worthwhile for a medical institution to take this on? Believe it or not, I've heard that from some doctors,

Al Musella 39:16
That's the biggest problem we have. Because a lot of these doctors make all their money on phase 3 trials. It's very expensive to run a phase 3 trial. I was just talking to a drug company today. They pay $1 million per patient to a hospital for a phase 3 clinical trial. That's going to be replaced by an office visit where you just prescribe the drug. So that's going to be a major problem. I don't really care about these doctors who do this, but that's where our biggest opposition is coming from.

But people win and people lose. I care about the patient in this particular case. I don't care about these rich facilities. Some people will win because they could now develop more drugs. If we're going to have four or five drug combinations, there'll be four or five different companies involved who are going to make a profit.

Roger Royse 40:11
They will be the cheerleaders, I guess, to get this done.

Al Musella 40:16
We’re the cheerleaders.

Vanessa Hugo 40:19
The patients are the cheerleaders.

Al Musella 40:22
The system was not designed to be a moneymaker for a hospital. That should be the least important thing. They'll make the money on the other cancers that are treatable. And wait until I say you don't need radiation anymore. Radiation oncologists are going to kill me.

Roger Royse 40:40
Does this mean that there are no or very few exclusionary criteria? That is, are the drug companies required to allow most or all patients?

Al Musella 40:55

Right now, if you get the conditional approval under the Promising Pathway Act, any doctor could prescribe it for the indication that it was approved for. They're not really going to allow off-label use of these drugs. For example, if it's approved for glioblastoma, anybody with a glioblastoma can get that drug. There are no exclusionary criteria.

Vanessa Hugo 41:22
It would include contraindications for whatever the treatment is. Those people will be able to get it.

Richard Anders 41:27
It's a complicated question because clinical trials are really carefully designed, as you already pointed out, to exclude people in a way that hopefully will make your trial results better. So are they going to be able to say things like, people who've been pretreated with four other things or people who are resistant to this? Or are they basically going to say, in a very broad category, if you have GBM, then you are eligible for the drug? Or are they going to slice and slice and slice the categories into very narrow criteria, so that basically, it's exclusionary criteria?

Al Musella 42:03
If you have a glioblastoma, you could get the drug. However, the way I envision this, and it hasn't been hammered out exactly yet, the drug company is going to be allowed to propose a few like a “data plan”, where for the endpoint of getting full approval, they'll say, “We only want to count patients who would meet these criteria.” Everybody could use a drug, but we'll only watch those patients for the purpose of getting the full approval. Like we won’t take patients who are on their deathbed, as a last ditch effort.

Richard Anders 42:46
That's brilliant. They'll pre-identify cohorts that they want to use as endpoints upfront, so that effectively they're creating virtual clinical trial endpoints. But the goal is that almost everybody. If you don't have a certain mutation, and it's a drug to hit a certain mutation, you want to exclude those patients, of course.

Al Musella 43:08
The doctor wouldn't prescribe that. That's where the check is: the doctor has to prescribe. He has to think that it's going to help.

Richard Anders 43:15
It's a much more complicated question than that. Because you could say, “What about a patient who doesn't have a certain level of immune marker in the cell, and the patient says, ‘I want to try it anyway.’” And they find a doctor who will do that. The drug company could, in theory, say, “We want to exclude those patients.” And biologically, it's a necessity. But the question is, can the drug company exclude on the basis of,”These are the things I feel like we should exclude.” As opposed to, “These are very scientifically-driven exclusions”?

Al Musella 43:47

The drug company would have no say on which individual patients get it. But what they do have is a say on who would be counted in that cohort.

Richard Anders 43:55
That's really interesting. Brilliant. Great idea.

Amit Gattani 44:06
This is an interesting topic, especially for some of us, who are trying to do some of these off-the-road treatments right now.

What really helps bring down the cost 10x?

You showed the standard pathway which is promising.

Al Musella 44:36
We're going to get rid of the phase 3 trials or minimize them. They could still run phase 3 trials, but it's not going to be required. Usually, a phase 1 trial is tiny. Phase 2 is small, and phase 3 is very large. They're the most expensive ones. By getting rid of the phase 3 trial, you get to cut out the most amount of time and you get to cut out the most amount of money. Also, you're not going to have to do multiple phase 2 trials. It's just like one relatively small phase 2 trial to get approval and you can start making money.

Amit Gattani 45:04
How many drugs have gone through this so far?

Is this focus primarily on brain cancer, or is it open to all other types of cancers? Has it been tried successfully, let's say in prostate cancer or something else?

Al Musella 45:29
It's not a law yet. It's a proposed law. They're just going to introduce it into Congress probably next week or the week after. Then it takes however long to actually get into a law.

It's not just brain cancer. I forget the exact wording used in the bill, but it's a serious disease with no effective treatment. The main ones that we were concentrating on are ALS – that's what the bill was originally written for – brain tumors, ovarian, and pancreatic.

In prostate cancer, I would think it'd be possible for a specific circumstance like maybe prostate cancer patients who failed whatever. Not just like a general prostate cancer diagnosis, because for most prostate cancer patients, they do very well. It's only a small percentage of you that have major problems. So if you could identify that subgroup that has the problems, you could probably argue for getting a drug approved for that.

Do you have any idea what that would be? It would be prostate cancer patients who what…? What would be bad?

“Reengineering Clinical Trials - The Promising Pathway Act” (Al Musella) [#90]

Amit Gattani 46:47
Is there a list of organizations that are supporting it?

Al Musella 46:53
We have a group of 100 organizations that are supporting it.

Vanessa Hugo (in the chat):
The link is here.
If you click on that, it lists 102 organizations that have endorsed it so far.
We're looking for more!

Al Musella
Unfortunately, the two biggest brain tumor organizations don't support it. We're working on them. They just don't agree with me. They don't think it's a good idea. But these 100 other organizations do. It's just a different way of thinking about it. It’s the scientifically correct way to do it, the tried and true method that we've been doing for these years if we have another 100 years to wait to get the cure. But we don't have time. I want to see this in my lifetime. I think we can make a major difference within months after getting this approved.

There are a few treatments that we want right now. For example, Michael has been trying to get Suboxone (a narcotic to treat opioid addiction), and he can't get it. A few of these other drugs, they just can't get it.

Brad Power 48:10
What can we do to support this?

Al Musella 48:19
I'll tell you when it's time. As soon as they reintroduce it, which is going to be in the next couple of weeks.

We have to contact all our senators and representatives. I have an easy way to email: if you go to our website, you put in your name, address, a couple of clicks, and you send it to your congress people.

I learned that this is really important. It's probably more important than even donating money. Vanessa's husband had a meeting with Bernie Sanders. He said he's not opposed to it, but nobody has really asked him to support this. He said that if he gets people in his district asking for him to support it, he will. We need patience. We need people to contact their representatives and push this. These congressmen get about 200 or 400 bills a year. They don't know any of this. They don't know the details of something like this. What they do is they look at who's getting the most push, and they look at those bills in detail. They won't even look at something like this unless the people tell them they want it.

Vanessa Hugo 49:27
This bill only applies to a small population of people. I mean, it's a large population, but relatively we're a small constituency group. We need everybody in our constituency group, everybody that is facing these terrible diseases, to call their senators and call their reps.

Al, correct me if I'm wrong, but we have a lot of support in the Senate. So I think we're trying to really rally support in the House now.

Al Musella 49:53
The same checkbox is easy for senators and representatives, because even though they say something now, you have got to keep this on their mind so that they know how important it is.

Amit Gattani 50:09
Is there any linkage to Biden's Cancer Moonshot program?
Can that be a catalyst for this?

Al Musella 50:27
One of the collaborations I'm in is part of the Cancer Moonshot program. They are asking ARPA-H (the Advanced Research Projects Agency for Health) for a huge grant to implement a brain tumor learning system, which is basically our patient navigation program. They're partnering with us to do a patient navigation program on a much larger scale and get a lot more support from programmers and artificial intelligence. They're going to do that through a large ARPA-H grant. If they could get this learning system going that's part of the Promising Pathway Act, they'll be a big part of the Cancer Moonshot deal. Unfortunately, I was not invited to the meeting. Hopefully, I'll be invited to the next one. But the Promising Pathway Act didn't come up. I'm sure the President would love something like this.

I would wait until I tell Brad, and he'll send out a message to the members.

Dan Moynehan 51:46
I like the idea of mentioning the Cancer Moonshot. That might be another way to get the attention, at least of some of the Democratic representatives and senators.

Al Musella 51:55
It's bipartisan. It's split 50/50 in the support of Democrats and Republicans. The first time we tried it was all Republicans. Now we finally have Democrats on our side.

Richard Anders 52:22
Is the database going to be publicly available? (De-identified)

Al Musella 52:26
We’re talking about this now. Theoretically, right now, any doctor or researcher can access it, and patients can access their own data. That's not de-identified, so it's identified. They'll have all

their history, and all the different treatments they did. We're also going to ask them to fill out surveys of patient-reported outcomes, and to verify what we have.

But let me step back. I'm associated with a company called xCures. They could take your basic information, like name, address, phone number, birthday, and get all your medical records and organize them within about 15 minutes right now for most people. That'll be the backbone of this registry. The patients will have access to that data, to be able to verify that everything's true or correct, and to the patient-reported outcomes. They'll have that all in one place, which is really nice. Because all these people go to all these different providers, and everything's disjointed. Here, you'll be able to have one thing. You could print out a quick report to show your doctor and say, “Yeah, this is my highlights.” Instead of having to remember everything,

Richard Anders 53:34
I think it would be immensely helpful if you would allow, not just doctors, but maybe some nonprofits or even biostatisticians, professors, a wide variety of people, to access the de-identified data, because it can be a goldmine of potentially useful semi-anecdotal information.

Al Musella 53:55
That's covered under researchers.

The system that we have for patient navigation is a learning system, where you could see patients like us: how they did, what treatment they did, and the outcomes. If this system is used for all the different drugs, like for brain cancer at least, I'm picturing that we'll have the majority of brain cancer patients, and here you would have about 10,000 patients a year to be able to mine that data to do so many different things.

Richard Anders 54:33
Would a drug company be able to say, “In order to take our drug that's in the Promising Pathway Act, you need to do a sed rate (sedimentation rate, a common blood test) once a month. That's a requirement of taking the drugs.” … so that they can populate the database?

Al Musella 54:47
No. They could suggest it, but there's no way right now to require that type of stuff. But they would have all the normal blood tests. All the blood test results would come in here. The test results will come in. The MRI results will come in.

Richard Anders 55:03
The ones that were being taken in the ordinary course. But the ones that weren't taken?

Al Musella 55:09
Exactly, yes. But if for some reason they needed a certain thing, like the sed rate or PSA or whatever, they could make it known. Maybe a good idea would be to have a newsletter going out to all the interested parties. But people could talk about these types of things and say, “For all patients who have this, this, and this, we need to do these types of tests regularly.”

Richard Anders 55:33
That would be very valuable if you could get certain desired data promoted, so that people would really use it. It could make a difference.

Al Musella 55:41
I'll tell you one example of how we use the database already. We just published a peer-reviewed paper on the use of Prilosec (a proton-pump inhibitor used to treat heartburn, a damaged esophagus, stomach ulcers, and gastroesophageal reflux disease) in brain tumor patients. Brain cancer patients get steroids that cause stomach problems, so they give Prilosec to prevent stomach problems. We looked at the patients in the database who took Prilosec versus the ones who didn't take Prilosec, and it had a bigger difference than Timolol (a beta blocker used to treat high blood pressure and migraine headaches), which is a normal drug. Taking Prilosec decreases your chances of living. Isn’t that wild?

Richard Anders 56:15
Decreases your chances?

Al Musella 56:18
Decreases. If you take Prilosec it decreases your chance of living. Do you have a link to that paper, Vanessa?

Vanessa Hugo 56:25
Via chat. Here is the article:
Proton pump inhibitors are detrimental to overall survival of patients with glioblastoma multiforme: results from a nationwide real-world evidence database | medRxiv

Al Musella 56:29
You could look at other associations like that.

What happened is one of the doctors saw this for his patients, and he wrote an abstract about it. He asked us to see if we could go through our database and prove it. They used propensity score matching to set up the comparisons. They said the difference in survival was significant.

Richard Anders 56:54
What was the p-value? Do you know?

Al Musella 56:56
We can check the paper. But it's such an easy thing because for these alternatives – I thought any proton pump inhibitor would be fine. So a study using a proton pump inhibitor and an H2 blocker works just as well, and you get to live longer.

Richard Anders 57:15
The data shows that?

Al Musella 57:16
The data shows that.

There was a report on that in a different type of cancer too that backs up what we said. There's a reasoning behind it in the paper. But it's interesting. We presented that at the Society of Oncology as an abstract that was published in a journal.

Chris Apfel 57:57
I'm still an adjunct professor at UCSF in the biostatistics department. You just mentioned, case-matched or propensity score matched analysis for the PPIs (proton pump inhibitors). I think that this case-matched analysis, especially when their propensity score matched, could look like a randomized controlled trial. So you really have very strong evidence that there is an effect. I'm happy to have an offline discussion with you on that.

The other part, which was actually interesting on the PPIs is, in our platform that we developed, which is a functional tumor cell profiling 3d microtumor platform, we are looking at repurposed drugs. And we are seeing impressive results from some of the repurposed drugs. I haven't seen anything on PPIs yet. I don't think it's in our panel at this point. We are planning to currently look at a 24-drug panel, so that we have a wider catch. There are some substances where I'm really concerned it might increase the risk of survival, or may nurture tumor growth. I'm very interested in not only if there is a benefit for it. I think you find in the internet everything under the sun, and when a patient dives into the internet, they can very easily, through their own confirmation bias, get into the wrong conclusions. Unless you really test this on the patient's tissue, you have no idea what's going to happen. And it may only be applicable for some patients, and not for others. Looking at the impact of repurposed drugs is really important. We'd love to have an offline discussion with you.

Al Musella 59:54
A learning system is a perfect place to test off-label drugs. If you're using off-label drugs, you need a large number of patients, and you have to be able to track them and have that data available. Just to get your institution – which is a big institution – helps, but imagine doing that nationwide. Check every patient who uses that combination?

Chris Apfel 1:00:16
Together with xCures, we may be able to do something there. Because the key is the case-match control. I was an executive director at Cadence Pharmaceuticals at some point. We did a health economic analysis on a 110,000 database on IV acetaminophen and what the impacts are on the patient's outcome undergoing hip and knee replacement surgeries. That was not cancer-related. But the interesting thing was, with propensity score case matching of 22,000 patients, we were able to show a $500 per patient cost savings. And even though this was bundled into the anesthesia reimbursement system, and therefore not reimbursable, no CPT code (Current Procedural Terminology codes are a uniform language for coding medical services and procedures), we were acquired by Mylan Corp. for $1.3 billion within four to six

months, when I came out with these results. So looking at real world evidence data, but applying rigorous statistical methods so that we really have a high level of evidence and certainty. That's actually a very, very important step. So let's just talk offline.

Al Musella 1:01:30
To wrap up by a show of hands, how many people would support the Promising Pathway Act? Most of them. Well, not Jeff.

Jeff Waldron 1:01:43
I just don't know enough to vote to be honest with you. I listened to everything, but I would like to research it further. I don't disagree. I don't not support it. I just need to research.