“Navigating Brain Cancer” (Al Musella) [#80]

Brad Power
January 3, 2024

“Everybody asks me, if I had a glioblastoma, what would I do? This is if access was not a problem. There's no way that anybody is going to get this treatment plan right now. Some of these are impossible to get, and you'll never find oncologists willing to prescribe this for you. But this is how I would approach it if I happened to have a glioblastoma right now.” – Al Musella

“For us as patients and caregivers, it's a very frustrating chess game. Right now, we don't have access to a lot of these things concurrently. You have to pick and choose which ones you're going to pursue. If you do pursue one, and it doesn't work, you have to pivot really quickly to the next one.” – Vanessa Hugo

“The Promising Pathway Act … creates a conditional approval pathway for the FDA, where after you see that drug is pretty safe, and it has the effect you want it to have, it gets a conditional approval where any doctor could prescribe it, and insurance will handle it like any other approved drug. But any patient who uses these drugs has to be followed as if they're in a clinical trial. We learn from every patient. You continue the research. The only difference from the standard pathway is it's more flexible, where you can do combinations if you like. And any patient could get access, whereas in clinical trials, it's only a very select few, like 5% of the population, who can get into clinical trials.” - Al Musella

Meeting Summary

Navigating brain cancer is a daunting challenge for patients and their loved ones, marked by shock, overwhelming choices, and the urgency to make informed decisions about treatment options. The medical team provides initial guidance, but the plethora of choices in doctors, treatment locations, tests, and clinical trials demands that patients quickly educate themselves to make rational decisions. Understanding the landscape of brain tumors, including information on medical experts, treatment options, and support sources, becomes crucial for navigating this difficult journey.

In response to this need, the Musella Foundation 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 Musella, the founder of the foundation, 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 treatments that patients and caregivers should consider for brain cancer?

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1. **Pick the most experienced surgeon**. More experienced surgeons could get the tumor out with less damage to you.
2. **Insert GammaTiles**. These are bioresorbable tiles implanted at the time of surgery that release radiation.
3. **Get DCVax (autologous tumor lysate-loaded dendritic cell vaccination) from the surgery tissue.**
4. **Get advanced genomic testing on the tissue.** If the genomic analysis finds a good targeted drug, take it.
5. **Defer external beam radiation.** External beam radiation is the standard, but there are long-term negative side effects, such as strokes.
6. **Start Optune.** Try for over 90% compliance with the new high power arrays.
7. **Start Keytruda (checkpoint inhibitor immunotherapy) and poly-ICLC (an immunotherapy targeted at glioblastoma).**
8. **Take temozolomide (the standard chemotherapy for glioblastoma) IF your cancer is MGMT methylated** (a test of the MGMT enzyme, which affects the DNA-repair function, which makes tumors more susceptible to temozolomide).
9. **Start sonodynamic therapy** (low intensity ultrasound combined with sonosensitizer selectively taken up in tumor cells).
10. **Get advanced imaging**, such as fractional tumor burden mapping.

For more information on each of these options, please see the meeting transcript here.

What are the challenges that patients with brain cancer and their caregivers face?

- There are 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, you have to pivot really quickly to the next one because the disease is very aggressive.
- The current drug development process is too slow and costly for rare diseases like glioblastoma.
- Only a very select few, like 5% of the population, can access clinical trials.

How can we overcome the regulatory hurdles to accessing treatments and accelerate treatment development?

You should support “The Promising Pathway Act”, pending legislation which will create a conditional approval pathway for the FDA. After you see that a drug is pretty safe, and it has the effect you want it to have, it would get a conditional approval. Any doctor could prescribe it, and insurance would handle it like any other approved drug. Any patient who uses 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.

medical treatment, product, or course of action. You should always consult a doctor about your specific situation before pursuing any health care program, treatment, product or other course of action that might affect your health.

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Meeting Notes

SUMMARY KEYWORDS

glioblastoma, patient, clinical trial, tumor, people, drug, treatment, cells, years, vaccine, good, radiation, talk, GBM, call, trial, pathway, question, working, vanessa

SPEAKERS

Al Musella (72%), Brad Power (12%), Vanessa Hugo (7%), Brian McCloskey (5%), Adrienne Nugent (2%), Ebrahim Nana (1%), Lisa Collman (1%), David Plunkett (1%)

OUTLINE

1. Brain cancer treatment and patient advocacy. (0:03)
2. Developing a platform for glioblastoma treatment. (2:18)
3. Glioblastoma treatment options and research. (8:16)
4. Personalized cancer treatment options. (14:29)
5. New brain tumor treatments with promising results. (18:55)
6. Personal journey with glioblastoma and treatment options. (23:27)
7. Cancer treatment options and advocacy. (28:11)
8. Genetic testing for glioblastoma. (34:02)
9. Optune mechanism of action and potential for other cancers. (39:25)
10. Cancer treatment options and clinical trials. (43:56)
11. Brain cancer treatments and advocacy. (48:54)

SUMMARY

- **Brain cancer treatment and patient advocacy.** 0:03
    - Co-founder of Cancer Patient Lab Brad Power introduces webinar on brain cancer, with guest speaker Al Musella sharing insights after decades of advocacy.
- **Developing a platform for glioblastoma treatment.** 2:18
    - Al Musella, president of the Musella Foundation, discusses the organization's vision for speeding up the search for a cure for glioblastoma, which involves collecting medical records, using AI to structure the data, and presenting treatment options to patients and doctors.
    - The organization's virtual tumor boards bring together world experts to suggest treatment plans for patients, and the registry records the rationales for these suggestions to feed back into the AI loop.
    - Al Musella proposes the "Promising Pathway Act" to provide easy access to experimental treatments for patients, including a conditional approval pathway for the FDA to approve drugs after they've shown safety and effectiveness in a smaller group of patients.
    - He believes that this approach would allow for more flexible combinations of drugs to be tried, and would provide valuable learning opportunities for doctors and researchers.

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- **Glioblastoma treatment options and research.** 8:16
  - The current drug development process is too slow and costly for rare diseases like glioblastoma.
  - Al Musella prioritizes experienced surgeons for glioblastoma surgery and advanced genomic testing.
  - He discusses the use of gamma tiles for glioblastoma treatment, including their effectiveness in recurrent cases and potential for combination with other therapies.
  - He also mentions the importance of advanced imaging modalities, such as fractional tumor burden mapping, for identifying effective treatment targets and monitoring patient response.
- **Personalized cancer treatment options.** 14:29
  - Vanessa Hugo discusses the challenges of accessing personalized cancer treatments, including the need for fresh dendritic cells for the DC-Vax vaccine and the requirement for the Compassionate Use program in the UK.
  - Al Musella provides updates on the availability of the vaccine under the Special Access Program in the UK and the potential for importation from the UK once approved.
  - Combining DC-Vax with Keytruda shows promising survival results for glioblastoma patients, with potential for further improvement with additional therapies.
- **New brain tumor treatments with promising results.** 18:55
  - Al Musella presents research on Optune therapy for brain tumors, showing doubled 5-year survival in a randomized phase 3 trial.
  - Combining Optune, with the new arrays and frequent use, and Keytruda, we may be able to get in the range of 50% 5-year survival, comparable to DCVax with a different mechanism.
  - Al Musella discusses a new technology (sonodynamic therapy) using FDA-approved dye and ultrasound to kill cancer cells in the brain with minimal side effects.
  - The technology involves repeating the treatment over time to target cells far away from the main tumor, with potential to treat glioblastoma.
- **Personal journey with glioblastoma and treatment options.** 23:27
  - Al Musella shared his family’s experience with brain cancer, and the importance of serial MRI scans to monitor tumor growth or shrinkage.
  - Al Musella's personal journey with brain tumors began when his sister-in-law was diagnosed in 1992, and he has since dedicated himself to advocating for patients and creating resources for them.
  - He has learned that the key to success in advocacy is to be proactive, persistent, and adaptable, and to be willing to take risks and challenge the status quo.
- **Cancer treatment options and advocacy.** 28:11
  - Al Musella discusses the challenges of clinical trials for rare diseases, including the risk of receiving a placebo instead of the actual drug.
  - He discusses the need for legislation to help patients access treatments outside of clinical trials.
  - Brian McCloskey discusses proton therapy for tricky places to treat, including glioblastoma, and the potential benefits and limitations of using radioligands for cancer treatment.
  - Brian McCloskey shares his personal experience with glioblastoma running in his family and asks for insights on proton therapy and radioligands.
- **Genetic testing for glioblastoma.** 34:02

    - Brian McCloskey asks if glioblastoma is a germline-based cancer, citing his aunt and son who also had the disease.
    - Al Musella explains that sequencing is important for diagnosis and treatment, but there are different types of sequencing and only a small percentage of patients have actionable results.
    - Vanessa Hugo mentions that xCures has a registry of 140,000 total patients, including over 1000 GBM patients.
    - Brian McCloskey asks if liquid biopsies are relevant in the brain cancer space, and Vanessa Hugo replies that tissue-based biopsies are more common.
- **Optune mechanism of action and potential for other cancers.** 39:25
    - Al Musella explains the mechanism of action for Optune, including how it disrupts cell division and exposes new antigens to the immune system.
    - He highlights the importance of using immune checkpoint inhibitors in combination with Optune to enhance the immune response.
    - Optune and sonodynamic therapy have potential to treat various cancers beyond GBM, including lung and pancreatic cancer.
- **Cancer treatment options and clinical trials.** 43:56
    - Lisa Collman asks about a new tumor treating field device called Voyager, which is in clinical trials but not yet available.
    - Al Musella discusses a magnetic device in Texas that is more promising but still early in development.
    - He expresses frustration with the clinical trial system and the lack of progress in developing a vaccine for cancer.
- **Brain cancer treatments and advocacy.** 48:54
    - Adrienne Nugent and Vanessa Hugo discuss the latest research on glioblastoma, including a Stanford study on familial GBM and a patient navigation program at Cancer Commons.
    - Lisa Collman shares insights on hyper-mutated TMZ and glioblastoma, and the group discusses how to stay informed and learn from each other.
    - Brad Power mentions the launch of an online discussion forum for a continuing conversation on brain cancer treatment ideas and questions.
    - Al Musella suggests passing the Promising Pathway Act to get rid of problems and make treatment easier, with a follow-up session planned for when it's reintroduced in Congress.

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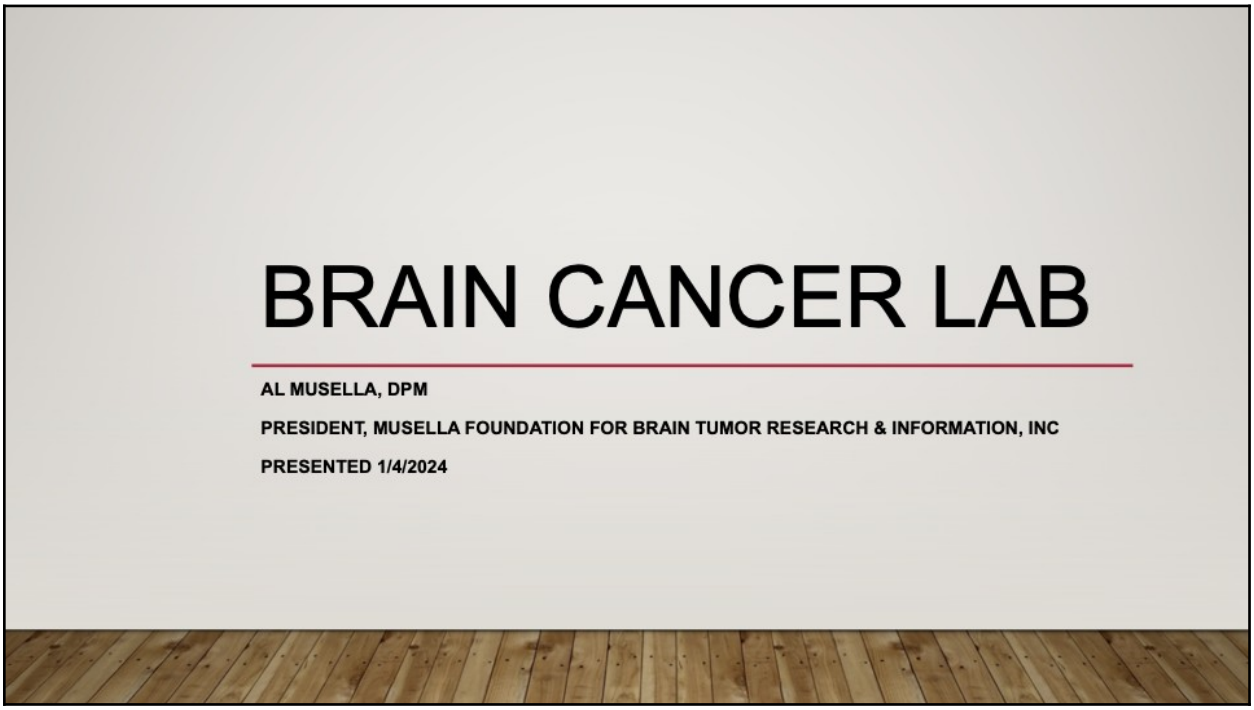
TRANSCRIPT

Brad Power
I'm the co-founder of the Cancer Patient Lab with Brian McCloskey and Rick Stanton. This is our first session of 2024. We typically have these weekly webinars. We’re kicking off the Brain Cancer Lab, which is an expansion for us since we've mostly been involved in prostate cancer to-date. We're branching out into brain cancer and pancreatic cancer, thanks to a collaboration with Cancer Commons.

The more I learn about Al, the more I am inspired by the fact that he's been doing what we're trying to do in the Cancer Patient Lab for decades. He's been a leader in helping patients navigate brain cancer. I'm very excited to hear what he has to say today.



Al Musella 2:18
I'm president of the Musella Foundation. I've been involved with the Musella Foundation for about 26 years now. I started because I had two family members who died of a glioblastoma.

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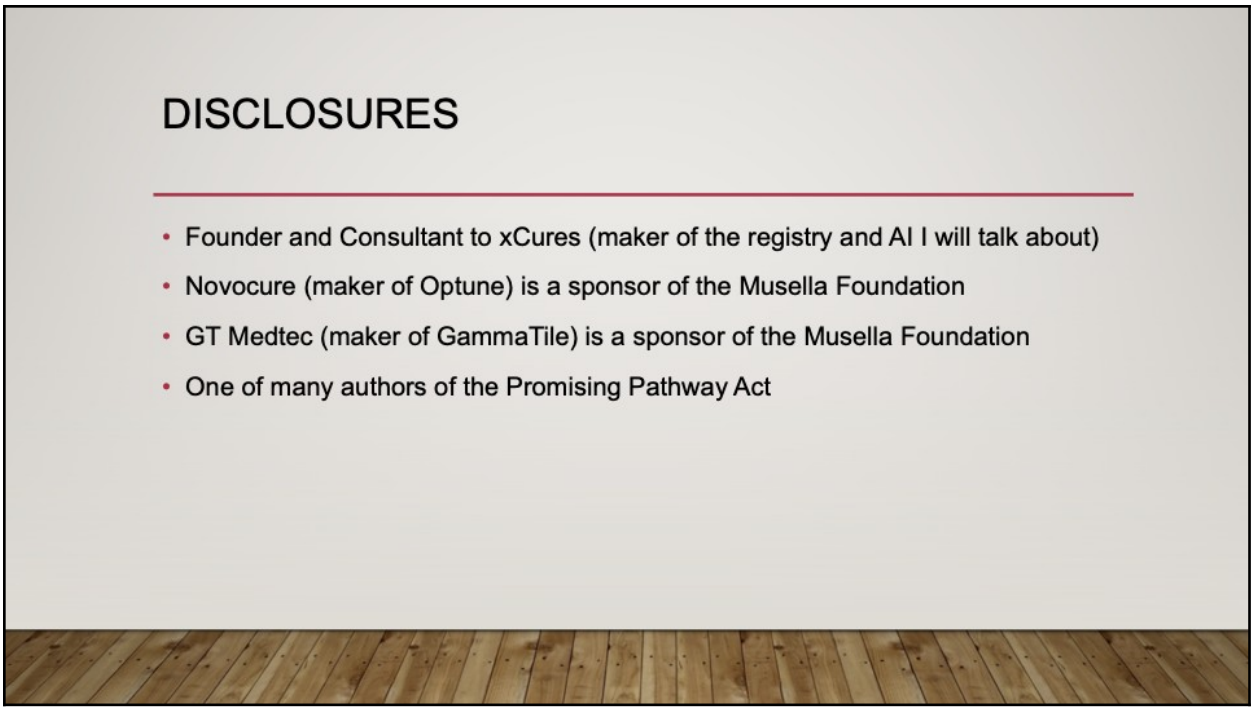
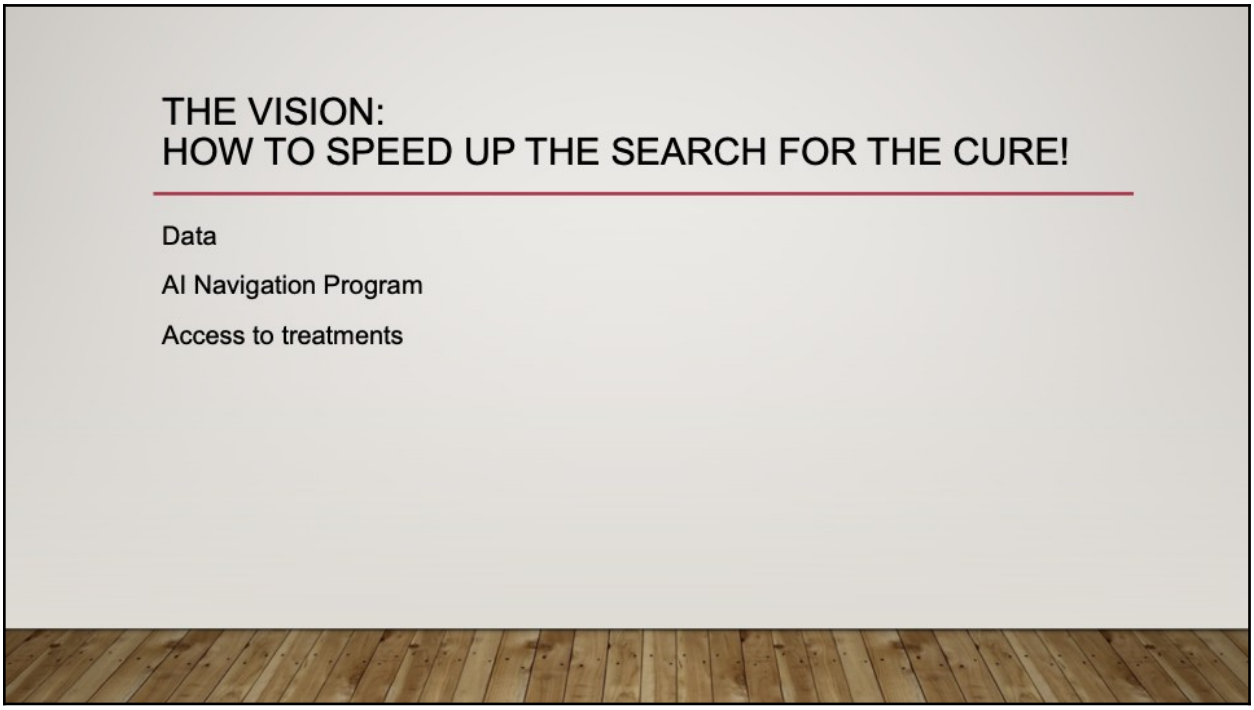


Al Musella 2:32
I have a couple of disclosures here. I will never let a sponsor change what I say.

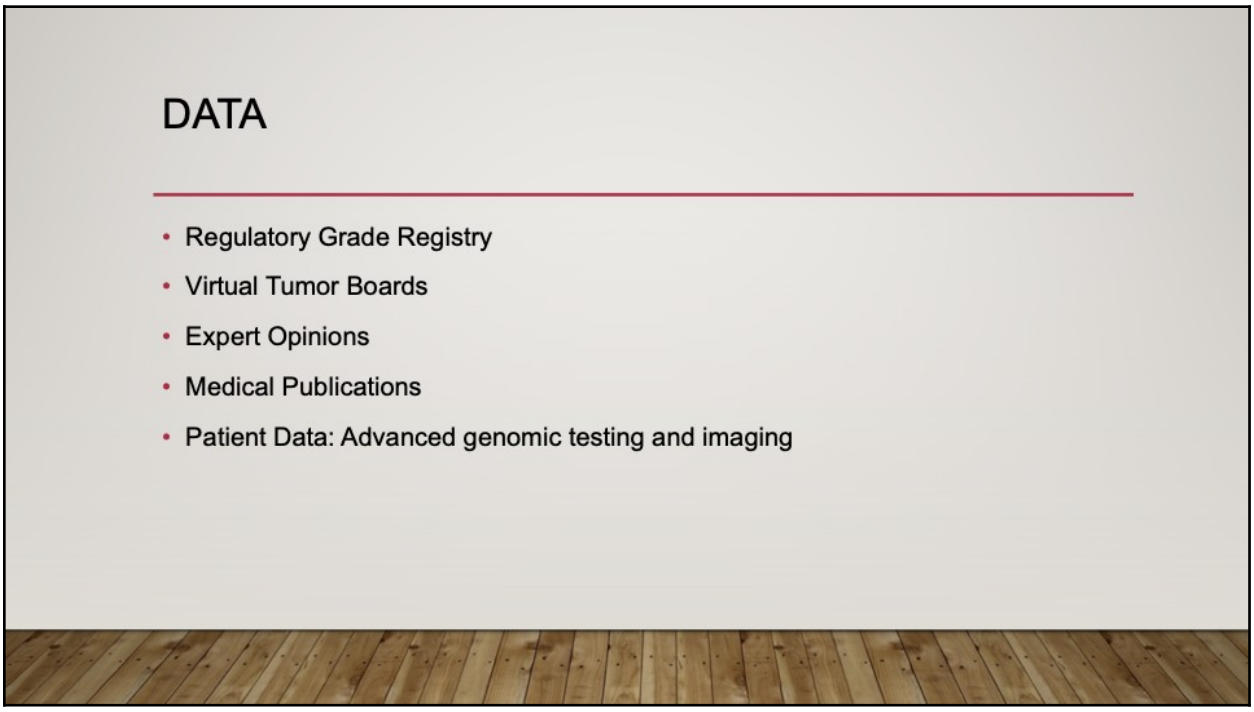


Al Musella 2:40
This is the vision of how to speed up the search for the cure. I say it's a vision because this is our plan. We've been working on it for years. We’re getting closer and closer, but it's just not

there yet. We could use some help. But we are at least three quarters of the way to completing this.

There are three parts to this:

- the data,
- the AI navigation program, and
- access to treatments.



First, the data: This is the important part. It starts with a regulatory grade registry that xCures is running. All they need is your permission, and a few details about you, and they can collect all of your medical records from every doctor, every medical facility, and every MRI place. They collect thousands of pages of records on each patient, and the artificial intelligence percolates that data and structures it, theoretically. It's not perfect yet. That's why I say it's a vision. But we're getting close. It picks up the important pieces so you can, at a glance, see the entire history of the patient. You’ve got all the biomarkers, the treatments, and the outcomes.

Then we have virtual tumor boards, where we present cases to some of the world's experts.

Then we record the rationales for what they're suggesting to the patient. We record the experts’ suggestions. Some of them are here, right now. I'll explain that role.

Then we have all the medical literature to search.

Then for each individual patient, we’ve got all the data, all that advanced genomic testing and imaging, all the treatments they did, what happened so far.

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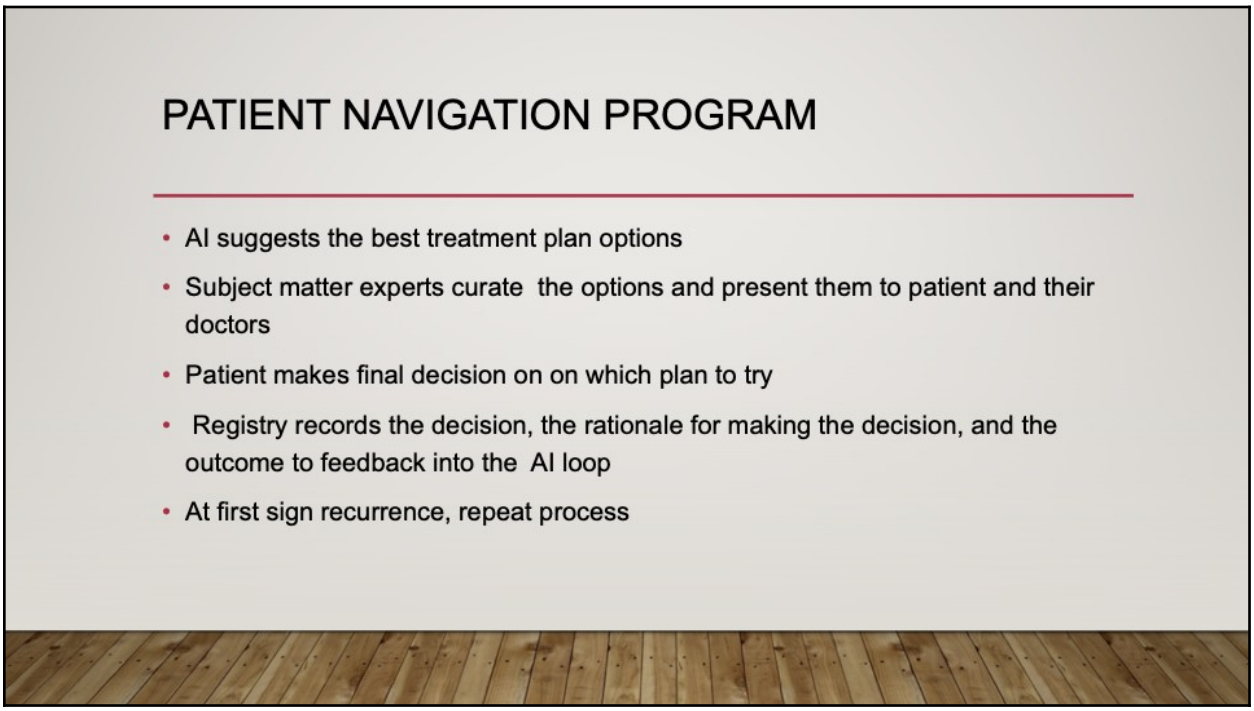

Next, the patient navigation program. The way the patient navigation program is supposed to work, and we're getting close, but it's not there yet:

1. The artificial intelligence suggests the best treatment plan options,
2. Then the subject matter experts curate the options. For example, they could take into consideration how the patient feels about treatments, like do they want to be cutting edge and try to go for a Home Run and risk losing out on current standard treatments, or do they want to be conservative? Are they willing to travel? Would they pay for options that might be expensive? They curate that out and present the options to the patients and the doctor.
3. The patient makes the final decision on what to try.
4. Then the registry records the decision, the rationale for making the decision, and then the outcome, to feed back into the AI loop.
5. At the first sign of recurrence, you repeat the process.

This way, we learn from every single patient. We basically get input from doctors across the whole entire country or actually the world and see what combinations they are trying. This system will be able to find the best combinations. Previously, doctors were trying these combinations, and nobody was tracking them. We never learned from these patients. Somebody might have the cure, and if they keep doing it on their own, if it doesn't get out to the general public, nobody else will benefit. We're going to keep track of all those options.

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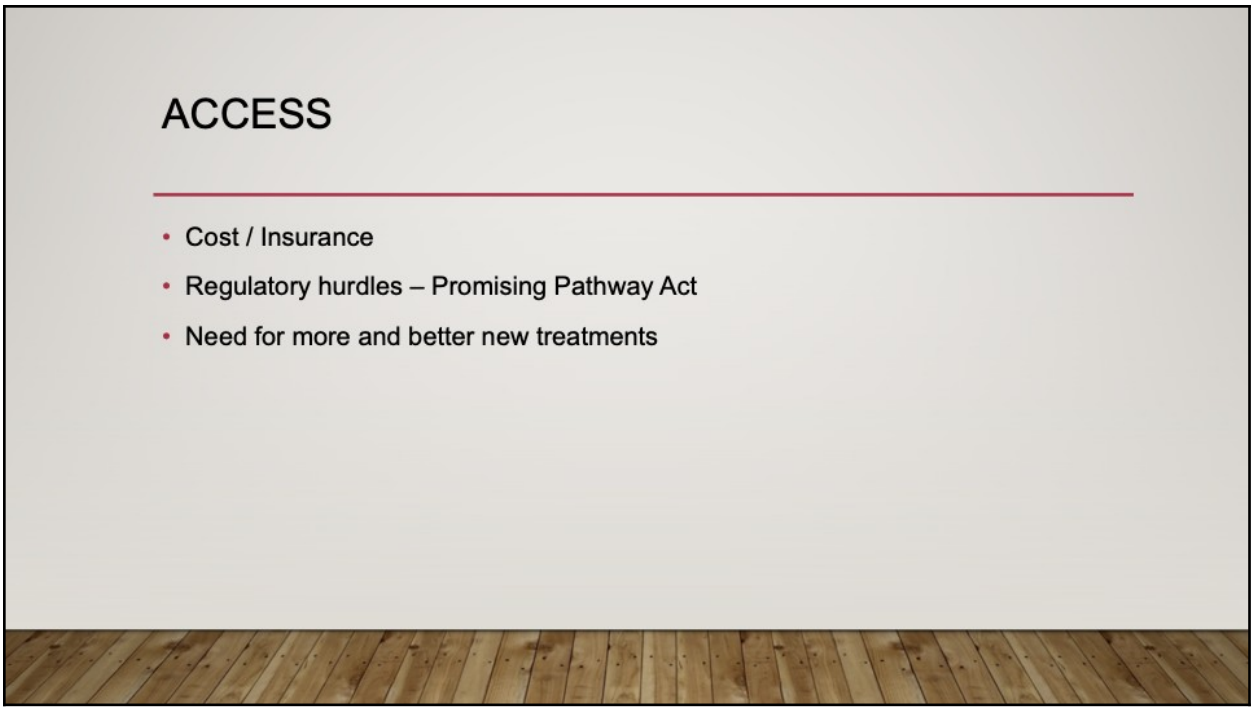
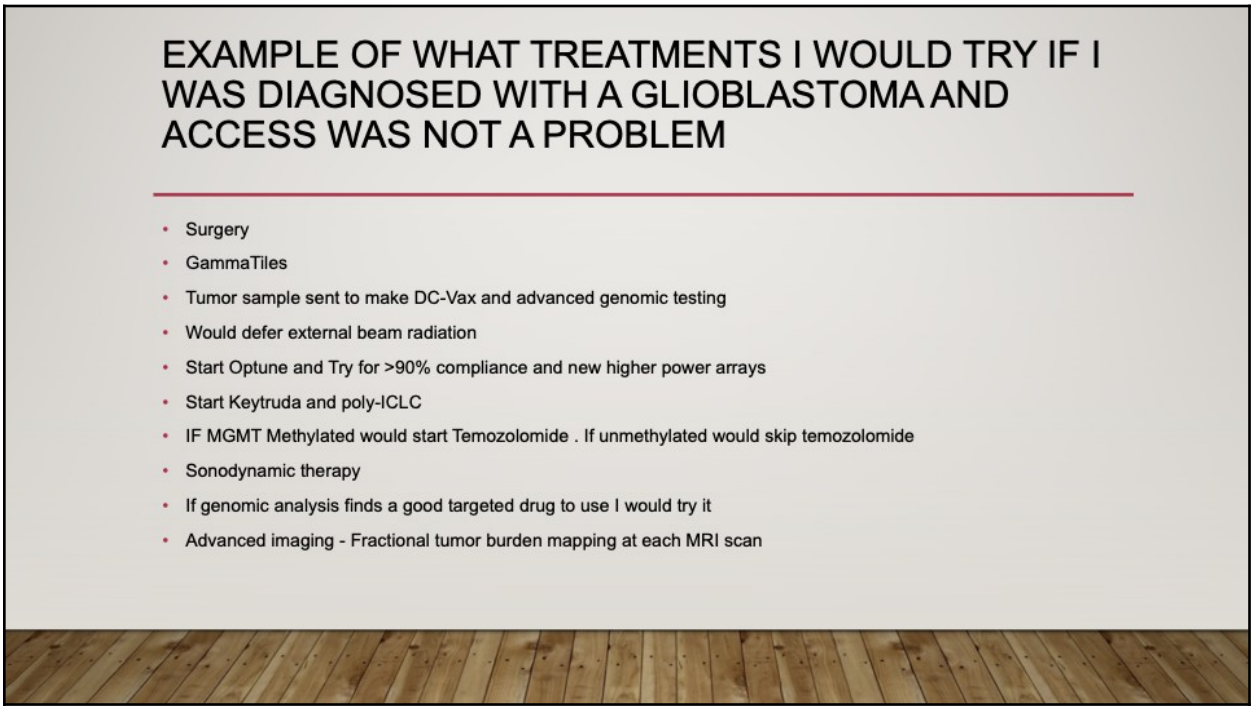


Access.

- If the drug is available, there are cost issues and insurance issues, especially for off label drugs. These drugs are expensive. They're like $20,000 a month for some of them, which is crazy. We have to work in different ways, but that's another topic.
- Regulatory hurdles: a lot of these drugs that we want to use are experimental, and you can only get them in clinical trials. The problem with clinical trials, first, some of them, my favorite ones actually, have a placebo component. I really hate placebos. I think we could get rid of those in the near future using the registry as an external control group. That's one big thing that we should all be working on as a group. Also, they're very rigid. You can't do the combinations that we want to do. There are so many exciting things right now that could help, like, a third of the patients. But a third of the patients is not enough to gamble your whole entire life on. If you're doing a clinical trial, where a third of the patients are helped. In my mind, I would say try three of these at the same time, and maybe you'll have a chance. But under current conditions, you can't. So we want to get easy access to these experimental treatments. That's why I came up with the Promising Pathway Act. This was my idea, but I had a lot of people help me write the actual act. The Promising Pathway Act, is in Congress right now. It has no chance of getting passed right now, but we're working on a new version. Basically, it creates a conditional approval pathway for the FDA, where after you see that drug is pretty safe, and it has the effect you want it to have, it gets a conditional approval where any doctor could prescribe it, insurance will handle it like any other approved drug. But any patient who uses these drugs has to be followed as if they're in a clinical trial. We learn from every patient. You continue the research. The only difference from the standard pathway is it's more flexible, where you can do combinations if you like. And any patient could get

access, whereas in clinical trials, it's only a very select few, like 5% of the population, who can get into clinical trials. We actually do more research with this because every patient that uses it, and all combinations are being tracked. Eventually we'll have enough data to say, “Yes, this should graduate to a fully approved drug, or no, we shouldn't be using this anymore.” So it would increase the amount of research, slash the cost to get a drug approved, slash the time to get a drug approved, and it’s more flexible. This is another topic in itself. We will do this at another meeting on The Promising Pathway Act. Right now, I'm helping the senator rewrite the Promising Pathway to account for some of the criticism that we've got about it. It was too perfect, and they want to water it down. And then there's a need for more and better treatments. With all these new genetic tests, we’re finding good targets. But there's no drugs that could hit those targets yet. The problem is with a small disease like glioblastoma, it's hard to commit $1 billion and 20 years of development time to hit a target that you're not sure of. With the Promising Pathway Act, instead of $1 billion and 10 to 20 years, you could do it with maybe $5 million and three or four years, which is more doable. Our organization and a few others could actually take researchers who have been funding grants for over the last few years that have good ideas and good products that have never gotten to people, and we could actually get those into people under the Promising Pathway Act. It's impossible under today's regulations. The Promising Pathway Act, aside from getting access to the current experimental drugs, it'll encourage the development of new experimental drugs. We'll get to the cure much faster.



Everybody asks me, if I had a glioblastoma, what would I do? This is if access was not a problem. There's no way that anybody is going to get this treatment plan right now. Some of

these are impossible to get, and you'll never find oncologists willing to prescribe this for you. But this is how I would approach it if I happened to have a glioblastoma right now. I would really try to get these treatments.

- It starts out with a surgery. I would pick the most experienced surgeon in our area. I get really scared when I see people go to local community hospitals to have brain tumor surgery. This is a place where it really matters that you have the expert. But things like chemotherapy, it doesn't matter as much, because it's all basically standard plan. But for surgery, the more experienced surgeons could get more tumor out with less damage to you. So it's important to go to the experienced places.
- I would have them insert GammaTiles. I'll explain what those are.
- I would take the tumor sample that is removed and have them make DCVax (autologous tumor lysate-loaded dendritic cell vaccination). I'll explain that. And do advanced genomic testing.
- This was a controversial one: I would defer external beam radiation. External beam radiation is the standard. It's almost unheard of to not do external beam radiation. I'm going to talk about that later with GammaTiles. But I have a lot of long term survivors as friends. Some of them are okay, but most of them have problems with small blood vessels in their brains being messed up, so they’re having little strokes. Some have other problems, like Alzheimer's disease, and other bad problems. I'm talking 20 years down the line. In the past, they never cared about that, because there were no long term survivors. So it didn't matter. But now, with a plan like this, I'm thinking we could get a majority of people into long-term survivorship. Now we have to start worrying about the future.
- Start Optune (patches that apply electric fields). Try for over 90% compliance with the new high power arrays.
- Start Keytruda (checkpoint inhibitor immunotherapy) and poly-ICLC (an immunotherapy targeted at glioblastoma).
- Take temozolomide (standard chemotherapy for glioblastoma) IF your cancer is MGMT methylated (a test of the MGMT enzyme, which affects the DNA-repair function, which makes tumors more susceptible to temozolomide).
- Start sonodynamic therapy.
- If the genomic analysis finds a good targeted drug, of course, I would use it.
- One of the keys is advanced imaging. There are a few different imaging modalities now that are very advanced. One of my favorites is called fractional tumor burden mapping.

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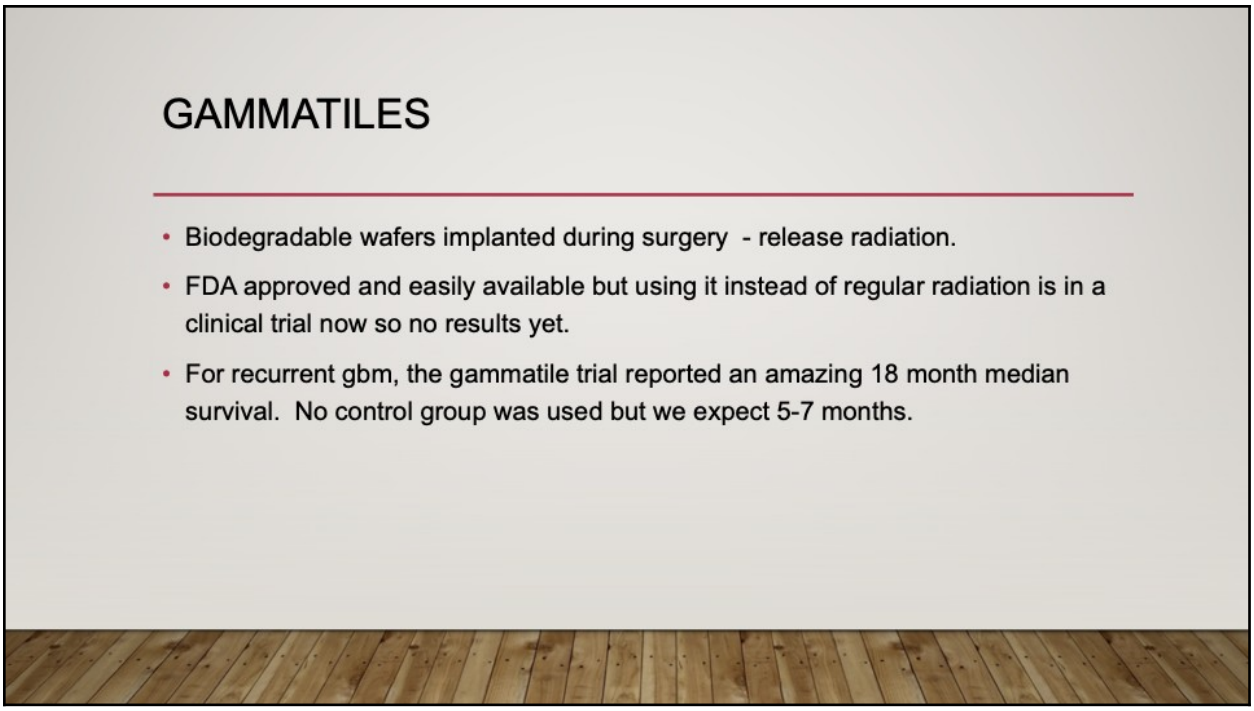


Al Musella 13:05
GammaTiles.
These are biodegradable wafers implanted at the time of surgery, and they release radiation, mostly for like two weeks. I had a little update: eight weeks, I think it is. But for the first two weeks, it's a high dose of radiation. They're FDA approved and easily available. But years ago, instead of regular radiation, it was in a clinical trial now, so nobody's really doing that right now. And you might have trouble finding somebody to do it. But I think it's worth a try. The publication for recurrent glioblastoma was amazing. They had 18 months median survival for recurrent glioblastoma. That's a surgery at the time of recurrence with implanting of GammaTiles. There was no control group for this trial, but we only expect five to seven months of survival after recurrent GBM. So it's way more than double survival.

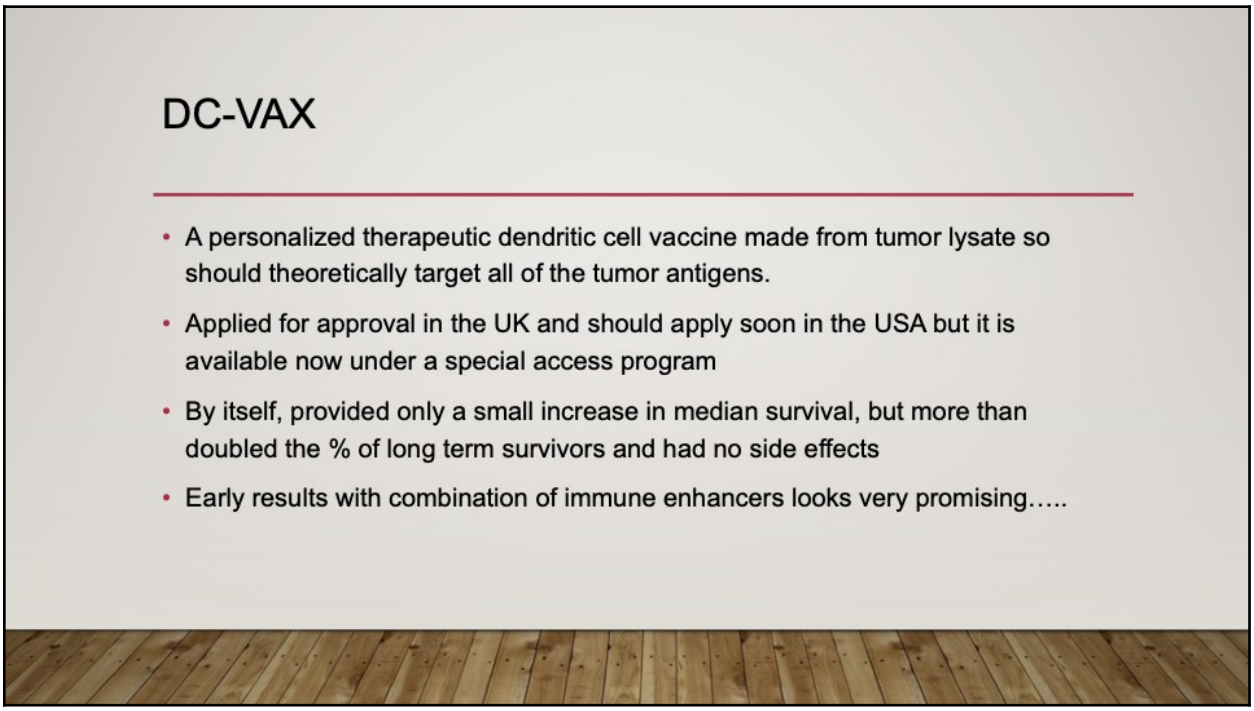
Of course, my hope is to combine all these things that each give a little benefit, hopefully to make a cure available.

Vanessa Hugo 13:55
One question on the GammaTiles: Is the FDA indication limited to just recurrent GBM, or is it also inclusive of newly diagnosed GBM?

Al Musella 14:06
It’s approved for newly diagnosed and recurrent GBM. Right now, they're doing the GammaTiles plus standard radiation. Of course, they're afraid of not doing the radiation. It's scary to not do it. There were trials like 30 years ago, where they skipped regular radiation. But the tumors grew so fast that it was overwhelming and people died so quickly that there's a tendency to avoid skipping radiation right now.

Vanessa Hugo 14:28
In an ideal world you could combine all these things, but I know some people's hesitation right now, they wouldn't necessarily want to get GammaTiles at the newly diagnosed stage because it may preclude them from joining another clinical trial later on down the line. In an ideal world, I'd be like, “Yes, go for this.” At this stage where things are right now, I would caution asking for these because it may rule out another option down the line.

Al Musella 15:03
You have to play like a chess game and figure out a few moves ahead.



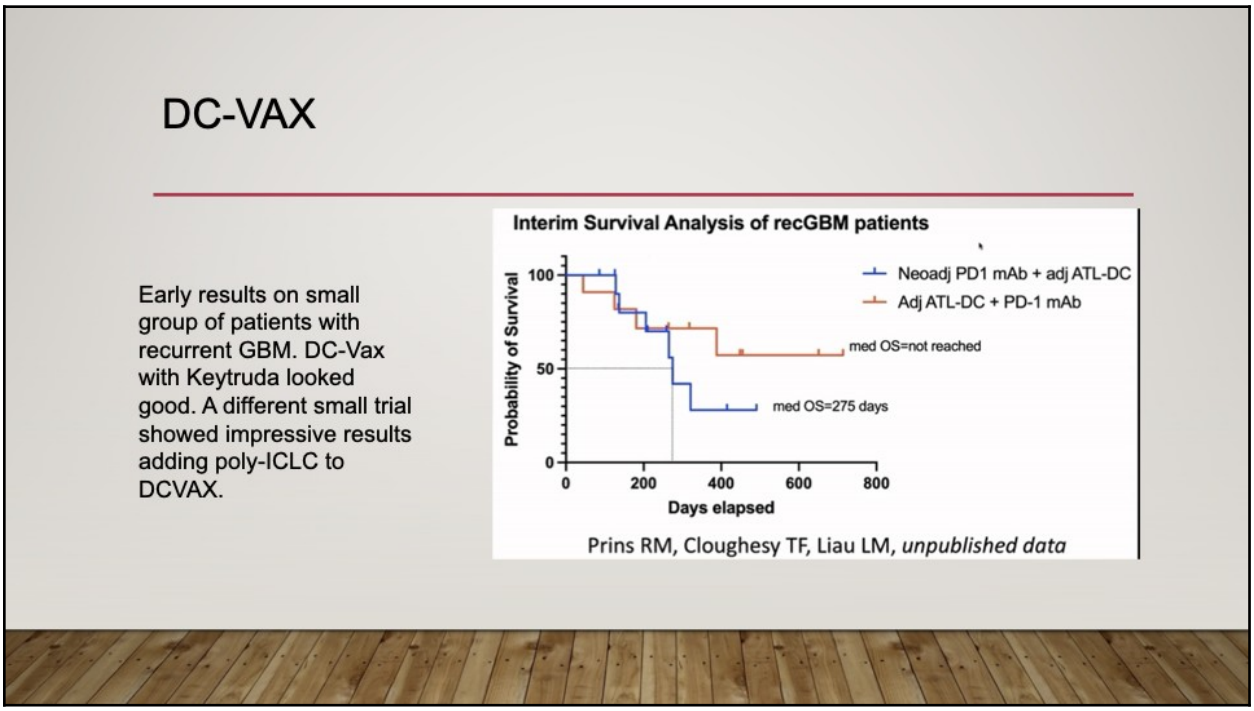
DCVax is a personalized therapeutic dendritic cell vaccine that's made from the tumor sample removed at the time of surgery. So it's personalized to your particular tumor. They have applied for approval in the UK and should apply for FDA approval in the USA, but it's available now under a Special Access Program in the UK. It's very expensive, like $200,000. You have to make like seven or eight trips to the UK. I heard some people are bringing it back home somehow. I certainly hope it gets approved in the UK. In theory, you should be able to order it and import it from the UK. It'll still be expensive, but at least it'll be easier.

Vanessa Hugo 15:53
I'll put a comment on that too, because that's something we've looked into for my husband, Michael, for the Special Access Program. The vaccine requires them to harvest your dendritic cells to make the vaccine. Because of the freshness of the dendritic cells, they require the apheresis process to extract those cells be done in the UK, at this time, under the

Compassionate Use program, in order to make the vaccine within the timeframe they need to make it. I don't know what that'll look like once they get approval for that process.

Al Musella 16:32
You will have to go there at the beginning for that part and the first injection. But then after that, hopefully you could get sent home. Because the expanded access program where you can input drugs is not available in the United States process. I think it's going to be possible. But right now you have to go there for each injection, and there are a lot of injections.

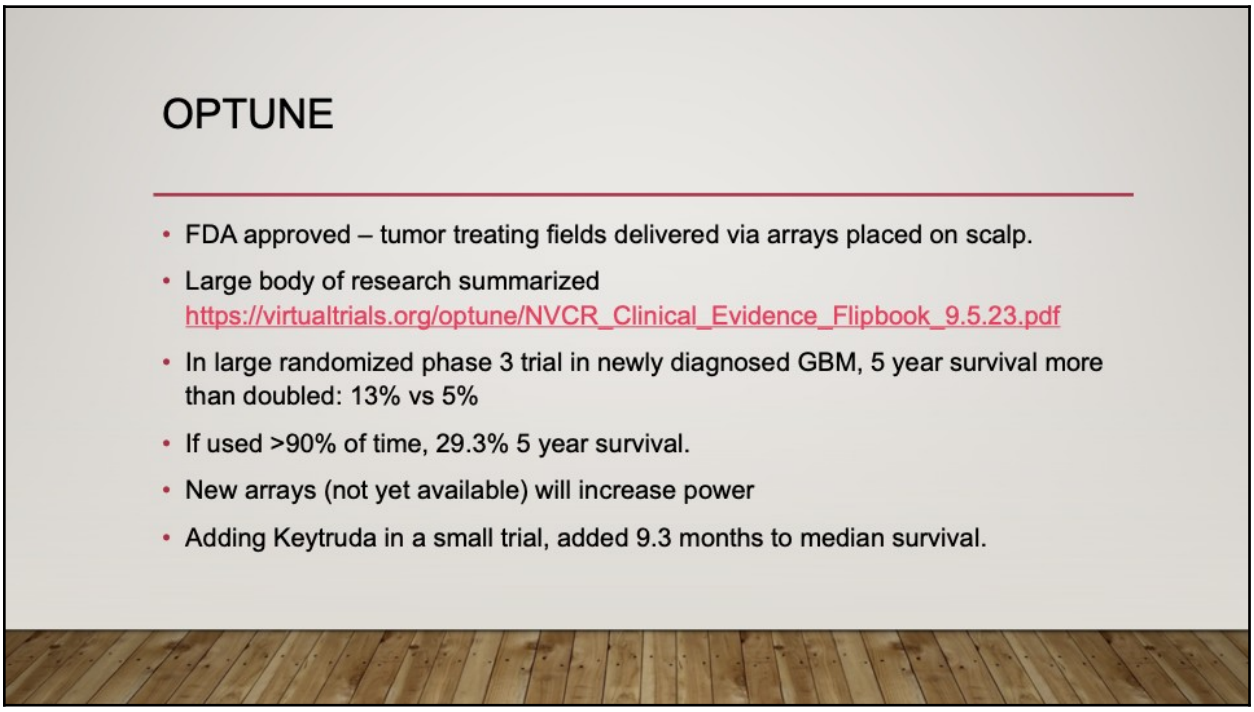
By itself, it only provided a small increase in median survival. It didn't help the typical person, but there's a long tail to the survival curve. It doubled the percentage of long term survivors. And none of these people have any side effects. I think of it as adding chances to you. By itself, it's good enough to use because of the risk-benefit ratio, but we can improve it.



Early results with combinations of immune enhancers look promising. Here's a survival graph of a small, very small, early trial. They wanted to combine DC-Vax, which they're calling ATL-DC, with Keytruda. These two lines are giving it before the surgery and after surgery. This is only after the surgery. This is amazing, because with recurrent glioblastoma, remember, the typical patient lives only five to seven months. So they would be down here someplace. This line is tremendous. Actually, it's not good enough, because only about half the people are long term survivors. I know some of the people in this group, and they are doing fantastically well.

But still 50% is not good enough. But if you could get 50% from Optune and combine them, you might be up here someplace. Then if you add the sonodynamic therapy, I think we're going to get really, really high on these things.

There's also a small study using a drug called poly-ICLC, which also had similar – not as good as this but similar – increase. And so if you could combine the DCVax with poly-ICLC and with Keytruda, I think we're going to get a higher line than this. And things are starting to look promising.



We have an actual Optune user here. You're going to love this.

There's a lot of research on Optune, probably more than just about any other treatment for brain tumors. Novocure put it all together into a clinical evidence flipbook, where they gave the highlights of each of the trials.

https://virtualtrials.org/optune/NVCR_Clinical_Evidence_Flipbook_9.5.23.pdf

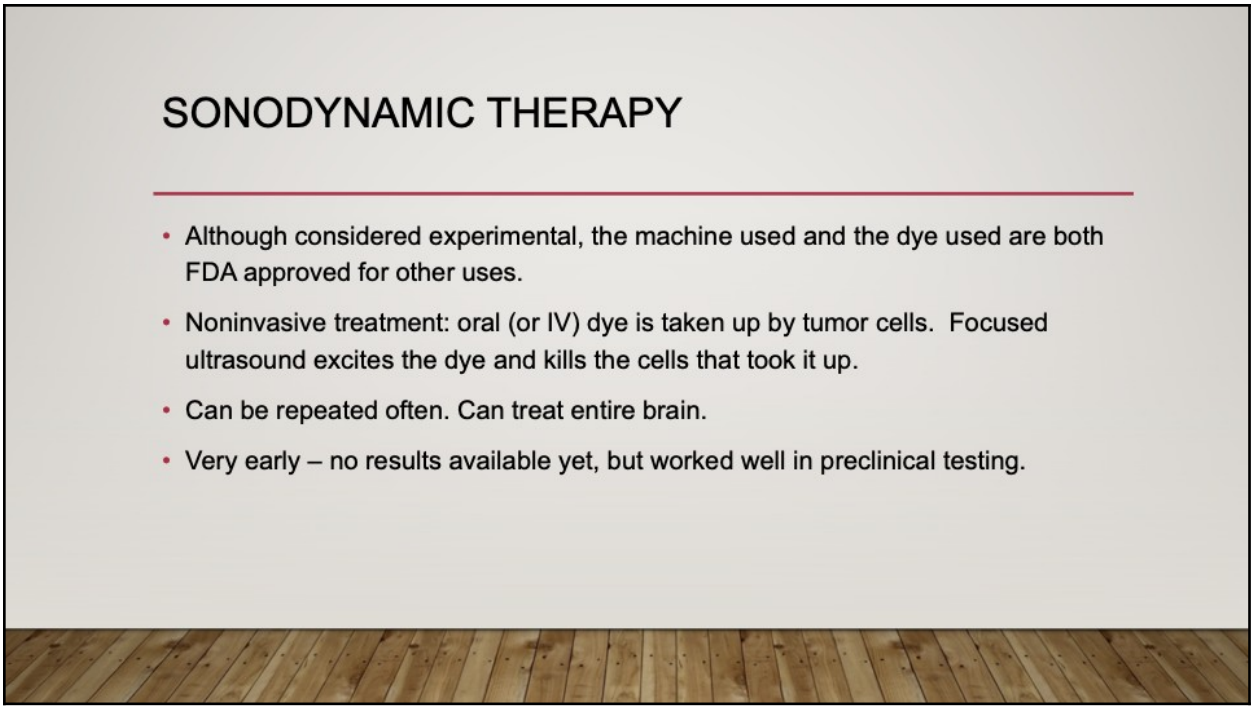
In a large randomized phase three trial for newly diagnosed glioblastoma, the five year survival was more than doubled. It was 13% versus 5% on the control arm, so that was a randomized trial, which is solid. It at least doubles – almost triples – survival.

It's basically arrays that are applied to the skull that are on all the time. You change them twice a week, maybe three times a week. It's connected to a device, the power unit. You don't have the device on all the time. You probably should have it on as much as possible because it only works while it's on, and when you turn it off, it stops working. It's not like a drug that has a half life. This is immediate. As soon as you turn it off, it stops. So you want it on as much as possible. If you use it more than 90% of the time, the five year survival rate jumps up to 29%, which is amazing.

There are new arrays that are not available yet that are going to increase the power. They're going to be more flexible, lighter, more comfortable, and should actually work better. So we should bump those numbers up a little bit higher.

There was another study where you add Keytruda, which is an immune checkpoint inhibitor, that added nine months to the median survival, which is also amazing.

Putting all this together, we have the Keytruda, the new arrays, using it frequently, I think you're going to get into the range of about a 50% five year survival, which is the same as the DCVax using a different mechanism. By combining them, maybe we get up to like 75% five year survival, which will be a major, major, major, major breakthrough.



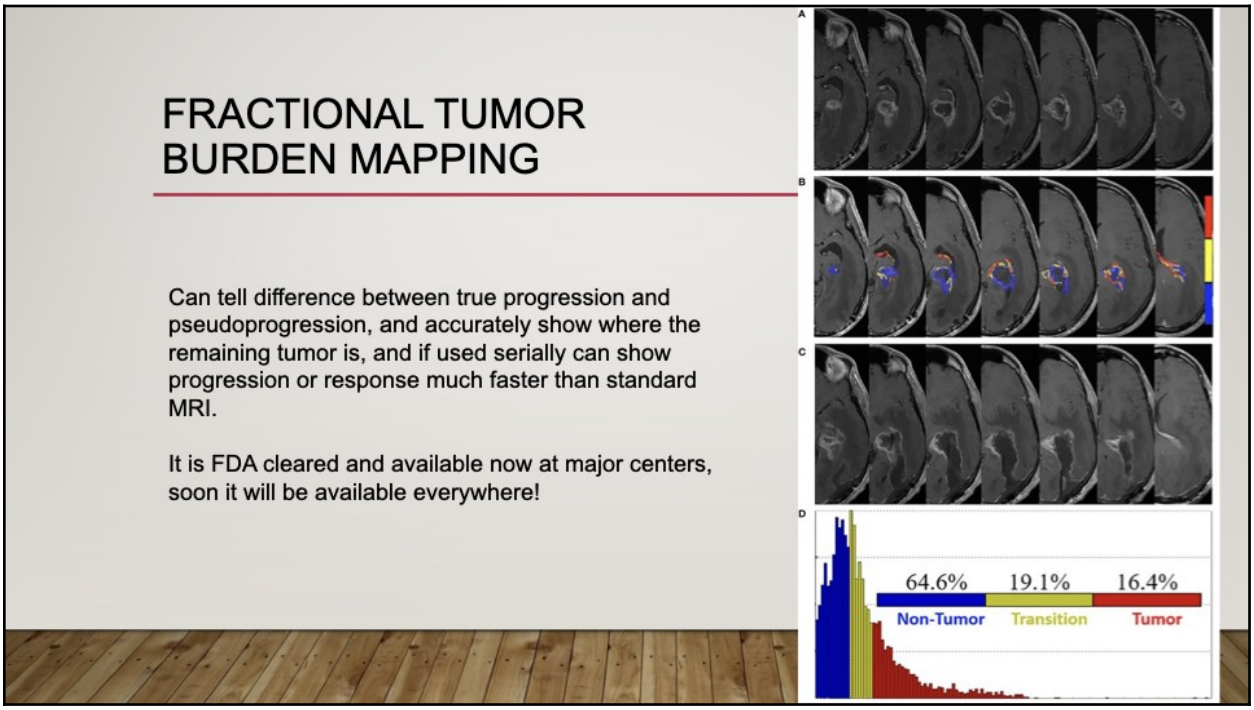
That gets us to sonodynamic therapy. This is my favorite new technology. It's experimental now. It's in clinical trials – very, very early clinical trials. I think they have only taken maybe 20 or 30 patients so far.

Basically, they use a dye that's FDA approved. It's the same dye that they use at the time of surgery to tell the difference between tumor and non-tumor. You put the dye in, you use a special light, and you could see the tumor glows, and normal tissue doesn't. They took that concept. They give you the dye, then instead of using light, they use ultrasound applied externally, just like when you're having a baby and they do the sonograms. The focused ultrasound excites the dye molecules and kills the cells that took it up. Basically it kills the cells that are cancerous and leaves the normal cells behind. The greatest thing about this is that you can repeat it over and over over again. Theoretically, it doesn't hurt. There are minimal to no side effects, maybe a little swelling, that can be taken care of with other drugs. By doing it over

and over again, you stop it from gaining a foothold. Right now, they plan I think to do it once a month. You could treat the entire brain.

There are two different ways of doing it. One does small areas at high intensity, and the other does a large area at lower intensity. We don't know which one works better. But the large area of low intensity treats half of the brain at a time. So you do one half one week and the other half the next week. It will hit any of the cells wherever they are. With a glioblastoma, we know you're going to have cells far away from the main tumor mass. This should theoretically help bump those up. Like I said, it's very early, no results available yet, but it worked great in preclinical testing.

So again, combining all these different things, I think we have got a chance.



Advanced imaging is one of my favorite new technologies. Fractional tumor burden imaging is available. It's FDA cleared, and it's available at some major centers. It'll be available everywhere soon.

If you look at the top and bottom images, you can see that there's something wrong. It looks like tumor here in the top image. This second image from the top could tell the difference. Like this area here in the middle, and this whole area here in the middle of the middle slice on the second row. There's not too much. It's just radiation effects and swelling. But if you look up here in the top row image, it looks like a tumor, and it looks the same as up here. But this is the only area of tumor.

The difference that this could make is, first of all, by serially doing this every month or two months, you can tell if it's growing or shrinking much more reliably than just looking at the regular MRI image. You'll be able to pick up a recurrence fast and change scores. Or you can see that it's actually working even though the area that is non-tumor is growing. That happens with pseudoprogression. Pseudoprogression means it looks like it's getting worse, but it's really not. The tumor is not growing; it's just dead materials collecting, and the swelling, and it makes it look like there's a tumor. Both DCVax and Optune triggered pseudoprogression in almost all of the long term survivors. So what's happening is when we give treatments like this, the doctor sees the tumors grow and they stop treatment. They say, “Stop. Forget it. It's not working.” When in reality it is working, and this imaging could prove that it's actually working or not working. This is very important.

Also, you'll see progression on this one or two scans before you would on a normal MRI. That could save plenty of time for patients to try something else. It could also be used to plot out stereotactic radiosurgery. You could do stereotactic radiosurgery in that area. Then hopefully the next scan, it's all blue. You could also plot out sonodynamic therapy with a high intensity one, and just make sure those areas are treated.

Brad Power 25:44
You just shared a lot of wisdom. You said you've been at this for 26 years. We're about two or three years into this, and you're 26 years into it. You've got 10x more experience. What's been your personal journey? You were a doctor in Long Island. You had family members with GBM.

Al Musella 26:19
Many, many years ago, my sister-in-law was diagnosed with glioblastoma. This was back in 1992. That was the year that the internet was invented. There were no internet resources. I started most of the internet resources. I did the first online support group and the first website for brain tumors. It snowballed from there. She happened to live eight-and-a-half years. We found a treatment that her doctors didn't know about. It was a clinical trial at a different hospital. Back then, there was no master list of clinical trials. So I helped set that up. But she was at Sloan Kettering in New York City, and she didn't know that hospital three miles away was doing something that might have helped. We found that, she did it, and the rest is history. She lived eight-and-a-half years.

A few years later, in 1999, my dad was diagnosed with glioblastoma. He didn't live that long. He couldn't even make it through radiation. He was much older and had a butterfly glioma on both sides. He died quickly. But I have a couple other relatives with other types of tumors, brain tumors, one of them is fighting a pituitary tumor right now, another one died of a central nervous system lymphoma last year. It hit us pretty hard. I retired from the podiatry office back many years ago to run the foundation full time. And now, Vanessa is helping me.

Brad Power 27:51

“Navigating Brain Cancer” (Al Musella) [#80]

What have been your key learnings? What's been your evolution? How would you describe your learning journey? What have you learned over time? What's important? What works? What doesn't?

Al Musella 28:06
This is going to sound controversial. I probably shouldn't say it in public. But for the first twenty years, I was always thinking that the best way forward is the clinical trial. Now I'm thinking that might not be correct, because the way clinical trials are set up right now, you can't do these combinations. We need the combinations. The only way to do that now is outside of trials. There are so many possibilities. You can’t even design a clinical trial, a rigid clinical trial, to do that. We have a clinical trial that is worthwhile. We are running our patient navigation program as a clinical study. And that type of treatment is perfect.
https://clinicaltrials.gov/study/NCT03793088?term=xcures&checkSpell=false&rank=1

Brad Power 29:07
I think that's very, very important. It was in your slides. We probably should schedule a separate session to talk about innovation in the drug discovery process or the translational medicine process.

Al Musella 29:29
My favorite example is somebody just called me yesterday, they have a diffuse midline glioma with the H3k27M mutation. And they want to know what to do. Right now, the best treatment for that is a drug called ONC201, and the only way to get it in the United States legally is in the clinical trial where they're testing it against an actual sugar pill placebo. Imagine having your child be told that there's a drug that's going to help. It helped about a third of the patients tremendously, and it helped about half the patients a little. It's an oral pill, not toxic. But your kid has a chance of getting a sugar pill instead. To me, that is devastating. I just can't handle things like that. There used to be a way to get it illegally in Germany. But the drug company had them shut down, so right now you can't even get it from Germany anymore. Right now, the only way to get it is a clinical trial where you're going to have a chance of getting a sugar pill placebo. That's the right science from the point of view of the drug company. But from the point of view of the patient, that's just not right. That's one of the reasons we have the Promising Pathway Act. Under the Promising Pathway Act, ONC201 would have been approved about five years ago. It would have saved hundreds of kids. It’s just a horrible situation. The FDA doesn't want them to apply for approval, yet. They want a phase three randomized trial. Even though every pediatric brain tumor doctor wants this drug.

Brad Power 31:06
I think we think that warrants a whole session in a follow up, just to understand that. And what we can do is as patients and patient advocates to lobby for that legislation.

Brian McCloskey 31:29

A two part question just in the area of radiotherapy. So first is surrounding proton therapy. There's some discussion about proton therapy being better for tricky places to treat. I'm curious what your thoughts are on that.

And then also, what about radio ligands? In the prostate cancer space, we have a treatment called Pluvicto, which is a radio ligand that targets the high expression of PSMA.

Al Musella 32:06
Let me start with the proton radiation. The trouble with a glioblastoma is that it’s diffuse. What you see on a target is only the main part of the tumor, but you're gonna have cells all over the place around it. So it's not one of those things where you want a very highly focused beam of radiation; proton is very, very precise. Wherever you shoot it, it'll work. But just a few millimeters away, you're not gonna have any effect, which is great when you have something vital like the optic nerve, you don't want to hit the optic nerve, that's perfect. But in general, for glioblastoma, I don't think there's that much benefit over standard radiation. Now for radioligands, I like the concept but I think there are safer ways. Instead of using radioligands, one of the projects that we've been trying to get into humans right now is a combination of a targeted antibody against Interleukin 13 receptor alpha 2 (IL13Rα2), and it attaches a pseudomonas exotoxin. So it's like a smart missile, inject it, and it only goes to cells that have the IL13Rα2, which in the human body is only found in cancer cells, and also in the testes and ovaries. So they inject directly into the brain to avoid the touches of the ovaries. So it brings the poison right to the cells that have it to get ingested, and they kill the cell. With radioligands, it’s the same principle; we just have to see which one is going to work the best.

Brian McCloskey 33:47
It sounds like a glioblastoma runs in your family. This is a really naive question: Is glioblastoma a germline-based cancer? The reason I ask is that my aunt and her son both had it as well.

Al Musella 34:16
There's a project going to test that; something like 5% are. It's not really the tumor, but it's a propensity to develop tumors. And it's some syndromes like Lynch syndrome, where you get glioblastoma. In my family's case, it was my sister-in-law and my father, so they're not related. It's just getting to be more common, I get at least five new calls a day. For a small group of people, it is hereditary. There's a good Facebook group that's exploring this to do an actual study. You might be interested in joining that group.

Brian McCloskey 35:07
To push on that a little bit further: you talked a little bit about sequencing. If they're going to go in, and they're going to do surgery, they could get some sequencing done. One of the things that we've learned in the prostate cancer space is there's a whole lot of different flavors of sequencing. It could just be a limited gene panel DNA. We could get into a whole exome or whole genome, etc. What are your thoughts in terms of the right diagnostics to apply?

Al Musella 35:41

We're trying to set up a meeting with a whole bunch of these companies to figure out the advantages and disadvantages of each. Right now, like my plan that I presented, it only requires the most basic of diagnostics like MGMT status and IDH mutation status. For the vast majority of people who have these tests, it's not going to really show something that's actionable. I forget the numbers, but maybe 10 to 15% of people will have something that's actionable. And it could change the treatment plan. Yeah, but it's still worth it to do it. If you find something like the BRAF mutations, it's really good, because there are drugs against that. As we get more drugs, it becomes more important. So we'll keep an eye on it.

Brian McCloskey 36:32
I'm gonna push on that just maybe a little bit more, in terms of the denote the number of patients that actually do get sequenced that glioblastoma patients that do get sequenced.

Vanessa Hugo 36:46
I hear two different numbers thrown around. So for those patients that enroll with xCures through our patient navigation partnership program, I think it's like 90 to 100 people have their genomic testing for their tumor, but that's part and parcel of just being part of our program and getting that recommendation and advocating for it. Outside of our virtual trial, I think it's a lot less and I think the percentage would really depend. At the major academic centers, I think it is fairly standard. If you're in the community based practices, it is far, far less common. I want to say I've heard like 10%.

Brian McCloskey 37:35
Could that include liquid biopsy as well? Is that relevant in the space or is it all tissue based?

Al Musella 37:44
It’s tissue-based. Liquid biopsies are experimental right now. New York State just passed a law that goes into effect next January that says that all insurers in New York have to pay for these genomic testings, which is a good step forward.

Just to add on to something Vanessa said, the people who call in to our project are much more highly motivated, like this group here. So they're more likely to have the test. And if they don't have it, we recommend that they do it and a lot of times, they’ll go back and do it.

Brian McCloskey 38:13
It seems to me like there's an opportunity for a Count Me In project to be dedicated to glioblastoma, like there is in prostate cancer. There's the metastatic prostate cancer project, which is part of Count Me In. It's very much for research focus. It's a very different application than what we're doing. But they are acquiring this knowledge to hopefully identify targets.

Al Musella 38:42
Well, we’re basically doing that with glioblastomas right now. We're working with a couple pediatric groups. But aside from doing all this, we're also collecting tissue samples that could be used for research.

Brad Power 38:52
For the record, how many patients do you have in your database, more or less?

Vanessa Hugo 39:04
Across xCures for all cancers? I hope I'm not quoting a wrong number, but I think 140,000 total patients in the registry, and then for GBM patients, I believe there's over 1000, but I could be wrong.

Al Musella 39:20
Do you know the number, Adrienne?

Adrienne Nugent 39:22
I want to say around 1000.

Al Musella 39:29
That's funny. I used to get weekly reports, but I don't get them anymore. I need to look into that.

Jeff Krolicik 39:35
What is the mechanism of action for Optune?

Vanessa Hugo 39:48
There's a fantastic paper that came out, I believe in 2022 that explored the mechanism of action. There's multiple and there's still a lot we don't know.
Here is a link to a paper about Optune mechanisms of action:
https://aacrjournals.org/cancerres/article/82/20/3650/709639/The-Mechanisms-of-Action-of-Tumor-Treating

Al Musella 39:59
The reason it got started was the alternating magnetic fields, electrical fields, but there's a magnetic component to it. So any cell that's dividing, as the spindles form and try to separate, it's very sensitive to these magnetic fields changing. And these fields change like 60 times, I forget the frequency, but they keep changing. And they actually stop these spindles from separating the right way. And there is a very nice video floating around where they show the cells, when they're at that stage, and they're trying to separate, they just blow up. Because they can't take it. Then once the cells blow up, it releases these new neoantigens into the environment, and they trigger an immune response. So it has the two mechanisms; first, it actually stops the magnetic dipole moments from working the way they're supposed to. And then, once they kill the cells, it exposes the antigens that were inside the cell to the body, and the body can then attack it. That's one of the reasons why we say to use Keytruda, which is an immune checkpoint inhibitor. Immune checkpoint inhibitors by themselves did nothing with glioblastoma. You have to trigger the immune response before you can enhance it. So the immune checkpoint inhibitors only increase the response, but they don't start it. So if you started

with like, DCVax and/or Optune, they could make it much more powerful. Then there's a whole bunch of other little mechanisms. And it's outlined in that paper.

Brad Power 41:37
Jeff, that answers your question, I presume? Okay. And I guess the other question, and it's a general question, and David Plunkett is up next. But looking across a number of the therapies you're talking about whether it's Optune or sonodynamic therapy, David, you can ask the question, but to what extent are they GBM specific, and to what extent might those same technologies be applied to other cancers?

Al Musella 42:03
Okay, Optune is being applied to many other cancers. Lung cancer, pancreatic cancer. It's actually easier to use on the body than on the head.

Al Musella 42:15
But the problem that it has is it's localized to where you can aim the arrays. So like if you have pancreatic cancer that hasn't spread yet, it can do pretty good. But once it has spread, you can't treat a whole body with Optune. As far as sonodynamic therapy, they started in the brain because it's so elegant. But it should theoretically apply anywhere, because it doesn't have to be this one specific dye. There are a lot of different dyes that can be used that have an affinity for different types of cancers. You just have to find the right dye, and then it should be easy. Really, the limiting factor is swelling within the brain. If you kill too many cells in the brain at one time, you get swelling and there's no space for it to expand. So you have to give steroids or Avastin to decrease the swelling. If you're doing a prostate case, for example, swelling there may hurt but it's not going to cause any problems.

David Plunkett 43:24
My initial impression is that that's a good opportunity for a PSMA ligand instead of a radioactive payload, a dye payload that’s sensitive to sonodynamic therapy.

Al Musella 43:40
Yeah, it's very similar to the photodynamic therapy that they do on the skin lesions. But the trouble with photodynamic is that it’s hard to get the light deep inside. So with ultrasound, they can hit any place in the body.

Brad Power 43:56
Next up, we have Lisa, Lisa Collman. Lisa, do you want to say your question which is in the chat?

Lisa Collman 44:05
I've seen a new tumor treating fields device where they refer to it, I think, as Voyager and you wear a band instead of the arrays. I believe it's in clinical trials, but I'm wondering, do you know anything about it? Do you think we'll see it in the next couple of years?

Al Musella 44:25
That's funny. My first reaction to it was that it can't possibly work. But some of my favorite doctors are on the board doing it. And I asked them, and they say they're not sure yet. But they say don't discount it yet. It's a much easier device to use, but they don't have the research behind it that Optune has. I don't think you can get fields as high strength as Optune without having the arrays on. I talked to the people who created Optune about this exact thing. I said, ‘look at this device.’ I showed them the device and I said, ‘Can you make something that you don't have to shave the head for or attach to the skin and irritate the skin?’ They said they tried it, but they just can't get the field strength high enough. So it's something to look at. There's also a magnetic device being tested down in Texas. That's even more promising, I think. But it's still way too early. It's another thing where you don't have to shave your head, you don't have to wear it all the time. It's only a few hours a day. That's the direct magnetic thing instead of electric. There's a lot of exciting stuff coming out, but Optune has way more research behind it. And I like the fact that it has research behind it.

Ebrahim Nana 45:57
My son is currently enrolled in the SurVaxM trial (an immunotherapy for glioblastoma). Which of your suggestions can be done concurrently? With the placebo, we only had a 60% chance of getting the real vaccine. So I want to cover all bases. Out of your suggestions, are there any actions that can be done concurrently?

Al Musella 46:23
That's a good question. The SurVaxM trial is one of my favorite trials. I love SurVaxM. As a matter of fact, we're trying to raise money right now to create an expanded access program for it. So people don't have that problem. The trouble with the SurvaxM trial, and I could be wrong, but right now, they're not combining it with Keytruda.

Al Musella 46:48
They did a small trial of combining it with Keytruda. That seemed to work a lot better than using SurVaxM alone. But then for some reason, they went back to SurVaxM alone for this trial. I have no idea why. If I couldn't get DCVax, I would try to get SurVaxM or one of the other vaccines. Another problem with SurvaxM is that it’s only against one target, although that target is theoretically ubiquitous in glioblastoma. I really can't say to add something to it, because they’re not going to let you and it's gonna be obvious. Like if you get on an immune checkpoint inhibitor, sometimes they have bad side effects. And there'll be questions. That's one of the problems with the current clinical trial system, but that's for another day.

Ebrahim Nana 47:43
So is it possible this pathway may happen earlier, so that he can make sure he does in fact get the vaccine? What's the timeline for not having to be on a placebo?

Al Musella 48:01
So it would require a lot of money to be raised. It's probably not going to happen this year.

I hope that he got the vaccine. At the first sign that it is not working – I would say, use advanced imaging to make sure that it's working – drop that and try to go onto something else. But the best thing, the easiest thing to use at the same time is Optune, but they'll know about that. You have to try to convince them. But if you can't do it now, do that at the first sign that there's any kind of progression. But that is one of our favorite trials.

Adrienne Nugent 49:06
Brian brought up the Count Me In project. I've seen that they're starting a brain tumor component. See https://braintumorproject.org/. We'll all learn about that next week. We'll learn more about the Count Me In project next week from Eli Van Allen. So definitely something to keep tabs on.

This link https://med.stanford.edu/news/all-news/2023/05/familial-brain-cancer.html?microsite=news&tab=news is to the Stanford study that I was referring to about familial GBM and the genomic or genetic underpinnings there.

Vanessa Hugo 49:45

I'll just chime in to follow up on Ebrahim's question. Al went over all these great new promising treatment strategies, but he said in the beginning – and I'll say it again right now – for us as patients and caregivers, it's a very frustrating chess game. Right now, we don't have access to a lot of these things concurrently. You have to pick and choose which ones you're going to pursue. If you do pursue one, and it doesn't work, you have to pivot really quickly to the next one. That's where I think our patient navigation program is very helpful. Because on a patient by patient basis, they'll help talk to you about, which one you want to pursue first, which one do you want to go after second? And if there are adjuvant therapies, whether that's repurposed meds or supplements, there are other things you can look at.

Brad Power 50:40
That patient navigation program you're referring to, can you say a bit more about that?

Adrienne Nugent 50:51
A lot of people on this call have worked with us at Cancer Commons. We work very closely with Vanessa and Al at the Musella Foundation to just stay on top of the latest resources, and talk with patients about what they're hearing. For example, on this call today Lisa brought up some really wonderful insights she'd gathered about hypermutated TMZ (Temozolomide) and glioblastoma. So honestly, we feel very privileged to hear such wonderful information and continue the discussion so we can all learn from each other.

Brad Power 51:22
Our online discussion forum that we're starting to launch and build up is partly also there for a continuing conversation. When people come up with ideas or questions, they can share them.

Al Musella 51:52

As a group, we should really try to get that Promising Pathway Act passed. Right now, we don't have to do anything, because we're in the process of rewriting it. It’s going to be reintroduced in a couple of months. But once it gets reintroduced, we should really be fighting as hard as we can. You'll be able to do whatever treatment you want, to have access to everything. We'll get a whole bunch of new treatments coming in. And we'll make our lives a lot easier.

Brad Power 52:19
Let’s definitely plan on a follow up session just on that.

Al Musella 52:23
We'll do that right at the time that it's reintroduced.

Brad Power 52:34
Do you think that's in like six months? Or how long do you think it'll be?

Al Musella 52:39
I think it's when the new Congress people get signed in. I don't remember. I think there's a change in the guard right now. The person I was working with is actually stepping away from Congress. So we have another person who's taking over, which is good. A whole new group of people come in, I think, mid January. So I figure about two months after that. So February, March, April maybe.

Brad Power 53:10
We'll calendar that.

It's been great to launch the Brain Cancer Lab. Thank you all for all of your wonderful insights. It's quite a menu. There is a lot to learn. I'm sure every one of those items on there is a deep dive in its own right. And we'll have to come back to this and discuss it further.