What is Personalized Medicine in Brain Tumors?

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- Priscilla Brastianos, MD, Massachusetts General Hospital, Harvard Medical School

Mr. DeVitto: Welcome back everyone, I hope you enjoyed a good lunch. We're now going to try to get started with the afternoon portion of the program. So thank you again for joining us here.

Our next session is "What is Personalized Medicine in Brain Tumors?" it's going to provide an overview on how recent scientific advancements are allowing us to develop new precision medicine approaches for brain tumors. And this presentation is going to be presented by Dr. Priscilla Brastianos who is a steady figure at these meetings over the years and she's joining us here two weeks out from her marriage, right? Congratulate her, wish her well, yes. And maybe 24 hours away from her bachelorette party I'm told.

Dr. Brastianos is Director of the Central Nervous System Metastasis Center at the Mass. General Hospital, Harvard Medical School. Her research focuses on understanding the molecular mechanisms that drive primary and metastatic brain tumors. She leads studies which identify novel therapeutic targets of meningiomas, craniopharyngiomas, and brain metastasis which have already been referenced today. Which have led to several national, multi-center, clinical trials.

So please join me in welcoming Dr. Brastianos. Thank you.
Dr. Brastianos: Thanks for the kind introduction and the invitation to be here. I love coming to these meetings; I always leave feeling very inspired by these ABTA meetings. So thank you for ABTA for putting this together every year. It's useful for patients but also for the clinicians too, so thank you.

So what I'm going to talk about is personalized medicine. So I could go on for many, many hours about this -- but I won't. So what I'd like to do is give you a highlight of personalized medicine and how it may impact how we manage primary brain tumors.

I'm going to focus on non-gliomas -- I'll talk a little bit about gliomas because a lot of the morning was on gliomas -- and I'll also talk about brain metastases. So these are my disclosures.

So you heard about this earlier. Personalized therapy has really revolutionized the management of many different types of cancers. So what do we mean by personalized medicine? And earlier some of the fantastic talks touched upon this, but how I'm going to define personalized medicine for this particular talk, is I'm going to focus on targeted therapy.

What is targeted therapy? It's therapy that we can now target specific genetic changes with drugs. So genetic changes often drive cancer, including brain tumors, and we can target those changes with specific drugs. So here's a list of just some of the different mutations that are found in different cancers and some of the cancers where we have some efficacy of some of these agents.

So here is an example; so you'll hear this -- and I'll talk more about Brap more a little bit later in my talk -- but Brap for example, it's a gene that's commonly mutated in a bunch of
different cancers, especially metastatic melanoma which is one of the poster childs [sic]\(^1\) of where we've seen targeted therapy have a dramatic change in where we manage these tumors.

And here's just one example; you can see here, this is a scan showing multiple melanoma lesions and then after targeted therapy, targeting Brap, you can see this dramatic change here.

So this knowledge of the efficacy of this targeted therapy along with the dramatic improvement in technologies to understand metastatic changes has really led to an explosion in the number of studies to try to understand what are the genetic mutations in cancer.

Just to give you a sense of how the technology really has improved in understanding genomics or genetics, this is a nice curve which highlights that. So the human genome project in 2001 where we sequenced all the genes of the human genome in one patient took 13 years and cost 3 billion dollars.

Sequencing then of another genome in 2007, of the Watson genome, cost 2 million dollars. So big cost difference there. A whole genome now in 2019 costs about a thousand dollars, so much cheaper. So the technology is improving.

We know that targeted therapy works in many different types of cancers. So now again, in the last 15 years we've really seen it's a revolution in how we manage cancers because of this.

The question is where are we at with brain tumors? So I just talked a lot about cancer in general, but what about brain tumors?

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\(^1\) [sic] is used to denote the typed material was transcribed exactly as spoken.
So Dr. Lesser alluded to this a little bit. I'm going to give some examples of where we have seen precision medicine approaches work or where there are approaches that are promising. So here's one approach. I'm going to start with craniopharyngiomas.

So you heard a lot about gliomas. I'm going to talk about this very rare brain tumors called craniopharyngiomas. So craniopharyngiomas, they're very rare tumors. They typically occur in children and adults and although considered "benign", they can cause significant impairment through compression of critical structures and through morbidity of treatment because of where they're located. So they can be located close to the pituitary gland, the hypothalamus, the optic phyism. And once surgery and radiation fail there hasn't been -- traditionally -- any effective treatment for this particular tumor.

So classically there's two subtypes. I'm not asking you to memorize these though (inaudible 00:07:07) does really roll off the tongue. So there's two subtypes. The first subtype, (inaudible 00:07:11) tends to occur in children and the papillary tend to occur in adults. Previously we knew that there was one particular genetic mutation that was common in (inaudible 00:07:20) but we didn't really know much about papillary craniopharyngiomas.

So this is a study from a few years ago. I do want to say that any time you're studying a very rare tumor -- this is a very rare tumor that occurs in about 300 cases per year in the U.S. -- you need a national and an international effort. So we actually got tissue samples for this particular study from Egypt, from Hopkins, from Pennsylvania. So it has been a really rewarding multi-disciplinary, international effort to study these tumors.
So what did we find? We used some of that newer technology that I talked about to see if we can find drivers, genetic drivers of this tumor. So we found first that the (inaudible) subtype has this particular mutation, the beta mutation, but more strikingly that 95% of this particular subtype have this Brap, V600 mutation. Which is that same mutation that I mentioned earlier that's a target in melanoma.

And these driver mutations were mutually exclusive between the two different subtypes. When we made the initial discovery of the Brap we actually who had a patient who came in that required urgent neuro surgical decompression for his tumor.

So here's his tumor presentation. He came in unfortunately unattended and had this large, very large cystic mass, right here. This very large tumor right here. He got urgent surgical decompression, and unfortunately, came in three different times with recurrence of his tumor. His tumor kept coming back. And at that point in discussion with the neurosurgeon we had to try something else because surgery wasn't quite working for him.

So he came in a fifth time and he required -- he had this large, solid tumor mass here. So you see here this very large tumor mass with visual loss. So we had just found the Brap mutation in this particular tumor which turned out to be a papillary craniopharyngioma. So we tested it, we found Brap, and then we started him on Brap inhibitor therapy. This was not on a clinical trial, we got Compassionate Use therapy to try the Brap inhibitor.

So this is his tumor before treating and then you can see here, the tumor is shrinking after just 17 days of therapy. And then after 34 days of therapy the tumor had shrank by more than 85%. So this was exciting because we had never seen medical therapy work for papillary
craniopharyngioma. So this was actually one of the most exciting moments in my career, I'd say personally. Seeing from lab to seeing a patient benefit and his vision improving. It did really well to clinic. So this is why we do the research that we do -- seeing patients benefit from the research.

Also strikingly, is when we looked at his blood, we can actually see circulating Brap in his blood on multiple occasions. As had previously been done in melanoma. So the other thing about the brain tumor mold is we can draw from what others have learned in cancer and we found Brap in his blood multiple times and then a sharp decrease after surgery. And when thinking about personalized medicine for brain tumors, the possibility of non-invasive detection and monitoring of these patients raises the possibility that you can actually maybe monitor and detect these tumors without surgery. We're still not there yet, but possibly if we can detect some of these mutations in the blood maybe in the future, we might be able to minimize the need for aggressive surgery. But again, that’s pie in the sky.

So since then, a number of responses have been published in the literature, so you can see here there are three other cases that were published and a few others now and you can see that their tumor is shrinking with the Brap inhibitor therapy. Obviously, you need to study this in a clinical trial and you heard about clinical trial designs this morning. So we've now initiated a national, multi-center trial. This is why Dr. Lesser was talking about with his patient who's enrolled in this trial. So this is an ongoing trial now and we're studying the effects of the Brap inhibitor therapy on these patients that have papillary craniopharyngiomas.

So more to come hopefully in the future.
What makes this tumor different from glioblastomas and I'll talk more about this in a little bit, is that these are simple, genetic tumors that don't have much in the way of mutations. These are simple genetic tumors where we found one driver event in that tumor. So this targeted therapy seems to be working in these tumors. So to summarize the first few minutes of my talk; so papillary craniopharyngiomas have Brap, B centered mutations, Brap tumors have demonstrated remarkable responses in patients with papillary craniopharyngioma -- again this is early, and we still have to see if the clinical trial will work, but a clinical trial is underway to further evaluate the underlying role of Brap and mech [sic] inhibitors in papillary craniopharyngiomas.

So let me briefly now talk about meningiomas, so I'm going from one of the rarest brain tumors to one of the most common, so meningiomas and where we're at for precision medicine with meningiomas? And that's a work in progress. And you saw a similar graph earlier from Dr. Lesser, showing the breakdown of primary CNS malignancies in the U.S. and though we hear a lot about gliomas, meningiomas are the most common primary brain tumor representing 36% or 37% of all primary brain tumors in the U.S.

So I always like to start with a historical point. In the early 1900s the father of modern neurosurgery published a 740-page textbook. It's riveting bedtime material, I promise. On how you classify and manage meningiomas. And at that time, surgery was the mainstay of therapy for these tumors. So most of these patients had -- required surgical resections to have them managed.

So surgery is still the mainstay of therapy for these tumors and when surgery fails, we have radiation to offer. Even after complete resections though, a subset of these tumors do
reoccur. About 20% of Grade 1. So there's three grades of meningiomas; 20% of those recur.
And Grade 1 tumors, particularly those in difficult locations are associated with decreased long-
term survivals. And then the recurrence rates for Grades 2 and 3 meningiomas are higher, but a
third of meningiomas are incompletely resected. Recurrence rates after subtotal resection are
quite high and five-year-old survival rates are still slightly decreased. Even among meningiomas
which have been considered a "benign" tumor. So they are certainly not benign in many
patients.

And medical therapies have had limited efficacy to date after surgery and radiation fail.
So here's just a graph or a chart showing how systemic therapy really hasn't done much for
meningiomas. Here's a list of different agents, different drugs, that have been looked at in
meningiomas. And here I just want to draw your attention to the response rates which have been
very close to zero percent in almost every study in recurrence; this is in Grade 1 meningiomas.

And similarly, response rates are very close to zero percent in Grade 2 and 3
meningiomas. The one thing meningioma field has suffered from is lack of trials. Actually,
even for some of these trials they were often arms of studies that were added to glioblastoma
trials. So there was very little science to drive some of these trials and part of it was because we
didn’t really understand what were the genetic changes driving meningioma? So we had very
little data but with the improvement of technology that we talked about earlier that hopefully will
change.

I'll give you a little bit of a preview what some of that work is showing. Prior to 2013
what did we know about meningiomas? I know Dr. Jaishri Blakeley will talk about NF
specifically and NF-2 specifically in her session but we knew that 60% of meningiomas had alterations in this gene called NF-2 and then this chromosome 22 was lost in about 40-70%. However this is an incredibly difficult gene to target and beyond that, we didn't know much else about what were the genetic drivers of meningiomas?

So the question is; do meningiomas have clinically actionable mutations that we can target? This is a study that we published a few years ago where we actually genetically characterized about 65 meningiomas. I won't go through this in too much detail, but we found targetable mutations in a gene called AKT1 -- and I don't expect you to remember any of this. I'm just going to highlight some of the important points.

So why is this important? AKT1 is a member of this pathway called the PI-3 Kinase Pathway. The AKT mutation is a known mutations [sic] in other cancers. So it's known to drive over cancers and more importantly, there are known inhibitors of AKT1 in clinical trials right now in other cancers.

So here's a study -- this is a study published by folks at MSK -- where they actually looked at an AKT inhibitor in solid tumors with AKT mutations. This highlights again, precision medicine or personalized therapy where we're targeting cancers based on the specific mutations that they have. This trial did not include meningioma patients but what they did see is that 25% of patients across all solid tumors that had these mutations benefitted from an AKT inhibitor.

That potentially highlighted a promising treatment that we could consider in meningiomas. Similarly, we found mutations of this gene called Smoothens. What is
Smoothens? It's a member of this pathway called the Hedgehog-Similian Pathway. These particular mutations -- again, we're drawing from the literature of other cancers. They've been linked to other cancers and there are FDA approved inhibitors to Smoothens in clinical use right now.

Sorry, this is right after lunch. Maybe should not have shown this figure. This is an example of a Smoothen inhibitor, (inaudible 00:17:33) which is showing high response rates in a cancer called Basil cell carcinoma. So we're finding some of those same mutations in meningiomas as in Basil cell carcinoma. Again, we're trying to use what we find in cancer to apply that to brain tumors.

What was also pretty striking is that these mutations do originate in the skull base. They seem to have a location predominant. What we're starting to see -- and this has been shown in other types of tumors -- is that genetics seem to correlate with clinical phenotypes. And we're seeing that these mutations do tend around the skull base which are often very surgically challenging tumors.

So based on this we have an actual precision medical trial in meningiomas. Getting this trial through NCI, getting to drug companies before the trial took a lot of effort as many, unfortunately, companies and Dr. Lesser alluded to this with brain tumors, do not want to support brain tumor research in general. So getting the meningioma trial was quite a challenge. We actually have already completed a tool for one of the arms. There's been a lot of support from the neurooncological and patient community for this trail which has been really rewarding to see.
So when we compare our control to this arm, this arm is going to be opening in the fall. This arm will also be opening in the fall and this one will be opening sometime probably early next year. So we have about 600 hospitals that are activated with this trial which is really exciting.

To summarize this piece, genomics uncovered potentially clinically significant alterations in meningiomas. We still have a long way to go with obviously -- are these trials going to show efficacy? We do have this national, multi-center, NCI sponsored trial underway and we're hoping that these therapies will play an increasingly important role in management of meningiomas. Specifically those meningiomas that fail surgery and radiation.

In brief, and some of this was already touched upon earlier today, what about precision medicine for high grade gliomas? As had been alluded to earlier -- and Dr. Lesser had that great figure showing how complicated tumors and pathways can be -- unfortunately, glioblastomas are quite complex, genomically. That doesn't mean that we won't still see efficacy for target therapies, but we still have a long way to go there.

This is actually data that was shared with you from Patrick Wen. So the Brap mutation that I told you about earlier that's present in melanomas and craniopharyngiomas is present in a subset of high-grade gliomas. This is just prelim data from a Phase 2 study looking at (inaudible 00:20:11). So these are Brap meth inhibitors in patients that have refractory Brap (inaudible) high grade gliomas. So this was one arm of this study, this was a Phase 2 study in rare cancers that included grade three and four gliomas. And we see that it's a huge overall response rate here at the bottom here. 22% of Grade 3 gliomas and 29% of Grade 4 gliomas or glioblastomas. Still
not good enough, but we are seeing some responses with Brap inhibitors in glioblastomas having these mutations. Unfortunately, it's only a very rare subset of glioblastomas that have these mutations.

But here's an example of a patient that did benefit -- and again, this is data provided from Dr. Wen. This is a 37-year-old patient that had a right, parietal, Brap, mutated glioblastoma. Got Brap inhibitors, tolerated the treatment well, had a response in one area but then they had another tumor progressed; but some promise in this patient.

And we heard about the GBM AGILE study from Dr. Cloughesy earlier today and this is another example of precision medicine effort in glioblastomas. This is the INSIGHT trial where again -- similar to the study earlier -- different arms of the study are going to look at different targeted therapies in glioblastomas. So that's an ongoing trial that's open at multiple institutions. More to come for glioblastomas whether precision medicine will show benefits in these tumors and we're absolutely hoping they do.

Finally, for the last ten minutes of my talk I'm going to shift gears and talk about brain metastases. Again, we haven't talked too much about brain metastases earlier today, but I do want to talk a little bit about precision medicine in brain metastases where we all are seeing a lot of promise.

So brain metastases; so why are they important? They're truly an unmet need in oncology. They're actually the most common cancer of the brain -- meningiomas are the most common primary brain tumor -- brain metastases are the most common cancer of the brain with
an incidence of about 2-300 thousand cases per year in the U.S. Most are lung, breast and melanoma and median survival in this is still quite low; 3-23 months, unfortunately.

Also unfortunately, clinical trials in the U.S. have historically excluded patients with brain metastases, which is a huge problem when you're trying to find better therapies for this patient population. Actually I do want to highlight this scan is from a 24-year-old patient of mine with brain metastases. We are seeing young patient's come in with brain metastases, so again, we do need to do more to find better treatments.

In 20 BC, Augustus Caesar said "All roads lead to Rome." Management of brain metastases between the 1950s to 2010, all roads led to whole brain radiation therapy. Pretty much, if you had a brain metastases, you received whole brain radiation therapy.

There's a lot of data emerging now that there's neurocognitive -- and actually, I'll go through this slide. Whole brain radiation therapy became the mainstay of brain metastases for about 50 years because of this early study from 1954 showed there was (inaudible 00:23:38) of symptoms in 24-38 cases. Survival was four to eight months. At that time, unfortunately, patients didn't live long enough to have the neurocognitive deficits that we're seeing now. Dr. Wefel and others have done really remarkable work in studying neurocognition in these patient populations. There have been a number of studies that have come out in the last two years showing neurocognitive decline after whole brain radiation. Patients will live longer but unfortunately a large percentage of patients do have memory and neurocognition issues after whole brain radiation.
We need better systemic therapies to improve the standard of care. There are more systemic therapies coming out. What are some of the challenges in precision medicine in brain metastases?

Number one; as I mentioned earlier, limited number of perspective trials in this patient population. A lot of clinical trials unfortunately exclude patients with brain metastases. Many are small studies. Most patients with brain metastases have progressed on several therapies; they're often sicker. It's challenging to treat patients who've already progressed on a lot of therapies.

The other is the extent to which brain meds share the genetic profile. I talked about genetic profiles earlier, the extent to which they share the genetic profiles of primary brain tumors is unknown. I'll spend about five minutes at the end of my talk briefly speaking about this work, which we've done, which was actually ABTA funded. I always like to present that here, because there's a lot of support for ABTA.

So targeted therapies are showing a lot of promises in brain metastases. Just as I was talking about targeted therapies in melanoma, we are seeing nice responses in the brain. Let's go start with melanoma. About 50% of patients with melanoma develop brain metastases, so a very large proportion of patients. Brap mutations affect about half of melanoma patients and Brap mutations, as I expressed earlier, predict a sensitivity to Brap inhibitors.

Here are some of the prospective studies again. I'm not going to go into too much detail, but some of the prospective studies of different systemic agents in melanoma. The first couple are actually chemotherapy. I want you to focus on that the response rates in the past were very
low. About 15 years ago, if a melanoma patient came into clinic with brain metastases, unfortunately it was a death sentence. Patients would die within a few month and it was terrible. We've seen a lot of promise in the last few years; part of it is because of immunotherapy -- which you heard about earlier today -- and targeted therapy.

You saw a similar slide earlier today with Dr. Lesser's talk, where he talked about targeting the immune system so I won't go into too much detail here. Other than, we're seeing great effects with immunotherapy in melanoma as well as non-small-scale lung cancer and other cancers. Basically, how it works, unfortunately cancer's smart, it forces your own immune system not to recognize it. How immunotherapy works is it puts a block on that block such that then the immune cells do recognize your cancer. There's a number of different immunotherapies that have come out and been FDA approved for different cancers.

You can see immunotherapy here. These are just different types of immunotherapy and response rates are much better then historically what we were seeing in melanoma. Now we're having patients who can live for several years on these immunotherapies. It's really wonderful to see.

Finally, targeted therapies. These are therapies that target Brap and again, you see response rates that are quite high with targeted therapy in melanoma brain metastases. Lots of promise, lots of good studies showing that these are good agents. That we're now using as standard of care in patients with brain metastases.

What about non-small cell lung cancer? About 40% of non-small cell lung cancer patients will develop brain metastases. Very common, just like melanoma. We're seeing that
targeted therapies have promise in brain metastases. Dr. Lesser talked about some of these earlier -- so EGFR and ALK inhibitors. These are targets in lung cancer and we're seeing targeted therapies having great effect. Again, this is a table just showing some of these studies and we can see -- you can see response rates are much better than what, historically, we were seeing.

Just like in melanoma, non-small cell lung cancer brain metastases patients are living much longer now too, because of this exciting work with targeted therapies.

And finally, breast cancer. About 30-40% of patients that have this type -- HER2 amplified breast cancer -- will develop brain metastases. We do see that some targeted therapies do have efficacy in the brain also.

However, what you might notice, although we're seeing promise many of these patients do progress in the brain. Even after initial responses we do see patients who progress in the brain. We need better therapies for brain metastases patients and for the last five minutes of my talk I'm going to focus on my ABTA related research. It was one of the first grants I got as a fellow was from ABTA. We actually did some research that led to a clinical trial. I'll show you some of that work now.

The unanswered research questions that we really tried to answer with our ABTA funded research is; what are the targetable mutations in brain metastases? Patients often do progress in the brain; can this be due to genetic changes that are different in the brain metastases compared to the primary tumor? Because the brain metastases, obviously, they come from the primary tumor. And can we rely on that primary tumor biopsy? For a patient that has a skin biopsy, can
we make decisions based on the skin biopsy for patients with brain metastases? Which is what standard of care is for brain metastases patients.

What we did over the last years and what we're doing this -- ongoing in my lab currently -- we're genomically characterizing hundreds of brain metastases. Meaning we're trying to understand how brain metastases differ from their primary tumor. What is driving that brain metastases? That's the question we're trying to answer.

ABTA actually provided support and we built this internal team of collaborators and before a few years ago the largest study to genomically characterize brain metastases had one patient sample. Now we have 1,500 patient samples that we're in the process of analyzing. This has again, been an incredible international effort. We've been sequencing and trying to understand the genetic mutations in brain metastases and why is this type of research challenging?

Why has this not really been previously done? Well, previously, brain metastases were not routinely banked. Normal tissue -- so you do need a blood sample or lymph node to compare to and that was not routinely collected, historically. Older samples are harder to analyze and patients -- we do need the consent of patients for this type of research. A lot of the wording is in the newer consent forms.

This is our study; it was funded by ABTA. Where we genomically characterized a hundred of these brain metastases matched with primary, normal tissue. And let me just geek it out with some science for a second. So for each brain metastases and primary tumor we tried to
understand what are the genetic mutations? Where are they? Are they in the brain metastases? Are they in the primary tumor or are they shared?

Red is a mutation exclusive to the brain metastasis, blue is exclusive the primary tumor and gray are shared. What we saw was that all the brain metastases had this significant divergent or branched evolution where the brain metastases of the primary tumor shared mutations, but there was continued significant evolution. Such that there were new mutations in the brain metastases.

Why is that even relevant? Why do we care about that? Well, we need to know if therapeutic targets are different in the brain compared to the primary tumor. We did see that this indeed was the case.

The pattern we saw in brain metastases was what Charles Darwin depicted in his notebook in 1837, this pattern of branched evolution. This is exactly what we see in brain metastases. Unfortunately, it's significant genetic divergent evolution, and this is what we see.

Let's take it back to the clinic. Is this clinically relevant? Do they have targetable mutations that are not in their primary tumor? And again, I'm going to geek it out and try to walk you through this.

This is an example of a patient who had a brain metastasis; a cerebellar metastasis in the back of her brain. She was stable on her (inaudible 00:32:20) therapy. So her disease from here down was well controlled. This is not an uncommon scenario where we often see patients who do develop brain metastases in the setting of their extra-cranial disease. The disease outside of the brain being well controlled and what I do want to draw your attention to; when we analyzed
her primary tumor sample and her brain metastasis, she had this new mutation called the EGFR mutation. Which I told you about, was in lung cancer, but it's not really in breast cancer. We found it in the brain metastases of this breast cancer patient.

Just to put this on the figure here. Her brain metastasis had this targetable mutation that was not in the primary tumor sample. When we looked across the samples, more than half the cases had this targetable alteration in the brain metastases that was not in the primary tumor.

What are the opportunities to target brain metastases for trials? There were and we found lots of alterations of this pathway called the CDK pathway, the PI3 Kinase pathway. Again, the point is we're seeing new mutations in the brain metastases that are not detected in the primary tumor.

How is this important? Well, I asked you some questions earlier; why does the brain metastases progress in the brain and why do patients have -- why do we see these heterogeneous responses in the brain compared to primary tumors?

This means that genetic drivers are new actual mutations in the brain likely lead to these difference we see in the responses. But it also means that if we were only to look at the primary tumor, we might miss potentially actual [sic] alterations in the brain metastases.

Based on this we've now initiated a biomarker driven trial in brain metastases. This is a national NCI sponsored trial. Just been activated about two weeks ago throughout the U.S. so we're excited to see if we're going to see benefits. Basically, we're going to be targeting patients based on what we see in the brain metastases. This is going to be an ongoing trial for the next few years. We'll see if personalized medicine will work for this patient population.
Just to conclude this part; targeted therapies are showing promise in brain metastases. Brain metastases harbor many targetable mutations not in the primary tumor and a precision trial is on the way.

To finalize the entire talk; what I hope I've conveyed to you today is mapping the genetic profiles of primary and metastatic brain tumors is critical. Is helping us uncover therapeutic targets and I do think -- when we were talking about what excites us and Dr. Lesser was talking about what excites him -- I do think that precision medicine is a promising approach for primary and metastatic brain tumors.

We still have a long way to go, but I do think that we're going to see real changes in how we manage these patients with this personalized medicine approach. I'd like to thank a lot of individuals who contributed to some of the work and specially to ABTA for supporting our work so early on.

I always like to -- this is a patient and family conference. I lost my mom to metastatic breast cancer a few years ago. Now I'm actually planning a wedding, I'm having a wedding soon. Her absence is even more striking to me. We often forget about why, as physicians, forget about what drives us. What drives me is that I miss my mom every day. Before she passed away, she asked me and my brother who's a radiation oncology resident to dedicate our lives to trying to help patients and do better. That's why I do what I do and everything I do is in honor of her. Thank you.

[Applause.]
I think I have a few minutes for questions? Five minutes for questions. Did I confuse everyone? I do talk fast, I know that. Yes.

Q: Where do you see this target therapy in 20 years? 30 years?

A: Yeah, what I hope to see and maybe I'm always an eternal optimist -- I hope to see that in 20 - 30 years, for each cancer we'll have the genetic mutation and we'll know how to target that patient. Based not just on their disease but what their particular cancer -- what mutation they harbor. We'll know what drives that cancer and we'll be able to target it. That's what I'd hope. I think that's probably simplistic for many types of cancers and I think it's ultimately going to be a combination of targeted therapy and immunotherapy.

We're seeing immunotherapy work beautifully in many types of cancers. We're still waiting to see -- work in progress -- if it's going to work for glioblastomas, for example. I do hope that in the future we'll be able to tailor patient's treatment based on the genetic biomarkers.

Even now for immunotherapy, we're starting to see what are the biomarkers that are working for that predict [sic] response to that immunotherapy. I think precision medicine is not going to be just targeted therapy, but we're also going to be able to predict who's going to respond to immunotherapy. Who's going to respond to targeted therapy? Then come up with a concoction that will be individualized for each patient.

That's my dream.

Q: Cure cancer.

A: Cure cancer, exactly.
Q: That's a solution, I think.

A: Agreed.

Q: Yes. Wanted to ask -- you had talked about meningiomas. Just wondering, is there any targeted therapies that are being looked at with regard to nerve sheath tumors, schwannomas?

A: Yeah, I think Dr. Blakely will be talking about that at your break-out session; is that right? There will be an entire breakout session on nerve sheath tumors, but there's definitely promise in that area with targeted therapies. I think there's going to be an entire session on that.

Q: Hi. This is maybe more of a logistical question.

A: Yeah.

Q: In your current research project, are you banking brain tissue? How do you go about doing that?

A: Oh, that's a several hour question. It's actually -- there's a lot of steps that are required. Number one, the first thing you do is ethics approval and IRB approval to actually do this.

The second, for a lot of the types of research that we're doing, we consent patients. When a patient comes into our clinic, we consent patients to have permission to -- what they are going to go get to the operating room for their tumor to be taken out, if we can take a piece for research. And then explain what we do with it.

For banking, it depends on what the type of research you want to do is. Some of the tissue we store in freezers, others we're making animal models. Taking the cell lines and making
animal models from tissue. Others are -- there are periphen embedded for purposes of pathology but then we can often use that discarded tissue for some of the research we're doing too. We try to bank as much as we can, so we can use it for current research efforts.

In the consent forms now for patients, we will consent them for future -- if many patients are okay with us using the tissue for future research. Then we'll bank it for some of the newer technologies that are going to come out in the future too.

Q: You don't put out an ABP to the medical community?

A: There are efforts now -- there's the huge effort in the breast cancer community called Count Me In, where patients are sending samples for research. I think there needs to be more of a push to create that in the brain tumor community too. Then patients can feel empowered. Maybe that's something we can discuss with ABTA about things we can think about doing. There's a huge need for that. Oh, perfect, good! I think having something like that for brain tumors is great.

Q: Hi, I wanted to know how do you consider your funding levels for all these studies?

A: How do I consider funding?

Q: Do you consider that you're dramatically underfunded? Do you consider that you're fairly funded?

A: So I think that as researchers we're always underfunded is the short answer. The problem with the current funding climate -- the NIH for example, doesn't fund a lot of these discovery
efforts. All the genomic efforts that we've been doing -- when we started the work it wasn't -- NIH doesn't fund these kind of things. These are fishing expeditions and whatnot.

We do rely on resources like ABTA and other philanthropic organizations for funding this kind of research. Because it's high risk research that potentially does have high rewards, but it's often not -- the NIH -- the funding limit right now for RO1s is eight or nine percent. Of all the researchers in the U.S. that apply for funding to the NCI, eight or nine percent of those people will get funding.

The funding climate is uber competitive. Again, organizations like ABTA have been really helpful. It was one of my first grants. I had a post-doc that got an ABTA grant, now I have another post-doc that's going to be funded by ABTA. These are the things that fuel our research, I can't emphasize that enough. Many of us here in this room have benefitted from ABTA funding.