“The Personalization Conundrum” (Brad Power) [#16]

July 6, 2022
Brad Power

How can physicians be convinced to overcome concerns of safety, reimbursement, and liability to prescribe novel regimens (personalized drug combinations, dosing, and sequences), without randomized clinical trial evidence?

Meeting Summary

In this meeting we had a lively dialogue on the "personalization conundrum" for advanced cancer patients – on the one hand, we can identify highly personalized treatments, such as drug combinations, but … on the other hand, high levels of personalization mean that it is unlikely there will be evidence from randomized clinical trials to support the uniquely targeted treatment. So clinicians may lack confidence to prescribe them and payers to cover them. Treating physicians have concerns about safety, reimbursement, and liability, which are heightened when there isn’t randomized clinical trial evidence.

We have learned about personalized treatment strategy thanks to insights from some amazing experts. Personalized drug combinations (Ally Perlina), dosing, and a strategic sequence of therapies based on evolutionary and game theory (Bob Gatenby) can provide better outcomes for advanced cancer patients.

However, access to personalized treatments is often hard. There are “expanded access” or “compassionate use” processes for patients to get access to drugs where they would not otherwise be eligible. But there are still other barriers and incentives to getting access to drugs or drug combinations that are “off label” (unapproved use of approved drugs). For example, if a patient gets access to a drug off label, providers are not able to mark up the drugs via the typical “buy and bill” paradigm, which is 6% to 600% for infused anticancer drugs. Physicians lose revenue, while also spending more time managing the process and the patient, including potential adverse side effects.

Clinicians make treatment decisions outside the guidelines, e.g., off-label uses of drugs, for individual patients all the time. When they do, they are guided by their own experience, and the experience of their colleagues. What are those dynamics, and can we encourage more of it? Testing, mathematical simulation models that predict response, and real world experience from longitudinal studies are three approaches that could give physicians, payers, and patients more confidence to prescribe more personalized therapies.

- **Testing**: We have heard from Tony Letai and Payel Chatterjee of SEngine about functional testing . Blood-based liquid biopsy using ctDNA and surrogate markers of efficacy can be used in cases where fresh tumor tissue is unavailable. (Peter Kuhn is scheduled to discuss.) Blood and other novel tests (Karin Rodland) can enable more frequent monitoring of disease progression, enabling fine-tuning of treatment and personalization.

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- **Predictive Models**: There is a lot of investment and effort in developing models that will predict drug response by large pharmaceutical companies and academics that can be repurposed.
- **Real World Evidence**: Every patient should be tracked in an observational trial to share results of their unique, personalized, N-of-1 experiments. GCTA (XCELSIOR) is one such unique registry (Jeff Schrager): It allows you to create "n-of-1" arms, does not drop the patients on the floor ever, has no exclusion criteria, and understands "arm" in a dynamic way not available to any other trial model.

Several other ideas were raised to address the personalization conundrum:

- Glenn Sabin proposed that the patient could consent to hold the clinician harmless, lowering liability concerns.
- An anonymous caregiver suggested that the job of patients is not to be a grateful consumer of an industry that serves itself, but rather a person with needs, and that you are seeking people who can help you, where your needs and your wishes are primary.
- Ally Perlina recommended having patients raise specific treatment options with their doctor and listen to the specific feedback.
- Saed Sayad pointed to creating a logical process that leverages existing public data.

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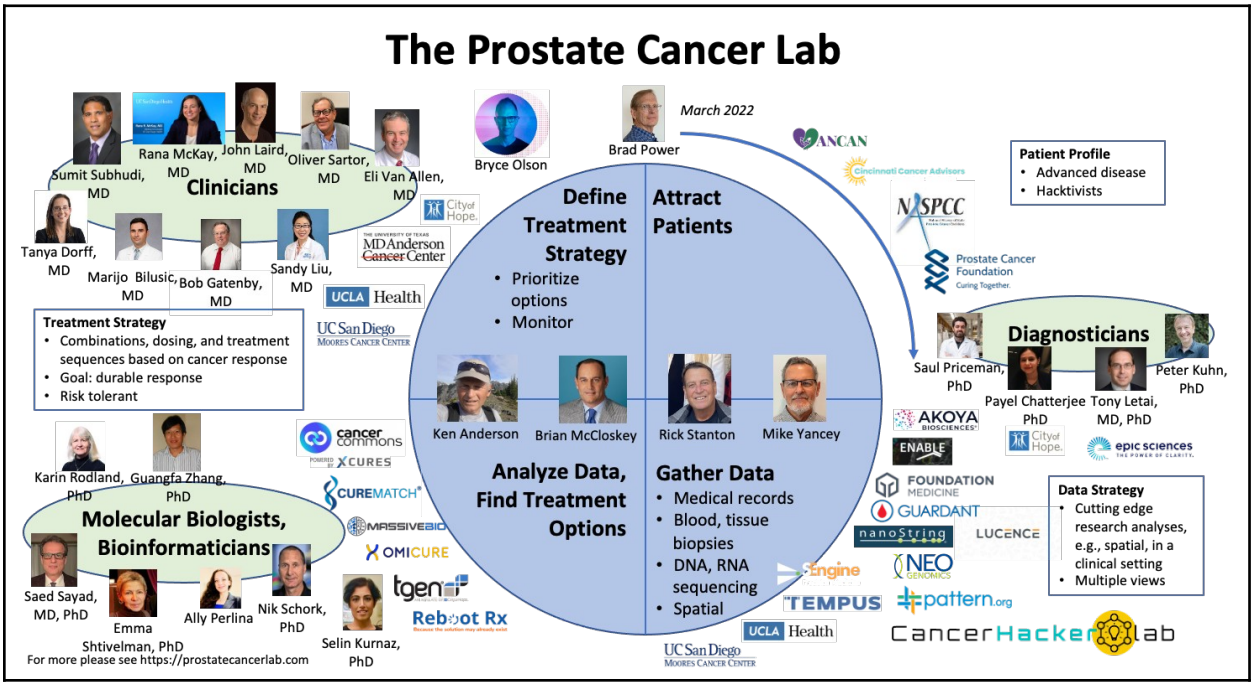
Meeting Notes

Brad Power: Today we're going to have a conversation about some of the things we've learned about various aspects of making complex testing and treatment decisions for advanced cancer patients, and to get your input on some countermeasures to the “personalization conundrum”. A lot of the things that we have been talking about, such as drug combinations, have been generally accepted by most people that we've spoken to as a better option. If you can hit multiple biomarkers at the same time, that’s better, but there's a concern around toxicity when you have drug combinations.

How can we balance this conundrum of, on the one hand having what appears to be better, more effective treatments, e.g., through drug combinations, and on the other hand, a concern around toxicity?



This is the Prostate Cancer Lab organization. We launched in March, so we're about four months in. This is a checkpoint for reflection.

This picture has changed almost every couple weeks because we've added another diagnostic company, another presenter (we have had 15 meetings with a variety of discussion leaders), or another patient, molecular biologist, bioinformatician, or physician.

This is our 16th meeting, and each time we've had various people lead discussions, many of whom have raised new ideas. We have a calendar going forward of meetings, about 10 or so scheduling into September. The discussion leaders are providing insights on this decision process of identifying treatment options, targeting them based on diagnostics and analysis, and then trying to reflect those and prioritize them.

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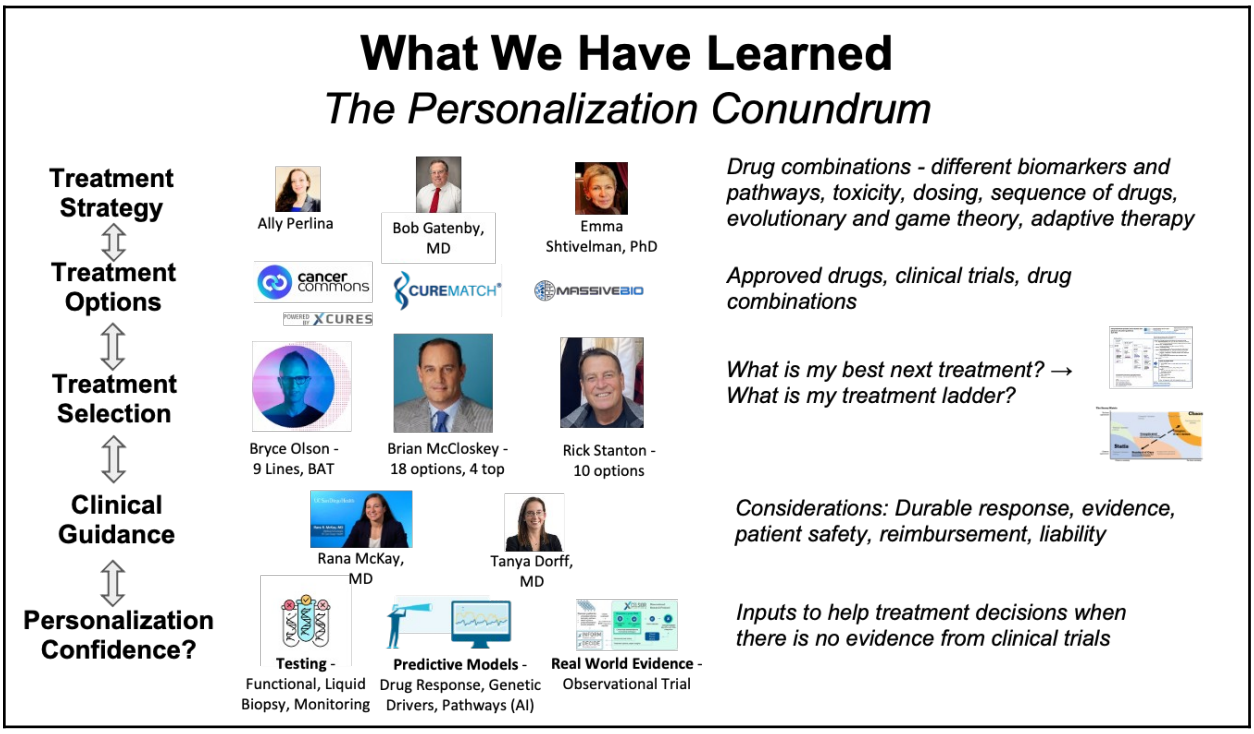


This slide summarizes what we've learned and what I'm calling “the personalization conundrum”.

Treatment Strategy: Ally Perlina of CureMatch has presented their recommendations for matching approved drugs indicated by the patient’s biomarkers. CureMatch’s distinctive contribution is drug combinations. Their premise is that hitting multiple biomarkers is better than hitting one at a time.

Saed Sayad has also made the point that more drugs at lower dosage is better than fewer drugs at higher dosages.

Bob Gatenby has been an influential, theoretical strategic guide for us with his ideas. Cancer is a heterogeneous population. Any drug or treatment is going to have an effect on that population and generate a resistant strain. If you administer drugs at maximum tolerable dose until resistance, you will breed resistant strains. Rather, we should think about knocking down the population using game theory, evolutionary theory, and adaptive therapy.

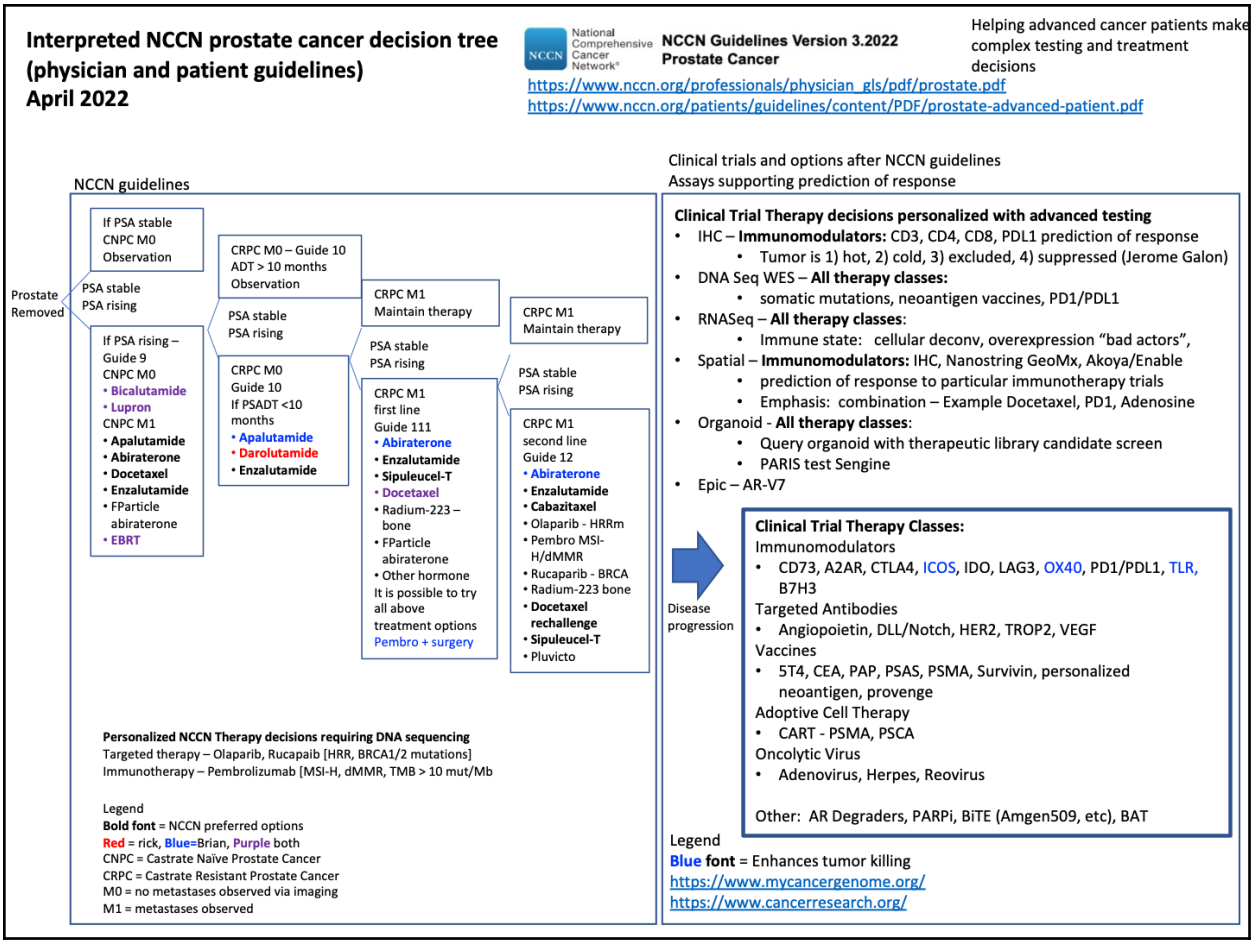
Emma Shtivelman has been a leader in giving us principles for choosing among treatment options and ideas about treatment. For example, a targeted CAR-T therapy may be in Brian’s future. It could target PSMA or a couple of other antigens. Therefore, if you have a drug that reduces the PSMA-presenting cancer cells in the population, then it might make the efficacy of that eventual CAR-T less. She also had ideas about choosing different pathways. A lot of the prostate cancer therapies are targeting androgen deprivation and androgen receptors. Can we

find drugs and treatments that would be targeting different pathways, and see what they can do, rather than continuing to pound the same pathway and get increasingly diminishing returns.

Treatment Options: Brian has submitted his data to Cancer Commons, xCures, CureMatch, and Massive Bio. CureMatch focuses on combinations of approved drugs. Massive Bio focuses on clinical trials. Cancer Commons is mostly Emma Shtivelman. xCures is the software engine that's running Cancer Commons, and they have come up with yet another set of options. Brian reviewed the treatment options they recommended for him last week. He had 18 options, of which four seemed to be on the top.

We need to give a shout out to our inspiration Bryce Olson, who has been through nine lines of treatment, though it could be more. He's currently on bipolar androgen therapy, which is an extreme version of adaptive therapy. It's being very effective.

Rick Stanton has presented previously that he's identified 10 options for his treatment. Rick's treatment options have largely come from his clinical team, which includes Tanya Dorff, Rana McKay, and doctors at UCLA.



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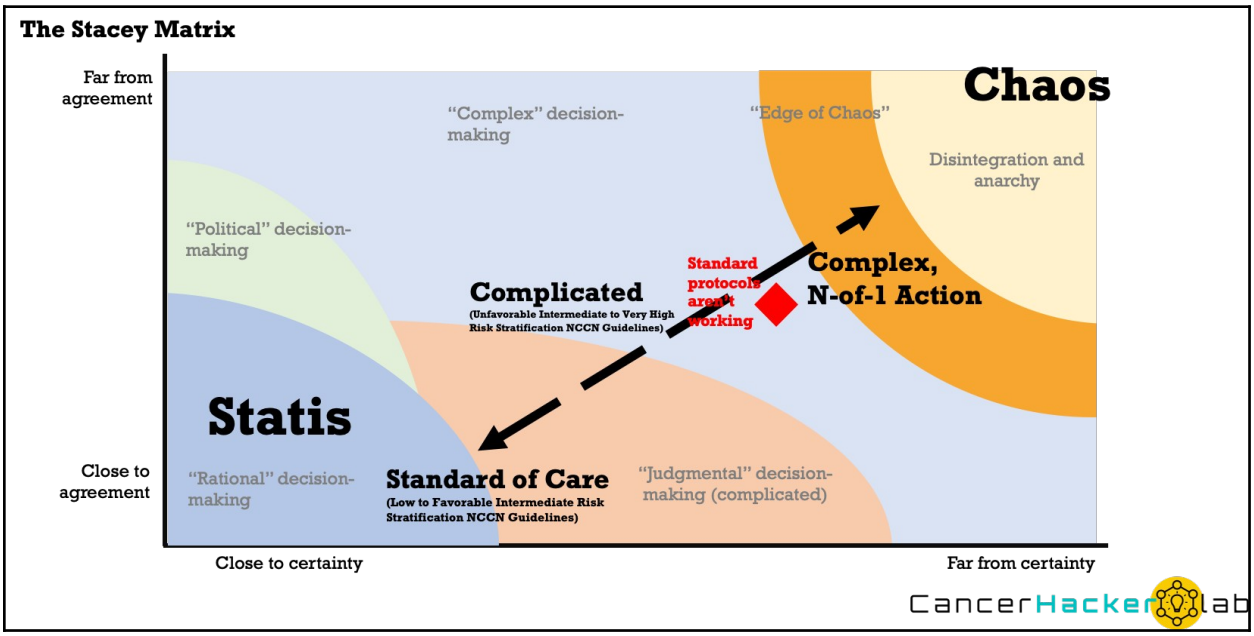
There are two little thumbnails of slides that you can't quite see off to the right. One is Rick's analysis of the NCCN guidelines. I included it to make the important point that we are beyond the standard of care. The discussion and decisions we're talking about are for patients who've exhausted the standard of care, and they've exhausted the obvious choices for drugs or treatments. Most have had a prostatectomy, radiation, and androgen deprivation, and they've failed all of those. They are in the zone of discretion, where there might be a dozen or 20 options, and a patient and his medical team needs to choose amongst them.



The second thumbnail slide is called “the Stacey matrix”, which says that we're in the zone of complex decisions, not straightforward and easy decisions.

Treatment Selection: The essence of this conversation is how we can make physicians and patients more confident in making personalized decisions, particularly drug combinations, but also dosing and sequencing. When Bob Gatenby reviewed Brian's case, he said that since Brian has a very low PSA, he is a candidate for an “extinction event". He recommended that Brian choose a ladder of three drugs in rapid succession or in a cocktail, and see if he could get an extinction event, to use the evolutionary terminology. But we run into the question of toxicity when we have combinations, because we're in uncharted territory, because there aren't clinical trials that have run that personalized combination at personalized dosing.

Personalization Confidence?: There are three tools that we could use to give patients and clinicians more confidence.

- **Testing**: We've had a discussion led by Tony Letai of Dana Farber about functional testing and what it can do. We've also had a presentation by Payal Chattergee of SEngine on functional testing. And we will have others from First Ascent Biomedical. Liquid biopsies are another source of information that could give confidence in choosing amongst options and to be more personalized. We're going to have Peter Kuhn

presenting on liquid biopsies in a couple of weeks. Another testing category is monitoring. We had Karin Rodland talk about identifying biomarkers through proteomics. Obviously PSA is a form of monitoring a biomarker, but there might be others that could be identified. The big idea is that if you could have more frequent testing of your response to a drug situation, a drug that you're being administered, then you could move more quickly.

- **Predictive Models**: AI and machine learning is getting better at making predictions. Drug companies are throwing lots of money at figuring out whether patients will respond to drugs that can be repurposed for patients. There's been a history of looking at genetic drivers. There are models that can be developed that would predict whether a patient is going to respond to a drug. Predictive models may be off in the future, but it could give one confidence in making a personalized treatment decision.
- **Real World Evidence**: Nic Schork in our last session said that we could develop a protocol and put everyone into an observational trial or registry. Jeff Schrager, who works with Cancer Commons, told me about a trial called XCELSIOR, which is a continuous trial that accepts all patients and then monitors their progress longitudinally. That could be plumbed by AI and ML or patients to figure out what's working. It's using real world evidence to get some confidence to see what is working.

Brian McCloskey: That was a perfect summary of where we've been. To add some color, last week I met with Rana McKay and presented my 18 options. She was amazing in that she went through all 18 of them. I spent a full hour with her. It's one of the things that makes her a different doctor, in such a great way. When we get into personalized medicine, we get into drug combinations, and the big issue for her was toxicity. How do we manage toxicity? How do we manage quality of life? How do we figure out what the right dosing is and sequencing for these drugs? I certainly subscribe to the idea that drug combinatorials are the right approach. But I'm in a zone where I don't know where to go. Dosing and toxicity are real issues. I appreciate her perspective that, as a physician, she lives by the creed that she will do no harm. You can easily get lost looking at all of these different approaches that are going to use these drugs to address these targets of opportunity that we've identified. But there are a lot of unknowns. I appreciate Rana’s guidance in putting the brakes on. We have to help her. The mission here is, how do we help? How do we help our physicians get over this hump, and do it in a way where it meets their standards of safety, meets my standard of quality of life, and helps us to get to better outcomes. For me right now, that's really the heart of the issue.

Kaumudi Bhawe: Thank you for providing this platform. Your slide outlining the different approaches and the three different aspects of moving the needle forward is very informative. We need decentralized, observational trials, such as XCELSIOR, with the ability to open up arms as necessary, and are also collecting patient tissue and liquid biopsy blood samples. It needs to be written into the trial protocol that that information is captured so that it can help future patients. Currently there are multiple observational trials, but we need trials where the intervention is screening itself. We need to get these companies, such as SEngine, and all the different types of testing companies that are out there, to overcome the typical limiting factor of patient tissue. Among the three options that you've listed for a doctor or an oncologist, if there is

evidence on the patient tissue that a certain combination of drugs is working, or some experimental treatment actually works on the tumor cells, then that would be a gold standard equivalent almost to having randomized clinical trial data for that combination, but in a more feasible way. Obviously it's not possible to conduct a randomized clinical trial for every single combination or new treatment.

Brad Power: I don't know the universe of registries as a naive patient. This gets into data privacy issues. Of the advanced cancer patients I know who are trying to survive, privacy is not an issue. They would be quite open to making all of their data available for research and not really care if their employer or anybody else knew about it. \I believe that that would be the vast majority of advanced cancer patients. So it's not for lack of willingness of patients to have a global registry that you could then see what works and what doesn't. The “patients like me" argument seems obvious. If 20 people have my situation, and 10 people tried this and 10 people didn't, and 10 people had something good happen and 10 people didn't, I want to do what worked for the 10 people. Therefore, more data is better in that registry. I don't know anything about the registry landscape. On the one hand, everybody should stand for a global registry that is a data vacuum cleaner. It should be very open source, like Wikipedia, a “good for the planet" model. Yet there are competing forces and incentives that cause academics to want to hold research data close, because that's the article that they're going to write about based on their data, et cetera. It sounds like you have some knowledge of XCELSIOR. What does that landscape of registries look like? We wouldn't want to reinvent the wheel. Nic Schork offered to create a protocol, but I wouldn't want to reinvent the registry wheel. There must be something out there. Is three one out there where we could just say, “this is what everybody should be using”?

Kaumudi Bhawe: There's currently no system in place that allows this to happen easily. A system needs to be created. Even something like XCELSIOR isn’t really there yet. There are multiple factors playing into this. There's the economics of it. There are different competing interests. I don't have an idea right now of who the right people would be to tap into creating a platform to make this happen. Because any interventional trials that are out there have to be led by the group that is instituting the intervention. There doesn't exist a third entity that initiates an open ended trial and then gets everyone on board.

Brad Power: In the past we have talked with Eli Van Allen at the “Count Me in” project at the Broad Institute. He's also at Dana Farber. They have a metastatic prostate cancer database. However, when we spoke to him about being able to use this registry for clinical use, he said they can't do that, that it's for “research use only” purposes. If he had to make it useful for clinical purposes, he would need a lot of money to get it suitable and available for clinical use. If anybody is going to do something like that with a broad societal benefit, it might be the Broad Institute, and yet, they're doing something like it, but as our healthcare system is often skewed, it's not directly for patients, it's for research and drug discovery.

Kaumudi Bhawe: Even if it's initially labeled as for research, because that's more kind of protecting the doctors and everyone. We don't want to claim that this is clinically relevant yet.

It's research. Glenn [Sabin] can speak to this a little bit too with some experience that even the testing companies have their limitations of what can be tested on patient tissue. There are those barriers as well.

Glenn Sabin: This is such a big, hairy, complex topic, and you got the legal regulatory exposure stuff, the toxicity, and the quality of life that Brian spoke about, but where does it start? We’re living in the U.S., and you have to start with the economics and the incentives because that just seems to drive everything. I worked with Kaumudi recently on a shared client, a woman 81 years old, metastatic, luminal hormonal breast cancer, that happened to be low amplification of HER2. She went through multiple combination targeted therapies and the tumor kept getting larger and larger. The treatments had no impact on it. We went through a process with Cancer Commons and we engaged with SEngine to test a cultured organoid. It pointed to a couple agents, mostly BTKIs (Bruton's tyrosine kinase inhibitors) and other agents that have no indication for this type of malignancy. I pushed to get the Georgetown Lombardi Cancer Center tumor board to have a discussion with all these top breast cancer experts. Because she was only in theory at a line three treatment, they just weren't comfortable. Then in the recent ASCO meeting that just passed there was a study that discussed the arm of low amplification HER2, and all of a sudden they were willing to give her a HER2 treatment outside of a trial. We were working hard on getting her into a HER2 trial. It was very difficult getting her onboarded. Then Georgetown just kind of came through and said, now that they knew about the embargo and they released the information at ASCO, which was available weeks prior to that, they decided to make it available for her.

She just went through her first treatment a few days ago. I'm sure it will have an impact on it because it's a fairly remarkable agent for this particular situation.

Here you have an NCI-designated comprehensive cancer center, but they're giving her this agent that Medicare won't pay for. It's off label, and all the money is in the infusion. It's not reimbursed for the administration of the drug. AstraZeneca made the drug available free of charge to this person. Georgetown Lombardi can't mark it up. Typically the markup is around 20%, or actually between 6% to 400%. That's the range of a markup on infused therapies, depending on where you get it. Institutions pay less for it, and they get reimbursed more. The community oncology practices pay more for the drug, and they get reimbursed less.

That's why they're rolling up all these smaller community oncology practices into these major institutions. As an institution, they could make that call. They know that they're getting revenue from higher paying folks that are getting other infused drugs. But what incentive would there have been for a healthy community oncology practice to go through this process with this woman to get her something off label, and then have the exposure of different toxicities and quality of life, and the additional energy it would take to manage the side effects, et cetera?

Brad Power: We were talking about registries. For that patient that you were working with, would her experience be tracked anywhere? Was she on a clinical trial or would her experience be available for future people publically?

Glenn Sabin: Not yet, but we could always go back and make it so. I'm sure Georgetown is paying attention to how she will do, and they have the case, and if she does remarkably well, I'll push for minimally a case report. Case reports are going to become more important as the low end of the totem pole of evidence. If we go to an N-of-1 model and track this stuff, everything should be published and indexed.

Anonymous Caregiver: I want to propose a mindset shift. Brian, at the end of your setup there was an intention to help physicians feel more comfortable. I want to step back from that a second. I'm trained on the doctoral side in clinical psychology, and we have principles as well of “do no harm”, but also beneficence, which is to help. I want to propose maybe as a setup for the rest of this conversation, moving forward, the notion that our job, or your job as patients, is not to be a grateful consumer of an industry that serves itself, AKA a “patient”, but rather a person with needs, and that you are seeking people who can help you, where your needs and your wishes are primary. Obviously, it needs to include willing participation of those who serve you, not coercive, but it's really important to put your own needs first. One of the best things that we can do in terms of adding other decisional factors is to consider the realm of what makes you comfortable with your treatment decisions, and really dive into the psychological factors, such as your appetite for risk. I know you come from an investment banking background. Any of us can look at how risk/reward calculus applies in other areas besides medicine, but to get really good at how people differ with their appetite and their goals, and what's going to feel like a life well lived to them, and what's going to feel like a birdie putt left short, and to flesh that out. Then you can bring that to physicians and say, “Hey, this is me. This is my life. This is how I make decisions.” Then your physicians can inherit and use that as their rationale for operating then within the context of their ethics guidelines, which includes “do help”.

Brian McCloskey: That was super insightful. The one quick thought I have is this idea of appetite for risk, and maybe that's not just on my part, but also on the part of the physician, because you have various physicians that are going to have very different appetites for risk, who want to push the envelope a little bit. I don't know where I stand on that right now, to be honest. I almost need a tool. Wearing my marketing hat, you could do a Myers Briggs test, or some other personality test, to understand the patient's appetite for risk, and the doctor’s’, and see if we are aligned. If you look at a scale, where do I sit? Where does my doctor sit? That's a really important alignment that needs to happen, and if you're not aligned, then that can really lead to bad outcomes.
I'm processing what you're saying. I love the fact that you're bringing in the psychology of the decision-making process into this conversation. You're an expert at it. Maybe there's a way to formalize that a little bit more.

Brad Power: We reflected on the passing of Kasey Altman today, and one of the things that she did before her molecular tumor board was to share a statement of the goals of the patient. Brian, I've been encouraging you to articulate your strategic intent and put it above your treatment options. Some of the strategic principles that you would apply would be this risk factor and quality of life. Kasey built that into the front end so that the doctors knew what the patient,

who is the customer of the process, wanted as an outcome. Risk orientation and quality of life are two obvious ones. And there may be more that would be personal and unique to each patient. That would be great to get explicit because the unspoken bias is that doctors are taught “safety first, do no harm”. That's going to be an overarching consideration. That risk factor is going to be pegged on the high end, and as Kerri was talking about in the balance with benefit, it may not always be the same orientation the patient has.

Glenn Sabin: It should be in the standard of care that your first clinical new patient appointment should be in combination with a clinical psychologist.

Anonymous Caregiver: It definitely needs to be more integrated. We need to solve the pipeline problem in behavioral health before we're going to do that.

Saed Sayad: To discuss the logical approach: This group has a set of questions, and we try to find answers. Discussion is secondary to the main goal. We have a set of real questions, and the first step is asking experts, physicians. They say, try drug A; if it doesn't work, then try drug B. Mostly the decision is a random process, or based on very limited clinical aesthetics. The next step is doing a search. Mostly what we are talking about is about research. This is a set of data, which is the right number? We have many patients, who are using many drugs, but we don't have those stages.
But before that type of research, we have a lot of data in the public domain. I mentioned this in the first meeting: we are not using that data. There are more than 5 million experiments in public data. For many of the questions we are asking, maybe we can find the answer in those experiments. Before asking this coalition how we can get the clinical data, which is going to be a five-year project, this is what we have and see how we can give access to those data, to our researchers, practitioners, and patients. If we have a coalition, and we cannot find that answer in those public data, then we go to the research. Then our focus should be mainly or say, these are my five top questions. Let's focus and try to find the answer for those questions. Three steps: experts, search, and research.

Mike Yancey: On the risk question: you need to look at it from the standpoint of the potential benefit for any potential treatment strategy, and then of course look at what are the risks, and then try to balance those. As your runway gets shorter, your appetite for risk is going to get greater, and you will be willing to maybe try things that are more risky, but may also provide more benefit. Because in the end, you're going to totally run out of runway.

Stacy Hurt: Brian, in that scenario that you outlined about the drug combination, have you found somebody that's willing to administer those drugs in combination? The reason I ask is because I'm in Pittsburgh, and I had a really rough time coloring outside the lines with a pancreatic cancer patient that I was working with through an academic medical center, an NCI-accredited cancer center, that was outside their scope of liability. Can you make some set of assumptions that you're willing to assume the risk of toxicity, et cetera? Do you have a clinician ready to administer that drug combination, and how are you doing that?

Brian McCloskey: I'm too early in that journey right now to know. I just got my feedback last week from Rana. Practically speaking, we're going to re-image where my disease is. That's the next step. Then I'm going to meet with her again after I go through a PSMA PET, CT scan, bone scans, all that stuff. I don't know yet whether or not she is on board. She was more prone to pursue some of the easier drugs, ones where there's a little bit more data or where there is a phase two clinical trial. We're not so far out on the branches just yet. We are still early in the conversation.

Jeff Waldron: I'm not a patient, as many of the people on this call are. One thing that always impresses me with oncology patients from a behavioral health or psychological standpoint is one of their bigger criteria is helping other patients like themselves not have to go through the same experience that they did, like to cause earlier diagnosis or earlier intervention. That's another important criterion in working with patients: so they can feel that they're giving back and changing the “standard of care” to be more reflective. That's why Stacy's question was so good about how you get greater access to lower doses of combination therapies, rather than a high dose monotherapy. Giving back is pretty important from a psychological standpoint.

Anonymous Caregiver: I love that. I would characterize that as purpose. Especially with cancer patients, among all the types of behavioral health patients, there's a real need for addressing the existential issues of life; meaning, purpose. There are natural times in people's lives where there are transitions: retirement, what should I do with myself, empty nest, all that kind of stuff, but especially, any of these factors that really play into quality of life. Quality of life isn't just minimization of medical side effects. It's about the positive. It's about the presence of things that matter to you.

Brad Power: John Laird, if you don't mind calling on you as a clinician. This question that I posed today is largely about physicians caught being concerned about drug combinations, which is one of the treatments that we've come up with that we believe is strategically a better approach, but then it runs in this resistance around toxicity. As a clinician, who's made these sorts of decisions for your patients over years, what do you think the forces are? What would your comments be?

John Laird: Just to be clear, I'm not a practicing clinician, I'm an advocate that looks for doctors who can deliver what we think might be best. So Stacy's question for me goes to the heart of the matter. I have two pancreatic cancer patients right now that I'm going to be “coloring outside the lines”. My question for the group is, does the group have any wisdom on how you find these practitioners? Because that's often the key. When you start working with combinations in general and then novel combinations, it's really hard to predict really what the actual risks are. If there's no data now, maybe from Saed’s point of view there are data on some of these more unusual combinations, but it is a legitimate issue.
One thing that may be missing from the conversation: have you guys talked about optimizing the patient's terrain so that it is more robust and has resilience to take on any given set of treatments? Because optimizing terrain can optimize results and minimize side effects. Maybe not for this conversation, but that's another important factor.

Brad Power: Let me drive down a little bit of detail on that. Could you please give us some examples? Because Rick, in a conversation we were having just recently, was talking about nutrition as something that's in the things you can control as a patient about your general health. What is terrain, and what would be the two or three major things you can do as a patient to improve your terrain?

John Laird: Terrain comes from the Latin for earth. All of us have probably planted plants, and we become intimately involved in questions of terrain, right from the beginning. What is the quality of the soil? Are there nitrogen fixing bacteria? What's the temperature? What's the amount of moisture? What is the amount of pathogens? Good guy bacteria, bad guy bacteria? Those are all questions of terrain, healthy terrain, healthy plants, diseased terrain, diseased plants. Probably more in the naturopathic literature, the concept is that cancer is only one factor. Another factor is the person in whom the cancer is growing. There's lots of mind-body evidence that suggests that emotional states, experience of loss, these kinds of things, that anything in a mind-body way that adversely impacts the immune system makes cancers more likely and makes it less likely that you can heal from it. There's a huge body of evidence. Nutrition is another terrain factor. Exercise is another terrain factor. Drilling down and looking at immune function, natural killer cells, looking at the factors that promote angiogenesis, the factors that promote or reduce apoptosis. There's lots of blood tests, for example, that can be done.
Keith Block and his book “Life over Cancer” has a couple really good chapters on terrain. There's a physician, Nasha Winters, who is a naturopathic doc who had stage three or maybe four ovarian cancer. She was doing so badly that she took herself off of treatment. There must be a better way. Out of her work over the last 10 years, she wrote a book called “The Metabolic Approach to Cancer”. She has a 10 factor terrain questionnaire, which is her way of beginning to look quickly at what the terrain factors are. She does very few consults with individual patients. Now she's trying to develop oncologists who are integrating a lot of what we're talking about now. I remember in one case I had with her -- it happened to be an ovarian cancer patient – she said, if you give this patient chemo it will kill her. What we need to do is optimize terrain, improving her bone marrow. The patient's gone 7, 8, 9 months. She has cancer, but it hasn't advanced, and her measurements are substantially improving. The whole area of terrain is – I'm not an expert in it – common sense, no brainer that has a lot of payoffs. Oncologists won't talk about terrain, but they'll say exercise, diet, and mind-body. Whether they know it or not, they're already in the terrain conversation.
There's a society of integrated oncologists. There are naturopathic oncologists. That's what I tend to look for.

Glenn Sabin: You’ve got your host environment, which John's speaking to, and you've got the tumor burden. If you're N-of-1, you're a unique host and you've got a unique tumor burden. It's a process of combining sensible evidence-based lifestyle medicine and the core tenets of integrative oncology to work on that host environment, psychological, emotional, physical, through nutrition, by creating a strong immune function and a very resilient individual who happens to be hosting disease. You've got the nutrients, of course, but you've got all kinds of different biomarkers of different areas. You've got oxidative stress and free radicals and

inflammatory markers, et cetera. It's just a sensible approach. I'm just as interested in the host environment as I am in these discussions around precision medicine, and they're not mutually exclusive at all. But getting back to the area of precision medicine, I think one huge area, obviously in addition to the economics, is the legal and regulatory exposure, and liability. What does that look like? Can you get patient waivers where a practitioner could be more comfortable working with a patient? As a patient gets a shortened runway, there's more pressure on the oncologist and oncologist team and those tumor boards. If there's a way to bring in an attorney that is really steeped in this particular area, that would be fantastic.

Brad Power: We've looked into that. It's kind of the flip side of a patient's consent. It's holding the clinician harmless for the advice they would give.

Ally Perlina: Drug combinations are a challenge like everybody's outlining, but it doesn't mean that it's impossible because many hundreds of patients were given some combinations. Three drug combinations that are novel are a bit more difficult to put on the table for consideration, but two drug combinations seem to be a little bit more realistic, to convince a physician. A patient needs to be very aware and open and informed. My inference is that if you are very clear about your request, then you can always hear if a doctor says, “no”, why do they say, “no”? They can reason with you. You need to have a request in mind when you go into a doctor's appointment. If you leave it open ended, of course the doctor will use the tried and true approach that maybe does not work. They may know that the odds are quite poor in terms of long term survival, but they've used it before, and they know that there's no opposition, and the system does not encourage them to look outside the box. If you go with an open-ended question, most likely the doctor will stick to what they did before. But if you say, “I would like to get this for me”, and then see if they have reasonable concerns. “This is specifically not good. I'm, I'm afraid about hemorrhaging for you specifically.” Then it sounds personalized, and it may be worth considering why they object to certain things. But if it's just a general apprehension then I've seen patients change doctors with persistence.

Brian McCloskey: To add a bit of color to that: I presented Rana McKay 18 different treatment options, of which close to half had come from CureMatch. The CureMatch treatment options were stacked up against treatments, such as an ADC targeting B7H3 clinical trial, going on Pluvicto, and another clinical trial with ARV-766. She thought carefully about each of the different options. She had some questions, like one of the drug combinations was Apalutamide plus two other drugs. She said, “well, you've already seen Apalutamide, why would we do that?” I give her credit because she went through all of them. But it was very easy for her to move into this position where there's not a lot of data in terms of how these drug combinations work together in terms of efficacy. And there's this overarching question about toxicity. When she was faced with the other options, I think it was probably easier for her to move in the direction of those other options. What I don't know is, is that the right decision? Is that the best path to go, particularly where I am in my treatment journey? We have to think about this strategically, not just my next best treatment. Is it better to do a three drug combination right now as opposed to Pluvicto or an ADC? Hopefully that helps to provide a little bit more context for you on the

challenge I'm facing with her. I haven't gotten feedback from Tanya Dorff, for example, or others, but that's the challenge.