“Tests and Treatments for Rick Stanton” [#3]

April 6, 2022
Brad Power

Meeting Summary

Advanced prostate cancer patient Rick Stanton shared details on his testing and medical history, treatment options being considered, and the tests he would like to see to inform his future treatment decisions.

- **Medical history:** Rick shared a table with his PSA measurements and treatment history. His PSA is currently under control, and he is looking to have his next treatment ready to go.
- **Treatment options:** Rick listed the treatment options that have been recommended to him. Dr. John Laird suggested that trying chemotherapy combinations in the lab of Bob Nagourney at the Nagourney Cancer Institute would have a greater assurance of efficacy (80-90%) than clinical trials (15%). Rick Davis endorsed treatments with more evidence, and recommended that Rick revisit his initial diagnosis, as well as considering Pluvicto (PSMA-targeted radiation nanoparticles).
- **Tests requested and analysis desired:** Rick has requested IHC stains that will provide indications on his likely responsiveness to immunotherapies. He is offering his extensive medical data to anyone who would like to hack on it.

We continue work on “right to see” – finding ways for patients to be able to access data from “research use only” tests run on them.

Requests

- Please let us know if you know anyone who might be interested in being a principal investigator, or any potential funding organizations, for an observational feasibility study on providing data from emerging (research use only) tests to patients to guide their prostate cancer treatment decisions (“right to see”).
- If you would like access to Rick or Brian’s data, please contact them.
- Please join our online discussion forum for 24/7 conversation.

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Meeting Notes

Brad Power: There are three agenda items we plan to cover in this meeting:

1. An update on our work on “right to see” - the idea that patients should have access to “research use only” data that is run on them.
2. Rick Stanton is going to lead us through his treatment situation, his history, and the decisions that he is facing now, as a setup for the issues facing people like him with advanced prostate cancer.
3. Rick will share the data that we have on him and Brian McCloskey and the additional tests he would like to see run.

“Right to See”

We spoke with Nik Schork, Peter Kuhn, and Marty Tenenbaum in the past week about various ways to get around the roadblocks to patients having access to data from “research use only” tests run on them.

One workaround is to have an IRB (Institutional Review Board), as Nik Schork talked about in our last meeting. Nik described in our last meeting how he helped get an IRB-approved protocol for Rick Stanton. So one path is to broaden or expand that as a template for others to use.

Another workaround is to set up an observational feasibility study, which is a research study with a lower barrier to set up than a classic randomized clinical trial, which is prospective, expensive, and slow. We are working to find principal investigators and organizations that would fund such a research activity.
If you know anyone who would potentially be a PI or an organization that would want to fund that kind of work, please let us know.

Rick is also trying to go through standard channels and a CLIA-certified lab to get the advanced testing he would like through City of Hope, where he is being treated by Tanya Dorff, and where they have access to his tissue.

Rick Stanton: TGen is moving ahead with approvals to work with Akoya and Enable. I can’t say for sure because Akoya and Enable don’t want to talk to a patient. They want to talk to TGen, which has the protocol in place. I’m boxed out. I get a little update that things are moving ahead. I’m very excited about that because I would like to be the first of many. I’d like this to be available to everyone who has the means. It’s fairly modest, I think a few thousand dollars. It’s getting closer.

Introductions of New Participants

Rick Stanton: I’d like to hear from some of the people I see on this call whom I don’t know. Could you please introduce yourselves?

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Dr. John Laird: An MD focusing on complex cancer patients and integrative treatments, recently relocated to Asheville, North Carolina.

Saed Sayad: An MD now focusing on AI, professor in the Computer Science department at Rutgers.

Alex Feltus: Biochemist, biomedical, genomics, professor at Clemson, crops, high end computation.

Chandra Kota: A medical physicist working in new radiation treatments. Currently working at Yale and looking beyond my day-to-day job and seeing how I can help patients with advanced radiation treatments.

Heather Messerly: At Certis Oncology in San Diego, creating PDx models using mice of patient cancer tumors to test different treatments on them to see which ones work and do not work. I’m not a scientist. Patient manager. Learning by sitting in. Happy to step in and help.

Jan Sobieralski: A patient with castration-resistant prostate cancer. I just asked my doctor if I could get Leutetium 177 (discussed in our last meeting), and they said “no”, because I have to be castration-resistant and have had the Taxol treatment, further along in my journey.

Rick Stanton Case

Rick Stanton: To start with how I’m doing. I just completed six rounds of docetaxel. In my last round I had an 80% dose since I had developed some tingling in my fingers (neuropathy), and I’m a guitarist.

When I got my infusion, they also took my PSA, and I learned that my PSA had gone down – not a lot, but it did – from 2.6 to 2.4. The time before that it was 2.4, so I’m bouncing around 2.5. My cancer is being controlled. I expect to get another round of chemo.

At the start of my chemo I was advised that I would have six to ten rounds. This is in an Arcus clinical trial. I was randomized to the docetaxel arm, not the arm with a PD1 inhibitor and an adenosine inhibitor from Arcus I had hoped to get. Sandy Liu of UCLA is the leader of this trial and my treating oncologist. The folks at Arcus are my friends from when we worked together at Amgen. They are a very good small molecule company.

I hope my decisions will be informed by an IHC (immunohistochemistry) stain at a minimum. This is the kind of test results I hope to get:

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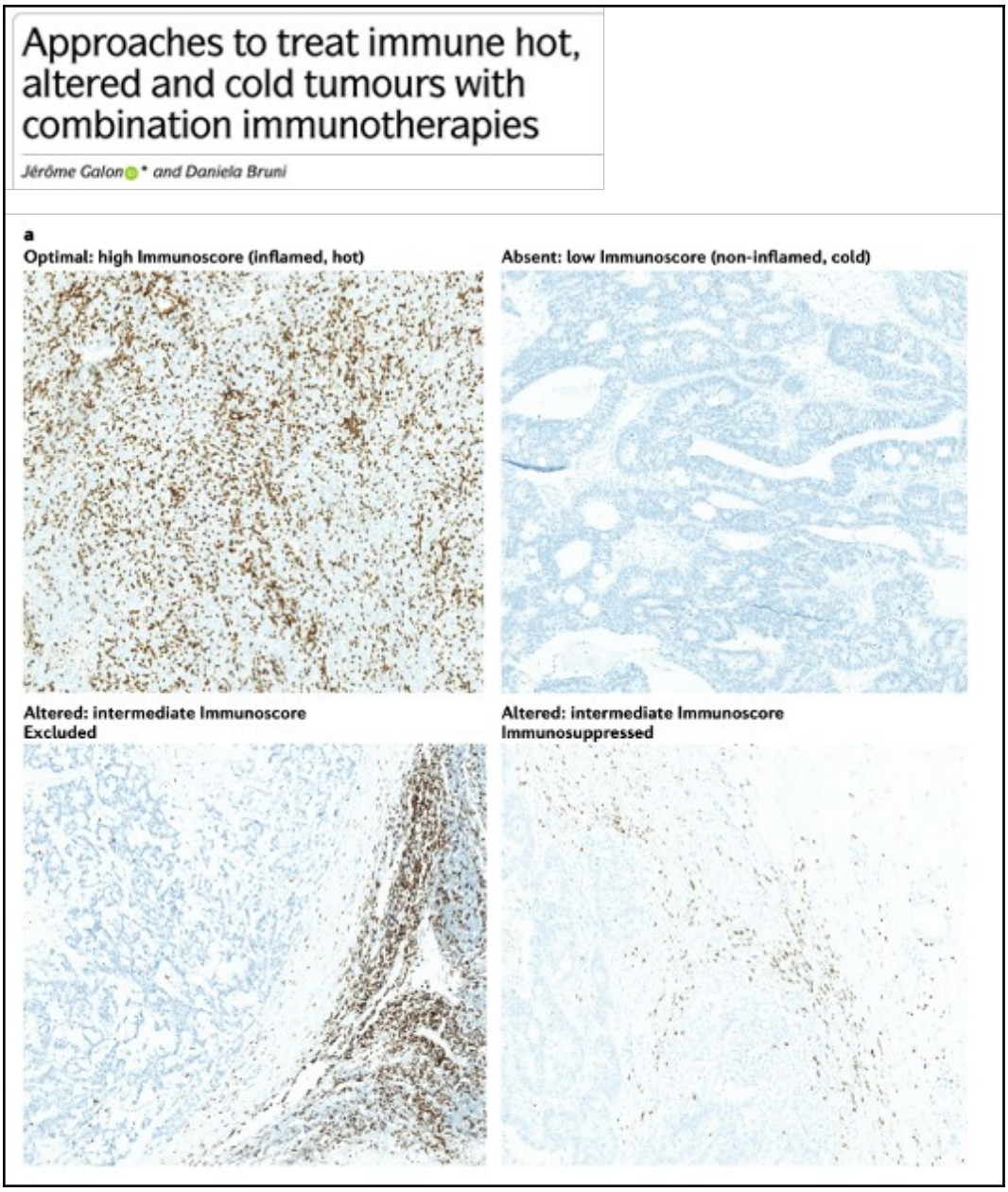

These are four tumor slices. This is a CD3 stain, that is looking at T-cells: CD4, CD8, and Tregs (regulatory T-cells). The brown pattern in the upper left tells you that this tumor is loaded with TILs (tumor infiltrating lymphocytes), which means it is “hot”. On the right you see that it is “cold”, T-cells are not infiltrating this tumor. On the lower left if you did an RNA-seq, you would think you had good infiltration, but the moat of exclusion means there is immunosuppression. In the lower right you see a low amount of infiltration, though they are there.

The reason I bring this up with the four states is that this IHC staining or spatial analysis would influence your selection of an immunotherapy. If you have low infiltration, either you need to do a prerequisite or hope for a miracle.

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Brad Power: Which do you look like?

Rick Stanton: I don’t know. I’m waiting on IHC - this stain. I asked Tanya Dorff to order it for me, and she agreed. I would call this spatial analysis. Akoya, Enable, and NanoString all do very deep queries using advanced technologies which are “research use only”. I want to do this with IHC, which is more standard.

I hope that I will be in the upper left. If you’re in the upper right, cold, with no tumor-infiltrating lymphocytes, PDL1 blockade inhibition is not going to work because there are no T-cells to modulate.

Dr. John Laird: As you said, with the upper right hand result, it would be a waste to try immunotherapy. Prepping that microenvironment would be key.

There is a group, not set up commercially, called Consultative Proteomics at the University of Texas, led by Dr. Robert Brown, that I’ve used. They do proteomics, IHC stains, 20 or 30 on any given tumor. Are you familiar with their work?

Rick Stanton: No, that’s beautiful.

Dr. John Laird: What they do that’s particularly relevant to this particular slide is assess CD8 cells, which are the ones that are going to be most helpful, from FOXP3 cells that put on the brakes. Anything that is 2/1 or over (CD8 to FOXP3) is considered good. Then they will look at CD163s, which are macrophages, and are also key. Macrophages can be in an M1 stage or an M2 stage, and they transform back and forth. If they are in the M1 stage, that is very positive; if they are in the M2 stage, then that is a brake on the system.

We can run the samples and get results, but they are not a high volume shop. It can take six weeks or more to get results back, but they’re very helpful.

This look at the microenvironment is something my mentor Mark Breniker had them set up a few years ago. You also get a protein fingerprint to give you a sense of which of these genetic changes are driving the tumor. No oncologists are going to make any treatment decisions based on this, but looking at the microenvironment terrain can often help in the off label environment.

Rick Stanton: I feel like going 20 deep in the IHC. Are these different slices of tissue, or are you able to stain and wash?

Dr. John Laird: They end up with 20 slides. They need a block. Offline I can help get you set up.

Rick Stanton: Are you acquainted with Akoya and NanoString’s spatial efforts?

Dr. John Laird: I’m not.

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Rick Stanton: You’re going to love them. It’s immunofluorescence, like an IHC. You’re able to do it on one slice of tissue. Immunofluorescence allows stain and wash. You are tagging the fluorescent molecule some color, typically red, green, or blue, to an antibody. You can go in three at a time with the three colors. You could pick CD3, CD4, CD8 and iteratively build up to their high dimensional, up to 100 plex. I know they’re operating at 35. This is both Akoya and Enable. It’s like what you said, except it’s on one slice. NanoString enables even deeper querying. In the slide on the lower left, you could query boundary areas.

Dr. John Laird: What was the extent of your disease and previous treatment?

Rick Stanton: Here is a one-page chart of my history and treatment considerations with my state, tests, treatment guidelines, and therapy options being considered.

id	date_notes	molEvid_notes	PSA_analysis	description
1	treatment strategy			patient desires aggressive treatment and so far, can handle side effects
2	treatments	popStudies	UCLA	salvage radiation, lupron, (casodex 13 months PSA 0.1->1.1), (darlutamide 4 months PSA 1.1 -> 2.5)(docetaxel 4 months P
3	next therapy options	CDK12 mutation	City of Hope	clinical trial: XmAb20717 (PD-1 x CTLA-4 bispecific antibody) + olaparib: https://clinicaltrials.gov/ct2/show/NCT0500572
4	next therapy options	RNASeq + popStudies	UCSD	-PSMA CART (Poseida).
5	next therapy options	RNASeq + popStudies	UCSD	-PSMA bispecific (Calibr)
6	next therapy options	popStudies	UCSD	-Immune checkpoint blockade (Impact, joint IIT with UM, JHH).
7	next therapy options	CDK12 mutation	UCSD	-Xencor (Immune checkpoint + X) - There is is an olaparib (PARP inhibitor in this trial). Currently not yet open.
8	next therapy options	RNASeq + popStudies	UCSD	-ARV-766 is an investigational orally bioavailable PROTAC protein degrader designed to selectively target and degrade A
9	next therapy options	RNASeq + popStudies	UCSD	-Daicchi antibody drug conjugate to B7H3. Not yet open at UCSD.
10	analysis	DNASeq WES	DNASeq - Ashion	TMB 1.4m/MB-low, MSI stable, CDK12 mutations(2), TPRSSD2-ERG fusion
11	analysis	DNASeq WES	TGenAnalysis1	HRD-tHRed=1.5=proficient, scarHRD=deficient, copy number gain ch8q
12	analysis	DNASeq WES	TGenAnalysis2	HLA class1, neoAntigens identified-prioritization in progress
13	analysis	RNASeq bulk	TGenAnalysis3	over expression: AR, KLK3(PSA), FOLH1(PSMA), KLK2, EPHA3, IGFR, CD276 (B7H3) - normalized to 45 in-house ref tissues
14	analysis	RNASeq bulk	TGenAnalysis4	connectivity map in progress
15	analysis	RNASeq bulk	TGenAnalysis5	low to very low CD4, CD8
16	analysis	RNASeq bulk	stantonBioscience	CD276 (B7H3)
17	analysis	IHC primary tumor	City of Hope	CD3, CD4, CD8, PDL1 stains wCOH pathology interp due 3/23
18	analysis	spatial phenotype	Akoya/Enable	seeking someday, somehow to get Akoya/Enable analysis
19	analysis	spatial phenotype	Nanostring GeoM:	seeking someday, somehow to get Nanostring GeoMx analysis
20	2019-10-01		4.1	yearly physical
21	2020-01-17	3 months	5.6	follow up local urologist
22	2020-05-04			prostatectomy City Of Hope, [4+3 Gleason], right and left seminal vesical as well as perineural invasion pT3bb
23	2020-06-16	6 weeks	0.6	Two CDK12 mutations noted on Ashion/TGen sequencing. MSI and TMB low
24	2020-07-16			PET PSMA scan UCLA: PSMA uptake left anterolateral 8th rib. Rib biopsy negative
25	2020-07-10	1 month doubling time	1.2	Lupron and Casodex start to respond to rising PSA
26	2021-04-01	8 months control	0.1	Lupron and Casodex - PSA held at ~.1 for 8 months on , then starts climbing
27	2021-08-09	4 months control	1.1	Darlutamide start, Casodex stop, stable PSA at ~1.2 for 2 months, then starts rising
28	2021-12-09	4 months doubling time	2.5	CT Scan - multiple prominent but mostly subcentimeter short axis left supraclavicular, mediastinal, bilateral common ilia previously with PSMA avidity and therefore most consistent with metastatic nodal disease.
29	2021-12-14	1 month washout rise	3.6	start round 1 Docetaxel under control arm of Arcus (Arc6) clinical trial of (Docetaxel + PD1 + dual adenosine receptor)
30	2022-01-04	3 weeks	3.1	Docetaxel round 2
31	2022-01-25	3 weeks	3.5	Docetaxel round 3
32	2022-02-15	3 weeks	2.4	Docetaxel round 4
33	2022-03-08	3 weeks	2.6	Docetaxel round 5
34	2022-03-29	3 weeks	2.4	Docetaxel round 6

From row 20 to the bottom is my PSA and the treatments I have received from my diagnosis in 2019. You can see I had Lupron, Casodex - which held me stable for 8 months, Darlutamide - which didn’t do much, and now Docetaxel - which took me from 3.6 to 2.4.

Brad Power: Dr. Laird asked about the extent of your disease? You’re metastatic?

Rick Stanton: I have nodal disease, 4 lymph nodes from my neck to my pelvis. These are picked up in a PSMA scan and confirmed in a CT scan. I am at nodal, Stage 4, castrate resistant. Lines 3 through 9 are my next therapy options.

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When I talked to Tanya Dorff, what evidence would influence her recommendations? CDK12 opens a lot of neoantigen fusions. She is advocating for this clinical trial which combines a bispecific PD1 and CTLA-4 with olaparib. Olaparib has been approved for CDK12 mutations, but subsequent data maybe shows not that great. It’s more for a BRCA-1 or BRCA-2. So I asked why she would recommend it. She said she wouldn’t recommend olaparib on its own, but in combination with the PD1 and CTLA-4, she thinks it might be a good fit for me.
Rana McKay gave her recommendations, including a PSMA-targeted CAR-T. Why would she add PSMA? There are three evidence notes on why it would be a fit for me. It fits from population studies. It was also confirmed in the RNA seq. I am a super high expressor of PSMA, and so is Brian. I light up.

Rick Davis added Pluvicto in our conversation last week.

Dr. Laird: Are you familiar with the work of Robert Nagourney down in Long Beach?

Rick Stanton: No.

Dr. Laird: Bob Nagourney in the 1990s started doing chemo sensitivity testing. He took live tumor tissue and exposed it in a test tube to multiple chemotherapy agents. There were many other people doing the same work at the same time. Some of the work was crappy, and the whole field was discredited. Nagourney has done good work over decades. In the test tube you can test various combinations. In general, if he finds that a tumor is sensitive, that will be borne out 80% of the time clinically. If he finds that a chemo is ineffective, that is borne out clinically 90% of the time. Nagourney is one of the smartest oncologists around. He is world class. He has a tough ego. He’s gotten a lot of hits from the profession. But his work has led to standard of care combinations, such as cabazitaxel and gemcitabine. The larger point is that trials are a crapshoot, and the percentage of success is maybe 15%. It would therefore be rational for my patients – and usually I don’t give any advice to patients unless I have reviewed their files for four or five hours, and I don’t really know your case, but this is a wide-open conversation – to go the Nagourney route, because you’re looking at 80% or 90% effective treatments vs. 15%. I would go that route first and get his assessment. He doesn’t care so much about genetics. He looks deeply. He’s more like Harrison Ford in Indian Jones who is confronted by a guy with swords and knives, and he pulls out his gun and shoots him. Nagourney cares about whether the treatment will kill the cancer. He cuts to the chase. He’s good to have on your team. If you have nodal disease, he would need a centimeter of tissue that you would have to get to him on the next day. Your tissue would probably be accessible. Whereas the proteomics can be frozen tissue, Nagourney needs fresh tissue. Nagourney Cancer Institute.

Rick Stanton: That sounds great.

Dr. Laird: He has a TED talk on his website. He is not just a lab, he is an active practicing oncologist. He knows the challenges. It would have advantages to do it onsite.

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Brad Power: Rick, what are the requests you would like to make? What are the questions you have?

Rick Stanton: Rick Davis, you gave the suggestion of Pluvicto. It was shocking to me because three out of three of my clinical oncologists hadn’t mentioned it. I queried them during the week. I got a beautiful response from Sandy Liu, my treating physician under the docetaxel Arcus trial. Her response was, “Yes. Pluvicto would be a very good option for you.” It’s so interesting that until I brought it up, because you brought it up, it wasn’t even on the radar. Suddenly it’s a very good option.

The other option is a crossover that I can go to and stay on the docetaxel and the PD1 inhibitor and adenosine.

Rick Davis: It’s a pleasure. It’s what we do. Sometimes you can’t see the wood from the trees. I also want to thank Dr. Laird because he’s saying the same thing. We can be looking around and running around in circles up the spiral staircase in the ivory tower and there’s some really good stuff out there. I don’t know how much experience Dr. Nagourney has with prostate cancer, but it doesn’t behave like other cancers.

In looking at your chart, something came to me that Dr. Laird mentioned: your disease was strange from the start. It showed up as very aggressive, 4 + 3. (The pathologist looking at a biopsy sample will assign one Gleason grade to the most predominant pattern in your biopsy and a second Gleason grade to the second most predominant pattern. The Gleason score classifies cancerous cells into 5 distinct patterns as they change from normal cells to tumor cells, graded on a scale of 1 to 5, where grade 1 cells resemble normal prostate tissue, and cells closest to 5 are considered “high-grade” and have mutated so much that they barely resemble normal cells.) It was relatively aggressive, but not over 8. I think if your slides ever got re-read might it have a much higher Gleason score? If you had intraductal disease and low PSA, from the outset your disease didn’t behave like an adenocarcinoma disease. There may have been mutations in there from the beginning that didn’t allow you to respond properly. One of the treatments we’ve seen used in that situation is adding platinum-based chemotherapy. I think you’re just getting docetaxel right now. I would be doing a little more work and see whether your cells had a bit of a neuroendocrine aspect earlier? Or even now? If they did, maybe we should add something else to the chemo.

This is separate from the PSMA discussion.

We go to these docs, and they don’t see the obvious. It makes me a little crazy.
Were you properly diagnosed in the first place?

When guys come into our group, we often push them back to their medical team to say, “have you done this, have you done that?” There is no one better than Epstein at Johns Hopkins to review those slides.

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I’m glad that we got you and Brian onto the PSMA path, especially when you say you’re super sensitive to PSMA. And Pluvicto is the best PSMA option. We have a guy whom we hooked into Bryce yesterday. His disease is running crazy – his tumor burden is around 39. He is certainly eligible to start Pluvicto, but he doesn’t want to wait the four to six weeks it would take to start. He is going into the Weill Cornell trial with alpha- plus beta-particles, starting next week, because time is so much of the essence for him. Fortunately, you don’t have that situation. Oliver Sartor thinks that alpha- plus beta- has some merit. But I would start with is tested.
I would be interested to hear from Dr. Liu about when Dr. Calais (at UCLA) is going to be able to start to take patients for Pluvicto.

On olaparib, these doctors are searching around to see how they can make a cold tumor hot. You have CD12. The problem with olaparib is that in the trial with Maha Hussain (PROfound ClinicalTrials.gov number, NCT02987543), they went for a basket approach and got a basket approval. They got all these mutations approved for the use of olaparib. They got a basket approval, but the only mutations that worked were for people with mutations in BRCA1, BRCA2, or maybe ATM. For the rest of the mutations, olaparib was not effective. But all these people with these other mutations got excited, e.g., with CDK12, and thought olaparib is the magic bullet, and it’s not.

We have to tie these guys back, and we have to stop these docs from treating some of our folks as fresh meat. That is driving me nuts.

Rick Stanton: It’s a beautiful soap box. At least I’m under control today, and that gives us a chance to be proactive.

If you’re falling and your parachute fails, you don’t even have that extra week or two to get the paperwork done to get scheduled, let alone figure out what to do.

Thank you to all of you so much.

I have been lucky to have TGen and Nik Schork help me.

We see these possibilities for my next treatment.
I have had extensive analysis for me, thanks to TGen.
I had a whole genome sequencing done, not just a whole exome.
We see the tumor burden, mutation.
I also had a neoantigen analysis, similar to what was done for Shirley Pepke.
My buddy Guang Fah at TGen did it. I have a lot of fusions.
TGen also identified my overexpression.
There is a connectivity map going on for me, and an organoid study.
It’s a very nice analysis that TGen has brought to the table.
Rana McKay suggested a B7H3 clinical trial. It is a clinical trial based on RNA seq, the first I’ve seen of a doc recommending a treatment based on RNA.

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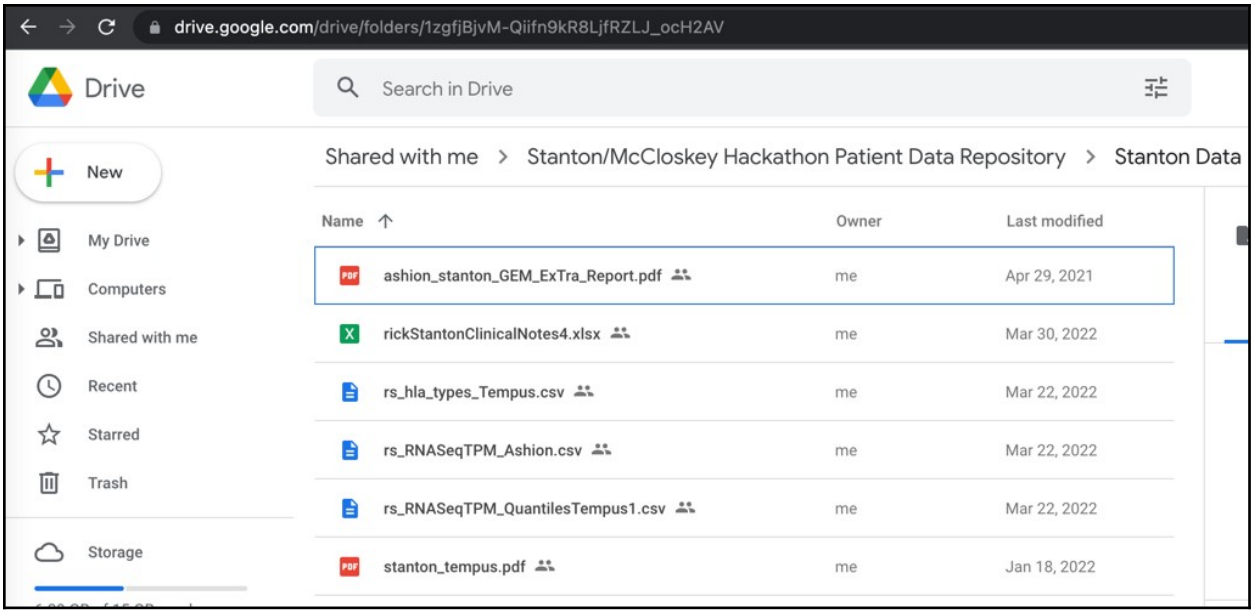
Brad Power: This is data that you have, or is in process, and will be ready sometime soon. If we were running a classic bioinformatics hackathon, like Alex Feltus knows, do we need to schedule a separate event for that? How would you like to proceed with what analysis on top of the data that you have?

Rick Stanton: I am a bioinformatician, so I am looking at my RNA seq data to do an assessment of my immune composition, using libraries in R.
This is my data, and it’s available on Google Drive.



Anyone who wants it can see my mutational reports, my clinical notes, my HLA types, RNA seq and transcripts per million, from both Ashion and Tempus, and my Tempus report.
This data is available for anyone who wants to hack on it.
I hope to be able to share my immune composition, which is a poor man’s view to answer the question of whether there are Tregs, or CD8s. You can estimate that rather exquisitely with this immune deconvolution. And if anyone wanted to help me, that would be great.

Saed Sayad: There are public databases that we should learn from. I have something to present. I will do it next week. We have analyses for drug repurposing, for example.

Brad Power: Let’s do that.