“Multi-omic Analysis Guides the Decisions of Brian McCloskey” (Rana McKay, MD, and BostonGene) [#98]

Brian McCloskey and Brad Power
May 22, 2024

“For the next four days, Dr. McKay completely quarterbacked my care across the emergency department, the urology team, the radiation oncology team, her team, and orthopedic surgery.” – Brian McCloskey, Cancer Patient Lab

“First, we noticed that a lot of tumor cells demonstrate expression of Synaptophysin in the metastatic sample, nearly 38%, and only 3% expression in the primary sample. We then reviewed H&E slides and images and revealed that in the metastatic sample, we also can find areas with neuroendocrine-like features.” – Kirill Kryukov, BostonGene

“The salient thing that I pulled from this report is the striking angiogenesis signature. There are multiple different VEGF pathway genes that are dysregulated. What's important to pull is that there are multiple different targets here, as opposed to just one that could all be targeted with a drug. When I see that, that's a very nice thing as a clinician to say, ‘Hey, this is not just one thing out of a sea of many; there are multiple targets in this pathway… This pathway seems to be off, and that may present a greater vulnerability for the tumor.’” – Rana McKay, MD, UCSD Health

“That's what precision medicine can do. It can help try to identify a specific vulnerability that we can take advantage of with drugs that we otherwise would not be able to.” – Rana McKay, MD, UCSD Health

Meeting Summary

Advanced prostate cancer patients want to know what their next treatment option should be if their current regimen fails. However, this is a moving target as new treatments are approved, clinical trials for new treatments begin, and experience is gained in old and new treatments. It is important to occasionally scan the field for newly approved treatments and research on treatments currently in clinical trials. For example, a number of new drug combinations and sequencing of systemic therapies in metastatic castrate-resistant prostate cancer can hit the cancer harder and earlier.

Dr. Rana McKay is uniquely qualified to discuss the latest personalized approaches to treating men with prostate cancer. She leads a multi-disciplinary prostate cancer clinic at UC San Diego Health, focused on delivering advanced cancer care. Her research interests include the design and implementation of clinical trials and novel biomarkers and therapeutic outcomes for patients with genitourinary (reproductive and urinary system) malignancies. She is interested in understanding mechanisms of response and resistance to specific cancer therapies. Before joining UC San Diego Health, Dr. McKay was a medical oncologist at the Dana-Farber/Brigham and Women's Cancer Center in Boston and an assistant professor at Harvard Medical School.

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Kirill Kryukov presented BostonGene’s analysis of Brian’s cancer, demonstrating the power of transcriptomic (RNA) analysis in identifying key biomarkers. Dr. McKay discussed her interpretation of the test results and considerations of various therapeutic approaches, illustrating the issues and art and science of treatment navigation.

What is Brian McCloskey’s situation?

- Advanced prostate cancer, diagnosed in 2016.
- Has had many tests over the years and has been through multiple lines of treatments including a radical prostatectomy, salvage radiation, six lines of systemic therapy, and two additional surgeries to remove metastatic lesions.
- Constriction of his right ureter (the tube that transports urine from the kidneys to the bladder) leading to kidney hydronephrosis (kidney swelling that happens when urine can't drain from a kidney and builds up in the kidney) and kidney damage, which affects his ability to pursue treatments that require full kidney function.
- Has had five operations since February 2023 to replace the ureter stent used to preserve as much kidney function as possible.
- In April 2024 the cancer spread to bone (typical for prostate cancer) in his spine (in the L2 vertebra, the second uppermost of the five lumbar vertebrae toward the lower end of the spinal column, within the lower back) leading to a compression fracture and spinal stenosis (the space inside the backbone is too small) requiring surgery to separate his spinal column from the spinal cord. He is recovering from that surgery.
- Suspended his most recent systemic therapy, a chemotherapy (docetaxel), in February to take a break from the side effects of a cytotoxic treatment.
- BostonGene completed extensive testing on Brian’s tumors in early 2024 and identified several targets to pursue.

What did the BostonGene analysis uncover?

- Some alterations were uncovered from the latest biopsy sample (amplification of androgen receptor, and co-amplification of KIT/PDGFRA/VEGFR2, along with a PTEN gene mutation), suggesting evolutionary divergence and potential targets as the disease progresses.
- A transcriptomic (RNA) analysis looked for biomarkers that are valuable as antibody-drug conjugates (ADCs bind to the tumor cell, a chemical linker takes a cytotoxic drug inside the tumor cell, which kills the cancer cell while sparing healthy tissue.) for therapy (TROP2, Nectin4, and SLFN11), and all of these markers in both samples demonstrated a medium or a high level of RNA expression.
- RNA analysis also uncovered a medium or high level of expression of some other potential biomarkers (HER2, HER3, and TGFb).
- The immune microenvironment has changed from an immune desert in Brian’s primary prostate sample to fibrotic in his metastatic sample.
- MxIF analysis revealed that a lot of the tumor cells demonstrate expression of synaptophysin (a specific and fairly sensitive marker for neuroendocrine tumors of both

low and high grades of malignancy) and in the metastatic sample near 38%, and only 3% expression in the primary sample.

What are the treatment options being considered for Brian?

- **Chemotherapies**: Brian’s synaptophysin (neuroendocrine marker) points to platinum therapies (such as carboplatin) and cabazitaxel.
- **Targeted drugs**: Drugs targeted at his gene mutations (e.g., VEGF and HER2), especially targeting the VEGF expression (KIT/PDGFRA/VEGFR2) with a tyrosine kinase inhibitor (cabozantinib) combined with an immune checkpoint inhibitor (nivolumab/Opdivo), which increases the efficacy over cabozantinib alone
- **Antibody drug conjugates**: to target Brian’s RNA biomakers (TROP2, NECTIN4, and HER2)
- **AR (androgen receptor) degraders** (a type of drug which interacts with the androgen receptor to downregulate this hormone activity, which feeds prostate cancer)
- **Radionuclides (drugs that contain radiation that bind to tumor targets)**: Alpha particle radionuclides (like actinium) are possible, but beta particle radionuclides (like Pluvicto) are not because of Brian’s kidney obstruction, which would hold the radiation in his kidneys for too long. (Actinium is not processed through the kidney.)

What are the strategic principles being applied to make a decision on Brian’s next treatment?

- **Outcome Goals**: Consider two main outcome goals: quality of life and delaying disease progression.
- **Integrate**: Balance and integrate data from the research and the test reports, considering patient history, current treatments and clinical context when interpreting reports.
- **Target**: Identify specific vulnerabilities in the tumor (VEGF, angiogenesis signature – formation of new blood vessels in cancer growth) and insights on the disease (neuroendocrine) to target with drugs. Consider possible agents and their compatibility with other agents.
- **Immune system**: Prefer immunotherapy over chemotherapy to maintain the strength of the immune system.
- **Safety**: Look at FDA approval evidence in other cancers and where there is evidence of safety and efficacy in prostate cancer. Avoid drug combinations that have high toxicity risks (such as two VEGF drugs).
- **Access**: Favor treatments with easy access.
- **Plan ahead**: Keep treatments in reserve for future rounds and allow for new, better therapies to come to market.
- **Validate**: Validate the test results and findings: If decisions are being made based on the increased expression of synaptophysin, VEGF pathway, etc. and these decisions are based on a single data point/test (there is a confidence risk for RNA expression tests.), consider confirmation through other tests, such as (in order of decreasing confidence):

(1) confirmation by IHC (immunohistochemistry - tissue staining) or a proteomic test, (2) a biological replicate showing the same signature (confirms the expression but does not unambiguously demonstrate a corresponding protein expression), and (3) molecular matching to similar patients who have shown increased expression and translation of the gene of interest.

- **Disease burden**: Keep the disease burden as low as possible.

What is Brian’s next treatment going to be?

Brian is planning to get a drug (cabozantinib) for inhibition of one of his biomarkers (VEGF) combined with an immunotherapy drug (nivolumab, brand name Opdivo, an immune checkpoint inhibitor). This combination has shown good efficacy in other cancers. Brian hopes to access this combination through a clinical trial being offered at UCSD.

What are Brian’s next steps?

- Procure nivolumab and cabozantinib for his treatment, either through a clinical trial or, if he fails the eligibility criteria, through patient assistance programs.
- Monitor his response to treatment and disease progression through various tests, including scans, PSA (prostate-specific antigen blood test), radiographic progression, blood tests for molecular changes and assessments of his symptoms and quality of life. PSA is a tricky marker to follow in castrate-resistant prostate cancer, especially with AR (androgen receptor) amplification and it's not as reliable as in metastatic hormone-sensitive settings. There are several ways to monitor disease progression with blood draws, using various approaches (e.g., minimum residual disease testing), such as fragmentomics, which looks at fragmentation patterns of cell-free DNA from a blood draw and identifying interesting markers (such as DLL3, a ligand highly expressed in neuroendocrine tumors, and STEAP, a prostate-specific cell-surface antigen highly expressed in human prostate tumors).

What can you learn from Brian that you can apply to your own care?

- Get an extensive diversity of tests to examine your cancer from different perspectives over time.
- Choose a quarterback for your care who is well-versed in the research and connected with you. (It may be hard to find medical oncologists like Dr. McKay who are willing or able to integrate complex molecular testing data into their practice).

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Meeting Notes

KEYWORDS

brian, tumor, therapy, report, patient, sample, mckay, cancer, target, data, prostate cancer, psa, analysis, drugs, question, carbo, agents, inhibitor, gene, amplification

SPEAKERS

Rana McKay (42%), Brian McCloskey (22%), Kirill Kryukov (15%), Brad Power (5%), Allen Morris (5%), Rick Davis (4%), Jonathan Starr (4%), Kaumudi Bhawe (1%), Saed Sayad (1%)

SUMMARY

Brian McCloskey shared his personal experience with cancer and Dr. Rana McKay provided an in-depth analysis of his cancer genomics. She presented a personalized treatment plan for Brian, combining VEGF inhibition with immunotherapy. The team discussed the potential synergies between different immunotherapies and emphasized the importance of delaying progression and enhancing the quality of life for patients undergoing cancer treatment. Later, the speakers discussed the potential of precision medicine in prostate cancer treatment, highlighting the importance of transcriptomic analysis, personalized treatment strategies and intelligent drug selection. Kirill Kryukov presented BostonGene’s analysis of Brian’s case, demonstrating the power of transcriptomic analysis in identifying key biomarkers. Dr. McKay discussed her interpretation of the test results and considerations of various therapeutic approaches.

OUTLINE

Prostate cancer treatment and research with patient Brian McCloskey.

- Brian McCloskey shares his cancer journey and introduces the topic of multi-omic insights.
- He expresses gratitude towards Dr. McKay for her exceptional care and support during a recent medical emergency. Dr. McKay has been Brian's doctor since 2017 and has been a source of comfort and strength throughout his cancer journey.
- He shares his cancer journey, including multiple systemic therapies and how BostonGene analyzed his cancer progression.
- Kirill Kiurkov of BostonGene will discuss multi-omic analysis and its implications for cancer treatment, followed by Rana's discussion of clinical implications.

Cancer analysis, including gene mutations and immune system changes.

- Brian McCloskey and Kirill Kiurkov discuss analysis of Brian’s primary and metastatic tumor samples, revealing alterations in androgen receptor and kit genes.
- Kirill Kiurkov highlights medium/high RNA expression in both samples, including potential biomarkers like TGF beta.
- He analyzes Brian’s immune system and proposes treatment options based on findings.

“Multi-omic Analysis Guides the Decisions of Brian McCloskey” (Rana McKay, MD, and BostonGene) [#98]

Targeted therapies for prostate cancer based on RNA sequencing report.

- Dr. McKay highlights the striking angiogenesis (the process of new blood vessels forming from existing blood vessels in the body) signature and multiple dysregulated VEGF pathway genes in prostate cancer.
- VEGF inhibition and immunotherapy combination shown to be effective in prostate cancer.
- She discussed potential treatment options for prostate cancer patient Brian, including “Nivo Cabo” (nivolumab plus cabozantinib).

Personalized cancer treatment strategies based on the patient's genetic data and clinical context.

- Dr. McKay explained how they analyzed omics data to develop an IO therapy (immunotherapy) for Brian's cancer.
- She discussed the use of single-cell analysis and bulk RNA sequencing to understand Brian's tumor.
- She provided additional context on the combination of Cabozantinib and immunotherapy, citing FDA approval and potential underlying mechanisms.
- She explained that their strategy involves integrating data from reports with patient information to create personalized treatment plans.
- She highlighted the importance of considering patient history, current treatments, and clinical context when interpreting reports.

Cancer treatment options for Brian, including immunotherapy and targeted therapy.

- Brian McCloskey shares his personal experience with cancer treatment and the importance of patient-clinician relationships.
- Dr. McKay explains how VEGF inhibitors and immunotherapy are used to treat cancer.
- She discusses the goal of therapy as delaying progression and maintaining quality of life.

Cancer treatment options for Brian, including treatments targeted to his cancer profile and radioactive particle drugs (theranostics, radioligands).

- Brian McCloskey wants to find a drug that preserves his quality of life while slowing cancer progression.
- Precision medicine can help identify a specific vulnerability in the tumor to target with drugs.
- Dr. McKay explains that PSA is a tricky marker to follow in CRPC, especially with AR amplification, and it's not as reliable as in metastatic hormone-sensitive settings.
- She monitors multiple factors beyond PSA, including symptoms, radiographic progression, and response to therapy, to make treatment decisions.
- She discusses the limitations of theranostics (compounds that contain radiation and that bind to specific tumor targets in the body) in treating Brian’s kidney obstruction, which would hold the radiation in his kidneys for too long, highlighting the need for practical considerations in drug selection.

“Multi-omic Analysis Guides the Decisions of Brian McCloskey” (Rana McKay, MD, and BostonGene) [#98]

- Participants discuss the potential of new radioactive agents, including actinium and PSMA, for castration-resistant prostate cancer treatment.

Prostate cancer treatment options, including neuroendocrine and AR-targeted therapies.

- Rick Davis expresses concern about potential neuroendocrine cancer and asks about treatment options.
- Dr. McKay discusses the challenges of defining neuroendocrine prostate cancer, including controversy around the use of IHC markers.
- She mentions the potential opportunity for Brian to participate in a degrader study for AR-mutated tumors.

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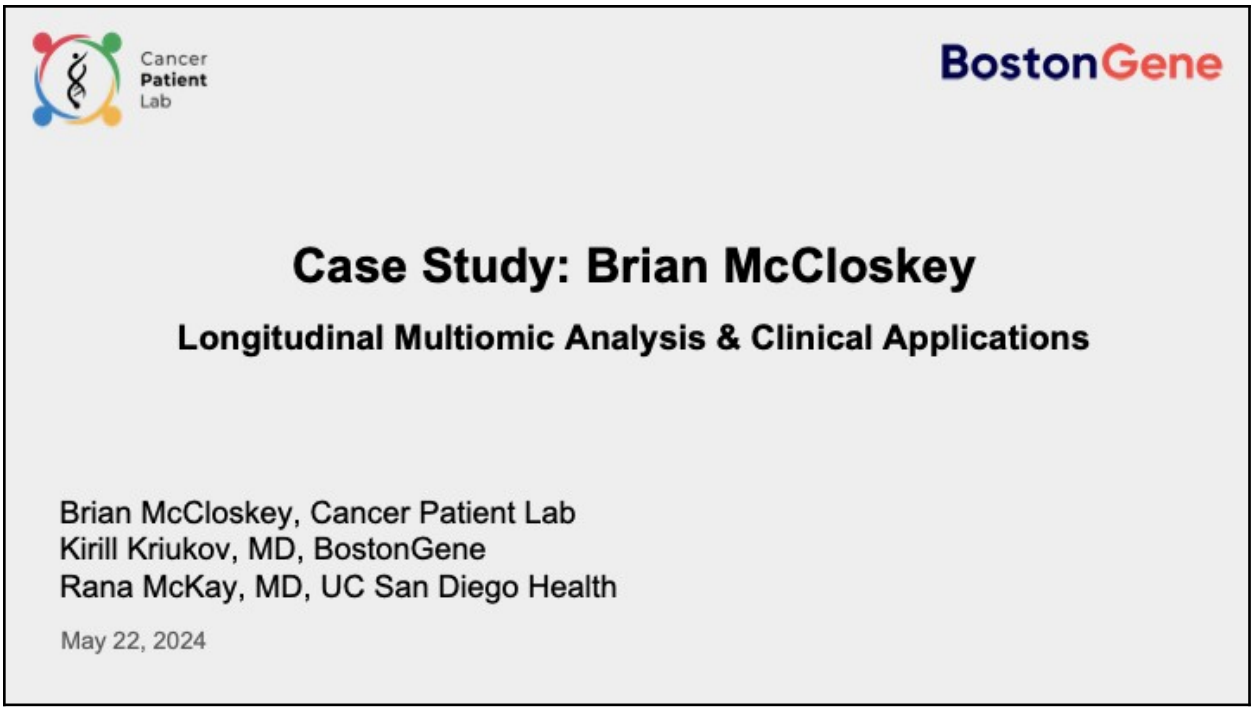
TRANSCRIPT

Brad Power
This is a meeting of the Prostate Cancer Lab or Cancer Patient Lab, where we're going to be focusing on Dr. Rana McKay's recent insights and particularly the case of Brian McCloskey, but I'll let him introduce that.

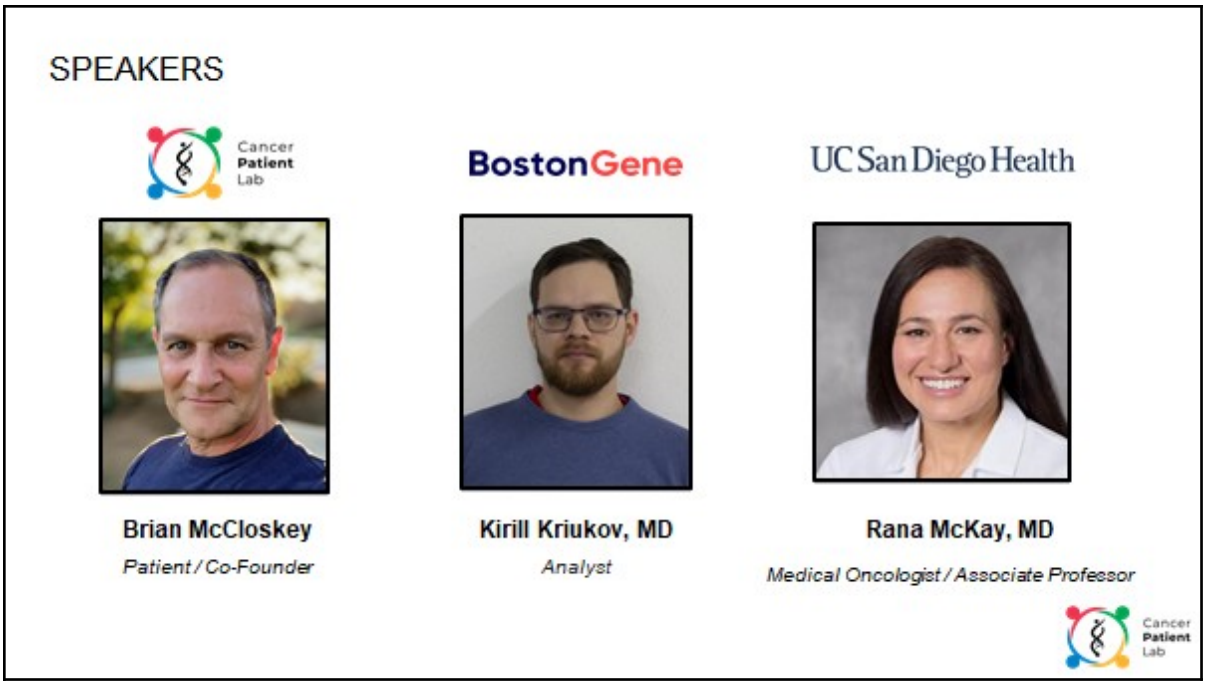
This is for information purposes only. This is not medical advice. We're trying to give patients and caregivers information they can take to their medical team.

And finally, we are a patient-led volunteer learning community, and we would appreciate any donations you can make, which you can do through our website.



Brian McCloskey 1:28
We're going to pivot here just a little bit. This session was set up as Dr. McKay was going to talk about novel therapeutics. But over the course of the past four or five days, there's been a change in my case, which warranted bringing together Dr. McKay and BostonGene with Kirill Kryukov that talks about the linkage between multi-omics and clinical decision-making. That's what we're going to talk about.

“Multi-omic Analysis Guides the Decisions of Brian McCloskey” (Rana McKay, MD, and BostonGene) [#98]



I'm going to set us up, give a brief introduction, and talk a little bit about my cancer journey. Kirill will discuss the multi-omics insights, which I think will be fascinating for many people. They are in depth, some of the most comprehensive, multi-omic insights that I've seen, and then Rana will talk about the clinical implications.

A quick word before we get into my cancer journey. I've wanted to say a few words about BostonGene and about Dr. McKay.

BostonGene has been absolutely incredible in their outreach to me, and pulling together, what you're going to see is just absolutely unbelievable information in terms of defining my cancer and tracking it over time. It's amazing. They invested a lot of time, resources and money in making it work. I'm incredibly grateful.

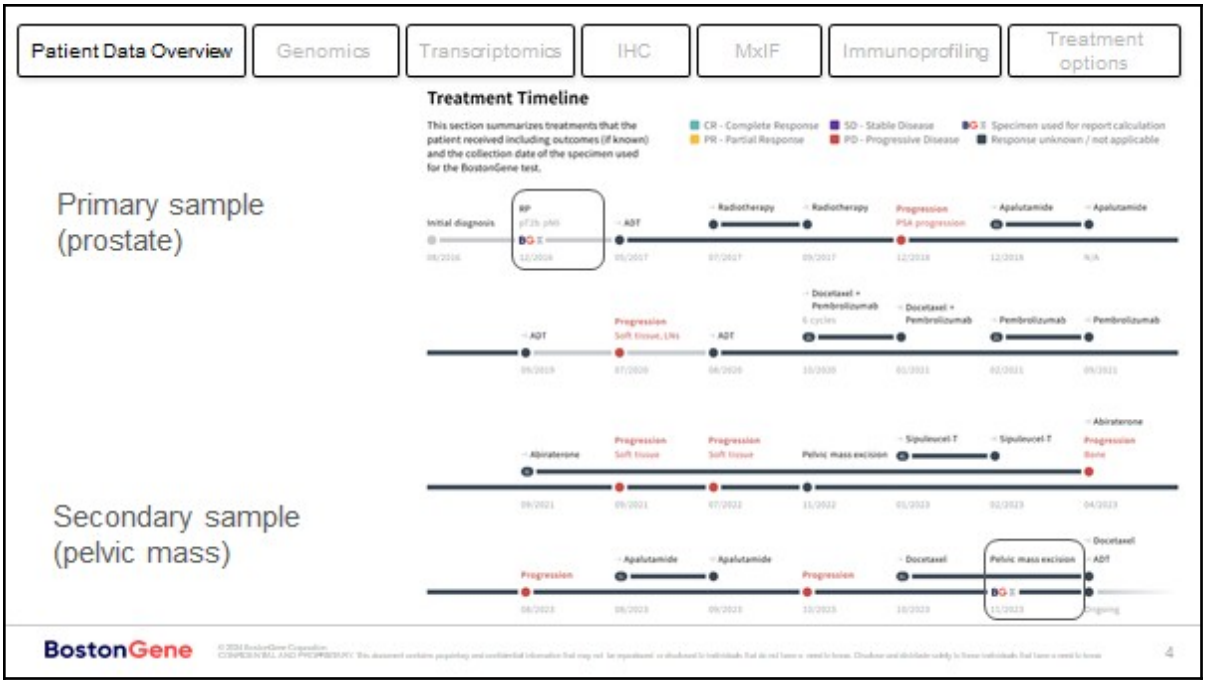
Finally, Dr. McKay is of course a brilliant medical oncologist. But just a brief story about her because it's relevant to this session. Just about a week and a half ago, on Mother's Day, I was writhing in pain in my bed. My wife sent an email to Dr. McKay which said, “Brian is having a lot of pain in his back.” We knew that it was related to a compression fracture that I had on my L2 vertebra that was the result of an infiltration of my cancer. So on Mother's Day, Rana said, ‘Hey, you have got to call an ambulance.’ And so of course, we did that. For the next four days, Dr. McKay completely quarterbacked my care across the emergency department, the urology team, the radiation oncology team, her team, and orthopedic surgery. I'm just so thankful to have her as my pilot in this endeavor. She has been my doctor ever since I was diagnosed in 2016. I think she came onboard in 2017, but I'm just so thankful that she's there for me and for my family for that matter. She's just courageous and an amazing doctor, and just an amazing person. I'm just so thankful. So thank you, Dr. McKay.

“Multi-omic Analysis Guides the Decisions of Brian McCloskey” (Rana McKay, MD, and BostonGene) [#98]

Rana McKay 5:09
You are fantastic. You're going to make me cry. Whatever it is that you need, buddy, whatever it is your family needs, I'm here for you. I know it was a very, very, very rocky weekend. I'm so glad Kristin sent me the email that she did.

Brian McCloskey 5:33
It was a harrowing story. I've got some recovery to do. But, medicine is not just about the bits and the bytes, which we're going to focus on today from a scientific perspective with multi omics. It's that care. And Rana is just on the next level. Thank you for being here.

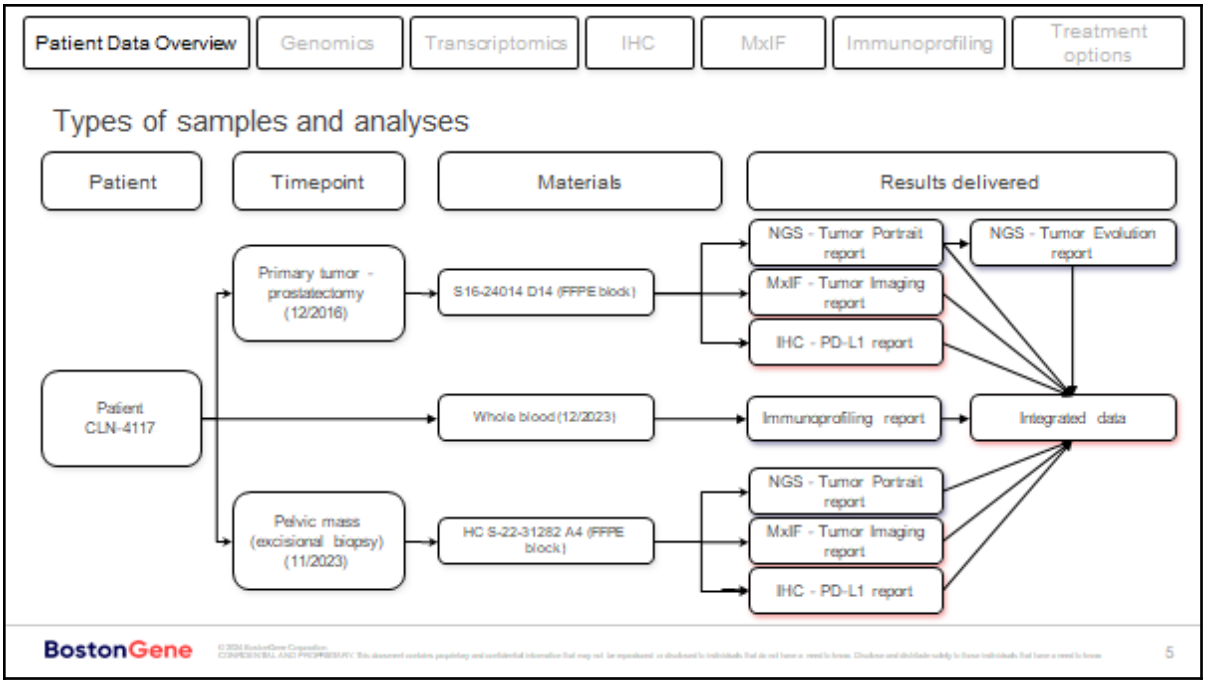
Kirill, thank you so much for all of your work. I'm looking forward to digging into this.



This is a busy slide. I'll just talk about the high level components of it. This is my cancer journey. On the left hand side, there are two anchors. As you see there's a primary sample of my prostate from 2016 and on the bottom left, you'll see there's a secondary sample, which represents the pelvic mass from November of 2022. These are sort of the book ends of tissue that BostonGene used to track the evolution of my cancer. And what you see on the right, is a very detailed view of my cancer journey starting in 2016 and all the various therapies that I've had, some of them are systemic therapies. Obviously, androgen deprivation (ADT) radiotherapy, there's a secondary hormone therapy with apalutamide. Then moving on to docetaxel plus Keytruda, or pembrolizumab. I'm not going take you through all of them. But I've had, I think, at least seven or eight different systemic therapies. We've just been basically batting my cancer down, as we've gone through this journey, which is really kind of coming up now on eight years. And this really is sort of like the footprint for how we've looked at my cancer and how BostonGene has specifically looked at my cancer and thinking about each of the different selective pressures, meaning those systemic therapies, and how they change my cancer over

time, and where it stands as of the end of this analysis, which was with a sample tumor, where the pelvic mass was in November of 2022. So we'll call it 2023. So that date is kind of getting a little bit old, but we're going to use it as we go into the next steps. So Kirill is going to talk a little bit about the multi-omic analysis. And then Rana will talk a little bit about the clinical implications, which I'm really happy to share with everybody.

Kirill Kryukov 8:37
Thank you. First I want to reinforce Brian also because it's a great pleasure to talk with such an interesting person and such an interesting patient who has such a detailed history as you present to us and of course we wanted to see such clinical history for all our patients. So about the thorough analysis that we performed in BostonGene here.



We had two different sample tissues for analysis: the primary tumor sample and a metastatic sample. For both of them, we performed several types of analysis with multiplex fluorescence, our new generation sequencing and IHC tests. From collected blood, we performed immune profiling. Together with this analysis, we created an integrated presentation with the most valuable findings.

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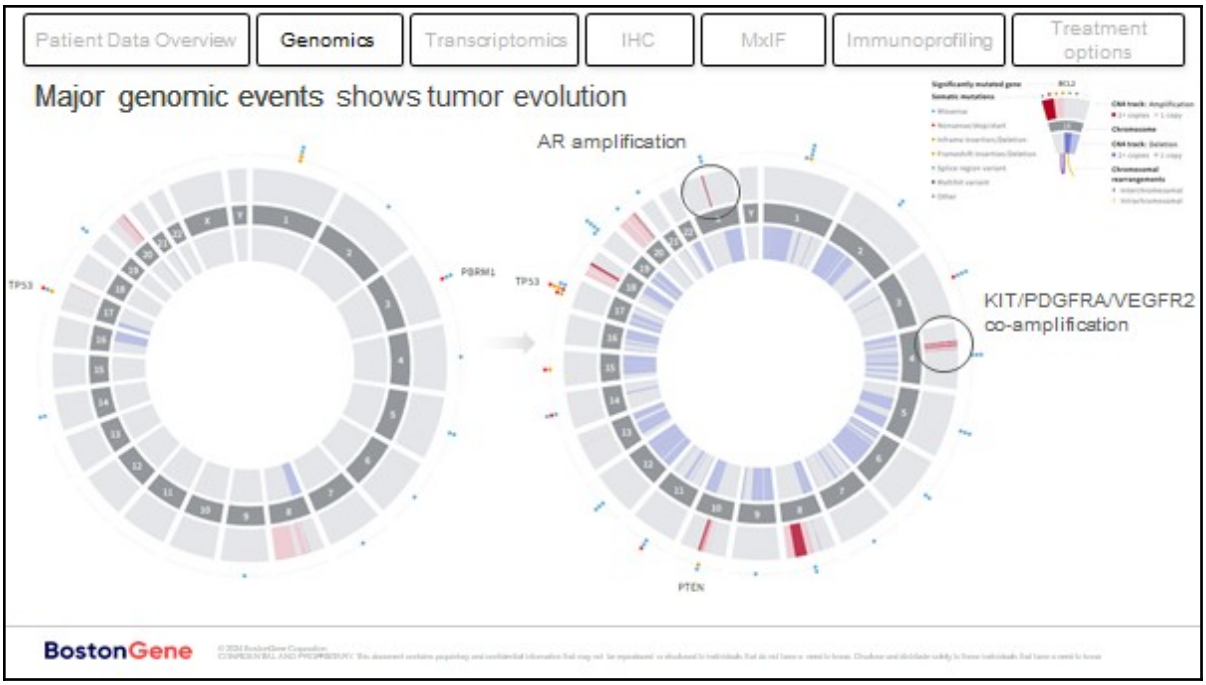
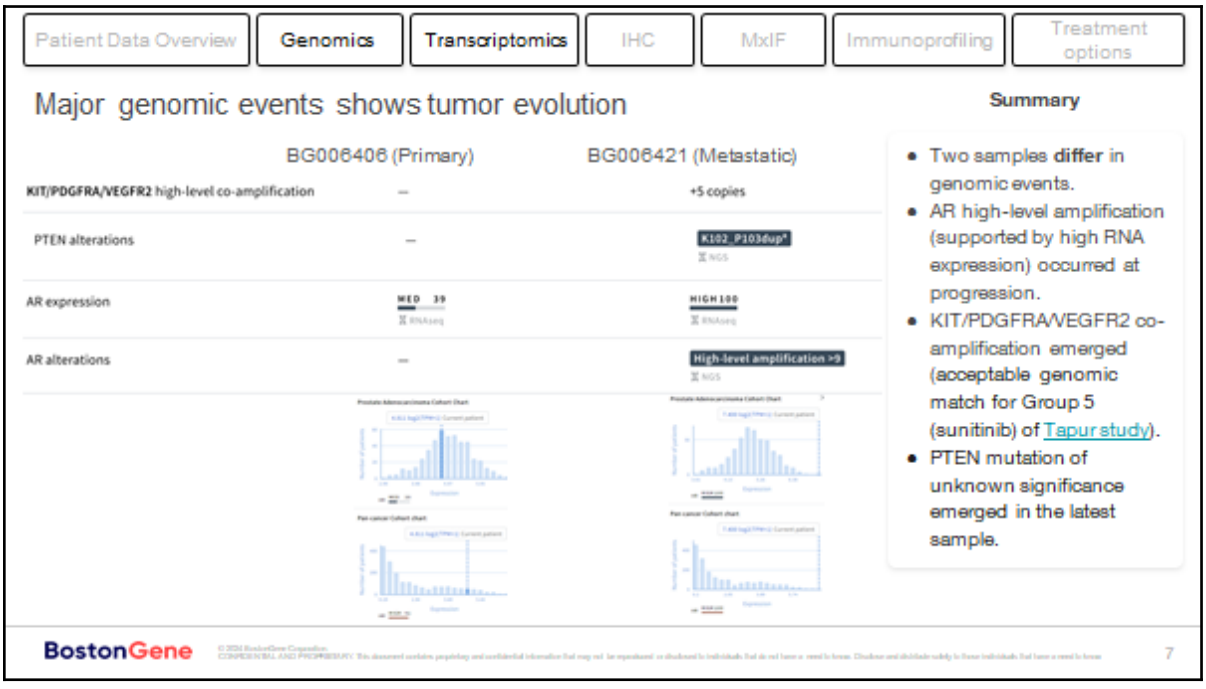


Kirill Kryukov 12:19
We saw some alterations as the cancer evolved in the second sample, and among them, amplification of androgen receptor, and co-amplification of KIT/PDGFRA/VEGFR2, along with a PTEN gene mutation. This iteration suggests evolutionary divergence and potential targets that may emerge as the disease progresses.



Here is a visual confirmation of this.

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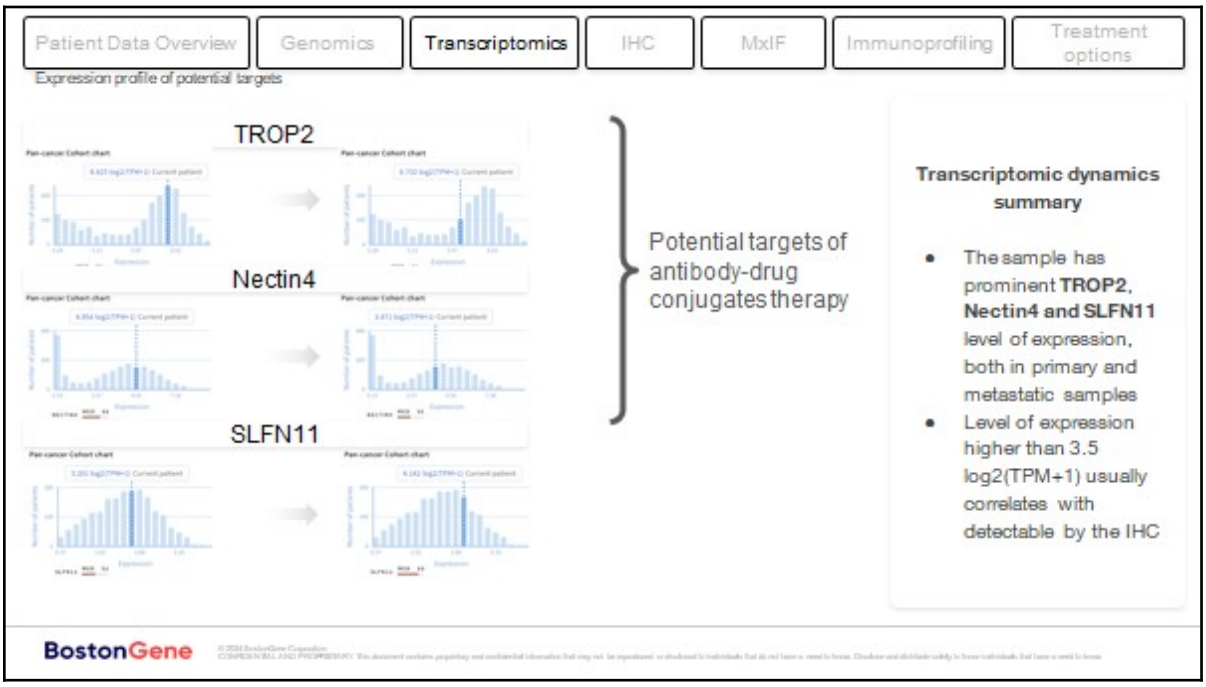
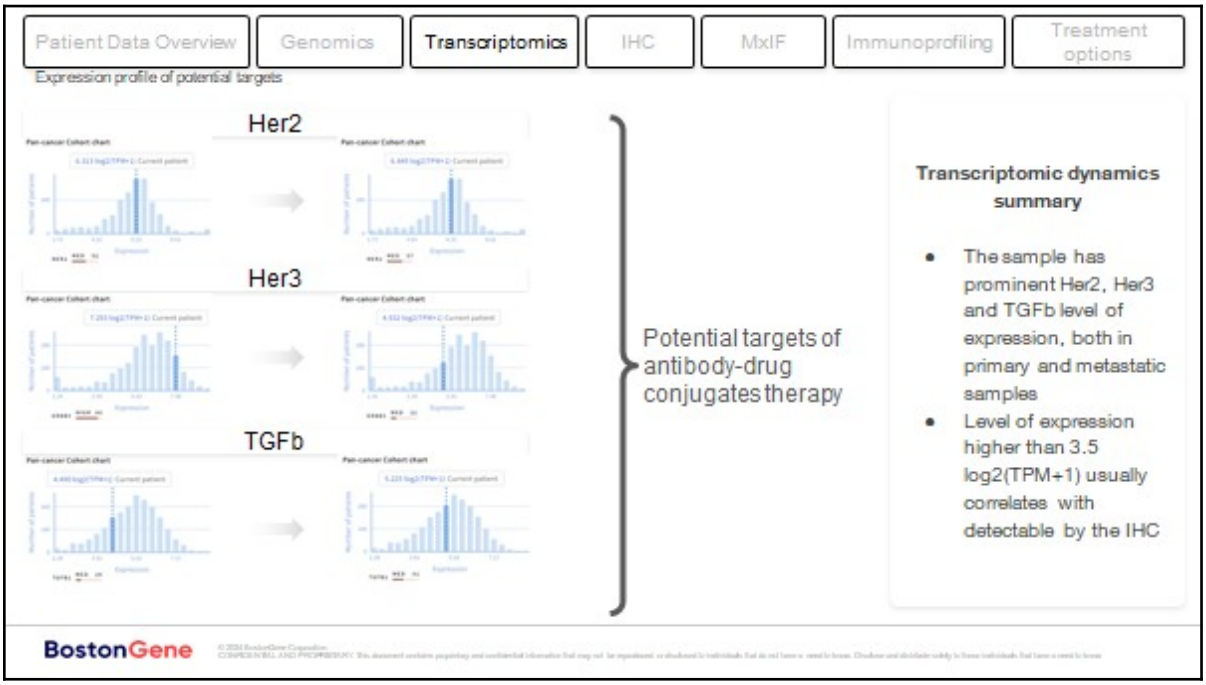
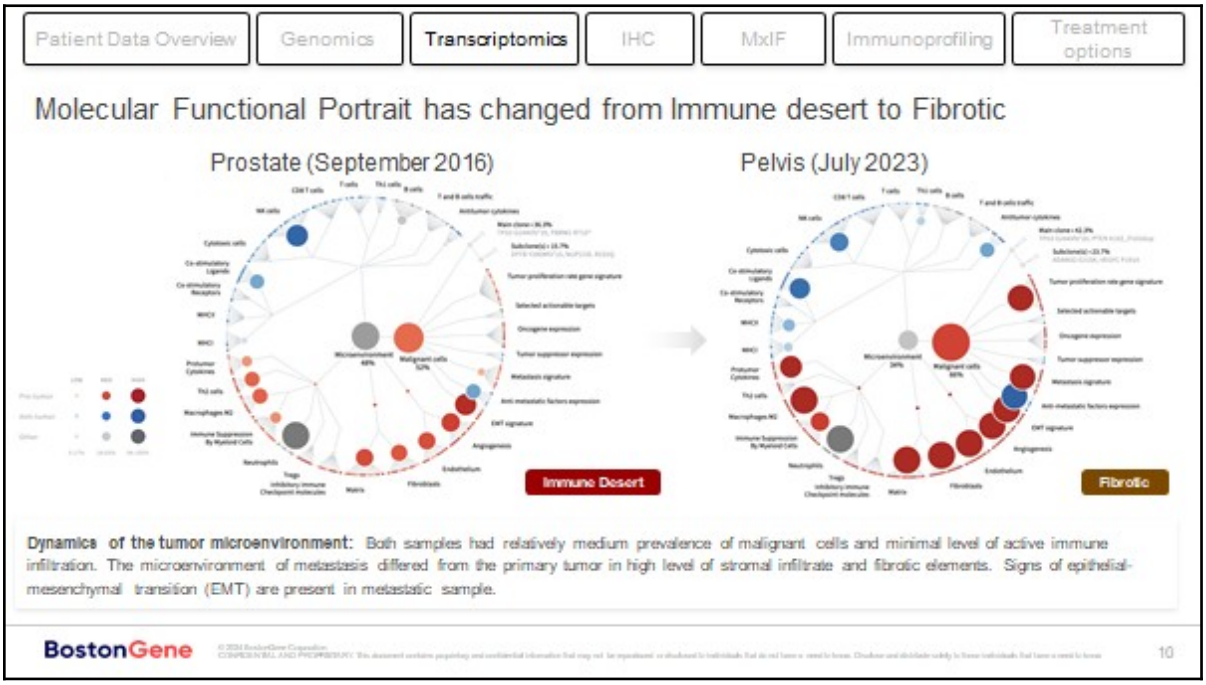


Our transcriptomic analysis also focused on some biomarkers that are valuable as antibody drug conjugates for therapy. Specifically, we looked at TROP2, Nectin4, and SLFN11. All of these markers in both samples demonstrate a medium or a high level of RNA expression, based on our pan-cancer cohort that includes most types of different types of cancers.

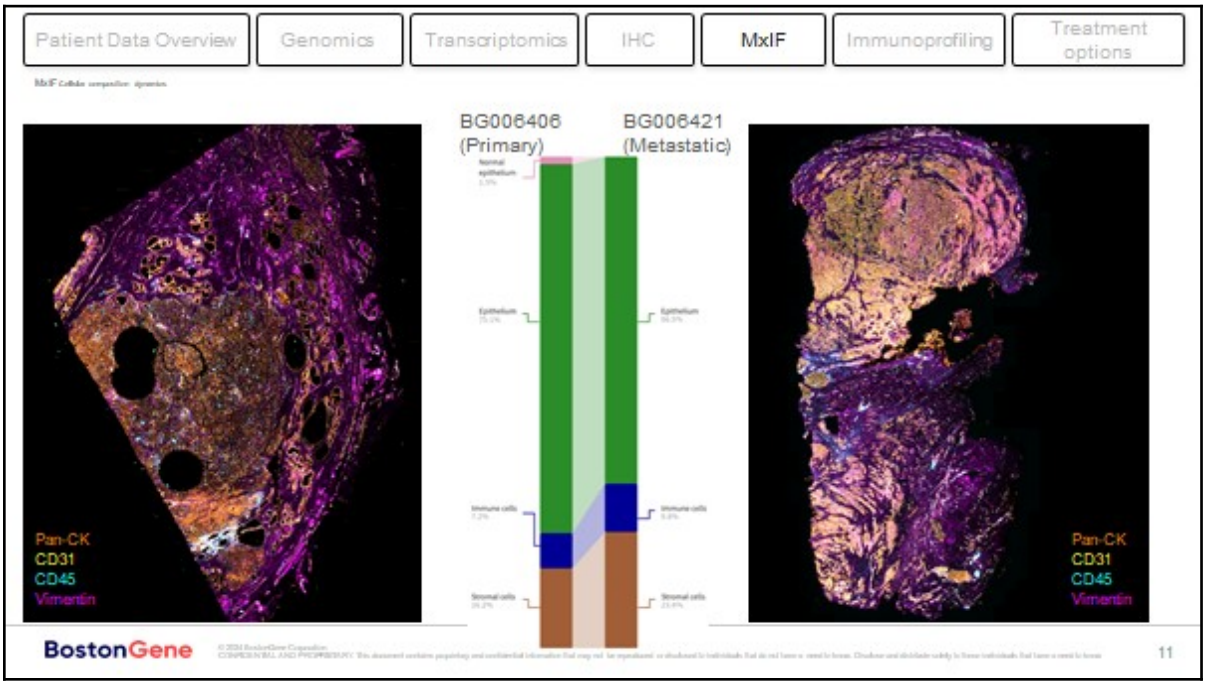


“Multi-omic Analysis Guides the Decisions of Brian McCloskey” (Rana McKay, MD, and BostonGene) [#98]

And that's one place and also we revealed a medium or high level of expression of some other potential biomarkers like HER2, HER3, and TGFb level of expression, both in primary and metastatic samples.

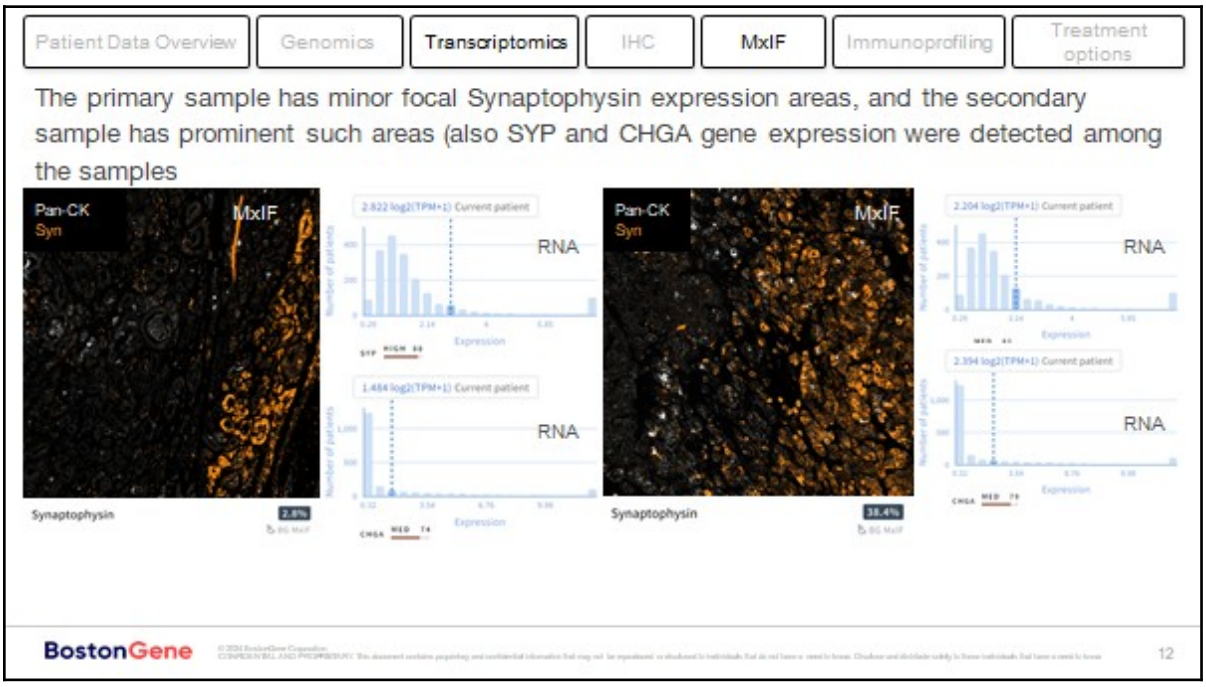


Also, our transcriptomic analysis allows us to create portraits, functional portraits of the immune environment. We revealed that it's changed from the immune desert in Brian’s prostate sample to fibrotic in his metastatic sample in pelvic mass, and this also can demonstrate that not only tumor levels, but the immune microenvironment has changed too.



“Multi-omic Analysis Guides the Decisions of Brian McCloskey” (Rana McKay, MD, and BostonGene) [#98]

And also we performed complex multiplex immunofluorescence analysis based on a lot of markers for the immune and tumor cells. And on this slide, you can see whether you have these two samples stained with major markers and changed in the composition of these two samples.



Here were several interesting findings. First, we noticed that a lot of tumor cells demonstrate expression of Synaptophysin and in the metastatic sample near 38%, and only 3% expression in the primary sample. We also confirmed that by RNA expression on synaptophysin and chromogranin from the primary sample to metastatic. We then reviewed H&E images that revealed that in the metastatic sample we also can find areas with morphologically neuroendocrine-like features.

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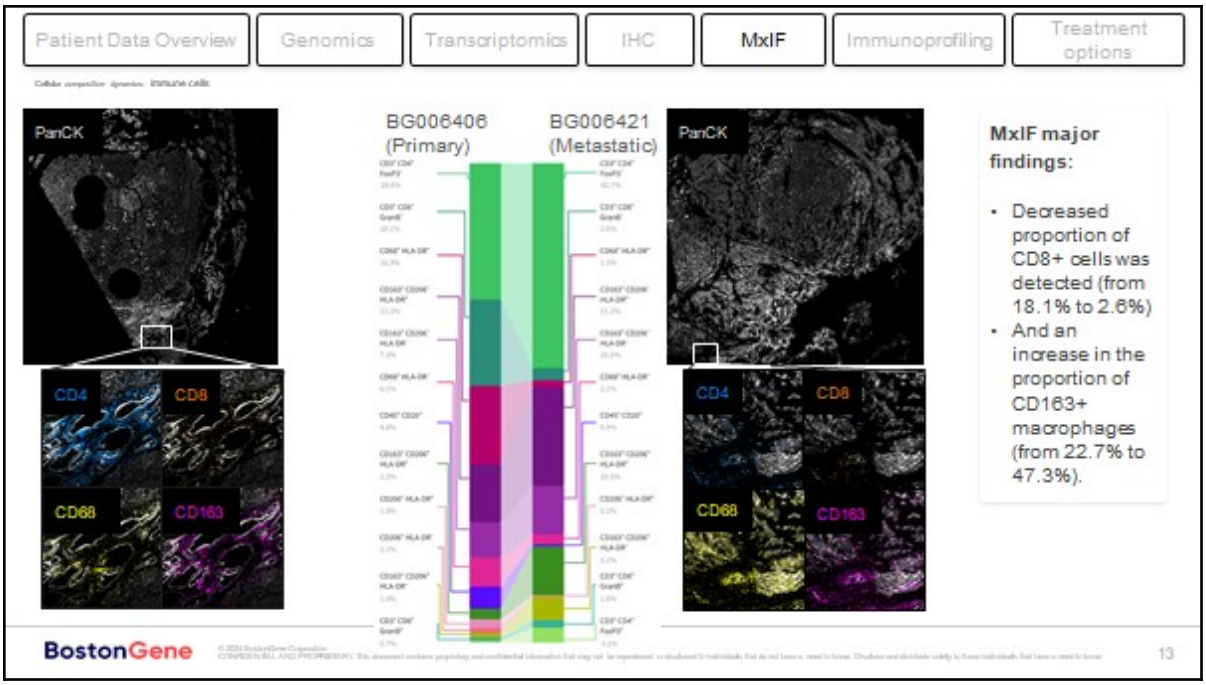
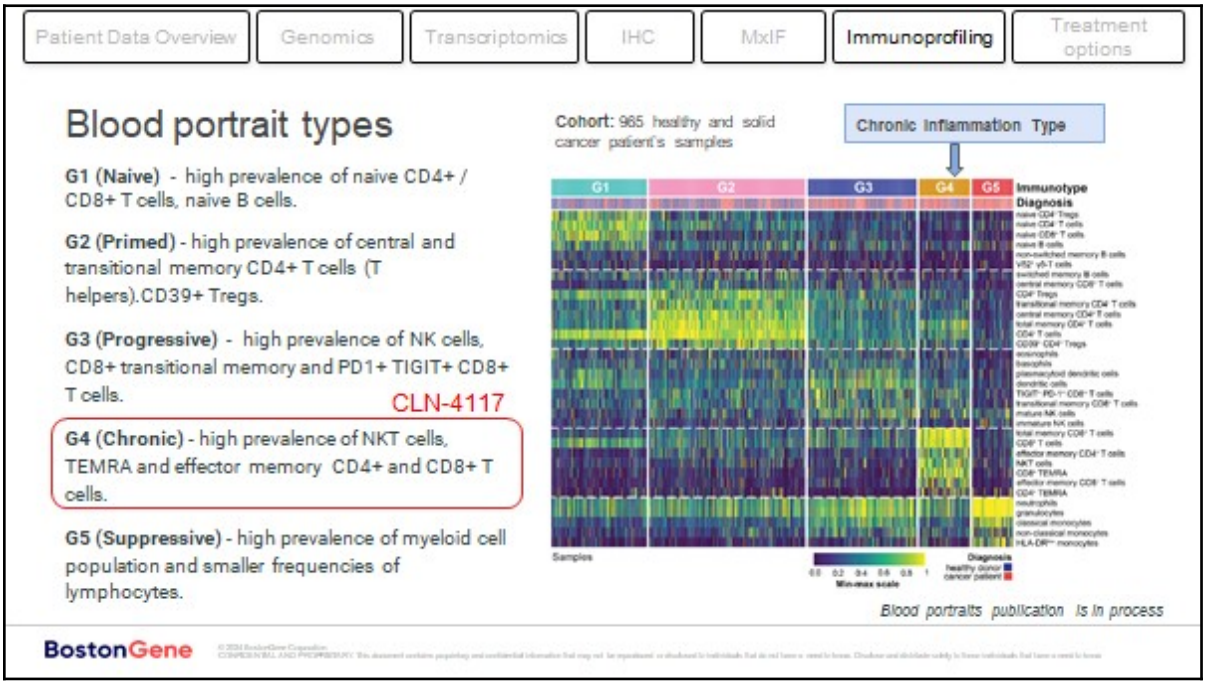


Then we performed an analysis based on an exam on the immune system of the samples. And also we can see some valuable findings. First, it changes the balance of macrophages. In the primary sample we've seen approximately similar amounts of an M1-like type macrophages and M2-like type and in the second one (metastatic), almost all macrophages and demonstrated expression of CD163 marker. Also we can see that the number of CD8-positive T cells decreased from the primary to the metastatic sample.

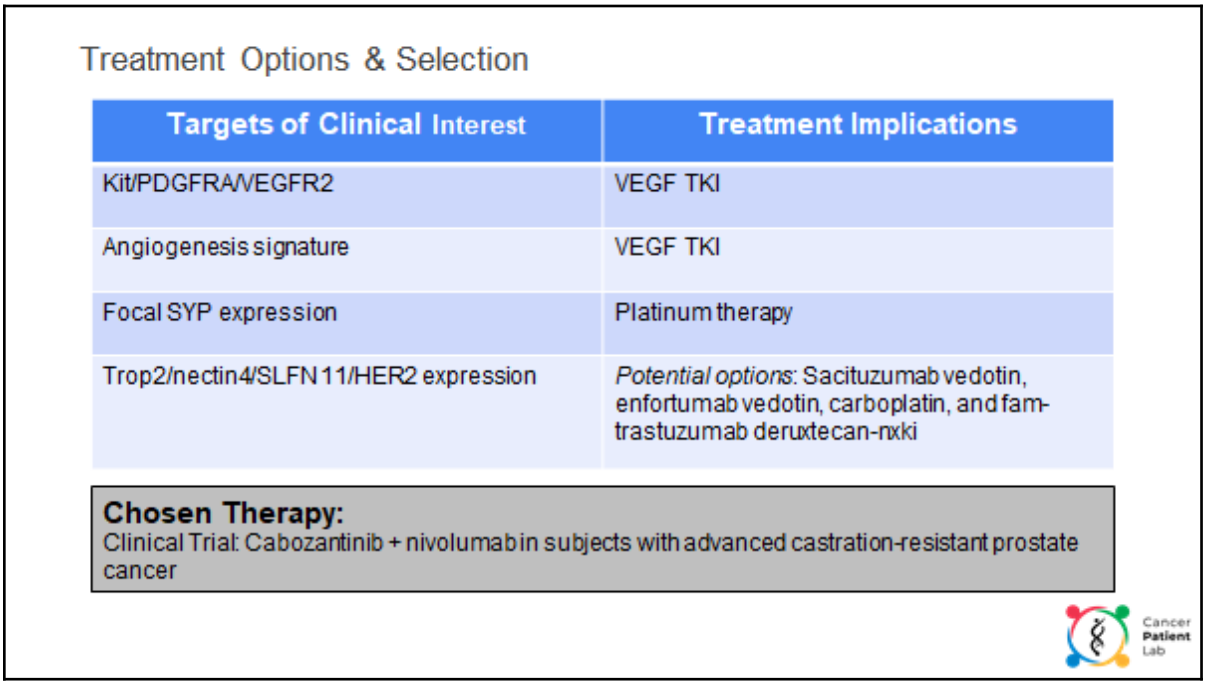


“Multi-omic Analysis Guides the Decisions of Brian McCloskey” (Rana McKay, MD, and BostonGene) [#98]

Our next step is in the profiling report that based on the number of cells collected from blood, and based on different levels of expression, we rate blood types that characterize the patient's immune system. And for Brian, it's G4, chronic blood portrait type with high prevalence of natural killer cells, memory effector cells and T cells of a CD4 and CD8.

So based on all these findings, we propose our treatment options and also present this data to Brian and his medical team. We are very interested in collecting feedback from you to listen to possible treatment decisions based on our analysis.

Rana McKay 18:39



Thank you so much for going through that. I think there's a lot of really exciting pearls to pull from the report and from the information. When I think about how we strategize selection of therapies for any given patient in the clinic and utilizing these precision medicine reports for guiding therapy selection, I think we need to really think long and hard about, well, what clinical data do we actually have available on whatever is identified as a target, or attempts at therapeutically targeting that target?

In prostate cancer thus far, we need to also think about, “What are the agents? What are their side effects? What's their compatibility with other agents? Access? There are a lot of pragmatic things to think about when we take this report that has 20 or 30 hits. How do you integrate that into something that we actually will end up giving a patient because I think there's a lot of really interesting things but at the end of the day, do you feel comfortable enough injecting said therapy in the patient or having somebody take that oral medication? Also availability of these agents really matters.

“Multi-omic Analysis Guides the Decisions of Brian McCloskey” (Rana McKay, MD, and BostonGene) [#98]

The salient thing that I pulled from this report is the striking angiogenesis signature (formation of new blood vessels from pre-existing blood vessels). There are multiple different VEGF pathway genes that are dysregulated. What's important to pull is that there are multiple different targets here, as opposed to just one that could all be targeted with a drug. So when I see that, that's a very nice thing as a clinician to say, “Hey, this is not just one thing out of a sea of many. There are multiple targets in this pathway. This pathway seems to be off, and that may present a greater vulnerability for the tumor.” Additionally, VEGF inhibition in prostate cancer has a long, long history of drug testing. And there's recent data that were presented from the COSMIC-021 study from phase one of cabozantinib/atezolizumab. There's a large phase two of CONTACT2. I think sometimes the design of these studies, it's not exactly the situation that Brian is in or the eligibility criteria aren't exactly the position that Brian is in, but we can take really important data about what we learned from the clinical testing of these agents.

The other salient thing is the angiogenesis signature, the KIT/PDGFR/VEGFR, which would suggest targeting with a VEGF TKI (tyrosine kinase inhibitor).

The focal synaptophysin expression with the SLFN 11 is a potential potential marker for platinum sensitivity, at least the data on SLFN 11 has suggested that and so one of the other things that we had been toying with is do we do pursue cabazitaxel or carboplatin, and go down that dual chemo route?

Or do we do a chemo-sparing strategy? There is data for the combination of that and of VEGF inhibition with IO.

For neuroendocrine tumors, there's a clinical trial currently ongoing with the combination of Lenvatinib (a kinase inhibitor that targets VEGF) and pembrolizumab (Keytruda, an immune checkpoint inhibitor), for neuroendocrine-differentiated tumors. The trial that we're thinking about for Brian is being amended to allow neuroendocrine tumors to enroll because of the fact that we've seen some signals and other datasets of activity of VEGF inhibition and immunotherapy in neuroendocrine tumors.

The TROP2, NECTIN4 and HER2 expressions are exciting, really just around the fact that there are ADCs (antibody drug conjucates) out there. But we need to keep in mind that this is RNA data. This is not necessarily protein data. I wish we could do multiplex IHC to actually look and see if it matters here.

For all the current ADCs that are being used, they're not necessarily biomarker-selected, per se, but I think this does open up the door to thinking about antibody drug conjugates. I think they're a little bit farther behind in prostate cancer than some of the other stuff that came up from the sequencing report.

So we were really again toying between cabazitaxel plus carboplatin versus “nivo Cabo” (nivolumab plus cabozantinib), and at the end of the day, we settled on nivo Cabo, just given the fact that we can likely get these agents and try to get them on trial. There's a lot of safety data

already on these agents. There's a lot of safety data on the combination of these agents. There is a track record for efficacy in prostate cancer. We are working on trying to procure these two drugs for Brian on a trial and if we can't get on the trial, going through a patient assistance program through these drug companies.

Saed Sayad 24:52
How do you connect the dots? This is an expensive and extensive analysis of omics data. I believe you had some early questions you were trying to answer. One of them is the final therapy.

How did you come up with this idea based on the analysis to reach that final decision about the treatment?

Rana McKay 25:28
This is what I do. It's based on knowing the data in the field, such as, what are the drugs that target VEGF? These are the drugs that target VEGF. What are the studies of those drugs in prostate cancer thus far? Okay, we have a signal. This is how they're being used. Brian's tumor doesn't have a strong immune signature. But what we've seen is that the VEGF inhibitors at least tend to work better in combination. We've seen with IO (immuno) therapy, and we've also seen data in small cell lung cancer of neuroendocrine-differentiated tumors, that they tend to respond better to IO therapy, or at least they're more responsive to IO therapy. This is where we came up with a concoction of an IO combined with a VEGF, based off of what we saw on the report.

Saed Sayad 26:34
So is it single cell data analysis?
Is this a commercial test that any doctor can order?

Rana McKay 26:39
I'll let Michael Hensley and the BostonGene team speak to this. This is just a next generation sequencing company. The reports are getting better and better. What is the information that's displayed? Everybody does this.

Saed Sayad 27:06
Is it the bulk analysis transcriptomics?

Rana McKay 27:13
This is bulk RNA seq.

Saed Sayad
Is that single cell analysis?

Rana McKay
This is not single cell analysis. This is bulk RNA seq from FFPE tissue.

Brad Power 27:41
Could you explain this at a level up? I don't speak maybe at the drug level, but I do speak immunotherapy, chemotherapy, and targeted therapy. So if I just play this back, Brian has a number of mutations that were identified, of which VEGF looks the most interesting. There's HER2 and other things, but you focused on VEGF and then you chose an immune checkpoint inhibitor – Opdivo or Nivolumab, which is a sort of immunotherapy. Immunotherapy is always problematic in cold tumors for immune checkpoint inhibitors. Why is it going to work? Then why combine it with a Tyrosine Kinase Inhibitor, TKI, which means it targets the pathway that VEGF is on?

Could you please abstract it up a level to talk about the strategy or the thought process? It's similar to Saed’s question, but if you could just do an eighth grade level version of this the treatment strategy?

Rana McKay 28:57
It's based off of the targeted sequencing report, but also based off of the data in the field thus far. The combination of Cabozantinib is being tested with immunotherapy in the field. And the regimen of “nivo Cabo” is already FDA-approved to treat another type of tumor where there was demonstrated efficacy and other kinds of cancers. The combination of immunotherapy and Cabozantinib is also being tested in prostate cancer. And the old school data of Cabo monotherapy was not as great. There's no comparative of looking at Cabo combined with atezo/nivo. So I think it's understanding the field that has also driven us around the decision for immunotherapy and also understanding that there could be some underlying neuroendocrine features of this with the synaptophysin expression. And neuroendocrine, like atezolizumab, for example, which is the same drug that was tested with Cabo is FDA-approved for neuroendocrine lung cancer. You could be a purist and just treat off of the report and be very myopic. That's not my strategy. My strategy integrates the data from the report, all the data that's available publicly in the domain of everything we do, also needs to be integrated. So I take what's in the report and integrate it with the data that's in the field to come up with the best strategy.

Brad Power 30:44
It sounds like this could be changing every six months, like the answer today, because of the results of those trials. Six months from now, you might come up with a different answer?

Rana McKay 31:00
It also depends on what's important for Brian and where he's at right now. And what has the patient gone through? What prior treatments has he had? What do we want to save for later and not use now and what like, so it may be this. You may generate the same exact report in a totally different patient with a totally different history, and we will come up with a different thing to do. The report may be exactly identical. But we will choose something else because of the clinical contexts in which we are seeing things. Maybe this individual hasn't received XYZ therapy. Or maybe they have. You can't interpret the reports in a silo. You've got to put them in

context with your patient. What are the goals for your patient? How are you going to strategize subsequent line therapies? What's your patient gone through? What's going on in the field? What's happening in the world of prostate cancer? What's happening in the world of solid tumor malignancies that I can apply to Brian's case?

Brad Power 32:03
Brian had Keytruda. So he's had an immune checkpoint inhibitor before, and he felt it didn't do a good job.

Rana McKay 32:10
He didn't fail that immune checkpoint inhibitor. We stopped the immune checkpoint inhibitor. Actually, that was an exclusion on this trial: you can't have failed a prior checkpoint inhibitor or go on this trial. But he didn't fail the checkpoint inhibitor, we ultimately decided to stop it and then after he stopped it, as a subsequent time point, he ultimately ended up progressing.

Brian McCloskey 32:35
This is part art and part science. Just understanding where the patient is in the journey is so critical. Rana and I went back and forth between these two options of Cabo plus nivo versus cabazitaxel and carboplatin. I was personally just very hesitant to go down the cabazitaxel carbo route because I was afraid of what it was going to do to my bone marrow and my immune system. I'm also very data-driven. I saw that Cabo plus nivo could target this angiogenesis signature in the VEGF. I really wanted to go in that direction, and save this other therapy for a later time. We also know that if I started with Cabo plus nivo, there are other therapies that could come after a cabo plus nivo, such as actinium, or maybe we go after HER2, whatever the case may be, we can save that for a later time. As a patient, we're trying to stay as healthy as possible while we're undergoing these treatments, which can be so detrimental in and of themselves.

Rana is really good at understanding all of those dynamics in the sense of what my clinical history is, and as me as a person, and so that that relationship is just absolutely key.

Jonathan Starr 34:37
Thanks for this presentation. It is pretty amazing. Having the patient and diagnostician, all of you together here and presenting is really remarkable.

However, I missed a step. Brian's filled it in a little bit just now you showed four different genomic oddities and things that treated them and somehow have some relationship to treating them. And then in the end, it was sort of an existing clinical trial that you went with. It sounds like you chose these because of some connection with VEGF. Is that right? Could you could you explain that a little more?

Rana McKay 35:39
The genes that were upregulated in Brian's tumor are all part of this angiogenic pathway, this like blood vessel growth pathway, and so VEGF is one of them, PDGFR. That pathway can be

targeted with inhibitors to VEGF, and many of the VEGF inhibitors also have activity at other kinase domains, such as the PDGFR. That's basically what we did.

Jonathan Starr 36:21
Cabo and nivolumab, one of those, or both of those, inhibit blood vessel growth?

Rana McKay 36:35
Correct. The cabo does.

Jonathan Starr 36:40
Then you're thrown in the nivolumab as another immunotherapy. Is that right?

Rana McKay 36:54
Yes. And the data in the field about the two being synergistic together.

Jonathan Starr 37:01
Okay, did you consider other angiogenesis inhibitors to add to cabo?

Rana McKay 37:14
No, it's going to be too toxic to do two different kinds of VEGF inhibitors and cabo has a track record of activity in prostate cancer. It also targets another protein called MYC, which is also predominant in bone disease and bone metastases, particularly in prostate cancer. It's just sort of knowing that data.

Jonathan Starr 37:46
What are you hoping to get? What are you expecting? What kind of response are you expecting, and realistically hoping for?

Rana McKay 38:06
The goal of therapy is to ensure that we can delay the time to progression and ensure that Brian has enhanced quality of life while he's on treatment, and can continue doing the things that he wants to do. Those are our two goals. We don't want them to progress. We want them to live longer. And we want him to do what he loves to do. You didn't hear me say the goal of therapy is to drop PSA. You didn't hear me say the goal of therapy is to make things shrink on a scan. You didn't hear me say that the goal of therapy is to decrease the SUV uptake on his PET scan. Those are not the goals of therapy. The goals of therapy are delaying the time for progression, whether it be clinical progression, or radiographic progression, like overtly progressing, and making sure that Brian has a great quality of life. There's a lot of stuff that happens in there that can detract us away from our goal of preventing progression. Brian may say, “my PSA is going up”, and I would say “but your scans look good and you feel good. Keep going.”

Brian McCloskey 39:32
Just to add a little bit of color. I couldn't say it any better than what you just did. But, my PSA has been on the march. One of the things we didn't really talk about is that my original Gleason

score was a 9. So we know that I have aggressive cancer. Often we get concerned about PSA rises. When I came off of docetaxel, I think I was at like 2.5. I think it's now up to 40 or 70, or whatever. To be honest with you, I'm not worried about that. I really am not. I'm more concerned about getting therapy that is going to stop or slow the progression of my disease and do it in an intelligent way. You know that I'm like, super data-driven. You just saw an amazing presentation from BostonGene, which is just replete with data.

I want to leverage that knowledge to the extent I can to pick drugs and drug combinations that are going to preserve my quality of life, and just keep this thing at bay while medicine continues to advance. Over the course of the past eight years, there have been new drugs that have been coming along. There's a lot of talk right now about actinium. We just had a patient-only discussion on Monday, where we spent a lot of time talking about actinium. Whatever the drug is, these are bridges to get us there.

It's a real issue trying to stay healthy while undergoing these therapies, as I think we all know, and the longer you go, the harder it is. You just get farther out on the branch. Finding the right drug that preserves that balance of quality of life and keeping this thing at bay, that's a touchdown for me.

Rana McKay 41:50
We are trying to, like Brian said, do this in an intelligent way, be smart about targeting. We're trying to understand a vulnerability in the tumor that can be leveraged with therapeutics. That's what precision medicine can do. It can help try to identify a specific vulnerability that we can take advantage of with drugs that we otherwise would not be able to.

On the comment about the PSA. PSA is a tough marker to follow in the CRPC setting. Brian has AR amplification. He's going to have a high PSA. It doesn't necessarily mean that you have more PSA producing cells; the cells you have just make more PSA. If you have AR amplification, the cells you have will make more PSA. So PSA can be a very tricky thing to follow and practice in CRPC. It's not as important as in the metastatic hormone sensitive setting and in the metastatic hormone sensitive setting, it's very reliable. But in the castration-resistant setting, it's not as reliable. And especially in somebody who's got AR amplification where you start seeing rapid rises in PSA, like we have patients and their PSA starts going haywire. I could almost guarantee you they just picked up an AR amplification when they just started going off the charts with their PSA.

Jonathan Starr 43:25
Following this going forward, will you just watch how Brian is feeling? Is that going to be the measure of success?

Rana McKay 43:33
Oh no, we do a ton of testing. We are data people and we watch how he’s feeling of course, but we do check PSA. It's one of many things we look at but we don't make unilateral decisions around PSA.

Jonathan Starr 43:48
Let's say some of that stuff goes bad, but Brian's feeling fine. Are you going to intervene or change therapy?

Rana McKay 43:57
If Brian is feeling great, but he's having radiographic progression, I would have to ask myself and Brian, “Okay, how many spots? Can they be radiated? Can we introduce another modality to treat the areas of progression that we see if there's more progression, then can actually be targeted with radiotherapy?” Then we're going to have a discussion and say, “Hey, I know you feel good on this therapy, which is a very good thing, but you've got some more lymph nodes that are growing, and the lymph nodes are enlarging and what do we want to do about it?” We may say that there are a lot of different paths that we can go, and we can decide to switch gears based on that.

Generally when there's radiographic progression that we can't target with some other means my goal is to keep his disease burden as low as possible on his scans.

Jonathan Starr 45:00
How often are you going to test? Or how often are you going to image?

Rana McKay 45:14
It depends. Usually it's about three months. We may do sooner, if needed, based on symptoms. We may do later if he's feeling fantastic, his PSA did decline, and he's feeling good. And maybe he was going on a trip and doesn't want to get scans before he goes because that's just always a bad idea. But we decide on those things together. I don't make those decisions unilaterally.

Kaumudi Bhawe 45:53
I want to thank Dr. McKay, Brian, of course, and BostonGene. All three angles coming together watching that happen here. It is very powerful.

What are your thoughts on theranostics (a medical technique that combines diagnosis and therapy for cancer using radioactive drugs and radiotracers) like lutetium?
In this case, is that approach even applicable?

Rana McKay 46:26
Theranostics have a lot of really exciting things that are coming down the pike. Lutetium PSMA is already FDA approved. But this is sort of the balancing act with any given therapy. Brian has an obstruction in his kidney that we've been dealing with. We don't want to put in a percutaneous (passing through the skin) drain to drain urine out. He's got a stent in place, and there's only so much we can do to help alleviate that obstruction. Having severe hydronephrosis, or severe swelling of the kidney, and not being able to clear that obstruction is a contraindication for Pluvicto because then this tracer is secreted in the urine. And if you're obstructed, you're just going to have radioactivity in your kidney just sitting there causing

damage to all of your organs. There are some radiotracers that are not cleared via the urine, like radium, for example. We could do radium, but it's only bone targeting.

These are very practical things that we have to contend with when we're thinking about therapeutics.

There are other other agents coming down the pike, actually, we're going to be having an actinium, PSMA through CONVERGE here at UCSD, hopefully, that'll get activated in the next three to six months and will be available in the castration-resistant setting. There are a lot of really cool radio therapies that are being developed.

Kaumudi Bhawe 48:05
If I understand correctly, that could be the next arrow in the quiver after this? You have that waiting in line?

Rana McKay 48:14
It could be. We'd have to make a decision around a nephrostomy tube if we want to go down that route.

Rick Davis 48:32
I went over to my FMI (Foundation Medicine, genomic testing company) meeting. I told him why I was late. They said, “Well, why don't you go back? We want to hear this meeting, too.” We reset the meeting for two hours later in the day. I'm thrilled to be back. God bless you. I mean, amazing. What you're doing for Brian, we love it.

I have a couple of questions for you on treatment options and interested to know what your thoughts are.

The first is you mentioned neuroendocrine. There's enough in this report that gives you some concern that maybe there's a neuroendocrine element creeping in. I wasn't smart enough to pick up all those but I heard “neuroendocrine”, and that's when my ears go up because we've lost some people very dear to me because we didn't catch the neuroendocrine early enough. I think it's fantastic that for Brian, we have caught it early so we can respond to that. On the neuroendocrine side, I was wondering whether there's any evidence in this DLL3 protein for Dr. Misha Beltran and Rahul’s trial?

You were talking about the amplification, and we've seen a couple of guys really respond well to the protein degrader ARV 766, because they had amplification, but they also looked like they've got some NEC disease. Just saw one guy and they haven't done the scans yet. I hate to see this after what you said, because I agree with you, but it did drop his PSA by 50% in three weeks.

What about those sort of two avenues, the DLL3 and the ARV. And what else can you do really early if you see the NEC disease?

Rana McKay 50:43
One, we don't know how to actually adequately define neuroendocrine prostate cancer right now. Right now, probably the definition is based on histologic assessment. And based on histologic assessment, Brian does not have neuroendocrine prostate cancer. We may have even done this on one of his prior biopsies, or tissue sampling, I can't remember which one. He doesn't have IHC positivity for synaptophysin or chromogranin, though there's a lot of controversy in the field, whether those should or shouldn't be used in defining neuroendocrine prostate cancer. What we saw, the little signal, was that there's increased RNA expression of synaptophysin, very focal increased RNA expression. So we're just conjecturing. What does that mean? We see that in people who have histologically identified neuroendocrine, which Brian does not have. He histologically has adenocarcinoma. And he's got an AR amplified adenocarcinoma. So that's the one potential thought around neuroendocrine.

For DLL3, I didn't actually see it in the report. I think it'd be nice to include it in the report. That was Rick who was talking about STEAP (A prostate-specific cell-surface antigen highly expressed in human prostate tumors) earlier. I don't think STEAP is in the report either.

It'd be good to think about all of the markers in prostate cancer and honestly, for tumors in general, just to make sure that there's reporting on that. I don't know what the DLL3 RNA expression is. Again, RNA is very different from protein.

The last question that you had was around the degraders. We have ARV 766 open here at our institution. But right now, they're only enrolling for AR-mutated tumors not amplified, mutated. You have to have an AR mutation, which Brian does not have. I think it would be great to try to get on a degrader study. There are a couple of different agents that are out there. Arvinas is going to be opening up this study and expanding the cohorts. There could potentially be an opportunity in the future to get on that agent. But I know that 766 development has been acquired by Novartis. So that's going to probably delay things. We'll see the field continue to evolve,

Rick Davis 53:33
It sounds like you're saying Brian doesn't have the right AR mutations for the ARV 766.

Rana McKay 53:43
Right now the study is enrolling patients with ligand-binding domain mutations like 702 and 787.

Allen Morris 54:27
Let me frame this in the context of the end-of-the-line patient; somebody who has presumably exhausted all standard of care measures. I am a pathologist. I'm starting to get the Foundation One reports, the Neogenomics reports, and Tempus reports, (but I do not get BostonGene reports). They're identifying (molecular) mutations, for example, within a vascular signaling pathway. These reports are getting so intricate and long, notably linking mutations to pertinent

clinical trials, or to already approved drugs targeting that mutation for other cancer types, but not approved for the patient’s cancer.

It sounds to me that what you're trying to do with Brian is to still remain within “standard of care”, at the fence between standard of care and right at the frontier. It seems to me when you use a phrase such as “data”, what you're trying to say is, “Hey, I want to stay somewhat within the limits or guardrails of evidence-based medicine: what's out there with collective experience, what's safe, etcetera.”

My question is, do you ever stray to phase 2 signals? [I should have said: stray further, beyond the immediate fenceline frontier] to things that maybe some people colloquially call “off label stuff”? For example, you stated that Brian has very strong vascular signals, and you already answered that you wouldn't dare go with a double vascular inhibitor that might be complementary and might be [synergistically, perhaps even Dr. Castro, Paris subway combinatory] effective, I suspect, because you're going to say there's no data.
This patient empowerment group is trying to reach for end-of-line patients in what's beyond, further in the frontier. Does UCSD actually have a “precision oncology protocol” [which functions that way: enabling a push further into the frontier than what may be available elsewhere], more than just matching patients to clinical trials? Do you really have something special at UCSD? Or do you just have the molecular data reports, for example the Foundation reports that by software link to candidate clinical studies and try to, for example, get patients into clinical studies?
[Of course, you and/or the UCSD molecular tumor board then use your considerable judgment from knowledge and experience, in and of itself special and unique, to make specific, personalized recommendations. But does this not happen at every academic medical center without a “UCSD Precision Oncology Protocol”?].

Rana McKay 56:58
Well, that is a question that I don't think we can answer in two minutes. That's a very multi-embedded question. It's not to say the level of it's not phase 3, or phase 2 or phase 1. Half the stuff we're talking about is all phase 1, or may not even be in testing.

The issue about dual VEGF inhibition is that it has been tried and it's incredibly toxic, and it doesn't work very well, even in tumors where they're addicted to VEGF. You just have to be very careful. I would never give that to Brian because I think it would hurt him. At UCSD we do have a very robust precision oncology program. We have an infrastructure with a molecular tumor board both for precision immuno-oncology and precision targeted therapy that meets very regularly to review and align around treatments and actually have a team that helps us procure drugs too because that's half the battle.

Brian McCloskey 58:06
Thank you, Rana.