“Repurposing Approved Drugs” (Saed Sayad) [#4]

April 13, 2022
Brad Power

Meeting Summary

Saed Sayad, MD, professor of computer science at Rutgers, and founder of Bioada Lab, presented a bioinformatics analysis of prostate cancer using public databases.

His main claim is that there is lots of useful data in the public domain which is under-utilized.

He shared several examples in prostate cancer where public data can be used to generate hypotheses for treatment options, including:

- Several drugs that could address a common gene (HOX) in prostate cancer (HXR9, sunitinib, aphidicolin, resveratrol).
- Only two sessions of radiation therapy may achieve the same result as the standard, which includes more sessions.
- Copper, in combination with other drugs, has been shown to kill prostate cancer cells.
- Prostate cancer with poor outcomes has a number of biomarkers, one of which (YOD-1) has been targeted by an oncogene (MicroRNA-373) in cervical cancer.
- Proteins found in a blood analysis (related to P53) could predict whether patients will respond to expensive therapies (anti-CTLA-4).
- A serum analysis can predict risk for 11 cancers, including prostate cancer.

His group is building a platform to make it easier for healthcare professionals to directly query these public databases, without having to use bioinformaticians or data scientists.

A rich - and at times heated - debate ensued about the merits of efforts to develop research hypotheses (especially for repurposed drugs) vs. getting them to clinical use for patients who need treatments today. The process of developing evidence to get promising treatments into the standard of care for patients can be expensive and hard to fund if it can't be funded by a pharmaceutical company with a proprietary drug that could benefit. Government and advocacy groups like the Leukemia and Lymphoma Society or Prostate Cancer Foundation were mentioned as the most likely avenues for funding.

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Meeting Notes

Brad Power: Saed Sayad teaches at Rutgers, but he's based in Toronto. He's going to share with us information that he's gotten from public sources and done data analysis on those sources to share with us today.
But first let’s do a round of introductions to get a sense of the people that are drawn to Prostate Cancer Lab.

Participant Introductions

Mike Yancey: I'm here as a prostate cancer patient. I'm out of the Northeast Oklahoma area.

Brad Power: When you were diagnosed in Oklahoma, where did you get treatment? It's easy when we're on the coast or near an academic cancer research center, like Boston, or Houston, MD Anderson, San Diego, UCSF, or Seattle.

Rick Davis: If he joins one of our groups, I'm sure we can help him solve that problem.
I run AnCan. We provide patient support to patients at all levels of prostate cancer from active surveillance, all the way up to advanced disease. And one of the things we do is navigate them if they are not getting the right sort of treatment.

Karin Rodland: I'm a PhD cancer biologist. I've been interested in cancer for about 50 years. My specialty is gynecological ovarian uterine, cervical cancer, but I've been involved at Pacific Northwest National Lab in a lot of tumor characterization studies organized by the Clinical Proteomic Tumor Analysis Consortium (CPTAC), which just covers a wide range of tumors. And we also have funding to do early detection and risk assessment in prostate cancer.
So basically I can help you navigate the literature. That's probably my most useful function.

Brad Power: You're based in the Portland, Oregon, area?

Karin Rodland: Yes. I'm an emeritus professor at Oregon Health Sciences University. And to answer Mike's question, no matter where you are, if you don't have one of those named places nearby like MD Anderson or Mass General, find your state's academic medical center and get your care at your state's medical school academic center, because they will be the most cognizant of the research level of findings of anywhere in your state. And every state has one just about.

Sophia Cornew: Hi, I'm with the company Ciitizen that was acquired by Invitae last fall. We've supported a number of Brad's hackathons, mostly from a data infrastructure perspective. Our product allows patients to gather all of their medical records from all places of care, and consolidate it in one place that's easy to share. I like to call it a digital file cabinet.

That sounds simple, but, when you've received tons of care and you're dispersed all over the place it can be quite helpful, especially for a hackathon like this, so that everyone can access it and work from the same clinical information. We are delighted to support these hackathons and would love the opportunity to support the patients participating. I haven't been able to join because I have a conflicting meeting with the Leukemia and Lymphoma Society. We host their national registry.

Now that we are part of Invitae, one of the things I'm excited to do is bring forth a lot of the research assays that may not necessarily be open to the general public yet. And there's definitely a lot of interest in the prostate cancer space from a hereditary and somatic perspective. And so would love to bring in some of those kinds of scientific minds on our extended team and see if our lab can't also be of service to the hackathon.

So wonderful to meet you all. And I'm so glad that I can be here in person versus watching the recordings and, and reading all the emails. It's so nice to meet everyone.

Ken Anderson: I've known Brian for quite a while. I'm a cancer patient who has been battling prostate cancer for almost six years now. I just got my first round of Lutetium. I have been pretty actively involved with AnCan.

Chandra Cota: I'm a medical physicist working in radiation therapy. Brad always confuses me with a radiologist who reads images in radiology departments. It just goes to show there are so many different subspecialties and niche fields within cancer care. It's just mind boggling for patients to keep track of who does what? In my day job I assist the doctors, as a radiation oncologist, delivering radiation treatments and think about better ways of radiation treatments, which are more effective for patients with fewer side effects. I’m currently working at Yale in Connecticut, and I'm always looking to learn and help patients outside the traditional healthcare setting. I'm here to see how I can help patients and leverage technologies and advance the field so we can hope for better cures.

Herb Geller: I am a prostate cancer patient. I'm also a researcher and lab chief at the National Institutes of Health, where my specialty is neurobiology, but we use lots of different techniques, and I have published in the cancer field when I was part of the Rutgers Cancer Institute when I was a professor at Rutgers. I'm very interested in how we move ahead.

Laura Kleiman: I'm the founder and CEO of RebootRx, a nonprofit that is repurposing generic drugs for cancer, using AI technology that we're developing.

Pradeep Mangalath: I'm the co-founder and CTO at RebootRx. We've worked with Brian in the past. I recognize most of you. It’s good to reconnect.

Ally Perlina: I'm the chief science officer at CureMatch here in San Diego. I'm a San Diegan. I've been attending quite a few of these hackathons and have been able to help in various ways and hoping to do more. I worked with Rick some time ago at Human Longevity. I’m the kind of

scientist who has very diverse, multifaceted expertise for about 20 years now, mostly with startups, specializing in systems biology approaches to impact clinical care.

Usually when we hear systems biology, it's very much computationally focused, but I've been very close to the actual patient-physician interactions and decisions. My mission has always been to take all of these expert interactions and then deliver them in ways that can be automated as much as possible to scale personalization with molecular level precision.
The way I always seek to help is to, first of all, provide input in any kind of analytics from bioinformatics to machine learning, to any sort of data science, even though I've never gotten very much technical and hands on, and I can't offer that right now, but I've done so much data analytics that I think I'll be able to at least chime in with input or questions because that goes for any type of data, from genomics to transcriptomics, of course, and metabolomics, even proteomics.

I also did a lot of work with the microbiome and actually invented some products that also do pathway and molecular profiling from different -omics, including microbiome and not only with pharmaceuticals, but nutraceutical agents. I was a primary inventor on a personalized supplements product, something I did before I came to CureMatch in 2020.

Happy to provide some insights there, but I just want to make sure that as, as a CureMatch representative, I seek to help get all of the markers that everybody deems as important, because I know this is a big part of these hackathons to figure out what is the list of markers that are important and then to take them into this many-to-many analysis, what are the drugs that best address most markers and what are the combinations that can be attempted and CureMatch will score that.

So I'm happy to run a report that will match basically any markers at any level.

Rick Stanton: Thank you, Ally. You're terrific. I know from working together, when you grab onto a task, you're the kind of person we want in our corner.

Brad Power: Ally will be doing an analysis of Rick and Brian's data and presenting that in the next week or two.

Rick Stanton: I wanted to give a quick shout out to Rick Davis. I got a communication from Dr. Tanya Dorff, saying that Pluvicto would be a great choice for me. Thank you so much, Rick, for bringing this to my attention. This seems to make sense, and it wasn't brought up by my clinical oncologist team, and when you brought it up, I asked them about it, and they all said that it seems to make sense. It was just flabbergasting to me.

Zsuszanna Devecseri: I am head of oncology at Sanofi. I have a big passion for prostate cancer research and finding a cure. I lost my father to prostate cancer, so I will do everything to help prostate cancer patients.

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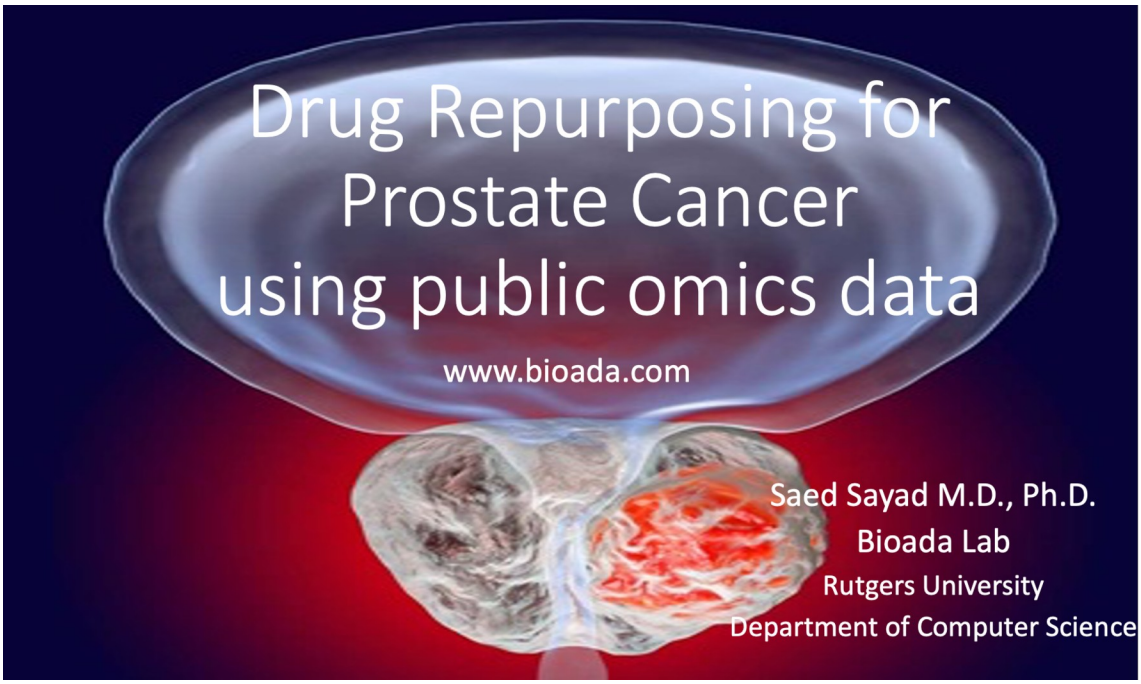
Saed Sayad - Drug Repurposing for Prostate Cancer Using Public -omics Data



Saed Sayad: I want to talk about drug repurposing for prostate cancer using public -omics data. In the last twenty years there is tons of data in the public domain. The NIH did a great job of encouraging researchers to upload their data into the GEO website. (It stores curated gene expression data in the Gene Expression Omnibus repository.)

I’m a professor of computer science and data science. My education is as a medical doctor and biochemist, and I did a post doc in AI.

Ten years ago I said, let’s put all the expertise in one place and see what we can get out of it. I believe that billions of dollars were spent assembling this data, but we are not using it. This is one example of how we can use that data.

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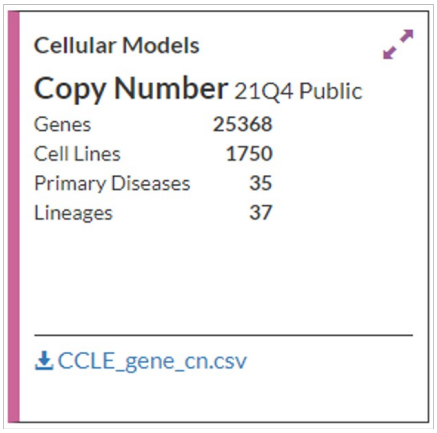
DepMap – Broad Institute

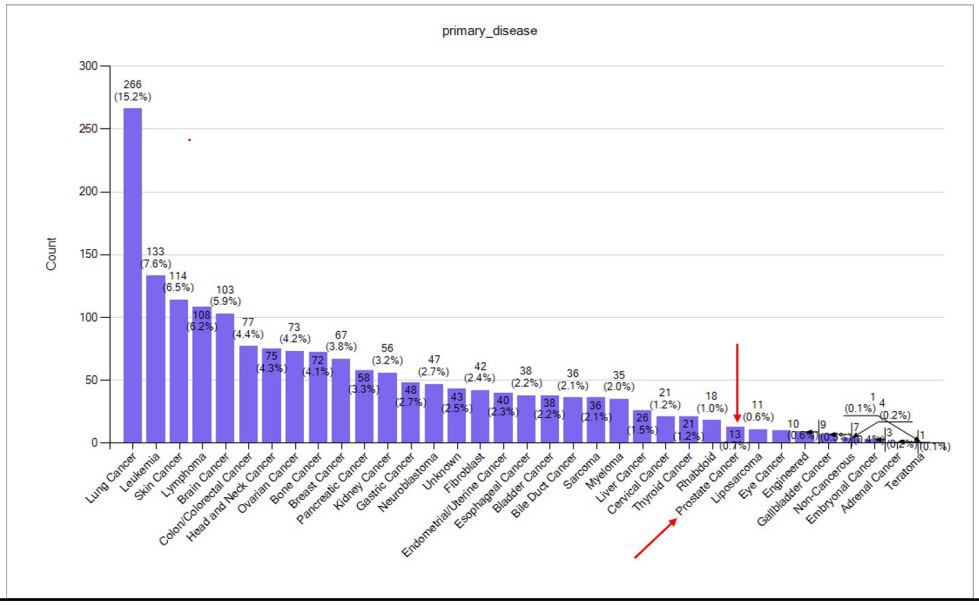
- Copy Number
- Expression
- CRISPR
- RNAi
- Drug Sensitivity
- Mutations
- Proteomics



https://depmap.org/

Another example besides NIH is the DepMap (Cancer Dependency Map) from the Broad Institute. They spent millions of dollars to generate this public data, mostly related to cancers, including the copy number, expression, CRISPR, RNAi, Drug Sensitivity, Mutations, Proteomics. For example, on the copy number data, there is data from more than 1700 cell lines.

DepMap – Primary Disease



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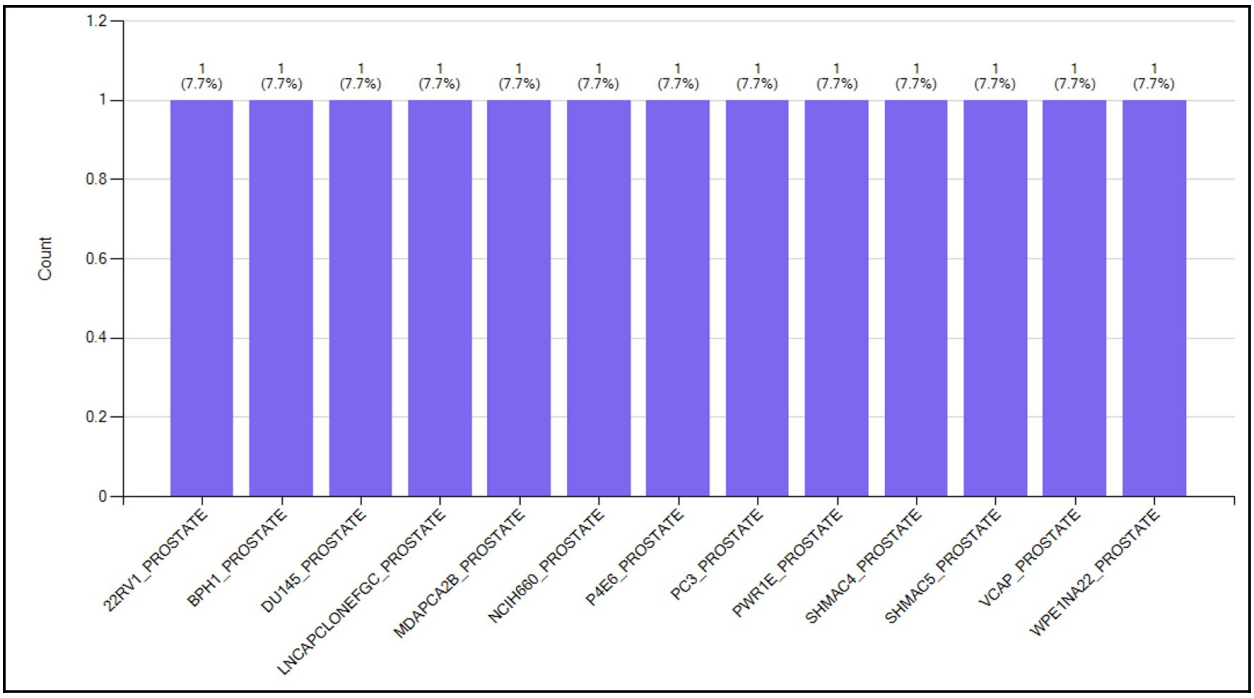
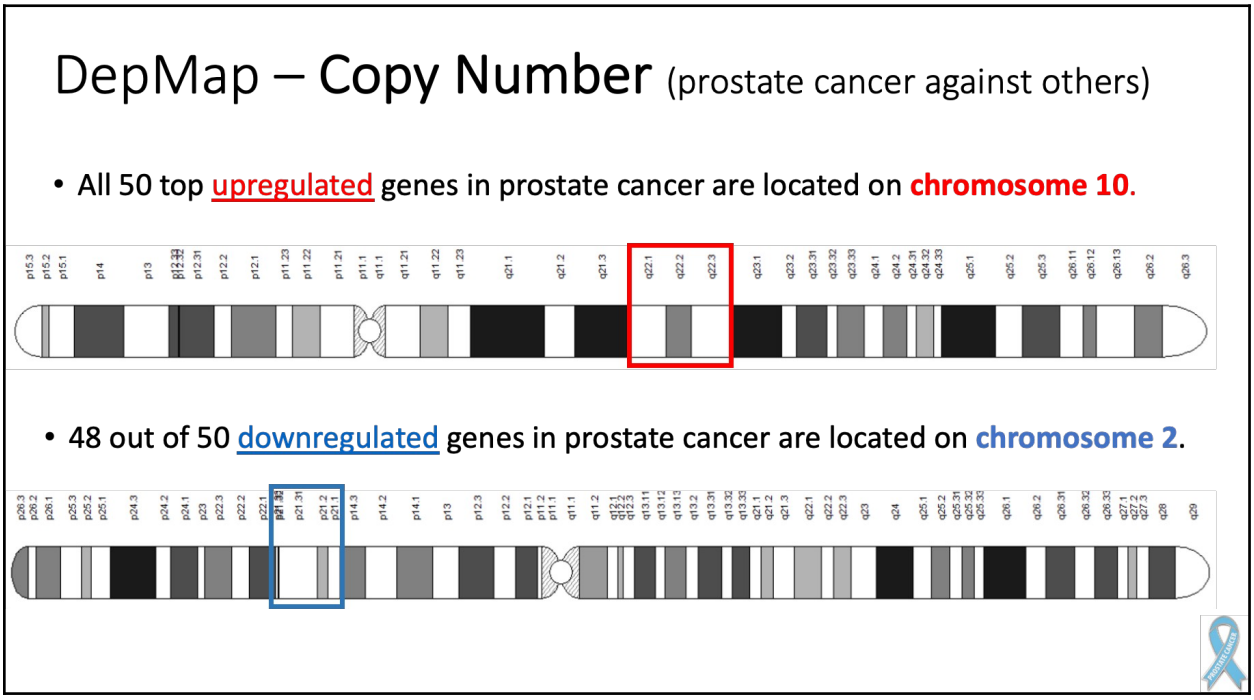


The data related to the prostate is about 12 cell lines.



All of the top 50 upregulated genes in prostate cancer are located on chromosome 10.
It might be because of the nature of the prostate tissue. We don’t know.
But having the top 50 upregulated genes in prostate cancer located on chromosome 10 is amazing.

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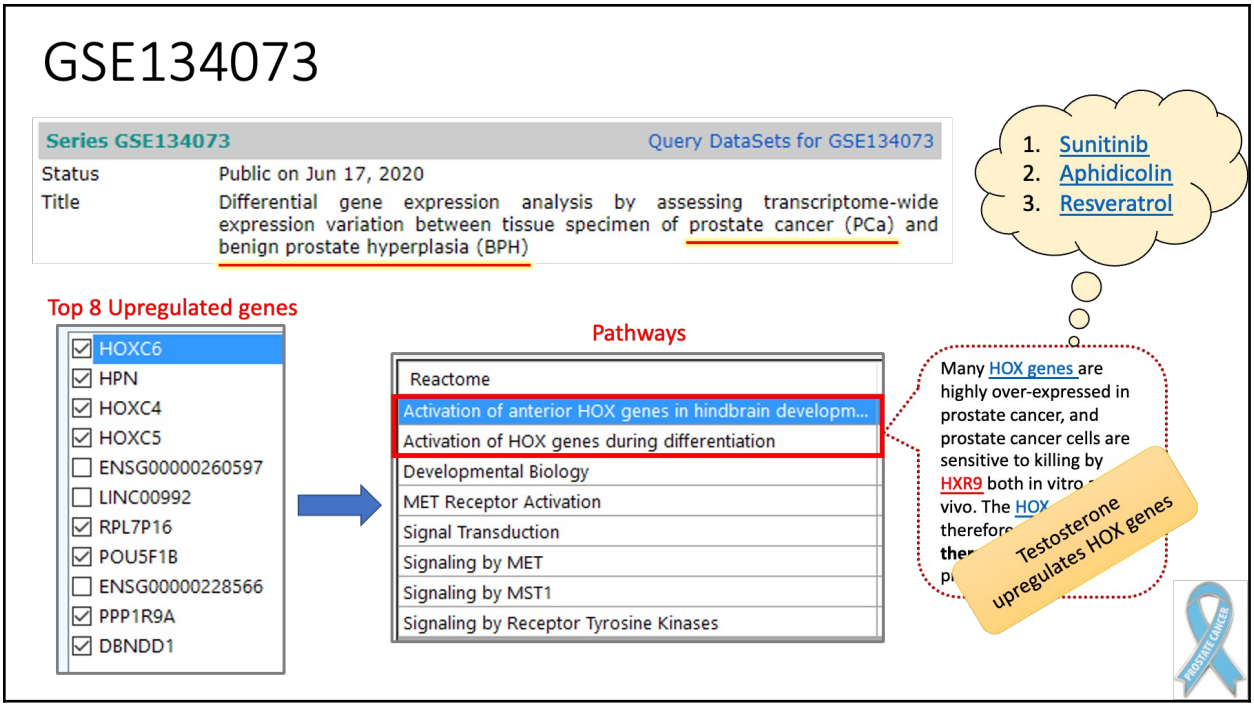
48 out of 50 downregulated genes are located on chromosome 2.
As a starting point, we can think about why we have this kind of aggregation.



Now we look at some of the data from the NIH GEO website as an example. This is prostate cancer and BPH (benign prostate hyperplasia). We want to see the differences between the -omics data, the gene expression data. For example, the top 8 upregulated genes between these two, if we check the HOX gene pathway, we found that there are research experiments using HXR9 to go after these genes, and they got some good results. At the same time, we found that testosterone upregulates HOX genes. From the public data of drug-gene interactions, we found three drugs, including resveratrol, which is a very non-toxic option. This is just a hypothesis. It needs to be tested.

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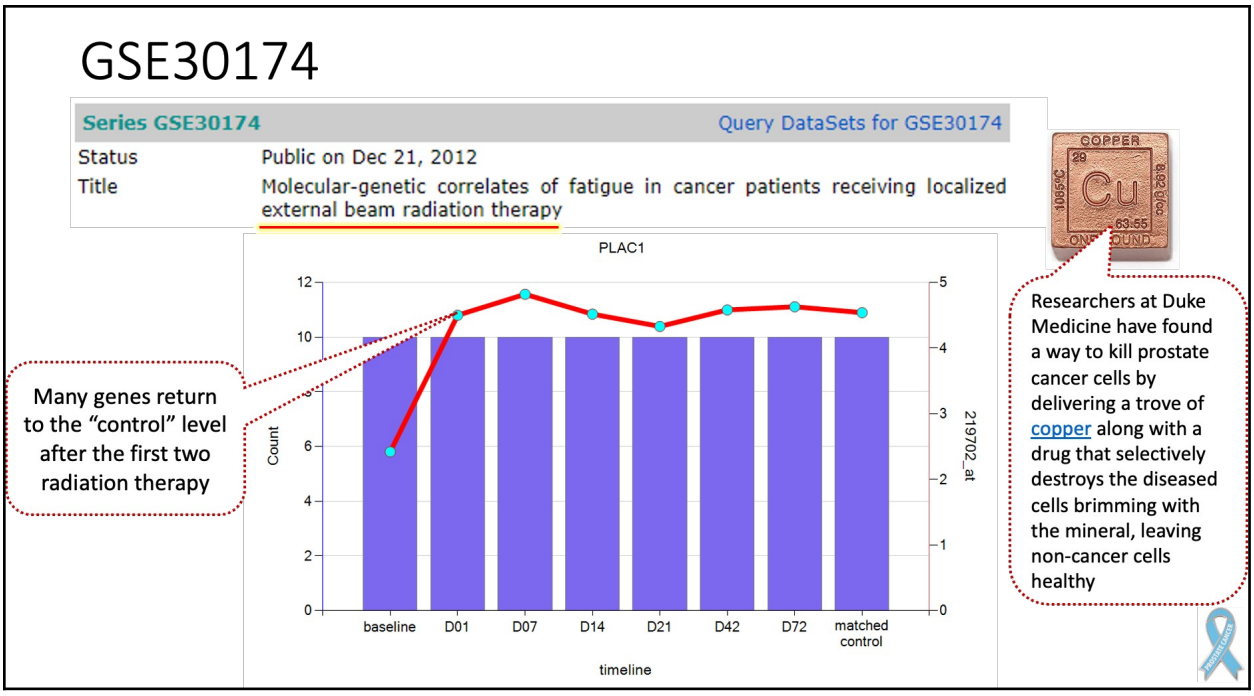
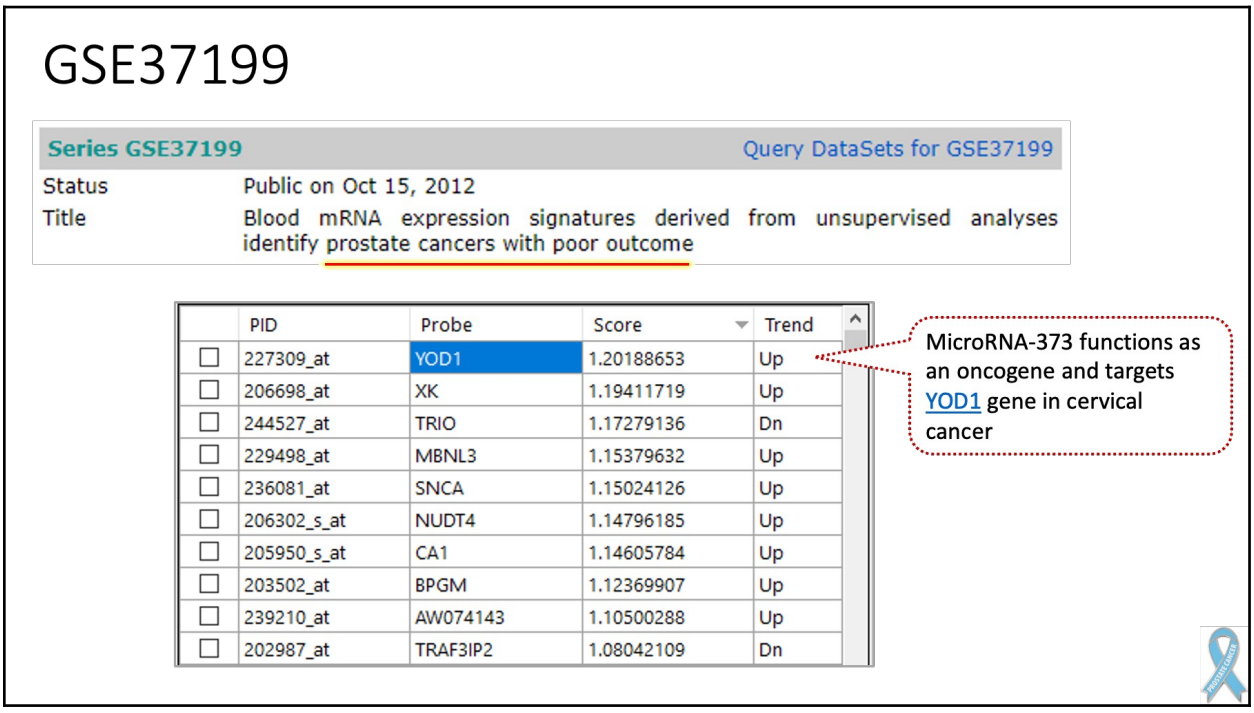


Another example is from radiation therapy. There is a baseline here that can be changed by this probe PLAC1, which can return it to the level of the matched control. I can show you 100 different genes that show this same behavior: after two sessions of the radiotherapy, you return to the matched control level. Do we really need so many sessions?

Similarly, copper has been found as a good chemical to affect prostate cancer.



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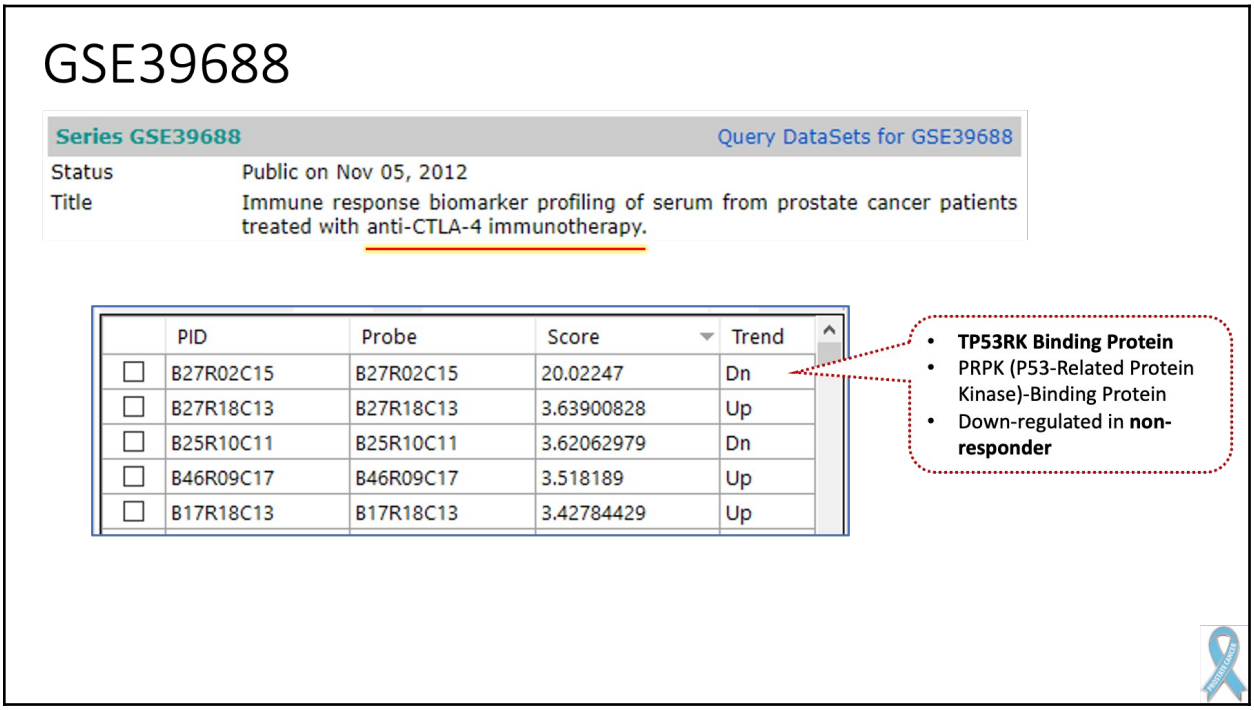
Another public domain experiment has been made to identify prostate cancer with poor outcomes.

Then we found research related to the MicroRNA-373, which targets this gene.
This is another hypothesis.



Another research study is on anti-CTLA-4. This is a very expensive treatment. Can we see who is going to respond, and who won’t respond? We found this protein in the blood of this non-responder, which is related to P53. This is another hypothesis to test.

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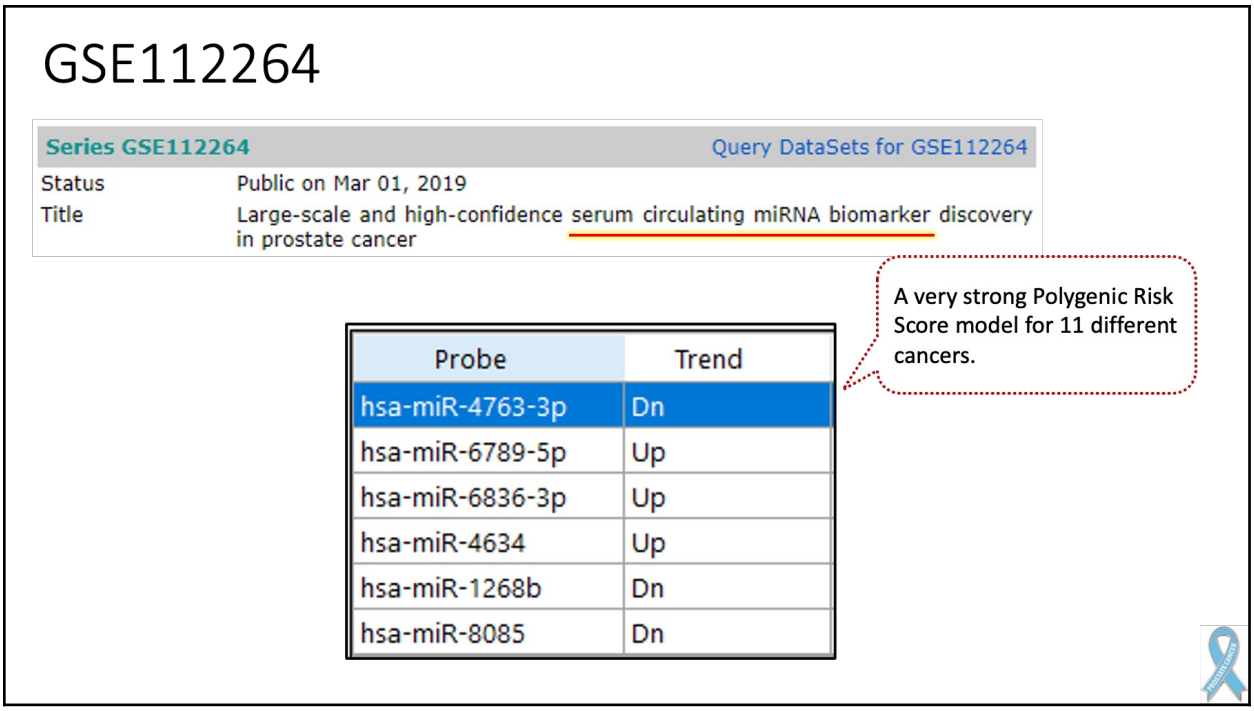
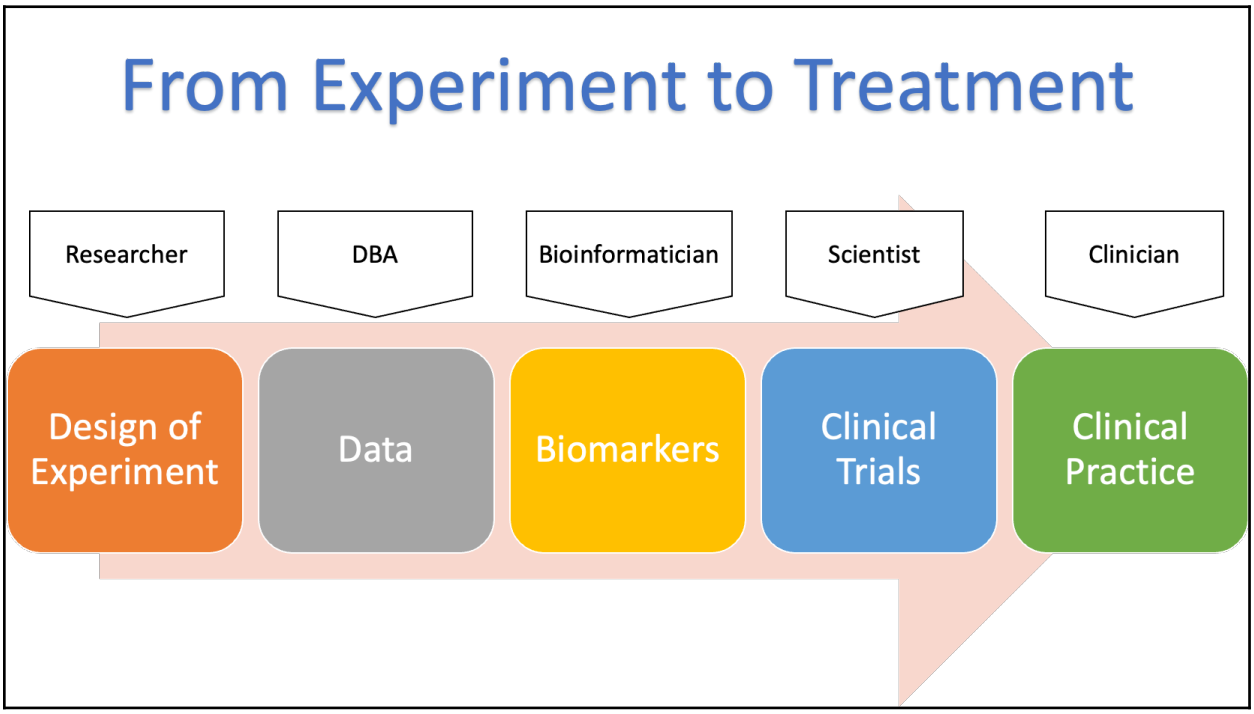


This analysis of serum circulating micro RNA biomarkers. It is an extensive experiment done by a team in Japan with more than 1500 cases. They found six biomarkers that can predict 11 different cancers. But there is a big problem with reproducibility. But you can surely have early prediction from the serum.



We have the full process from experiment to clinical practice. Now everybody is here.

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The darkest area is the data. We have a huge amount of data, but we are not using it.
In our group we are trying to solve this issue, and create a new layer on top of data that 80% of people in healthcare can easily ask and answer questions by using this platform, instead of asking for help from bioinformaticians, data scientists, and database experts.

Brad Power: I’d like to learn a bit more about you. You have Bioada, which is your startup. And you have your teaching.

Saed Sayad: I teach data science and computer science. 10 years ago I started doing research in this area. But there was so much work to get access. That is why I wanted to build a platform. And working on biomarkers.

Brad Power: Laura and Pradeep, your work at RebootRx is also on repurposing approved drugs. Did you have any comments?

Laura Kleiman: Our approach is slightly different. Pradeep spoke with Saed yesterday. We start with clinical data on drugs. It is very complementary.

Pradeep Mangalath: There are lots of hypotheses in the data we see, and validating that in the public databases would be very helpful. And for stratifying patients who might benefit from certain drugs. We are looking forward to seeing the Bioada platform, and see how we can tie the two ends of our analyses.

Saed Sayad: We are talking about private data, as well as public domain data. We are trying to avoid having to write tons of code to use the data. I can give you 50 possible drugs with potential effects on prostate cancer from the DepMap. 99% of people in this field don’t know about this data.

Karin Rodland: By accessing all these different data sources, both public and private, do you think you have solved the power problems so that you could apply AI or deep learning so you can have not a lot of false discovery? That you actually have more samples than features?

Saed Sayad; Bioada created three layers: data management, exploration, and modeling.
The biggest issue we have for clinical use is reproducibility. We are giving the healthcare researchers and practitioners the tools to access this data.

Rick Stanton: That sounds like a “no” to Karin’s question. You don’t have enough data.

Saed Sayad: No, we have enough data. We have more than 1,000 different experiments. When you find the biomarkers, or any useful data, you need to reproduce it.

Karin Rodland: Since you are acreting data from a number of preclinical studies or clinical trials. Suppose I have a biomarker that is centered around TGF, osteopontin, and spark. I want to go out and validate that in an independent population, and that requires a lot of money. But

probably somebody has already done a study on prostate cancer RNA seq, but they haven’t looked at osteopontin, TGF, and spark, but those data are there in the public domain. Are you looking at tools that would allow you to do the reproducibility experiment, looking at independent cohorts?

Saed Sayad: Yes. We can find similar experiments to answer the same question.

Brad Power: I’d like to get some reactions to the hypotheses Saed uncovered.

Rick Davis: These discussions are noble, and I pick up something. I look at the relevance of these discussions to patients today. I’m familiar with the Duke research with copper. The concept was that prostate cancer has a particular affiliation with copper. They absorb copper. If you give copper with drugs, which are attracted to the copper, it will destroy the prostate cells. Dan George spent a lot of money in 2014 to run experiments. But it had no legs because they needed millions to run a trial. We need to do more than develop research protocols.

Laura Kleiman: You said there is no value in using generic drugs for prostate cancer patients. Who are we talking about?

Rick Davis: I didn’t say there is no value. How do you move something like copper to be available practically for patients.

Laura Kleiman: The main issue is funding the clinical trial. That’s what we do at RebootRx. There are ways to fund these clinical trials. And then there’s the issue of changing the standard of care once you have that evidence. Maybe a quick example is an initiative in the UK to address these specific challenges: the NHS England Repurposing Medicines program.

Rick Davis: I’m frustrated. Some of you have lost touch with reality.

Saed Sayad: We should be patient.

Rick Davis: What about Duke’s study on copper?

Saed Sayad: I totally agree. Moving to an experiment is a difficult job. Let me show you another example to see the potential. There is a drug for psoriasis. That’s why we need a group for this.

Rick Davis: I agree that the drug is effective. We know that what you are discovering can work. But Duke couldn’t move the copper for prostate cancer forward. How do we take that to a practical application?

Karin Rodland: I’m an academic researcher. The question Rick is asking is, “When you get a great preclinical result, how do you turn that into clinical practice?” The standard of care requires that you do a defined clinical trial. The issue that Rick is raising is, “How do you fund the clinical trial?” In this country most clinical trials are funded by the pharmaceutical company

that owns the drug that they are testing because they are very expensive. However, in the UK, Canada, and other countries with a national health system, where everybody gets their healthcare from the government, that is not necessarily the case. Although the pharmaceutical companies tap into those populations because they have great metadata. One of the people on this call is working with the Leukemia and Lymphoma Society. Here is how you can do this without having a proprietary interest in the drugs that are being tested. The Leukemia and Lymphoma Society has funded a program called “Beat AML.” It has a master IRB to test 106 drugs. The concept is that a patient is going to come in, they’re going to be profiled for their DNA, their RNA seq, their imaging data, their proteomics, and this knowledge base is going to be applied to that individual patients data, and in “Beat AML 2” they’ll be given the standard of care, and when they don’t respond to the standard of care, there will be a precision pathway chosen for that patient based on their -omic data. The Cancer Moonshot is also looking at NIH-sponsored clinical trials to run around this.

Herb Geller: I agree with you 100%. You’re looking at repurposed drugs that are off patent. Nobody has any financial interest in getting them to market. Where do you get the money from? The NIH sponsors clinical trials for things like this. There are SBIRs.
Data from cell lines is a very risky process. Cell lines don’t represent patients. It’s a major lift. You need a lot more evidence.

Saed Sayad: Cell lines are used by the Broad Institute and Sanger Institute. They are moving to the organoids. The rest of the research I showed you were on human beings. The clinical trials piece is hard.

Ally Perlina: I share some of the impatience of being grounded in reality. Much as love the data and analytics, having worked on the clinical side, I realize that even when something is very promising, it is not going to cut it to give it to somebody in our lifetime. The problem is that with the around 300 known cancer drugs, there are 4.5 million ways to combine them in 2- or 3-drug combos. Not just off-label, but autoimmune and other drugs which can be repurposed lead to millions more combinations. It is very rare that just one drug will address the molecular profile of a patient. It’s not just practical to wait for millions of trials to be run. What has been done at CureMatch, founded by Razelle Kurzrock, is to prove through clinical studies that molecular matching is predictive of outcomes. It’s a paradigm shift. You can’t prove in advance all the combinations, but you can prove that the algorithm and the knowledge base that matches the molecular profile of each patient to a combination of 2 or 3 drugs can impact PFS and OS, and that’s the measure of validity in this lifetime. I’m happy to contribute to some sort of guideline development for what we would consider promising that would have merit. It has to bind and inhibit. We have to be realistic. Pharmacological efficacy is a big deal. We can define what needs to be met to be clinically useful.

Brian McCloskey: I wonder if there is a way to bundle up these promising repurposed drugs to go to NIH or Cancer Moonshot to review them?

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Herb Geller: That’s what the job is of program managers at NIH. They need to talk to people who have ideas and whether they have merit. There will be a booth at a conference of people from the NIH.

Brian McCloskey: My sense is that the government is going to be the source for funding this.

Herb Geller: Or an advocacy foundation, like Zero.

Rick Davis: Or the Prostate Cancer Foundation. Maybe this group should push on copper and disulfiram.

Brian McCloskey: I’ve made a note of that and will follow up.