“Drug Combinations and Off-Label Drugs” (Ally Perlina) [#7]

May 4, 2022
Brad Power

Meeting Summary

“We have done many simulations on genomic data, and all of them show that using more drugs is better than fewer drugs, and less concentration is better than more concentration.” Saed Sayad

In this meeting we discussed the strengths and weaknesses of using combinations of approved drugs to better fit a patient’s unique molecular profile and thereby achieve better outcomes, and the use of off-label drugs targeted at molecular biomarkers. The main concerns were around toxicity from combinations and the possibility that off-label drugs might behave differently in different disease contexts (something that worked in one cancer might not in another). (For more background, please see the notes from our meeting #5 on April 20, where Ally Perlina, Chief Science Officer at CureMatch, presented combinations of approved drugs that are the best fit for advanced prostate cancer patient Brian McCloskey based on his cancer’s unique molecular profile.)

Question/Concern	**Answer/Response**
Should a combination of drugs be administered sequentially vs. all at once?	● Leaving mutations untargeted enables progression. ● Higher matching results in better outcomes.
Are drug combinations more expensive than monotherapies?	● Providing the molecular rationale is evidence that can persuade payers to reimburse. ● Alternative drugs are identified that affect the same pathway. Some will be cheaper yet have the same effect. ● Dosages for drugs within a combination can be reduced vs. when the drug is administered as a monotherapy. ● By targeting the molecular profile, better outcomes are achieved, which are cheaper.
Do you have any experience or data in having patients cycle on and off drugs?	● We don’t. ● It’s hard enough getting physicians to consider drug combinations.
Do you include therapies that are in clinical trials in your recommendations?	● We don’t. ● Adding drugs that are in clinical trials would be too complicated and too risky for most physicians.
Is there evidence to support using a MEK inhibitor for a BRAF mutation?	● I will have to look it up to find the evidence. ● It depends on the situation whether to use the indirect MEK pathway.

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Is off-label use of a drug potentially a mistake? What about the example of a BRAF drug not working in colon cancer?	● If a drug that targets a mutation didn’t work, it was because the whole molecular picture wasn’t taken into account.
How should a physician manage doses with a novel drug combination?	● There are links to papers with combination dosing strategies provided in the report. ● We will provide report reviews on request.

Brian McCloskey asked about on-off cycling through drugs, an idea promoted by Dr. Bob Gatenby.

Saed Sayad and Dr. John Laird observed that our guidelines, which push to maximum tolerated doses, are driving cancers to resistance – a flawed strategy.

Saed Sayad presented a hypothesis that RCC1 could be a biomarker to predict cancer recurrence after prostate surgery.

Requests

- Do you have any feedback on drug combinations and off-label uses of approved drugs?

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Meeting Transcript

Brad Power: We are going to start today with feedback on Ally Perlina's presentation about CureMatch. For those who don’t recall Ally’s presentation, the CureMatch approach has two key features: combinations of drugs and off-label use of approved drugs, and there was some conversation about people being interested in clinical trials.

Brian McCloskey: As Brad mentioned, we were able to circulate Ally’s presentation about the CureMatch report based on my profile and get comments from some of my oncologists, Emma Shtivelman, who's on the call today, and Peter Kuhn. I grabbed a few snippets of feedback that came in and we can take these one by one.

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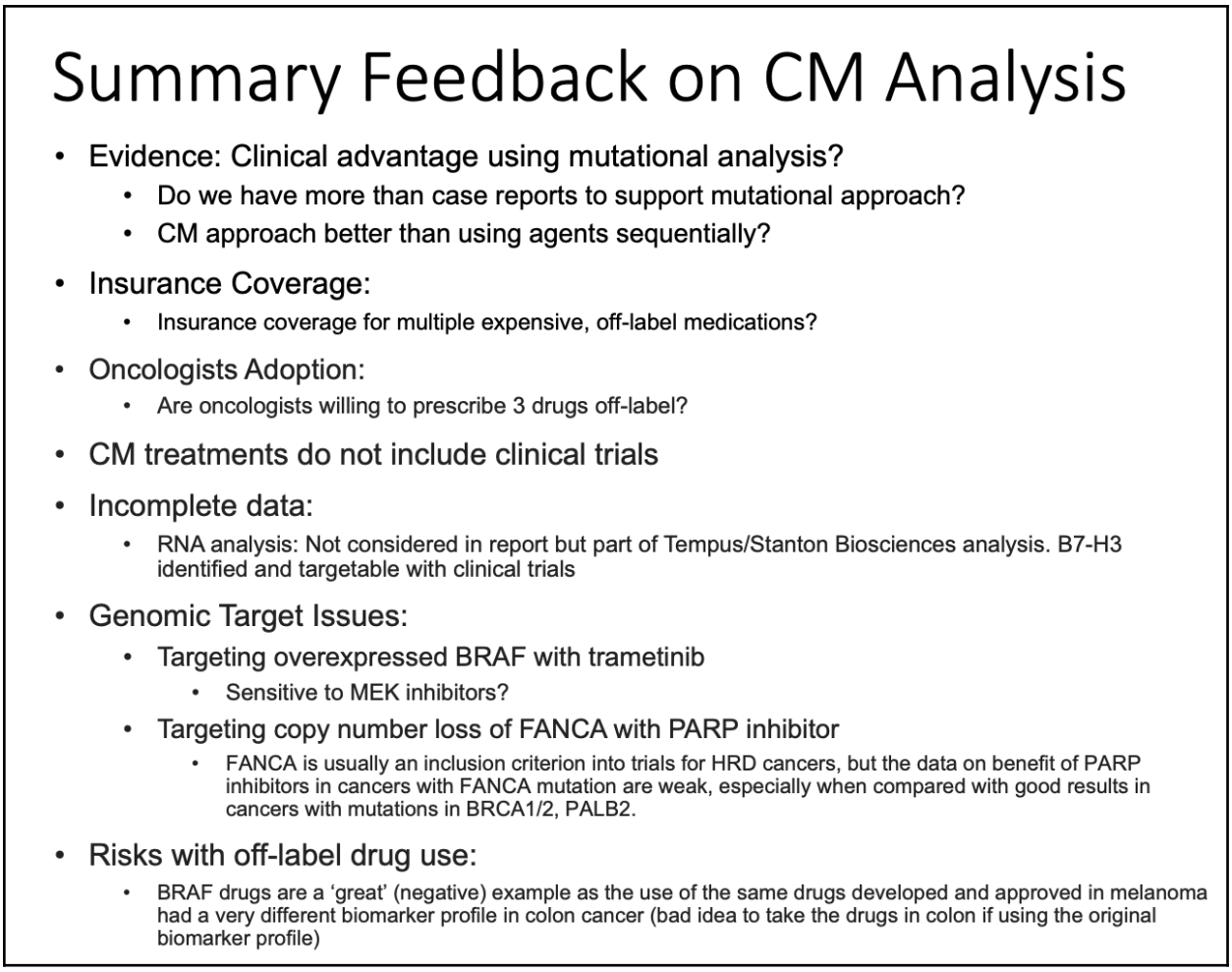

Brian McCloskey: Ally, I'd love to get your feedback in terms of whether or not these are issues that you have come across, or if these are new, and what your thoughts are in terms of how to address them. The first came in from Tanya Dorff, who is an oncologist at the City of Hope. She liked looking at the mutational analysis, but she questioned whether or not there was a clinical advantage to using an all-in strategy or looking at these agents sequentially.

Ally Perlina: That's surprising to hear from somebody at City of Hope. We don't usually need to convince anybody when we deliver our reports that it's better to cover as many bases as possible of what's driving a patient's cancer. In the many dozens, if not over a hundred, reports that we delivered where I was participating and reviewing, I haven't once met an oncologist who said, “why would we want to target all the mutations that are driving the patient's cancer as opposed to one at a time?” I think that's old age thinking that you can just target one at a time. The evidence is pretty clear that when the drivers are left untargeted, they most often promote the next set of clonal expansion of those cancer cells that have the drivers that are not targeted. The motivation to try to target as many of the markers at once as possible seems well accepted. We have evidence that patients that are partially matched or have a lot of mutations left unmatched don't do as well in terms of progression-free-survival and overall survival. We've had

several study results showing that it's the degree of matching that actually matters. It's like how many birds can you shoot with as few stones as possible, which is why we have the score. Since the beginning of the company in 2015 by Dr. Razelle Kurzrock, we've had clinical evidence showing that no matter what the cancer is, no matter what the data set is, the higher the matching, the better the outcomes, and the worse the matching, the worse the outcomes. Nobody wants to turn a blind eye on a cancer driver and leave it untargeted. The industry may struggle to deliver multiple drugs in an affordable way. It’s not the standard way to get three drugs at a time. We still see a lot of physicians will opt for two different drugs, and see how the patient does. And then they will add another one. Or if a patient is already on a drug and responding, they'll keep their patient on the treatment because they're seemingly doing okay. Our recommendations include immunotherapy, chemotherapy, and all kinds of targeted therapies that are approved. I shared a slide with evidence, and we're going to be publishing more with even bigger data sets with the latest algorithms that show that the higher the score, the more markers you cover, the better patients do.

Brian McCloskey: You mentioned the expense of off-label drugs, which was another issue that Tanya mentioned. Do you have any data that compares the cost of the combinatorial approach with off-label drugs versus standard care monotherapies?

Ally Perlina: I'll send a link to an independent evaluation that priced out our recommendations. There are choices and options that follow the molecular rationale. This will help make a case for a physician to get it covered or partially covered. Under our targeting description there are always alternative drugs that have the same therapy type and the same targeting mechanism. With these alternatives the score can be almost the same or exactly the same, but one treatment would cost a lot more versus the other one. We have this model where we include the molecular matching and clinical value with the financial feasibility – getting the highest score for the least money. Plus, when combining multiple drugs physicians often opt to start with much lower dosages, e.g., one third on a three-drug combination, or a half dose on a two-drug combination, then titrate up as much as makes sense. We have a calculator, which can be used to estimate the most impact with the smallest price of the drugs. Finally, we show that having three-drug and two-drug combinations is a lot less costly and less of a burden on the patient, the doctor, and the medical system, than having one drug that has no molecular basis. Cancer centers have drug acquisition specialists, who are trained to make appeals to compel drug coverage and reimbursement, and having this molecular rationale in the report to attach helps them.

Brian McCloskey: You talked about lowering the dosage when you combine several drugs. Have you looked at cycling on and off a therapy, e.g., on for three months, take a holiday for three months, get back on for three months? Do you have any data that supports that? The reason I'm asking is that we had a really interesting conversation with Bob Gatenby yesterday. He is an evolutionary biologist at the Moffitt Cancer Center in Florida. He has spoken and written a fair bit about adaptive therapy. When you mention going for lower dosage, which makes sense when you're doing drug combinations, it raised this question in my mind of how he approaches it, where he lowers dosage. He doesn't go for the kill shot.

Ally Perlina: No, we don't have any evidence that would support it. Maybe this is something new and emerging, but we only have evidence to show that you should target more markers at once. There's no other data. Everything we put in our system is extremely well curated, and it's all under the guidance of Dr. Razelle Kurzrock. It's not like there is just some independent AI that just comes up with some serious predictions. It's not machine learning, and it's completely based on evidence. If we don't have clinical level evidence, we don't put it in the system. That doesn't mean that there isn't some exploratory angle that we may not be covering. Coming up with novel combinations of existing drugs is already outside the box enough, and as much as the medical system is ready for nowadays. They are more ready compared to our Human Longevity days, when we did have the same off-label combinations being tried, but not as frequently and not as willingly. That was in 2015, and now the world is different. Oncology is reaching this pivotal point and turning the corner to realize that precision oncology that addresses the mutations, and as many as possible, is really the way to go. That's a great point, but we don't have any reason to believe that going off and then cycling back on is necessarily better.

Brian McCloskey: We're going to try to get Dr. Gatenby on to lead a discussion about his approach. He did some clinical trials with abiraterone, which is what I'm on right now. There's a podcast that he did with Peter Attia, “The Drive”. He definitely has a different take in terms of how to approach the delivery of treatments.

Ally Perlina: We do not include investigational compounds. If it's a novel compound that has not been approved for anything, that drug will not be in our system. If we included novel combinations of approved and novel drugs, that would be a bit too much novelty. Things like drugs for B7H3, according to what we do, aren’t included since they aren’t yet approved. If there is a trial that's wonderful, and we're not saying it's not a suitable option. We consider RNA, proteins, and DNA, and we can consider it from multiple labs and multiple reports at once.

Brian McCloskey: We had talked about that before in terms of clinical trials, and B7H3 being one of those that was identified in some RNA-Seq analysis that Rick and I did with Tempus. I think you've got that.
Emma, I think you had some questions about BRAF and targeting copy number loss with PARP inhibitors. Do you want to elaborate on anything there?

Emma Shtivelman: I couldn’t find any solid evidence that overexpressed BRAF is something that responds to treatment with a MEK inhibitor. It makes sense because it's in the pathway.

Ally Perlina: I have some follow up to do. I can pull up the evidence that we have, but if there wasn't any clinical evidence, this connection would not have been made. Our system doesn't have the freedom to make connections. Everything is based on a drug target, or marker drug sensitivity, or resistance associations that are curated when it's a direct drug target. We actually even have IC50 values play into the score. This is not the case here. This is more about the mechanism of sensitivity through DNA damage response and the role of PARP inhibitors. And

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we do discriminate between PARP inhibitors and other inhibitors and chemotherapy in general versus platinum agents. Some markers can trigger one, but not the other. In this case, I'll just pull up whatever evidence we have. But there was enough clinical evidence to suggest that this can be included in the system.

Emma Shtivelman: I'm working with a patient who has BRAF amplification in a completely different type of cancer. I have difficulties suggesting a MEK inhibitor for this patient. So I will benefit if you can find the data.

[Ally subsequently provided Emma with the following references, which she found helpful:

Recommendation of regorafenib in patient with BRAF overexpression:

- The FDA label for regorafenib, a multi-targeting kinase inhibitor with a broad range of therapeutic targets includes kinases involved in regulation of tumor angiogenesis [VEGFR1 (also known as FLT1), VEGFR2 (KDR), VEGFR3 (FLT4), TIE2 (TEK)], oncogenesis (KIT, RET, RAF1, BRAF, and BRAFV600E), and the tumor microenvironment (PDGFR and FGFR), does not have contraindication against its use in presence of wild-type BRAF as seen on the FDA labels for the selective inhibitors dabrafenib, encorafenib and vemurafenib.
    - https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203085Orig1s014lbl.pdf
    - https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/202806s019lbl.pdf
    - https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/210496s013lbl.pdf
    - https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202429s019lbl.pdf

- A study in which biomarkers, including clinicopathological and molecular values, were evaluated to predict the outcomes of regorafenib in patients with refractory mCRC using NGS testing of tumor tissues.
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7649869/
        - In a subgroup analysis of an LCCC1029 trial, addition of regorafenib to chemotherapy improved survival times among the patient population with KRAS and BRAF dual wild-type CRC. Patients with BRAF mutation alone did not realize any survival benefit after adding regorafenib.
        - Patients with BRAF mutation demonstrated a tumor response of progressive disease (PD) and significantly worse PFS compared to those without BRAF mutation.
        - Based on findings from a LCCC1029 trial and this analysis, the presence of a BRAF mutation might be a negative biomarker for survival in patients treated with regorafenib.

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- Unlike the BRAF-selective inhibitors, dabrafenib, encorafenib, and vemurafenib, which can induce activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells, in preclinical and clinical studies, regorafenib demonstrated anti-tumor activity irrespective of RAS and BRAF mutation status.
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4182691/
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6291325/
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7513622/
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7649869/

Recommendation of PARP inhibitors in patient with FANCA mutation:

A Phase II study which evaluated the synthetic lethality with rucaparib in mCRPC patients with non-*BRCA*DDR genes reported responses in a patient harboring FANCA alteration. Of 4 patients with a*FANCA*alteration, 1 patient with a monoallelic truncating alteration had complete radiographic and PSA responses

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8435354/

A case report of a relapsed epithelial OC patient harboring germline*FANCA*p. P615Hfs*25 heterozygous mutation reported response to the niraparib treatment with PFS of over 21 months.

- https://www.frontiersin.org/articles/10.3389/fonc.2022.778545/full

A preclinical study which evaluated the effect of homologous recombination protein and PARP sensitivity, reported that the FANCA deficiency could induce sensitivity to PARP in mouse fibroblast cell line model

- https://doi.org/10.1158/0008-5472.CAN-06-0140

PubMed Central (PMC)

Non-BRCA DNA Damage Repair Gene Alterations and Response to the PARP Inhibitor Rucaparib in Metastatic Castration-Resistant Prostate Cancer: analysis from the phase 2 TRITON2 study

TRITON2 enrolled 78 patients with a non-BRCA DDR gene alteration (ATM [n = 49], CDK12 [n = 15], CHEK2 [n = 12], and other DDR genes [n = 14]). Among patients evaluable for each endpoint, radiographic and PSA responses were observed in a limited number of patients with an alteration in ATM (2/19[10.5%] and 2/49 [4.1%], respectively), CDK12 (0/10 [0%] and1/15[6.7%], respectively), or CHEK2 (1/9 [11.1%] and2/12[16.7%], respectively), including no radiographic or PSA responses in 11 patients with confirmed biallelic ATM loss or 11 patients with ATM germline mutations. Responses were observed in patients with alterations in the DDR genes PALB2, FANCA, BRIP1, and RAD51B.]

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Ally Perlina: If there is a molecule that is upregulated and oncogenic, you should target it, but with BRAF, you don't have to target it with indirect MEK inhibitors. It very much depends on what else is going on.

Saed Sayad: We have done many simulations on genomics data, and all of them show that using more drugs is better than fewer drugs, and less concentration is better than the more concentration.
And I have a gut feeling, not scientific, a theory, that we shouldn't go after cancer cells with maximum force. If we do, we are going to create a lot of resistance because of the interaction between pathways. You are just pushing one knob to the max, and those cells are going to react the same way. And that's the reason we see the resistance. We see the side effects, but if we can change a few knobs at the same time, we can make life for those cancer cells uncomfortable. And that's the key. There's going to be less side effects and less resistance because you are attacking from different points. Based on the simulation we see more drugs and less concentration as a better choice.

Brian McCloskey: Your simulation doesn't look at scenarios where you deliver a drug, then you take a holiday, then you re-deliver, off and on?

Saed Sayad: I’m not making the time management argument. Say you have one upregulated gene, and you are trying to downregulate it. When you increase the concentration of your drugs, the other genes are going to react, and instead of going down, they're going to go up, and all those other side effects are going to go up. But when you start to play with different genes at the same time, now you have a good balance, and you don't need that much of the drugs. It means to me, just a scientific guess, that having five drugs with 20% concentration is better than one drug with a 100% concentration.

Brian McCloskey: This is fascinating. There are definitely some opportunities to look at combining knowledge from your approach and Bob Gatenby's approach. We wii bring him into this conversation.
Peter Kuhn raised the risk of off-label drug use.

Ally Perlina: First of all, we do show some examples of combinations being used that are novel combinations. Tumor boards often suggest novel combinations. We're trying to systematically provide the same type of knowledge and rationale in the form of a report. What gets given to the patient is up to the physician to judge how clinically appropriate it is, considering what state the patient is in, what else they're taking, what other diseases they suffer from, their medical history, things that they responded to or didn't respond to. We provide the best molecular matching that considers and scores and filters all of these novel combinations. We filter out those combinations or individual drugs for which there are known toxic reasons not to give them. It can be due to the level of drug combination, toxicity, drug mechanism, combination toxicity, or it can be on the level of resistance. If some marker confers resistance to a certain drug, then no combinations with that drug will be considered. That doesn't mean that if there's no evidence of something being potentially harmful that any and all combinations are completely entirely safe.

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We don't have our algorithm trying to analyze toxicity risks; if there's evidence to not match a certain drug or combination, then we filter it out.
With this particular BRAF question, I spoke to Dr. Kurzrock. When a marker has drugs, then no matter what cancer it shows up in, we don't see any evidence not to target it. And as Sayad was saying as well, if you have a driver, and you don't target it, it's going to go on and drive, especially when others are being targeted. It's enhancing the chances of hyper-progression or that the cancer will stick to the only mechanism that allows it to thrive that hasn't yet been suppressed by drugs.
In the specific case where BRAF was upregulated, you drugged it, and it didn’t work for colon cancer, the reason is because you didn't take the other parts of the molecular picture into account. What we show is that if you have a marker and you can drug it, it should be almost medically negligible, to not at least consider drugging it.

Nik Schork: With these novel combinations and the kind of dose-finding exercise that one would have to go through, does CureMatch provide a recipe for how to do this? You could imagine not wanting to give someone drugs that aren't effective, but you have to start somewhere with these novel combinations in order not to create a toxic situation. On what basis would a physician based on your criteria decide when to ramp up or ramp down doses in these novel combinations?

Ally Perlina: I defer to Dr. Kurzrock and others with clinical expertise. They've used four drug combinations that were novel, starting at a lower dose. In our product we don't give any kind of a recipe because this gets into the doctoring space, which we try to stay out of. We do the molecular matching, and then we can say, there is a page in there that shows published examples with dosage strategies. Some of these examples have Dr. Kurzrock as a co-author. We don't go too far into saying, give your patient this and this, because that's making final recommendations.

Nik Schork: I was just thinking of someone who isn't as experienced as Rozelle Kurzrock in monitoring outcomes, but who's been giving advice through CureMatch to start out with these drugs. Without some recipe or understanding of how one could adjust the dosages, it just might get complicated, especially without a protocol that someone could follow.

Ally Perlina: The best way is provided in the references which are part of the report. It's about dosage combination strategies. We also offer report reviews. During a conversation we can refer to somebody's clinical experience, but we don't put it in the report. It doesn't mean that we leave people high and dry. We do provide guidance if we're asked.

John Laird: Our guidelines are consistently driving cancers to resistance and this is not being addressed with all of the resources that are available. I think Saed is raising some valuable points. Bringing in Dr. Gatenby is hugely important. He is saying that the science is clear and our oncologists are constantly telling people your cancers aren't cured or are incurable, And we're going to continue using this strategy that we know is not curative. We might give you

some increased months or a few years. We need to name it for what it is, and Dr. Gatenby has some great ideas.

Rick Stanton: I wanted to mention that Ally kindly offered to do an analysis on my data as well. The data from Brian that Ally used to come up with a CureMatch report for him was dependent on about three mutations and about five over-expressions. I got the same Tempus report, but my report only noted about three mutations. It did not note the five over-expressions, and Ally said that she can't work with such sparse input. It shows what CureMatch can do is dependent on the input, and it's inconsistent. I will try to fish out my data.

Ally Perlina: If there's one mutation, and you already know how to target it, you don't need CureMatch to go and score that. We can do it, but it won't be valuable, which is why I offered to look at your expression data. Let's see what the whole picture tells us. Maybe there are some biomarkers to put in and get some value out of a CureMatch report for your case.

Jeff Waldron: I've preached on this before, but I think that patients with advanced disease probably won't qualify for clinical trials. I know they're not part of the CureMatch engine, but I think expanded access programs (EAP) can give patients access at no cost to investigational therapies. You have to rely on your clinicians at academic medical centers to make the recommendation for a therapy, given that it is investigational and the trials are underway. But they're usually in stage two or stage three trials at that point, so the dosing is fairly established, and it’s just more efficacy that they're working on. I think it's something patients should consider. There's been a huge increase in EAP programs in the last 18 months, and the FDA and particularly oncology has the Reagan-Udall system that steers cancer patients to EAP therapies.

Saed Sayad: Upregulated and downregulated genes are very important. If we take care of the driver gene, the passenger genes are going to follow. The other aspect is whether what is upregulated or downregulated is offensive or defensive. If we see something upregulated it is because something bad is happening. Something is pushing these genes to be upregulated, and we need to downregulate it. Some of the co-occurring pathways that get instigated by certain cancers and drugs can involve growth factor receptors.
For instance, if there's any co-expression with EGFR then pembrolizumab and analogous checkpoint inhibitor-focusing drugs cannot be given without EGFR inhibitors. If you see a PDL1 marker or tumor mutation burden, and think you're going to give pembro, thereby addressing the marker, but if EGFR is upregulated, it needs to be addressed, even if it is secondary like a passenger, or if it's an outcome of something that happened earlier in the cancer evolution. If you give pembro without EGFR inhibition in these situations, then it leads to hyperprogression, which is really scary.
But what if our system is trying to upregulate our defense, then we cannot downregulate that. This is gonna add another dimension to the whole complexity of this interaction between genes and diseases.
I really like that flow chart presented by Rick in the last meeting.

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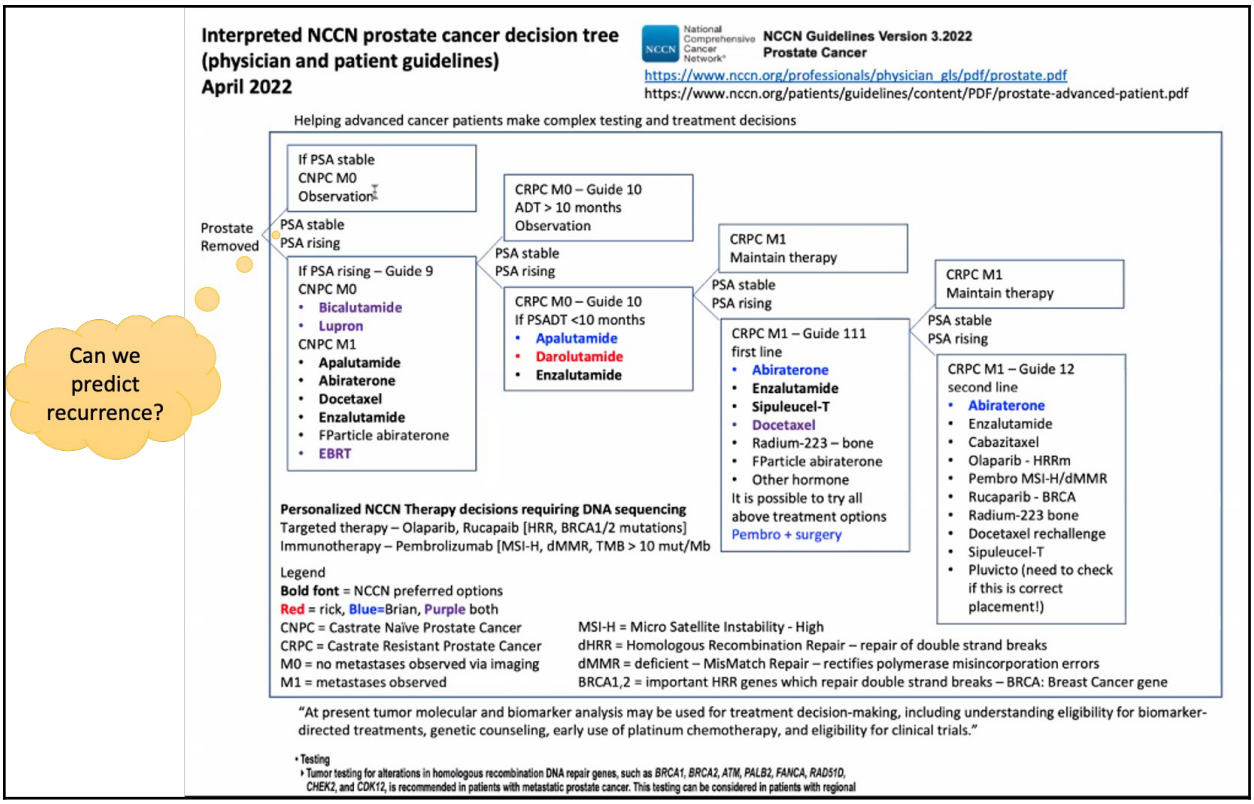
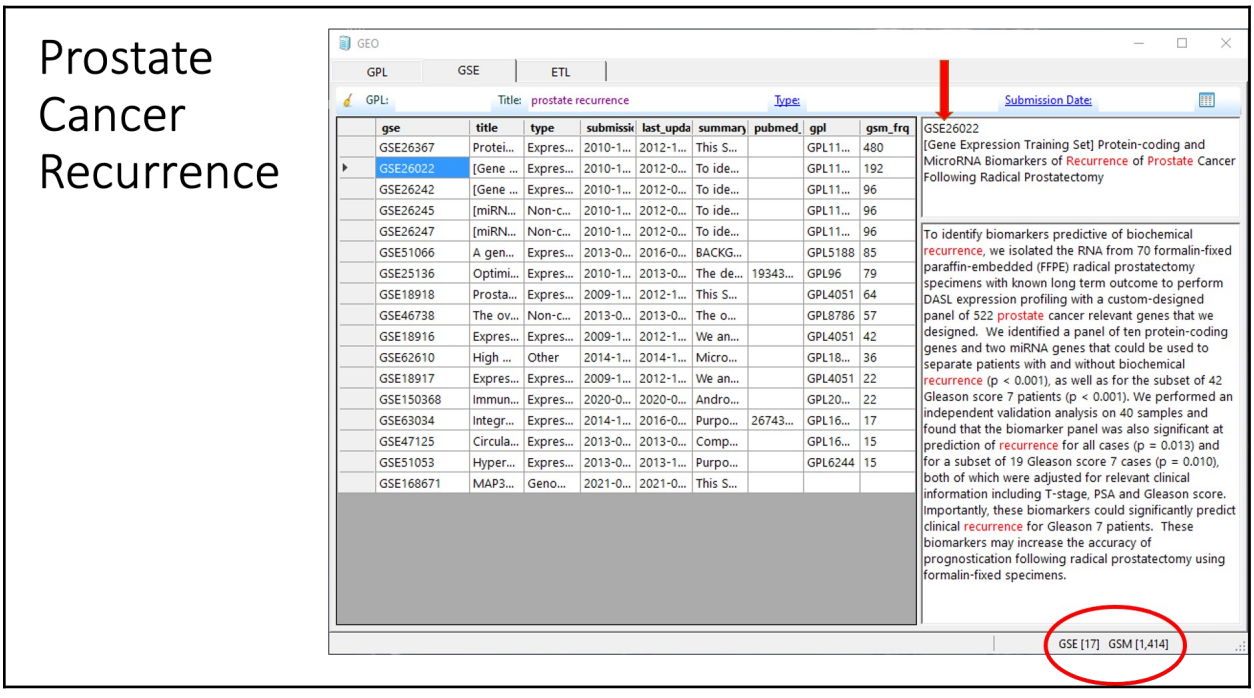


Hopefully we can make this chart dynamic and another layer after making it dynamic is moving from descriptive and exploration to prediction. For example, if we start with “Prostate Removed”, the first thing I asked was, “can we predict recurrence?”



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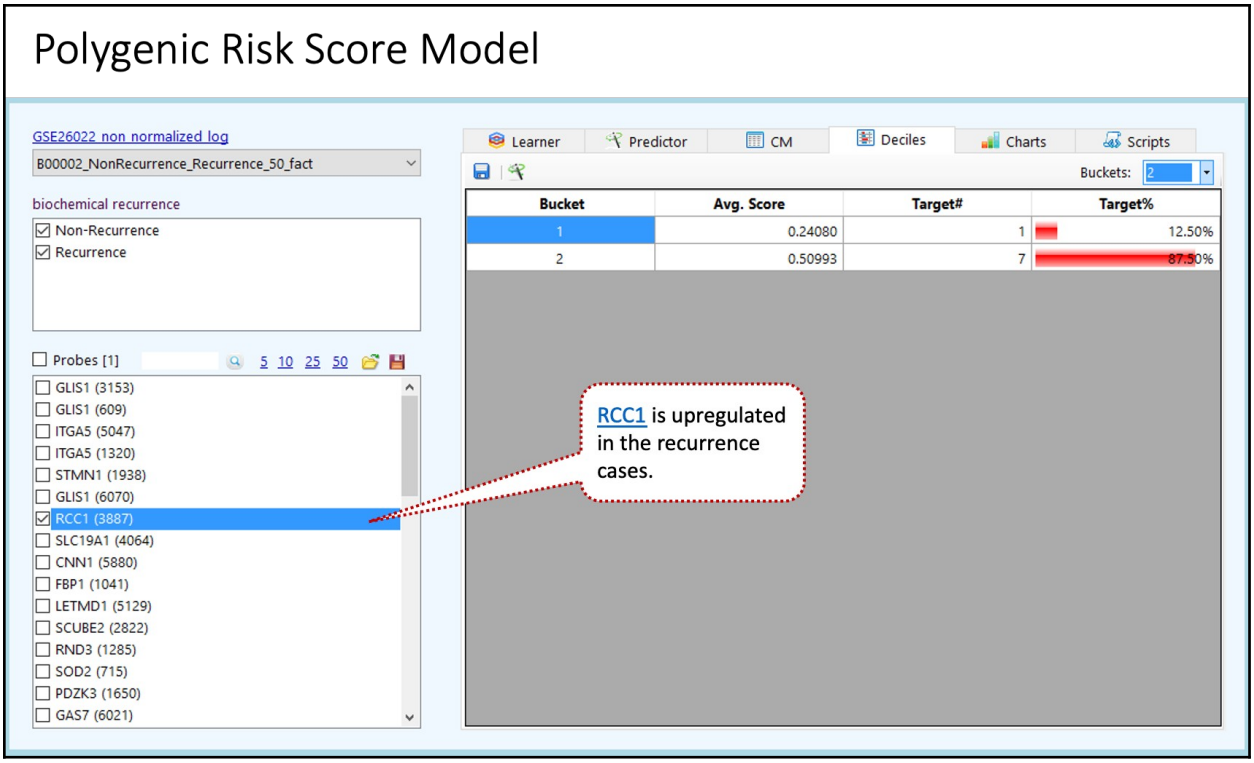
When somebody has had their prostate removed, we will want to know if we can predict recurrence because it's going to change the approach. This is going to be important. So we searched on the public domain data for “prostate” and “recurrence”, and found 17 public domain experiments. We chose one of them, GSE26022, which is related to the recurrence of prostate cancer following a radical prostatectomy.



And then we analyzed this data and we found only one gene, RCC1 (regulator of chromosome condensation 1), can be a very good predictor of recurrence. Now at this stage, we can pass this one to the clinical researcher.

Rick Stanton: What is this gene expression?

Saed Sayad: This RCC is amazing. It is operating the recurrence cases. When we searched on the internet we found many papers on the multifaceted roles of the RCC, one of which is in tumorigenesis (the transformation of normal cells into cancer cells). This is something to go after. Maybe this one can be a biomarker to predict recurrence. And that could completely change the way we are going to manage the patient.

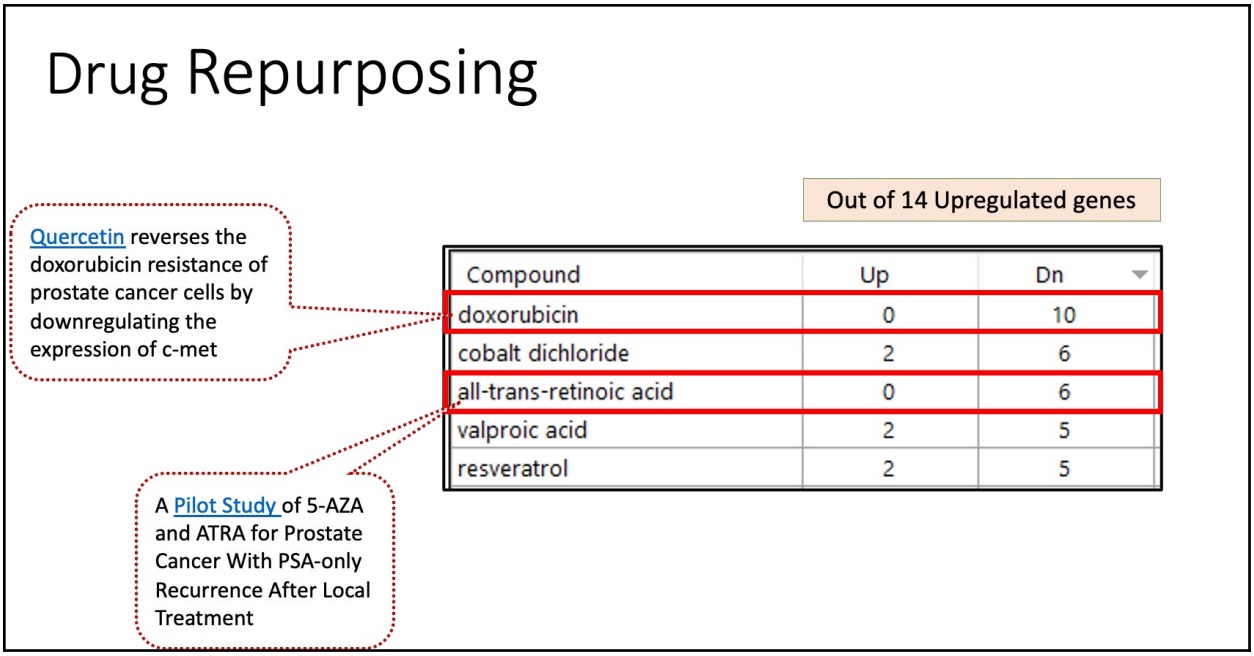
Rick Stanton: Why did this gene appear? Was it over-regulated? Was it upregulated? How was this determined? Was it in the transcripts?

Saed Sayad: That's an issue of having a single gene for a single patient, because you need to compare if this is more than normal. What is normal for one patient? We need to solve this issue. With two groups of patients, we can easily say, this is correlated with recurrence. How do

we know if this has been upregulated, for example, in your case? This is something we need to work on, but at least based on this experiment, we know this is a signal we have.

Emma Shtivelman: RCC is a marker of progression in more than just prostate cancer. It's involved in chromosome condensation, an important step in cell proliferation. I'm not sure that it's either targetable or useful.

Saed Sayad: We can use it as a biomarker for the probability of recurrence.



Saed Sayad: When we looked at the data, we saw that doxorubicin and ATRA (all-trans-retinoic acid) are going to downregulate in the 14 upregulated genes.

Emma Shtivelman: Those are cytotoxic or cytostatic agents. It depends on the circumstances. Of course they will downregulate RCC1, if cells stop dividing.

Saed Sayad: But how do you know this is specific? I can show you many other drugs which don't do that. The point here is this is just a hypothesis. If this is true for patients who are positive for the RCC1 biomarker, maybe after their surgery, they need to take this drug. Maybe that can affect the rate of recurrence. This is all a hypothesis.

Brad Power: I see in our conversation today the importance of the multidimensionality of the crowd that we've assembled here. Bob Gatenby said he wanted mathematical models and simulations that will in advance predict what's going to happen if I give this combination of drugs. We need CureMatch to suggest a combination of drugs. Then we need a dosing strategy, et cetera.

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The hypotheses that are underlying the strategies that clinicians are using are not explicit. Saed said this very directly, Bob Gatenby also said, and Dr. Laird pointed out the underlying strategy is to hit the cancer with a maximum tolerable dose until you get resistance. That's what they're doing. And yet nobody says it, and it's not in the NCCN guidelines.
We've identified this other layer, a strategy that sits on top of the NCCN guidelines. And that requires the sophistication of simulation models that Saed is talking about. Predictions, running experiments, and then figuring out what's working and what isn't. We've got a whole new frontier that's opened up based on the conversation we've had today, and reinforced with what we talked about with Bob Gatenby.

Saed Sayad: Having these flow charts is going to be a great help for the other patients because we can pinpoint where someone is and make it dynamic. For every decision, we can question why this branch, why that branch, and we can predict what will happen. We cannot just go for a description. We need to predict which path is a better path. And we need a prediction model.

Brad Power: We talked with Ryon Graf of Foundation Medicine yesterday about whether we could introduce our confidence level in those decisions. Where there's a fork in the road, and we recommend where you go, how much confidence do we have in that? How much can we predict effectiveness? And if we could do that, then the learning would be much more. You would have to track longitudinally what the results are and the outcomes.
Learning happens when you set up experiments and you predict results, and then you either get them or you don't. And so if you want to have a thorough learning system around progressing the state of the art, we need a lot more math and we need to lean a lot more on bioinformatics. It's going to get a lot more complicated too, because, for example, we were talking about dosing today. Brian kept asking questions about on-off cycling, and that's part of this too. And so each patient starts to look more and more like an N-of-one, and we're going to have to get comfortable with very N-of-one art, as opposed to following a regimented batch consistent approach.