“The Gut Microbiome and Cancer” (Michael Liss, MD, PhD) [#128]

Brad Power and Kayla Yup
January 22, 2025

“Hopefully I gave you a little bit of Gestalt on what's coming and how your microbes can interact with your immune system and how you can manipulate it with your diet and things like that that are coming. It's always a sensitive topic in that you have to be careful, especially with patients that are in the cancer journey, because it's a vulnerable time and you're looking for stuff. I want to make sure that I'm an advocate for you when you're looking at the microbiome and making sure we're not overselling something. Because this is a vulnerable spot, we need to make sure we're making good recommendations and doing good research to make sure that you are benefiting.” – Michael Liss, MD, PhD, MAS, MBA, FACS

Meeting Summary

Cancer is a complex disease that can be caused by a variety of factors, including: your genetics (e.g., gene mutations, such as BRCA1 and BRCA2); environmental factors (exposure to harmful substances in the environment, such as chemicals in tobacco smoke, ultraviolet rays from the sun, and asbestos); infections; lifestyle factors (being overweight or obese, not having a healthy diet, not getting enough physical activity, or drinking alcohol); hormones; and stress or a poor mental health state. Beyond the prevention of cancer, patients also have challenges with managing cancer symptoms, such as pain, depression and anxiety, fatigue and weakness, loss of appetite, weight changes, nausea and vomiting, constipation.

Both the prevention of cancer and the management of cancer symptoms can be influenced by your gut microbiome. Your microbiome regulates cancer initiation, progression, and responses to therapy. An altered microbiome has been tied to specific types of cancer and to the effectiveness of cancer treatments, suggesting that the profile of your microbiome could be a biomarker for your cancer diagnosis or prognosis.

According to research from the American Cancer Society, approximately 40% of cancer cases in the United States are linked to modifiable lifestyle factors, meaning they could potentially be prevented through lifestyle changes. Lifestyle choices, particularly diet and exercise, significantly impact the microbiome, which in turn can influence your development and progression of cancer.

Michael Liss, MD, PhD, is uniquely qualified to lead a discussion about the role of the microbiome in cancer, especially prostate cancer. He is a urologic oncologist (a doctor who specializes in diagnosing and treating cancers of the urinary tract and male reproductive organs), and has a PhD in translational science, with a focus on natural products and the microbiome. He has a masters degree in clinical trials and is a professor at UCSD.

What is the microbiome?

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The microbiome is the collection of microorganisms that live on or inside a person, animal, or plant. These microorganisms include bacteria, viruses, and fungi. The microbiome is dynamic and changes over time in response to environmental factors like diet, exercise, and medication.

How can the microbiome influence your development of cancer (for good or bad)?

The microbiome, particularly the gut microbiome, can significantly influence cancer development by either promoting tumor growth through inflammation and harmful metabolites produced by certain bacteria, or by suppressing tumor development through immune regulation and anti-tumorigenic metabolites produced by beneficial bacteria, essentially acting as a double-edged sword depending on the microbial composition and balance present; a disrupted microbiome is often linked to increased cancer risk.

Your microbiome can promote cancer through:

- **Inflammation**: Certain bacteria can trigger chronic inflammation in the gut lining, which can create a favorable environment for tumor development.
- **Toxins**: Some bacteria produce toxins and small molecules (metabolites) that are created when food, drugs, or chemicals are broken down that can directly damage DNA and promote cancer cell growth.
- **Immune modulation**: By influencing immune cell function, certain bacteria can suppress anti-tumor immune responses, allowing cancer cells to evade immune surveillance.

Your microbiome can fight cancer through:

- **Immune system support**: A balanced microbiome can stimulate the development and function of immune cells, which can help detect and destroy cancer cells.
- **Anticancer molecules**: Some bacteria produce compounds that can directly inhibit tumor cell growth and proliferation.
- **Barrier function**: A healthy microbiome can help maintain the integrity of the gut lining, preventing harmful substances from entering the bloodstream and promoting overall health.

What steps can you take to influence your microbiome?

- **Diet**: Try to eat 30 different types of vegetables per week: celery, green beans, spinach, etc. That is the easiest way to not only get all your vitamins, but increase the diversity of bacteria in your gut. You don't have to take any probiotics.
- **Prebiotics**: Prebiotics are non-digestible fibers that function as a food source for your gut bacteria. Some studies found that intake of non-digestible fibers was inversely associated with prostate cancer risk. To increase the count of prevotella, a favorable type of bacteria, in your gut, you can eat fermented foods.

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- **Probiotics**: Probiotics are live microorganisms that benefit the health of a host. Not all probiotics sold on the market are effective, so it is important to look out for a few factors when vetting products. Take note of CFU counts (the number of viable bacteria in a sample), the variety of bacteria included, and the ability of the bacteria to survive past the stomach acid (do they have delayed release capsules?) Some types of probiotics could be used to increase the count of Bifidobacterium.
- **Postbiotics**: Postbiotics are beneficial compounds produced by bacteria. It has been shown that Lactobacillus paracasei-derived postbiotics are capable of preserving the intestinal barrier integrity.

What’s next in microbiome research?

- Use the microbiome for personalized treatment and to manage side effects.
- Develop predictive models.
- Explore using vaccines to target specific microbes in the prostate
- Investigate the use of fecal transplants to boost immunotherapy response in prostate cancer
- Develop rationally designed microbial consortia for cancer treatment
- Continue research on the impact of the microbiome on treatment side effects, such as GI symptoms
- Conduct further studies on the use of probiotics and prebiotics to manipulate the gut microbiome for cancer outcomes

How can you learn more?

- Contact Dr. Liss at liss@health.ucsd.edu
- See other discussions that touch on the microbiome:
    - "Terrain and the Whole Person in Cancer Care” (Nasha Winters, ND, FABNO) [#95]
    - “Starving Cancer - Beyond the Metro Map” (Jane McLelland) [#113]
    - “Remote Monitoring and Deep Data” (Mike Snyder) [#52]
    - “Precision Medicine, AI, and Metabolic Interventions for Cancer Control" (Chris Gregg) [#53]

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Meeting Notes

KEYWORDS

Gut microbiome, prostate cancer, dietary changes, fecal transplant, immune system, microbiome diversity, B vitamins, inflammatory bowel disease, probiotics, natural supplements, cancer treatment, microbiome research, dietary recommendations, microbiome testing, cancer prevention.

SPEAKERS

Michael Liss (91%), Allen Morris (4%), Brad Power (3%), Robb Owen (3%)

CHAT CONTRIBUTORS

Allen Morris, Roger Royse, Alane Watkins, Rick Davis, Chad Magnussen, Cindy Ness, Vic Paglisotti, David Plunkett, Tom Binnings, Brad Power, Robb Owen

SUMMARY

Dr. Michael Liss from UC San Diego discussed the gut microbiome's impact on cancer, particularly prostate cancer. He explained the concepts of Alpha and Beta diversity in microbiomes and how dietary changes can influence bacterial mechanisms. Liss highlighted a 2017 study showing differences in gut microbiomes between cancer patients and healthy individuals, noting the role of B vitamins and dietary components. He also discussed potential therapeutic approaches like fecal transplants and probiotics, emphasizing the need for rigorous research and individualized treatment plans. Liss stressed the importance of a balanced diet, including 30 different vegetables weekly, to support gut health and overall well-being.

OUTLINE

Introductions

- Dr. Michael Liss is a professor at UCSD and director of clinical trials for the Center of Microbiome Innovation.
- He discussed the gut microbiome and its impact on cancer, particularly prostate cancer.

Overview of the Gut Microbiome

- Microbiome research started in the 1800s to examine gut bacteria.
- Biomes are a biological concept.
- Different environments (e.g., gut, skin) have different microbiomes.
- The microbiome has Alpha and Beta diversity.
- Microbiome samples are compared using different axes to identify similarities and differences.
- The Human Microbiome Project classifies different organ sites, including the prostate.
- There is a link between gut inflammation and prostate cancer, suggesting that gut bacteria may influence prostate health.

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Impact of Diet on Microbiome and Cancer

- Research shows differences in gut microbiomes between cancer patients and healthy individuals.
- B vitamins (folate and biotin) in the gut microbiome impact cancer risk.
- Dietary changes, such as reducing sugar and carbohydrates, can affect bacterial mechanisms in the gut.
- The microbiome can be a biosensor with the potential for developing prediction models for disease types.

Therapeutic Applications of Microbiome Research

- Vaccines and fecal transplants are potential treatments for cancer.
- Microbiome-based immunotherapy can enhance the body's immune response to cancer.
- Ongoing research has the potential for developing personalized microbiome-based treatments.

Challenges and Future Directions

- There are challenges of using fecal transplants and there is a need for rigorous safety measures.
- There is potential for using microbiome research to improve treatment outcomes and manage side effects.
- Approaches to microbiome research and treatment must be individualized.
- The future direction of microbiome research includes the development of predictive models and personalized treatments.
- Supplements need rigorous research to prove their effectiveness.
- Commercial microbiome tests face challenges.

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TRANSCRIPT

Brad Power
This is the Cancer Patient Lab.

We're honored today to have Michael Liss with us. Dr. Liss is at UC San Diego. He was referred to us by Cancer Patient Lab co-founder Brian McCloskey. He's going to be talking about the gut microbiome and how it impacts cancer, prostate cancer, specifically, but in general, for other cancers and what's at the cutting edge of the connection with the microbiome.

This is for information purposes only. This is not medical advice. We try to arm patients with information that they can take to their medical team.

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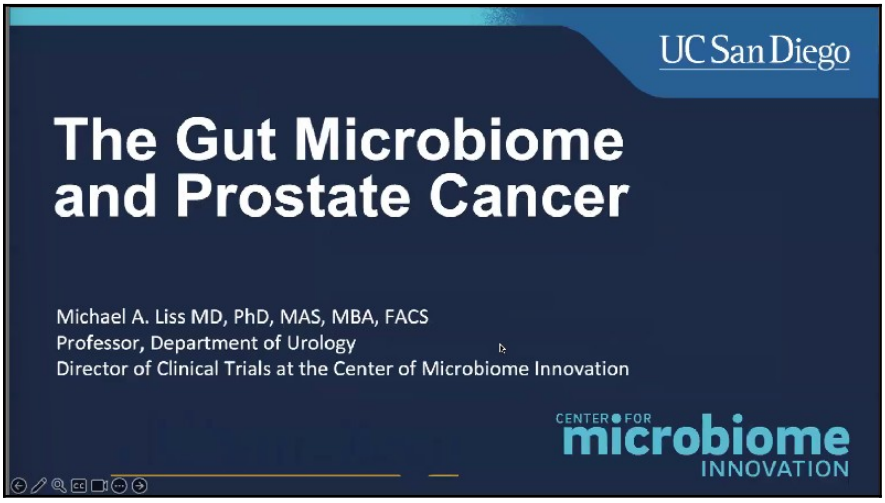

Michael Liss 1:16
I'll talk about the gut microbiome. You've probably heard a lot about this in the comings and goings and in the news.

I'm a professor at UCSD, and I'm the director of clinical trials for the center of microbiome innovation. I have a company focused on this particular topic, but I won't go into the very specifics until the end, when I'll make a couple comments about it.

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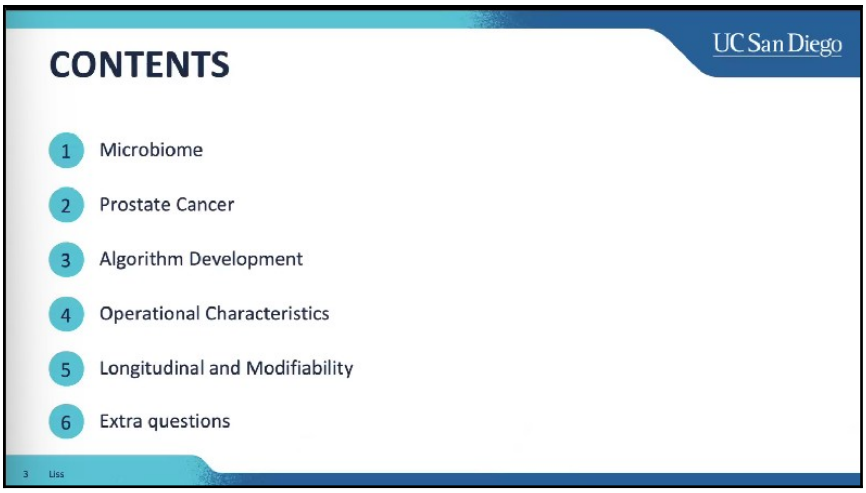

This is the agenda. [We’ll talk about] the microbiome, a little bit about prostate cancer algorithms, and how we may be able to use this information. And then we'll get into the questions.

This is how we think about microbes. This is a museum, actually, in Amsterdam. Of course, somebody like me would go to something like this. That's why it exists. It's called “Micropia.” It takes us all the way back to the 1800s when we start looking at bacteria. We had them out on these little plates. You had to have very specific plates to grow certain bacteria, and so we were a little bit limited.

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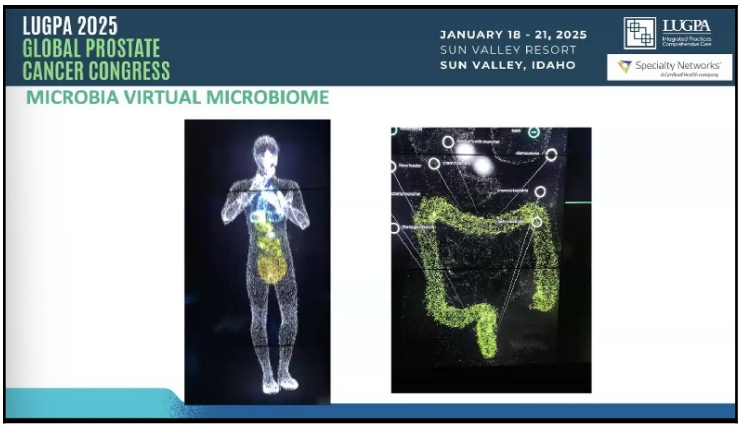

This is one of these virtual things you stand in front of and go, ‘Whoa, where's all the bacteria in your body?’ Well, most of it's in the gut. That's where a lot of the action happens. So a lot of these bacteria are there. And they're not all bad.

I usually show this slide because these particular birds clean the teeth of alligators, and they're not going to eat this bird, because it's basically its toothbrush, and it prevents disease and things like that. So we think something is maybe horrible when we see these names, right, but it actually may be beneficial. And I think that's where the microbiome (the community of microorganisms that exist in a particular environment) and all these microbes with fancy names get a little bit confusing when we start talking about them. Not all of them are bad.

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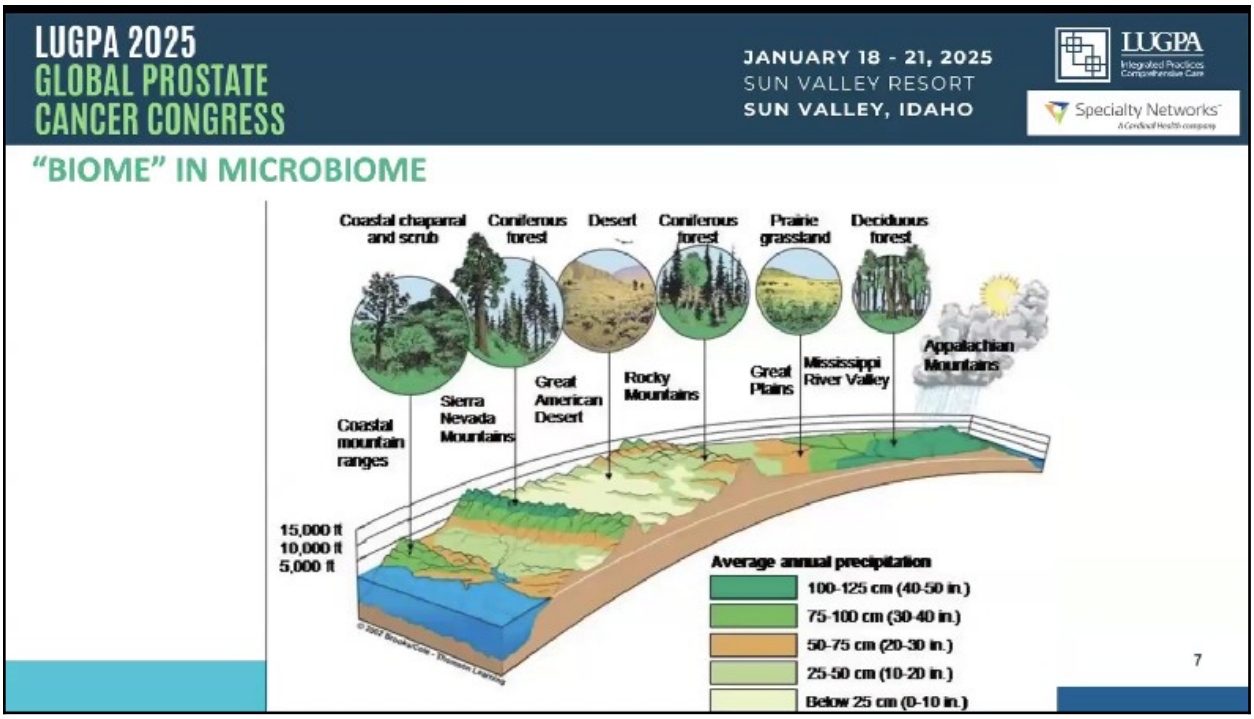

When we say biome, we have to go back to fourth grade biology. If you live in the Mississippi River Valley, you're going to have different bacteria or plants and things like that than you would if you're living on the mountain coast. This concept goes throughout our body, like what is in our colon is not the same as our skin, and we could use those differences now and we can start comparing diseases. Even within the Sierra Nevada Mountains, if I put in or take out a wolf, well, that changes the whole ecosystem. That's how we start thinking about the microbiome, is that it's not just one bacteria, they're all communicating.

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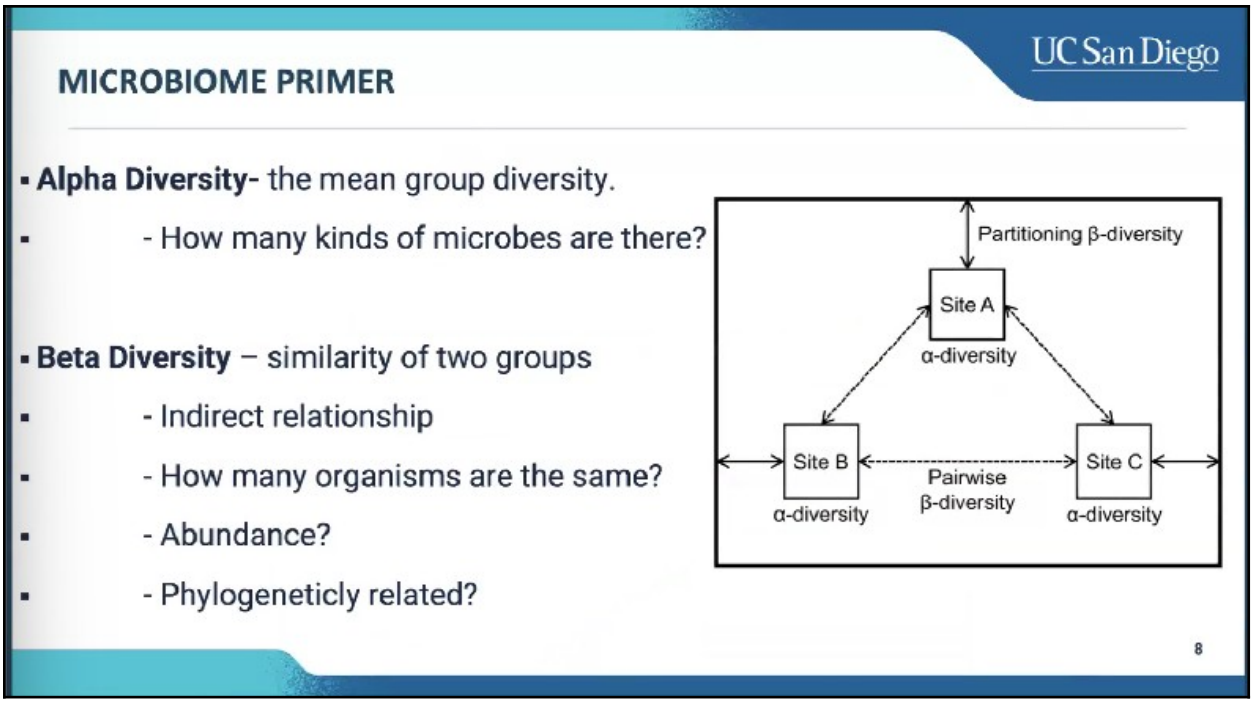
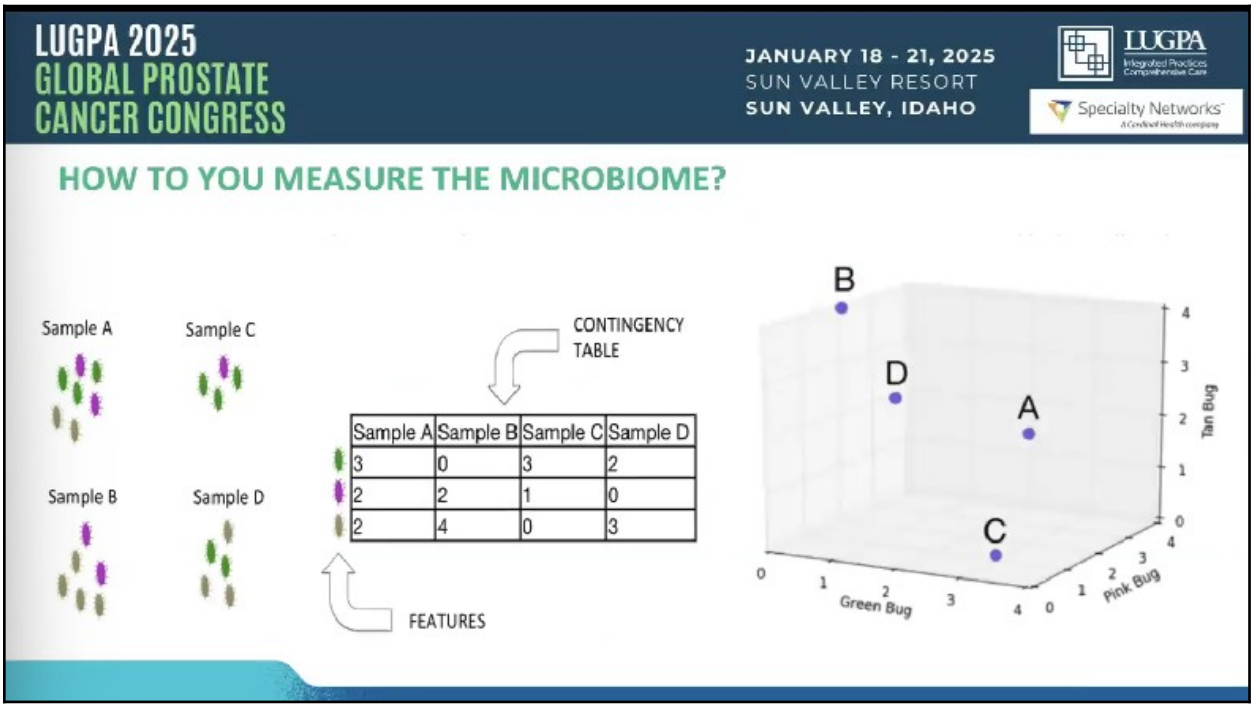


Here’s a little primer on, ‘well, what do we look at when we talk about the microbiome?’ A lot of it is diversity, or ‘how many.’ So there's alpha diversity, meaning ‘how many kinds of microbes are there?’ and beta diversity, which is, ‘what are the relationships with these particular bacteria.’



When you see some of the [research] papers come out, this is how we compare different things. If we have samples from different patients, and we want to compare them. Well, we take sample

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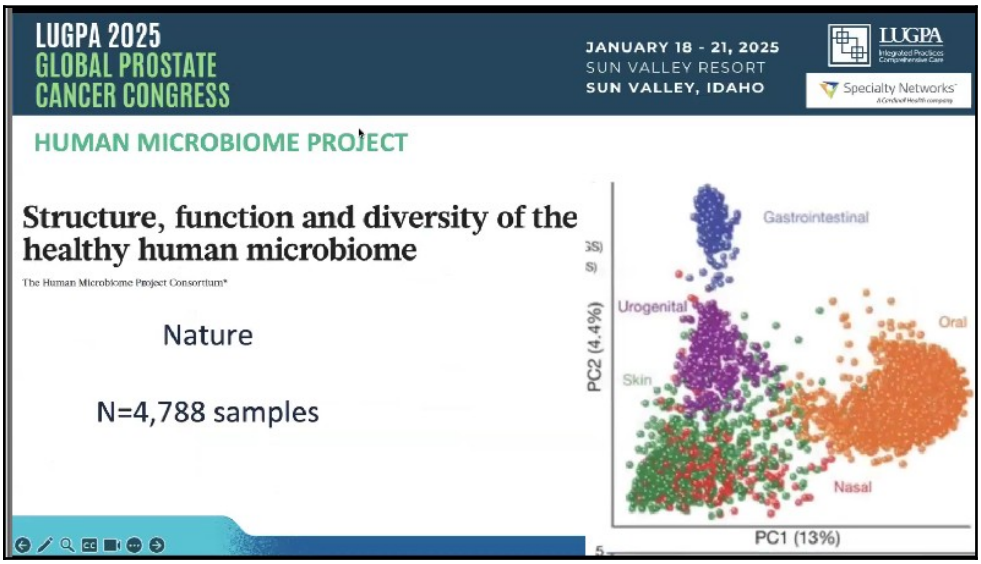
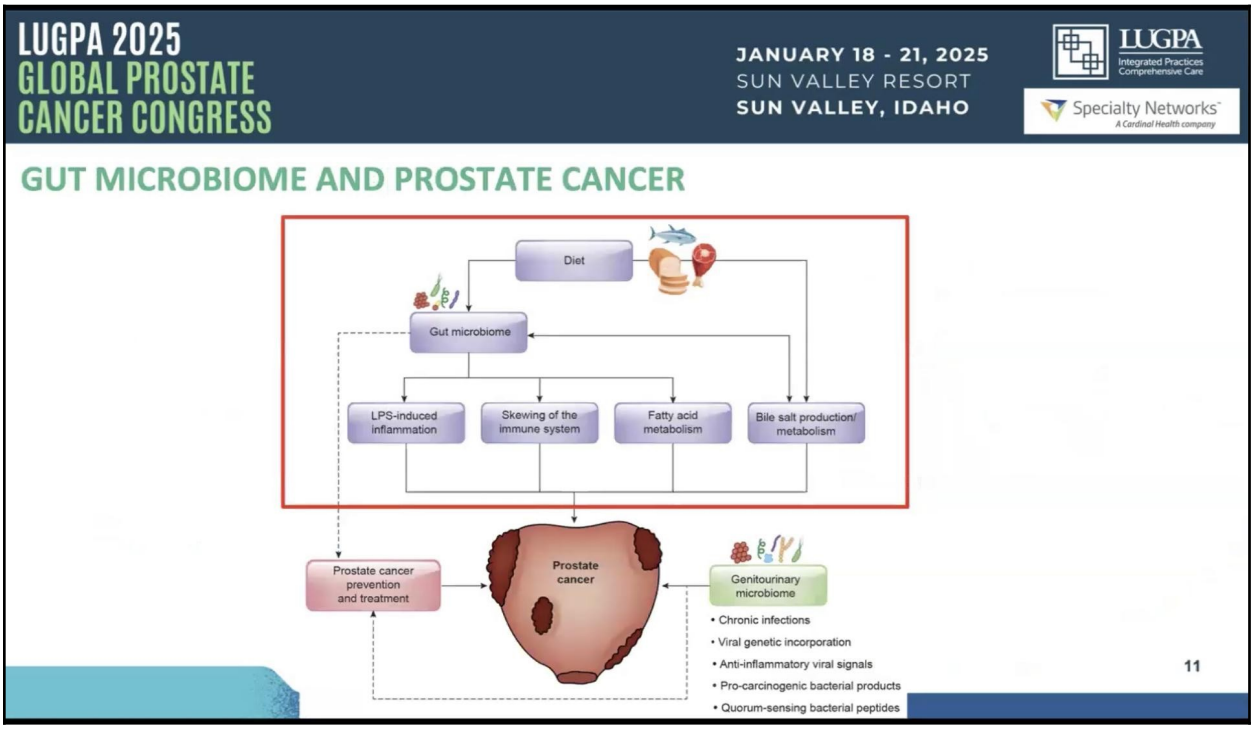
A, we count three greens, two purples and two browns. Okay, that's that. And we kind of set up a whole table like this, and now we set it on three different axes to see, okay, where, in three dimensions, does this person lie? And we can see that B and D are more closely related than B and A. And so that's how we can do these, some of these comparisons of different microbes.



This is the Human Microbiome Project. So this came out quite a while ago, using 4000 samples, and that's how we grouped different organ sites, essentially.



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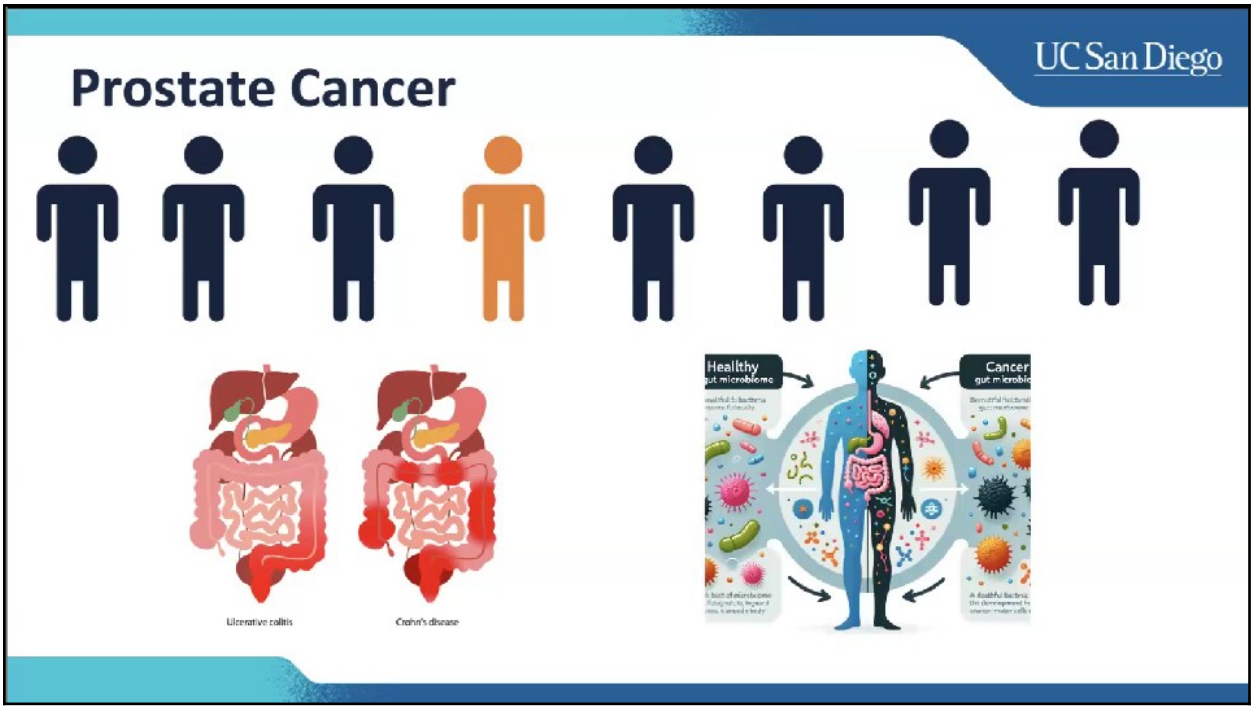
When we talk about the microbiome, there are different sites, right? So if we're talking about prostate cancer, at the very bottom of this slide, the very degenerative urinary microbiome that we can get from directly in the tissue or in the urine is very different from what we're talking about in the gut. So the gut can be manipulated by diet and things like that, whereas the urinary stuff may be manipulated in a different way.



When we moved to prostate cancer, we knew it's a very common disease, and when I first started thinking about this, I had a lot of microbiology background, and I was looking for a way to kind of marry these things, because I felt like they were related. And I started looking at inflammatory bowel disease, and there were some papers that had come out saying that there's this link between gut inflammation and prostate cancer. [I had been wondering] ‘how does bacteria in your gut somehow relate to a prostate?’ They're not connected. They're close to each other, but there's no connection between the colon and the prostate. And so this inflammatory aspect piqued my attention. And then basically, we said, okay, there's a healthy microbiome and a cancerous microbiome. Can this start impacting what we're looking at?

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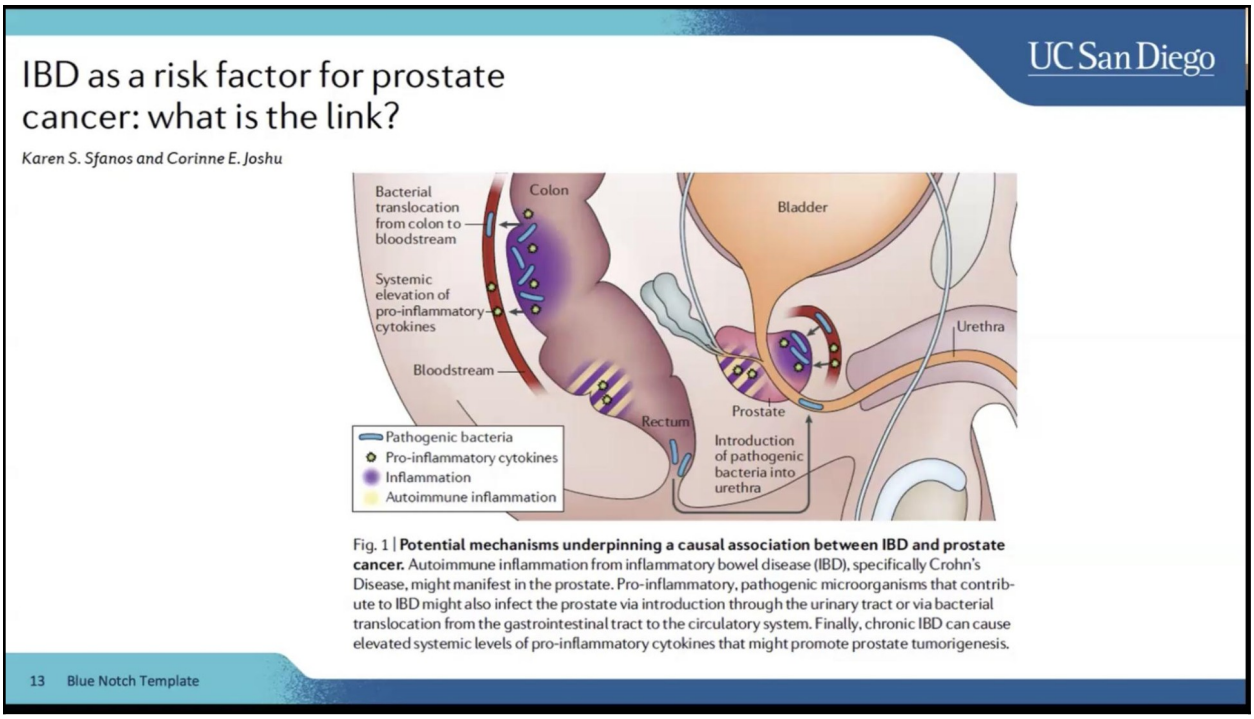

This is a diagram showing the colon, the prostate, and the bladder, and how we void out the urethra. There's different concepts of things going on here. So within the prostate, there can be various organisms. [Some questions about the microbiome here are] can they cause DNA damage? Can they make certain substances that are within the prostate? Or is it a chicken or the egg situation where a cancer can form and then maybe the microbes that can live in that environment are different than if there wasn't a cancer there. So can we use that as a biosensor?

The other aspect in the gut is, as we get older, men can have urinary tract infections or inflammation or something like that, and those bacteria usually communicate from the rectum over to the urethral urinary system. And so things that are in the colon can directly impact the prostate, but they also can make microbes and cause generic inflammation and things like that that we want to watch for.

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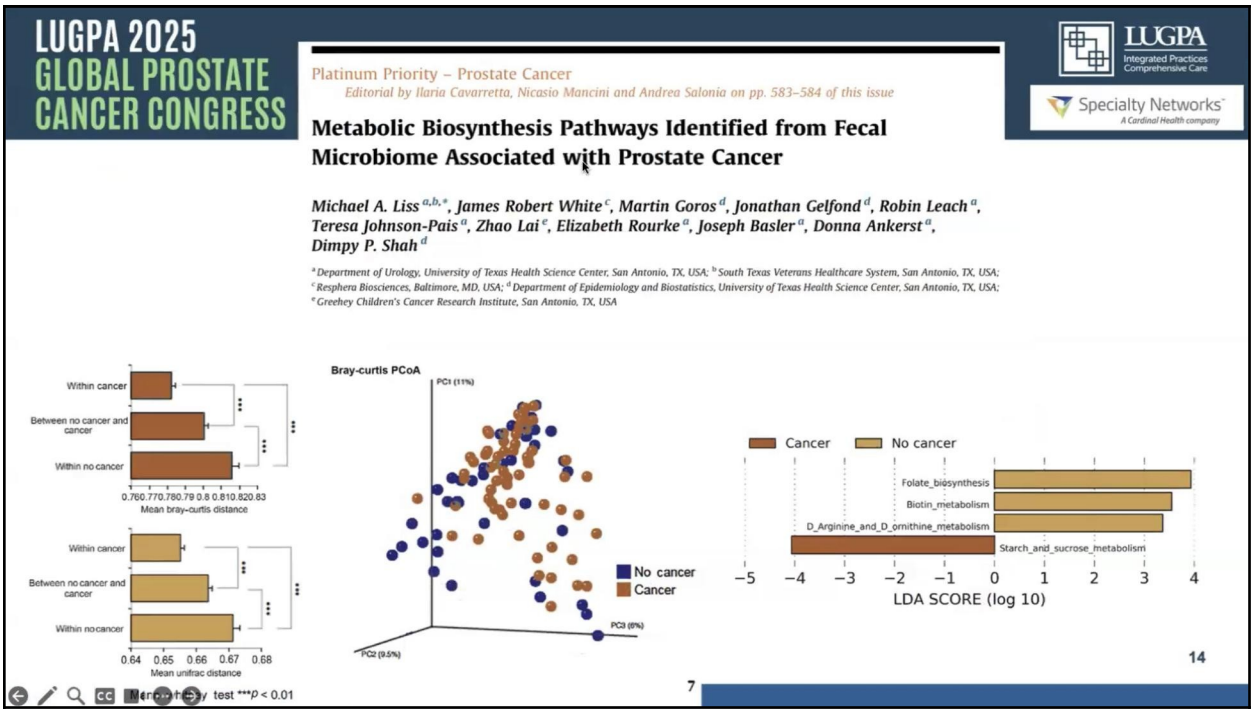

We first published on this topic back in 2017. I basically used patients that had cancer versus not, and I used their gut microbiome, and we showed that there were some differences. And if you kind of make a line diagonally through this, you can see a lot more orange on one side and more blue on the left side. And so that told us, ‘Okay, some of these patients are grouping around so they have similar bacteria.’ And then I looked at their function (what are these particular bacteria doing?) and we came up with B vitamins, which are folate and biotin. Now, [folate] is not something that you take. [It is] created through biosynthesis mechanisms. So the bacteria that actually make folate for you, we want to feed those types of bacteria. You don't necessarily want to take folate. You just want to feed the bacteria that can make it for you. And then biotin metabolism was ‘okay, do increase things that have biotin, not necessarily the pills themselves, but the dietary components, so the bacteria can break down the biotin themselves.’ And then what was more common on the cancer side were these starches and sucrose. So a lot of sugar, carbohydrates, common things that we think of. We don't have to eliminate [these] but maybe take a look at your diet and say, ‘well, okay, what are the sugary stuff I'm eating? How much carbs am I eating?’ You don’t have to make drastic changes, even small changes in diet can change these bacterial mechanisms.

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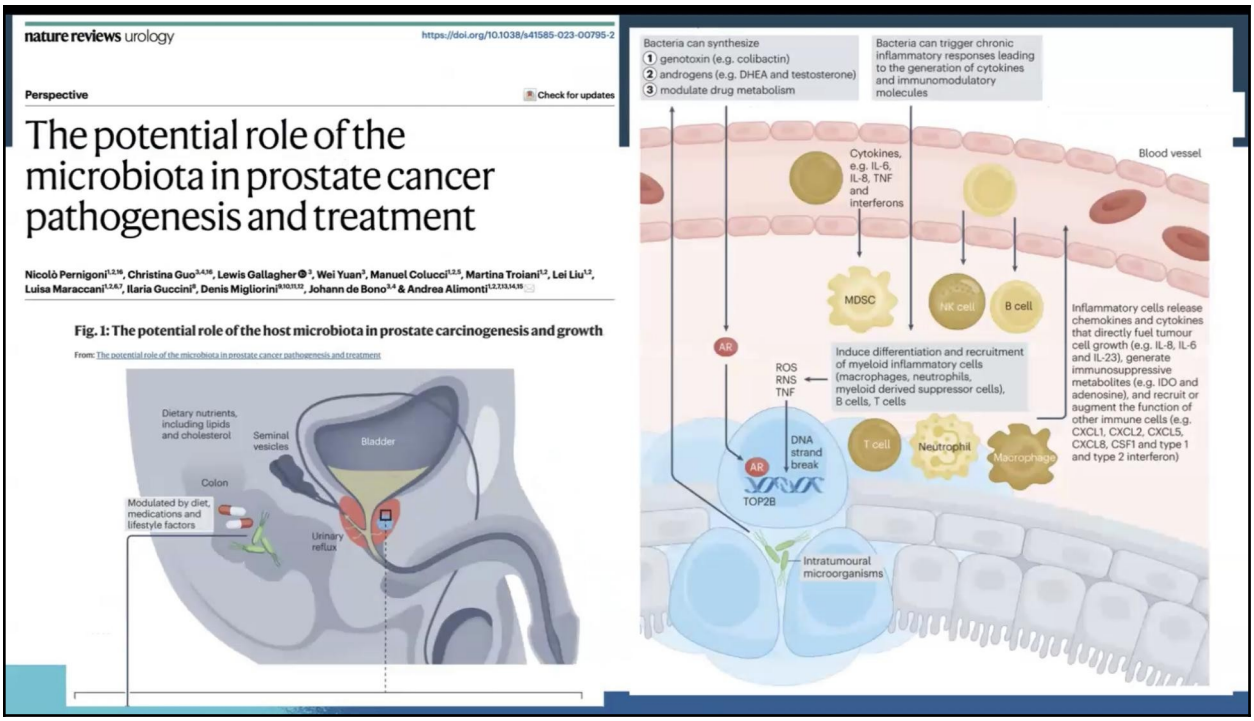

So [this is] kind of a similar concept that I showed on the last slide. What I wanted to say was, we're starting to understand, on the right here, the interaction with the immune system. So now what is the real function of all these bacteria in our gut? Well, it can do stuff for us. It can make vitamins, it can digest our food, but then it also has a function in that it goes into our antigen-presenting cells (note: Antigens are substances the body recognizes as foreign and mounts an immune response against. Antigen-presenting cells are immune cells that present these antigens to T cells, which are other cells of the immune system responsible for recognizing threats) that are in our colon. It takes these bacteria and shows it to our immune system and it trains it in a certain way. So we're just kind of touching the surface on ‘how exactly is this done, and can we manipulate that system to show it certain bacteria and train our immune system in certain ways?’ And so I think that's where a lot of this research currently is heading.

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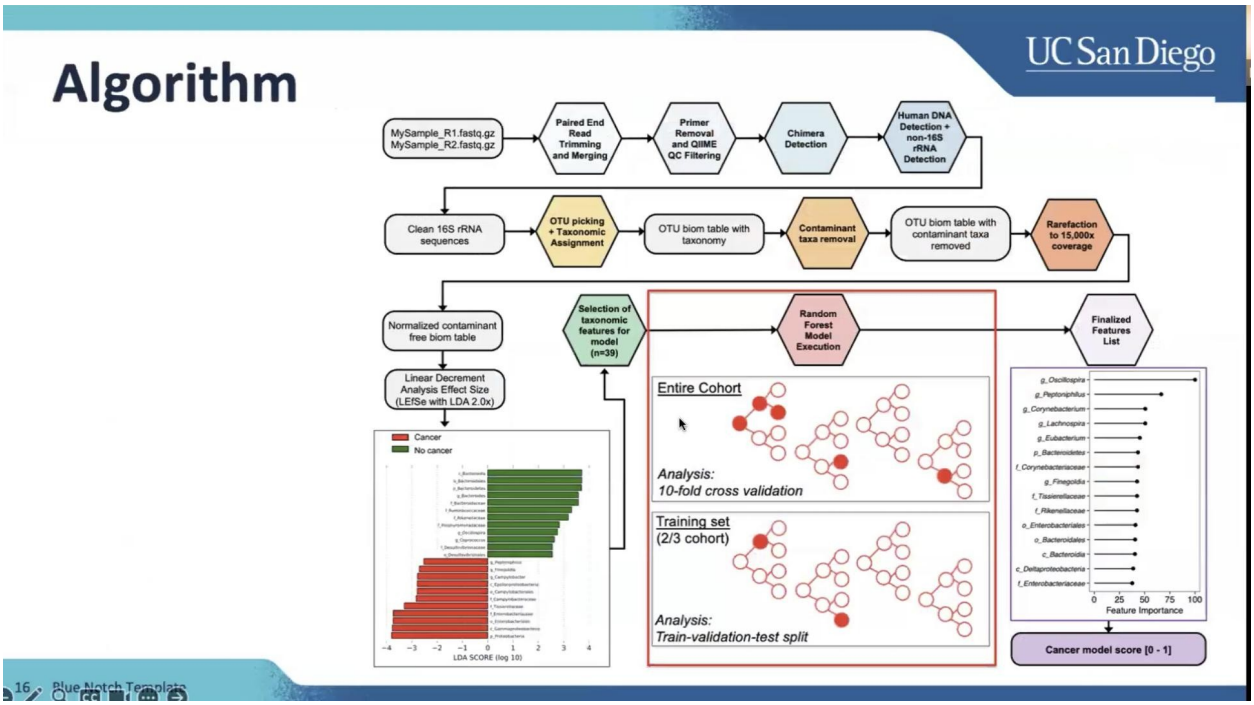


This is a complex thing, but what I wanted to show was that we can take this down all these different avenues. We take a bacteria and then we show what types of bacteria are there, and then we have to use all these different steps to select the certain bacteria that are there, to confirm which bacteria are present there, and remove contaminants. But then we can start using this pathway down here in the lower left. [In this pathway, the questions would be:] What are the bacteria that are good, what are the bacteria that are bad? And now, with AI, we can develop cohorts and say, ‘Okay, is this particular bacteria present or absent, yes or no? And two, is this bacteria abundant? What abundance level is it at? Is it 50% or is it 1%? And so all those yeses and nos can be put in an algorithm to start figuring out, on the right side, can we develop prediction models for disease types?

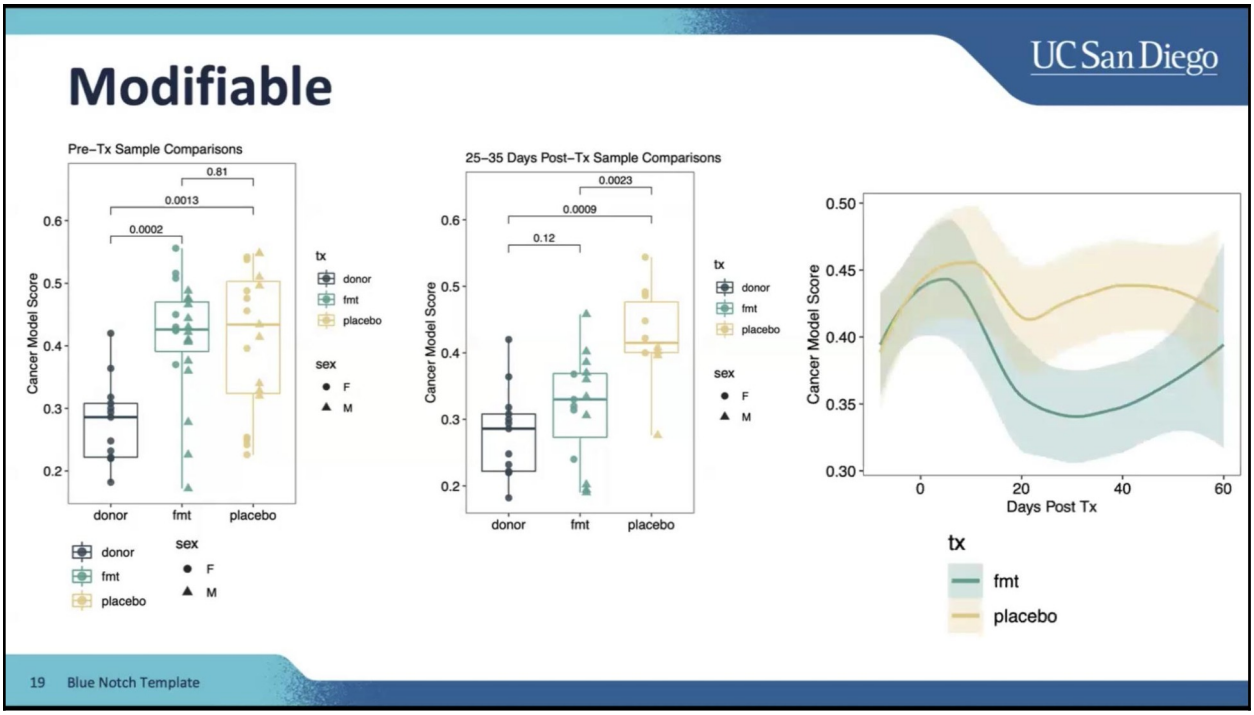
[Slide deleted because paper not published yet.]

This was the paper that isn't published yet, so hopefully nobody posts it. I know that a lot of the stuff is recorded. But I did want to show that we have some biologic gradients here showing cancer, and based on our scores over time, the likelihood or risk of cancer in the future can go up. So we can actually build biomarkers based on some of these bacterial groups.

[Slide deleted because paper not published yet.]

Over time, we compared predicted events versus probability, and the gray is like your usual clinical risk factors, and we want to be close to that. [To show that the microbiome could potentially be used to predict risk of cancer.] Just the microbiome alone can actually mimic what we can find clinically. Over time, these graphs on the bottom show that if you have a poorer

microbiome score, you may be at increased risk for certain cancers, and this is for prostate specifically.



But can we manipulate it? Could it be modifiable? This is a study of inflammatory bowel disease. The teal and yellow groups are people with inflammatory bowel disease, and they're going to get randomized to getting donor stool. So this donor will give to the teal group, and you can see over time that the teal group then lowered their cancer score. Just by changing their microbiome, you can actually manipulate these scores.

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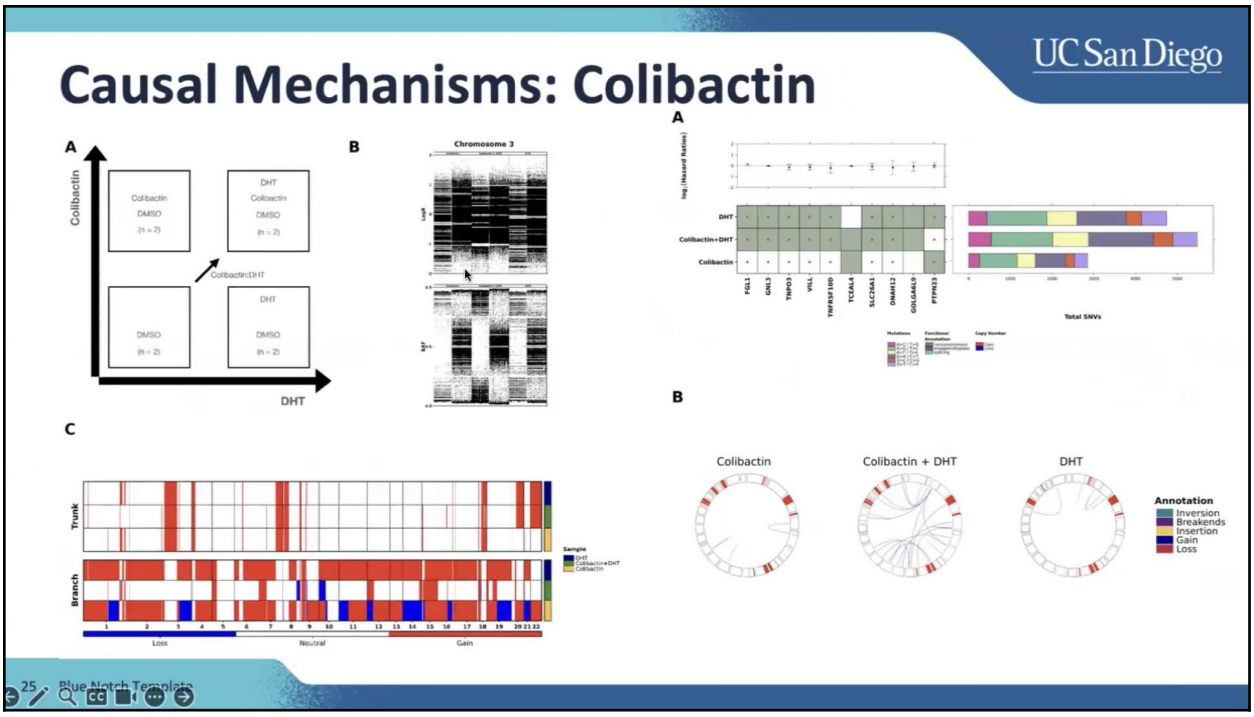
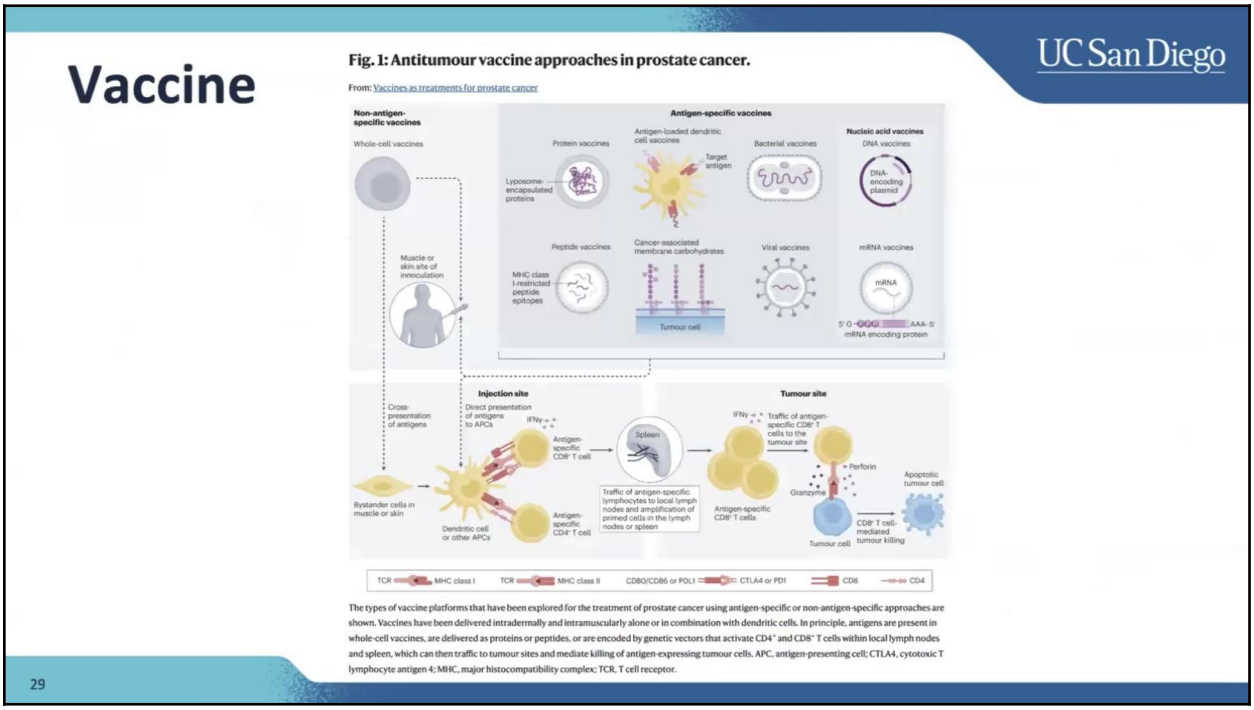


Here is how complex some of these things are. This is causal mechanisms with genotoxins (substances that can induce DNA damage). What we're showing here, at the bottom right, is that when we're using colibactin, which is a genotoxin, with hormones, and you combine the two, they can cause a lot of DNA damage. So these are types of bacteria that maybe we want to find and in the future research, try to get rid of these types.



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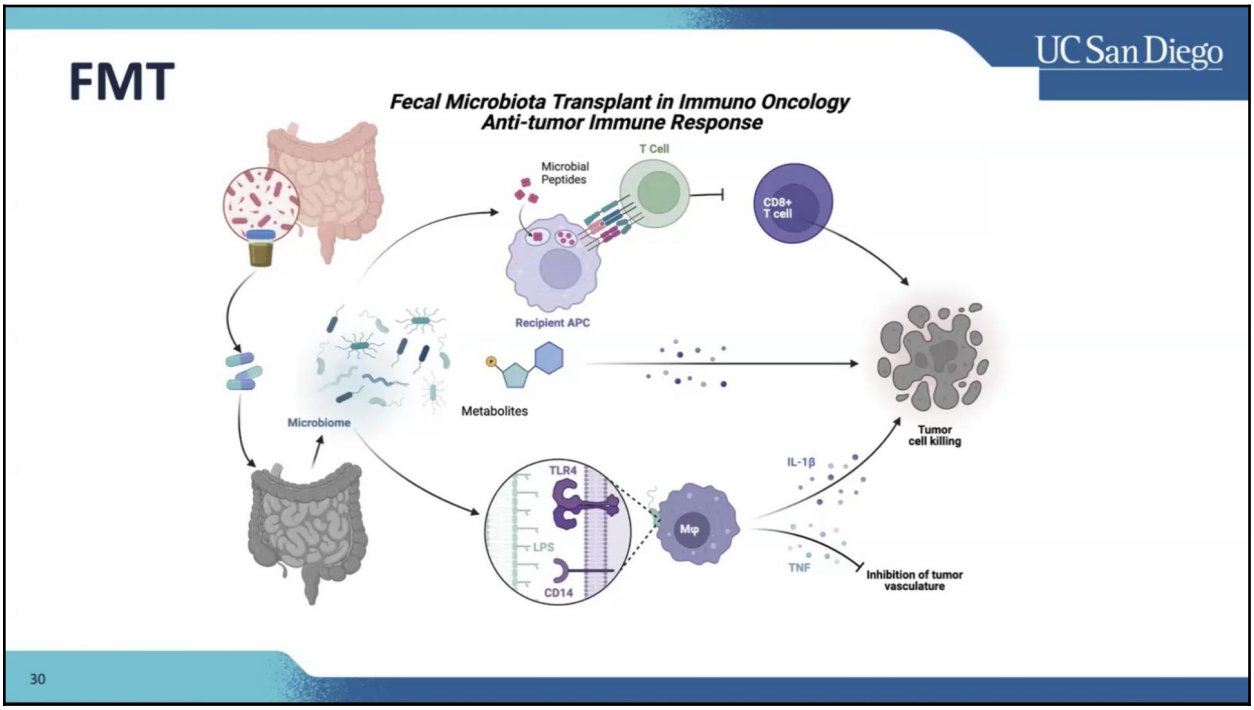
What are different ways we can use particular microbes? One, vaccines are coming out. And when I say microbiome, that could include viruses and other things like that. You can use vaccines to inject into the prostate or into a local site that could increase the body's awareness of certain peptides (short chains of amino acids) that are carried by microbes that can expose right to that immune system that we're talking about. That's one way that you can use the microbiome.



[Another method is] fecal transplant. This is a common question: can we start using fecal transplant? This is a donor—they collect their stool, they can make pills, and give it to a certain person with cancer. And then what happens there? The mechanism is what we're still trying to figure out. But there are some studies in immunotherapy, specifically for kidney cancer, lung cancer, melanoma, that have shown that if you do this, you can actually boost immunotherapy. One of my goals is to try and do that with prostate cancer, because it's considered a non-immunogenic tumor (tumors that do not trigger immune responses, may lack T-cell infiltration and instead have an immunosuppressive environment, and typically do not respond well to immunotherapy. Also known as ‘cold’ tumors. In contrast, ‘hot’ tumors are characterized by the presence of strong immune responses). Can we increase it into a hot tumor or an immunogenic system where now there's microbial peptides that are training our T cells in a certain way that then enhance that immunotherapy.

The top is the T cells and the bottom is the macrophages. These are all things that enhance tumor killing. There are also metabolites that those microbes can produce that can go into, potentially, therapeutic intent.

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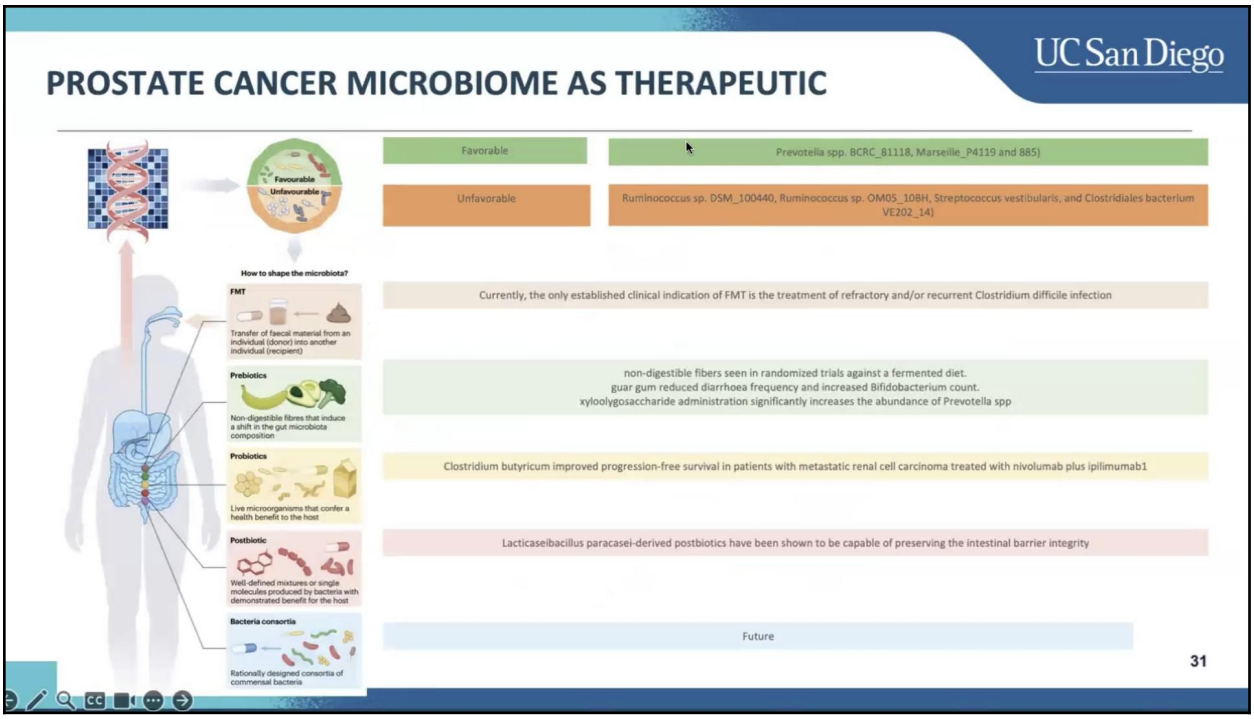


This is the future of microbiome as a therapeutic. Can we identify the favorable microbes and the unfavorable microbes? Some of these things I posted here are in published data about the types of bacteria. I said some of those names [of bacteria that] you can't produce, like Ruminococcus, but some are streptococcus, prevotella. And these aren't things that are, ‘oh, I can go grab a probiotic and take it and have these particularly grow’ per se, or ‘I can get rid of them with a certain antibiotic some way.’ So these are all being tested in various ways because taking antibiotics has its own issues.

As we look down here, what are the different things we can do to help our immune system? Fecal transplant (FMT) is one, but just like in the early days of when we say transplant, getting a kidney, or even blood transfusion, we have to figure out what is in that. There are parasites, there are viruses, there's COVID, there's HIV, there's multidrug-resistant organisms, and you're taking all these things and putting it in someone else.

There's a really great Netflix show that you can watch, called ‘Hack Your Health,’ about this particular topic.

There are other things that we don't fully understand about the microbes, because it can even impact mood, depression, obesity. Is long term FMT the answer? I say, “probably not”. We can rationally develop certain probiotics for treatment. That's the way things would probably go, just because the regulatory aspect of doing FMT is quite challenging.

For prebiotics, this is a great way to use our diet to enhance fibers and things like that to enhance those bacteria to grow the ones that we want. I put a little note in here about prevotella, that's the favorable one. So how do we increase that? You know, fermented foods.

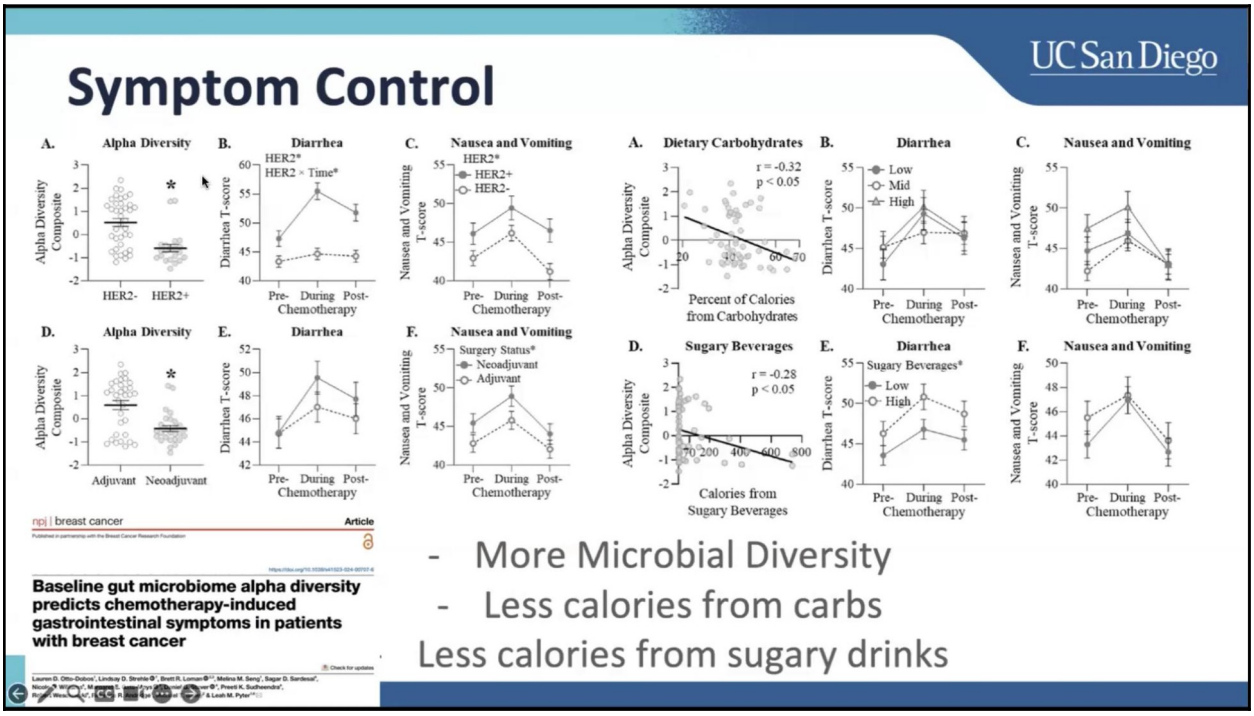
“The Gut Microbiome and Cancer” (Michael Liss, MD, PhD) [#128]

For increasing the count of Bifidobacterium, some types of probiotics can help. But when getting a pre- and then a post- you have to do something, you test it, you do something, and then you gotta retest it to know if it is actually working or not. I get a lot of phone calls [where people say] ‘Okay, which one should I take or not?’ And it really depends on where you're starting. You know, a farmer just doesn't go to the desert and lay down seeds. If you have a desert type of gut, well, we need to find cactuses and things that grow right in that particular environment, rather than trying to plant corn in an area. Or how do we transfer that gut from a desert to more fertile ground. So I think all these things are just starting to come out.

Probiotics are a pretty common one that I get asked about. And again, it depends on bacterial CFU counts (CFU stands for colony forming units and is a measure of the number of viable bacteria in a sample). It depends on how the pill was made. Does it get past your gastric acid or just, does it die there? And, you know, sometimes they can be costly, so [they are] things that we have to monitor, but I do think, one of those is an option.

Postbiotic means, can I just take what we are trying to get from those bacteria? A lot of times, it's like butyrate (a short-chain fatty acid generated from microbial fermentation of fiber) or different types of fatty acids. Can I just take that and then skip the whole bacterial side of things? And that is an option for some things, but again, it depends on how stable it is, and whether it gets absorbed in the system because your bacteria do a really good job at kind of accessing their metabolites to the bloodstream, rather than just taking it.

And then this last [section of the figure on the slide], bacterial consortium, kind of a rationally designed consortia. So, as we study different types of cancers, can we figure out which bacteria are more important and then just focus on those particular ones? So I think that's the future.



“The Gut Microbiome and Cancer” (Michael Liss, MD, PhD) [#128]

I threw this in here too because I get asked a lot about how the microbiome impacts symptom control. This study was done on breast cancer, and I know there's some survivors here. And so they were looking at alpha diversity, which we talked about, [and is a concept referring to] how many different bacteria are there. And then they used diarrhea and nausea and vomiting as gastrointestinal (GI) side effects. And so the people who had more diverse bacteria had less diarrhea in the second one and less nausea and vomiting, right? So, before we start a treatment, is there a way to diversify our bacteria? And same thing with the bottom one. Alpha diversity composite for neoadjuvant versus adjuvant, that's kind of how they broke it up. But pretty much, if you had a more diverse [composition], with different types of bacteria in your gut, you were kind of doing better on those GI symptoms. On the right side, we took dietary stuff — and remember way in the beginning of this talk, I talked about carbohydrates and sugars — same thing with GI side effects. If you're really high in carbohydrates and sugars, then you may have more GI side effects. And this was the paper in the lower left hand corner. So I think that is kind of a universal finding.

That was pretty much it from my standpoint. Hopefully I didn't go over too far, and I can go back to some of the slides, but hopefully it gives you an idea of what the microbiome is and how we're studying it. I wish there was more of a definitive ‘this is what you do,’ and I know that's what a lot of people are looking for, but I have to be very cautious about that because we don't really know. This is the beginning of this topic and how we can particularly use it. I'm happy to answer questions from people.

Michael Liss 22:45
[Question from the chat:] Over-the-counter probiotics frequently contain lactobacillus. --- Do you recommend over-the-counter probiotics?

I'm going to say this about natural supplements. I have a PhD in translational science, and I work on natural supplements, and I'm not against it by any means, but I think what the issue with the industry was is that if they're already selling it, then they don't have to do the research to prove anything's working, right? We have to design studies, which I'm doing, using natural products, probiotics, things like that, to test them before and after, to see ‘okay, if this person takes it, is there really a change?’ [When] trying over-the-counter probiotics, the things to look out for are the CFU counts, the different variety of bacteria that are in there, and then, if they make it past the stomach acid (do they have delayed release capsule?) That's super important. And then it's a bit of symptom control, right? Are we using it for prevention or progression? To reduce progression, I can't recommend anything like that.

[Question from the chat:] Clostridium study with double checkpoint inhibitor in met. renal cell carcinoma --- is that a phase 2 study re: improvement in progression free survival?

So that's the CBM, Clostridium butyricum. That's why I mentioned butyrate. That was a Phase II City of Hope trial using a probiotic. We're hoping more of those studies come but again, it is a phase two. So we gotta get that to phase three. That's being planned for in SWOG, which is our Southwest Oncology Group NCTN. I think that was approved to move ahead. I think we will be moving to a phase three study. I'm really interested in that particular probiotic.

[Question from the chat:] How about akkermansia?

There are pluses and minuses on akkermansia. It's universally thought to be okay for immunotherapy. An akkermansia probiotic is actually quite difficult to make, and the ones that are out there have different variations on a theme here. So we have to try to get what the exact akkermansia is, and then what level do you want. Some people have akkermansia levels that go really high when they have inflammation.

Why is that? Why is that elevated when I have inflammatory bowel disease, let’s say, but they're not benefiting necessarily from their immunotherapy? We have to learn a little bit more about akkermansia. I know people are jumping on it and companies are jumping on it, but I think the jury's still out a little bit. And when I was saying, AI, you know, it's not akkermansia by itself, it's interacting with something else, right? So, I don't think that there's going to be one probiotic with one thing in it [would be enough]. I mean, it was nice to see that Clostridium butyricum study, but I do think it's going to [have to] be a conglomerate.

[Question from the chat:] Is it true that probiotics are destroyed by acids in the stomach? Seed is a company that claims they have a work-around for this - as an example

Yes [it is true that probiotics can be destroyed by acids in the stomach]. Yes, I have looked at theirs [Seed’s], they have a double capsule probiotic. It is being studied. There is some pre/post data on seed, as well as VSL, which is the other probiotics. So those do get into the colon, which is nice to see, but you have to keep taking it. It will kind of go away within a week or two if

you stop taking it. And Seed is quite expensive, so not all of you know my patients can afford that per se. Now, just because the bacteria that is in the pill gets in the colon, is it having the intended effect that you want? If you're doing it for symptom control, you can definitely do that on your own. If you're trying to do it for something else, it's a lot more complicated. They have to be careful with the claims, right? They're never going to say curing something or doing something like that. So I think that's our issue with natural products, probiotics.

[Question from the chat:] How far are we commercially from taking a stool sample of a cancer patient then prescribing supplements/treatments to improve outcomes and tackle Tx side effects?

So I said I wasn't going to talk too much about that, but that's exactly what I'm trying to do with my company. So, not necessarily taking stool from patients (again, that's the fecal microbiota transplant), and a lot of the studies are in Europe because our FDA is very strict on what we can give. And the reason for that — it's not because there's like, an anti-government issue going on here and they're restricting some type of treatment — it's because when we did the C. difficile trials, and they did do FMT, the problem was that a couple people had got really sick, septic some people had passed away. And why was that? Because they got transferred a multidrug-resistant organism, and they got an infection in an immunocompromised person. So this is very sensitive stuff, and we were right to go, ‘okay, hey, we should treat this like you're getting an organ transplant or getting a blood transfusion. We need to make sure it's really, really safe.’ So I think as we go, I think starting with treatment side effects is a very reasonable one. Start in the beginning, allow you to take something and then test you again, and kind of see your progress over time. So that's where I'm starting as well. And then as far as improving outcomes, we would need to start learning, taking that data going ‘okay in six months, are you on to the next treatment, or are you in remission,’ right? And then that feeds back to the loop, okay, what bacteria were beneficial, which ones were not? So as we start teaching that system, then we can start learning, okay, these are the bacteria that are really controlling this particular treatment outcome, then we can start developing. So how far away are we? I think probably within the next three to four years, we could start developing trials on this particular thing. And so that's what I'm really focused on lately, is trying to get to that point.

[Question from the chat:] Your thoughts on Akkermansia as a probiotic supplement?

I talked about that one. As far as treatment outcomes, we don't quite know yet. A lot of the akkermansia data is case control, right? These people did well, and they seem to have akkermansia there. Do we know how that works? Nope. Do we know why that person did well? Well, maybe they were exercising and healthy and had a great diet beforehand, and they were bound to do well. In those case control studies where you're looking at benefits, people who did well and people who didn't do well, there's a lot of stuff in the background that you gotta account for, and we have to be careful, because these microbiome studies are not very big. If you're comparing 30 people to 30 people, you're going to find stuff that maybe is not true.

“The Gut Microbiome and Cancer” (Michael Liss, MD, PhD) [#128]

[Question from the chat:] Is there a correlation between frequent stomach issues and the microbiome?

Not necessarily stomach issues. So if you already have, you know, a GI issue going into a treatment — we know those who have IBD and or even GERD, if you have upper tract — if you're like getting esophageal cancer treatment, and you already have GERD, you already have Barrett’s esophagus, obviously, that's kind of a difference. So, each patient's a bit unique, and that's why I talked about the desert biome versus the rainforest biome. So if you're starting out with the desert, well, how do we move you into a different category first? And then we can start manipulating things. And everyone's starting at a different rung on that ladder. And so just taking stuff, to me, doesn't quite make a lot of sense. And there's a lot of companies out there that will definitely send you a gut microbiome thing. They also happen to sell a lot of the products that you can buy. And so those aren't quite tested for this particular situation. And so a lot of it is experimental, if you will, to see if these things help. But I do think that the pre/post testing would probably be important.

[Question from the chat:] What is your process for making recommendations for a patient? 1. What tests do you use to personalize a recommendation? It is important to match the recommendations to the particular microbiome and not just recommend generally. 2. Or are their general recommendations that can be made?

I'll start with general recommendations because those are the easiest, and that's usually what we all get. And, you know, I've had family members go through the cancer journey as well, and you get home and you're like, ‘Okay, what do I do? Like, I want to take some power here, you know, control my situation.’ And then you just get “diet and exercise.” You're like, well, like what diet? And some people go all the way from vegan to paleo to whatever. There's a lot of options. So I think that the thing here at UCSD we've been really focused on was the number of different vegetables you take per week. Okay, so we try to get to 30 different types of vegetables per week. Just make a list on your fridge, right, celery, green beans, salad, spinach, whatever. You just list 30 of them down that are completely different, and that is the easiest way to not only get all your vitamins, but increase your diversity of bacteria in your gut, and it doesn't have to be overwhelmingly a diet change. So that's where I think the easiest, that's what I recommend, basically, is that you don't have to take any probiotics, you don’t have to take any supplements. If you're just eating 30 different types of plants, you're automatically going to increase your plant intake, and plant-based diets are known to come on board here. But it's really hard for us to go, ‘Okay, if you like steak, or you have an alcoholic drink every once in a while, or whatever, are those completely bad’ — not necessarily. A lot of it also depends on what rung of the ladder you're on, right? If your microbiome is just needing a lot of help, you're going to have to be a little bit more strict on that than others.

[Question from the chat:] Is raw veggies better than cooked?
You can do it raw or cooked, it just depends. I think sometimes we leach a little bit out. They don't all have to be raw. But however you can eat them, it should be enjoyable, right? We have

to also live life, and we want to make sure that we're enjoying it, so doing really restrictive diets, I just don't think are helpful, because it changes our mood.

[Question from the chat:] Do all cancers benefit from bifido strains ?

We don't know about all of the different types of bifidobacteria. Some of them are beneficial. Bifidobacterium came up from infants, essentially, that's where it all kind of came from. So do infantile bacteria help us with cancer outcomes? Not necessarily. We do see trends that may help and some bifidobacteria actually help other bacteria grow, right? So I think that's probably the more important piece, is that it's not necessarily the Bifidobacterium doing something, but it is them interacting.

Robb Owen 35:42
With the work that I do with cancer coaching, we do something very, very similar to what you're working on now. I use AI to derive micronutrient deficiencies that may have initiated the DNA mutation of the cancers, and so we work backwards from that by developing a whole food, well balanced diet to help build the immune system, help with the gut microbiome, natural, prebiotic foods, probiotic foods, and then hydration, stress mitigation, physical activity. And what we've been seeing is, if we're able to work with a client at least three to four weeks prior to them starting their treatment, and be able to get the microbiome in a position where it's functioning properly, we're seeing similar results as what you're seeing, where they manage treatment better, no side effects from chemo, or less side effects and whatnot. It also allows us to target certain supplements and a very small range of supplements that directly work with the gut microbiome and the DNA. So based on that information, it correlates greatly to what you're doing, along with hydration as a key component to it. So, I would love to actually talk to you.

Michael Liss 37:13
We'll have a separate thing, but we do use — so we're on the same page — because we use basically dietary questionnaires. There are three components that I like to use. One is your diet. Your current diet, where are you at?
Second is your baseline microbiome,
and the third is your daily log.
As simple as ‘I had a good gut day’ or ‘I had a bad gut day, right?’ And if you're lining up a lot of bad days together, we're doing something wrong. And because everyone is so individual, and everybody wants these magic bullets, this is the thing that everybody should be doing. And when you do microbiome research, I can move you a little bit, [but] your microbiome is very resistant to change. And you have fluctuations throughout the year, right, in the summertime you’re eating more berries and whatever, and in the wintertime you’re eating more potatoes or something, so there's little variations in it, but over the long term, they stay pretty consistent. And I can tell one person varied from the other person, more than this group of cancer patients and this group of cancer patients. It's more aligned with yourself. So it’s harder to make big changes in that. That's how I think we have to go forward with this, is treating what we call the ‘N of one.’ That’s what the Cancer Patient Lab is doing, right? That's what you guys are doing, which is why I was excited to talk to this group.

Allen Morris 38:55
I believe you recommended 30 vegetables, and I take it, therefore — do you agree with this statement? — you say that if you eat 30 vegetables, you do not need supplements. Is that correct?

Michael Liss 39:21
Your gut is extremely good at taking out what it wants. And so a lot of times we're eating supplements that are really high in stuff that we don't need. I either say you're making very expensive poop, or we could be doing some harm there. Why don't I increase the vegetable intake [instead].

And somebody asked about fruits [a question in the chat asked, “Are fruits part of the 30 list?”] and not necessarily fruits, because fruits have a lot of sugar. So we can add fruits in there to flavor things and whatnot, but really it's the vegetables that are doing it. And so those different types of vegetables have zinc, they have these things in it. You still may need [supplements] — a lot of us have to take calcium supplements if you're on hormone therapy, a lot of us have to watch your iron if you have low iron, right? So, not all of it has to be from that. This is combined with your routine, right? You're going to be measuring these things. If you have low blood counts [and you’re] eating 30 vegetables, you still need iron, you know? So it's not going to replace this stuff, but I do think that [for] managing the symptoms and then later, hopefully getting to treatment outcomes, this is just an easy recommendation that people can follow.

I'm not telling you to completely change your whole diet, right? You just print out a list, you put it on the fridge, and you check it off during the week. It's like, instead of [thinking], ‘well, man, I got five left in the week, looks like we're having a big salad for dinner today, or something like that,’ instead of going, ‘alright, do I need the big prime rib,’ or something like that if that's what they like, you can still have those things, right? I think taking away things that people enjoy is actually harmful because they enjoy those things. The other part is, if your family history is from Norway and all those genes, all those 1000s of years, [your ancestors] ate a lot of fish, and now you go totally vegan, your particular microbiome may not agree well with that particular diet, right? Or if your family grew up in the Mediterranean and you go to an all meat diet, you're probably going to have horrible gut issues for that, right? So that's why I think establishing a base, measuring ‘what are we doing, and how do you feel’ baseline, will then help the future stuff. So, the recommendation was just merely to help out. Walking, that's the other thing I recommend. At least go for a mile walk if you do anything else. Okay, we can go up from there. You walk a mile a day and eat 30 different vegetables a week. You're doing more than what 90% of people are doing right now, and I know that it's going to help people. So how can I get people moved in that direction?

Allen Morris 42:33
Just one more time to drive it home. If you do 30 vegetables and you walk a mile a day — and some people believe there's mineral deficiencies, and you did talk about iron and of course, we can become iron deficient, we can become B12 and folate deficient, and if we're on hormones,

we may need calcium supplementation — but in general, for example, this population in the United States is not zinc deficient in general. Tell me if you agree with this statement: we're not deficient in zinc in general, but especially if we walk a mile a day and we do 30 vegetables, we do not need to do zinc supplementation. Is that correct?

Michael Liss 43:25
Like I said, it depends on your baseline. In general, maybe if you had a pretty well-balanced diet beforehand. But if you're on the tea-and-toast diet for years because you have a gut issue, you're going to have deficiencies and stuff. And so I think this isn't an all or none thing, right? It's [more like] ‘okay, [for] this particular patient, I have to be concerned about certain things.’ We're talking about microbiome, gut here, and what I responded to was, what is an easy way, what is a general recommendation I give my patients before I can get into the real specifics of a certain person. The general is that. That's our baseline. Can we get that stuff going? Then we go, ‘okay, you're micro deficient in this, you’re macro deficient in this, we need to shift these things over. And this is a whole team approach. And this happens over time. This is not a one time thing. I don't like to make those blanket statements because someone will prove me wrong, right, and I don't mind it, but we gotta work [at an] individual patient level, rather than just saying, ‘Yeah, you're never going to need to take a vitamin if you do that.’ That would be a not true statement. I know it's not maybe what people wanted to hear, but I think it's an individual aspect that depends on your baseline.

Allen Morris 44:56
The other question is, I talked to my GI doctor, and I asked him, ‘What has made it to prime time in the gut biome world?’ And he told me that fecal transplants for C. difficile colitis is the only thing that has made it to prime time in, not academic medical centers, in mainstream community hospital GI pathology practices. Is that correct? Or have other microbiome things made it to prime time? And what I mean by ‘made it to prime time’ is, have been entered into practice guidelines.

Michael Liss 45:50
That's correct, only C. diff, right? And if you've ever had C. diff, you'll do anything to stop the diarrhea, right? So, that makes sense, right? Those are the extreme messed up gut [cases], right? Can we improve that? Yes, again, we have to be super careful with these fecal transplant things. And so Europe has done some—and all these are phase one and phase two—we're seeing some signals [that] have not made it in. None of the actual things that you can test right now, if you're going to get off this Zoom and try to go order a kit, have really been shown to help. We are still in the midst of studying this. That's why I gave the general recommendations because we have data to show that plant-based diets and exercise help outcomes. We know that. What are the particular bacteria that are driving these things? That's what we're trying to research and then maximize those things. So we don't have that yet, but that's what people like me are really trying to focus and hone in on. And obviously, we've hit on a topic, right? I think we all say we want to have this particular diet, and then when rubber meets the road two weeks in, you're like, ‘Man, I can't do that.’ You end up going back to what you've been doing. Somebody asked about the portion sizes [a question in the chat asked “What is your portion

size each of 30 vegetables?”] and to me, whatever you can get of 30 different vegetables. If it's one celery, it's one celery. If you have three, awesome, right? I'm just trying to get you to think, okay, if I'm putting in my lunch for the day, what do I got in there? Okay, got carrots, celery and spinach, sweet. Got three checked off already. Awesome. [It’s] not the bacteria that are in there (they may not survive through), but it's the micronutrients and the prebiotics, right, the food for the different bacteria that go into your gut that are helpful.

Some are asking about Turkey trail mushrooms [a question in the chat asked “Has Turkey Tail Mushrooms been shown to improve the immune response?”]. We'll all have this one off. I had a patient say I ate grapes for 30 days straight, and my PSA went down. Okay, I don't know how I can transfer that to someone else. And maybe you're on the rung of the ladder where somehow grapes expanded a certain type of bacteria, and then you felt better and the PSA came down. But like I said, we have to test each one of these things. So mushrooms is one of the vegetables, great. It has a lot of different vitamins and mushrooms, depending on how you cook it. Try not to do too much butter, stuff like that. But there's definitely a lot of food as medicine stuff going on, research going on in that. We just have to be careful about saying this is the one thing right, because it may respond differently in different patients.

[Question from the chat:] How do you measure a good gut day?

I don't get to measure that. You get to measure that. And by the end of the day, if you're having bloating and diarrhea, that’s a bad day, right? If you had cramps, bad day. If you had normal you know, if you look at a Bristol Stool Chart, you can see if you're constipated or not. But usually, if you have a stool that's long and kind of gently curves into the toilet, that's a good bowel movement, right? [If we have] clumpy stuff, a lot of floating stuff, small balls that are hard, we know we gotta increase our water [intake], right? So that's what I mean. We gotta be measuring this over time, because you could eat something that worked amazing for somebody else. You know, I think one of my patients brought in a vegan pizza once. Well, if you're not used to a vegan diet, right, you're going to have some bloating and stuff like that. And to get you to change, you may have to go through a little uncomfort first to get to a good place. So that's what I'm saying. This is a longitudinal and directed patient specific plan that we need to get to for patients.

[Comment from the chat:] FDA Approves Turkey Tail Trial for Cancer Patients | Bastyr University

There's [a comment] about FDA approved Turkey Tail trial for cancer patients. Yeah, again, [these are] trials. This one's not in the US. Memorial Sloan Kettering is looking at that [too].

There are a lot of curcumin studies out there. There are a lot of different supplements. Like I said, I have a PhD, and that's what we did in drug development. How do we take natural products and move into drug development? Well, you need good manufacturing practice. They have to be held to the standards of the pharmaceuticals, and right now they are not. They just have to not contain bad stuff, essentially, and they have to be GRAS, which is “generally

recognized as safe”. There's a lower bar for natural products than when we're using for therapeutics. We just have to be careful that some of these things may or may not work for certain people. That's where I'm coming in going ‘Okay, let me test combinations of these things.’ I gave it to a randomized clinical trial, using Good Manufacturing Practice, using pill design, measuring blood levels (because a lot of this stuff you take and it gets metabolized really, really quickly, and it actually doesn't even get into your bloodstream.) Curcumin is one of those things. It just gets glucuronidated in the liver really, really fast. And so you can never get really high levels of blood curcumin levels. So you just can't do it. And so, that may be the same with different mushrooms and things like that. There may be a component of it that's driving it,, and, you know, more research is needed. And that's always a hated comment from patients who are going through cancer because people want stuff now, right? We want to get things going. And [we’re thinking], what can I do to help myself that may be being overlooked? And so I think that's what a lot of the microbiome industry hasn't really focused on yet, which is what I'm kind of taking on, basically.

[Question from the chat:] Do you have a blanket inventory of labs with which you to check patients for any deficiencies?

I work with heme/onc (blood cancers), or oncology. As a surgeon. I don't necessarily need to check a lot of those things, and most people aren't deficient in some of those. But I know Vitamin D is a pretty common one we check. I started checking folate levels, red blood cell folate, especially if it's a longer term measurement. Serum folate can be quite variable day to day, and depends on the diet that you're eating. Folate, in some instances, is good if you're really low, and if you're really, really high, that's not good either, right? So it's kind of this bell shaped curve where you kind of want to be in the middle with folate. And I have another talk I did, if you look that up, on folate and prostate cancer, I think it was in Grand Rounds in Urology (link here, scroll down to the lecture “Folic Acid Concerns and Men’s Health”).

I don't do blanket testing now, because I don't necessarily know of particular things that impact the outcomes, but it will matter, depending on what chemotherapy or what treatment you're doing. There are certain drugs that can chelate those particular nutrients or vitamins and things like that, so you can get deficient in certain treatments. So I think that is something that we need to cover. I know there are companies out there that check all this stuff, but when you bring it to us, it's kind of like, ‘well, okay, how do we necessarily fix that?’ How long are you on a vitamin to correct that for? It's kind of challenging. A lot of the stuff comes from vegetables, so that’s why I say a lot of these small changes that may look big on a piece of paper, [that make you think] ‘oh my god, I'm deficient in x’, if we just kind of increase our diet, sometimes those small variations can can go to green.

[Question from the chat:] Are there any commercial tests you recommend for measuring the flora in the gut?
There's a lot of competition. It's complicated. Some of it is like 23andme in the early days. When you can go check your ancestry, you kind of get this report that can show your diversity, it'll give your diversity scores and things like that. But I wouldn't necessarily endorse a particular one or

not, because none have been tested, necessarily, in particular in the cancer space. A lot of it is for generic health and well being so some of the ones that are out there have been focused on things like athletes, dietary things. There's Biome, Sun Genomics, and my company, Oncobiomics, but I haven't released my kit yet, only because I'm really focused on this particular cancer patient journey, not only forming biomarkers for prevention, right? Because we know that diet and lifestyle choices are about 30 to 40% of cancers. Okay, so why is no one working on that? Well, we did a bunch of prevention trials, we spent a lot of money, and they didn't work. I said, ‘Well, we did it on a population level. We didn't look at individual patients who are more likely to get cancer.’ Can we combine genetics and maybe microbiome and lifestyle changes together to do prevention studies? That's one arm. The other arm is to do this pre/post testing and kind of these different during or before treatment, preferably, kind of like what Rob is alluding to. You know, can we do assessment beforehand or at the time of problem. Companies that kind of say, ‘well, hey, we happen to also sell this probiotic, and this thing,’ we have to [consider], well, is it really tested to prove to increase that or not? So I kind of like it when they give you, ‘well, these are things that could increase these types of bacteria,’ and then let you kind of go search for things that may impact that, right? Because maybe you can't afford the monthly probiotic that they want to send you, and you don't really know if it's going to work or not. And then the last part is the kind of the daily management, or log, of managing over time to see, ‘okay, hey, I changed something, but it doesn't look like it's working. I need to pivot, maybe retest, and then try something new.’

So there is stuff out there. How useful is it? There's been a lot of complaints on the reports that are generated that are like, ‘well, they're a little confusing to understand, and what exactly am I supposed to do here with this information?’ So I'm always a little hesitant to recommend particular companies because I haven't seen that quite solved yet.

Brad Power 58:24
Do you have any closing thoughts you'd like to share with us? Any summary?

Michael Liss 58:33
This is a new aspect. Hopefully I gave you a little bit of Gestalt on what's coming and how your microbes can interact with your immune system and how you can manipulate it with your diet and things like that that are coming. It's always a sensitive topic in that you have to be careful, especially with patients that are in the cancer journey, because it's a vulnerable time and you're looking for stuff. I want to make sure that I'm an advocate for you when you're looking at the microbiome and making sure we're not overselling something. Because this is a vulnerable spot, we need to make sure we're making good recommendations and doing good research to make sure that you are benefiting.

“The Gut Microbiome and Cancer” (Michael Liss, MD, PhD) [#128]

CHAT DISCUSSION

00:32:03 Allen Morris: Over the counter probiotics frequently contain lactobacillus. --- Do you recommend over the counter probiotics?
00:33:16 Allen Morris: Clostridium study with double checkpoint inhibitor in met. renal cell carcinoma --- is that a phase 2 study re: improvement in progression free survival?
00:36:17 Roger Royse: How about akkermansia?
00:36:20 Alane Watkins: Question: Is it true that probiotics are destroyed by acids in the stomach? Seed is a company that claims they have a work-around for this - as an example
00:36:59 Rick Davis, AnCan Foundation: How far are we commercially from taking a stool sample of a cancer patient then prescribing supplements/treatments to improve outcomes and tackle Tx side effects?
00:37:14 Alane Watkins: Question: Your thoughts on Akkermansia as a probiotic supplement?
00:37:17 chad magnussen: Is there a correlation between frequent stomach issues and the microbiome?
00:39:52 Cindy Ness: What is your process for making recommendations for a patient? 1. What tests do you use to personalize a recommendation. So important to match the recommendations to the particular microbiome and not just recommend generally. 2. Or are their general recommendations that can be made?
00:40:57 Alane Watkins: Question: Do all cancers benefit from bifido strains ?
00:46:48 Roger Royse: Is raw veggies better than cooked?
00:47:48 Vic Paglisotti (he/him): Are fruits part of the 30 list?
00:47:57 Cindy Ness: What is your portion size each of 30 vegetables? Do you have a position on organic?
00:51:47 David Plunkett: I think that a better understanding of what makes it past the stomach is something I need to work on.
00:54:15 Tom Binnings: Has Turkey Tail Mushrooms been shown to improve the immune response?
00:55:20 Brad Power: How do you measure a good gut day?
00:55:29 Robb Owen: Dr. Liss, my email is robb.owen@hotmail.com. I would love to share the data we are collecting from our clients as we are approaching cancer from the same perspective, targeting diet to assist in correcting the gut microbiome to assist in making conventional treatment more effective and we are seeing very positive results.
00:55:48 Brad Power: How does the microbiome relate to immune system health?
00:56:18 Brad Power: Is the microbiome more important for some cancers over others, e.g., blood cancers?
00:56:47 Rick Davis, AnCan Foundation: FDA Approves Turkey Tail Trial for Cancer Patients | Bastyr University
00:56:54 Rick Davis, AnCan Foundation: Turkey Tail Coriolus versicolor | MSKCC
00:57:53 Cindy Ness: Do you have a blanket inventory of labs with which you to check patients for any deficiencies?
01:03:07 Alane Watkins: Are there any commercial tests you recommend for measuring the flora in the gut?

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01:11:44 Alane Watkins: Thank you - very helpful!