# “The Latest Tests for Personalized CancerCare” (Tony Magliocco) [#89]

Brad Power
March 20, 2024

*“We're in a revolution in medicine: the change from traditional medicine, where it was essentially surgery and chemotherapy, to a more focused approach to cancer and individualizing treatment, which gives us better results and fewer side effects.”* – Tony Magliocco

*“We've got a whole host of stuff that's in the experimental stage that would be interesting. We're looking at proteins in the blood instead of looking at nucleic acid, and so on, that may indicate things.”* – Tony Magliocco

*“Liquid biopsy is your friend… It is very important to keep track of what's happening in real time… A combination of radioimaging and liquid biopsy can be really important. But you need the newer technologies. The older ones can't do it. They're too crude.”* – Tony Magliocco

**Meeting Summary**

How can information from diagnostic tests help cancer patients, caregivers, and their doctors make personalized treatment decisions?

Advanced cancer patients, their caregivers, and their medical teams face difficult challenges in accessing and interpreting data from tests to build an integrated picture of an individual patient's disease and interpret the results for treatment decisions. These challenges include interpretation of new tests, treatment complexity, obsolescence of information, conflicts between test results, and integrating data from multiple tests. This becomes an even larger challenge/opportunity as more diagnostic tests become available, like RNA sequencing, liquid biopsies, proteomics, single cell analysis, and functional testing.

Tony Magliocco, MD, President and CEO at Protean BioDiagnostics Inc., is uniquely qualified to talk about these issues since he spans the boundaries between medical specialties – pathology, clinical care, molecular biology, and testing. He was trained as a medical doctor in Canada and spent 20 years as a surgical pathologist and implemented new technologies in hospitals. He was recruited to Moffitt Cancer Center to bring next generation sequencing and liquid biopsies to their labs. Building on this experience and a desire to make a difference in community cancer care (where 80% of patients are treated), he launched Protean Biodiagnostics, a "one stop shop" for testing. Protean's goal is to manage the patient's journey over their life with a focus on test data to deliver personalized medicine with advanced testing, data management, and software to make it easy to interact remotely. They also work with companies to bring new testing technologies to market.

***What is personalized cancer care?***

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“Precision medicine” is the population-based selection of targeted therapies based on a diagnostic test, e.g., you have an EGFR mutation, and there is an anti-EGFR drug.

“Personalized medicine” is taking a holistic view of you as a patient, including your wellness, preferences, and expectations. You put your test results together to make the right treatment path for you, including how to sequence and organize treatments if you have more than one treatment option, and decide how to manage your wellness with nutrition or complementary approaches.

***Why would you want to pursue more personalized cancer care?***

- Better outcomes
- Less toxicity, safer
- Avoid treatments that won’t work
- Better fit with your preferences
- Give you a feeling of agency

***What are the top ten challenges in accessing personalized cancer care?***

1. **Treatment complexity**: A few decades ago there were only one or two new treatments that became available every few years. But in the last year, there were over 100 approvals from the FDA, many of them targeted therapies that need companion diagnostics. How do you and your medical team decide what is the right therapy for you? How do you bridge between insights in molecular biology and your treatment decisions?
2. **Treatment obsolescence**: The treatment landscape can completely change every six months. Whatever you thought you knew was the best next treatment option for you can be wrong based on the latest evidence.
3. **Testing access**: Every cancer patient should get standard tests for their disease, e.g., an EGFR test for lung cancer, but many do not. Rapid growth of targeted treatments has created an explosion in demand for companion diagnostics. What tests should you get? How can you access all of the tests that are needed to point to your personalized treatments?
4. **Test interpretation**: Up to 30% of patients have an incorrect or incomplete diagnosis. Over 60% of oncologists say they have difficulty trying to understand what tests to use, and what the results mean. It is very confusing for anyone trying to keep up with this. Different test results may conflict. How do you interpret your test results? Does your doctor know what to do with all the possible test results, such as RNA sequencing and proteomics? What do you do if the tests seem to contradict each other? How do you bring together all of your test results into a comprehensive view of your disease and which treatments are best for you?
5. **Expense**: How do you pay for the additional tests and test integration?
6. **Information technology**: How do you take advantage of what new information technology makes possible?

7. **Doctor incentives:** Some oncologists are like fundamentalists in a religion: they read their Bible and say, “This is what the trial said,” and they can only treat it according to what the trial said. When they deviate from that, that's putting them at risk.
8. **Resources access**: Over 85% of patients are treated at community hospitals, which don’t have the resources of major academic research cancer centers.
9. **Fragmented care**: Different institutions don’t speak to each other, and often departments and individuals on your medical team don’t speak to each other.
10. **Clinical trials consideration and access**: Less than 5% of cancer patients are treated through a clinical trial, which usually provide access to the standard of care plus a new and better treatment option. Some people say, “I don't want to be an experimental animal.” The medical system is biased to favor the standard treatment. But the outcomes from clinical trials are better, even if you get the standard of care (the control arm) in a clinical trial. Should you consider clinical trials?

***What do you need to do to get personalized cancer care?***

1. **Test**: Get a wide and deep range of tests about your disease. For example, liquid biopsies are becoming more accurate and predictive and can be easily and inexpensively accessed.
2. **Tissue**: Manage your tissue so that there is adequate raw material available for tests.
3. **Multidisciplinary medical team:** You need multidisciplinary care: a surgeon, a radiation oncologist, a medical oncologist, a pathologist, a radiologist, and you may also need a social worker, a mental health specialist, and a pharmacist.
4. **Consult**: Get “second opinions” (reviews by experts) about what tests and treatments you should get.
5. **Engage**: Be the integrator of your care to overcome fragmentation. Use software agents and AI tools to interpret your data to uncover insights about your disease to share with your medical team.
6. **Integrate**: Look across all your test data to get a comprehensive view of your disease. Develop theories and models that integrate data across tests.
7. **Decision support**: Use software tools to match your profile with treatment options, including drugs, drug combinations, and clinical trials.
8. **Telemedicine**: Access services electronically wherever possible to take advantage of global resources.
9. **Data**: Gather all your medical and test data in one place for ease of access and sharing. You want to have a longitudinal view of your journey and capture and keep all test data along the way.
10. **Monitor**: As your disease evolves and medical practice evolves, you should continuously check to ensure you are getting the latest guidance. For example, new blood tests for circulating RNA and exosomes can monitor your disease progression (“minimum residual disease“) in very small amounts and help predict how to treat your cancer.

***How can you access a full range of tests to guide your personalized care?***

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Protean Biodiagnostics, BostonGene, and Tempus, among others, provide many diagnostic tests and test integration.

For example, you can work directly with Protean. They charge $400 to review your data, give an opinion on what testing might be needed to fill gaps, and pointers to treatment options. If there are any gaps, Protean can run additional tests. They will create an integrated report for you and your doctor. They can also monitor you through your journey. Because Tony is a licensed physician, he can prescribe and consult with your doctor, and advocate for tests and treatments. They can also run a “virtual tumor board” (review of your case by a group of experts). They lean into new tests. For example, they are the only lab doing a test using very new three-dimensional bulk DNA folding, and their single cell testing allows useful analysis on scarce tissue.

You can learn more about testing and personalized treatment guidance by watching Tony’s YouTube channel, “The Cancer Informant”, which you can see here.

***What does the future hold?***

The future of cancer care is not just treating your disease, but personalized wellness. How do you manage your health holistically?

Advances in imaging and liquid biopsies will allow you to visualize your cancer as it's going through its evolution almost in real time, so that you can manage your cancer as a chronic disease. If you see it escaping, you will be able to adjust your treatment and push it back.

***What can you do to accelerate the transition to more personalized cancer care?***

You can get early access today through Cancer Patient Lab to several tests in the experimental stage through special arrangements with test providers, such as mProbe, Travera, and Sage Medic.

You could also help create a formal cohort with a universal IRB (Institutional Review Board, a mechanism to protect patients) to coordinate testing, manage a biobank, and aggregate and manage our data. We would collectively evaluate new companies as they come along and decide if we want to use them as a group. You would have the option to volunteer to give urine, blood, or whatever. You would get the research grade test results back, and you would decide how to use the information. We could see what works, and promote the ones that are useful.

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**Meeting Notes**

## KEYWORDS

patient, liquid biopsy, oncologist, pathologist, cancer, tumor, work, treatment, happening, therapy, data, diagnostic, rna, pathology, neuro endocrine, doctor, clinical trials, disease, test, testing

## SPEAKERS

Tony Magliocco (72%), Brad Power (10%), Brian McCloskey (10%), Amit Gattani (7%), Allen Morris (1%), Roger Royce (1%), Paul Van Camp (<1%).

## OUTLINE

1. Integrating diverse perspectives for cancer patient care.
2. Precision oncology and its challenges in the healthcare system. (3:06)
3. Improving cancer care through telemedicine and AI-powered diagnostics. (7:10)
4. Personalized medicine, clinical trials, and business model. (11:35)
5. Personalized cancer treatment and genetic testing. (18:24)
6. Medical testing and interpretation with a pathologist. (22:38)
7. Personalized cancer treatment and multidisciplinary care. (26:25)
8. Conflicting cancer diagnoses and treatment options. (33:35)
9. Personalized cancer treatment and liquid biopsy. (36:13)
10. Liquid biopsies, CTCs, and RNA in cancer treatment. (41:37)
11. Cancer diagnosis and treatment using advanced genomics and AI. (46:02)
12. Liquid biopsy and personalized cancer treatment. (52:09)
13. Liquid biopsy companies and their capabilities. (57:41)
14. Genetic testing and cancer treatment. (1:03:39)

## SUMMARY

- **Integrating diverse perspectives for cancer patient care.**
    - Brad Power and Brian McCloskey introduce the Cancer Patient Lab, a platform for advanced cancer patients to access educational seminars, a community of patients and industry experts, and testing services.
    - Tony Magliocco, the guest speaker, is introduced as a person who can help integrate diverse perspectives on cancer treatment through whole exome sequencing, liquid biopsies, RNA sequencing, and proteomics.
- **Precision oncology and its challenges in the healthcare system.** 3:06
    - Tony Magliocco shares his expertise in molecular pathology and precision oncology, highlighting advancements and challenges in the field.
    - He warns of complexity in precision oncology due to numerous new treatments and lack of coordination in the healthcare system.
- **Improving cancer care through telemedicine and AI-powered diagnostics.** 7:10

    - Tony Magliocco highlights the challenges in cancer care, including difficulty understanding test results and incorrect diagnoses, e.g., the significant gap in EGFR testing for lung cancer patients.
    - His company, Protean Biodiagnostics, aims to address these gaps with a telemedicine-based system called MAPS, which includes oncology consultation, diagnostic decision support, and clinical trial matching.
    - He describes a comprehensive cancer management system that integrates multiple data sources, including tissue pathology and molecular testing, to provide personalized guidance for oncologists and patients.
    - The system uses advanced tools, such as CureMatch, to predict optimal therapeutic combinations based on molecular data, and provides a virtual tumor board for discussions among doctors and patients.
- **Personalized medicine, clinical trials, and business model.** 11:35
    - Tony Magliocco discusses the potential of precision medicine for stratifying clinical trials and personalized therapy, highlighting the use of liquid biopsies and ultra-rapid tests for faster diagnosis and treatment planning.
    - Brad Power raises the distinction between precision medicine and personalized medicine, inquiring about Tony Magliocco's approach to integrating both concepts in their work.
    - Tony Magliocco highlights the challenges of personalized medicine, including sequencing and combining treatments, and considering a patient's overall wellness.
    - He emphasizes the importance of a doctor-patient dialogue to determine the best treatment plan for each individual patient.
    - His company makes money by selling diagnostic testing services directly to patients.
- **Personalized cancer treatment and genetic testing.** 18:24
    - Tony Magliocco listens to patients' concerns and goals, then provides personalized advice on current services, research services, and non-conventional services.
    - He prioritizes evidence-based medicine, but also considers unproven and experimental therapies, providing an open and informed approach to patient care.
    - Amit Gattani asks how many patients Tony Magliocco has helped with their service, and Tony Magliocco mentions dealing with hundreds of patients, including a young man in Australia who was in hospice but was able to go into remission after testing and trial.
    - Tony Magliocco also shares another case in Australia where a patient had a KRAS test result that was not actionable, but Tony Magliocco identified a PK3 mutation and advised the doctor on what the result meant, helping the patient go on a trial without needing additional testing.
- **Medical testing and interpretation with a pathologist.** 22:38
    - Tony Magliocco is an experienced clinician who has lived on both sides of the medical field, providing personalized advice to patients based on his judgment and experience.
    - His company offers its own testing services, but also utilizes other labs for additional testing, prioritizing what's best for the patient.
    - He provides expert interpretation of glass slides and encourages patients to seek alternative opinions.
- **Personalized cancer treatment and multidisciplinary care.** 26:25

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    - Tony Magliocco explains how his company works with patients, offering personalized recommendations and tests based on their genetic data.
    - He becomes a patient's coach or advisor, providing opinion and guidance on interpreting test results and making decisions about their health.
    - Amit Gattani explains that oncologists are hesitant to trust his cancer diagnosis reports due to lack of understanding or discrepancies between tests.
    - Tony Magliocco acknowledges that building trust with a pathologist is crucial for accurate diagnosis and treatment, and they are willing to work with Amit to gain that trust.
    - Tony Magliocco emphasizes the importance of multidisciplinary care in cancer treatment, highlighting the need for a team of professionals from different fields to work together to provide the best possible care for patients.
    - His experience working in oncology has given them a unique perspective on the field, allowing them to understand the treatment choices available and advise oncologists on the best course of action for each patient.
- **Conflicting cancer diagnoses and treatment options.** 33:35
    - Brian McCloskey, an advanced prostate cancer patient, seeks advice on treatment decisions based on conflicting pathology and transcriptomics results.
- **Personalized cancer treatment and liquid biopsy.** 36:13
    - Brian McCloskey asks about the volume of data collected on a patient, and Tony Magliocco explains that cancer is a 4D disease that evolves over time, with driver mutations that drive its growth and change.
    - Tony Magliocco uses the metaphor of a tree to describe how cancer grows and evolves, and how treatment can lead to resistance and the need for balance in cancer therapy.
    - He discusses the importance of understanding the evolution of cancer, including the use of liquid biopsy to monitor changes in real-time.
    - He highlights the challenges of treating cancer as a chronic disease, including the need for forward-thinking oncologists who are comfortable deviating from trial protocols to provide personalized care.
- **Liquid biopsies, CTCs, and RNA in cancer treatment.** 41:37
    - Brian McCloskey discusses the importance of liquid biopsies in tracking cancer progression and resistance to treatment, highlighting the challenges of obtaining enough circulating tumor cells (CTCs) for analysis.
    - Tony Magliocco mentions the potential of exosomes and onco-zones as rich sources of membrane markers and RNA indicators, which could be used to track cancer progression and response to treatment.
    - He emphasizes the importance of newer technologies in liquid biopsy and imaging, as standard pathology is limited in its ability to provide accurate diagnoses.
- **Cancer diagnosis and treatment using advanced genomics and AI.** 46:02
    - Tony Magliocco discusses the challenges of analyzing cancer data, including integrating data from different sources and dealing with the complexity of single-cell analysis.
    - He also mentions the importance of considering the overall health and wellness of cancer patients, rather than just focusing on tumor response.
    - Tony Magliocco: "We have telemedicine, video conferences, virtual tumor boards, and we do our own liquid biopsy labs."
- **Liquid biopsy and personalized cancer treatment.** 52:09

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    - Tony Magliocco has a large network of experts in various cancer types, including lung, breast, and sarcoma, and is willing to connect patients with the right specialist for their specific needs.
    - He discusses the limitations of liquid biopsy in detecting resistance to anti-androgen therapy in prostate cancer, but highlights new methods that can look at RNA for deeper profiling.
    - He mentions using Guardant 360 and Tempus for more comprehensive profiling, and offers to discuss offline for personalized insights.
- **Liquid biopsy companies and their capabilities.** 57:41
    - Tony Magliocco mentions several liquid biopsy companies, including the Genomic Testing Cooperative, which evaluates over 1500 RNA in liquid biopsies, and Angle Parsortix, which can harvest living cells from blood for further analysis.
    - He emphasizes the importance of balancing the strength of data with novel approaches, and taking into consideration the patient's hunch or intuition when making decisions.
    - He expresses interest in early access to novel diagnostic tests and suggests creating a cohort for data collection and management.
    - He mentions several experimental technologies, including protein analysis in blood, and offers to work with the group on early access studies under an IRB.
- **Genetic testing and cancer treatment.** 1:03:39
    - Tony Magliocco emphasizes the importance of differentiating between germ cell and somatic mutations for treatment decisions, as they carry different types of information and may impact future health risks for the individual and their children.
    - Genetic counseling is recommended to help individuals understand their results and manage their health, as genetic testing can provide valuable information about the presence of mutations and their potential impact.
    - Tony Magliocco favors Natera for minimal residual disease monitoring due to its high specificity and data support.
    - Other companies like Grail, LabCorp, and Neo Genomics are also developing similar tests, but Tony Magliocco is cautious about their sensitivity and specificity issues.

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## Meeting Transcript

Brad Power
This is the Cancer Patient Lab.

Our standard disclaimers: this is not medical advice, and everything will be made public.

Brian McCloskey 0:56
The Cancer Patient Lab is designed for advanced cancer patients, to give them access to educational seminars, like what we're about ready to do, and to get access to our community, where there are a range of patients and industry experts that can provide advice. The third thing that we offer is access to testing services, whether it's DNA testing, transcriptomics, functional testing, etc. What I would encourage you to do, if you haven't done it already, is to go to this link: community.cancerpatientlab.org, where you can register with us. We're in the process of redesigning our collaboration platform, which is at the link. You'll see different areas where you can ask questions and get answers from the community.

Brad Power 1:58
A quick introduction to Tony, before we get started. It was Brian who raised the question, “We're big advocates of getting lots of tests – whole exome sequencing, liquid biopsies, spatial phenotyping, RNA sequencing, proteomics – How do you pull all this together and integrate these diverse perspectives?” I always think of it as like the blind men and the elephant, who are touching different parts of that elephant, and they're trying to figure out, what is this thing? What is this disease? How should I guide my treatment? Several people, including Marty Tenenbaum, and I think Glenn Sabin, recommended Tony as a person who's been working in this space of pulling things together, so you get an integrated view of your disease.

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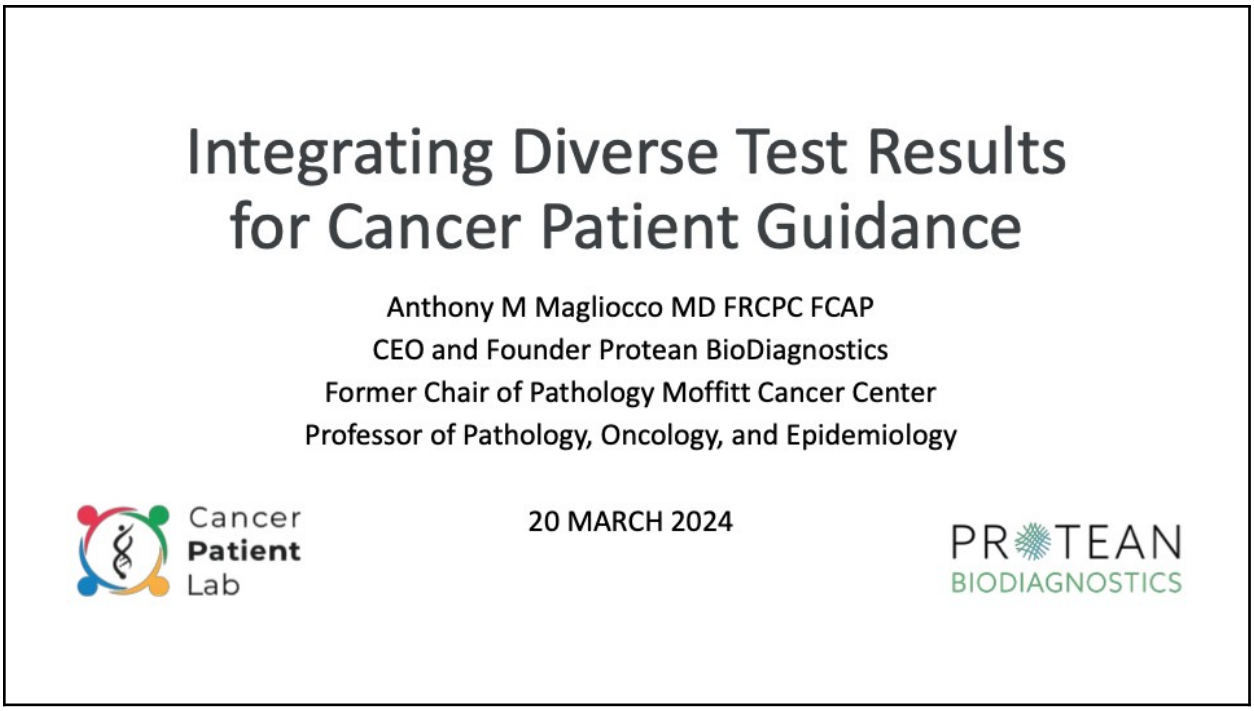


Tony Magliocco 3:46
Thank you so much for inviting me to speak today.

For those that don't know me, I was trained as a doctor in Canada about 35 years ago in the British tradition, which is a holistic approach to medicine. I became interested in pathology and particularly molecular pathology, but it was before molecular pathology was a thing. So I ended up being one of the first pathologists trained in molecular at Fox Chase (a cancer center in Philadelphia). Then I went back to Canada and had a variety of roles doing everything in surgical path, forensics, etc. In Calgary, I was appointed to be head of the pathology program at the Tom Baker (a cancer center in Calgary, Alberta). I did a lot of work with clinical trials, coordinating cancer care in Alberta and so on. Then I was fortunate to obtain a position at Moffitt Cancer Center as chair of Pathology. For those that don't know about Moffitt, Moffitt is a major U.S. NCI-designated cancer center, running a large precision oncology program, and so on.

Over the years, I was able to have a front row seat to the advances in everything from immunohistochemistry through to molecular analysis and through to all of the opportunities and challenges of precision medicine.

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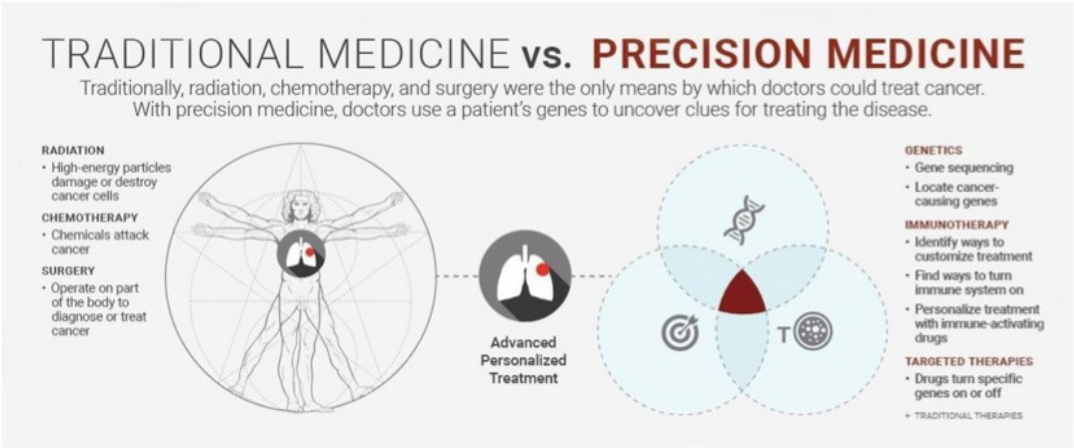
PROTEAN BIODIAGNOSTICS™

Improving outcomes for cancer patients everywhere.

I left Moffitt seven years ago to form Protean Diagnostics. Protean is a technology company that's focused on trying to solve the cancer problem more broadly and with a holistic approach.

Precision Medicine Has Revolutionized Cancer Treatments

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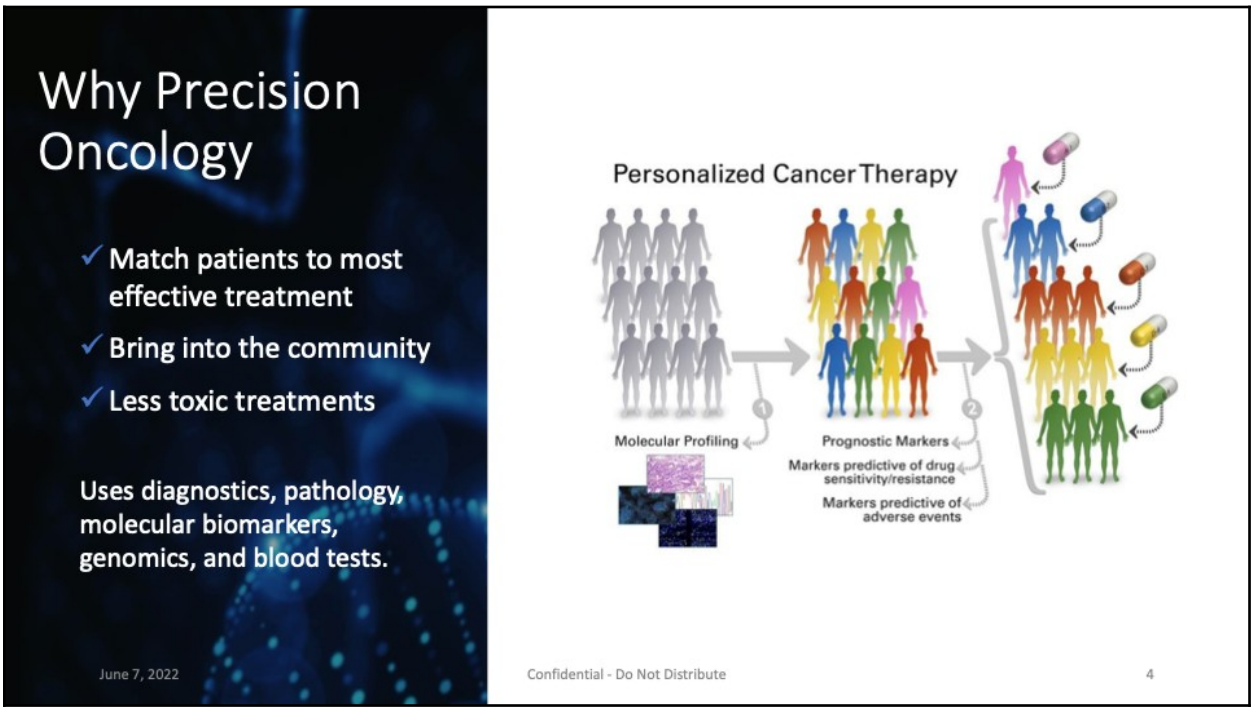
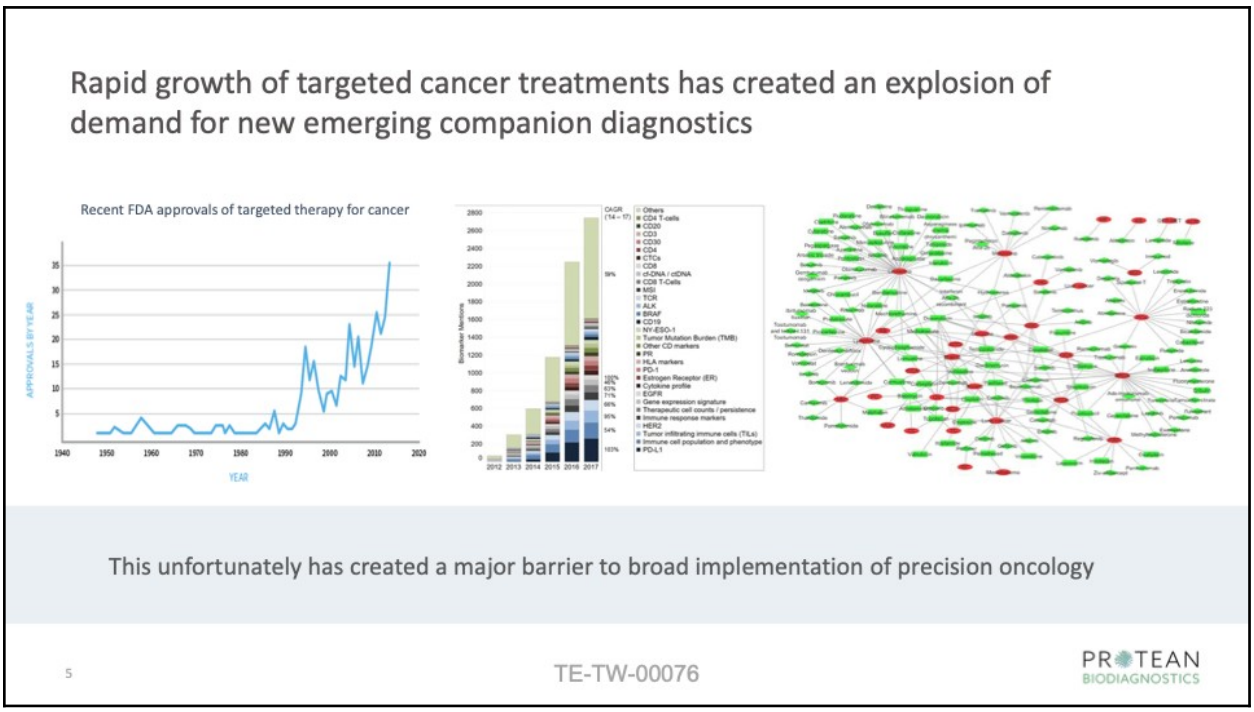



The challenge of precision oncology is essentially to match patients to the correct therapy, so that we can get an ideal response. If we're going to give a therapy to the whole population, only a few patients would respond. But if we can match the patients with the right therapy, we get a much better outcome and response.



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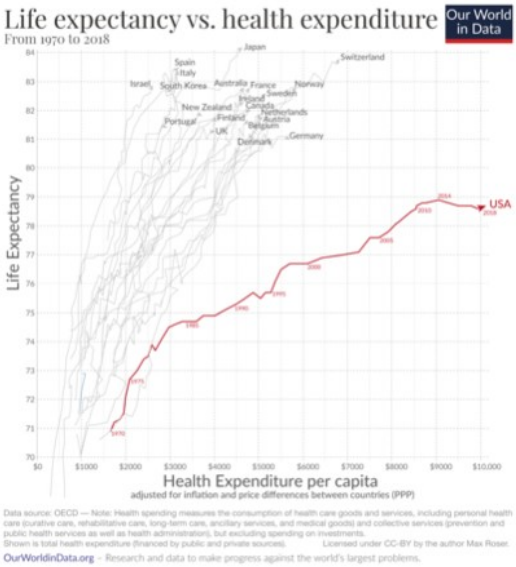
This is all well and good, but the system has become very complicated. Back in the 1980s and 90s when I trained, there were only one or two new treatments that became available every few years. But in the last year, there were over 100 approvals from the FDA, many of them targeted therapies that need companion diagnostics.

This creates an immense challenge for the system. How do we deliver all of these companion diagnostics? How do doctors decide what is the right drug to use for a particular patient? This has become a very problematic issue.




When we look at U.S. healthcare spending, we see that the U.S. has deviated from most of the other economically advanced countries. The U.S. spends more money than anybody, but seems to have worse outcomes, in terms of survival, etc. This is an interesting challenge, where we really need to think about how to solve that.

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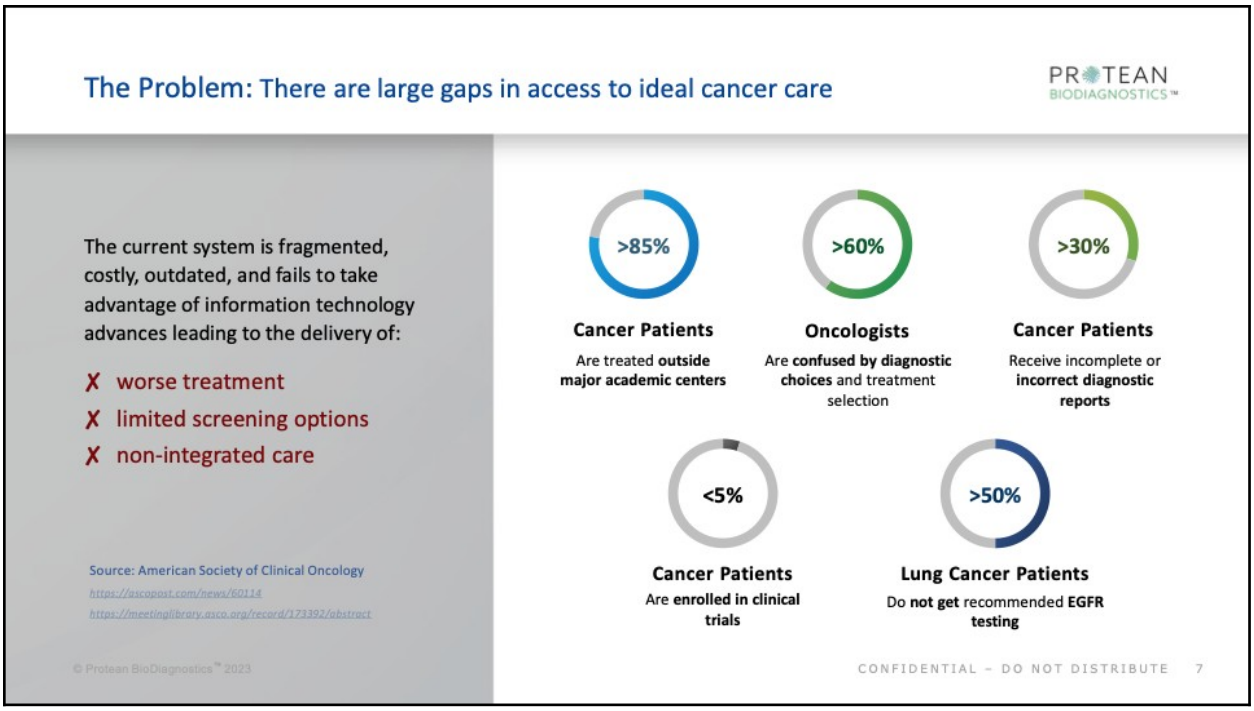


If we look at the cancer situation in America, we see that about 85% of cancer patients are treated outside of major academic centers in community oncology groups, hospital systems, like Baptist, or Advent, et cetera. The majority of cancer patients are in non-academic centers.

If we query oncologists, over 60% say they're having difficulty trying to understand what tests to use, and what the results mean, and this is getting worse. A lot of the 40% are just not admitting that it is very confusing for anyone trying to keep up with this.

One of the other problems is that up to 30% of people have incorrect or incomplete diagnosis. When you go to an academic medical center, the first thing you do is review it to make sure the diagnosis is correct.

Another problem is that only 5% of people are getting onto clinical trials. Some people say, “I don't want to be an experimental animal.” You're not an experimental animal. Clinical trials are delivering very high quality for very high quality treatments, you get access to first-in-human studies, and so on. The outcomes are actually better, even if you're on the control arm of a study. Getting involved in clinical trials is important, and can improve survival and reduce costs.

If we take an example of how poorly we're delivering cancer care, lung cancer is a good example. Every lung cancer patient should have a chance to have EGFR (Epidermal Growth Factor Receptor, a protein expressed on the surface of cells) testing, and treatment (targeted to the EGFR mutation) as a standard of therapy. It's been around for over a decade, yet more than 50% of patients are not getting the diagnostics and not getting the treatment.

There's a very large gap to fill here.

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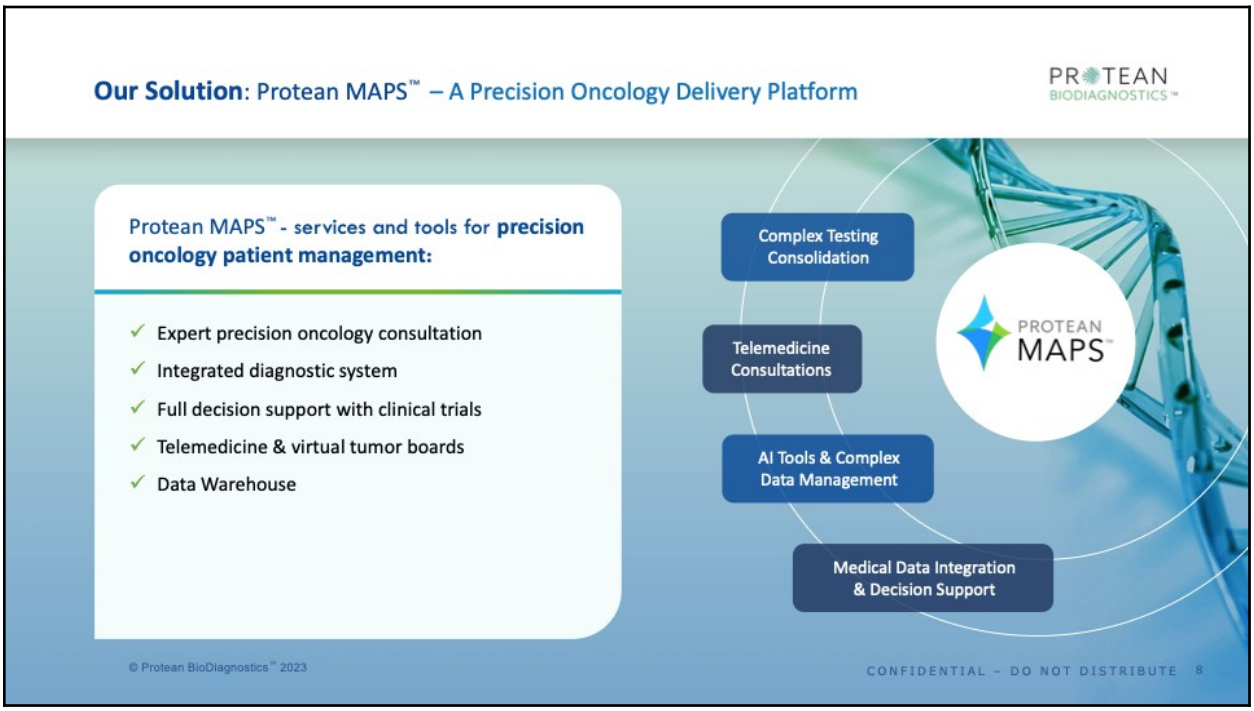
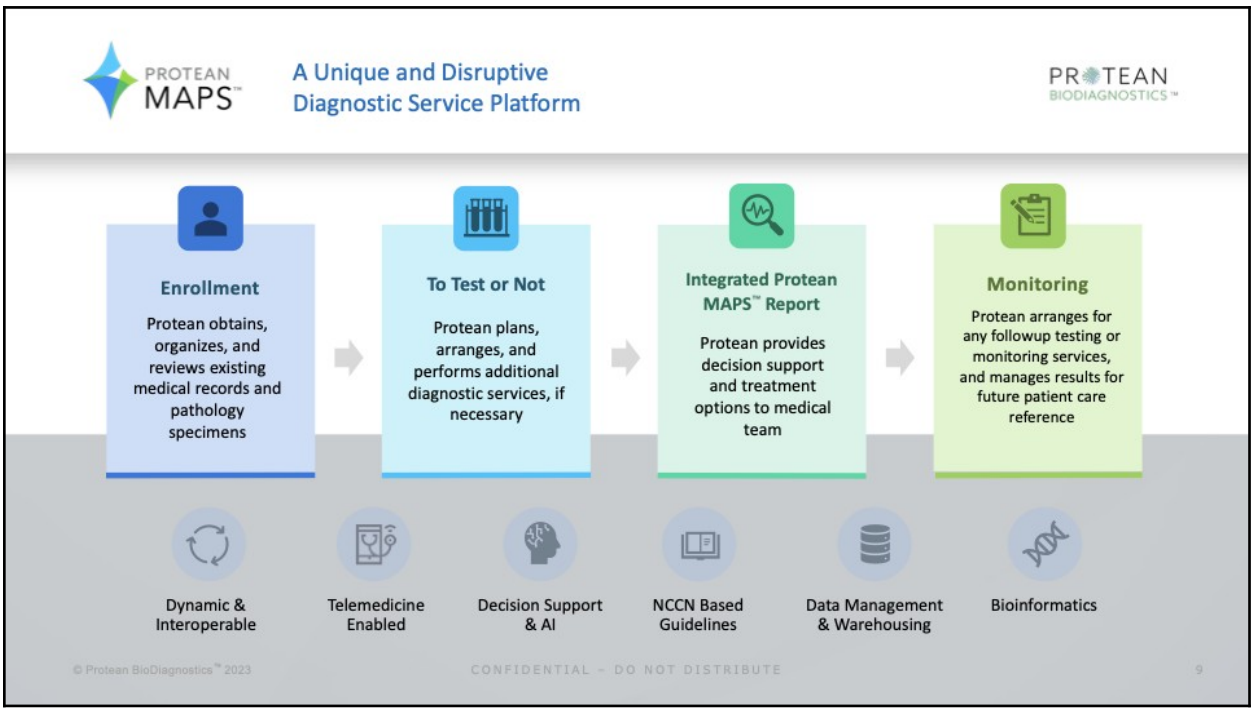



At Protean we try to solve this gap with a system called MAPS. It's a one-stop system, where we include aspects of oncology consultation, integrating the diagnostic systems, have decision support, including clinical trial matching, and deliver it all via telemedicine. On top of that we manage all the data.



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Our system is easy to use. Patients get enrolled. A patient can come to us directly, a health system can come to us, or a doctor can use it.

When you get enrolled, we review all of the path (pathology) records, medical records, and determine if tests were done accurately, and if there were any gaps. If there are gaps, since Protean runs CAP/CLIA labs (College of American Pathology Clinical Laboratory Improvement Amendments quality certifications), we fill the gaps with testing. We then have an integrated report that I'll show you where we put all this information together, including guidance for the oncologist or the patient. We also have a monitoring program, so that we can monitor a patient through their journey with cancer and continuously go back to them should they have a recurrence. We keep track of what's happening with their treatment. The system is continuously updated with the NCCN (National Comprehensive Cancer Network) guidelines (the standard of care). We are telemedicine-based. We have AI tools, and so on. That's our MAPS system.


This is the way we integrate our reports. We take very complex information and distill it down into a simple A5 (A5 size paper is 5.8 x 8.3 inches) report that's designed for an oncologist. They only need to look at the front part of it.

We always do a tissue review to make sure the diagnosis is correct. Sometimes you'll find, they think this is metastatic prostate cancer, and it turns out it was actually metastatic lung cancer. Or they think it's a malignant cancer of the liver that turns out is a benign nodule. The tissue pathology is very important.

We then look at the key actionability across the molecular tests, try to harmonize them, and then give guidance in a very simplified way.

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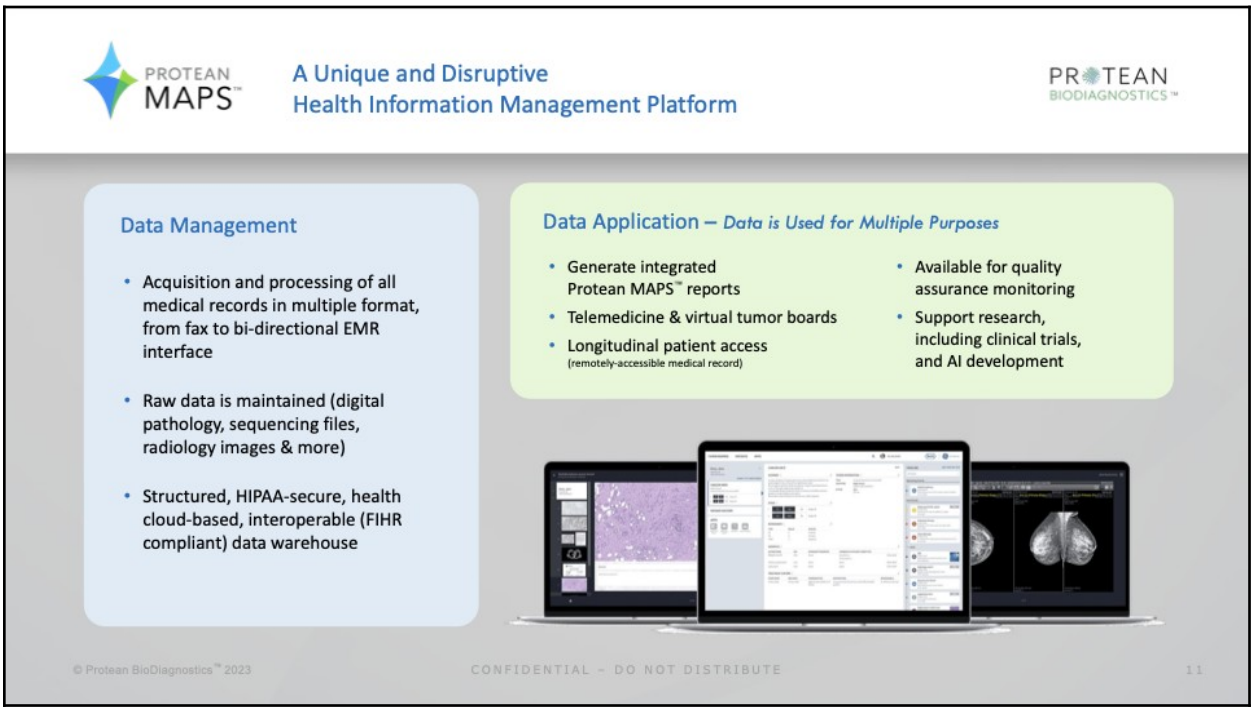
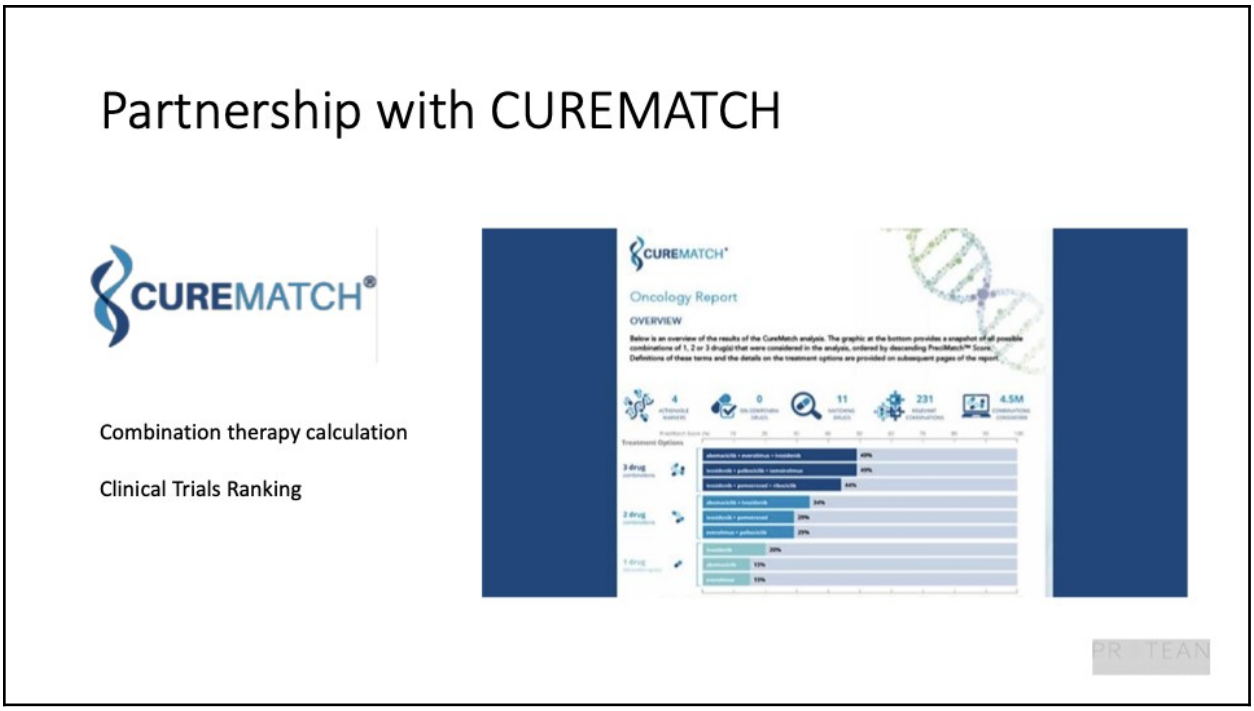



We also have a virtual tumor board, where we can discuss with the doctor and the patient. This is all loaded into our tumor board platform. The results are organized here chronologically.

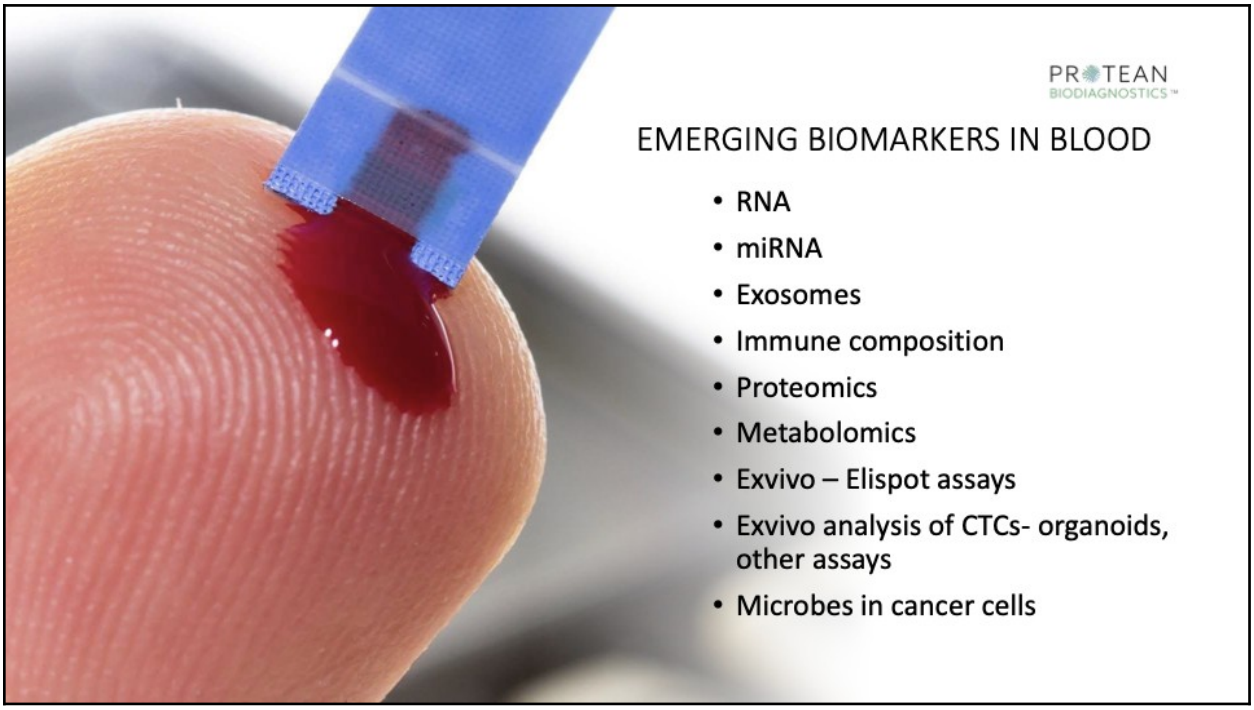
There are tools here including trial matching, guideline tools, and others.

This is the way an EMR should look, but it doesn't. An EMR is really about billing. This is about information management. It's available asynchronously. It's protected. It's HIPAA-secure. We can control who has access to it. We can work with a practice to organize their patients. We can work with a family where we coordinate tumor boards for a particular family, and they may want to see different doctors and go to different medical centers.

**“The Latest Tests for Personalized CancerCare” (Tony Magliocco) [#89]**

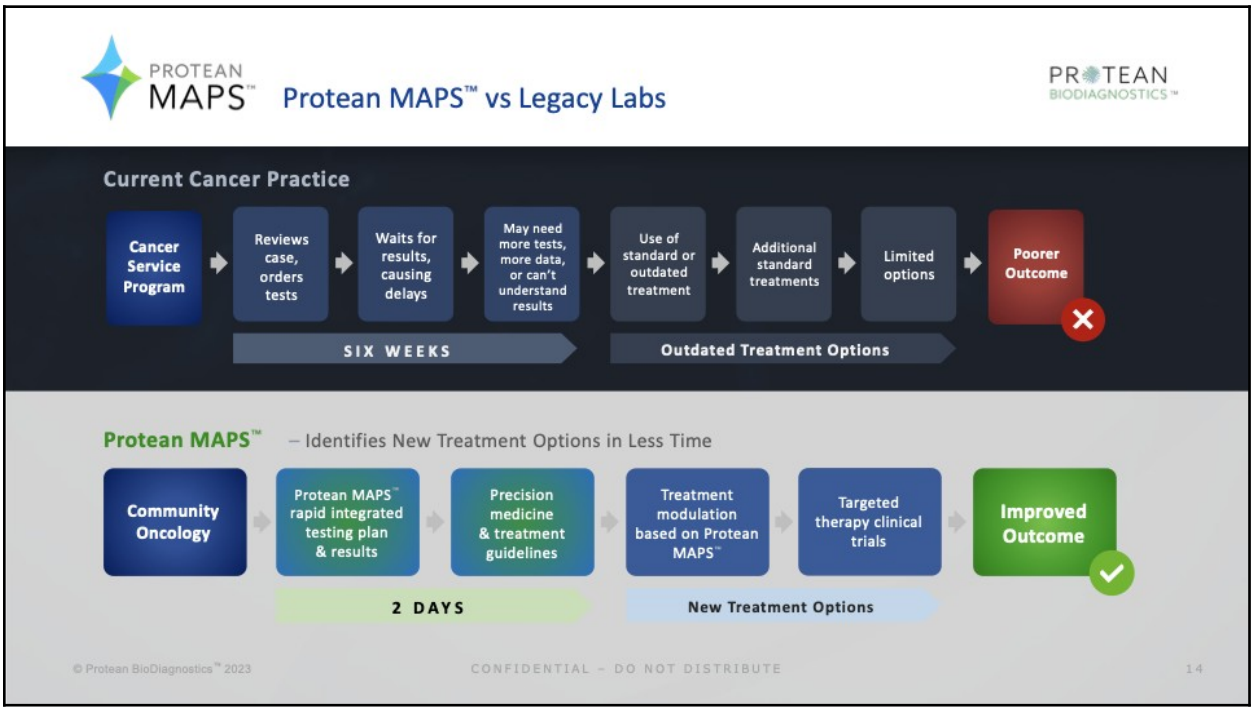



We also use advanced tools. A good example is CureMatch. CureMatch has an algorithm that looks at the molecular data, compares it to millions of combinations of therapeutics, and then it predicts optimal combinations. This can be useful for stratifying clinical trials or considering off label therapy. Tools like this can be really helpful for people who have gone beyond guideline-based care.



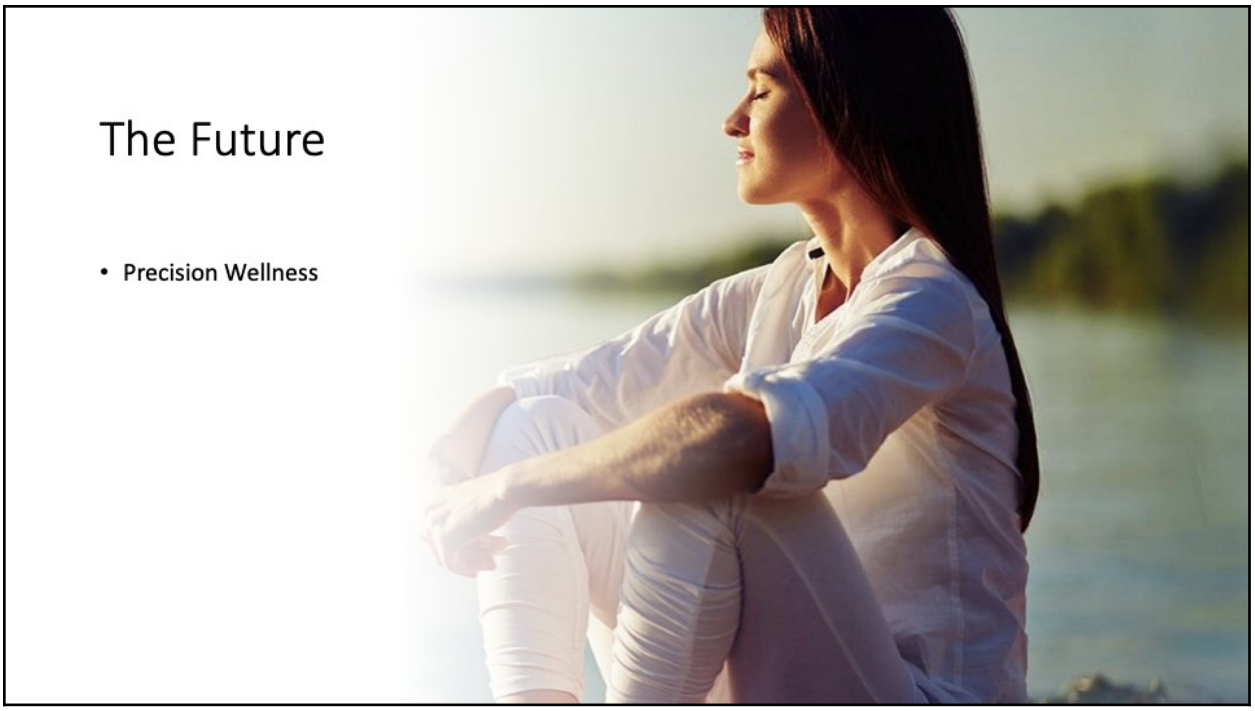
**“The Latest Tests for Personalized CancerCare” (Tony Magliocco) [#89]**

We're also doing a lot of work on liquid biopsies. This allows us to monitor a patient over time to see what's happening. There are a lot of emerging molecular markers, including circulating RNA, exosomes, and other things that can be found in very small amounts and help predict how to treat a cancer.

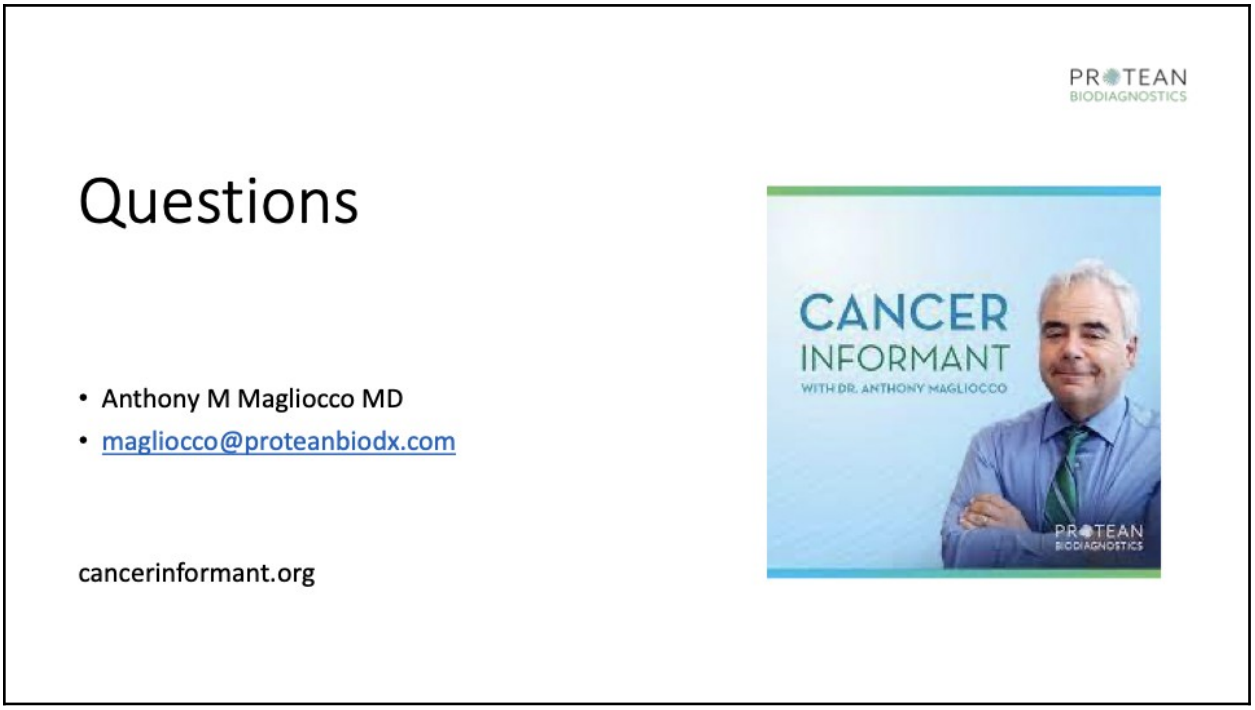



The conventional way of testing can take weeks to get a result. At Protean, we have ultra-rapid tests that have results within a day. We put a treatment plan together very fast. We also have full services, with full sequencing, genetics, molecular, etc., and access to new innovative diagnostics and clinical trials.

**“The Latest Tests for Personalized CancerCare” (Tony Magliocco) [#89]**




The future is about not just treating disease, but precision wellness. How do we preserve health? How do we treat patients holistically?




For those that are interested, I run a podcast called the “Cancer Informant”. It's also a YouTube channel.

**“The Latest Tests for Personalized CancerCare” (Tony Magliocco) [#89]**

Brad Power 12:56
One of my pet issues is the distinction between “precision medicine” and “personalized medicine”, where precision medicine is population-based, and is what people in the medical industry refer to as “targeted therapies”, where you have a diagnostic, and then you have a treatment that's lined up with that; as distinct from personalized medicine, where it's really getting deep into all of the tests for a patient, and then integrating it for a personalized treatment option. It sounds like you're doing both.

How do you think about the distinction between “precision medicine” versus “personalized medicine”?

Tony Magliocco 13:49
One is guideline-based, like you described, in terms of saying, “Here's anti-EGFR drug. It's used on people who have an EGFR mutation.” You need to test, and if this patient has a tumor that's got an EGFR mutation, we should give that to them.

If you're more of an integrated physician, you start thinking about, “What's the wellness of this patient? Do they have other coexisting conditions? How does this patient think? What is their insurance coverage? Are they eligible for this? Are they even interested in these kinds of things?”

Most of the things you described are one-offs, “You have this. You've got that. You're eligible for EGFR, but you're also eligible for immunotherapy. You're also eligible for this other targeted therapy.” How do you sequence them? How do you put them in order? It's often lacking data as well. What is the correct order to utilize?

Unfortunately, the way that clinical trials are designed, they generally put new therapies against the traditional, but they're not put against each other, and often the doctor is left confused as to what we should use because there's a gap in knowledge. Often pharma companies don't necessarily want their drugs compared head-to-head to show one flavor of this drug is better than the other one, that this can have an impact on care.

You've raised an issue about matching a patient to a treatment because of the advanced testing that we have. A patient may have multiple treatment choices. They have to think about how to sequence them and organize them. We don't quite know how they're going to work in combination. That's one thing.

The other thing is thinking about the overall wellness of the patient. Do they have other coexisting comorbidities, like diabetes or mental illness? Do they have ideas about how to manage their wellness with nutrition or complementary approaches, and so on? It's a challenging field.

**“The Latest Tests for Personalized CancerCare” (Tony Magliocco) [#89]**

As a care provider, the first thing is to think about the overall wellness of the patient and have that dialogue with the patient as to where they are. What are their expectations? How do you put this data together to make the right path for each individual patient?

All medicine is personalized medicine. It is about a doctor and a patient, and about what's best for this patient. We don't know the answers to everything. Sometimes we have to use our best judgment.

Brad Power 16:29
One more stage setting: your business model. You've talked about how you might be working with a provider. You've talked about how you might be working with a diagnostic company or a matching service, like CureMatch. I know from our previous conversations that you also will be a pioneer in bringing a test to market and making it available through your CLIA-certified lab.

Of course, this community is interested in, “If I'm a patient, how can I access your services? Are your services direct to patients and caregivers?”

Can you talk a little bit about your relationships and your business model? How do you make money?

Tony Magliocco 17:10
At the end of the day, we make money by selling our services, which are basically testing services. We have a CAP/CLIA lab, and all of our services are diagnostic services that could be paid for directly by a patient. Many of them are covered by Medicare. They can be purchased by a hospital or pharma. We essentially make money by providing diagnostic services and advice.

If we start with a patient – that's probably the best way to start, since this audience is patients – patients come to us. They can come to us directly. They can self-refer to us. We take them on board. I would work with them directly, or another member of the Protean team would take them on board. If they're interested in our services, we take them on as a patient.

Then they would sign on to share whatever they felt appropriate sharing with us. They could send us their medical records. They could send us their test results. We would have an interview with them to see what services they need. Sometimes they say, “I want to make sure my diagnosis is correct.” So we would review their pathology or review their treatment. Other times it may be, “I've heard about this test. What do you think of it?” I may not have heard of it, and I'll investigate. “That seems to have some evidence, or that seems to be a new thing, and it doesn't have a lot of evidence, but it doesn't look like it might cause any harm.” There may be dialogues like that.

In other cases, a patient may say, “I need access to genetic testing. I can't get it where I am.” We can provide that testing for them and explain the results. Patients work with us in a variety of ways. Being a physician, I will talk to the patient and say, “Tell me about yourself. Tell me about where you are, and what your goals are. What are your concerns?” Then we try to put a plan

together for that particular patient to see where they're at. Some patients don't want to have conventional treatment; they're interested in other things. They're more interested in monitoring saying, “Do you have a test that can tell me if my cancer is responding or not?” “Yes. I have blood tests for that.” “Is my diagnosis correct?”

When I work with a patient, I have a very open mind to hearing about what a patient needs and then trying to advise them as best I can about what are current services. What are research services? What are non-conventional services, and what do I think of them? We try to work with the patient in that way and try to deliver a high quality service for them.

Obviously, I am a physician. I'm subject to malpractice. I have to recommend things within the current standard, and in my thinking in medicine things are either (1) proven – if they are, those are therapies; or they're (2) unproven – those are things that are experimental; we're collecting data in our trials; or they're (3) disproven, I'd say, “It looks like there isn't much evidence about that.” I have to say that as well. So that's how I practice as a physician.

Amit Gattani 20:26
As patients we get all these different tests done. They don't match exactly. They lead to different conclusions. We don't have a comparative service.

How many patients have you done this on?

You've been around for eight years, what are the outcomes and results from the service that you have been providing?

Tony Magliocco 21:08
We have dealt with hundreds of patients.

I'll give you an example: one of the patients we dealt with was a young fellow in Australia who was 18. I heard from his mom, who said, “He's in hospice. We can't do anything with him.” They wouldn't trust him in Australia. Long story short, we organized some testing and found that he had an embryonal rhabdomyosarcoma that was driven by NRAS (neuroblastoma ras viral oncogene homolog, a cancer driver gene) mutations in a PD-L1. It turned out there was a trial. We were able to get him on it in Australia, and he went into a full remission. He's still in remission four years later.

We work with a lot of patients and with doctors, because a lot of the doctors are generalists, and they're unaware of what the results mean.

I did another case, I think it was in Australia as well – I've got a lot of Australians – where they had run a Caris (Caris Life Sciences, a testing company) test. They said, “I don't know what to do with this result. There's nothing actionable.” I read it and said, “There's a PK3CA mutation, and there's a PD-L1.” They hadn't picked that out. They were able to go on a trial. We didn't have to do another test. They had not really understood what the result meant. So we were able

to help advise their doctor saying, “This is what it means.” Because a lot of the generalist oncologists are not geneticists; they're not molecular biologists. They're none of those things.

The other side of the problem is molecular biologists are not doctors. They feel very uncomfortable advising on that. I happen to be old enough to have lived on both sides. I understand that medicine is an art. I can put both together and make advice. I'm not scared to do that, because I understand that's the practice of medicine. I can put it together and advise a patient with what I think in my judgment is the best option for that particular patient. I've worked with dozens and dozens of patients and their families over the last number of years in a variety of situations.

Amit Gattani 23:07
Initially, I thought that you were like CureMatch, that you were not doing any of the actual testing, that you were integrating all the test data from different tests to provide a 360-degree view of the situation. But later on, I understand that you are providing your own testing services.

Does that create a conflict? Does that bring a bias in your system that your own testing services now are mixed with other testing services and might create a bias?

Tony Magliocco 23:50
There is a bias because, “No, mine are best. Otherwise, we wouldn't offer them.” But we also take in the others. We will ingest all the data, and if additional testing is not needed, we don't do it. I review. We have our own lab that can do testing. We often use other labs. I will send stuff to Tempus, Natera, or Foundation. I will utilize whatever lab is necessary. I like to think of myself as an ethical physician, where I do what's best for the patient. In terms of what's best for that patient, that's what we recommend. Some of the tests that we have at Protean, no other lab has. We have 3D genomics. We're only allowed to have that commercially available. We have certain types of methylation profiling no other lab has. If the patient already has data, I'll take that data. Some of the practices that we work with say we can only use Foundation. I'll take Foundation. I am a pathologist. I will look at the glass slides and make my own interpretation. I have been a pathologist for 35 years and a specialist in surgical pathology. I've run cancer departments for a long time. I've been a PI on clinical trials. I've been a basic researcher. I give you my best possible judgment. Like every human I am biased. I try not to be and try to give you my opinion. I encourage every patient to seek alternative opinions. You might go to someone else and say, “They think this or that, or the other thing.” I provide my opinion, my expertise, and my interpretation of the results, and you can take it for what it's worth.

Amit Gattani 25:29
Your slides were very impressive. They had a lot of really good data.

As a patient, I have maybe half a dozen reports from the past 18 months, from RNA sequencing for the immune system to everything else. So I come to you, and you will give me a no cost estimate or a cost estimate for the service?

How much time does it take for me to get a response back from you guys?

Tony Magliocco 26:24
It's right away, basically. You contact us. We sign you up within 24 hours. You send us everything you have. As part of the $400 consultation fee, we review all of the paper you have and put it all together as an initial assessment. Then if you also have the raw data, and say, “We want to download raw data from Tempus,” or wherever, we'll pull all that raw data in for you as well. Then I'll say I want to see the glass slides. So you send us the path report. We pull all the glass slides together. That's our initial onboarding. We take you on and look at where you are in your journey and consolidate everything.

Then it's, “What's going on with you?. “I'm trying to consider between these studies,” or “Am I responding?” We will say, “I think maybe you need a new liquid biopsy.” or “I've reviewed all your stuff, and there's a new biomarker that wasn't run,” or, “I looked at your PD-L1, and I disagree with the result. I think that it's really positive, it's not negative.” I would have the discussion with you and then make some recommendations, saying, “You ran a genetic test, but they only looked at 50 genes. I really think you probably have a genetic predisposition, because everyone in your family had cancer. So we should do the whole exome, and really look at it. And we should do a polygenetic risk score.” That's how it works.

Those additional tests might cost more. If you have Medicare, this will cover it. If you have to pay out of pocket, then maybe this test is going to cost $500. Maybe this one's going to cost $1,000. Maybe we need to work with you, if you're economically disadvantaged, and there's a limit to the payment that you can do, or we spread it out, or however. Or we have a novel test saying, “Here's an experimental one. I can give it to you for free, but you're going to have to give me an informed consent. We can use your data for a part of a clinical study. We can give you access to this brand new test. You can utilize it as you see fit. I can also talk to your doctor about what it all means.” So that's generally how we work with a patient. I become your coach or your advisor. You can take my advice for what it's worth. You can ask me stuff, and I'll give you my opinion. I tend to be fairly outspoken. I say what I think, and obviously, you have to use your own judgment if it makes sense to you or not.

Amit Gattani 28:46
I've taken these reports to my various oncologists, and they take a look at it, and they never can put full trust in it because partly they don't understand it, or partly they see some discrepancy between one test to the other.

Is it better for me to have my oncologist approach you for that analysis?

Then they will be more invested in that or more keen to get that? As a patient, at the end of the day, the action will come from the oncologist. They will have to be a critical part of the decision-making to what we do next or not. They have to believe in the test results and the outcome. Where do you find best: whether it's patient-led or oncologist-led?

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Tony Magliocco 29:49
It depends on the oncologist, but generally oncologists are well connected to their patient. If the patient says, “I really want to look at this.” Often the oncologist will take an effort to look at that. They have to determine, “Is this legitimate or not?” If they look me up, they'll realize that I'm probably legitimate. They'll recognize who I am, and what we're doing. I'm more than happy to work with the oncologist because the oncologist is the treating physician.

That oncologist in Australia felt I was some sort of a scam operation. But after I presented him with tumor boards and everything, he now calls me and says, “This is what's going on with the patient, what do you think I should do next?”

With a doctor, obviously, they're going to have a certain amount of skepticism because there's a lot of stuff out there. They have to gain trust with the advising. “Does this pathologist know what they're doing?” Because the doctor doesn't necessarily know how to interpret all this stuff. They're relying on the pathologist. The doctor doesn't look at the slides, or the oncologist doesn't look at the slides. They have to have a lot of trust in the quality of their pathologist and electrodiagnostic person. I'm more than happy to talk to them. I like to talk to them. Because often after I do, I find they start sending me all of their patients. They understand that I'm not here to mess with them and their patient. I'm here to help them navigate this wilderness of all of this stuff, because nobody can keep track of it.

We all have to work as a team. The best approach for a patient is multidisciplinary care. You need a surgeon. You need a radiation oncologist. You need a medical oncologist. You need a pathologist. You need a radiologist. You may also need a social worker. You may need a mental health specialist. You may need a pharmacist. Having that team is important. I'm all about multidisciplinary care, pulling people together.

Every patient has a different goal and a different belief. We have to take care of our patients so that they can't be hammered into a square peg in a round hole. We really need to think about our patients and how we take care of them the best I can. If you have an oncologist that doesn't want to talk to you, that'd be a warning sign, I would think, that this oncologist is a little bit closed-minded about it.

One of the things that I had the opportunity to do when I was in Calgary was work with oncologists. I was the only pathologist in the oncology department. I was in that department for 13 years. I spent day-in and day-out working with oncologists. I understand what they have to deal with. I created the reports, not for other pathologists, but for oncologists. That's why oncologists like to work with me. A lot of the oncologists think I am an oncologist because I have been working in the field for a long time and understand what the treatment choices are. Because a lot of pathologists are focused on the diagnostics, saying, “What kind of butterfly is it?” Whereas I'm saying, “How do we kill that butterfly?” I don't care what kind of butterfly it is, we’ve got to kill it. I'm a little bit more about the treatments. “How do we pick the right treatment?” Because I've had the privilege to work in a lot of clinical trials, I know the treatments

and the companion markers. I can help advise oncologists on the tasks and how to match them to treatments. But I don't treat people. I'm there to help back up the oncologist.

Brian McCloskey 33:35
I've been an advanced prostate cancer patient for seven-and-a-half years.

My question is about something you discussed regarding the art of decision-making. You have a very interesting background in the sense that you're a pathologist and a microbiologist. I happen to have data that fits into both camps, but they conflict. I just recently had a full analysis done by BostonGene where they compared tumor tissue from my 2016 prostatectomy to a metastatic lesion that was resected in December of 2022. They did whole exome sequencing and a tumor evolution report. If you're familiar with BostonGene, they did immune profiling, transcriptomics, and spatial phenotyping. The interesting thing is that, in 2022, pathology indicated that my disease was just simply adenocarcinoma. There was no mention of neuroendocrine disease. However, in combining my transcriptomics with spatial phenotyping, there were biomarkers that had changed between 2016 and 2022, which indicated that I was developing a subclone, demonstrating signs of neuroendocrine transformation.

I have been validating these findings with a bioinformatician at UCSD, who's looked up the profiles of neuroendocrine disease, regarding TCGA data. There seems to be some concordance with that information and my profile. However, it didn't show up on standard pathology. So as I'm sitting here making a decision about what my next treatment is, that's a really, really important bit of data that can tell me to continue to take androgen deprivation treatments, or to avoid them because they could lead to a progression of the neuroendocrine subclones.

This is a real life example, which fits into this art of decision-making.

I'm curious, have you ever seen this much data on a patient? I've got proteomics, too, which I can talk about later.

What do you do in this situation where standard pathology and microbiology don't necessarily conform?

Tony Magliocco 36:30
If you take a step back, cancer is a four-dimensional disease. There are snapshots in time.

You can imagine cancer like a tree as it grows through time. You start at the beginning. It starts as a single seed. Most cancers start as one cell. Then they grow and grow and grow. In that cell there are driver mutations that drive it. Those are the things that cause it. As it grows it evolves. Sometimes it gets more mutations, and the branches come off, and they change. Some branches may be going in the neuroendocrine direction, another branch may be going in another direction, and so on. A cancer will evolve over time.

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We have to create a timeline of your cancer and say, “How did we evaluate it at different snapshots in time?” If you treat a cancer, it will change. Cancers are like ecosystems. It's like if you watch “The Lion King”, all of the animals live in harmony. But if the lion leaves, then the hyenas take over, and chaos ensues. In a cancer, all of the cells are of different types. When we do different things to them with chemo, or endocrine, there's pressure on them and other ones escape. Cancers go through this dynamic process of evolution.

It's interesting.There are investigators at Moffitt that looked at this and said, “You have to trick an endocrine responsive tumor. You can't pressure it too much because it'll become endocrine-resistant if you put too much pressure on it. It's like if you put too much weed killer on a field, you get pesticide resistance, but if you keep the balance, the normal stuff will kill the weeds.” It's about trying to achieve that balance. Tumors are a balance, and you're looking at snapshots. You have a reductionist view on each part of it. You're saying, “Part of this tumor is evolving, but what's happening to the bulk?”

One of the principles is, first of all, we want to treat what is in the patient, not what is in the bucket. What was taken out two years ago tells us stuff about where your disease was two or four years ago. That's important. That's the ancestry of that. It gives us information. What was taken out two years ago and said, “How did it change? Did something happen? Is that only an isolated example? Because maybe you've got 20 mets (metastatic lesions)? Maybe this is only one of them? What about the other 19? What happened in the last week?”

Liquid biopsy is your friend. With liquid biopsy, we get to figure out what's happening today. So we can say, “Do you have cancer today? Is it going up? Is it going down? Do your cancer cells have a neuroendocrine type or not? Do we have to think about harmonizing this treatment and sort of pulsing it, and then reviewing what's happening to the circulating tumor cells, so we can tune it?” Those are all of the things that we have to think about when we're putting this data together because we have to visualize the cancer as it's going through its evolution. We have to understand how we avoid pushing it into crisis. “How do we manage it?”

It becomes a complicated problem that doesn't necessarily have easy solutions. But when we put it together, there are a lot of opportunities in treating a cancer. We have to think about them.

We also have really advanced imaging now where we have radionuclide therapies, lutetium, other kinds of things where we can visualize what's happening to a tumor in real time. The future of prostate cancer care is a combination of radio imaging, of really understanding therapeutic choices, and also liquid biopsy so that we would manage the disease as a chronic disease, so that if we're seeing it's escaping this way, maybe we have to adjust it and push it back the other way.

The problem is that oncologists are like fundamentalists in a religion: they read their Bible and say, “This is what the trial said”, and they can only treat it according to what the trial said. When they deviate from that, that's putting them at risk. They're a little bit concerned about, “I'm off track. How do I adjust that?” Sometimes you need a more forward-thinking oncologist that feels

comfortable moving beyond the trials, and saying, “Is this within the practice of medicine? Is this safe? Am I doing it within standards?” All of those kinds of things. Those are the challenges of treating a patient.

It's not surprising that neuroendocrine resistance is occurring. That's what happens. You kill out the cells that are androgen, and the neuroendocrine ones take over. That's expected. Then you need to switch treatment over to an anti-neuroendocrine or to another treatment because tumors will progressively evade treatment. But one thing that we learned that oncologists don't believe is sometimes they can go backwards, because tumors are kind of lazy, and say, “Now I've removed the endocrine treatment, maybe I can drive endocrine again. Say, wait a minute, this tumor went back, maybe the endocrine will work again.” You have to know that. The only way you can know that is by doing a liquid biopsy. Liquid biopsy is very important to keep track of what's happening in real time with the patient.

Brian McCloskey 42:23
Liquid biopsies would be phenomenal. Patients can give blood frequently. You can't give up tissue, particularly, bone is very difficult for a lot of prostate cancer patients. Mine happens to be soft tissue, which is a little bit easier. But still, it's not like I'm giving it every week. The challenge with liquid biopsies is just getting enough CTCs (circulating tumor cells). Even though my PSA should technically yield enough CTCs to identify changes in my genomics, possibly even transcriptomics, which BostonGene is pursuing. It's just difficult to get that. You're always going to be working in this situation where you don't have perfect data,

Tony Magliocco 43:14
About CTCs: we're learning now that exosomes and oncosomes (vehicles for intercellular communication and cell regulation) could be very rich sources of membrane markers, and also indicators of RNA. If you imagine a cancer cell, it's only got two copies of the DNA, but it may make 10,000 copies of RNA, and it's leaking all that RNA out, and sometimes it's packaging them. We're learning more about how RNA could be very important in tracking what's happening. There may only be one tumor cell, but there could be a million oncosomes in that tube of blood, and we can measure stuff on those oncosomes, like PD-L1, or we could measure if they are showing endocrine response markers or neuroendocrine differentiation. There are newer tools that will help make liquid biopsy more valuable in the future. The CTCs are kind of crude. They're pretty useful, but they were developed 30 years ago. There's a lot more advances in this field that are pretty exciting about a newer technology.

The other area where there's a ton of advancement is in imaging. We love imaging because then obviously, you're just looking at PET scans or radionuclides, and you can see what's happening with the treatments as the metabolic activity is going down. But again, they're nonspecific. A combination of radioimaging and liquid biopsy can be really important. But you need the newer technologies. The older ones can't do it. They're too crude.

Brian McCloskey 44:48

What I heard from you, and this is a big generalization, is that you would put more weight in what I'm learning from transcriptomics and spatial instead of standard pathology, which is just classifying it as an adenocarcinoma.

Tony Magliocco 45:08
Absolutely, because standard pathology is a morphological discipline, where they just look at the pattern. They make a stain. “Let's stay in it for neuroendocrine markers. Oh, they are there. There are a few cells that are showing that.” It depends how deep the pathologist went. They could also take that paraffin and sequence it and do transcriptomics and other things. Those are all complementary. The standard pathologist is taking a look at a high level, like at a 50,000 foot level, and saying, “This is the way all the cells are arranged.” Then they might stain it with a protein. “These are the patterns.” But if you start getting down to “We're going down to the molecular level of the tumor”, most pathologists don't deal with that. That goes over to the molecular pathology division, and then they don't necessarily put it together. Say, “Does this make any sense?” And say, “Wow. That makes no sense. What happened?” “Crap. We mixed the sample up.” There can be lots of reasons why things don't make sense. You have to make sure that they all come together.

This was one of the reasons I left academia because I was trying at my academic center to put the molecular with the surgical, and I couldn't, because the data systems wouldn't talk to each other. So when I founded Protean, I created a cloud-based Azure web system, where I can integrate all of the data and look at all the data and put it all together. That sounds simple. But it's actually not. It's very hard to do that because the data standards are quite different across each silo of medicine. Our goal is to try to harmonize the data and make it interoperable and connect it with EMRs, and then organize it in a way that tools like AI can sit on top and look at it.

Brian McCloskey 46:49
Having definitive models, looking at genomics, transcriptomics, or proteomics is a challenge. Then you need to have a reference model that aggregates those three disciplines. We're not even close to having that.

Tony Magliocco 47:07
When you look at a patient on a trial, you don't necessarily have to know what's happening to every cell in their body. You have to think about how much data do we need, and at what level, because there are so many levels. When you get down to a single cell, it's, “Okay, I know everything about this single cell, but there's a billion cancer cells in this patient. How much is that representative of the other 999 million?” That's where things like global analysis come in, like what's happening to the liver and brain, and everything else. Where you have to take that holistic approach and say, “What's the wellness of this patient? How is their immune system? What's going on? How do we measure tumor response?” You can't be super reductionist, otherwise you go down a rabbit hole, and it may not be fully representative of the disease. You have to take a step back and say, “What about my overall health and wellness?”

Brian McCloskey 48:01

**“The Latest Tests for Personalized CancerCare” (Tony Magliocco) [#89]**

The Cancer Patient Lab is about trying to get advanced diagnostics so that we can bring data to our decision-making as a patient as well as an oncologist. Your point about it being part art and part science, we fully appreciate that.

We're big believers in Bob Gatenby, evolutionary biology, and adaptive therapy. I just wish I knew about it six years ago when I was earlier in my disease.

Tony Magliocco 48:37
The two Bobs. Unfortunately Bob Gillies passed away. Bob Gatenby is in mathematical oncology. I was at Moffitt for years listening to them preach there about that. It was quite an interesting bit of lectures on bat populations, and how squirrels change color, and stuff, and how all of those apply back to tumors and evolutionary biology. It's very interesting stuff.

Brad Power 49:06
It's “bat” in both senses, the animal and Bipolar Androgen Therapy.

Roger Royse 49:43
I gather from your discussion that you can do this remotely, that you don't need to have in-person visits?

Tony Magliocco 49:50
Yes. We never have in-person contact. They're all remote. We have telemedicine. We do video conferences. We do virtual tumor boards. We can get all the doctors together and so on. It's all very remote and virtual. The lab is real, and it is in Orlando. We also have a network of liquid biopsy labs. We work with all of them. We know them all. We know Natera, Guardant, Foundation, Neo, Menarini, and a dozen others you've never heard of. We know which ones are the right one for the right situation. We do our own as well. We've got all of the tools available here, and we're open-minded about how to utilize them.

I've got the YouTube channels and the Protean website. There's a lot of information for patients. You can see all the different tests we run. We are doing a lot of work in epigenetics now, looking at global methylation profiling. Those are the switches that turn genes on and off. That's how a prostate cancer would decide whether it's a neuroendocrine versus non. Global methylation profiling can be quite helpful there. We're also the only lab that does 3D structural genomics, in which we look at folding and DNA structural changes that other assays miss. There's a lot of interest in that from many leading academic centers to run those to uncover actionable targets that other technologies miss. We look at things like RNA profiling, proteomics, and other things. We've got every test you can imagine, and we can work with other labs. We're doing stuff in ex vivo organoids and other things as well. We have partners that help us with those. There are lots of opportunities if you want to talk to us.

Allen Morris 52:08
Who are your top patients?
I’m guessing they are lung and breast cancer patients.

## “The Latest Tests for Personalized CancerCare” (Tony Magliocco) [#89]

What is the profile of the kind of patients who you work with?

Tony Magliocco 52:45
We've got a lot of sarcoma, brain, prostate, ovary, and breast patients. I am a breast pathologist. I know breast cancer inside out, but I get a lot of lung and solid tumors. My expertise is less in hematology. But we can still help, and we have consultants in those areas. To me a cell is a cell, and a cancer is a cancer. I've had the opportunity to work with all types over the years. I am more than happy to try to discuss, and if I don't have the answer, I've got quite a large network. We have over 30 affiliated with Protean, and I know hundreds of people beyond that that we usually reach out to with strange tumors to get advice on them. And if they don't know, they know someone, and we connect with a global expert on those kinds of things. We'll quickly get to the bottom of who the experts are on what we're dealing with. I'm the first to say I don't know something if I don't, and we'll connect it to someone else.

Amit Gattani 53:50
I'm also one of those lucky patients here that has neuroendocrine differentiation. I've had a bunch of liquid biopsies done over the past four or five years of my journey. You said that liquid biopsy is really good at differentiating to help guide the neuroendocrine disease. I have not seen that from all the liquid biopsy output that I have gotten.

Could you unpack that a little bit and help me understand exactly what part of liquid biopsy testing helps guide the neuroendocrine disease and diagnostic slash treatment.

Tony Magliocco 54:50
One point about liquid biopsy is that it depends on what kind you're using. It can be limited in terms of if they are just looking at total cell count, or are they looking at markers on the cell. Because you could start looking at, “Is this cell showing loss of androgen receptors and showing other markers that are implying a neuroendocrine differentiation?” Those are additional tools that can be added to a liquid biopsy that many ordering physicians don't know that might be there.

The other thing is on the circulating cell free nucleic acid, a lot of the labs focus on DNA. But now there are new methods that can look at RNA. And looking at RNA, you can start looking at expression profiles and see if those are changing as well. The differentiator is limited, because it's not in widespread use. But the tools are there that you can get in and start looking at what is happening in terms of the evolution of the tumor towards resistance to anti-androgen therapy and development of other potential targetable markers there as well.

If we look at companies like Natera, Natera doesn't tell us anything. It's kind of interesting. It's informed, but it's not really informed. It's just telling you whether the cancer is there or not. It's not really telling you how to treat it. Guardant is similar because they have a limited menu. Foundation is focused around targetable therapies. Tempus is more about RNA, and so on. You have to be a little bit more looking at some of the newer technologies for some of those things.

Amit Gattani 56:40
I have used Guardant 360 and Tempus. Tempus does a much deeper profiling, and Guardant for consistency of tracking my disease.

Is this a topic that you cover in any of your podcasts, or is there a white paper on this?

Tony Magliocco 57:03
I’ve got a podcast on prostate cancer. I've talked about it, but we could talk offline as well because you may be in a place that is an N-of-1 situation, where we want to look at your data and see where we're at and then think about what makes sense for you. Because, like I say, generally, as you get further in your disease, you're dealing with a heterogeneous disease you're trying to manage.

I'm managing some women with breast cancer. Some of them have the ESR1 mutation, but not, and they're going back and forth between using an anti-ESR1 versus a standard. They're trying to balance that by looking at what's going on with their CTCs, and so on. It goes into the art, because these different clones are doing different things. It's like whack a mole: you're trying to knock one down, and another one comes up, and you're trying to balance them out.

You may need to look at other types of liquid biopsies that give you that additional information that you may not have readily available in these ones. We can talk about that separately.

Brad Power 58:23
You said you can work with all of the liquid biopsy companies and take your input from all of them. You've mentioned that some of them can analyze RNA from the liquid biopsies.

Can you give some names about ones you find that are at the cutting edge that you would recommend?

Tony Magliocco 58:45
The one that I'm working with is the Genomic Testing Cooperative. We use them and are in partnership with them. They evaluate over 1500 RNA in the liquid, including immune response, markers, HLA, and other things. They'll give us that data back, and we can look at it. I'm impressed with their test. It sort of lacks a little bit in terms of evidence, but they are publishing on it.

Then we are looking at Menarini, which is developing new approaches to CTCs, then looking at downstream markers where you can isolate the cells. Then in the research environment they can start staining it with other things.

There are other companies that are emerging, like ANGLE Parsortix, and others, that can harvest living cells out of the blood and explore them. You can stain them. You can grow them, and you can do all kinds of things with them, as well.

There are over 30 or 40 liquid biopsy companies that are emerging, and they all can do a variety of different things. So it's a matter of finding the right one for the problem that you have. Taking an old school country doctor’s, like, “What are we primarily trying to fix here? Let's think about what are the right tools for solving this immediate problem.” Some of them are experimental, so you have to take those a little bit more carefully because they haven't been fully proven. You say, “We may find that we were being misled by the data.” You also have to look at the gravitas of the data, and how strong it is with making a decision. Sometimes a patient just has to go on a hunch, as well, when you're at the forefront of some of these things. Anyway, we take all of those into consideration, balancing the strength of the data, and then looking at novel things, and you have to balance it all up. That's just part of the art of it.

Brad Power 1:00:46
We are very actively interested in helping novel diagnostics transition from research use to clinical use. We like to be early adopters and guinea pigs for those tests with the caveats of not really having an evidence base to support them, but they might be helpful at the margin. We've had several such companies present to us – for example, Cliff Reid was on earlier, and he was previously associated with Travera, which is one of those companies.

Tony Magliocco 1:01:16
We are associated with Travera. We love those companies.

There might be an opportunity with your group to create a cohort, where there's a universal IRB and where you could help coordinate. We do this all the time, and then coordinate other centers. We can coordinate the blood testing or help fractionate the samples, do conventional testing, do experimental testing. We can aggregate all that data and manage it. That might be something that your organization might be interested in doing, creating a data warehouse just for you. It can give you all that data. Your people all sign up for it and manage it for you, biobanks, all that kind of stuff. You could act as a group and say, “What do we think about this group? Should we all contribute or not?” You could evaluate new companies as they come along and be something like the Nurses Health cohort or something like that, as well, and be able to do that as a group and take control of your own destiny.

Brad Power 1:02:14
This is very much our thinking. We've been educated about the observational registry by the folks at Cancer Commons, Marty Tenenbaum, who I think recommended you. They definitely follow that.

Brian is very focused on accelerating translational medicine for diagnostics. That would be very interesting. We can cover this offline. But it would be interesting to get contacts from those two companies you recommended, and we'd like to put them on stage on this forum. We'd like to learn about it, and then raise our hands and say, “I'd like that test. I'd be happy to be an early adopter and give you some more data.”

Tony Magliocco 1:02:57

We've got a whole host of stuff that's in the experimental stage that would be interesting. We're looking at proteins in the blood instead of looking at nucleic acid, and so on, that may indicate things. There are a lot of technologies there, and we are happy to work with you.

I like the federated model, where you take your own destiny, but then we can offer you and say, “Are you interested in this?” And if you are, “Here are some people that are volunteering to give urine or blood or whatever.” That'd be great to get you on board on those kinds of early access studies. Say this is under an IRB. We do all of our experimental stuff under IRBs. You get the data back, and so on. It's a research grade thing, and you can choose how to use it yourself.

Allen Morris 1:03:45
Is there any importance to differentiate whether a mutation is a germ cell variant versus a somatic tumor mutation in providing treatment decisions? How do you think about that?

Tony Magliocco 1:03:59
A germ cell tells you not only about yourself and your whole body. In a germ cell, every cell in your body is affected with that. The other thing is your children might be affected with it as well and your first degree relatives. That's something to keep in mind with a germ cell. For example, in prostate cancer, we know that many of them are driven by BRCA1 and others and homologous recombination. If we happen to know that you do have that, that guides you to PARP inhibitors and other types of therapy. Also, if you know you're at a hereditary predisposition, you might also be at risk of colon cancer or other cancers. So it might guide your screening. Knowing something about the germline is important, not only for treatment, but also for managing your own future because it may impact other organs and also your children.

Now at a somatic level, it's also important because that guides therapy specifically for that clone of tumors and so on. They both carry different types of information. It's definitely important to know the difference.

You always should have genetic counseling. You don't necessarily need it, but I recommend it. Genetic counseling is important. They can answer questions and get results. Just because you carry a mutation doesn't mean you're going to get the tumor. The mutations are all different types with different penetrances. They all interact with one another, and so on. I always advise getting genetic counseling. We provide that at Protean as well. We do genetic testing. We offer whole exome sequencing. We can even do whole genomes, if you want it, etc. We're quite familiar with genetics, as well.

Brian McCloskey 1:05:40
Back to the weighting issue, if you've got germline testing that identifies certain biomarkers for treatment decisions, and you've got somatic testing that does the same, what's the weighting in terms of predicted response of each of those different types of testing?

Tony Magliocco 1:06:06

Somatic is more important, a little bit, for one reason, because it's in the tumor. You might have a BRCA predisposition, but the other one doesn't get knocked out. Your tumor may not actually have the phenotype of homologous recombination deficiency. You're trying to kill the tumor. The somatic has priority in the tumor. You always go with somatic in the tumor. But like I say, you may have cut out the tumor, and now the part that's behind is different. You need this somatic in what's left behind. The key to proper effective therapy is knowing where you are. Somatic always trumps germline.

Paul Van Camp 1:06:47
Any particular test for minimal residual disease monitoring that you favor?

Tony Magliocco 1:06:59
The best one right now is Natera, simply because they’ve got the evidence. They sequence and find passenger mutations, and then they build a highly specific assay for it. They got a bunch of data on it that shows that it's pretty good, particularly in colon and other tumor types. Natera has got the most data on residual disease. But it doesn't guide you in treatment. It just tells you that cancer is there or not. It doesn't help you pick a therapy.

There are other ones that are trying to do that.

I wouldn't go with Grail. Grail has a huge problem with sensitivity and specificity. It looks like methylation markers might be better than nothing. It's not really designed to be quantitative. I'd look at the other ones like Radar and other things that are designed for minimal residual disease. Natera is leading the field in that. There are other ones that are available: Guardant, and also there's some coming out from LabCorp and NeoGenomics. I forget the flavors of them. Menarini is also pretty good at some of that as well. But Natera is the best one right now in terms of being able to detect minimal residual disease.