“Identifying the Most Effective Treatment on the Tumor Rather than Trying It Out on the Patient” (Dr. Chris Apfel) [#84]

Brad Power
January 31, 2024

“What really drove me was my personal experience and the realization that, while we often like to believe at major institutions that the future is here now, the reality is, if one of you is affected, and you have been, that we often are still living in the past. We're not leveraging all the possibilities and technologies that are currently in development.” – Chris Apfel

“If a patient gets treated according to what demonstrates sensitivity (a test's ability to designate an individual as positive), or if we are avoiding resistance for this patient, the likelihood … is that you double your odds to have a tumor response.” – Chris Apfel

Meeting Summary

As an advanced cancer patient you want a wide range of treatment options and a good idea whether you will respond to any treatment. As we have heard in our discussions with Tony Letai, Robert Nagourney, First Ascent, Travera, and SEngine, "functional testing" directly tests cancer drugs on your live cancer cells to see what the drugs do. It is a way to identify treatment options and predict which treatment is going to be best for you. It bases your decisions on trying it, not on theorizing about what might work.

Chris Apfel, MD, PhD, MBA is uniquely qualified to talk about the latest practices in functional testing. He was a successful anesthesiologist, intensivist, and clinical researcher whose work has been cited over 20,000 times by other doctors and whose clinical prediction model has several million hits on Google and is now standard of care in many institutions, including Stanford. He was surprised that genomic testing wasn’t the answer when his father was diagnosed with late-stage lung cancer. Moreover, his father, who had taken care of his wife when she struggled with ovarian cancer, refused therapy unless he could tell his father with great certainty that a treatment would work. The experiences of his parents drove Dr. Apfel to search for more effective approaches for cancer patients. He left his faculty position as a practicing clinician at UCSF, got an MBA from Wharton to complement his scientific and medical experience, and, together with his wife, Dr. Brigitte Apfel, also a physician, founded SageMedic Corp. and developed the SAGE Oncotest™ with the latest in functional testing technology.

How is the SAGE Oncotest similar to other functional tests?

The reason why functional testing has the power to make a prediction on what will work is because it's done on live tissue. Like other functional tests, the SAGE Oncotest requires live tumor tissue or “malignant fluids” (excess fluids with cancer cells that accumulate in the body). Patients who show low or no evidence of disease, or have hard-to-reach tumors, will have trouble getting enough fresh cancer cells.

SageMedic and others apply the candidate drugs at various doses, including in amounts greater than normally found in the body, such that if there is no response at that level, that drug can be ruled out, and if the tumor cells die, then that drug is a good candidate.

How is the SAGE Oncotest different from other functional tests?

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Rather than older methods of growing organoids (cancer cells multiplied in the lab) for functional testing, SageMedic has developed a process and platform to create hundreds of “microtumors” (copies of the tumor tissue) in their lab in a day. They can then test dozens of drugs and drug combinations with results in 7 to 10 days. Other tests using older organoid technology are accurate if you get a result, but often you don't get a result, and it can take months.

Rather than looking at single cells as in some other functional tests, SageMedic’s microtumors retain the tumor microenvironment and heterogeneity of the biopsy and the three dimensionality that is emphasized these days to understand not just the cancer cells but what is going on around them. Single cell functional tests claim results in two days, but these results haven’t been proven in clinical trials.

How can you access the SAGE Oncotest and work with SageMedic?

- You can request the test for your care, especially if you have solid tumors that cannot be surgically removed or have recurred and have failed first- or second-line therapies.
- You can collaborate in pilot validation or tissue donation studies.

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Meeting Notes

SUMMARY KEYWORDS

patient, tumor, oncologist, drugs, tissue, assay, dose, functional testing, therapies, biopsy, test, treatments, cells, question, chris, developed, sensitivity, dose response curves, number, results

SPEAKERS

Chris Apfel (72%), Brad Power (9%), Glenn Sabin (5%), Arra Yerganian (4%), Amit Gattani (4%), Brian McCloskey (3%), Roger Royse (1%), John Powers (1%), Jeff Krolick (1%)

OUTLINE

SUMMARY

- **Functional testing services for cancer patients.** 0:00
    - Chris Apfel, a scientist and MD by background, co-founded a startup to provide functional testing services after experiencing the challenges of his parents' cancer treatment.
    - He shares his personal story and discusses how functional testing can help patients make informed decisions about their treatments, with examples from his work at UCSF.
- **Cancer research and personalized medicine.** 2:52
    - Chris Apfel thanks others for introductions, shares personal experience with cancer research.
    - His personal experience with cancer treatment inspires him to create a unique solution for personalized chemotherapy treatment.
    - Cancer patients often lack effective treatments due to lack of driver mutations and tumor heterogeneity.
- **Using in vitro assays to predict cancer treatment response.** 9:14
    - Chris Apfel highlights the potential of in vitro testing for cancer treatment personalization, citing study with 90% negative predictive value.
    - In vitro tumor growth is challenging due to limited proliferative materials, with low success rates (30% in some cases) and long growth times (3-6 weeks).

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    - An oncologist's belief that a treatment doesn't work may be due to lack of data, not actually testing its effectiveness.
- **Personalized cancer treatment using tumor microenvironment.** 15:54
    - Chris Apfel highlights the need for clinical trials to prove the effectiveness of chemosensitivity testing, with over 75% of oncologists surveyed expressing interest in using the test despite potential lack of insurance coverage.
    - He suggests developing a new assay to improve upon existing chemosensitivity testing methods, citing the need to better understand tumor resistance and improve patient outcomes.
    - He explains that their method uses fresh cancer biopsies to create live 3D microtumors within a day, mimicking the patient's body and retaining the microenvironment and heterogeneity of the biopsy.
    - The method aims to double the tumor response, significantly improve progression-free survival, and improve quality of life, while reducing costs.
- **Personalized cancer treatment using AI-powered drug sensitivity analysis.** 22:04
    - Researchers use confocal microscopy to analyze drug effectiveness in multiple myeloma cells, predicting high accuracy in tumor resistance prediction.
    - Dr. Konieczny's team tested various drugs for a patient with lung metastasis, finding that doxorubicin and cyclophosphamide were most effective.
    - Developer of Sage direct tests for non-resectable solid tumors, including ovarian, glioblastoma, and pancreatic cancer.
- **Cancer testing and treatment options.** 29:09
    - Brad Power asks Chris about the input source needed for functional testing and the types of treatments tested, mentioning chemo and targeted therapies.
    - Chris Apfel explains that functional testing requires fresh tissue, as fixed or formalin-preserved tissue is not viable, and their technology can work with minimal tissue samples, including tumor samples from pleural effusions or corneal biopsies.
    - He explains that tissue samples can be obtained from bone for cancer diagnosis and treatment.
    - Roger Royse questions the effectiveness of using tumor tissue for cancer treatment, citing preciousness of pancreatic tissue and limited predictive value of liquid biopsies.
- **Personalized cancer treatment using tissue samples.** 36:11
    - Researchers need 100 milligrams of tissue to test six main drugs on pancreatic cancer cells, but often have difficulty obtaining enough tissue due to limited access to tumor tissue.
    - Patient with prostate cancer discusses the potential for keeping biological tissue alive in the lab for drug resistance testing.
    - Researchers have not yet tested whether exposing tissue to drug X in a lab setting can accurately predict its effectiveness in a patient's body.
- **Personalized cancer treatment dosing.** 42:43
    - Patients can have vastly different plasma concentrations of the same drug dose due to individual factors such as body fat, metabolism, and gender.
    - Chris Apfel emphasizes the importance of personalized dosing for cancer treatment, citing their own family experience.
    - A researcher advocates for low-dose combination therapy to reduce side effects and improve cancer treatment outcomes.
- **Personalized cancer treatment strategies.** 49:21
    - Nik Schork, a key figure in the Aveiro trial, can provide valuable insights on precision medicine for bone cancer.

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    - Early-stage tumors are more likely to be eradicated with adjuvant therapy, while later-stage tumors may have different sensitivity profiles and require personalized combination therapies.
    - Oncologists face hurdles in using innovative treatments due to insurance coverage and liability concerns.
- **Cancer diagnostic test development and commercialization.** 55:42
    - Chris Apfel discusses potential strategies for commercializing their cancer treatment assay, including partnering with oncologists and developing a high-quality registry.
    - Oncologists and researchers discuss developing a nonprofit-for-profit hybrid model to address unmet needs in cancer care.
- **Cancer treatment and drug development.** 1:01:18
    - Chris Apfel discussed the challenges of treating rhabdomyosarcoma, including the lack of effective treatment options and the potential for cancer to return after initial remission.
    - He also mentioned that there is a need to eradicate cancer cells as much as possible and get them below the detection level, but the standard of care for high-grade tumors is chemotherapy with a 30% success rate.
    - He explains that the company is not focused on analyzing individual tumor cells, rather their test is mimicking the tumor microenvironment of the tissue sample.
    - He notes that the company's approach can provide treatment effectiveness within a few hours, but most drugs require at least 2-3 days to show a reliable treatment effect.

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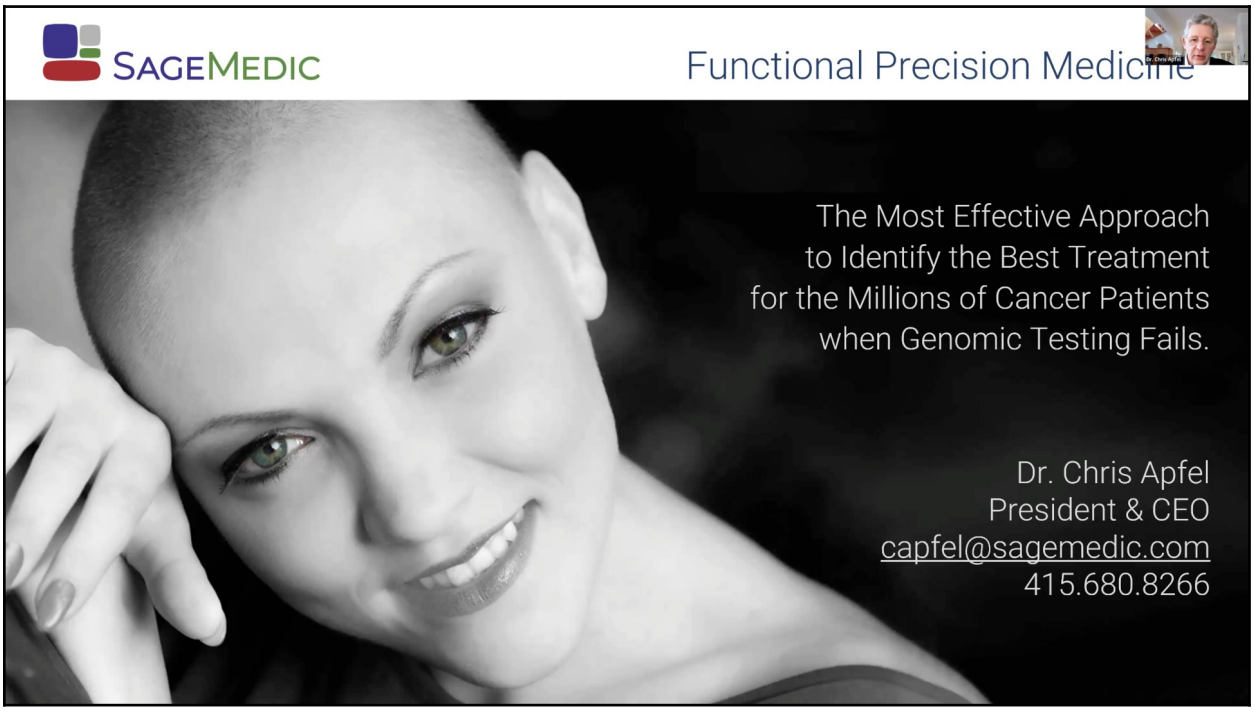
TRANSCRIPT

Brad Power 0:00
I'm Co-founder and CEO of the Cancer Patient Lab. This is another weekly session of our webinar series. Today, we're pleased to have Chris Apfel and colleagues to talk to us about his company and the functional testing services that they provide. Chris is a scientist and MD by background. I'm sure he will tell his personal story. He saw some experiences with his parents that encouraged him to try and solve some of the problems that patients face. He was at UCSF and then decided to launch a startup to provide functional testing services.

We've had half a dozen sessions on functional testing, including one with Robert Nagourney of the Nagourney Cancer Institute. Chris got to know Robert Nagourney in his learning about this area. There are a lot of resources that we have if you're interested in functional testing. I got functional testing from Tony Letai’s lab at Dana Farber. I shared those results last week. You can see examples of how a functional test can help you make decisions about some of the treatments you may be considering, especially the ones that look like they might be more effective.



Chris Apfel 2:51
Thank you very much for the wonderful introduction. I also have Arra Yerganian here. He is our board member and an advisor. We are working very closely together. And we have Rajesh Nitianandan, who is our cancer scientist in our lab. He is doing a lot of the hard work with colleagues and the team that we have at Sage Medic.

Arra Yerganian 3:44

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I was struck by the introductions of many of you on the call. I know that cancer touches just about everybody in some way, shape, or form. I was fortunate enough to grow up in a home where I was exposed to the science of cancer research literally every day. My dad ran the Children's Cancer Research Labs at Children's Hospital in Boston for 47 years. He was the chief scientist at the Jimmy Fund, which is the Dana Farber Cancer Institute today, and I saw his tireless efforts in trying to eradicate something that was devastating, and made great strides in lessening the impact and improving longevity for young young people as they grow older.

I met Chris about a year and a half ago.

I had previously been in healthcare but as a business and strategy and marketing leader. I was the Chief Marketing Officer at One Medical (One Medical is a membership-based primary care service with in-person care and online resources, including a mobile app. In February 2023, it was acquired by Amazon.), then I was in the same role at Sutter Health. I was struck by how frustrating the standard of care is for those who are really trying to do something different, and create pharmacotherapies, or treatment options, that are unique.

Chris impressed me because I saw something that was quite genuine. His personal story is remarkable. Both parents succumbed to cancer. His father refused treatment because he saw how badly the treatment went for his mother. It was an eye opener. As opposed to just clenching his fists and moving on, Chris decided to try to solve the problem.

What he's done over the past many years is through tireless efforts create an impact project that enables individuals to have at the time of tumor biopsy, a sample brought to the Sage labs in Redwood City, and within a very short period of time tested against many chemotherapies, and then ensuring that the right chemotherapy treatment is then provided. We look at this and say, “Wow! How simple is this idea?” But many have tried, and many have failed. What Chris is going to describe to you is really how Sage Medic has made this quite unique. I'm thoroughly impressed with Chris and the team for what they've been able to accomplish. I'm a friend of Chris, but also a board member, and really feel that this passion play of his can change patient outcomes across the globe. He's getting some pretty wild attention as a result.

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Chris Apfel 6:42
You mentioned a number of important points. What really drove me was my personal experience and the realization that, while we often like to believe at major institutions that the future is here now, the reality is, if one of you is affected, and you have been, that we often are still living in the past. We're not leveraging all the possibilities and technologies that are currently in development.

We have developed the next generation of an extreme drug resistance assay. We believe that this will make a huge difference for the millions of cancer patients where genomic testing often doesn't work.

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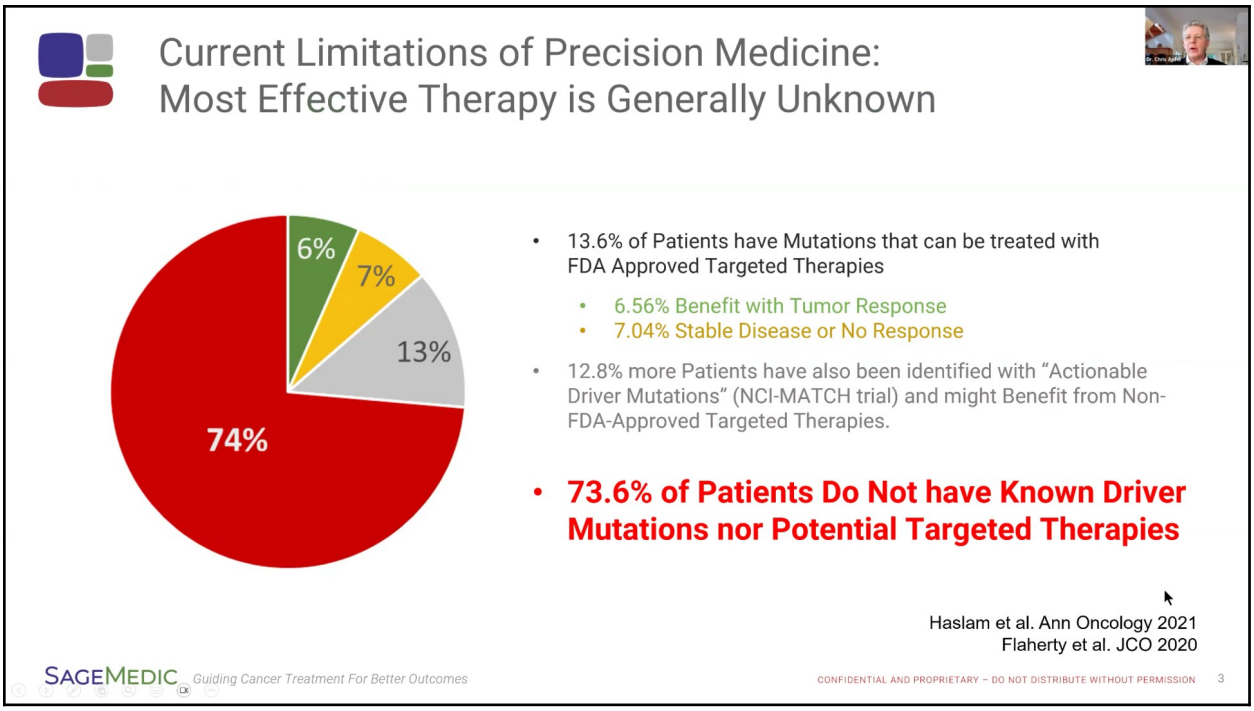

That's one important message that you are probably all aware of, but few others are: in the majority of cases patients do not have driver mutations. We all believe that with genomic testing, we often call it “precision medicine”, but the reality is that only one out of four patients has driver mutations according to the National Cancer Institute's MATCH trial, as Dr. Letai mentioned in one of his presentations. Then if you look at how many patients get FDA-approved targeted therapies, and how many really benefit from it, we are getting below 10%. So the majority of patients do not have driver mutations nor potential target therapies. That's the devastating state. Most will get therapies where we actually don't know which therapies are likely to work best.

When my dad was diagnosed with lung cancer, I was asking Dr. Johann from UCSF, who is a key opinion leader and has also written the NCCN guidelines, “Why don't we just test it on the tumor instead of trying it out on the patient?” His response was, “People have tried that before, and it doesn't work.” One of the arguments was tumor heterogeneity and the tumor microenvironment. Probably somewhere if you put it in vitro (in a test tube), it's different. It's surprising to me because as an anesthesiologist and intensivist, when somebody has an infection, what we often do is culture the specimen of the bacteria in order to understand which antibiotics are likely to be most effective. We do those in vitro live cells, basically live cell assays, but we don't do it in the oncology space. So I took a look myself. I spent about over a year going through all the papers that have been published in the past to understand why it did not work.

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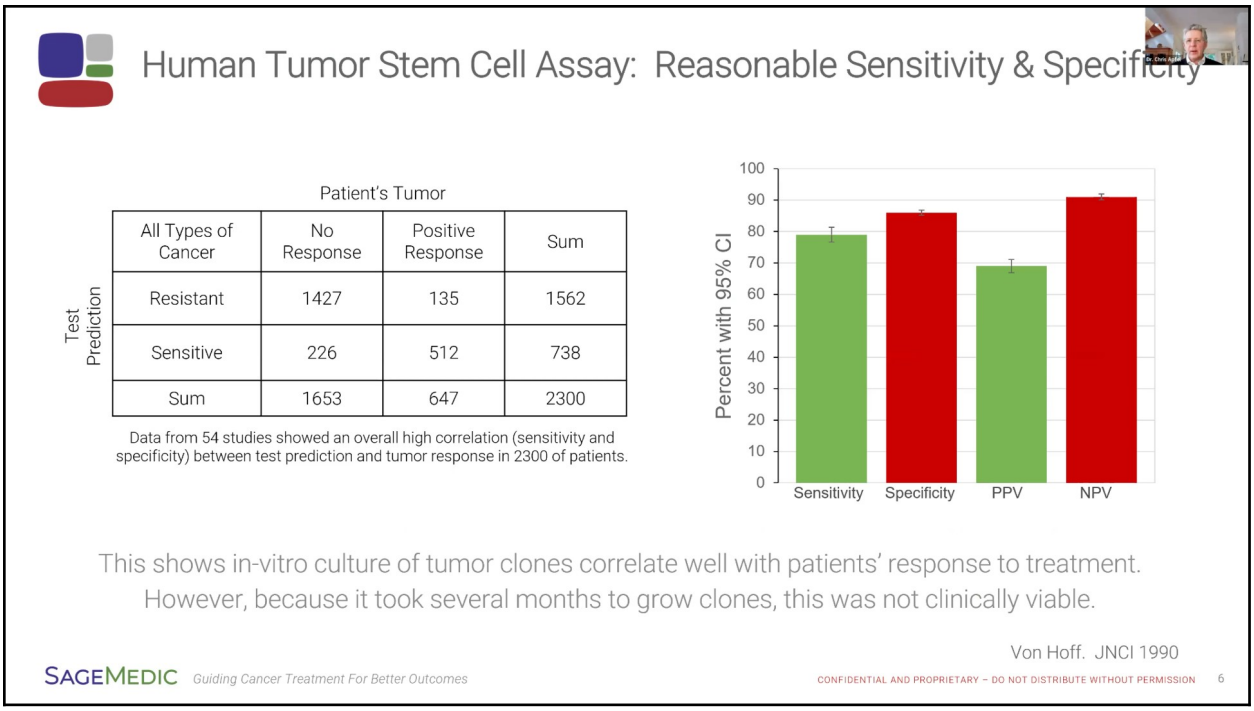

I will give you a few examples here that will give you hope. First of all, there is this concept that if you put something in vitro, it doesn't translate to in vivo (in the body). This is not accurate if you look at the data objectively. This is a paper published by Daniel Von Hoff over 30 years ago. They were able to grow tumors on agar, have a control group, and have others growing with different treatments. They were able to show that they have basically negative predictive values of over 90%. So that comes from those numbers. I don't want to bother you with the statistics, but the negative predictive value, that's the reason why I colored it red. So that's where the patient doesn't respond, you want to avoid that. For the specificity, which predicts which patient will not respond, as well that is also therefore red. Sensitivity and positive predictive value are in green, which is which drugs will work. The patient will correctly be identified that this will work. So 80%.

So the question is, “Why is it not here now?” One of the reasons is – and that's a problem with whenever you're trying to grow the tumor – growing tumors in vitro is very, very hard. You have heard from SEngine that the organoid models usually take three to four weeks, sometimes six weeks. Very often they don't grow at all because you may not have enough proliferative materials in the biopsy. So one of the limitations of those assays were, they were accurate if you got a result, but very often, you didn't get a result. And it took way too long.

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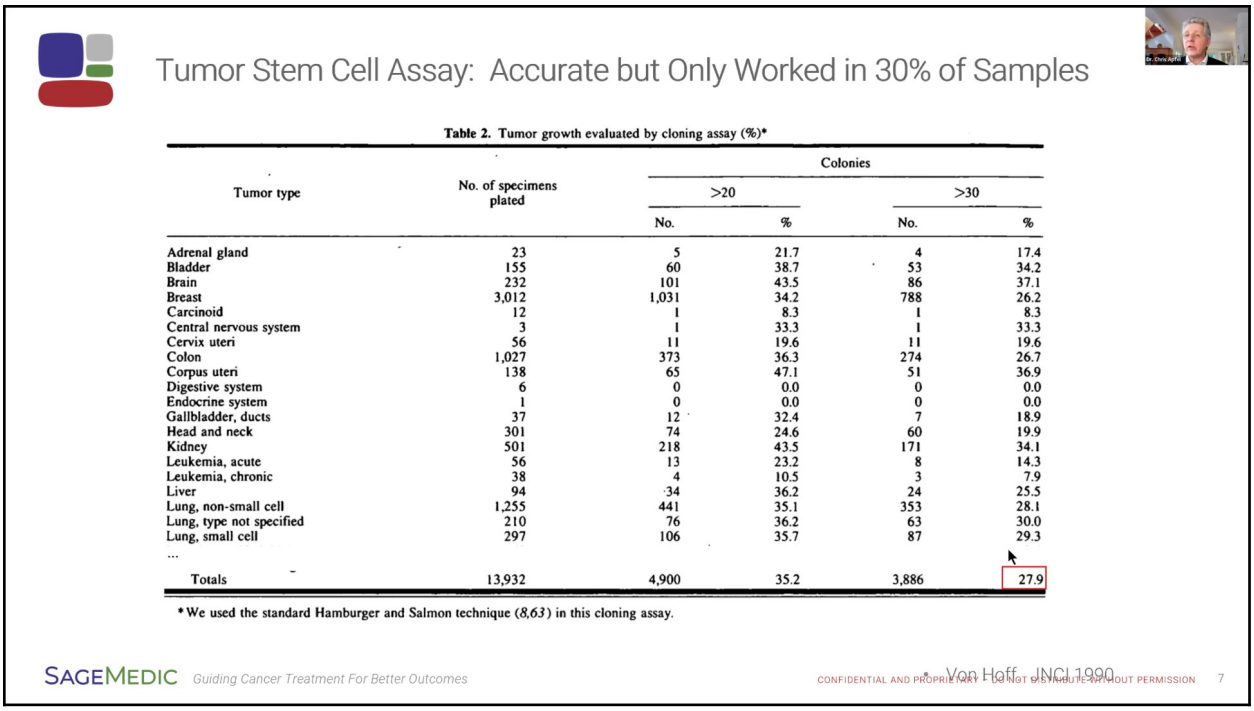

Tumor Stem Cell Assay: Accurate but Only Worked in 30% of Samples

Table 2. Tumor growth evaluated by cloning assay (%)*

Tumor type	No. of specimens plated	Colonies >20 No.	Colonies >20 %	Colonies >30 No.	Colonies >30 %
Adrenal gland	23	5	21.7	4	17.4
Bladder	155	60	38.7	53	34.2
Brain	232	101	43.5	86	37.1
Breast	3,012	1,031	34.2	788	26.2
Carcinoid	12	1	8.3	1	8.3
Central nervous system	3	1	33.3	1	33.3
Cervix uteri	56	11	19.6	11	19.6
Colon	1,027	373	36.3	274	26.7
Corpus uteri	138	65	47.1	51	36.9
Digestive system	6	0	0.0	0	0.0
Endocrine system	1	0	0.0	0	0.0
Gallbladder, ducts	37	12	32.4	7	18.9
Head and neck	301	74	24.6	60	19.9
Kidney	501	218	43.5	171	34.1
Leukemia, acute	56	13	23.2	8	14.3
Leukemia, chronic	38	4	10.5	3	7.9
Liver	94	34	36.2	24	25.5
Lung, non-small cell	1,255	441	35.1	353	28.1
Lung, type not specified	210	76	36.2	63	30.0
Lung, small cell	297	106	35.7	87	29.3
...					
Totals	13,932	4,900	35.2	3,886	27.9

*We used the standard Hamburger and Salmon technique (*8,63*) in this cloning assay.

SAGEMEDIC Guiding Cancer Treatment For Better Outcomes

• Von Hoff, JNCI 1990

This is an example. They only had 30% get a good result at that time. It depends on the tumor type. If we're talking about breast and prostate cancer, the rates are usually in the range of 20%. It's very, very difficult to grow tumors in vitro.

I've also looked at many other assays. Robert Nagourney was mentioned. He did enormous work and has a ton of experience. He was a fellow of Larry Weisenthal who developed the DISC assay (differential staining cytotoxicity). He founded Oncotech (a national clinical laboratory corporation) in the early days, and is one of the key figures in functional profiling.

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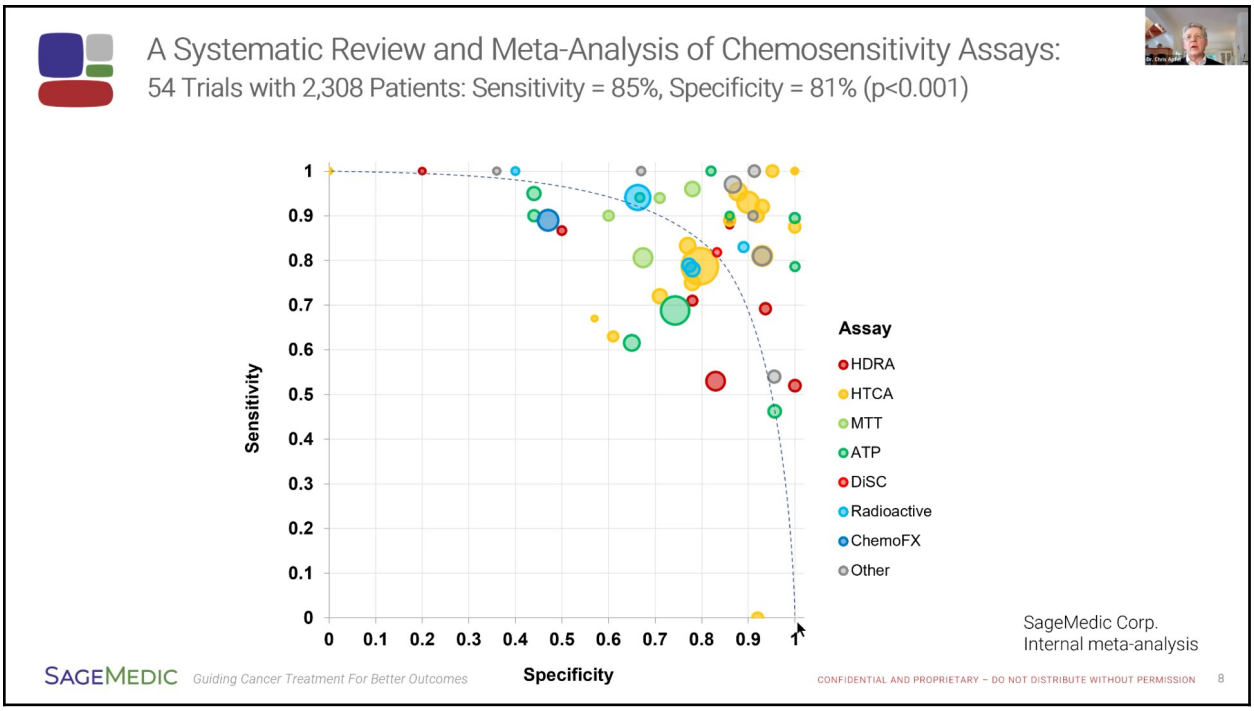

I analyzed all the data because I have a quantitative background. I'm still an adjunct professor of epidemiology and biostatistics at UCSF. I looked into the data, and I saw in the area under the curve, which is basically the tradeoff of sensitivity and specificity for all the assays I could find in all the published papers at the time, I was able to see that sensitivity and specificity to predict a tumor response was over 80%, on average. So if an oncologist tells you we know it doesn't work, then it's because the oncologist has never dared to look at the data. That's frustrating to me. Because oncologists nowadays very much adhere to the standard of care for good reasons. There is a good reason for the standard of care in general. It improves the average outcome. But there are situations where you actually have to go beyond, especially when the standard of care is failing.

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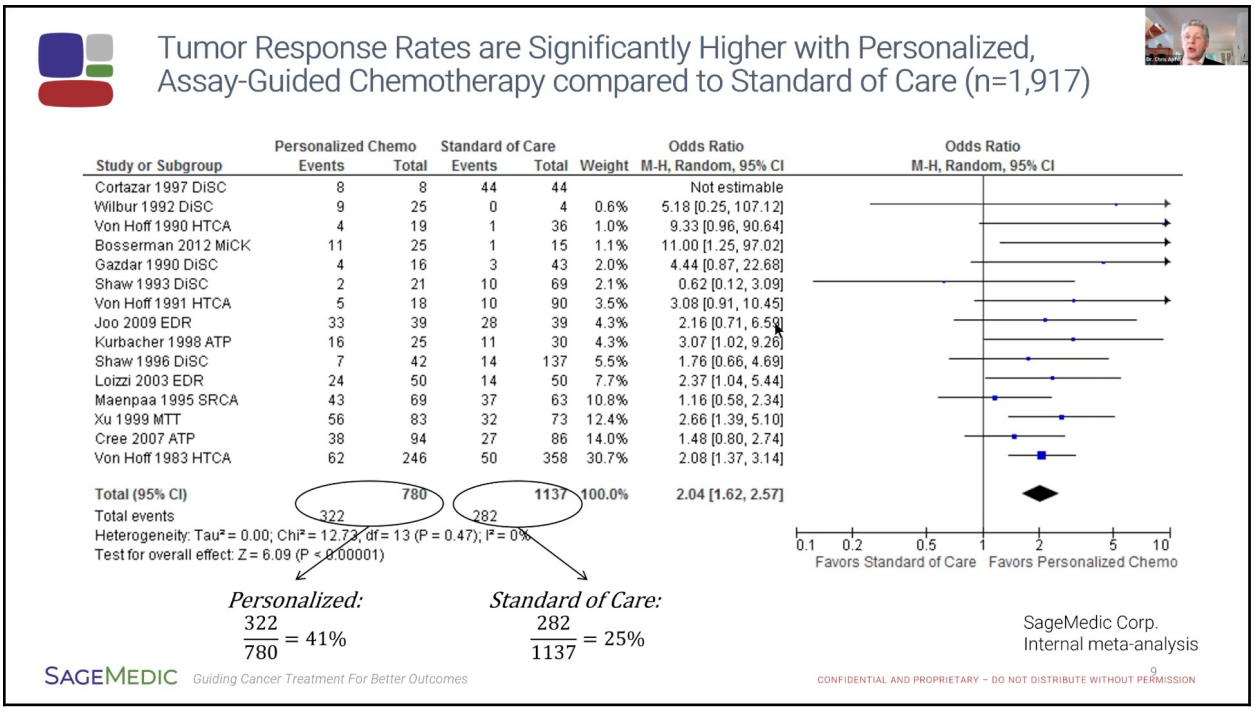

This one only shows a correlation that could be prognostic. What you really want to know is whether you can improve a patient's outcome if you are using that information, by then selecting a drug that is more effective. You can only know that if you have a comparative effectiveness trial, where you compare two different groups. I presented this to Robert Nagourney. I showed this also to Larry Weisenthal. We submitted this as an abstract to ASCO almost 10 years ago. We know that if a patient gets treated according to what demonstrates sensitivity (a test's ability to designate an individual as positive), or if we are avoiding resistance for this patient, the likelihood, if you look here at the data, is that you double your odds to have a tumor response. That is based on roughly 2000 patients.

The reason why most oncologists, even today, believe that this doesn't work is because if you look at most of the studies, they are underpowered to show a statistically significant difference. If the error bars of the 95% confidence interval that you see here – you don't want to cross the vertical line labeled with the number one – the result is statistically significant, or others are statistically not significant. Often, the bottom line conclusion is, the assay didn't work. If you look at those papers, and you only read the abstracts, or the conclusions, you will read that most of the papers more or less say, “We were not able to show it's a difference.” But there is a difference between the lack of evidence or the evidence for the lack of an effect. That's confused here. When I saw these results, it was very clear to me: “Yes. It can be done.” That's why we know this can make a huge, huge difference.

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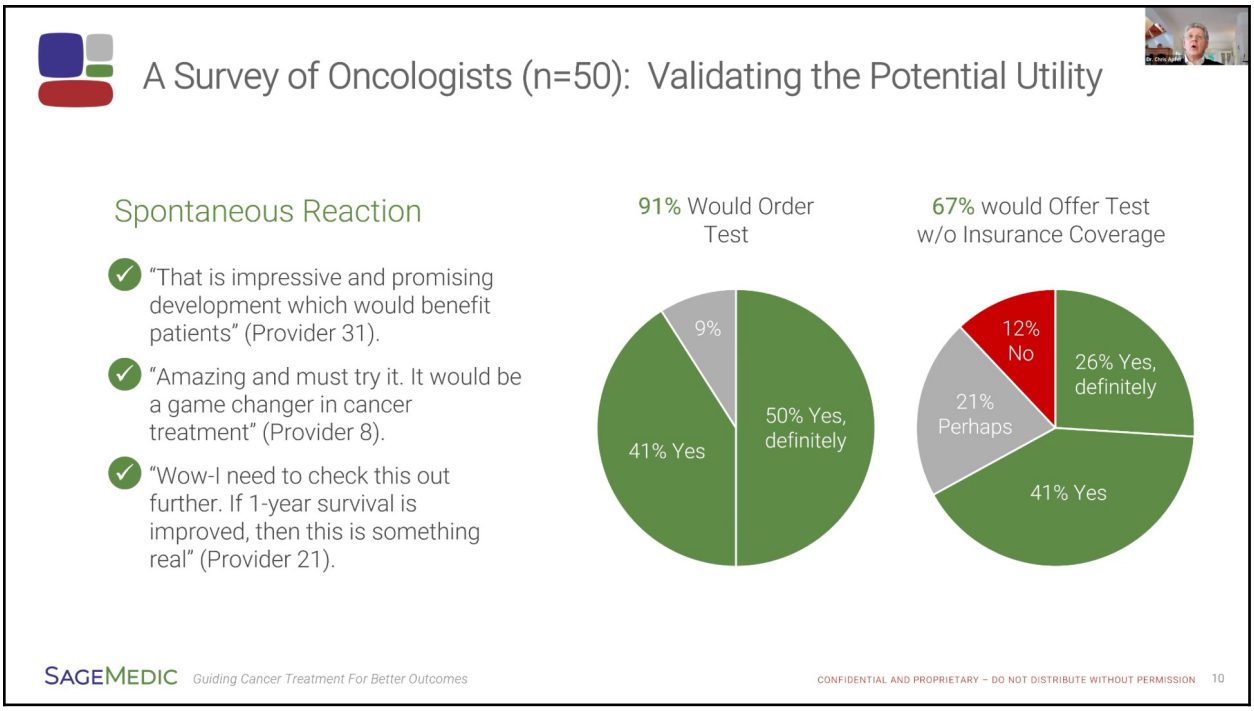

Chris Apfel 16:09
What is really needed are clinical trials to convince oncologists that this is an important part of tailoring the cancer therapy to the patient so that the right drug is given to the right patient at the right time.

We conducted a survey (of oncologists). We asked them whether they would prescribe or order a test that had those characteristics that I just showed you. Basically, everybody said, “Yes.” Then I said, “Even if there were no insurance coverage, and you might think that the patient might be able to afford it?” Then two-thirds would still say, “Yes, or definitely, yes.” It's very clear that there is a need. Then in the survey, we asked, “What do you think about chemosensitivity testing?” And then some oncologists just stopped the survey or just said, “No.” Or they said, “This is a hoax.” It's quite interesting how strong the opinions are, to a degree that you really need to have data to get there.

I have, therefore, suggested to Robert Nagourney and Larry Weisenthal to conduct clinical trials because clinical trials are part of my expertise. I've published over 100 papers on this in my field. I know how to do that. But they were reluctant to randomize patients with either assay-guided therapy, or what's considered standard of care, because Robert Nagourney felt the standard of care is kind of unethical. But on the other hand, if we don't show it in clinical trials, then at the end of the day, we will never get traction, so that it will be universally accepted.

That's when I started to realize that we need to develop our own assay. The assay that Robert Nagourney developed is quite dated. The biology is still true, but there are a lot of things that could have been or we have improved.

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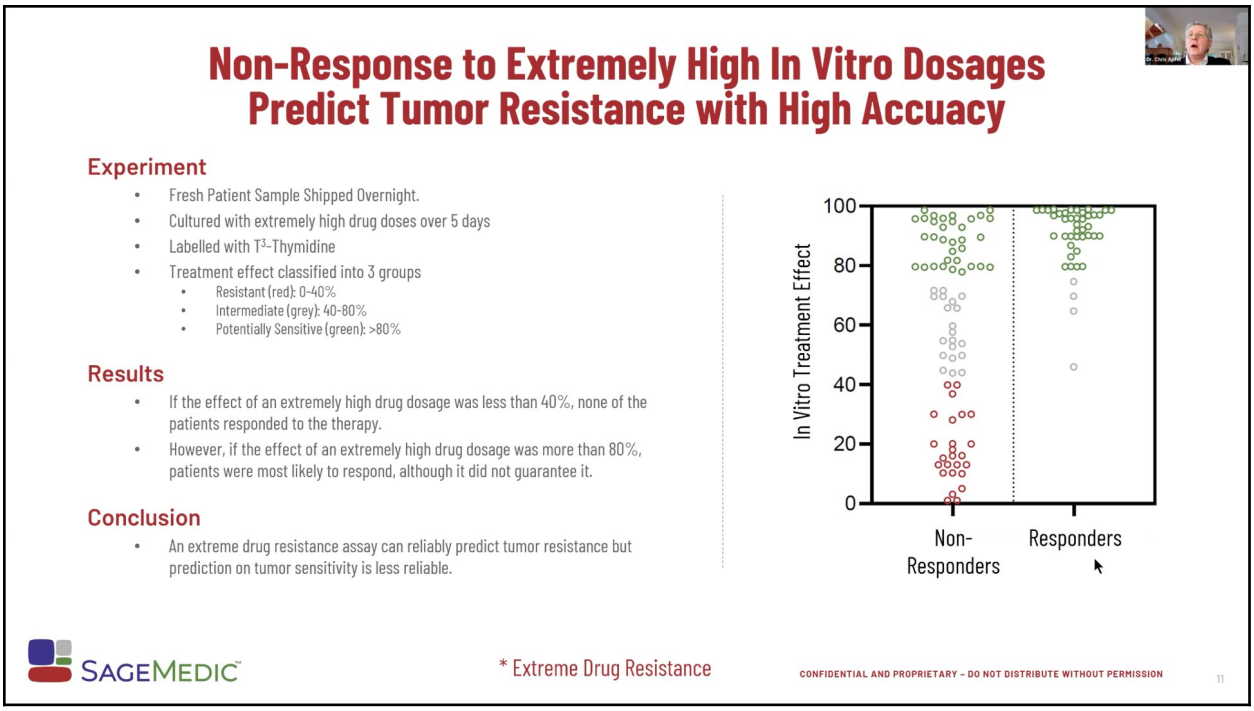
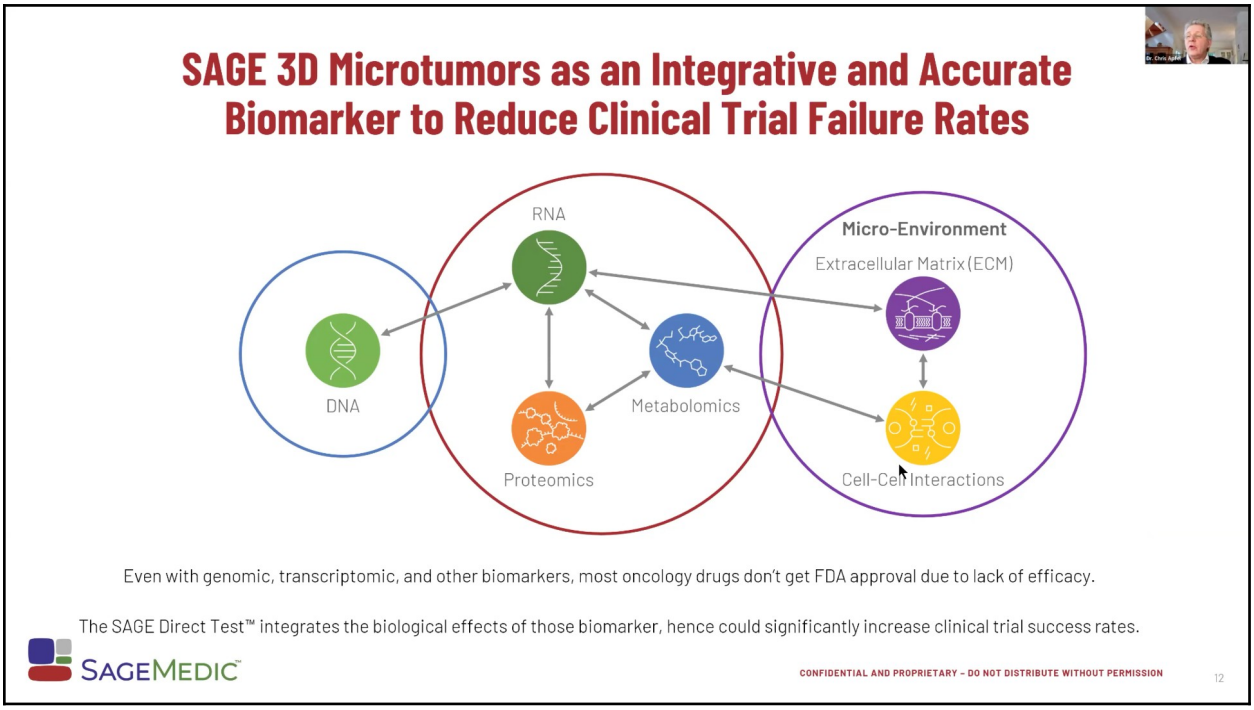


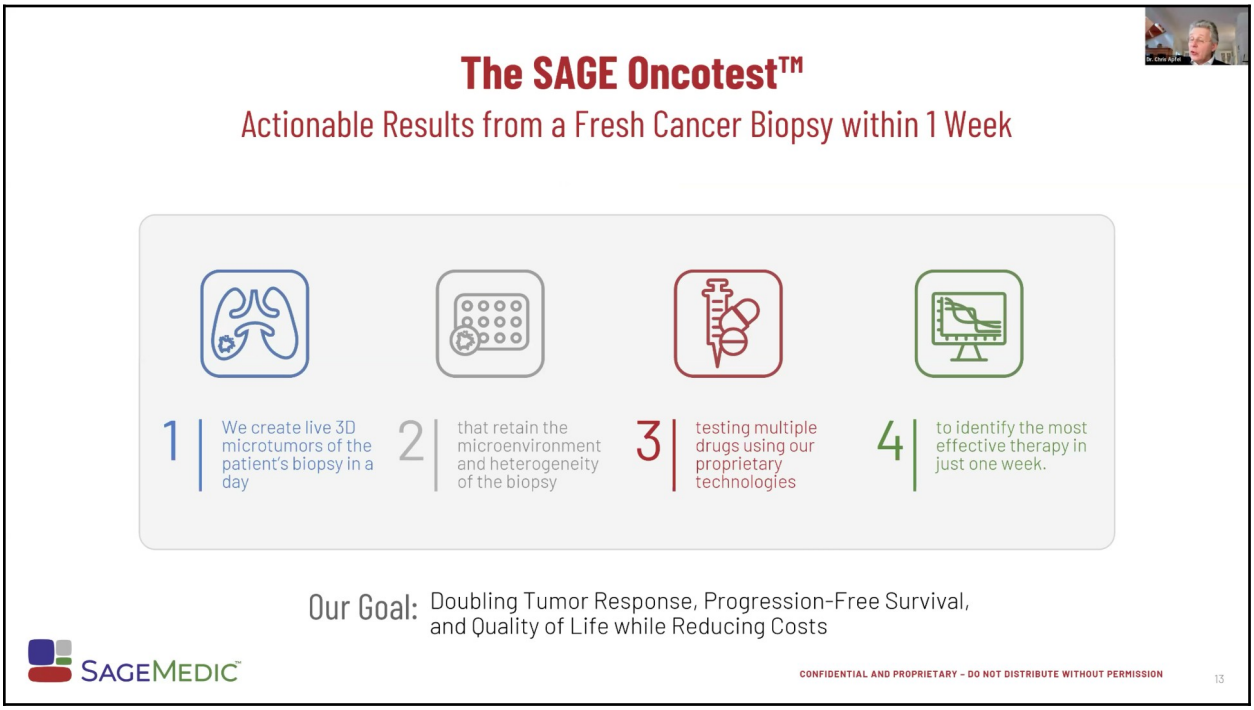
We have now developed an assay that can go beyond what was possible before. We can look at tumor resistance.



We know from our proprietary assay here that when a patient's tumor does not respond, ex vivo, towards the therapy, and the supraphysiological doses, then it can also not respond in the patient. That's generally known. We apply the drugs in the microtumors that we are creating at

various doses. Therefore, we can also use supraphysiological doses. We can see that if the patient's tumor is still viable, that this cannot work. We also know that taking the tumor as a whole, the whole is more than the sum of its parts. It's more than just the DNA. It's more than RNA or a metabolic pathway. Especially when we're not just taking single cells, but we also can consider the extracellular matrix and cell-cell interaction, and therefore mimic the microenvironment, that we have a fairly good surrogate for how this tumor would respond in the patient.

That could also be used for drug development, which this slide was referring to.



Our goal was to be able to have actionable results from a fresh cancer biopsy within one week or 10 days, and that's the key message. We need to make sure we get this for virtually every patient. It can't be that we need to wait for weeks or months until the tumor has grown and then find out it hasn't grown. We should mimic this to as close as possible to the patient's body and not just look at the single cells. We can now create live 3D microtumors of the patient's biopsy within just a day that retain the microenvironment and heterogeneity of the biopsy, so that we can test multiple drugs to identify the most effective treatment within just one week. Our prediction is that we can double the tumor response, significantly improve the progression-free survival, and improve quality of life, which may or might also be reducing costs. We are very bullish on believing that we can do at least that because our meta analysis already shows that previous assays have such a treatment effect. And our assay, which is now much more advanced than has previously been on the market, therefore should do at least that.

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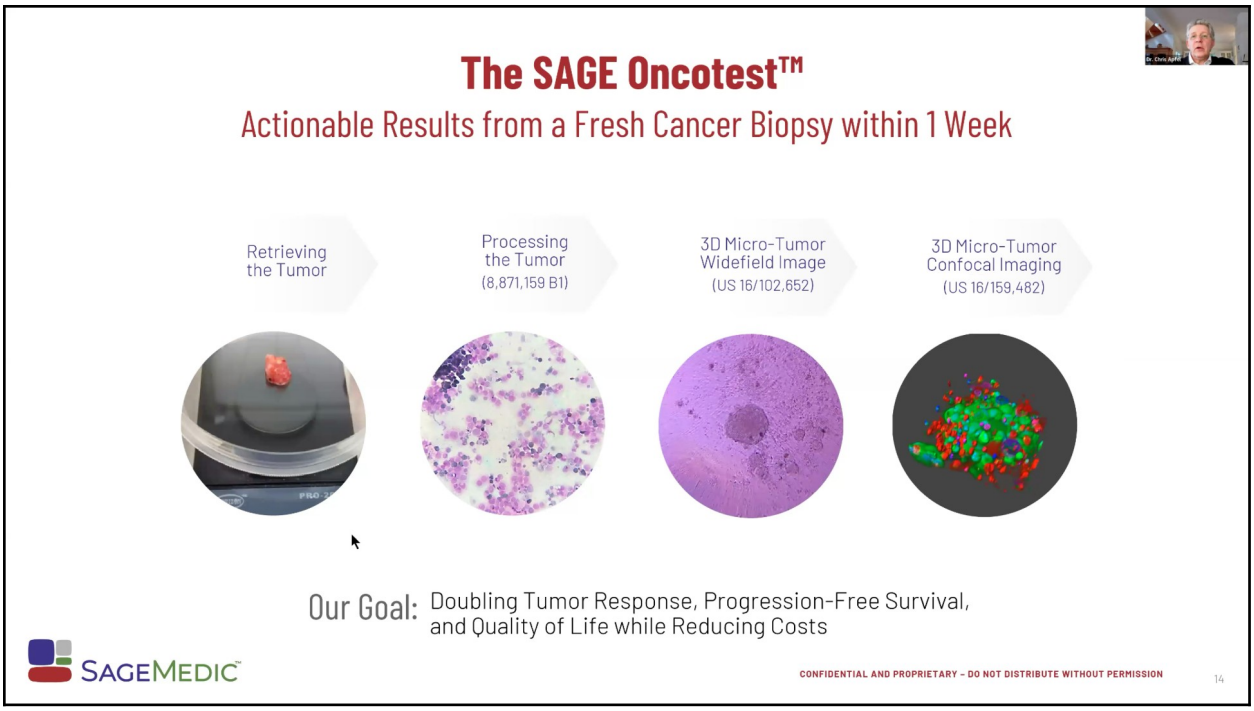
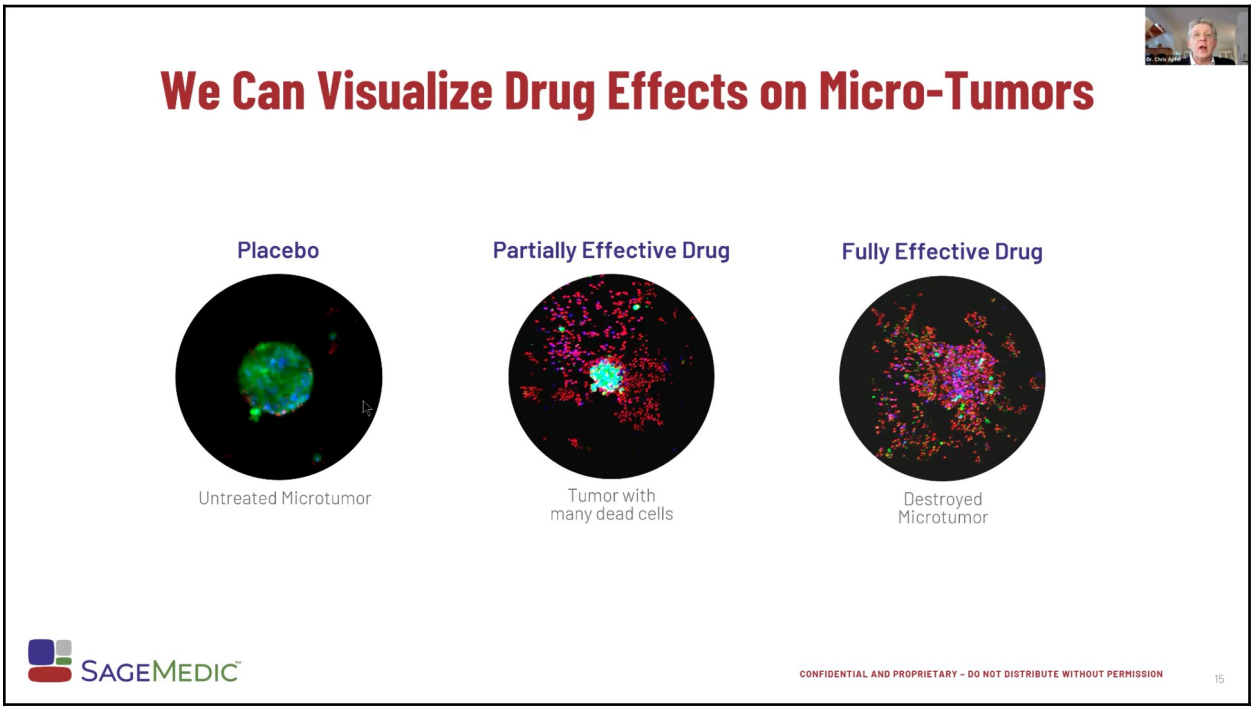
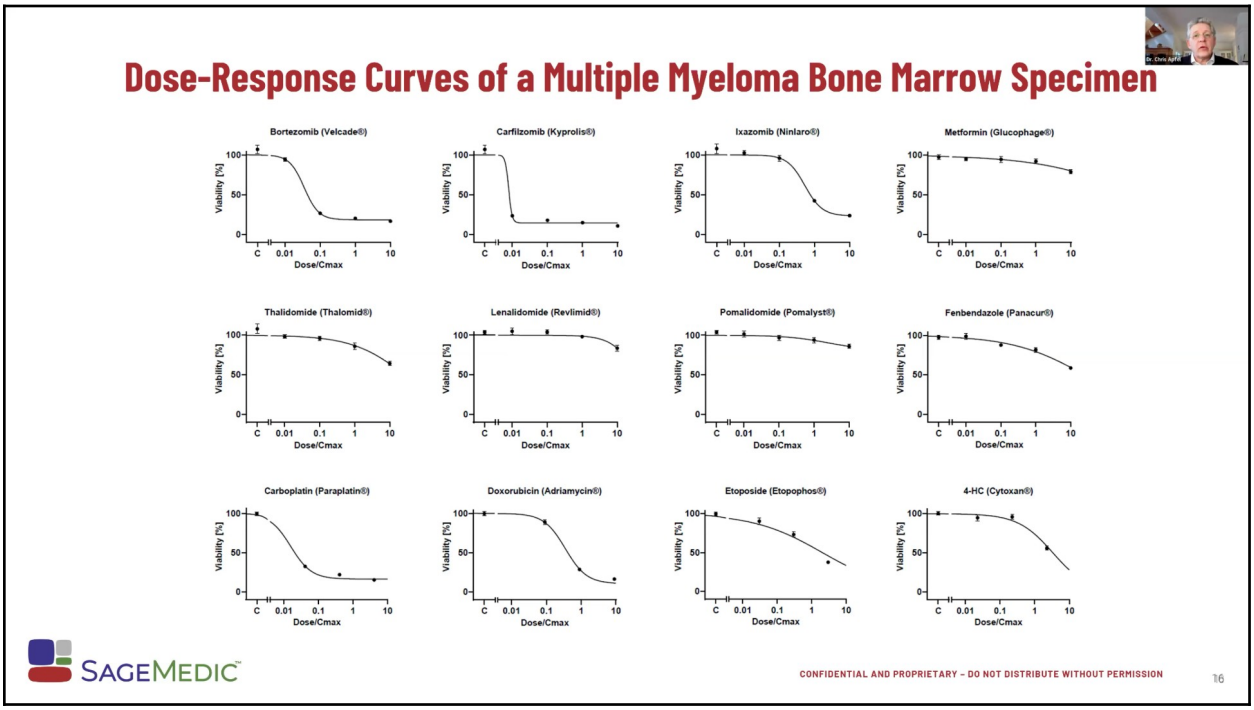


This gives you a rough idea on how we do it. We maximize the use of tumor fragments that have the original cell-cell interactions, the original matrix, and tumor microenvironment. That is, it is in suspension. Then we have an aggregation step, where within one day, we have the formation of these microtumors, where each of the wells reflect the tumor biology, the microenvironment, and the heterogeneity of the biopsy sample within each well. And then we can have different readouts.



“Identifying the Most Effective Treatment on the Tumor Rather than Trying It Out on the Patient” (Dr. Chris Apfel) [#84]

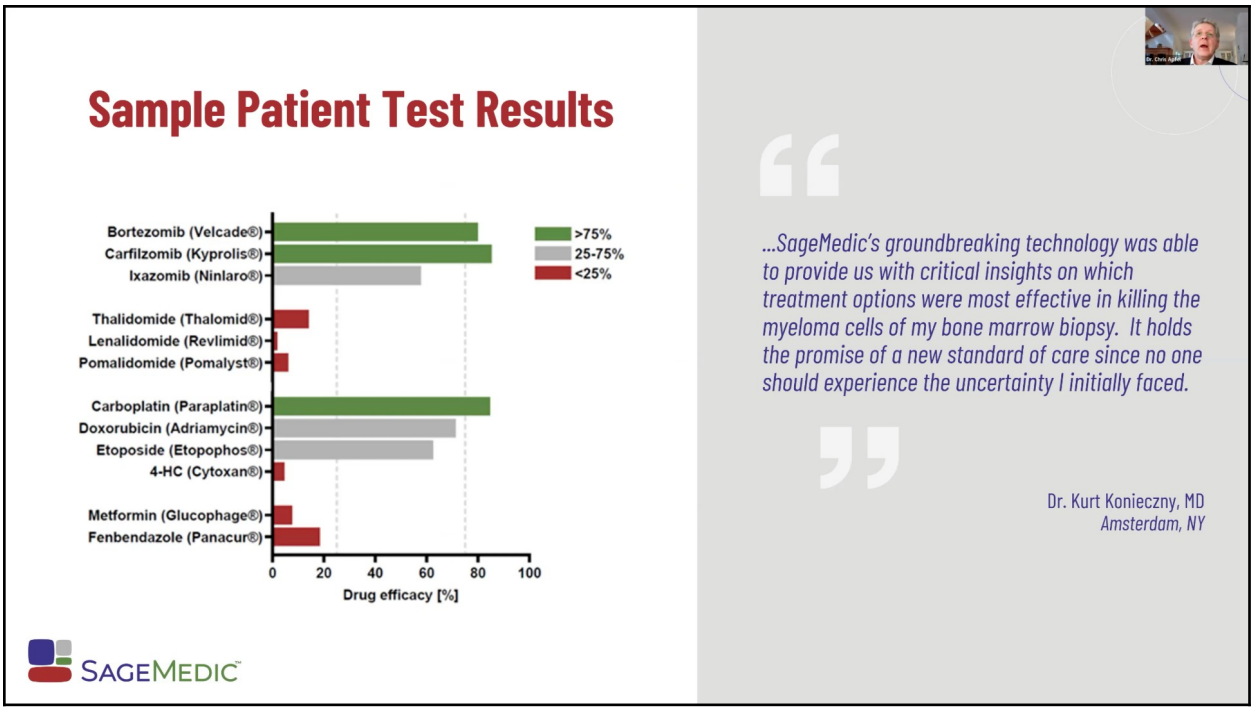
One of the readouts is looking at – with a confocal microscope (a confocal microscope produces a point source of light and rejects out-of-focus light, which provides the ability to image deep into tissues with high resolution, and optical sectioning for 3D reconstructions of imaged samples) – how many cells are dead or alive, which you can see here. You can see a tumor that is treated with its control group. Then you see one that is completely destroyed by a fully effective drug.



We do full dose response curves. It's very easy just to pick one dose and be wrong. When it comes to patient lives, it's really important that we know the data points are reliable and reproducible. We've worked a lot on reproducibility, also working with quite a number of replicates.

This is an example of a multiple myeloma patient, where we can see here with Velcade (bortezomib). You can see that it reduces the viability at a certain concentration, as opposed to lenalidomide (Revlimid), or Metformin, which somebody else also wanted us to test. Those drugs are not effective, as opposed to those that can significantly reduce the viability of those multiple myeloma cells in the tumor.

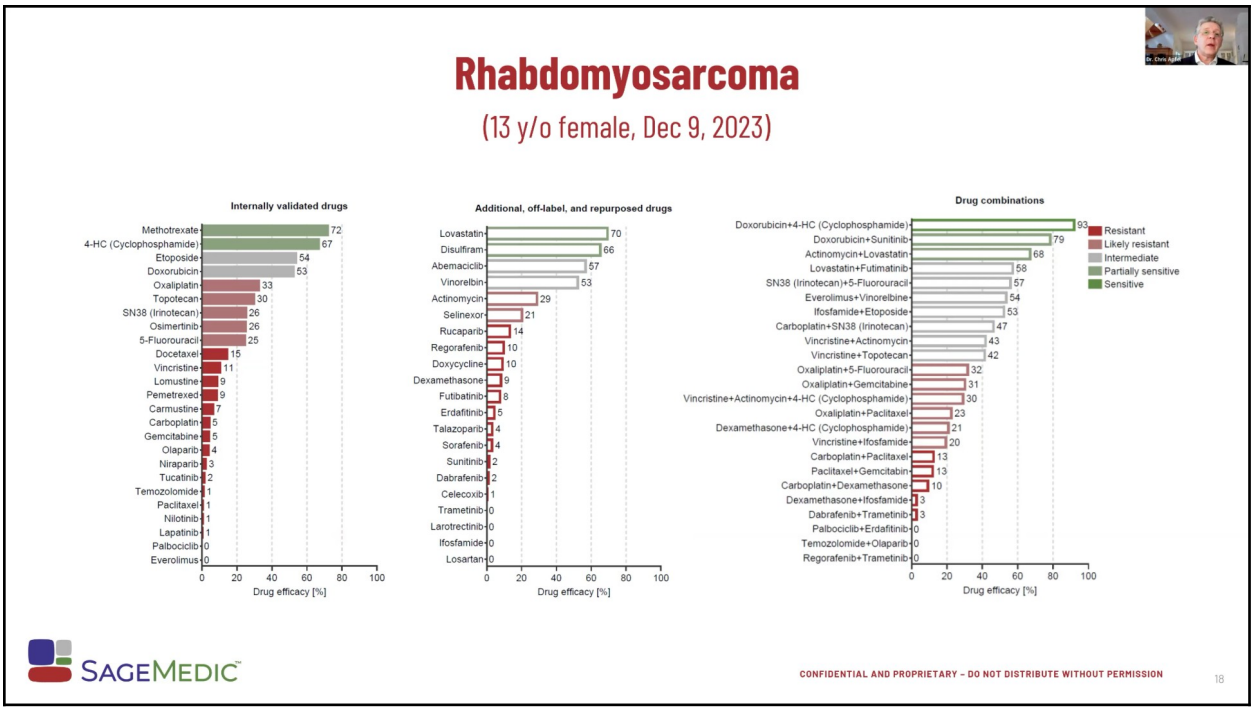
“Identifying the Most Effective Treatment on the Tumor Rather than Trying It Out on the Patient” (Dr. Chris Apfel) [#84]



We then aggregate those results to a bar chart, so that the oncologist can directly come up with a conclusion and have actionable information. Because we are also going to extreme drug concentrations that could not be tolerated by a patient physiologically, we are very certain about the prediction of tumor resistance. We believe that our prediction in our prospective studies that we're planning will be above 90%, probably enough above 95%, that we can predict tumor resistance in patients. Then we also have information on the sensitivity, but the sensitivity information requires calibration, so whether Bortezomib is really more effective than Carfilzomib, I don't think one can actually make that claim. But at least one has an idea on which drugs are likely to be most effective.

This was done for Dr. Konieczny, who was both the patient and a pediatrician, and he really appreciated having information that otherwise would not be possible.

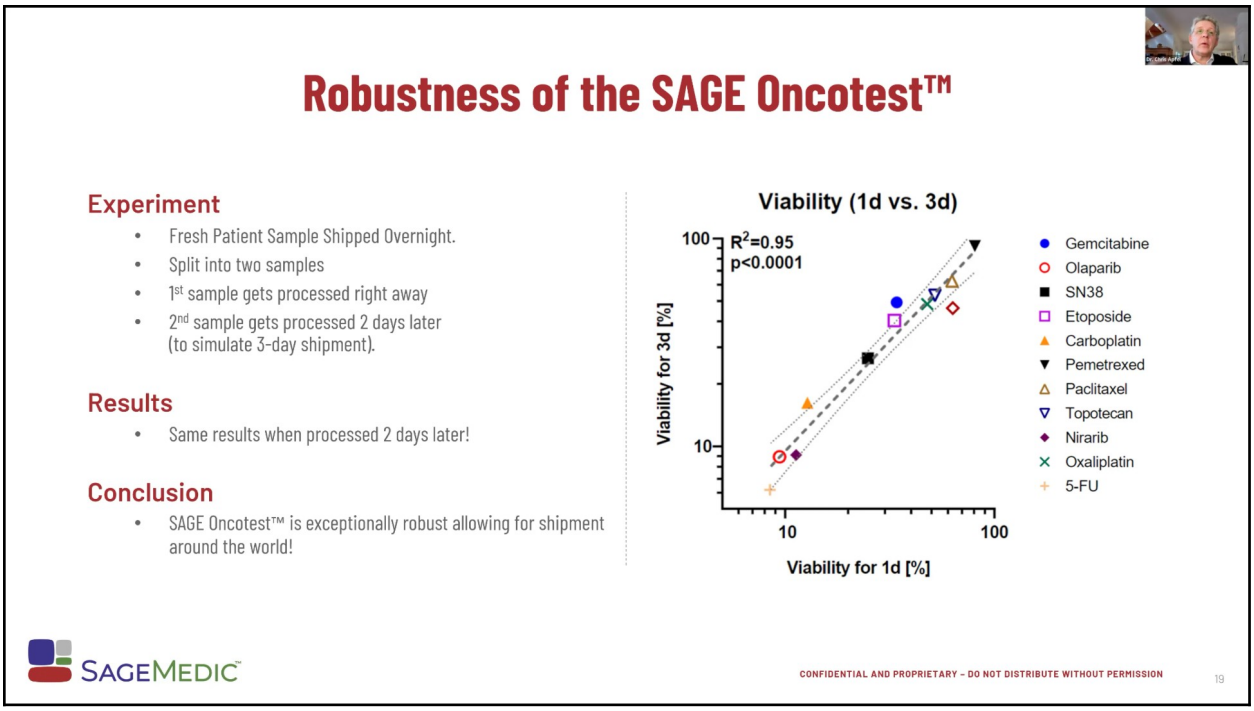
“Identifying the Most Effective Treatment on the Tumor Rather than Trying It Out on the Patient” (Dr. Chris Apfel) [#84]



This is a recent result where we went beyond our call of duty – beyond just testing standard of care drugs – because the mother of the patient really wanted us to try whatever is potentially available and possible. On the one hand we tested drugs that are used for rhabdomyosarcoma and looked at the sensitivity and resistance. We also tested repurposed drugs. For example, integrative oncologists often talk about Lovastatin, Disulfiram, Losartan, Celecoxib. Depending on the patient, they may actually have some effectiveness. We were very, very surprised to see that Lovastatin and Disulfiram had those cytotoxic activities at physiological concentrations. We were quite impressed with that. We are not suggesting to substitute this, but this was on a lung metastasis of this patient. We really need to find the best possible treatment and combinations into what's clear here is doxorubicin and cyclophosphamide showed the highest effectiveness, and that's what this patient is now going to get.

That's what Sage can do in order to make sure that the patient is getting the best possible treatment and is not hurt by treatments that we know cannot work ahead of time. So for example, Ifosfamide, that is down here, is not effective at all. Often also different combinations, that would only lead to side effects for this patient, would be completely unnecessary.

“Identifying the Most Effective Treatment on the Tumor Rather than Trying It Out on the Patient” (Dr. Chris Apfel) [#84]



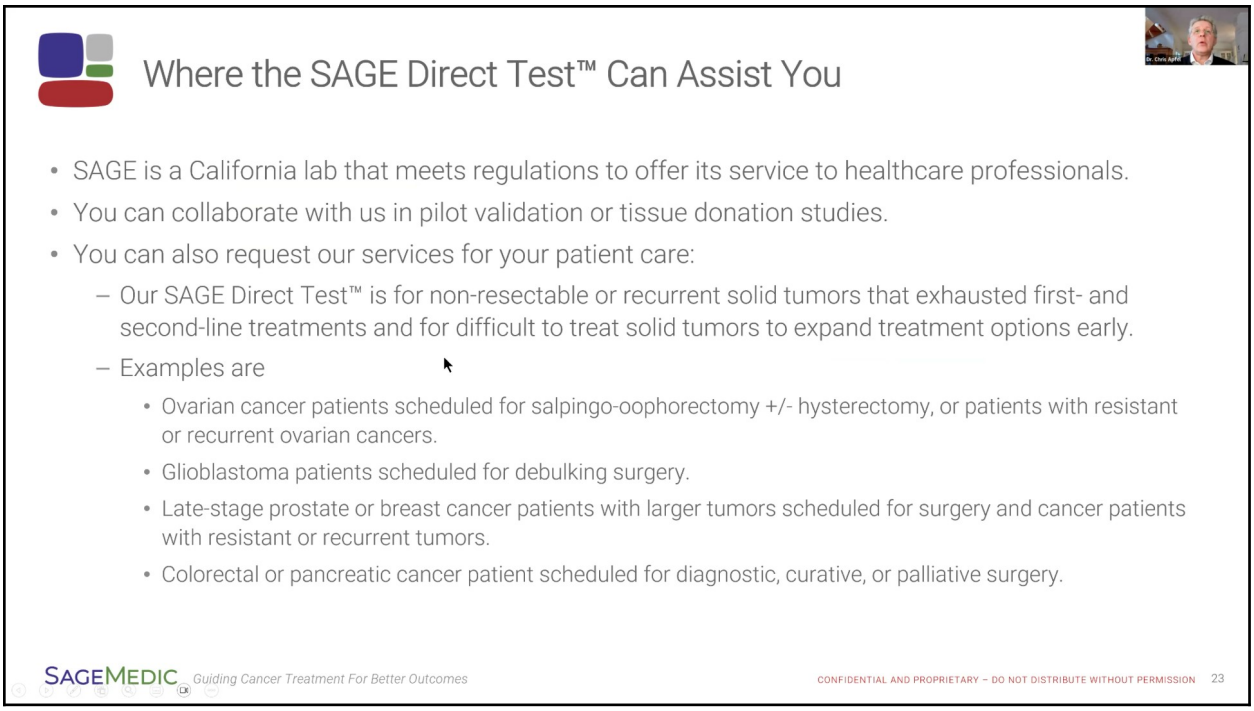
One important part for us is reproducibility. We are very proud to say that even if we have shipment delays, etc., because this is fresh tissue, there's always a concern that it is still valid. We know that our assays are very, very robust.

During the times of COVID, we have spent a lot of time making sure we have all the SOPs (standard operating procedures) in place. Establishing a CLIA lab (certification by the Secretary

of the Department of Health and Human Services per the Clinical Laboratory Improvement Amendments of 1988 for any facility performing examinations of human specimens, e.g., tissue, blood, urine, for diagnosis, prevention, or treatment purposes) is non-trivial if you're not coming out of an academic center that already has a pathology lab or a CLIA lab running there. We're very proud that we are now a California registered, CLIA registered, and CMS accredited lab that can report patient results.

I would like to come to a conclusion. This would not have been possible without our wonderful team, including Arra Yerganian, and including my wife Dr. Brigitte Apfel, who really has supported me throughout the years in getting this off the ground. We invested most of our savings in getting this started and developing IP. We have raised some more angel capital. We have not been as lucky yet to get the big venture capital funding like other companies that have a cooler technology out of a major institution because we have developed the technology all on our own and all the IP. But we are very proud that we have such a wonderful team that has made this possible without which this would not be possible.

“Identifying the Most Effective Treatment on the Tumor Rather than Trying It Out on the Patient” (Dr. Chris Apfel) [#84]



We can use our SAGE Direct test, that we now call the “SAGE Oncotest”, for non-resectable or recurrent solid tumors that have usually exhausted first- and second-line treatments. There are a number of examples from ovarian cancer to glioblastoma, late stage prostate or breast cancer patients or colorectal and pancreatic patients as well.

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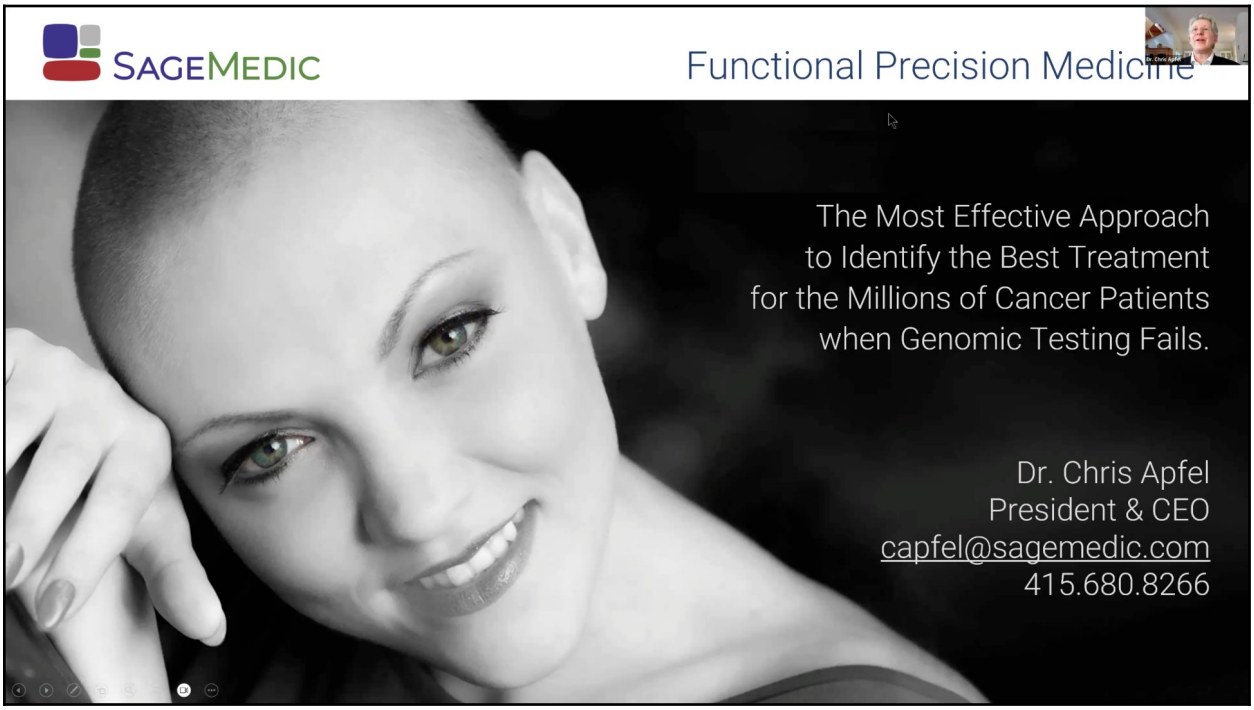
There is a lot that we can do here. The next steps are to collaborate on pilot studies, or tissue donation studies. Late stage patients really need these results. We can run those results anytime.



Brad Power 29:09
To put things in context, it seems like you have a better, more modern approach, and a better lab pipeline to do functional testing than, as you said, maybe some older technologies, but I would assume that you would still have the same issues that a patient needs fresh tissue because a lot of our patients are in remission, or they have bone mets where it's hard to get tissue?

The other thing is that I assume this is largely for chemo or targeted therapies. Historically, functional testing was used for chemosensitivity. Either chemo or targeted therapies are the main therapies you would be testing, which would leave out things like immunotherapy?

What's the input source that you need to run your test?
And what kinds of treatments might this be applied to?

Chris Apfel 30:21
Number one, yes, we need fresh tissue. It doesn't work with paraffin-fixed (wax) tissue, or if it's already in formalin (a preservative), which is basically the standard nowadays. If a tissue is removed from surgery, and it's thrown into formalin, then the tumor is dead, and you cannot do functional testing. That is true. The reason why functional testing has this power to make a prediction on what would work is because it's alive. So you need to have live tissue.

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One of the advantages of our technology is that we need very little tissue. We have been able to obtain and work with samples from ascites or from a pleural effusion. (In pleural effusions and ascites, excess fluid that can no longer be removed accumulates inside the body. In a pleural effusion, the fluid accumulates in the space between the lungs and ribs; in ascites it accumulates inside the peritoneal cavity.) We can get reproducible results from those patients as well. For patients who have that need to be drained, you don't need an additional biopsy. We have refined our technique so that we can also work with core needle biopsies, provided that they have a high tumor content. If we have a core needle biopsy, that is another possibility, in particular if this is a high grade tumor.

Usually what makes more sense is if a patient is scheduled for surgery, it's important that we get informed ahead of time, ideally at least a week, but we actually need at least two days to provide them with the shipment kits so that we can get the specimen. In gynecological cancers it's very important that patients are scheduled. For ovarian cancer, the ovarian cancer oncologists and surgeons are very open to that, because they know the situation. They have access to the tissue, but they often also do the chemotherapy or targeted therapies, let's say PARP inhibitors, for patients with BRCA mutations. They also do the chemo or targeted therapies on the patients later on. So they therefore know how important it is to have it. They are very happy to provide the samples to us.

Immunotherapy we are currently not testing. I think I'm very skeptical if somebody makes a claim in that regard. That is still an area that needs development. But let's keep in mind in immunotherapy, only one out of five patients are responding to it, no matter how much you might test. It would be nice to know. But most patients do not respond to immunotherapy.

Brad Power 33:17
What if someone has active cancer, but it's in the bone? Is there a way to access your test with tissue from the bone?

Chris Apfel 33:36
Yes. We can access tissue from the bone from a bone biopsy. We have done bone marrow biopsies, which of course is slightly different. We can also do soft tissue sarcomas. We haven't done osteosarcomas. The fear is if it's a real tumor from the bone that usually it is not calcified. Prostate cancer is a typical example of that. That should not be a problem, but we have not tested prostate tissues from the bone. So just as a caveat, there is no reason why it shouldn't work. What really matters is how aggressive the tumors are. If you have an aggressive tumor – and most bone tumors are aggressive – you should get at least some of those options that can make a huge difference to you.

Roger Royse 34:45
I just want to make sure you have to have live cancer cells to do this? They can't be frozen or on a slide. It has to happen fairly immediately after a biopsy or surgery?

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I've come to find out that this tumor tissue is really precious, especially in pancreatic cancer, because it tends not to have as many cancer cells. Is it a large amount that you need? Am I as a patient going to have to make a choice between using my tissue for this or something else? Or is it a relatively small amount?

Finally, what are the prospects that you might be able to do this with a liquid biopsy or a blood test at some point in the future?

Chris Apfel 35:42
That's hard with liquid biopsies. Liquid biopsies are primarily focused on cell-free DNA. Those have not been shown to be predictive, They can only identify existing mutations, and often they don't correlate with the tissue biopsy very well. That's an issue with liquid biopsies.

There are some efforts from a German group that is looking at circulating tumor cells. That is a possibility to grow those if you can find them, but they are exceptionally rare. It would likely take months to grow organoids. If there is somebody who isolates those single cells from circulating tumor cells, or through circulating tumor cells, and is able to grow them to organoids, then an approach like SEngine has would be the most appropriate one.

Brad Power 36:57
How much tissue do you need?

Chris Apfel 37:00
We need about 100 milligrams to test the four to six main drugs on it. In a pancreatic cancer case, if you would go through the gastric route, and do a fine needle biopsy, then it would likely not be enough. Often, they don't have any tissue at all. There are often very many attempts to get to the tumor tissue. I'm not an oncologist, but what is possible in pancreatic cases is to do a laparoscopic staging, and then get a specimen. Half a gram would be plenty. We could test quite a number of drugs. The advantage would be to be able to see whether it is gemcitabine, FOLFIRINOX, or naparitaxel. There are different treatments, often even in first line treatment for pancreatic cancers. Therefore having an exploratory laparoscopy even if it's not operable at this point, in order to get it tested, so that one can hopefully convert this tumor from an inoperable one to an operable tumor, and then have a surgery in order to overcome that.

Amit Gattani 38:40
I’m a prostate cancer patient with bone mets. As you're hearing from many other comments, getting tissue from bones is really, really hard. Bone biopsies are not that easy.

If I am able to get bone tissue, and you do some testing on that, is it possible to keep that tissue alive and keep my biological twin going in your lab for testing of multiple drug resistances over periods of time? Suppose you said this chemotherapy is going to work, or this drug is going to work, and nine months later things change. Is it possible to keep a biological twin of my tumor microenvironment going in the lab that can continuously be used, as opposed to regular new tissue?

Chris Apfel 39:47
Our advantage is that we can. We can freeze it and thaw it again. During this freezing and thawing conversion, some cells won't make it. In principle you get a certain proportion of cells that you can revive. Then you can do testing on that. You get very similar results.

One of the reasons why it makes sense to access the tissue – I'm coming back to the ovarian cancer case – Dr. Friedhof has actually shown that if you have tumor resistance in the first place, on drug ABCDE, you will also have it later – a year later, nine months later, or one-and-a-half years later – on drugs ABCDE. The tumor resistance is a relatively constant signal. The sensitivity is a signal that may change because tumors under therapy develop their own resistance. That's even harder to predict. We would at least know what the resistant part is.

Amit Gattani 41:05
Suppose that based on your study you say carboplatin will work for me, given six doses of carboplatin. You can maintain that in your lab and expose my tissue to six doses of carboplatin. Nine months later down the line my tissue is a close reflection of my actual body and how my body has evolved?

Chris Apfel 41:36
We haven't done it yet. We could. It would be a separate project. It's really R&D. It would be outside of what would be a clear, approved standard of care. You would need to be aware that this is an experimental setup, and we don't have validation for it. Because the question is also, whether the tumor is changing in the same way, over the period of time, as it would be in your body.

Amit Gattani 42:12
That hasn't been tried yet. Okay.

Brian McCloskey 42:19
I would imagine that it would be difficult to mimic the dosing ex vivo versus in vitro? I'm sure there are a lot of complicating factors, but that seems to be probably one of the top ones.

Chris Apfel 42:45
That's one of the reasons why we calibrate our dose response curves in order to compare the drugs by the Cmax concentration (the maximum serum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administered and before the administration of a second dose) that you can have in the plasma. But even that is a crude approach, because the plasma concentration has different curves on how fast they get redistributed or metabolized. Even that comparison has limitations.

There is also another interesting thing that I wasn't aware of for a long period of time. If you look at plasma concentrations that patients have with the same dosing, sometimes they vary plus or minus 200 or 300%. One patient has a 300% higher concentration than the other one, and they

get the same dose. They have different distributions, different body fat, different body mass index, whatever there is. Women sometimes metabolize differently in their liver, and have different metabolic pathways than men. Dosing is very, very difficult.

The standard of care in clinical practice is usually you start off with a very high dose. With this very high dose, if the patient can tolerate it, fine. If the patient can't, you dial it back because of the side effects. That's brutal. I'm in discussion with a very senior key opinion leader to devise a study where we would use low dose combination treatments of those drugs that show sensitivity in our lab, and they will then be combined at a dose that is a fraction of the dose that's usually given. So let's say if you actually do half the dose, you have a fraction of the side effects, even if you have a combination of drugs. It's hard to say which dose is necessary. I'm very optimistic on this approach to use low dose combination therapies of those drugs to which the tumor is sensitive to.

Brad Power 45:20
We had a whole session on personalized dosing.

Brian McCloskey 45:27
The dosing is a really interesting component of getting these drugs. There seems to be a proclivity to go for a “kill shot”. But the kill shots rarely work. What happens is that some patients, like prostate cancer patients, who can live with the disease, even in an advanced state for quite a long time, get exposed to a lot of therapies, and then you just get a heterogeneous mess of cancer cells, and they become really difficult to treat.

When you think about the recommended drugs, are you also thinking about dosing? Are you factoring in our adaptive therapy, for example, which I think that we're pretty big proponents of, particularly in the prostate cancer setting? Are you thinking about that? Or are you thinking about the kill shot?

Chris Apfel 46:36
I also had other family members being affected by cancer. I know what this kill shot does to patients. One of my best research fellows at UCSF was a BRCA1 patient. Last year she was diagnosed, had a prophylactic hysterectomy, and was diagnosed with stage four ovarian. The neuropathy that she's developed is not nice. There are enormous side effects. There are many high dosages that can also be lethal, and bone marrow suppression, that leads to sepsis. It's going very, very quickly. Trying to dose it to the maximum dose is not what I would favor. I'm more on your end. One of the reasons is, if you look at the dose response curves, they're actually pretty flat. That means if you have only half the dose, you may have a 10% difference in how many cells survived. So that was half the dose.

We have seen some effects in combination treatments on synergies. Sometimes they're completely independent, and sometimes they potentiate one another. We can see this because we are running those dose response curves. I'm a big fan of dosing as low as we can, and then use the combination of the drugs that are most effective. Interestingly, it also makes sense to

test the combinations. Because you may have one drug that has a good effectiveness, you have another drug that has a good effectiveness. But if you combine them, it's a lot better than if you give just one. We see this in our lab. Finding the right combination, and therefore reducing the dose, in my mind is promising, but one needs to be aware. Dr. Brian Leyland-Jones is a person I'm in communication with at the Avera Cancer Institute. He is a leading oncologist, and he is one of those individuals who believes in low dose combination therapy.

John Powers 49:33
Nik Schork has really been the key guy for working with Avera on their dosing. He did a lot with setting up their precision medicine trials. He's very familiar with it. You've already got someone that's in the group that knows that stuff very well.

I've got a long term relationship with Avera as well, so I can get you in to the right people there.

Jeff Krolick 50:23
How similar or dissimilar are, say for prostate cancer, a bone tumor, or a soft tissue tumor? Are you going to see more similarity in terms of drug response? Or are two samples better, or even from different bone metastatic sites? Is there enough similarity so that one sample will be beneficial or mostly beneficial?

Chris Apfel 51:00
That comes to the question of tumor heterogeneity, and late stage. Early stage tumors are usually monoclonal. If you can get it at stage one or stage two, you may actually have a higher chance of eradicating it. If you think of adjuvant therapy that's given for patients that have just nodal disease, and you have an effective therapy, you sometimes have a separation of survival curves of about 20%. That means one out of five patients will have long term benefit from this.

As soon as we are talking about later stage disease, we have different tumor clones that may or may not have different sensitivity profiles, and therefore you sometimes see the tumor is shrinking in one part and is growing on another part. That's what brings us awareness of tumor heterogeneity, which makes it so difficult to be precision medicine, because you can't just give this drug to those cells and this drug to that cell. You have to give it systemically.

That's another argument for low dose combination therapy of those drugs that you are sensitive to. If you're talking about late stage tumors, it would be good to know, which are the combinations, and then test those combinations as well, in order to know if there is synergy between combining those drugs.

On where they are different in different spots, we have looked at some colon cancer patients where we had the primary and the one that metastasized to the liver. The sensitivity profile was basically very similar.

Glenn Sabin 53:13
Are there many oncologists prescribing based on what your report informs?

“Identifying the Most Effective Treatment on the Tumor Rather than Trying It Out on the Patient” (Dr. Chris Apfel) [#84]

Chris Apfel 53:21
Oncologists in general are under significant pressure to practice within the standard of care. One question is insurance coverage. Oncologists, often, even within the standard of care, have difficulties with getting coverage. Because of that, they're reluctant to go with something that's not covered by insurance. This is hurdle number one.

Hurdle number two is: there's always a concern on liability, that they feel restricted by. For example, with a pediatric patient, especially because pediatric patients are a vulnerable population, getting beyond standard of care, what's not mentioned in the guidelines, is really difficult. In order to maximize the benefit for patients in an early stage, we often just report the standard guidelines around choices. There are often, especially at a certain stage, five to ten to twelve choices, and that allows the oncologist to treat and choose that. If you go outside of that, you need to find an oncologist who is comfortable with that, and the patient should know this ahead of time. If we are testing a drug that is, let's say, a repurposed drug, one would have to make sure that the oncologist is also comfortable with it.

Glenn Sabin 55:06
If the patient is able to get access to the drug, let's say through compassionate use, as one example, and the reimbursement and everything related to that is a non-issue, do you have a small group of community and or academic oncologists that have delivered these drugs and combinations for patients that have been informed by the report?

Chris Apfel 55:41
I know that Dr. Leyland-Jones is open to that. The number of oncologists is really limited.

I was thinking whether I should approach Dr. Nagourney again, on whether we should do that, and whether he would be open to it. When we developed our assay, and I showed him what we have done, I offered to collaborate with him and to even do a cross validation. For whatever reason, he said, “No. You would drive us out of business.” That's what his concern was. That's how it came across to me.

Glenn Sabin 56:25
If you had a network of open-minded experts willing to prescribe off-label, which is already about 40% of the anti-cancer agents anyway, that would be useful for you. Correct?

Chris Apfel 56:42
Very useful.

Glenn Sabin 56:48
Are you pre-revenue?

Chris Apfel 56:58

“Identifying the Most Effective Treatment on the Tumor Rather than Trying It Out on the Patient” (Dr. Chris Apfel) [#84]

We have started to offer our assay commercially. Our MSRP (manufacturers suggested retail price) is $4800. We give a discount for oncologists who are working with us collaboratively, and where we get patient outcome data, because that's actually what's important to us to really demonstrate that.

Glenn Sabin 57:28
These cases that moved forward and utilized these agents and combinations thereof through the management of an oncologist, would it be useful for you then to have all these cases in a high quality registry? And a Learning Health System overlaid on that?

Chris Apfel 57:41
Yes.

Glenn Sabin 57:43
How close are you to a category three, like CPT (insurance reimbursement code)? Are you nowhere near getting a code?

Chris Apfel 57:59
This depends on the health economics. I think that insurance companies are not only looking for an improved outcome. They are also looking for cost savings in order to get the CPT codes. That's my sense. We'll need a separate study on getting a CPT code.

Glenn Sabin 58:23
Are you willing to sell directly to consumers? Patients without a order? As long as they're working with an oncologist that they're communicating with and bringing them the results of the report?

Chris Apfel 58:41
We would like to see oncologists to be on board for this to be a first benefit of the patient.

Glenn Sabin 58:48
That's the only way it would be delivered. Otherwise, it's just information that may or may not be acted on.

Chris Apfel 58:55
The patient himself cannot order the tests. The patient needs a physician. Technically, if the patient were in California, I could do it myself. But we haven't gone down that path.

Glenn Sabin 59:13
There will be options for you to explore.

Chris Apfel 59:19

It can be any physician. It could be the general practitioner. It could be the concierge physician. It doesn't have to be the oncologist. Sometimes the surgeon says, “Why not?” Let's move forward with that.

Glenn Sabin 59:39
What kind of validation data are you developing now?

Chris Apfel 59:46
The first step would be the case series to demonstrate and correlate the sensitivity and resistance results with the patient tumor response.

Glenn Sabin 59:59
Combinations of case reports across pan cancer?

Chris Apfel 1:00:04
Yes.

Glenn Sabin 1:00:05
Have you already started developing these?

Chris Apfel 1:00:09
We have some protocols in the pipeline.

Tell me about your background. What triggered your curiosity?

Glenn Sabin 1:00:26
We're working on developing an end-to-end service with a hybrid nonprofit and for-profit that would essentially address all of this unmet need and rate limiting factors, several of which we've discussed. We're actively developing this and an N-of-1 physician network is just one piece of that. Maybe Brad or Brian can connect us, and we can have a conversation that digs into that.

Brad Power 1:01:43
You flashed an experience you had with a rhabdomyosarcoma patient. We ran a hackathon for another rhabdomyosarcoma patient. I recall that they respond to the chemo, and then it fails. It's a number of cycles, but every time the chemo works, there's no evidence of disease, and then the cancer comes back. It’s an endless cycle, unfortunately.

Is there anything in your testing that can look at the durability of the response? In your example there was a drug combination that had like 97% response. But is there anything in that prediction that would look at durability?

Chris Apfel 1:02:41
That's a tough one. The key would be to try to eradicate it as much as possible. And then get it below the detection level. But I'm not sure whether that pattern is known for high grade tumors.

They tend to be more sensitive to a drug, but then they develop resistance. Because they're high grade, they may then still have sensitivity to other drugs until they develop resistance there. I'm not sure whether that's typical for rhabdomyosarcoma.

Brad Power 1:03:29
I recall there's about a 30% success rate with the standard of care, which is chemo.

Chris Apfel 1:03:35
Right. And that's not good. We can do much better than that.

Amit Gattani 1:03:48
Travera presented to us a few months back, and they seem to be in similar space. I'm sure you know them better than we do. Can you help us understand the difference between what you're doing versus what Travera is offering?

Chris Apfel 1:04:04
Travera, as far as I understand is, they're looking at single cells, so not at the tumor as a whole. And so they don't have the tumor microenvironment and the three dimensionality that is nowadays very much emphasized. That's number one.

Number two, they make a claim to measure or be able to detect effects in a very short period of time, which may be true for typical cytotoxic drugs that are cytotoxic, irrespective of replication. But there are many other drugs that just need days or and weeks until they become effective in a patient's body. The concept of being able to measure the effectiveness of a wide range of drugs within a few hours or within a day needs to be shown. What we do know is, we have looked at how long we need exposure until the cells start to die. What we have seen is we have done one day, two days, three days, four days, and beyond five days. We see that for most of the drugs, for 90% of the drugs, they need at least two days, if not three days, to really see a treatment effect. Usually when a cell is starting to die, and it's entering apoptosis, that can be for example, measured with this BH3 assay that Tony Letai has developed. Once they enter this cascade, they usually die within a few hours. So if it decides to die, that decision will have a treatment effect relatively quickly within a few hours. That's generally accepted. We see in our lab that you need at least two days, usually three days to see that effect in a reliable fashion.

Amit Gattani 1:06:28
Going back to your first point that they are focused on single cells versus the tumor microenvironment: as a patient, what I understand is that it's the tissue sample that they are getting, so they are getting exactly the same thing that I would be sending to you or to them. Are you saying that they are isolating and working only on a very small part of it?

Chris Apfel 1:06:51
They're isolating the individual cells, and then they're measuring the effect on the individual cells, irrespective of the tumor microenvironment and irrespective of the extracellular matrix, etc.