# ‘Organoids Guide Treatment Decisions“ (Payel Chatterjee, SEngine) [#13]

June 15, 2022
Brad Power

“*We design our drug panel so that it is comprehensive enough that we would be able to find at least one exceptional drug in the majority of cases.*” – Payel Chatterjee, SEngine

**Meeting Summary**

Payel Chatterjee, Chief Scientist, SEngine Precision Medicine, led a discussion on the role of organoids in guiding cancer treatment decisions. The value proposition of “functional testing” (applying 100 or more drugs to fresh tumor tissue and seeing how the cancer responds) is that this very direct approach can identify unexpected drugs to try, and extraordinary results, for some patients. The drugs in the panel that SEngine tests are unique because they pay attention to the genomics and FDA-approved drugs for that cancer, but also include drugs that have been approved for other cancers to make a very comprehensive list to test. This broader range of drug options leads to surprises every day. The lesson from their experience is that you should never be too biased to the typical treatments because you don't know if a surprise might come up. Some of their surprises and successes have been in cancers with very difficult prognoses, such as pancreatic and ovarian cancer.

Payel shared several stories, including unexpected and exceptional responses:

- A pancreatic cancer patient with a HER2 amplification had an amazing response. For 1.5 years, they have been scanning her, and they can’t believe it, but there is no evidence of disease.
- A woman who was in hospice with a very late stage of ovarian cancer tried the SEngine organoid test. The test indicated a top candidate of an approved drug that was normally indicated for a blood cancer, but not for her cancer. The doctors were surprised, but tried it, and she experienced an exceptional response. She was able to get out of hospice and travel.
- A very terminally ill cholangiocarcinoma patient had progressed through five lines of treatment, but nothing was working. A SEngine organoid test identified Dasatinib, which was used mostly in leukemias, as a top drug. It had an exceptional response. The patient’s pain and tumor markers were controlled for several months when her life expectancy would've been measured in weeks.
- A colon cancer patient’s doctor was struggling to find a therapy after several lines of therapy. SEngine PARIS test identified gemcitabine, which is a common chemotherapy. The patient took it, the tumor was reduced, and the patient lived for nine months, instead of weeks.
- A prostate cancer patient had failed four lines of treatment. SEngine identified 9 drugs with relatively high scores, showing potential. The patient chose Azacitidine because he learned it had fewer side effects.

Organoids maintain the tumor heterogeneity and physiology.

## ‘Organoids Guide Treatment Decisions“ (Payel Chatterjee, SEngine) [#13]

43 drugs can be tested on a full plate, drawn from physician recommendations, the standard of care, the genomic landscape, and FDA-approved drugs, to create a comprehensive targetable list.
In 70% of cases, including patients who have had multiple lines of therapy and have no known druggable biomarkers, SEngine could still identify an actionable candidate therapy, beyond the patient’s genomic report.

**Questions for Further Discussion**

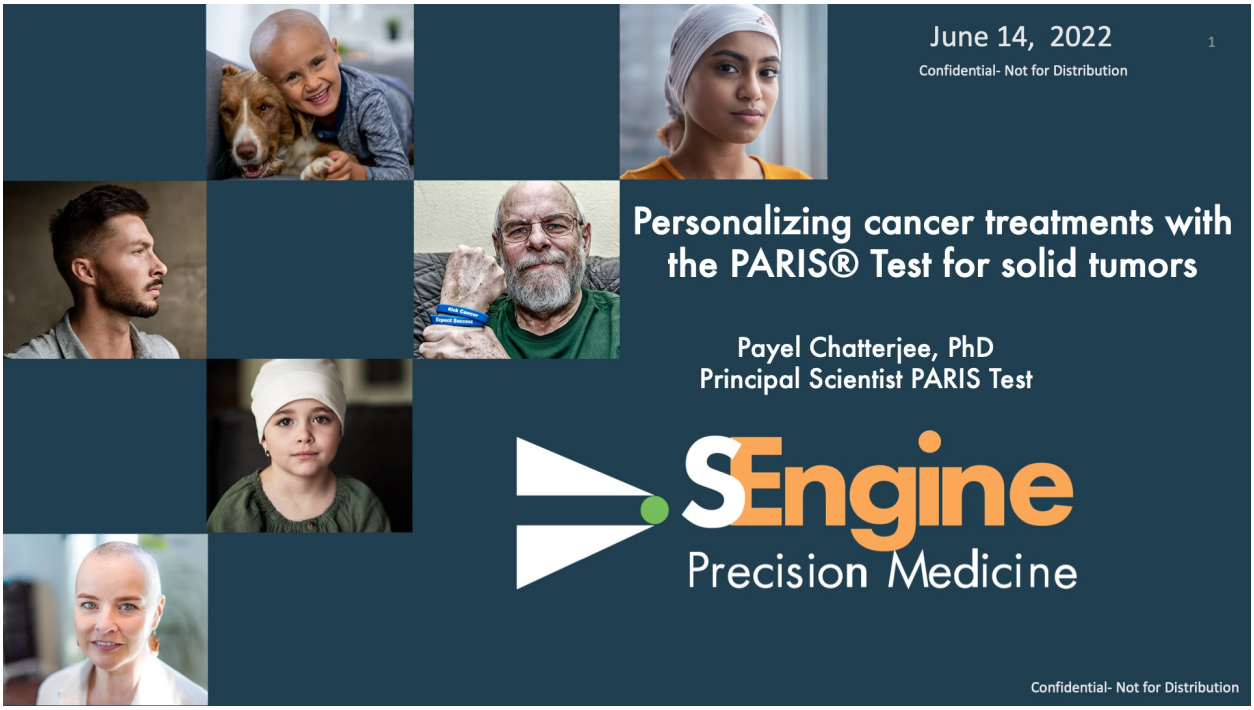
- Functional testing seems like it offers useful information to guide complex treatment decisions and may uncover unexpected treatment candidates. Do you agree?
- How can we accelerate adoption? What are the barriers to wider use?

**‘Organoids Guide Treatment Decisions“ (Payel Chatterjee, SEngine) [#13]**

—

**Meeting Notes**

Brad Power: Payel Chatterjee of SEngine will be leading a discussion on using organoids to guide cancer treatment decisions.




Payel Chatterjee: I'm the principal scientist at SEngine, where I manage drug selection and reporting for the PARIS test. My presentation will be about personalizing cancer treatment with the PARIS test for solid tumors. The name Paris comes from mythology – Paris killed Achilles by shooting him in his heel because that's the place Achilles was most vulnerable. That's the concept of SEngine Precision Medicine: finding the unique vulnerabilities of every patient's tumor so that we can target and treat the patient with those unique drugs.

**‘Organoids Guide Treatment Decisions“ (Payel Chatterjee, SEngine) [#13]**


Even though there have been advancements through DNA sequencing or through FDA-approved therapies or different treatment approaches, like the proton beam or Gamma Knife, we still lose a lot of people every year from this disease. A lot more still has to be done.


We believe that every individual's cancer is a unique mosaic of molecular changes. Cancer happens when we are having a lot of molecular changes, either gene mutations, amplifications,

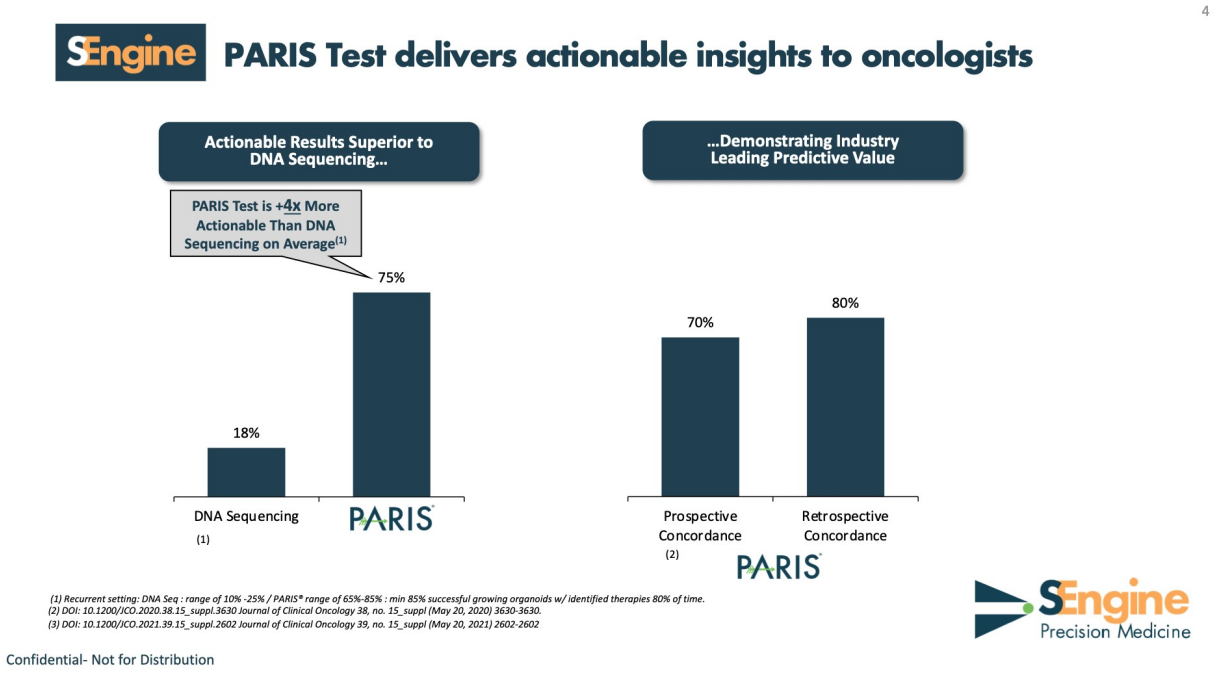
fusions, or maybe some other mutations, but every patient's tumor, no matter which type of cancer we are looking at, always presents us with a unique constellation of genetic changes. For example, if we see colorectal cancer with a KRAS mutation, no two patients are the same. We have seen KRAS mutations along with P53. We have seen KRAS mutations with CDK12 and 2AB loss for prostate cancer. We have seen androgen amplification with a BRCA1 mutation, ATM, and other mutations. There are plenty of permutations and combinations of different genetic changes that make every individual's cancer almost like a unique disease.


At SEngine our CEO and the chief scientific officer is Dr. Carla Grandori. SEngine was founded based on scientific research that happened at the Fred Hutch Cancer Center. Our co-founders were principal investigators and professors at Fred Hutch. Besides Dr. Carla Grandori, they included Dr. Chris Kemp, Dr. VK Gadi, who is a breast cancer surgeon, and Dr. Eddie Mendez, whom we lost due to cancer, unfortunately, but his vision still continues through SEngine.

We grow tumor organoids in the lab, outside the body. We get the patient sample and grow it in the form of clumps of tumor cells in a 3D structure. We merge that with robotics technology for drug screening. We treat the organoids with drugs over six days. Then we merge this result with our unique bioinformatics technology. We rank all the drugs from 15 to one. Every drug gets a unique proprietary score, which we call the “SPM score,” the SEngine Precision Medicine score. Our test is unique because it's a CLIA-certified, first-in-class, pan-cancer assay. It's a functional assay rather than a predictive assay. We test the drugs on which we are reporting. We don't discriminate against patients based on their previous lines of therapy, meaning we have patients who have had multiple lines of therapy, even up to seven or eight lines of therapy.

## ‘Organoids Guide Treatment Decisions“ (Payel Chatterjee, SEngine) [#13]

We look for an exceptional drug for the patient. We provide a report to the oncologist which gives the drug sensitivity unique for that patient. We are CLIA-certified in all states except in New York State, where certification is pending. We are trying for insurance reimbursement. It might still take a little over a year, but we are taking baby steps towards it.
We are also involved in multiple clinical studies across the world. We have a clinical trial for colorectal cancer in France with Gustave Roussy, one of the leading cancer institutes there. We are part of two cholangiocarcinoma clinical trials at the University of Washington and University of Chicago. We are regular members of the University of Washington's gynecology and oncology departments’ tumor board, where we discuss with the doctor what might be the next step for the patient.

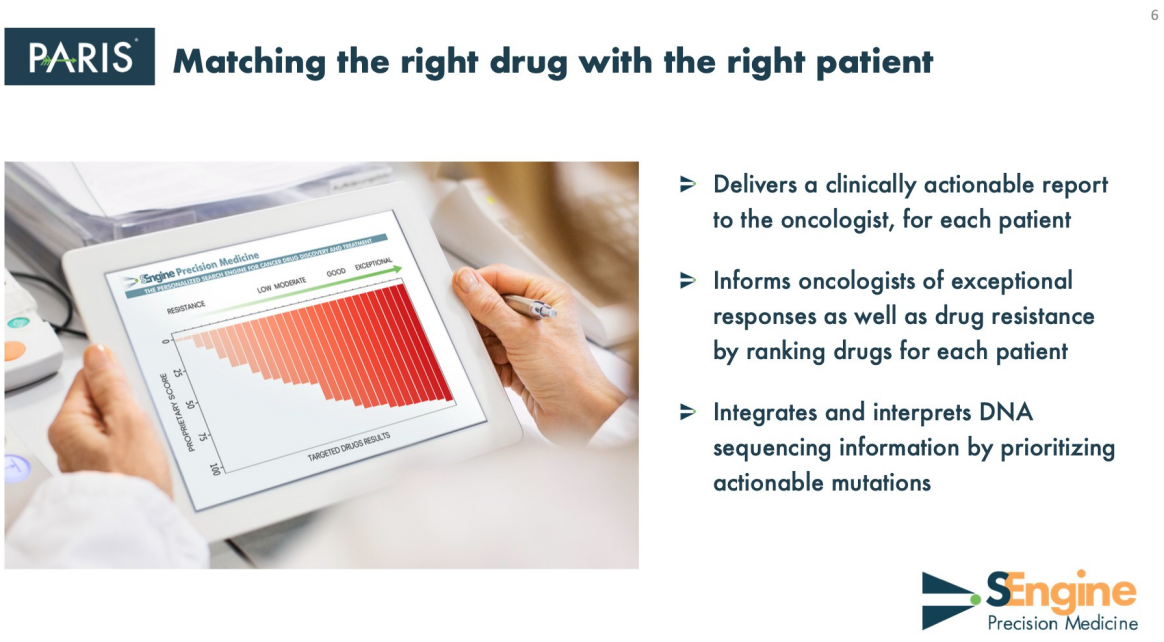



We think our test is superior to DNA sequencing. Nowadays it's common practice that if a patient comes to the clinic, they will get genetic testing. But only 18% of patients with a DNA sequencing get a drug prediction, while for us, at least 75% of patients get a drug prediction. For example, if a patient gets DNA sequencing, and BRCA1 or BRCA2 mutations are present, then the DNA sequencing can predict that a PARP inhibitor might be beneficial, but you don't know which PARP inhibitor would be beneficial. There are four different PARP inhibitors. One might be better for a patient or for your tumor type or your stage of the disease, compared to the other three. We test all four along with an ATR inhibitor or platinum, and we can tell you which PARP inhibitor would be best for your tumor.
That gives the power and that cuts out the whole guessing game, because from the beginning you know which drug would be best for that patient's tumor.

Rick Stanton: Is your testing limited to small molecules?

## ‘Organoids Guide Treatment Decisions“ (Payel Chatterjee, SEngine) [#13]

Payel Chatterjee: Currently we only do small molecules. We do both targeted therapies as well as chemotherapy. We don't do immunotherapy yet. That's in process. We just hired someone who has unique experience in immunotherapy and culturing immune cells with tumor cells. Same for monoclonal antibodies. We have tried before for HER2 with trastuzumab (herceptin), but it's trickier to test it in an ex vivo or in vitro system.
For prospective and retrospective concordance, we could predict a drug in almost 75 of percent of cases. We see a very high concordance with prospective studies, where the patient received a drug guided by the PARIS test. We have also seen over 80% retrospective concordance for patients where the patient has seen a drug already and progressed on that drug. We could see that our SPM score would be very low for that drug. We have also seen if a combination didn't work, for example, if FOLFOX (a combination chemotherapy regimen that includes the drugs FOLinic acid, Fluorouracil, and OXaliplatin) didn't work for the patient, we see either the Flu and FOL part, or the OX part, when tested separately, either both of them performed poorly, or at least one performed very poorly in our test. And that's when you know the combination is not going to work. We see this very regularly across the tumor type, and we also do very rare tumor types.
Before SEngine, I did prostate cancer research. Then after coming to SEngine, within two years I got exposed to so many different types of cancer that I never knew existed.
We don't discriminate. We even make organoids even if it’s a cancer we have never heard of. That's our test’s strength.




Our motto is matching the right drug with the right patient because we deliver a clinically actionable report within the clinically relevant timeframe. It generally takes four to six weeks, although it depends on the starting material, meaning if the surgical recept resection or the biopsy material is very poor in quality or very limited amount, then the chances of success obviously would be lower. And also the time frame might be extended. In certain specific tumor

types, as it is a little tricky to grow, it might take a little longer, but in general, it is four to six weeks. Along with the proprietary SPM score, which ranks from 15 to one, we also give the categories for each drug: exceptional, good, moderate, to low. Exceptional is where the scores are 15 and 14. Good is 13 and 12. That's why we curate every single drug, even if it is actually curated through our algorithm. There are at least two or three reporting members who are scientists who have immense knowledge of cancer biology. They curate every single drug and check if it is actually matching with our call. We give that conclusion in the report in the written format.
If there is any genomics information available, then we also integrate that in our conclusion portion. For example, if a patient has a BRCA2 mutation, we saw one PARP inhibitor over others. We would explain that we have seen PARP inhibitors and the patient has a BRCA1 or BRCA2 mutation. Sometimes those concordances help the oncologist to choose the drug or give the oncologist maybe better confidence in our test. We have seen that a lot of time. They believe more if you see a genomic concordance, but even if the patient doesn't have genomics we are still able to match a drug. We regularly get samples without genomic testing, especially from the University of Washington, where, as soon as the patient is diagnosed, they sometimes send us the sample, or we get a sample where they're on the first line of therapy and genomic testing has not been done yet. Later on, maybe after four weeks, the genomic report comes, and they would be surprised to see the result that this drug came up on our report. It has happened multiple times.

Brian McCloskey: Does the accuracy of the test change based upon where the patient is in the journey? If they've been under more selective pressures versus less, does that impact the accuracy?

Payel Chatterjee: No. I will show you some examples today of our exceptional cases, and one prostate cancer case. We have seen newly diagnosed cases for our cholangio trial, as I mentioned, where the patient would receive the first line of therapy, and they would do our test right when the diagnosis happened. Then when the patient progressed through the first line of therapy, they would use our test result to give the second line. And we see that very regularly, for example, one patient never received gemcitabine (chemotherapy). They normally give gemcitabine and pavlotaxid, or gemcitabine and cisplatin. The patient had never seen either of those. We would see resistance in one. And after some months when we spoke to the doctor, they would say, “that patient progressed, so we put the patient on your top drug.” We have also seen patients who have come along after a really long time, for example, a patient was in hospice, but still got our drug as monotherapy. I'm going to show that case. They are still surviving after two years.

Rick Stanton: This is fabulous. I hope to get some fresh tissue to you.

Payel Chatterjee: We need fresh tissue from a biopsy sample or fluids.

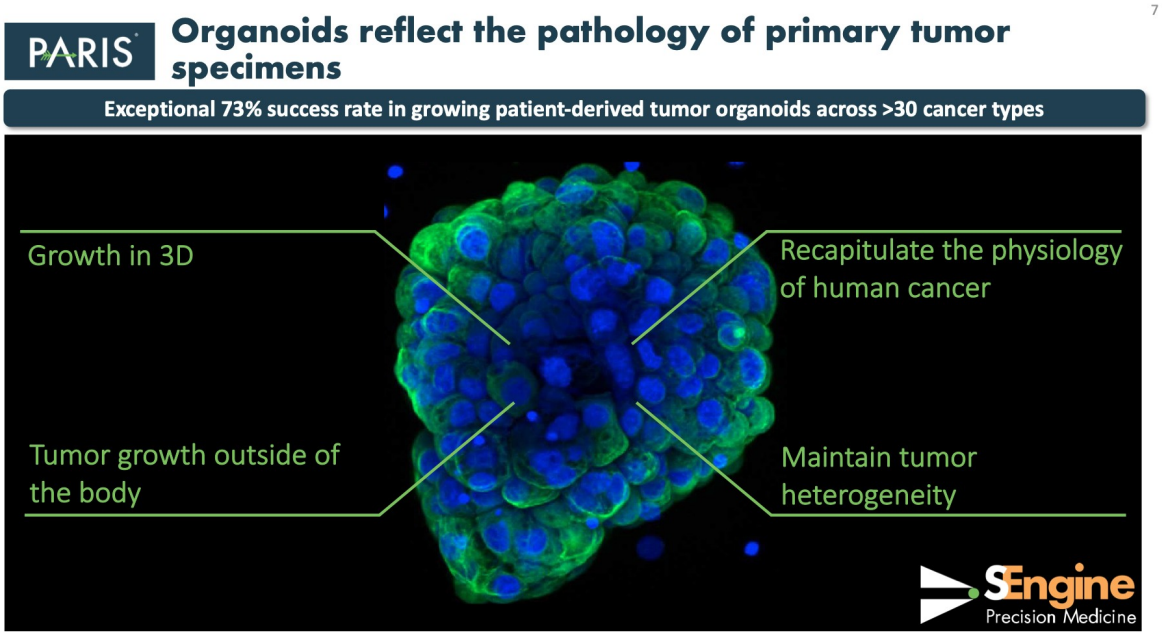
Rick Stanton: Is there a sample record report that you could share?

## ‘Organoids Guide Treatment Decisions“ (Payel Chatterjee, SEngine) [#13]

Payel Chatterjee: I'm going to show some exceptional cases. One of the exceptional cases is a pancreatic cancer patient with a HER2 amplification, and the tumor got cured. They're calling her, and they're scanning her, and they can’t believe it, but it's been five years. They couldn't find anything. I can share the links and those reports.

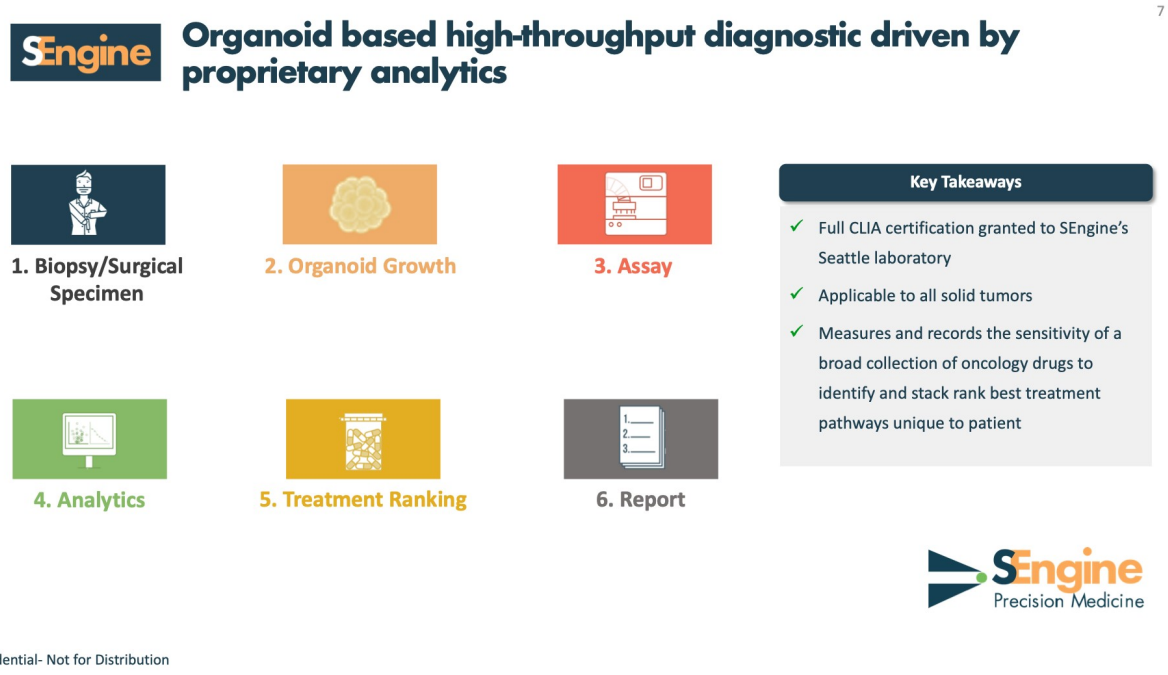
Brad Power: Rick has identified seven therapies that he's gotten from various sources. Brian has 17, and these include drug combinations. If their PSA were to rise, and they were to need to go onto a next therapy, they have a ready-made list of drugs that they would want to test.
Is that a use case for organoid testing?

Payel Chatterjee: Yes. We always give priority to doctors' choices. If the doctor has some drugs, which they want to test, or if the patient would like to test some drugs on an organoid first, we will always give that priority. We have a drug library of 200 drugs, from which we choose. I'm going to explain the workflow.
We do combination studies, but it's a little limited now just because we are also very small. We are trying to expand this year so that we can do more. It's mostly one drug at IC 30 concentration, meaning 30% of cells get killed, and then we combine drugs B, C, and D with it, in multiple doses.
For example, for prostate cancer, you might try to combine it with enzalutamide as the first drug at 30% concentration because most patients must have seen that drug at some point. Then it can be combined with other drugs, such as a PARP inhibitor or some chemo.




This is a pretty structure of an organoid. It's basically clumps of cells. There are no immune cells or any other confounders we select. We enrich the sample for tumor cells. We have seen that it maintains tumor heterogeneity and recapitulates the physiology of human cancer. We have to

send every tumor organoid we culture for whole exome sequencing. We confirm the mutation we see in the patients in the tumor organoids. Only then are we allowed to send a CLIA-certified report. We confirm that whatever we are growing is at least a tumor.
We have an exceptional 73% success rate in growing patient-derived tumor organoids across 30 different tumor types. We have grown organoids in close to 800 cases, not a very minute number.




This is a general workflow of each test, where

1. The first step is obviously to collect the sample. Two criteria are that the sample has to be fresh, and it needs to be received within 48 hours. That's generally not a problem unless there is a big snowstorm. We have received samples from France, Switzerland, Norway, India, Australia, and Canada, and it has not been a problem.
2. After we receive the sample, we purify it, and enrich it for tumor cells, and grow the organoid generally for two to three weeks to be ready for our drug stain.
3. Then we use a robot to deliver the drugs to the organoids over six days. The organoids are incubated with the drugs. For a full plate, we generally test almost 42 to 43 drugs, which can be either FDA-approved drugs, or other small molecules, if the doctor has some request. It's also based on, if available, the patient's genomics. Drugs which are in clinical trials are available if they are in our library. Because our test is CLIA-certified, we have to validate every single drug we use. At least twice a year, we have to send it to separate labs, so that they would also test and give us the proficiency testing result. We can't test a drug which is in a clinical trial but is not in our drug library, but generally that is a very rare problem because most of the time we either have that exact same drug or maybe at least the same pathway-targeting drugs, a very close match.

4. Then our bioinformatics team analyzes the results. We have an internal app where the data gets stored, and all the drugs get ranked for each patient, from 15 to one. We give exceptional, good, moderate, and low ratings for each drug in the report. We provide a multiple-page report with the top drug table with a conclusion and explain the results. If needed, we also sit on tumor boards and with the doctor and the patient to explain the results. Mostly it’s with the doctor to explain and to guide them if they need any help.

Brian McCloskey: Relative to the treatment ranking: do you factor in response time? For example, if I'm considering carboplatin versus Apalutamide, would you be able to say, “we expect you would get X months of benefit before a PSA rise with one drug versus another drug?”

Payel Chatterjee: We can't say the exact time, but we can say if the drug has a full response or a partial response. If a drug has a partial response, there is a significantly higher chance that you probably will develop resistance much sooner than a drug where we are seeing a complete response, meaning one hundred percent.
Just yesterday I had a talk with a patient who was on paclitaxel, and we saw that it had a only 50% response, so a very huge amount of the cells are resistant, compared to another targeted drug, which had a hundred percent response. In a case like this, we would be able to tell you that there is a very high chance that you will develop resistance much sooner.
The exact number of months would be harder because our bodies are not the same.

Brian McCloskey: Maybe there's a distribution curve?

Payel Chatterjee: The problem is that drugs metabolize differently, and it differs from patient to patient. Every patient is in different states of health to tolerate the side effects.

Brian McCloskey: Regarding drug combinations: for example, I have treatment options of three-drug combinations, two-drug combinations, and single drugs. Can you look at the predicted response of 3-, 2-, or 1-drug combinations?

Payel Chatterjee: We can do one and two. Three we have only done in very limited cases. Three might be a little harder. One drug is our standard test. To test two drugs, we still have to first do the one to know the concentration for that particular patient. What is the concentration or how is the response for the single agent? Then we can do the combo. For example, to test carbo and enzalutamide, we would have to do a single agent first, and then we can do them together.

Brian McCloskey: This may be a little bit advanced, but can you look at effects over time? Can the organoids be preserved, so that you can test an adaptive therapy? For example, what is the right dose, and when is the right time to use it?

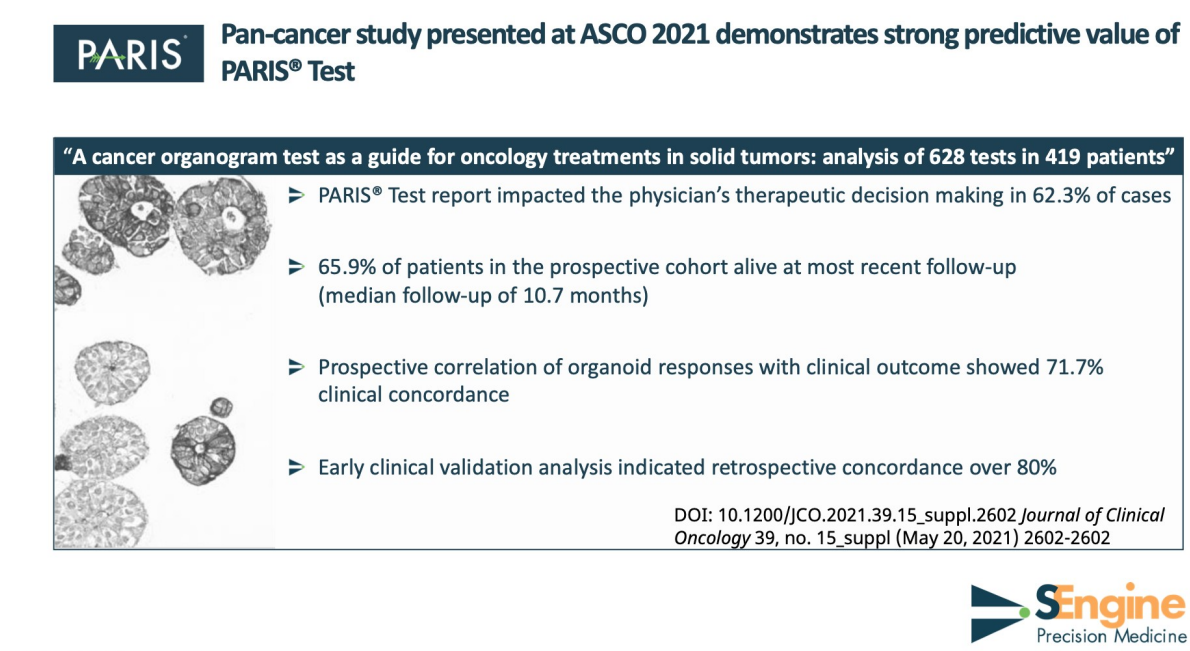
Payel Chatterjee: Most of the time we use up all the sample because the biopsy sample is very small. If we have some sample left, we definitely keep it. In the journey of the patient's tumor,

when you have been treated with some of the drugs, sometimes the response changes, though not very dramatically. We have seen patients where we did the test two and a half years ago, and we did it again after the same patient had seen multiple therapies. You could see some of the drugs which were rated “exceptional” before now dropped towards “low”, while some pathways which were “good” before are still rated “good”. In that case, we had two different samples collected in two different times of disease. At one point of time, those pathways were the driver pathways, but with time that changed.
We also had a patient who went on our guided therapy and was doing fine for a year, and then they progressed. So the doctor sent us a sample again, and we tested it. We could see the drug, which was 15 or 14 before, now it's 12. There was a shift.
Maybe the combination would be best if we see some other drugs coming up as a 14, and that's the time to change. Unfortunately, the previous frozen sample won't be very beneficial then, because that was the disease at the time you collected it.
We might need fresh tissue at that point of time.

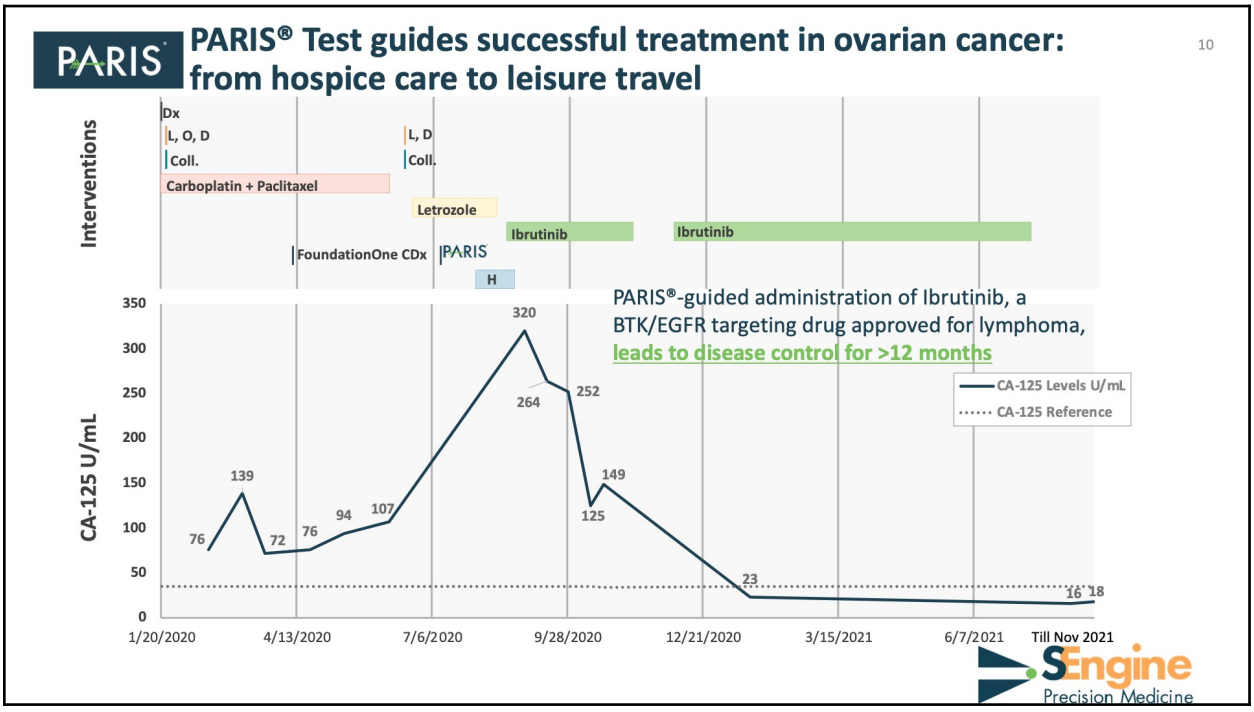
Ally Perlina: How do you measure toxicity?

Payel Chatterjee: It's outside the system, so we can't measure the exact toxicity profile. Because we sit in the tumor words regularly with multiple cases, we have an understanding of which drugs might be generally toxic for patients or hard to tolerate. If those drugs come up as top drugs, and we are part of the discussion, we always tell the patient that this might be toxic. Sometimes it’s hard to say, because we have some patients who are doing fine in a toxic combination for many months. For example, we recently had a patient who went on a MEK inhibitor and EGFR inhibitor combo, and generally MEK inhibitors are known to be toxic, but he's doing extremely fine. Over six months, his wife is constantly sending us messages and is extremely thankful. Sometimes it depends on the patient.
At this point we can't measure toxicity for a particular tumor, but maybe over time we will be able to.

## ‘Organoids Guide Treatment Decisions“ (Payel Chatterjee, SEngine) [#13]




We have shown that a PARIS test report impacted the physician's decision-making in 62.3% of cases. We've done a prospective cohort on our live patients. The median followup is 10.7 months. The clinical outcome showed clinical concordance in almost 72% of cases.




This is one of our star case reports, an ovarian cancer case. The patient came to us in the mid-2020. For prostate cancer, PSA is the biomarker, and for ovarian cancer, CA-125 is the

biomarker. You can see that during the PARIS test the patient's CA-125 was at 320 and the normal level is around 30. The patient was in hospice. Nothing had worked. She was not able to eat properly. She had obstructions in her stomach and bowel. She was getting a very high dose of pain management medication. We did the PARIS test, and the top drug was ibrutinib, which is a BTK inhibitor and generally used in liquid tumors, not in solid tumors.
When we saw the test result, the doctors were also very surprised, but the patient luckily was a part of the VA Health program, so she could receive the drug very quickly. Within a month after she went on the drug, she had some drop. She initially had a little bit of trouble tolerating the drug. So she took a small pause, in early December. She started using the ibrutinib again as a single agent therapy. On the timeline you can see her CA-125 dropped from 320 to 16 and 18.
The patient is still alive. She visited New Orleans last year, when her CA-125 was so low.
We heard from her doctor at ASCO that she started showing signs of progression. It's been from August 2020 until now. She was on that monotherapy out of hospice with no pain medication.
Her CA-125 recently rose to 200, but they put her on the second best therapy revealed by the PARIS test, which was ibrutinib, another EGFR-targeted drug, and her CA-125 already dropped below 90, after just one month of use.
She's still on a PARIS-guided therapy, and she's still out of hospice. Let's see what happens next. We would say that this is a really amazing story that she was in hospice, but because of our top drug selection, she's still living and doing fine.

Emma Shtivelman: What was the indication to try ibrutinib?

Payel Chatterjee: Our panel is unique because we pay attention to the genomics and FDA-approved drugs for that cancer, but also include drugs that have been approved for other cancers to make a very comprehensive list.
Almost 10% of our cases were responsive to ibrutinib.
I went to ASCO and met a prostate cancer surgeon from Cleveland Clinic. He told us that for prostate cancer they are also seeing it. We keep a close eye on our patient cohort.
Initially they used to test all 200 or a hundred plus drugs for every patient’s tumor. We have a database and an understanding of which drugs might be beneficial, even if it's not approved for that cancer.
That's how we see a couple of drugs which come up, I won't say for every single patient, but often. We always make the list very comprehensive so that we include those drugs. If we can do a full plate, then we would definitely, even if there isn’t an EGFR mutation, we would have an EGFR-targeted drug just because you don't know if that patient tumor is uniquely vulnerable to the EGFR pathway.

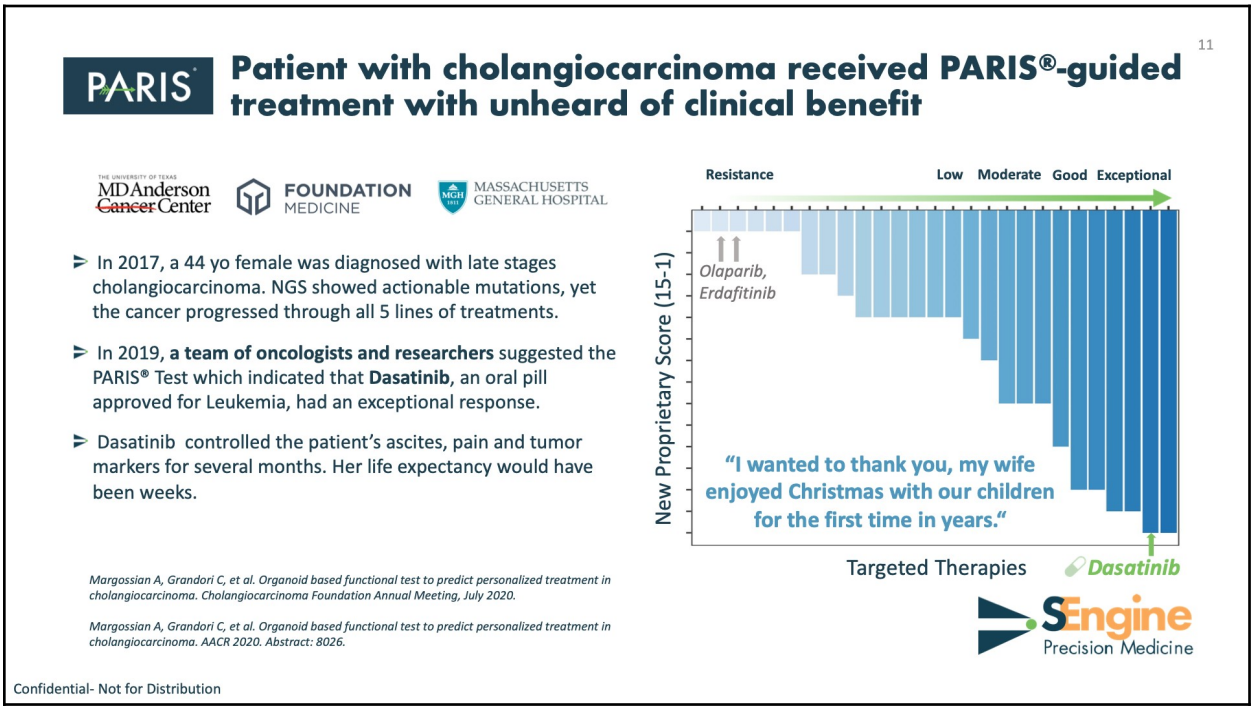
Emma Shtivelman: You're saying there was no particular mutation?

Payel Chatterjee: The patient only had a CHK2 mutation.
We checked the vTK, and there was no mutation per se. There has been only one report where a patient had a concurrent CLL as well as ovarian cancer. In that case, they were using ibrutinib for CLL management and the CA-125 dropped. So there had been only one case, but the

genetic mutations didn't match. Our University of Washington ovarian group is starting a clinical trial on ibrutinib.
Without the PARIS test, there would have been no way to find it. The same thing happened yesterday. There was a gastro cancer case, and belinostat was the top drug. They were also very surprised. We worked with a small management group and they had no idea that without the PARIS test, they would never have predicted that belinostat would be beneficial. We design our drug panel so that it is comprehensive enough that we would be able to find at least one exceptional drug in each case.

Emma Shtivelman: I heard of a case of ovarian cancer where she had an unusual mutation in STK11. I was surprised at the drug recommendation.

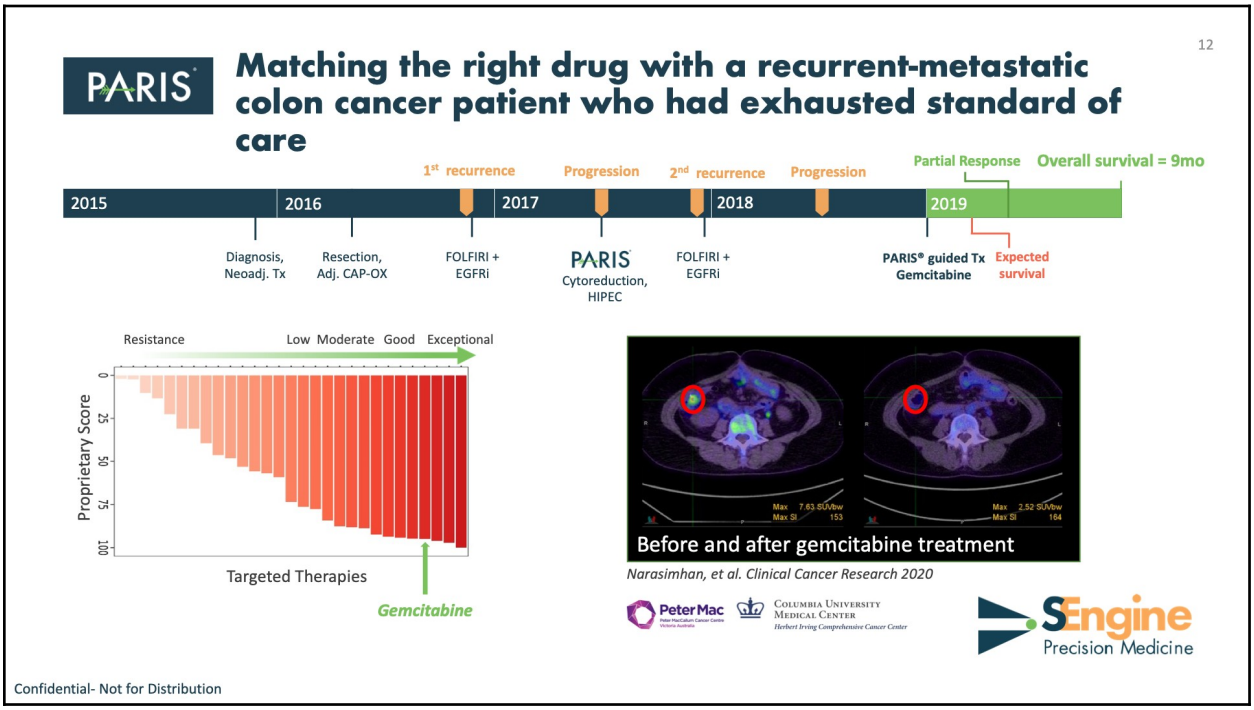
Payel Chatterjee: We get surprised pretty much every day. It's very hard to train a new person because they think someone with ovarian cancer responds to certain drugs. The next patient had a very similar mutation, so she thought the patient would respond to similar drugs. When she saw the PARIS test result, she called me to ask if everything was right. The lesson is that you should never be biased while you are doing a SEngine test because you don't know which surprise might come up.




This is another case of a very terminally ill cholangiocarcinoma patient. The patient had an FGFR mutation, which is targetable for cholangiocarcinoma. The patient had seen an FGFR-targeted therapy, and progressed through five lines of treatment, but nothing was working. In 2019 a team of oncologists suggested a PARIS test. When we did the test, the top drug was the Dasartinib, which was used in BCR-ABL-mutated tumors, mostly in leukemias. That had an exceptional response. The patient was able to receive the drug, and her pain and tumor

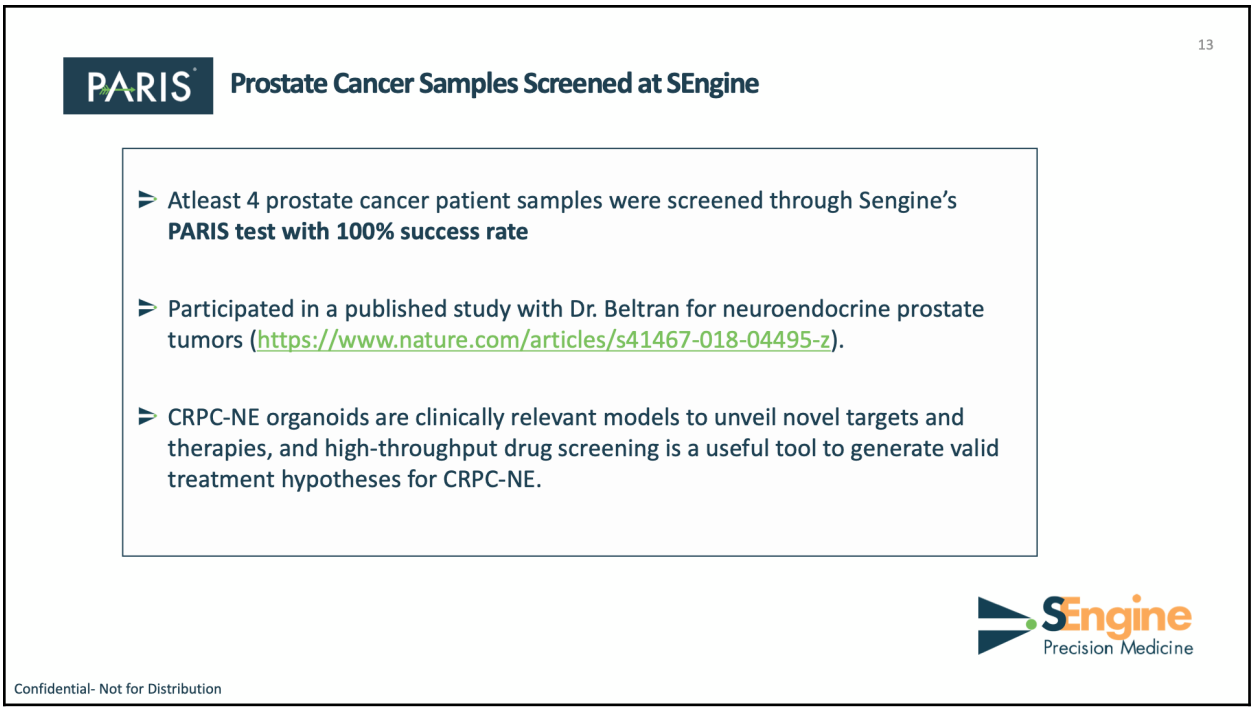
## ‘Organoids Guide Treatment Decisions“ (Payel Chatterjee, SEngine) [#13]

markers were controlled for several months. If we would've had more time, it would've been more beneficial, but she lived for several months when her life expectancy would've been just weeks since the patient was very terminally ill and cholangiocarcinomas are aggressive.

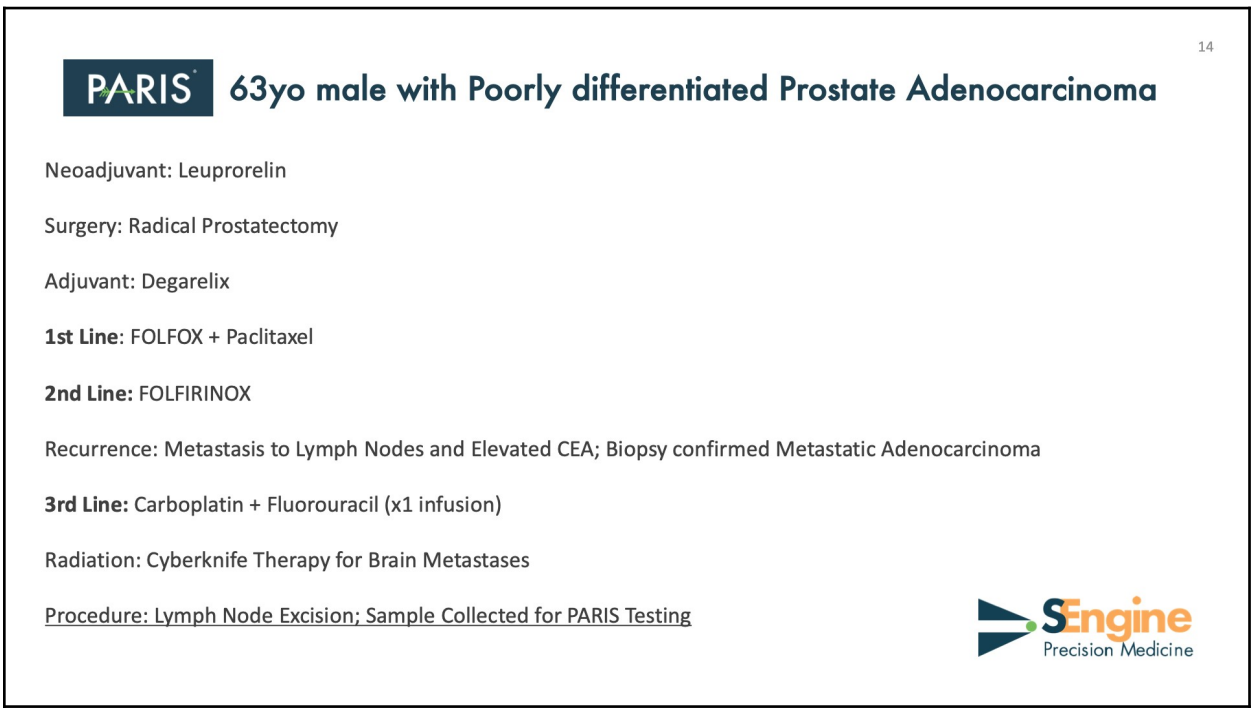



This is a case of a colon cancer patient. Her doctor almost gave up. There was no therapy they could choose or predict. Her doctor expected her to survive for weeks.
We found gemcitabine, which is a common chemotherapy. The patient took it. As you can see in the scan, the tumor was reduced. The patient lived after that for nine months.

## ‘Organoids Guide Treatment Decisions“ (Payel Chatterjee, SEngine) [#13]

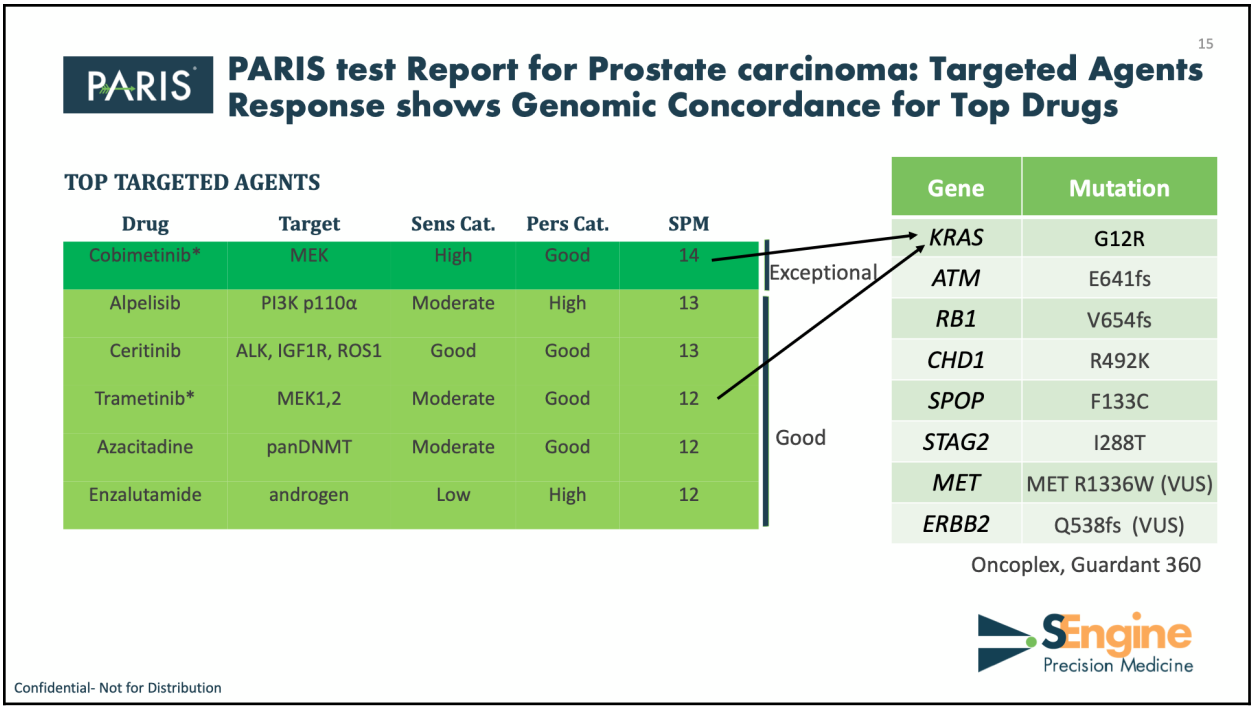



This is an interesting prostate case. We don't have an established relationship with a prostate cancer group. We participated in a study with Dr. Himisha Beltran where they started the organoid. We grew it again in our lab and did the drug screening for neuroendocrine tumors. Other than that, we have done at least four prostate cancer patient samples through SEngine. For each of the four we received we were able to run them through our process.
We also do a lot of sarcoma, ovarian, melanoma, breast, and others.



**‘Organoids Guide Treatment Decisions“ (Payel Chatterjee, SEngine) [#13]**

Here is an example of a prostate cancer case. This patient was a 63 year old male with poorly differentiated prostate carcinoma. As you can see, the patient had received FOLFOX + paclitaxel as a first line therapy, then had FOLFIRINOX second line, then a recurrence, then received carboplatin and Fluorouracil for the third line therapy, and then had radiation. Next, he received a lymph node excision, and a sample was collected for PARIS testing.




Even in this case, after these many lines of therapy, we saw an exceptional drug with a score of 14, which was Cobimetinib. It was in concordance with the patient's genomics. The patient has a KRAS mutation. As you can see, other than the Cobimetinib, there are multiple other drugs which also came up. We saw enzalutamide with a score of 12, which the patient can still get it maybe in combination, which would be better in this case, because it is not the top drug.

## ‘Organoids Guide Treatment Decisions“ (Payel Chatterjee, SEngine) [#13]

16

### PARIS test Report Targeted Agents Response shows Genomic Concordance for Top Drugs

**TOP TARGETED AGENTS**

| Drug | Target | Sens. | Pers. | SPM |
|---|---|---|---|---|
| Venetoclax | BCL2 | Low | Good | 11 |
| Capivasertib | Akt | Low | Good | 11 |
| Adavosertib | Wee1 | Moderate | Moderate | 11 |
| Midostaurin | FLT3, PKCα/β/γ, SYK, Flk-1, Akt, PKA, c- KIT, FGFR, SRC, PDFRβ, VEGFR1, VEGFR2 | Good | Low | 11 |
| Derazantinib | FGFR1/2, PDGFRa, PDGFRb, KIT, RET | Moderate | Low | 10 |
| Ulixertinib* | ERK1,2 | Moderate | Low | 10 |
| Niraparib Tosylate* | PARP1, PARP2 | Low | Low | 9 |

Moderate

Moderate/Low

| Gene | Mutation |
|---|---|
| *KRAS* | G12R |
| *RB1* | V654fs |
| *CHD1* | R492K |
| *SPOP* | F133C |
| *ATM* | E641fs |
| *STAG2* | I288T |
| *MET* | MET R1336W (VUS) |
| *ERBB2* | Q538fs (VUS) |

Oncoplex, Guardant 360

SEngine Precision Medicine

We also saw other indications; for example, the patient had an ATM mutation, and it's always controversial whether a PARP inhibitor would work or not. In this case, we tested both Niraparib and Olaparib, and we saw Niraparib had a low score, meaning it should be used in combination, but we could still detect the sensitivity in the top drug.

17

### PARIS test Report for Prostate Adenocrcinoma: Targeted Agents Identified by PARIS Test independent of Genomics

**Top Targeted Pathways revealed by PARIS TEST**

| PI3K/AKT/IGF | Apoptotic | Epigenetic | AR | TKI | Wee1 |
|---|---|---|---|---|---|
| Alpelisib (13) | Venetoclax (11) | Azacitadine (12) | Enzalutamide (12) | Midostaurin (11) | Adavosertib (11) |
| Ceritinib (13) | | | | Derazantinib (11) | |
| Capivasertib (11) | | | | | |

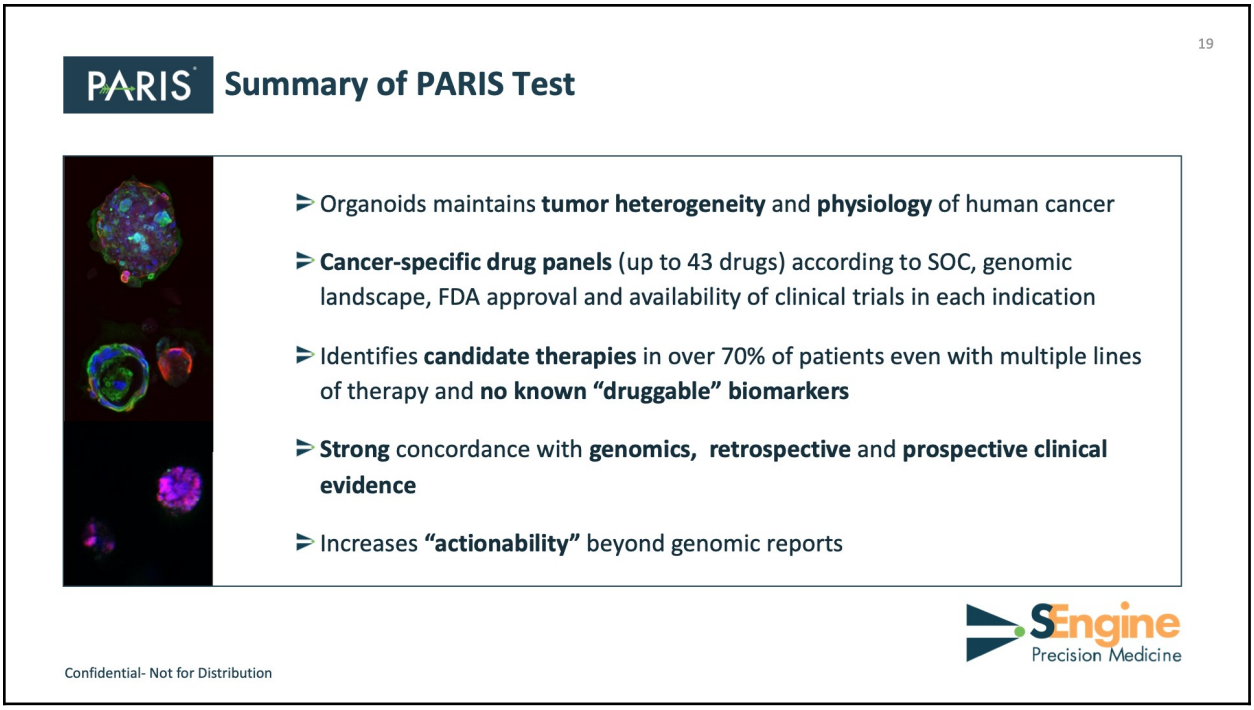
SEngine Precision Medicine



Without the genomic information, we revealed the sensitivity for these other pathways.

## ‘Organoids Guide Treatment Decisions“ (Payel Chatterjee, SEngine) [#13]

So you can see the PI3K/AKT pathway was one of the prominent ones for this patient’s tumor. We had Alpelisib targeting PI3K, Ceritinib targeting IGF1R, and Capivasertib targeting AKT. Azacitadine was indicated as an epigenetic drug. The patient was very interested in receiving Azacitidine, because he learned it had less side effects. That's what he was planning to get as the next line of therapy when I last spoke to him.
For the chemotherapies, the patient saw FOLFOX and FOLFIRINOX. If one of the drugs in a combination does not work, then we don't see a response. The fluorouracil, for example, had a score of only four, which is very low and poor. You saw that the patient progressed on FOLFOX, while Carboplatin was low, but still had a score of 10. We give scores for top drugs up to nine. The SN38, which is the renal thickener in the FOLFIRI part, also had a score of 11, but fluorouracil was really poor. That's why that combination never worked for him.




To summarize, organoids maintain the tumor heterogeneity and physiology. We confirmed that through genomic sequencing.
We test up to 43 drugs for a full plate, including doctor recommendations, standard of care, genomic landscape, FDA approval, and more of a comprehensive targetable list.
In 70% of cases, including patients with multiple lines of therapy and no known druggable biomarkers, we could still identify a candidate therapy, which can be actionable beyond their genomic report.

## ‘Organoids Guide Treatment Decisions“ (Payel Chatterjee, SEngine) [#13]

20

### PARIS® Test sample requirements

| Collection Type | Quantity Requirements | Collection Requirements |
|---|---|---|
| Core Biopsy | At least 4 cylinders | During Sample Collection:<br>☐ Sample should be refrigerated and not be left at room temperature for longer than 1 – 2 hours<br>☐ High tumor cellularity preferred<br>☐ ‘PARIS® Test Sample Collection Form completed (each specimen type should have its own form)<br><br>Sending Sample Collection:<br>☐ Must arrive to SEngine’s lab in 48 hours or less<br>☐ Try to avoid sample collections on Fridays<br>☐ Kit properly prepared for shipment to SEngine and Clinical Team notified of shipment tracking number |
| Punch Biopsy | At least 2 cylinders | |
| Surgical Excision | At least 1 $cm^3$ of tissue<br><br>Lymph Nodes: At least 1 whole lymph node | |
| Fluids<br>(Ascites/Pleural Effusions) | At least 250 mL | |
| Endoscopic<br>(Bronchoscopy, Colonoscopy, etc.) | At least 4 cylinders or 1 $cm^3$ of tissue | |

care@senginemedicine.com
1-833-736-4163

SEngine Precision Medicine

This is our sample requirement. We ask for at least four cylinders for the core biopsy. The punch biopsy is the hardest one to grow. Fluids at least 250 mL. If there is a surgical resection, one centimeter of tissue. The lymph nodes are harder. The example I showed you was a lymph node case, but in that case, close to a whole lymph node would be better because it is normally infiltrated with blood cells.

21

### SEngine Distinguished Scientific Advisory Board

**LELAND HARTWELL, PHD, NOBEL LAUREATE**
**Scientific Advisor, Board of Directors**
President of the Fred Hutchinson Cancer Research center from 1997 to 2010, Nobel Prize in Physiology and Medicine in 2001

**CHANTAL PAULI, MD, PHD**
**Scientific Advisor**
Pathologist at the Institute of Pathology and Molecular Pathology, University Hospital Zurich, pioneer in organoid development, provided Pathology oversight to the organoid platform

**SIDDHARTHA MUKHERJEE, MD, PHD**
**Scientific Advisor**
Winner of the 2011 Pulitzer Prize for his book, *The Emperor of All Maladies: A Biography of Cancer*, Assistant Professor of Medicine at Columbia University

**WILLIAM GRADY, MD**
**Scientific Advisor**
Professor, Division of Gastroenterology at the UW School of Medicine, Medical Director, GI Cancer Prevention Program Clinic with Seattle Cancer Care Alliance

**JONATHAN BAELL, PHD**
**Scientific Advisor**
Co-Director of the Australian Translational Medicinal Chemistry Facility and NHMRC Senior Research Fellow at Monash Institute of Pharmaceutical Sciences

**VK GADI, MD, PHD**
**Medical Advisor, Co-Founder**
Oncologist and Associate Member Fred Hutchinson CRC, Professor and Director of Medical Oncology at the University of Illinois at Chicago

**BRADY BERNARD, PHD**
**Scientific Advisor, Co-Founder**
Director of Bioinformatics and Clinical Genomics at Providence St Joseph Health, Assistant Member at the Earle A. Chiles Research Institute

**CHRISTOPHER KEMP, PHD**
**Scientific Director, Co-Founder**
Full Member at the Fred Hutchinson CRC Developed IP related to novel drug targets; awarded NCI grant support toward development of the SEngine Platform

SEngine Precision Medicine

**‘Organoids Guide Treatment Decisions“ (Payel Chatterjee, SEngine) [#13]**


Ally Perlina: What is your pricing?

Payel Chatterjee: It's somewhere between $5,000 and $7,000. We are trying to get reinsurance reimbursement, and sometimes it can be talked through. If the patient really needs it, it's not like just because of money, we don't do it.

Ally Perlina: Do you have a list of drugs that you would test each time?

Payel Chatterjee: We have a drug library of 200 drugs. I do the drug designing part. I'm normally in contact with the doctors or whoever wants to be part of the care team for the patient. I would provide a proposed full plate with a 43 drug list. If we can't do 43, we have to reduce the number. I'm in constant touch with the doctor, the patient, or the care team about what they would prefer. Together we come up with a solid list.

Ally Perlina: Can a patient order it without doctors or a care team involved? Can they just say, I'm going to get the tissue to you one way or another. Can you do the test if I pay?

Payel Chatterjee: At least one doctor needs to be signing our order form or the requisition form. It doesn't matter if that doctor is the treating oncologist. We have had multiple cases where the patient is not from Seattle. They could not get a doctor. We arranged for a doctor here locally so that they can get a biopsy, and that doctor would sign the form and send us the sample. We recently did it for an international patient. She would get her drug treatment in the U.S., but it was hard for her to travel, so she got a local doctor to sign the form and send it to us.

## ‘Organoids Guide Treatment Decisions“ (Payel Chatterjee, SEngine) [#13]

Rick Stanton: Olaparib is a drug that's being proposed by my oncologist Tanya Dorff from the City of Hope for my CDK12 mutation. I don't know whether it's really a match, nor is anyone sure. Is Olaparib something you can test?

Payel Chatterjee: Yes. We test four different PARP inhibitors: Niraparib, Olaparib, Talazoparib, and Rucaparib. We also test Veliparib, which is not very effective now.

Rick Staton: I’d rather have you test it than me. “It didn’t work. Sorry, bub.”