Will Precision Medicine work for me? Advances and Challenges in Cancer Research

Precision medicine is an emerging approach in cancer treatment and prevention. It is a shift away from a one-size-fits-all approach and requires sharing of information across research settings and community. Precision Medicine's central principle revolves around the ability to identify personal gene characteristics and match them to specific treatment options. We are exploring advances and challenges of precision medicine in cancer care with Dr. Luke Gilbert and Dr. Eric Collisson of UCSFs Helen Diller Family Comprehensive Cancer Center.

Full Transcript:

Priya Menon: Good afternoon and welcome to another episode of CureTalks. I'm Priya Menon, your host and today the topic of our discussion is Will Precision Medicine Work For Me? We are joined by Dr Eric A Collisson and Dr Luke Gilbert from UCSFs Helen Diller Family Comprehensive Cancer Center. On the patient panel, to discuss the patient perspective, we have patient advocates, Heidi Floyd and Adam Hayden. Welcome to CureTalks everyone. So to get the show started, we have with us physician scientist, Dr Eric A Collisson and cancer biologist, Dr Luke Gilbert from UCSFs Helen Diller Family Comprehensive Cancer Center and we are talking about a very complicated subject, which we are going to try and make simple for everybody to listen and realize the burgeoning importance of precision medicine. Dr Collisson, Dr. Gilbert, great to have you with us and welcome once again to CureTalks. I want to kick off the discussion with the most basic question to both of you. Can you help us understand what precision or personalized medicine is? Maybe they are both one and the same or there's a difference and we'll start with Dr Collisson and then Dr. Gilbert, you can chime in.

Dr Eric A Collisson: Sure, sure. I can start. I think, you mentioned precision medicine and personalized medicine and I think they are a spectrum of the same phenomenon. Precision medicine I think refers to treating the molecular underpinning of a disease and what Dr. Gilbert and I work on mostly is cancer. And what that means most of the time is a mutant gene or a mutant gene product. And so precision means that we're looking for chemical matter most often drugs, sometimes other treatments like cells or other proteins that attack the underlying cause precisely. So in contrast to chemicals that kill many different kinds of cells, we would like to be precise in what we do with the treatments we give. And that is called precision medicine.

And I think personalized medicine is along that spectrum, but folding in the diagnostic angle, which is increasingly important in the clinic it was fine years ago to sequence one genome over 20 different centers over 20 years with close to a billion dollars. Now our challenge is to do that in one human being in 48 to 72 hours so that we can figure out what mutations that patient's tumor harbors in enough time to get the treatment on board when it's needed. So, I think precision medicine is the overarching goal and personalized medicine is the reduction to practice with the diagnostics in the clinic.

Priya: That's easy to understand.

Dr Luke Gilbert: Yeah that's definitely well said. From my perspective, I think what cancer biologists do is more precision medicine focused and what clinician scientists do is both. So we think more about precision medicine on the level of targeting specific mutations or specific tumor genotypes or tumor genetic spectrum. And then the implementation is an enormous challenge to something that I'm frankly quite blind to.

Priya: So, so what we are saying is that precision medicine is an approach to the care of cancer since you're talking about cancer here in which we are trying to match probably the best therapy with the optimal

patient. And for this we look at all possible information about the patient and the disease. Is that right?

Dr Luke Gilbert: Dr. Collisson may disagree with me, but I think precision medicine is a combination of science and medicine and personalized medicine is medicine. I don't know, would you simplify it that far.

Dr Eric A Collisson: Yeah, no, I think that's well said. With precision we seek to gain is really at the molecular level in cancer that we want to know the underlying cause. And that's just essentially a scientific enterprise testing hypotheses, personalized medicine is you can't always test a hypothesis in the clinic. You've got to practice medicine and that's both art and science and personalized medicine falls in that spectrum.

Priya: Thank you doctor. So I'll just ask one more question on the basic before we actually address the topic that we're discussing today, whether am I eligible for precision medicine. Dr Collisson, it would be great if you can very briefly, this is for the benefit of the audience so they know what we're talking about here. Very briefly summarize the kind of categories that are presently available under the precision medicine umbrella for cancer. Just a brief idea of some terms that probably the listeners are quite familiar with but would like to hear.

Dr Eric A Collisson: Sure, sure. I'll give three examples and I'll be brief. And they all involve therapeutics because that's usually if cancer is left alone, unless you treat it with the therapeutic, then it usually ends in death. Not always, but quite often. So we're interested in treating cancer because the results of not doing so are lethal. So the three therapies can be broken down into basically small molecules. So these are drugs like antibiotics or aspirin that many patients are familiar with. They come in pills or in infusions. And these drugs often bind to proteins that we know drive cancer proliferation. So this is the equivalent of a broken accelerator that cannot be lifted off the car floor. And the cancer cell is essentially floored and always accelerating. So if you can design a piece of chemical matter to fit into that accelerator, you can pull it off the floor and get the acceleration to stop.

And there are great examples of that that Dr. Gilbert uses in his lab, Imatinib for CML for leukemia is an example. We have many other examples in melanoma and Lung cancer that that we work on as well. A second example would be a marker, like a protein on a cancer cell. So it may not drive the cancer cell, but it flags to the therapy that this is a cancer cell. And there we've been able to attack those markers with antibodies like Herceptin or Rituximab. These are antibodies that attack the cancer cell by the identification of this protein on the cancer cell itself. And then the cancer cell gets killed by the immune system.

Or increasingly we skip the middleman and we make the immune cells ourselves. And this is exciting work happening at UCSFs by some of our colleagues where they actually engineer the patient's own immune cell to attack the cancer through a similar recognition of this cancer specific epitope and their CD19 and other liquid cancers have been successful early examples, but we expect more so. So the idea is always to achieve a therapeutic index, meaning that the cancer cell dies, the normal cells don't, based on a molecular level meaning that the cancer cells have this thing the scientists discovered it and studied it and then a pharmacologist or other person has figured out how to make a therapy to block it.

Priya: Thank you Dr Collisson. It looks like we have already started getting a few questions in my email. So this one I think I'm going to take now – a person wants to know what cancers can be treated with precision medicine. I know you just mentioned leukemia, melanoma and lymphoma. So what else, what are the other cancers that can be treated with precision medicine this person wants to know?

Dr Eric A Collisson: Sure, great question. Well, I think at the level of a cancer, we're increasingly trying to do the first step in precision medicine that we talked about, at least in personalized medicine, which is diagnosis. We want to achieve precision diagnosis so that we don't get into this scenario where we don't know what this cancer is. We don't know what's driving it. We don't know what's going on. That's obviously not a good starting point. So I will say all cancers and maybe Dr. Gilbert will disagree, but all cancers are amenable to a precision approach to diagnostics. And that today I think includes imaging of the

tumor using PET scanning and CT and MRI scanning. These are precision imaging approaches as well as genomic characterization of all tumors. All tumors have DNA.

All tumors have at least one mutation in them. And figuring out the mutations that drive the cancer is a key first step. Then the treatment is the next step. And we have FDA approved quote, precision treatments in many diseases. Certainly the biggest cancer killers, lung cancer, breast cancer and colon cancer all have precision approaches in various degrees. There's still some pretty egregious omissions on that list. Pancreas cancer that we work on a lot in the lab, hepatocellular cancer, these are cancers that killed millions of people worldwide and for which we haven't really made a lot of progress on the precision medicine front yet, although that's changing.

Priya: Thank you, Dr Collisson. Now my next question is for Dr. Gilbert. Dr. Gilbert, what is it different within genetic and genomic testing and sequencing? The reason why I'm asking this question is when we were just preparing for this talk and getting some feedback from patients, advocates, there seem to be a big confusion around the difference between these two. It'd be great if you could just clarify this.

Dr Luke Gilbert: Yeah. I think many people do use them interchangeably. There are more specific definitions that can be applied, but the confusion in part relates to the fact that as we diagnose cancer, our methods for diagnosing the underlying alterations have changed over the years. And so, my definition for this is for genetic testing, you can be looking at a single gene or all genes and for genomics, sort of by definition you're looking at thousands of genes where all genes encoded by the genome. And so older tests in the late nineties, would, for example, look at a single gene that was known to be associated with cancer and ask, is that gene mutated in an individual patient or a cohort of patients where currently we're moving towards not looking at single genes in patient sample, but instead looking at either a large fraction of the genome or the whole genome. So if you are at a cutting edge cancer institute, often as you enter you can be given the option to have a test run on all genes known to be associated with cancer, for example.

There are companies that do this like Foundation Medicine. And so I don't, we may, because of our change in methodologies, we're losing what we would have historically defined as genetic medicine and everything's becoming genomic medicine in my estimation.

Dr Eric A Collisson: Yeah, I would agree. I would add another possible distinction between the two terms and I agree with Luke that they're used I don't want to say sloppily, but these are new terms to the word genomic didn't exist a decade ago. So I think we're learning, we're trying to fit where it fits. One thing we use in cancer genetics often refers to the genes you came with, meaning your mom's and your dad's. So germline genetics is a term that's often used. And these are the heritable components of cancer, which we know are many, whereas genomics may refer to the somatic changes, the changes that the cigarettes or the UV rays or the bad luck that your cells had afterbirth and resulted in a spectrum of mutations that you were not born with. So some people use the term genomics in cancer genomics to say, oh, these are somatic changes. I don't know if this works in the dictionary yet.

Dr Luke Gilbert: Actually. Maybe it is, I'm not sure. Yeah, no, that's, well, that's a nice way of looking at it.

Priya: So when we talk about genetic testing, most of the time we're talking about genes that have been inherited from family members. And when we talk about genomic testing we are talking about our own tumor and somatic changes from our tumor.

Dr Eric A Collisson: Yeah. So ideally to add to that, your genetics doesn't change over the course of your life whereas the genomics of a tumor can change between your normal cells versus your tumor cells, but also during the course of treatment a tumor can change. And so you would want to get just genomic profiling ideally throughout the course of tumor treatment.

Priya: We have a question that just came in, I think based on what we're just talking. The question is, will genomic sequencing show if I have a hereditary risk for cancer?

Dr Luke Gilbert: Yeah, it's a great question. Like most tests, you only know what you test. And so some of these panels, they interrogate 50 genes or 90 genes at UCSF. Our in-house panel looks at 500 genes and there's more than 20,000, I think it's now 28,000 genes in the genome and we don't sequence all those. So but you do inherit all of those times two from your parents. So we think a large amount of cancer risk is inherited, meaning, up to 50% in some cancers and certainly 10% in most common cancers there's a familial risk component, meaning you're born with it. The genetic tests that we do today identify the major risk genes, but don't identify every gene that impacts risk. So we encourage people who have a family history, meaning mother, father, brother or sister to undergo germline testing in most heritable cancers.

And those include pancreas, breast, melanoma in some cases, other colon cancer and other cases. So in those patients, we always recommend that you provide a saliva or a blood sample, send it off, see what mutations you have, and if something's found that is suspicious for the cancer that you have, then we work out from there. And if there is the appropriate consent and counseling in place, we talk to the brother, we talk to the mother, we talked to the children about their usually 50%, but not always 50% risk of inheriting that allele from you, if that makes sense.

Priya: Yes, that does. Dr. Collisson, maybe if we could just talk a little bit about who is a good candidate to get tested and what exactly do they get tested for and what might you hope would come out of that test?

Dr Eric A Collisson: I'm assuming you mean a germline genetic test. So this is a really the wild west today. I think as recently as about three years ago, the answer would have been very easy. If you have breast cancer or ovarian cancer or colon cancer and you had a family history then or your tumor looked a certain way under the microscope in the case of colon cancer, then you should get a genetic testing. That's still true and, and unassailable and absolutely true. We've now included other cancers under that rubric. Prostate cancer, pancreas cancer, others in which we know that there are inherited mutations. So I would say any patient with metastatic prostate cancer, any patient with pancreatic cancer, any patient under 50 with colorectal cancer, any patient with ovarian cancer and patients under, I believe 50 with breast cancer have certain kinds should get germline testing, less so for diseases like lung cancer and some brain cancers.

But now we're also seeing the direct to consumer movement pioneered by Silicon Valley and other places where we're both getting – are you related to aunt Josephine in Pittsburgh? So a relatedness test to kind of build interesting networks of long lost cousins, but also spontaneously on discovering deleterious cancer genes at the same time. And this is a bit of an ethical struggle of how to deal with these. If this patient just wanted to know is she 20% Irish like mom says or is she actually from Germany, but actually finds out that she has a 50% chance of getting breast cancer, that's not really what she signed up for. So that's difficult to know how to deal with that. And then a third scenario is there's a bunch of companies coming through that are proposing to build blood tests to actually find cancer before it's clinically evident. And those look very encouraging but are definitely too early for prime time. But this is a rapidly moving area.

Priya: Thank you Dr. So I, I believe when we last spoke, we discussed how it's definitely not just about the information, it's what you do with that information. It's about how appropriate a treatment is. And when we are especially not sure of the gene mutation will respond or not respond. So Dr how do you address the situation about appropriateness of selecting treatment? And how do you address this with your patients?

Dr Eric A Collisson: Well, I try to look at first, clinical evidence – has an experiment been done in patients like this, patient with this drug. That's the highest level evidence. But I think there's unfortunately the vast majority of the diseases in the cancer clinic today, we don't have good treatments for. And I increasingly looked at people like Dr. Gilbert to tell us, what, what are we not thinking of here in the clinic. I'll let him explain how he finds some new therapies for cancers and actually how he figures out how certain drugs we use all the time actually work.

Dr Luke Gilbert: Yeah. So I think as a background piece of information, and Dr. Collisson alluded to this, we only defined what the genes are in the human genome at around 2001. So it's only, it's been less than 20 years since we do know for a single genome what was encoded in our genome. Since then we've come a

long way due in part to advances in technology. And we've now sequenced hundreds of thousands of healthy individuals from across the globe, which defines what the natural genetic variation in the human population is. We've also looked at many hundreds to thousands of genomes from individual diseases and defined what the genetic alterations are that are associated with individual diseases, not just cancer, Crohn's disease, Lupus, all kinds of neurodegenerative diseases. In the context of cancer we've sequenced hundreds to thousands of genomes from individual cancers and that number continues to grow.

So for any common cancer, we now have a very advanced draft genome of the mutations that are associated with disease at diagnosis. For I'd say a fraction of those changes we as a scientific and medical community have built precision drugs. One of the more recent examples of this is a gene that is called KRAS that's mutated very commonly in lung cancer, pancreatic cancer and colon cancer as well as sporadically in other cancers like leukemia has. And it's been a really a holy grail of thinking of new ways to target this gene. We know this gene drives tumor progression and it drives a poor response to conventional therapies. And so our colleagues at UCSF a couple of years ago came up with a really innovative way to target this protein and that's progressed through startups and big Pharma to a series of molecules that were presented this year at ASCO, which is the main clinical trial conference in the US for cancer therapy with Amgen announcing that they have pretty dramatic responses in using this molecule to treat lung cancer patients that have a specific mutation.

Despite the promise of these approaches, we have a long way still to go. So there for, I'd say most of the genetic alterations that we see in an individual patient, we don't have a specific precision therapies to target these mutations. And even worse, we often don't even have an advanced understanding of what these genes do or how these genes work together with other changes we see in tumors to drive complex biology within an individual patient. And so there's much to do. And there are many people working very hard on this. I mean, this is the fundamental challenge in cancer biology at this point.

Priya: Dr. Gilbert but isn't it true that there are reports that confirm that the majority of individuals who have contributed their DNA to genomic research are Caucasian and therefore minorities under represented in the genome database. Can you comment on this as well?

Dr Luke Gilbert: Yeah, that's – to my understanding. That's absolutely true that the majority of the genomic information we have for cancer is derived from the US or from Europe or to some degree from Japan and China. But there that doesn't cover the global spectrum of genetic diversity in humans. We do have intentionally collected normal human genome information from across the globe. So we have that part in place, but I think it for sure in the context of many cancers, we don't understand how the mutations that are associated with liver cancer in Southeast Asia are similar or different from the mutations associated with liver cancer in North America. And one of the examples of why I bring this up as an example because there are global differences that don't relate necessarily to race, but instead to even to diet.

So there are known toxins associated with peanuts in Southeast Asia that drive mutations in liver cancer, which gives those people in that region of the world a different mutational profiles than what we have in the US where we have liver cancers that are more associated with obesity and alcohol consumption and other influences. So definitely important we need like your whole podcast is pointing out, we need both precision and a personalized approach here and that applies to each individual's family history as well as their personal life history.

Dr Eric A Collisson: I'll just chime in and say that's one of the shortcomings for all the excitement around genomics that we talked about – putting things into the DNA sequencing machine and getting lots of data. That's all very exciting. But what we often forget what we don't gain from that. And what we don't fully get out of the sequencing machine is, where did this patient come from? Is this patient born in the US does this patient have a virus she had as a child. Is this a smoker, a nonsmoker? What are the effects of environmental toxins or other practices? And so I think increasingly we're trying to get these well annotated datasets that go beyond just genomics. So it's putting that cancer genome from that patient in the setting of who she is and what, how did she grow up and what was her diet like and her exercise like, and it's only

with that complete picture that we're able to really educate the next patient.

In patients like you with this mutation, we found that a high fat diet is especially deleterious, for example. We can't give that advice if we don't have the dietary information with the genomic information. And that's a major challenge. We're somewhat handcuffed in the medical centers today, unfortunately due to the privacy with which we all guard our medical information. And that's probably appropriate certainly for diseases with more social stigma to them. But I think in metastatic cancer, there's a group of us who are trying to loosen those privacy rules, patients being at the front of this charge and trying to liberate their data for study on a broader scale to put their genomics in context with who they actually are and get it out there. So that's something we're trying to do more of in the cancer community.

Priya: Thank you. I do have some more questions, but I think I need to stop now, looking at the time and open it up for our patient panel. I'm going to hand it over to Heidi Floyd. Heidi is breast cancer survivor and advocate. She highlights treatment options, quality of life and community concerns. Heidi, over to you.

Heidi Floyd: Hi, thank you very much. Thank you doctor. I just want to say thank you for your work in this field. This is obviously crucial. My first question focuses on accessibility and briefly touches on what Priya had mentioned earlier. There are so many people groups out there that just simply don't have access to larger institutions that are conducting this kind of work. But it really is, I mean it's incandescent and life changing this arena. How do you, do you have any ideas on how to propose that we can reach the underserved where they are, so that because if they have cancer for example, they can't they have such financial toxicity, they don't have the wherewithal to get to organizations that might be conducting precision medicine. Do you, can you speak to that just briefly?

Dr Eric A Collisson: So I think there are really exciting things happening right now in diagnostics where we would measure the genetic or genomic changes associated with an individual tumor. The cost of some of these tests, whether they're DNA sequencing based or I'll highlight another version have dropped dramatically. There's a specific startup company, I'm thinking of that as an example that is leveraging new enzymes. So not DNA sequencing, but a new form of a test that relies on specific enzymes that we can harvest from bacteria that we can program to detect mutations. And this has been demonstrated in field trials in Africa to be able to differentiate between different subtypes of Ebola or in Southeast Asia, between dengue subtypes as well as in the US to differentiate between different serotypes of HPV that are associated with cervical and head and neck cancer.

Dr Luke Gilbert: And the appeal of these approaches is that they're very low cost and they can be done in the field with no specialized equipment. So the estimated costs right now for these tests, about $10, no specialized equipment, no refrigeration. You get results within half an hour. So if we can implement these at scale and we turn this from a small startup of 10 people, I'm not financially involved in any way, so I'm not trying to plug that for that. Just to be full disclosure. I think that these, these enzymatic tests can be implemented in any clinic across the world really. And I think that would be amazing for medicine outside of North America.

Dr Eric A Collisson: Yeah. And I'll just to speak to that question. I think, what we don't see often is, is the etiology, the cause of the cancers that we think we know a lot about in other countries. One of my colleagues, Catherine Van Lone here at the UCSF Cancer Center goes to Tanzania twice a year. Every year. She's a medical oncologist and we've now sequenced 200 genomes from Tanzania and squamous Cell Esophageal cancer here at UCSF. And we think that some of the causes of esophageal cancer in Africa may be different than those here in the US and so I think at a very fundamental level this isn't the kind of high tech fancy state of the art kind of medical center you think about. But actually using the power of technology to go global as Dr Gilbert is alluding to is really the first step to use technology to pull these populations up to a minimal standard of care and then building on that

Heidi: Going global. Would that not be just fantastic? What is your dream? I had a question but based on what I can't remember which one of you said this earlier, I kind of want to dive into this instead. One of you

were talking about the quote was exactly, we got our medical info where we're really tight on that because of the different laws and everything here in this country. But we want to liberate our data. I'm not sure which one of you was talking, which one is Dr Eric or Dr Luke. But it was, that was brilliant to me. As a patient, as a two time, someone who's been diagnosed with cancer, two times going into, let's say a patient is going into a surgery ahead of time and they know that they've been diagnosed with cancer, now they're going into remove their tumor or tumors, if the onus were on the patient, what can we do before we go in to say, we want to free this tumor. I want to make sure that it all the precision medicine that needs to be done on it can be done so that you can dive in and all the functional testing, make sure that you test those tumors with outside drugs, so I know what will work. Is there something that we as a patient can do before we go into those surgeries so that we get precision medicine?

Dr Eric A Collisson: Yeah. So, so there are a few of these projects that are growing. My colleague Nikhil Walgle at Dana Farber has a great project in breast cancer called the MBC Metastatic Breast Cancer project where patients are consented and, and they send their tumors in and he and his colleagues in Boston sequence that tumor and a proviso for participating I believe is that that data becomes public. And so the germline component is kept private, but the somatic mutations are shared with the public so that clever researchers in the Czech Republic for example, who may not be hanging out in Harvard Square that afternoon can have access and think about those data. We're aspiring to that in other diseases, pancreas cancer being one of them. And it is a delicate balance because a lot of these diseases like we just talked about have a very strong family risk.

So it's fine if the patient says, yeah, I want to share my data. But that doesn't mean her daughter feels the same way or sister feels the same way. And genes are tricky things. They get mutated in cancer, but they also get shared in families. So finding the right spot between transparency and privacy is something we just need communication, we just need dialogue and I feel, unfortunately we've kind of locked down the dialogue a little bit too much on the privacy side with some of the election shenanigans. But hopefully that will open back up and we can actually have a civil discourse on this topic.

Heidi: I agree completely as I as a very passionate patient advocate and as a breast cancer community organizer, how can we might even my little narrowly focused group, what can we do to help both of you as this progresses and the other groups that are out there in the precision medicine space, everybody that's out there working on testing everything. What can we do to help you?

Dr Luke Gilbert: Hmm, that's a tough question. There are a lot of these trials coming up that have to do more with you, what can we do to help you as a breast cancer patient, survivor, etcetera. I think we haven't done as good of a job beyond saying, send a check of what can we actively do to enroll patients. Some colleagues at UC Santa Cruz are trying to gather all the BRCA alleles called the BRCA challenge. I'd encourage you to Google that. And it is especially for Asian women with breast cancer who don't happen to be Ashkenazi Jewish. They have an allele of the BRCA 1/2 gene that looks like it might be cancer, but we don't sequence a lot of Vietnamese women, so we're not quite sure what to do with this. And so it's through this kind of crowdsourcing approach that we're trying to adjudicate what alleles are deleterious. And that's very much community driven. In other diseases where we're also trying to certainly support each other more through traditional meals and rides to clinics and donating a room so people can participate in a clinical trial. But I do agree we need to be more active on the genomics side and we're trying to build the infrastructure for that.

Heidi: Very good. I'd love to stay connected with you as if I could do anything to help. Please consider me at disposal.

Dr Luke Gilbert: Well, thanks for so much you already do.

Dr Eric A Collisson: I would add at a national level, a lot of research in medicine, research in science and research in medicine is funded by American taxpayers. And so they, I think 60 years ago there was, or 50 years ago, there was a decision by politicians and American citizens to fund cancer research. And this is

worth it. We've made a lot of progress, but I'd say it's been reassuring over the last couple of years, that commitment to cancer research has been renewed or is continued to be renewed. But it's something that politicians do need to hear that people care about and it's important to communities.

Dr Luke Gilbert: Yeah. It's pretty incredible in 2019 that there's any topic with universal agreement. But I would say that supporting cancer research, from the far right to the leading left side both are firmly supportive and there's just no disagreement on that topic.

Heidi: Full disclosure, I sit on the Department of Defense Grants Review Board for cancer research and I did not pay you to say that. It is just absolutely wonderful. Priya, thank you for letting me participate. Can I ask you one more question while we wait to see if we're all gonna get connected back up? So I have a question about functional testing. If they test a tumor outside, like during surgery what is the accuracy level when they do the testing do they know if a drug will work inside the patient, if it's outside the patient versus inside?

Dr Luke Gilbert: That is a really tall, challenging question. What I tell people is that everything except for a real human tumor is a model. And there's, we've learned a lot from models, from simple models than from complicated models. But in the end, any model doesn't recapitulate the complexity of a tumor in a human. And so I think we've come a long way in our understanding of how to use various models to predict drug efficacy. But it's one of the central challenges of cancer research is how to pick appropriate models and it's a balance of complexity and cost and throughput and which questions you want to ask. It's very, very challenging.

Dr Eric A Collisson: Yeah. I will say, I'm a consumer. I like trying new things as an oncologist and I like gadgets and new tests. I will say I haven't seen a commercial product that proposes to grow cells and treat them in a way that I think is currently clinically useful. That certainly doesn't mean it will never be a true statement. But today I don't think we're there yet. And largely because it's kind of at least two problems. It's one is getting the cells to grow, which is not at all trivial. And then second is the testing you do on the cells predictive of what's going to actually have to happen. And unfortunately that's a conditional question. If they don't grow then you can't even ask the second question. And we've learned that not all cells grow in that that is not random. So some of the patients in whom we most need this kind of a service. Again, pancreas cancer for example, are actually pretty tough to grow in a dish compared to leukemia cells for example, which can be grown relatively easily.

So yeah, I think, I think it's a promising model. I will add that that a lot of Luke's research is a similar version of functional testing where he actually tells us on a genetic level what kind of mutations should we expect if this therapy works and then the cancer recurs. So that's another kind of functional analysis where we're using a known medicine but we know it's not going to work forever. And I think Luke's research actually tells us what trouble lies ahead so that we can plan the next therapy appropriately. And that's another functional medicine that is very helpful.

Dr Luke Gilbert: Or even better, as a best case scenario, our research predicts for new medicines, how they should be combined with existing medicines to have synergistic anticancer activity. And so one of my goals is to continue working with clinician scientists and chemists to build innovative medicines that are really nontoxic, but which enables them to be combined with other therapies. So going back to this KRAS example that I have highlighted, this drug in people or in animal models is completely nontoxic. It's safer than Tylenol or aspirin. They've never had a dose limiting toxicity in people. And so that's my 2019 example of direction we want to be going in kinesiology

Heidi: Fantastic. This is like words to my ears as having been through so many different types of chemotherapy. That's amazing. Can you speak a little bit? I assume I'm just going to progress as if we're still kind of out there on the air. I was speaking recently at a clinical trials event in Philadelphia and one of the questions kind of surrounded what I mentioned earlier about underserved populations and how they may or may not be reticent to come forward or simply can't come forward. Can you kind of just elucidate the steps we've taken – I know that that's kind of the pendulum has swung pretty far about keeping privacy and things

like that, but how far have we come from like the Henrietta Lacks situation where we're not gonna do anything serious with your tumors, but we really want to help you. Can kind of just speak about what has been put in place to encourage people to participate?

Dr Eric A Collisson: Yeah, sure. I will. I will say there's more sticks than there are carrots unfortunately today, so it is against the law to discriminate against people based on a mutation they have. And that means I can't refuse to insure you based on a mutation for example. I can't not give you a job because you have a mutation in gene x and, and that's a fine law to enact, and in well-intended unfortunately it's not totally symmetrical with what Luke and I are telling you today. We were just talking about privacy and the laws preventing genomic privacy – requiring, I'm sorry non-discrimination based on genetics.

And at the same time, Dr. Gilbert and I are telling you that it's genetics that causes all this stuff or a great deal of it. So at some point it certainly not all genetics, but to say that genetics is equal amongst everyone and that there is no increased risk in person A versus B, it's scientifically not true? So I don't think we've had a high level discussion over how to reasonably factor in genetic risk into things like insurance premiums and stuff like that. It is clearly non zero, but our laws today assume that it is zero and I think we need to have a bit of a mature, a more mature discussion over that.

Heidi: Right. I agree.

Priya: Thank you Heidi. We have some questions that are coming in from our listeners that would probably be just go over those now. One of the questions is Dr. Collisson and Dr. Gilbert, how affordable is genetic and genomic sequencing and what is the attitude are the insurance companies to these costs? I think they're getting a bunch of questions on the cost of physician medicine right now.

Dr Luke Gilbert: So if the technology continues to change like Dr. Collisson said to sequence the first human genome was more than a billion dollars. The last estimates that I've heard for sequencing all the genes in your genome currently is roughly a thousand dollars little less than a thousand dollars maybe. And it's anticipated that that should continue to drop over the next two or three years. I think a good goal would be closer to $100. We don't have to sequence all of the genome or so we can save costs by sequencing of part of the genome that we know is highly correlated with disease. So in certain cancers we know that say 95% of patients have these hundred mutations, so we can just sequence those a hundred genes and gather most of the information we need. And then like I said, there are even newer technologies that don't use sequencing but instead used other enzymes and other, other newer methods to get at part of this information.

Dr Eric A Collisson: Yeah. And I'll say just because I think the listener asks for dollar amounts, US dollar amounts to do a germline test -what genes were you born with. The Internet will sell you that for around a hundred dollars. And those tests are not horrible. They're not medical grade per se, that the medical grade versions of those with all the insurance and stuff often goes up to around a thousand. That cancer test we're talking about with lots of genes is usually closer to two to 5,000. And the other part of the question was what does insurance pay for that? And the answer is it depends and it really depends on whether the disease – lung cancer often reimbursed colon cancer sometimes. It's really adjudicated on the insurance level by what disease the testing is being done in.

Because a lot of our reimbursements are still built on the lung cancer module versus the colon cancer module whereas I think a lot of us oncologists think more about mutations than diseases of origin. But we try to do both.

Dr Luke Gilbert: I think the related answer to this sort of vein of questions is how much, so diagnosis is one part, but how much do the therapies costs for precision medicine and there that in some ways is a discussion between the drug makers and the individual countries that they're being applied to. And so you see discrepancies in costs between countries that relate to the negotiation between for profit companies and national governments. There's a subtlety to this as well but in my opinion science sort of is designed to

show you what could be done. And then it's up to engineers and production and another means to scale this to be able to treat like a global population. And so in some, some of the things that we're talking about today like cellular therapies are currently extraordinarily expensive. And my hope is that as they become, as they're proven to be useful, and as they're scaled up, we'll find clever ways to decrease the costs. But that remains to be seen.

Priya: So we have Adam with us now. Adam Hayden is a brain tumor advocate and survivor and actually his personal blog called Glioblastology is a popular peer-to-peer resource and is in syndication with the Cancer Health magazine. Adam, please ask your questions.

Adam Hayden: Terrific. Thanks so much. And I was speaking into their best, so it's nice to hear your voice Priya and Heidi, nice to share the panel with you. I'm going to just I think a play off of what you were just discussing around cost. So the cost of therapeutic and CAR-T cell therapy, et cetera. We know it's extraordinarily expensive and we've had some good news that CMS is going to cover some of that. So hopefully we'll move in that direction. But I want to ask actually the flip of this. So last year Siddhartha Mukherjee wrote a cool piece for New York Times magazine saying that you can compare to blood thinning medications after a heart attack, one costs six bucks a pill, the other is a quarter a pill. He said that things like using the tools of genomics might help us prescribe cheaper medication when it will be as effective in some patient populations as opposed to others. So that was a call for cost savings through what I take to be personalized medicine. So I'd love you just to remark on is there an opportunity for savings in the long run around this practice of medicine?

Dr Eric A Collisson: I would, I'll comment on that. This is Eric. I think yes. You're talking about efficacy and that's certainly appropriate. You know, does this drug work better than the other drug? I would add even a more obvious and first baby step layer. In medical oncology, what I do is I talk to a patient about their treatment. We're going to do x, we're going to put our head down, walk uphill in the snow for two months, and then we're going to do another set of scans and see if the tumor shrinks. And if it does, then we'll keep doing that. And if it doesn't, we'll do something else. And so that's fine, but, but that takes two months and these things are charged by the dose. That's often four to eight doses of this medicine. It at two to $5,000 a pop and these things add up. What if we could tell after one dose with a blood draw rather than waiting two months. So I think that's an emergent area where actually precision diagnostics might prevent expensive ineffective therapy much more quickly than the slower diagnostics we use today, which are insurance reimbursed.

So paradoxically it may be cost effective to pay more for diagnostics to save more on drugs. And then the other example, I'll let Luke comment on. I think he's found many times that a cheap drug actually in a given genetic system works better than an expensive one. And that that bias is really in the system here.

Dr Luke Gilbert: Yeah. I think part of the problem is that the way drugs are approved is based off of their activity across a diverse set of patients. So you need to show efficacy in a given disease or at least within a given disease subtype, which often I think obscures exceptional responders and exceptional non-responders. We don't benefit at all from a given drug. And so a lot of my research is around trying to explore this using models because it's very difficult to design – Eric will have to correct me here, but we don't usually design personalized clinical trials at a single person level or I don't know how you would design that. And so this is an ongoing science and medicine problem that has sort of legal FDA ramifications too with how do you prove something as effective and safe for an individual versus a population of patients?

Dr Eric A Collisson: Yeah. And there's been some really exciting approaches to that. From some of our colleagues in the UC system that the UC San Diego Group for example, had published an interesting paper using given one patient Susie Q down in San Diego, she got first treatment x and then she got treatment y and it's the same person. And if she was on treatment x longer than treatment y, then maybe it's fair to compare treatment x and y with her genome and say this is kind of a clinical trial of one person, but done sequentially rather than simultaneously. There's caveats to that, right? The tumor has grown in that ensuing time. And it may not be a fair comparison, but I think we're learning ways to do these single patient and

personalized trials as we go.

Adam: Okay, terrific. So here's within the world of brain tumor and brain cancer advocacy what we see sometimes is that our newly diagnosed patients or not yet diagnosed patients will show up to the emergency department with some emergent symptom, seizure or something. And oftentimes they're sort of admitted and whisked into the standard of care protocols quickly. Making them ineligible for newly diagnosed clinical trials or unable to spend the time on the diagnostic screening that you're addressing. So I'm curious, something we think a lot about in the advocacy community is how do we help folks that are not yet even diagnosed, understand options before pursuing with the standard of care protocol when something more precise, maybe appropriate or available. Could you remark on that just in the settings of clinical care, how do we better inform people to make these choices?

Dr Eric A Collisson: Yeah, I'd say it's a huge problem. We have the same thing in pancreas cancer, this late presentation problem. My colleague Brian Wolpin at Dana-Farber presented some really compelling data looking having teaching a robot how to look at CT scans through the whole partner's health system. And it was really exciting that they could actually find some cases of pancreas cancer before just on the imaging that they had done for other reasons. And, so where I think that this is going is, is that we're going to have systems working in the background while the radiologists are still going to have a job. There are going to be computers looking at the brains of these people and setting off alarms when there's a tumor scene, hopefully to the glioblastoma network. And that will trigger let's get the consent team down there in real time, kind of on the equivalent of the 2019 back phone to consent them in real time. I can't think of another way of doing it because we just can't post an advocate in every emergency room 24/7.

Adam: That's exciting work. And I love the back phone. Yeah. Picking up in Glioblastoma. I'm not sure that good to good or bad. That's terrific. One other thing that actually just came up during the discussion and we talked a little bit about the KRAS case earlier. I'm curious, do you think that we are already moving in the direction of treating the molecular profiles or rather than the tissues of origin when trying to better understand treatment plans? It seems like we had some conversations, so I'd just like to hear more about that.

Dr Luke Gilbert: So I think that that idea was popularized that we can move away from a tissue based understanding of disease towards just a molecular profile. I sort of disagree with this idea. I don't think it's it's been born out, in some cases it has, in many cases it hasn't. And so I think that we need to consider the molecular profile of a given tumor type and stratify our treatment decisions based off that. But I'd love to know what Eric…

Dr Eric A Collisson: Yeah, I agree. I think the bloom is not entirely off the rose on that, but it's not a slam dunk. And Glioblastoma is a perfect example where we had drugs to treat some of the common mutations that we saw in lung cancer and Glioblastoma, but it just turns out due to brain penetration and the biologies being different, they just weren't as successful in Glioblastoma as they were in lung cancer. And to be honest, we didn't really ever figure out why we're still working on that. So I think as with all breakthroughs, it comes with footnotes and to really know it, you got to read the whole book and get to the bottom of it and keep going. So we're getting there. We do have medicines that are used across cancers, gastric cancer and breast cancer shared mutations. Melanoma and colon cancer have FDA approved drugs that are the same, but how well they work and how they're combined with other drugs differs.

Adam: Great. Terrific. Thank you. Really valuable.

Priya: It's like kind of time to wrap up now, but I have just one more question because this is exciting. I believe Dr Collisson and Dr. Gilbert, you folks have just recently moved into the new UCSF center, which is exclusively for precision medicine. So it'd be great if you could let us know what the new center offers in terms of trial research, etcetera, and then we can wrap it up.

Dr Eric A Collisson: Well, it's a beautiful building. We moved in last it's been a month now and I've had about four or five clinics in the new building. I think some of the perks are that every level has its own

treatment level there. So you can actually see the patients getting the treatment on the same floor. Often they'll go away and we won't see them again until the next visit, two weeks. So that's, that's a nice feature. And also the intermingling of different professions – radiation oncology surgeons are much more interspersed than they have been. And I think that's the key to success in these diseases, the multidisciplinary approach.

Dr Luke Gilbert: I would add, I think there's one thing that may maybe missing here is that I've never set foot in this building. So we need rich history of intermixing basic researchers who are not MDs with clinician sciences. And so I think that our current, the cancer research building is a wonderful mix of PhD MD and MD, PhD scientists. And I think I should go over to the new cancer building and say hi.

Priya: This is great. Congratulations to both of you to be in a new building now. So thank you so much. More than a decade ago, the science fiction author William Gibson said, the future's here and it's just that it's not evenly distributed. And the statement I feel could just as easily be applied to the field of precision medicine. And as we continue to explore and learn more, the future is definitely brighter with improved understanding and the breakthrough therapies for cancer. Dr. Gilbert. Dr. Collisson, thank you so very much for sharing all this information with us today. Thank you for your time. Heidi and Adam, thanks a lot for your participation and bringing the patient's perspective into the discussion. And we also, thank the UCSFs Helen Diller Family Comprehensive Cancer Center and the audience. Thank you and have a great day.