This transcript has been edited for clarity.

Philip E. Castle, PhD, MPH: Good afternoon, good evening. I don't think anybody's in the morning. My name is Philip Castle. I'm the Director of the Division of Cancer Prevention, and I am serving as a moderator for this very timely session, entitled, Cancer Screening Big Question: Are Multitumor or Multicancer Blood Tests More Hype Than Help?

My three distinguished panelists are Elizabeth O'Donnell, Chyke Doubeni, and Tomasz Beer. Let me just frame the question here, which is first of all, what are multi-tumor, multicancer blood tests?

Why do we need them? These are tests that use molecular profiling, and that can be a variety of markers to detect more than one cancer signature in blood. And why do we need them? Well, for many cancers, we still do not have a screening or preventive strategy. Some of the most lethal cancers that we are faced with today, like pancreatic and ovarian cancer, we do not have means to prevent or control them. We are in desperate need of strategies to find them early and prevent them from causing cancer-related mortality.

The real questions that we will be addressing today are what's the state of the field of multicancer detection? What do we know? What don't we know? And what are the key aspects of these tests that we are looking for, to move forward and offer this to the general public? So, I'm going to turn this over to our three panelists to make some opening comments. From there, we will launch into what I think will be a vigorous discussion. First, I'm going to introduce Elizabeth O'Donnell, who will tell you more about herself, and she will make some opening comments.

Elizabeth O'Donnell, MD: Thank you so much for the introduction and for the opportunity to be here and discuss this very important topic. My name is Betsy O'Donnell. I'm at the Dana Farber Cancer Institute. I'm a medical oncologist, and most of my career has been in the treatment of plasma cell dyscrasias. I have started a program at Dana Farber, the Multicancer Early Detection Program, focused on multicancer early detection testing, with the recognition that we need to take the same type of intensity and academic rigor to the study of types of early detection tests that might help to ultimately cure more patients. We've done a tremendous job over the course of the past two decades, extending lives through therapeutic interventions. We've revolutionized the types of therapies that we have. Yet, we're not seeing dramatic improvements in cancer mortality.

I believe that curing more cancers starts with earlier detection. I think the focus of our academic enterprise and pursuits needs to focus on this space, and that's what we're trying to do with our program.

Castle: Thank you, Betsy. Tom, I'll ask you to go next. Please.

Tomasz Beer, MD: Thank you so much. It's such a pleasure to be here with my distinguished fellow panelists and with our audience members. My name is Tom Beer. I'm a medical oncologist. I primarily have been focused on the care of men with prostate cancer and on prostate cancer clinical research. In the past 5 years or so, I got involved in the early detection of cancer and really began to fully appreciate the need and the promise of that approach.

About a year and a half ago, I joined Exact Sciences as chief medical officer for multicancer early detection.

I think my "why" for being involved in this work is similar to what's already been articulated. We face about 600,000 Americans dying from cancer every year, and the proportion of deaths due to cancer continues to increase as other medical conditions are managed with greater success.

We know that when proven, early detection can have a substantial impact on human health. We know that only about one third of incident cancers today even have a screening test that is guideline-recommended and universally endorsed. Only about 1 in 6 cancers are actually detected through screening, and 5 in 6 are detected clinically. So there's a great need for improvements in cancer screening that will broadly extend our ability to detect cancers beyond the four or five cancers that we can detect today.

Castle: Thank you, Tom. Chyke, please.

Chyke A. Doubeni, MD, MPH: Thanks, Phil, for the partnership to be on this panel. I am Chyke Doubeni. I'm a professor of family medicine at Ohio State University here in Columbus, Ohio. I'm a family doc, and I'm a cancer researcher. My career has been devoted to understanding the effectiveness of cancer screening in the general population. We've done seminal work around how to improve the delivery of cancer screening.

Multicancer early detection tests (MCEDs) have been a focus of public attention, and investigator attention and the research community for the past few years now. I think the interest has increased quite a bit recently. The reason, as stated earlier, is that we don't have screening tests for the majority of people who suffer from cancer.

I do want to make a couple of points here. Cancer is a very important condition, but not all cancers are the same. Knowing that some cancers can be very lethal — some of them, like pancreatic cancer, can kill very quickly — we need to be able to detect and treat them well. But some are indolent, meaning that they are just there and they will not actually cause harm in someone's lifetime. Cancer screening is tricky because for people who are screened, if we do it correctly, they are not symptomatic. They don't have any symptoms of the disease or condition we are screening for. But even in that condition, we still don't have ways to be able to tell what is actually more important and less important from a screening perspective.

Multicancer detection tests are really important if we get them right. I think we can get them right in the long-run, to be able to detect the majority of cancers for which we don't have a current screening test. That's just really, I think, the thrust of our conversation here. But I think the more important issue is that what do primary care doctors like me do? What do we tell our patients? When they ask for these tests, which are really in the public domain and interest — that's a really thorny question that I think we would be very interested to discuss here.

Castle: Thank you, Chyke; thank you, Betsy; and thank you, Tom. Let me let me start off with probably the most controversial topic that I can get things going here. There's often discussions about performance metrics, like sensitivity, specificity, false positive, false negative. I will weigh in, with my own opinion on this at the end, but tell us what you think we know about the performance of these tests and the critical metrics.

I'll start with Chyke, since you got to go last the first time, we'll go ahead, but please jump in any of the panelists at any point here. An open debate is, I think, valuable to our audience.

Evaluating Metrics, Relevance, and Validity

Doubeni: Now, Phil, this is a really important question because it underlies a lot of the questions that we need to answer around the tests, because in cancer screening, we talk about sensitivity and specificity, predictive value, or other parameters, which are measures that we use to describe cancer screening. For the most part, for us to know what these are, we have to do tests or studies that evaluate these tests in populations for which we screen generally. Currently, a lot of the studies, if not all of the studies that have been done to date, have studied people with cancer and have compared them to controls that are with known status.

If you look at the literature, it's reported that some of them have sensitivities as good as 50% or higher. I don't think those are useful right now because the studies aren't there for us to be able to understand clearly what the sensitivity and specificity of these tests are.

We need to be able to do those studies in the general population to understand; but I do need listeners to understand that we do not understand the sensitivity and specificity of these tests.

Castle: To that point, it's not just sensitivity and specificity. It's what stage are you detecting, right? For many of the multicancer tests — and I will say that there are probably 50 of these tests in various levels of development out there, at least 50 — their performance differs greatly by the organ or tissue type and by the stage. I want to focus this a little bit more and have Tom and Betsy weigh in here, which is what the real purpose of cancer screening is and what the real metrics of cancer screening are; in my opinion, it is certainly the prevention of death if not the extension of life. Could you two please jump in here and agree or disagree?

O'Donnell: I'm happy to jump in. There are a lot of questions that come up, especially as it pertains to trying to get tests like these approved, in terms of what the right endpoints are to be looking at. Is it mortality? Is it stage shift? These are really important considerations. How long can we wait to see a survival benefit? These could take decades to roll out. We're thinking about these tests in terms of what information they can give us and what information we need to have them become clinically relevant. It's hard because, as Dr Doubeni pointed out, these tests aggregate different types of cancer: some of them more rare, some of them more lethal. So you're mixing information about different cancers at different stages. When we think about these tests, there's actually a lot of information being gathered. It becomes a hard analysis to do when you think about how you approve these and how you recommend their use.

One of the critically important things that we have not talked about yet that you brought up is also the positive predictive value. When you do have a positive test, what is the probability based on the prevalence of that cancer in the population that that positive test will in fact demonstrate a cancer diagnosis? And from a primary care or population-based perspective, what do you do with those patients who have positive tests but have negative diagnostic workup? What should the threshold be for a positive predictive value for a test as well?

All of these are complicated and unanswered questions. I think it's our duty and responsibility to try and think through and sort them out even though they're complicated because what they hold is the promise of potentially finding lethal cancers earlier, which is what we need to do, and therefore being able to cure them.

Beer: Yeah. The goal of these programs is to reduce the burden of cancer, including cancer mortality; living with advanced cancer; and the need for advance complex, toxic, and expensive therapies for advanced cancer. There's no question that that is what everyone is trying to achieve in the field. The more difficult question is how do we efficiently demonstrate that? To what level of certainty do we need to get? The first step is to evaluate, basically, the clinical validity of these tests. The ability of these tests is to detect cancers, to detect them at early stages, characterize their performance across a broad range of cancers, understand the false-positive rate, the consequences of false-positive results, workups, and so forth. That's generally speaking in the scope of the FDA evaluation of safety and test performance. Then, over time, we gather additional data about things like outcomes with initial cancer treatment for screen-detected cancers. Are we seeing early-stage cancers recommended for treatment with curative intent? Receiving successful therapy? It isn't the end of the evidence train, but it's the beginning and it's an important beginning.

Are we seeing a reduction in more advanced stages in favor of earlier diagnosis? That's going to take a little bit longer. Can we predict mortality before we get to the mortality endpoint, recognizing that mortality can take a very long time to sort out and that as a society, we're going to have to look at the totality of the data and make decisions about whether the data convincing enough? A public health benefit is likely, and we should engage in using these tests. That may be somewhere, short of a definitive mortality demonstration. But along the way, where we have enough data to demonstrate a significant clinical impact.

Doubeni: Is it okay to jump in for a minute? I agree completely with the points made. I'm a primary care doctor, seeing people who come to me asking for a test to detect cancers that they may be worried about. That's really important for us to underscore. But cancer screening is a very complex process. And it seems simple enough: You do a test; it's positive, and people are happy if it's negative, and the workup is negative. But I think, as we all know, once you do a test, there is a series of things that happen, from getting the test to getting the workup that could be invasive, as in procedures that require much more invasive interventions than just a single test alone.

To that point that I'm sure we would have got to also, is that you have overdiagnosis, and I think it is a point that we've raised already. When you do a test to find things that are red herrings, and this can lead to procedures that some of the studies done already have shown that you can detect things and cause unnecessary procedures.

Where I'm headed with this is this: If we think about treatments, we don't administer treatments without knowing that they are effective and safe. Tom made that point very clearly. I just wanted to reinforce that. I know that the pathway to demonstrating that mortality reduction can be found within a good test, and is quite long because cancers take a long time in natural history to get the outcomes — like colon cancer, cervical cancer, thyroid cancer. It can be very challenging to do.

But, you know, these are people who don't have any symptoms. That's really important for us to keep our focus on understanding — to Betsy's point —that these tests can reduce the benefit to improve outcomes. The key here to understand the U.S. Preventive Services Task Force, which has been very important in making recommendations, uses this framework of benefit and harm, and for a reason. Because these tests may seem harmless, and it may seem to do something useful. But when you do randomized trials, oftentimes — pancreatic cancer is a good example, ovarian cancer is a good example — they can lead to harm because the

procedures to treat them are very invasive and very fraught with potential complications. I agree completely, but just wanted to frame that importance of mortality outcomes.

Beer: Can I just jump in a little bit? Because I think those points are so well taken. We still have a lot of work to understand some of the downsides, Chyke, that you mention, things like, how often do we get a false-positive result? One of the features of these tests is that they're being designed with a high level of specificity so that the false-positive burden is relatively low. That doesn't mean it's unimportant, but when you think about the false-positive rates for current accepted single-cancer screening tests, they tend to be around 10% or 11%. Here, we're looking at 1% or so. There's good reason for that. The consequences of a false-positive test that has the potential to detect many different cancers are more complex than a false-positive test for a single cancer, where the diagnostic journey is well worn and well understood.

But it is important for the audience to understand that the folks working on this are highly cognizant of that risk and are building in a high specificity to manage that risk hopefully with some success. The issue of overdiagnosis of nonaggressive cancers — time will tell. Some of the early signals would suggest that the type of DNA biomarkers that many of these tests include tend to be at higher concentrations in more aggressive cancers. So there's some hope, early days, but hope that the overdiagnosis, overdetection problem that we encountered on a large scale with prostate-specific antigen (PSA) prostate cancer screening may not be a significant challenge for these tests. But again, that's the sort of data that needs to come from prospective interventional studies and does not come fully from case-control studies, which is most of the data that we have today.

Castle: Right. It's great that you pointed out the PSA story, which highlights the introduction of a test without sufficient data to understand those benefits to harms. That's really the key. When we go into an asymptomatic healthy population, the bar for what we do is very high because ultimately, our goal is to keep healthy people healthy. And if we cause harm — more harms than benefits — then we've started defeated our purpose.

So, can any one of you talk about, what do we actually know about these tests, for example. Have any of them been proven to reduce advanced stage cancer? have any of them been proven to reduce mortality? I think we need to be very clear with our audience what we actually know today, which isn't to say that they don't have tremendous promise, but we need to be very, very clear what is the state of knowledge today.

Beer: Betsy, do you want to take that one?

O'Donnell: So, you know, our state of knowledge is very early. As has been mentioned several times, most of the work that's been done are case-control studies. We have two prospective studies. One is the PATHFINDER study and the other is the DETECT-A study. We're looking at the use of these tests in asymptomatic populations to discover the incident rate of cancers found using these tests. So we don't have mortality benefit. We don't have comparative stage shift benefit yet. Those are the types of questions that are unanswered that need to be answered. This is such an exciting field for the very reason that it's wide open with promise and opportunity. But there are a lot of critical questions that require the same type of rigor that we've applied to drug approvals for our test approvals. That's the paradigm that I look forward to doing over the next decade of my career. Certainly, Tom can speak very well to the prospective data that has been published thus far, especially for the Exact Sciences DETECT-A study.

Beer: Maybe I could just add to that. I think Betsy did a wonderful job pointing out what we don't know. We have learned some things from the two relatively small prospective studies. One is that a single application of the prototype assays that were evaluated, which are not the final assays, was able to detect some cancers, including cancers that don't currently have screening tests available. In the cases of both studies, PATHFINDER and DETECT-A, roughly speaking, the MCED test detected about as many cancer cases as were detected through standard-of-care screening for all the cancers that we have standard-of-care screening for. Now this was not a comparative study to compete between the two but just order of magnitude–wise, we saw about a doubling of the so-called screened detected cancers that could be attributed to the MCED test.

Then, we began to learn a bit about workups, complications, how many scans were required, and so forth, early days on that, but a little bit of data on that. We saw some detection of early-stage cancers, and we now know, from DETECT-A, with some 4+ years of follow up, when cancer was diagnosed at stage 1 and 2 untreated — it's only eight patients — but all eight of those patients are alive and cancer-free 4.5 years later. Some preliminary evidence was that the tests, in some cases, were capable of detecting cancer at a point where clinicians felt treatment was warranted and that treatment was successfully administered. Those are very preliminary evidence sets really for the field, and we await much larger studies with endpoints, such as stage shift and beyond, of course.

Doubeni: I agree with all of the points made. I just want to make a couple of points that, maybe to clarify your question about the current state of the evidence — the state of the science, as we might want to say. There are no randomized trials that I'm aware of comparing people who are screened and unscreened using the MCED test.

NCI has launched the VANGUARD study, which is really an important study to look at the visibility and the diagnostic pathway of these tests. That study is rolling out. Thanks, Phil and your group, for leading that effort, and I'm glad to be involved in that process. This is promising, and we're learning more about what the tests can detect. We know that they can, for the most part, distinguish cancer from non-cancer. We're in the stage where we're trying to understand if we can actually understand the performance characteristics in a way that helps us, then plan or do modeling studies.

One exercise that Ruth Etzioni and her group did around stage shift, this was published in *Cancer Epidemiology Biomarkers and Prevention*, the conclusion is what to expect? Using stage shift as the measure of outcome is not a reliable way to understand the long-term benefit of this test. It doesn't mean it might not be useful because let me be clear, the long time that it would take for us to demonstrate mortality benefit may not be feasible or practical.

We need some other ways to do it. Is it that way? I don't know. I'm a clinical epidemiologist. I think I know my field fairly well. But we don't know very well.

But I do think there's an opportunity for us as a society to learn how to best evaluate these tests to be safe and effective. Because the real key here is to be safe and effective.

Because just those two things are needed: the safety of the tests and effectiveness in reducing mortality or improving quality of life to be able to use them in a meaningful way. But the tests, some of them are out there. So Galleri and Exact Sciences have been very good at working on their tests. Galleri is one that I think that's out there, and some people are ordering it. I'm sure

it's really complex for primary care docs like myself to figure out how to navigate this space given that the evidence is quite premature.

O'Donnell: You used a really important word that I'd like to pick up on: this idea of efficacy and effectiveness. There are really macro issues within MCED testing and micro issues. The efficacy, how well does the test work, is an important question. The effectiveness, how well does screening work in a population… We know that there are huge deficits in screening in the United States and globally. And it's multifactorial. It has to do with location, socioeconomics. Part of the promise, or the hope of MCED testing, is the opportunity to increase the effectiveness of screening, meaning, how can we get more patients screened? How can we find more early-stage cancers? I think that that's an important component of this. There's such a tendency to focus on the negatives of MCEDs. I don't think, in the half an hour that we've been on this call, we focused on the potential positives quite enough.

Even if we use every possible gastroenterologist to do colonoscopies all day long, I think it's been demonstrated that we don't have the capacity to screen every single person in the United States who qualifies for screening. That was before we dropped the age down to 45. We have to think about this in terms of making sure we have appropriate academic vetted metrics for the use of these tests. And, yes, we've brought up the example of prostate cancer and PSA. But we also have to balance that with recognizing we're falling short for our patients in terms of offering effective screening techniques.

So, how do we marry both of these ambitions—to provide high-quality, evidence-based recommendations for testing, but still live within the pragmatic space of medicine in the United States, where we don't have equal access, we don't have equal opportunity, and we need coverage, so that tests are not only for those who can afford them?

Health Equity and Access to Care

Castle: That actually brings us to a great point, which is health equity, and I really want to cover that. But before we go there, I will say that we were just talking about access to colonoscopy. But keep in mind that there were other tests out there that do not require immediate colonoscopy, and even if you're positive on an MCED for colon cancer, you would still have to get colonoscopy. And, in fact, not to put an ad out for Exact Sciences, but they have a great test for colon cancer.

Beer: Thanks, Phil.

Castle: You know, I got to call it as I see it, okay? But let's talk about health equity because this is a critical issue. We're at a critical point in America in terms of healthcare delivery. How do we steal ourselves against the introduction of these very promising technologies when we show that they actually work or have enough evidence to suggest that they might work? How do we steal ourselves against inequities in access to these promising technologies? So, Chyke, I know this is something you've spent a long, long, long time thinking about, not just for multicancer but for screening tests in general. So I'm going to give you the first crack at this.

Doubeni: I'm going to try. Now, this is an important topic. Maybe I should go back to prostate cancer and PSA for a second. Some of the argument made for the potential, for MCEDs to address health equities, is that it is a blood test, right? Anybody can get it in a doctor's office. But I think we should do a reality check. I agree that there is really an important role —

potentially important role — when these tests have been shown to be effective and safe. I hope for that day to come. But there's a reality check here.

The health inequities occur in people who don't typically have access to care. When they are in the care setting, they don't often have that access or the personal communication that allows them to get the tests and care they need. While there's a really high potential — that if this test were available, it would make testing easier, if you look at the data on PSA testing, which is that blood tests and keep in mind that African American men have higher risk, guess what? There's still a gap between — and if you say White as a comparison — between White and Black. I don't think it's going to be a panacea or the answer to closing that gap.

Can it contribute? Everything that increases screening is a plus. There's no doubt about it. If this adds some more people getting screened then yes, it's fewer people who might die from cancer.

But I don't think that we should hang our hopes on the fact that if MCEDs were available today, it would solve the equity problem.

Castle: Could it exacerbate it, Chyke?

Doubeni: For a number of reasons yes. I was hoping to leave that for Betsy and Tom to talk about the cost of the test. Trust, right? Besides access, trust, cost… I don't want to say that Black people or other groups don't have interest in getting tested effectively. I think it's the contrary: They are interested, but they tend to adopt technology somewhat slower and tentatively. So, I think that at least initially, we will probably see an increase in disparities if this test were found to be effective.

Castle: Tom?

Beer: Yeah. I appreciate the chance. Just to key off what you said Chyke, I think anyone who thinks blood is easy and will solve all problems hasn't really looked at it. Blood tests can have a convenience advantage. But that adherence with blood testing is not a panacea for healthcare. This is a really complex set of issues, and some of the things that we've been thinking hard about is, first of all, really incorporating that thinking from day 1, before the test is even designed. These tests are unique in that they're being designed using human specimens. We talked about it a little earlier, cases and controls, people with cancer and people without cancer. Really important that those case control studies involve a representative sample of our population, so that we can be confident that our tests work for everyone. And everyone can be confident that our tests work for everyone. That confidence begins with having a test that's designed, from the ground up, in an inclusive manner. Then, the clinical trials that evaluate these tests need to include everyone. That's true for drug trials as well. But what's unique for diagnostics is that you really have to start even earlier when you're designing the test. We need to have evidence from prospective studies that are enrolled in a US-based diverse population that represents the folks that we're intending to serve with these tests and subject those trials to the sort of subset analyses that allow us to take a careful look at performance across groups, by risk factor, by race, by ethnicity, by whatever we think is appropriate to evaluate.

The next step is really assuming that we cross all of these bars and have a test that we're confident in. Really, there is no universal access without universal reimbursement. So, that's precisely why we are so laser focused on developing a test that will get FDA approval. We

think an FDA approval is really likely a prerequisite for broad-based reimbursement. It doesn't guarantee it, we all know that. But without it, it's very difficult to secure Medicare reimbursement and broad commercial payer reimbursement, Medicaid reimbursement, where we can even begin to have a conversation about universal access.

Now, we need to produce data of clinical benefit that would be convincing to guideline makers and to payers, so that they not only have an FDA approved product that they're considering but the evidence that is convincing. So those are the sort of blocking and tackling type things that need to be done. But we can't forget those, because without a test that's reliable, that people have confidence in and that's reimbursed for, we can't even think about equitable access.

Then, of course, the work begins of making sure that everyone is educated on it, has access to it in a culturally sensitive manner, that folks with economic disadvantage have access to it for our current products that are on the market. If you're below four times the federal poverty level, you automatically qualify for tests without copay. That would be the sort of work that we would expect to implement as well. There are dozens of other initiatives to bring this test to everyone in the country.

But what I can commit to is a central value of our program and defines the core goals before us.

Castle: Thank you, Tom. Betsy, do you want to weigh in on this one?

O'Donnell: I think this is one of the most critical issues and something from an academic standpoint, that we need to ensure that we have true representation in all the clinical trials that are being done. I think we have to — when we think about programs from a clinical standpoint — what does a program look like, and who is welcomed into that program? Because these tests — the available tests — are quite expensive, so we do not want to exacerbate disparities in the name of trying to eliminate them. And so being really sensitive to that, I think, from a clinical standpoint, is critical as well.

Going back to Chyke's comments, I think the challenge with oncology in general is that there is no "one bullet fixes all." We're not going to cure cancer. It is many different diseases, and there are many facets to it. My hope in pursuing MCED testing is that we will identify some portion of the population, whether it be 10% or 20%, that over time, with better innovation and with validation, we're able to identify patients who have lethal cancers, where we can find them at an earlier stage, and potentially cure them. There are some cancers where stage does correlate with outcome. You know, where we think colon cancer, for example, where we have certain metrics that we understand what a stage 2 colorectal cancer is, and if we find it there vs the stage 4, we know that the definitive intervention will change the outcome. But our goal in all of this is not the cure of all cancers. It's really trying to say: We're coming at this from every angle, and so much of oncology is devoted to pharmaceutical development, new drugs that extend lives.

That comes at multiple costs: the cost to the healthcare system and the personal cost. What it's like to spend your life in a cancer center, the time not spent working, the time that's stopped working for caregivers? I really feel that one of the main goals of pursuing MCED testing is to focus on the front end of cancer care rather than strictly on the back end and give that our energy and purpose, which we've done so effectively in cancer therapeutic development.

Castle: Well, I'll just say it in a different way: prevention and control are the answer.

O'Donnell: That's right.

Castle: I'm a little biased as a Director of the Division of Cancer Prevention, but take it as it is. But I also want to point out that it isn't just the access of the test; it's the downstream care that has to go along with it.

Doubeni: That's what I was actually going to try to point out. We talked about colorectal cancer earlier, and prior to the panel, we were talking about cell sampling for several cancer screenings. One of the features that I love about colon cancer, not just because I study it, is that you can get a test of people anywhere they are, and then the question always is, what do you do after the test is positive? Right? This is an area in which we're really laser focused to try to get people from when a test is positive to follow-up testing needed to confirm, and when it's cancer to get them treated. We know that there's a real drop off — a huge drop off — when it comes to this follow-up testing, even for colon cancer that we have done for many, many, many years. Then we talk about rural populations with limited access to a lot of this technology because of distance to care — it's huge.

I really love this conversation, and it's really an important conversation. All the design and inclusion approaches are really important and critical to understanding and making sure that trust exists, for people to immediately see themselves in the test development process and have the processes in place to ensure that there's awareness and the mission is completed with us culturally aligned or appropriate, navigation or some sort of advocacy to help them understand the test and use it. They have access to care. They have insurance to be able to pay for it, and they find the tests acceptable. I do think that one of the areas as a nation, a society, that we have to focus on is this. What happens after? It's like a day after — what happens? This is a really important area. I know Tom, you guys are also focused on, is that we have to begin to shift that tension to this first step for the screening process. That's why, when I started as a process, we have to think and, and look at a process, that consider equity access to all populations in this test. So, I do think Phil—thanks for sort of jumping in—that it is really important for us to put that in a picture to talk about access to the MCEDs in the years to come.

Beer: Just a quick comment, that this issue of ensuring access to follow-up care is so important. And it is really hard work. I mean, the one thing that Exact Science has been involved with a lot is stool-based colorectal cancer screening. There was a multiyear effort by many people, advocacy organizations, and others to get us to where we are today, where follow up colonoscopy for somebody with a positive stool test is done without a copay.

These kinds of things, you'd hope that the country could solve them faster. But that was a multiyear effort. There's dozens and dozens of issues like that that we're going to continue to work very hard on in a public-private advocacy partnership to continue to chip away at these problems. But there have been some successes, like, for example, what I just mentioned.

Standardizing Clinical Framework and Follow-up Care

Castle: I'm going to pivot because we're going to run out of time here. I want to pivot to the elephant in the room, which is that one of these tests, Galleri, is being offered to the public through the laboratory-developed tests pathway. It's not FDA approved, but it's being offered. It's not covered by insurance. Yet, many people are getting the test. I've gone from cancer

center to cancer center, and people are showing up with their positive result. We should talk a little bit about what we know and don't know and some of the challenges around the diagnostic pathway. Then, there's a question online, which is, what do we hope to learn from the UK NHS trial, which is evaluating the Galleri test in a randomized controlled trial? I'm going to open this up, anybody can jump in. But I felt like we needed to address this because clinicians are actually faced with this.

Primary care providers and the oncologists are getting these results. Patients are coming in, going, "What do I do with this?" And they may or may not know what to do with this. I'm going to ask Betsy to go first because she's established her center is probably wrestled with some of these issues directly. Go ahead, Betsy, please.

O'Donnell: We have a program, a clinical program, for just that, for the adjudication of positive tests. How can one access a Grail Galleri test? There are a couple of different ways you can obtain them through your primary care practice if your physician is aware of these tests and has set up the opportunity to order them. You can also get them directly from the company using their own telemedicine health. The issue becomes what happens if you have a positive test. So presumably, if you have a primary care physician who's ordering the test, they know how to do the diagnostic workup, which, you know, can be variable depending upon the practice.

But if you have gotten this directly from a provider, you then have to go to your own primary care physician and ask them to work up this test, which, if they're not familiar with the test, they may or may not be able to do. We see patients who have positive tests. We see, kind of, a broad range of evaluations that have been done in the communities. Some of them have been successful, some less successful, and there are two issues that come up.

One is doing the proper diagnostic work up. These tests, the Grail Galleri test, comes with a tissue of origin signal, sometimes one sometimes two, that is suggestive of what a potential cancer might be, remembering that these are screening diagnostic tests. That start is a starting point. The goal is to use the least number and the least invasive test to make a cancer diagnosis.

But then a really important question comes up; it's pretty easy if you establish a diagnosis and anybody who's done internal medicine training should have some facility in doing that. Once you have a tissue diagnosis, you can refer to the appropriate oncologist. But what if you don't, and how do you follow those patients? There's another really a critical question: Where do these patients live? Screening belongs in primary care. We want patients. That's the home of it, but when you have these in-between states, where patients have a positive test but a negative workup, where do those patients live and are we mitigating the burden on primary care providers by adding these easier blood-based tests? Or are we adding because we've added technologies that require follow-up and have uncertainty about what to do once you have a positive result and a negative workup. We follow these patients; it's a research question of ours where we bank on them, in terms of tissue, but we follow them over time longitudinally. Grail does offer free repeat testing if a patient has a positive workup. But beyond that, there are existing questions too, if you've had a negative test, what is the cadence for another one?

These are all unanswered and unstudied questions at this point, so to sum it all up, I think it's important to have some type of a clinical framework for MCED testing; have some

standardization so that you can understand the processes that are going into place and the back end of it as well. What is the reimbursement?

Because it is important to point out that in both the PATHFINDER and the DETECT-A studies, these were industry sponsored studies, so the clinical diagnostic evaluations were covered by the insurance company. It's important in practice, and particularly in the broader applicability of these tests, to understand what is or is not getting paid for by the third-party payers. That's a critical question that we're very interested in.

Castle: Chyke, Tom, do you want to weigh in on some of this?

Doubeni: The Galleri test is a very interesting example of the rollout of a test that feels like PSA — years gone by, right? But I think the potential value is that it may allow us to understand how the test has been used in practice. Let's face it. It's very expensive. This is a test that really is stratifying the population by income and social status in some ways. From my experience and knowledge of the tests, I offer some guidance if it's useful to folks. One is that when patients ask for the tests, it's really important to understand why they're asking for it. That's really important. What information are they seeking that's prompted them to ask for the tests. Did they see it on TV or other places? — but also understanding the test can detect arguably, about 50 cancers.

It is about understanding to at least have a conversation with the patient about what it means when it's positive, and what do false-positives mean.

The key important thing though, Phil, is that, even if patients are ultimately getting the test, it should not be in place of the tests that we know are effective in reducing cancer mortality risk, quality improvement, or quality of life. So that's really important to do.

I do think that, ultimately, this is a patient decision because I believe in shared decision-making. These are tests that I would encourage primary care physicians to use a framework — the US Preventive Services Task Force — around "I" recommendations, "I" statements, or "insufficient evidence" on D recommendations, meaning that we don't have the evidence to know whether or not it's going to work, in which case you need to have that shared decision-making and have the patient understand very clearly.

You also ask a question about the UK NHS study. Because this study has been done in a fairly large population, and people like it, and sometimes recommended their screening tests, I think it has the potential to help us understand some of the performance characteristics. Is it adequate? No. Because I do think that ultimately, for us to really understand the performance characteristics of these tests, as in sensitivity and specificity, we need to know if a person at that point in time has cancer, yes or no. That's the question we often can't really answer, but I think this one study might get close to that question.

One other study that we haven't talked about, the Vanguard study, that, Phil, your branch is doing, which also is an initial feasibility study. Seeing what trials can be conducted, what methods can be applied — all of those are important for us to learn more clearly or at least inform the approach and use of, say, the Galleri test. Folks need to understand that the evidence, for now — it is not clear what are the effectiveness of the tests and there are risks associated with the tests.

Castle: Before we go, Tom, it's also important, in regard to, the last question in the UK trial, that the UK has an organized healthcare system. Across the US, we do not have such a system, so the challenges of making sure that people get completion of care are very different.

I'm hopeful, even if they see a benefit in the UK setting, that doesn't necessarily guarantee that we would see the same impact in the US population because people fall through the systems in a very different way. It's an unfortunate reality of our healthcare system, but it is a reality. Tom, go ahead if you have anything to add to that Galleri discussion.

Beer: Sure. I do want to just take one minute to talk about PSA, because it's been mentioned a couple of times, and I just would like to share the perspective that, in the end, I think, PSA's a success story. It's a very complicated success story. It was introduced into practice prior to good evidence being available, which is why I think people are pointing to it. Ultimately, the European study, which was the one study that was not contaminated by routine screening, did show a benefit. The PLCO showed the challenges of trials, how long it took, and how difficult it is to do a good study over a long term as practice standards change. And it did lead to overdetection and overdiagnosis, which the field learned from and established strategies for such as active surveillance.

We're coming into this a lot smarter, having learned from both the promise and the mistakes of the PSA. But as a prostate oncologist, I do feel like I do need to stand up for the PSA just a little bit, and we could probably spend an hour talking about it. In terms of the question that you asked, Phil, about the workup. I don't have a lot to add, but I might just say that now, all we know today about the Galleri test and its work up is from the PATHFINDER study — about 6600 patients, about 35 MCED-detected cancers. It's important that clinicians know the basic numbers. About 1%-1.5% of patients who undergo the testing will have a positive result, 98.5%-99% could expect a negative result. Once you have a positive result, about two out of five end up with a cancer diagnosis. That's a high positive-predictive value. That's why a workup is warranted.

As Betsy alluded to, the workup gets pretty complicated. It's probably beyond what I can comment on here. But if the initial suggested tissue of origin location yields a diagnosis, that is the easiest path, what I think is clear to most is that, if a cancer is not found in a directed workup, then some sort of a rule out imaging study should be done because one can't just look for the suggested locations and call it good, the residual risk for cancer is sufficiently high to warrant some imaging. Then, the issue of how to follow these folks up long-term is quite challenging.

What I can contribute to this discussion is from the DETECT-A study, which is not Galleri.

We do have 4 years of follow-up, and the simple recommendation I would make based on these data today is that folks should continue the standard-of-care, guideline-recommended screening, and that's all we can say. We don't have data on retest frequency and so forth. That's something that needs to be done.

Standard-of-Care Screening

Castle: Let me build off of that point. We're getting to the end here, which is the standard-of care-screening that is currently offered, which has variable effectiveness, I think, is a fair statement. I will say that, and I'll let others chime in, one of my concerns is the access — if

somebody gets a multicancer detection test, particularly if they test negative, they may not get their routine screening. Any comments on that?

Beer: Can I jump in on that? This is a really important topic and, on a net basis as a public health impact, if that were to happen, that could be quite detrimental. But I am hoping that we can reverse that, and engaging a patient in any screening tests should be an opportunity to engage them in a broad-based cancer risk reduction effort that includes those other things. So, I hope that it won't be too long before we can put that discussion to bed.

I will say that serious voices were raising concerns about lung cancer screening, suggesting that maybe people wouldn't bother with smoking cessation if we offered lung cancer screening. We've gone past that debate. I hope we get past this one. Absolutely. Those data need to be gathered. We need to understand whether such effects happen. Hopefully, we can actually improve and not decrease access to standard-of-care screening.

Castle: …And educate both providers and the individuals to stick with it. I'm going to take a liberty here and remind everybody that for screening tests like cervical cancer screening and colorectal cancer screening, the primary benefit isn't early cancer detection. Their primary benefit is actually preventing incident cancer, and that would be lost if they discontinued sort of falsely reassured from the multicancer. So I think education, education, education is going to be the key thing. Betsy, you look like you're wanted to chime in on this point.

O'Donnell: In fairness to the work that's already been done, there's been no suggestion that this is a replacement for standard-of-care screening. I think that the people who would likely be pursuing are also the people who would be more likely to be adhering to screening. I think that's what we'll see in an early bias. What you're really worried about is, as time goes on and people become more confident in the abilities of these tests, will we see a falloff of standard-of-care screening? I do think that later fear is a concern, but at this point, I don't think that there's anything to substantiate that concern, and certainly not coming from, the work that's being done to say that this is a replacement. Rather, it is strictly being billed as a complement thus far.

Castle: I want to be careful here because what's happened in the past is underinformed consent. I assume that those with informed consent say, "Get your routine screening." Now, imagine this out into the wild here. I'm not saying it's going to happen. I'm saying we have to guard against it. That's what I'm saying. Chyke, do you want to add anything?

Doubeni: I think the urgency of clinical practice as primary care is that our time to submissions continues to dwindle. The convenience of a blood test can lull the primary care physician to say, "Hey, I've done a blood test to screen for cancer. I'm done, right?"

Also, we know that people will tend to do the tests that give them longer intervals. Not to make it too focused on Exact Sciences, but they'd probably prefer to do Cologuard. That will give them 3 years. The interval for colonoscopy is 10 years, then to have repeated testing when it comes down to really the brass tacks. I think this is real. It's a real concern. I agree with Betsy. It's a real concern. Once we roll something out there that becomes accessible, and potentially affordable, then there's a real concern that people will do it, and say, "Well, I'm done with my screening, and it's all over." One caveat, though, is that these measures may protect us, as long as we undermine the US Preventive Services Task Force process, which means that the quality measures are based on those tests. And, as long as they're based on those tests, then

we still safeguard the possibility that people will continue to recommend and encourage people to do the standard of care testing.

Final Remarks

Castle: We have less than 3 minutes. I'm going to ask each of you to take 20-30 seconds and give me a take home message. Tom, you're leading off here,

Beer: I was just going to make one follow-up comment to what was just said, which is that I think it's critically important that everyone in the field, test manufacturers included, are real clear that blood-based tests are not a replacement for organ-specific proven screening tests. They're unlikely to achieve the same level of sensitivity for early-stage disease, and certainly for precancer. So, it is a critically important message. Otherwise, I would just close by saying that there's a ton of promise and excitement in this field. The public-private advocacy partnerships that are emerging are critical, and we really need to innovate on how we can study these tests efficiently and get the evidence that we need, that we can get us comfortable with what these tests can and can't do. It is also important that we get that done in a timeframe that is realistic for these tests to be developed and addresses the pressing need that we have to reduce cancer mortality and morbidity. I don't see us achieving the Cancer Moonshot national goals without better early detection of cancer.

Castle: Betsy, 20 seconds.

O'Donnell: I'm stealing a line: The light bulb was not the result of incremental improvement to the candle. If we really want to change the course of people's lives in cancer, then we have to take the same energy and commitment to early detection that we've taken to therapeutic enhancements. We now have technology that far exceeds what we've had in the past. We need to study it rigorously, and we need to support industry, academic, and government institutions to make validated tests available to patients as they're proven.

Castle: Alright, Chyke, last words here

Doubeni: Cancer is really important, it's a very heterogeneous condition; MCEDs are very promising, but not quite ready for prime time yet. We should not get ahead of ourselves in primary care. To begin to use them, I recommend against using them at this time until the evidence is seen to help us understand how to use them well. At the same time, please let's work very hard to develop the methods needed to understand very quickly what their role will be. Don't use them in place of standard-of-care testing because that would deprive patients of the benefits of screening Thank you.

Castle: Thank you so much. I want to thank my panelists for a very excellent conversation. I want to remind the folks online that there's a survey that will pop up after you log off, and thanks again for your attendance and for your participation. Have a good evening, everyone.