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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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MOLECULAR AND CLINICAL GENETICS PANEL OF THE MEDICAL DEVICES

ADVISORY COMMITTEE

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Call to Order

Dr. Gallagher: I would like to call this meeting of the Molecular and Clinical Genetics Panel to order. I am Dr. Colleen Gallagher, the chairperson of this Panel. I am a senior counselor for bioethics and health policy at the University of Texas MD Anderson Cancer Center.

I note for the record that the members present constitute a quorum as required by 21 CFR Part 14. I would also like to add that the panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss and make recommendations on the design of multi-cancer detection (MCD) in vitro diagnostic devices or tests, as well as potential study designs and study outcomes of interest that could inform the assessment of the probable benefits and risks of MCD screening tests. The committee's discussion and recommendations from this meeting will help inform future agency regulatory efforts for these novel tests. Before we begin, I would like to remind the public and panelists that this is a non-voting meeting and ask our distinguished Committee Members and FDA attending virtually to introduce themselves. Committee members, please turn on your video monitors if you have not already done so and unmute your phone before you speak.

Panel Introductions

I will call your name; please state your area of expertise, your position, and affiliation. Dr. Philip Castle.

Dr. Castle: Yes, hi. I'm Philip Castle. I'm the Director of the Division of Cancer Prevention and a Senior Investigator in the Division of Cancer Epidemiology and Genetics at the US National Cancer Institute, and my expertise is in cancer prevention and cancer screening. Thank you.

Dr. Gallagher: Thank you. Dr. Edward Bujold. Dr. Bujold? Okay, we'll move forward. Dr. Peter Carroll?

Dr. Carroll: My name is Peter Carroll. I'm a professor of urology at UCSF and a member of the Cancer Center. My expertise is early detection of prostate cancer and its treatment.

Dr. Gallagher: Thank you. Dr. Mitchell Gail?

Dr. Gail: Yes, I'm Mitchell Gail. I'm a medical statistician in the Division of Cancer Epidemiology and Genetics at the National Cancer Institute, and I'm a senior investigator.

Dr. Gallagher: Thank you. Dr. Daniel Swerdlow.

Dr. Swerdlow: I'm Daniel Swerdlow. I'm a professor of radiology at Georgetown University. I'm in the abdominal imaging section, and I run the CT colonography program for screening for colorectal cancer.

Dr. Gallagher: Thank you. Dr. Deb Schrag.

Dr. Schrag: Hi, good morning. I'm a medical oncologist, gastrointestinal medical oncologist, and health services researcher, and I am the chair of the Department of Medicine at Memorial Sloan Kettering.

Dr. Gallagher: Very good. Dr. Stanley Lipkowitz.

Dr. Lipkowitz: Hi. I'm Stan Lipkowitz. I'm the Chief of the Women's Malignancies Branch in the Intramural Program of the National Cancer Institute, where we do basic translational and clinical research. My expertise on the clinical side is in the treatment and management of breast cancer patients.

Dr. Gallagher: Thank you. Dr. Rebecca Perkins.

Dr. Perkins: Hi, I'm Rebecca Perkins. I'm a professor of obstetrics and gynecology at Boston University and Boston Medical Center. I work closely with the National Cancer Institute, doing

cervical cancer screening and management guidelines, as well as with the American Cancer Society. It's a pleasure to be here.

Dr. Gallagher: Thank you. Dr. Carla Ballman.

Dr. Ballman: Hi, I'm Carla Ballman. I'm a professor of biostatistics at Mayo Clinic. I'm also an associate director of quantitative health sciences for the cancer center at Mayo. And my expertise area is clinical trial design.

Dr. Gallagher: Thank you. Dr. Mary Margaret Kemeny.

Dr. Kemeny: Hi, I'm Margaret Kemeny. I'm a professor of surgery at Mount Sinai Medical School, I'm a surgical oncologist, and the director of the Queens Cancer Center.

Dr. Gallagher: Thank you. Nathan Winslow.

Mr. Winslow: Hi, I'm Nathan Winslow. I'm the industry rep for the panel, and I'm the global head of regulatory affairs with Roche Diagnostics.

Dr. Gallagher: Very good. And, Deneen Hesser.

Ms. Hesser: Good morning. I'm Deneen Hesser. I'm the patient representative for this meeting. I'm a two-time cancer survivor. I'm an oncology nurse by profession, and my most recent affiliation is the National Cancer Institute Center for Strategic Scientific Initiatives, CSSI.

Dr. Gallagher: Thank you. Dr. Timothy Stenzel.

Dr. Stenzel: Hi, I'm Tim Stenzel. I direct the Office of In Vitro Diagnostics at the FDA. I am a molecular pathologist, and I have an extensive history of laboratory medicine in cancer. Thank you.

Dr. Gallagher: Thank you. And Dr. Donna Roscoe.

Dr. Roscoe: Hi, I'm Donna Roscoe. I'm the Acting Division Director for the Division of Molecular Genetics and Pathology in the Office of In Vitro Diagnostics, and we review these

types of tests if they come in seeking marketization.

Dr. Gallagher: And Karen Rue.

Ms. Rue: Hi, I'm Karen Rue. I'm the owner of Halen Consulting. I'm the consumer representative, and I have expertise in women's and children's health and geriatrics.

Dr. Gallagher: OK. And again, to Dr. Edward Bujold.

Dr. Bujold: Hi, I'm Ed Bujold. I'm a primary care physician in an independent practice in Western North Carolina, and I am representing the American Academy of Family Practice here.

Dr. Gallagher: Thank you. Candace Nalls, the Designated Federal Officer for today's Microbiology Devices Panel, will make some introductory remarks.

Conflict of Interest Statement

Ms. Nalls: The Food and Drug Administration (FDA) is convening today's meeting of the Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict-of-interest laws covered by, but not limited to, those found at 18 U.S.C. §208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this panel are in compliance with Federal ethics and conflict-of-interest laws. Under 18 U.S.C. §208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's

services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. §208, their employers. These interests may include investments, consulting, expert witness testimony, contracts/grants/CRADAs, teaching/speaking/writing, patents and royalties, and primary employment.

For today's agenda, the Panel will discuss and make recommendations on the design of multi-cancer detection (MCD) in vitro diagnostic devices (tests) as well as potential study designs and study outcomes of interest that could inform the assessment of the probable benefits and risks of MCD screening tests. The Panel's discussion and recommendations from this meeting will help inform future agency regulatory efforts for these novel tests.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict-of-interest waivers have been issued in accordance with 18 U.S.C. §208.

Mr. Nathan Winslow is serving as the industry representative, acting on behalf of all related industries. Mr. Winslow is employed by Roche Diagnostic Solutions. For the record, the Agency notes that Dr. Colleen Gallagher has consented to serve as Chairperson for the duration of this meeting.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement,

and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships they may have with any firms at issue. A copy of this statement will be available for review and will be included as part of the official transcript. Thank you.

For the duration of the Molecular and Clinical Genetics Panel Meeting on November 29, 2023, Dr. Stanley Lipkowitz has been appointed to serve as a Temporary Non-Voting Member. For the record, Dr. Lipkowitz serves as a consultant to the Oncologic Drugs Advisory Committee (ODAC) in the Center for Drug Evaluation and Research (CDER). This individual is a regular Federal employee who has undergone the customary conflict of interest review and has reviewed the materials to be considered at this meeting. The appointment was authorized by Rachel Bressler, Acting Director, Advisory Committee Oversight and Management Staff, on October 30th 2023.

Before I turn the meeting back over to Dr. Gallagher, I'd like to make a few general announcements. In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak. The press contact for today's meeting is James McKinney. Thank you very much. Dr. Gallagher.

Dr. Gallagher: Thank you, Ms. Nalls. At this time, I would like to invite Dr. Timothy Stenzel to give some opening remarks. Dr. Stenzel.

Welcome: Dr. Timothy Stenzel

Dr. Stenzel: Thank you, Candace, and thank you, Dr. Gallagher. Good morning, and welcome, everyone. Again, I'm Tim Stenzel. I direct the Office of In Vitro Diagnostics at the FDA, the office that receives submissions of the type of tests that we're going to be discussing today. I want to thank Dr. Gallagher for agreeing to be the chair of this meeting. I want to thank all of our

distinguished panelists. I want to thank all of our speakers who will speak during the open period today. And I want to thank all of you who are tuning in today.

We sought a wide variety of experts for this panel, and we selected them very carefully. They represent many different areas of the oncology space from primary care, individuals who may end up ordering such tests, therefore, are important, and then all the way up to the very specialist of specialists who take care of cancer patients. Also included on this panel are patients and patient advocates.

I do want to make one note about a gap in our panel. We tried very hard to include pathologists and laboratory medicine colleagues on this panel but were unsuccessful. We do invite those professionals, as well as anyone else, public and professional, to submit comments to the docket for this meeting. That docket remains open.

Thank you again for joining us today. Today's topic is on the front of mind for many people today as we seek to identify cancers, more cancers across many types, and early enough, hopefully, for them to achieve a therapeutic or interventional cure. And so it is a very important topic. We have a full agenda. So I say let's get started. Thank you.

FDA Presentation

Dr. Gallagher: At this time, we will view FDA's presentation on today's meeting topic. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel chair. FDA, you may now begin your presentation.

Dr. Stenzel: Welcome everyone to today's meeting. I want to welcome the chair of the panel, panelists, any public speakers, the general public, and other interested parties who have joined us today. We have a meeting of the Medical Devices Advisory Committee, specifically the

Molecular and Clinical Genetics Devices Panel.

The topic today is in vitro diagnostic multi-cancer detection tests. Today's speakers are myself and Dr. Donna Roscoe. I direct the Office of In Vitro Diagnostics at the FDA, and Donna is the Acting Director of the Division of Molecular Genetics and Pathology within our office.

By way of introduction, of course, FDA's mission is to advance and protect public health. We do this in a number of different ways and in a myriad of different areas. Today's topic is obviously cancer. We know that almost 2 million cancers will be diagnosed in the US this year. We know that current screening programs have helped lower the mortality rate for certain cancers, but not all. And then there are many cancers for which there is no screening program.

The FDA is heavily invested obviously in improving outcomes for patients with cancer, both involving diagnostics and other products. FDA has created the Oncology Center of Excellence to accelerate cancer progress. And, of course, we have health equity initiatives, which try to deliver on the promise of improvements across all people.

We know that there are routine screening programs in the United States. They cover approximately 30% of the incident cancers. And roughly about 30% are involved in colorectal screening, cervical cancer screening, breast cancer screening, lung cancer screening, and prostate cancer screening.

Not all programs are IVD-based. At least at this time, but many are. Conversely, we know that about 70% of incident cancers have no standard-of-care screening tests that are performed and, therefore not authorized at the current time as well for these tests. It's estimated that for the cancers that are routinely screened, and this is an overall number, only 14% of incident cancers are detected each year. And in part, that's due to the fact that there is less than 100% adherence to preventative screening programs, which is a related topic.

I'd like to briefly discuss the current preventative screening methods. For breast cancer, obviously, the most common method is mammography. For colorectal cancer, there is a variety of stool-based tests that are used, as well as colonoscopy. For cervical cancer, there are HPV tests, now quite a few, and then there are the routine Pap tests, as well as computer-aided Pap screening methods.

For lung cancer, low-dose computed tomography (CT) scans are currently recommended for certain populations. And for prostate cancer, the PSA test has been commonly used for this, and please see the USPSTF recommendations for prostate cancer if you're interested. At this point, I'm going to turn it over to Dr. Donna Roscoe, who will dive into the details of both single-cancer screening programs and tests as well as multi-cancer tests. With that, I turn it over to you, Donna.

Dr. Donna Roscoe: Thank you. Good morning, and thank you, Dr. Stenzel, for that introduction to our advisory panel meeting today. Before we jump into the topic of multi-cancer detection tests, it's important to discuss how FDA currently reviews diagnostic tests for cancer screening to help us prepare for some of the questions in the later sessions.

To date, the FDA has only reviewed and approved tests for single cancers. Review of any test always starts with the intended use and indications for use statement. All analytical and clinical validation is based on this intended use statement. The intended use statement will include the identification of the analyte, such as DNA, proteins, circulating tumor cells, or algorithms, which may be applied to various combinations of these analytes.

The intended use statement also includes the human specimen type, which may be tumor tissue, saliva, whole blood, or plasma. It includes identification of the technology and identification of the target population. Generally, for cancer screening diagnostics, the target

population is characterized by a range and level of risk, which is consistent with the management of patients for any particular cancer type. Finally, the intended use includes the clinical indication, which in this case is screening, and any other limitations that might be part of the intended use. Pre-analytical and clinical validation studies are based on the intended use as stated and are designed to cover the range of specimens and measurements that would be tested in the clinical setting.

The study is usually conducted in large prospective studies, which enroll subjects at multiple sites across the US to ensure a demographically diverse population. Enrollment is generally for asymptomatic subjects, and high-risk patients may be excluded because the test poses an unacceptable risk to these patients, who, in general, should have more frequent surveillance.

High risk is generally predefined and is based on the cancer type and clinical practice in these populations. But generally, it includes patients with a family history or patients with preexisting conditions, which predispose them to a greater likelihood of developing any particular cancer.

The study size is based on the prevalence of disease. However, we do allow for enrichment strategies, such as enrolling patients based on increased age, to help get a larger number of cancer cases. Designation of how the histopathological diagnosis will be determined is pre-specified for the purpose of calculating the sensitivity and specificity of the assay.

These designations are largely based on the benefit-risk assessment in consideration of the risks of follow-up procedures when the results are positive. The review of single cancer screening assays also includes a pre-specified statistical analysis plan that accounts for sources of bias, such as missing data, consideration of patient demographics, and comorbidities. The

analysis may also be adjusted for the enrichment that was used. Additional subset analysis is performed for stages and histologies, and as mentioned, the key demographics. This data provides valuable insight into the ability to detect early-stage disease and performance across different characteristics of the target population.

The study will also investigate test performance in subjects who have related comorbidities. For example, an evaluation of a pancreatic cancer screening assay would evaluate the performance of diabetic subjects. Or an ovarian cancer screening test study would include patients with endometriosis, and so forth.

This information is critical to inform patients and their physicians of various conditions that may cause false results, typically false positive results. Finally, the clinical performance of the test should cover the intended use population. Sensitivity and specificity inform the test performance of subjects. However, positive predictive value is also a very important performance metric, particularly in diseases with very low prevalence, such as rare cancers. For example, let's consider a cancer with a prevalence of one in a thousand and a test that has 100% sensitivity and nearly 99.9% specificity. For every 10,000 cases, 20 cases will be reported positive by the test, and half of those will be false positive for a positive predictive value or PPV of 50%.

So, you can see it is important for physicians to understand the importance of PPV for tests used in populations with disease, where the disease is a low prevalence to understand the potential that a test positive is a false positive. Having a full assessment of the performance of the assay, including any limitations of the assay and performance, FDA will determine whether a cancer screening test provides a reasonable assurance of safety and effectiveness by weighing any probable benefit to health from the use of the device against any probable risk of injury or

illness due to false results, in addition to other relevant factors. Both the nature of the risks and the magnitude of the risks are considered, and together with the level of uncertainty, various risk mitigations may be used to reduce these risks. This includes, for example, physician labeling, warnings and limitation statements, and post-market studies when appropriate.

So, let's now take a quick look at an example of a single cancer screening test, which has been approved by FDA. The Exact Cologuard test is a screening test for colorectal cancer. The intended use shown here highlights the biomarkers detected, which includes both select DNA biomarkers and hemoglobin; the platform; the specimen type, which is stool; the cancer; the target population, which here indicates average risk; and the age, which is shown as 45, and both are aligned with current guidelines. The appropriate follow-up for positive results is also indicated. As noted, this target population is aligned with the USPSTF guidelines based on benefit-risk assessments for screening for colorectal cancer.

The labeling also includes a description of who the test is not indicated for because the performance has not been evaluated in these subjects. This includes patients with a family history, prior cancer, inflammatory bowel disease, and other related types of conditions. The study that was conducted to support the approval of the Exact Cologuard test was a prospective cross-sectional study that enrolled men and women ages 50 to 84 from over 90 sites across the US and Canada who were at average risk for colorectal cancer. The primary analysis included a little over 10,000 patients, and the results of the Cologuard test, as well as the results of a fecal immunochemical test referred to as FIT, which was the alternative acceptable method for detecting blood in stool, were compared to the results of colonoscopy and histopathological diagnosis.

The histopathological findings were sorted into six categories for the purpose of

determining the sensitivity and specificity of the assay. Category 1 included the cancer cases. Categories 2 through 5 were adenomas, which were further subdivided based on histology, size, and number. And category 6 was the absence of any neoplastic findings.

As stated, for the purpose of analyzing sensitivity and specificity, Categories 3 through 6 were considered as non-malignant, and again, this was based on guidelines that refer to the relative benefit-risk for the follow-up procedures, given the number of people who present with these non-malignant lesions, and the low percentage that become cancer prior to the next screening interval.

The data showed that Cologuard had a sensitivity for detecting colorectal cancer at 92.3% of patients and a specificity of 86.6% when compared to FIT, which demonstrated 73.8% for sensitivity and 93.4% for specificity. Additional analyses were conducted, which demonstrated the performance by stage, histology, and other patient characteristics.

Overall, the data obtained from this large, controlled study, which was obtained with a locked-down version of the device and pre-specified cut-offs, was shown to be better than the existing alternative acceptable method, which in this case was FIT, used to screen patients. So, with the subset analysis and the appropriate labeling, a favorable decision and approval of the test was possible.

Now, moving our discussion to multi-cancer detection tests. Multi-cancer detection tests, which many of you are also familiar with as multi-cancer early detection assays or tests or MCEDs, are tests that measure biological substances that are shed into bodily fluids by cancer cells. These tests may be detecting circulating tumor DNA in the blood or protein analytes or both.

For the purpose of this meeting, we will consider multi-cancer detection tests as blood-

based tests. Multi-cancer detection tests offer many potential advantages, and chief among them is the potential to expand the number of cancers which can be detected with a single test, hopefully at a time when they may be treated and improve survival outcomes.

Blood-based tests may also improve patient adherence to cancer screening due to the ease and convenience of a blood-based test. As noted by Dr. Stenzel earlier, there's a real window of opportunity for multi-cancer detection tests, the overall number of patients who are screened, and the cancers that are detected, and hopefully improve overall health and outcomes for patients. However, there are many challenges with multi-cancer detection tests that are introduced by this "one test to detect them all" concept. With multi-cancer detection tests, there is a need to locate the cancer. The number and types of follow-up procedures present risks as well.

In addition to the potential for cumulative radiation exposure from repeated imaging procedures, findings upon imaging may lead to unnecessary biopsies, which may then lead to overdiagnosis and concomitant over-treatment. Understanding the risks associated with the diagnostic procedure for the follow up cannot easily be measured and may differ by cancer type.

Assessment of the benefit-risk may not be appropriate when aggregating cancers for this reason. Multi-cancer detection tests may also widen the gap for health disparities and underserved and underrepresented populations due to their limited access to resources and follow-up care or simply for financial reasons.

So, as we move forward in this emerging arena, it is important to determine best practices when validating multi-cancer detection tests. The purpose of this panel meeting is to seek expert advice and recommendations on the types of clinical validation study designs that should be conducted in support of multi-cancer detection tests, including how clinical truth is assessed, the value of per-cancer assessments, and what is needed for a balanced consideration of benefits and

risk.

So quickly, I'll move through the questions and the topics. For topic 1, we will focus on key clinical study design considerations for FDA submissions, evaluation of per-cancer performance, and per-cancer performance expectations. Because these tests are intended to detect multiple cancers, including those with low prevalence in the US, a large study is likely needed to demonstrate clinical validity. Even screening for prevalent cancer in the general population may necessitate large studies when considering the statistical power needed to capture and evaluate each individual cancer.

We therefore seek the Panel's opinion on the advantages and disadvantages of different study designs. Notably, case controls always over-inflate performance and control arms may be valuable to benefit the net benefit, but do lead to extremely, much larger sized studies. We asked for the Panel's opinion on size and enrollment strategies and include considerations for the use of non-US sites.

We ask the Panel to weigh on what are useful enrichment strategies. Should we enable the inclusion of high-risk to gather more cancer cases and, whether there should be an age restriction for the population based on the risks of the follow-up procedures and the ability to detect cancer, and what kind of evidence is needed to support an early cancer detection claim. While it is logical to report aggregated performance for a multi-cancer detection test, the benefit-risk profile is likely to be unique for each cancer. We seek the Panel's opinion on providing evidence of per-cancer performance. And also request comments on the minimum sensitivity and specificity measurements for the aggregated analysis, early-stage cancer, and per-cancer performance, as these may all go into having to determine risk mitigation measures and inform physicians appropriately about the limitations of the assay so they can determine the risks of the

follow-up procedures for their particular cancer patients.

As we noted for select cancers, there are other alternative screening methods. Multi-cancer detection test developers have made it very clear that an MCED test is not intended to replace current cancer screening methods. But in the absence of any comparison, it will not be clear whether the multi-cancer detection test contributes to the detection of cancers or merely decreases specificity overall for any screening program. We are seeking the Panel's opinion on the evaluation of per-cancer performance with attention to whether there should be data comparing the performance of the test to alternative screening methods.

Further, historical information about biomarkers previously investigated for their potential for screening, such as those in ovarian cancer, has provided information about the risks of such use and over diagnosis. We seek the Panel's expertise on the minimum per-cancer performance needed to minimize the risk of overdiagnosis and over-treatment based on our historical knowledge of the inappropriate use of tests in this setting.

Finally, for topic 1, potentially confounding variables are assessed to identify potential sources of bias in a cancer screening study. For multi-cancer detection tests, the clinical performance of the test is evaluated for different types of cancer simultaneously, and studies may neglect to assess the performance of the test in patients with other non-malignant comorbidities relevant to a specific cancer, such as inflammatory bowel disease, diabetes, emphysema, or other cancer-specific risk factors. We asked the Panel's opinion to discuss the need for assessing nonmalignant comorbidities and cancer-specific risk factors in the clinical performance study for multi-cancer detection tests, and any recommendations you may have for how this should be done would be appreciated.

All right, so moving on to topic 2, we focus on methods needed to locate the tumor and

appropriate sources for clinical truth.

When patients receive a positive multi-cancer detection test result, follow-up with an initial tumor-of-origin tests and/or radiographic imaging is needed. The complexity of the diagnostic workup presents uncertainty with the risks to patients. We ask the Panel to weigh in on the acceptable types of follow-up, whether tumor-of-origin tests are required, and the risks for repeated testing. We also ask about the risks to patients when not being able to identify a tumor and what mitigation measures might be employed.

We also ask the Panel to consider how clinical truth should be evaluated for a multi-cancer detection test. As noted, in the single cancer screening test validation, positives and a sampling of negatives may undergo a diagnostic procedure. However, for most cancers, a biopsy will be required upon positive imaging findings. How should the truth be assessed? And in particular, how should it be assessed for test negatives? The use of medical records at a later interval may rely on patients having symptoms, that they consult with a physician on these symptoms, and the physicians will actually treat them and work them up as a potential cancer case, which may not occur within one year of having received the multi-cancer detection test. Is there a minimum follow-up period for confirming test negatives? And how should the test be rerun at the end of the yearly interval to support the timely accuracy of the result?

Finally, as noted, FDA will evaluate the total evidence provided in support of the benefit-risk assessment of the test. Assessment of benefit includes both the type of benefit, the magnitude of the benefit, and the severity of the harms. In the case of multi-cancer detection tests, FDA seeks the Panel's opinion on the level of evidence needed to support a positive benefit-risk assessment, what level of uncertainty is acceptable, and what post-market studies should be conducted to further support the safety and effectiveness of the device. In this last set

of questions, we are particularly interested in the assessment of performance and early detection and the risks of false positive and false negative results.

We ask that the Panel weigh in on their opinion about what level of performance is needed to mitigate these risks and to conclude that this test is safe and effective for the aggregated and per-cancer performance. We ask that the Panel also weigh in on whether a fixed specificity is appropriate to support a low false positive rate at the exclusion of perhaps an improved sensitivity across all cancers. We ask them to weigh in on what is a reasonable number of follow up procedures and the frequency with which a multi-cancer detection test might be ordered. Does this depend on having received positive or negative results? And what are the harms from unresolved positive results? Are there appropriate risk mitigation strategies that could be employed?

FDA may employ risk mitigation strategies for cancer screening tasks, and we asked the Panel to weigh in on acceptable risk mitigation strategies. The FDA has generally not requested a demonstration of clinical utility for approval of tests, which is actual improvement in patient outcome. FDA has generally only requested clinical validation, which is a demonstration that the result correlates with the clinical status of the patient. However, for multi-cancer detection tests, for which the risk of follow-up procedures differs across cancer types, we seek the panel's input as to whether the evaluation of, for example, stage shift, should be incorporated into the study design and what the metric for success would be for such a study.

Stage shift refers to the decreased incidence in the diagnosis of cancer at later stages due to the increased detection and treatment at earlier stages. Stage shift, however, requires accounting for the sources of bias in the assessment, which can be challenging. FDA requests the Panel to weigh in on the value of clinical utility endpoints for the benefit-risk assessment of

multi-cancer detection tests.

Finally, with the understanding that it would be extremely difficult to obtain performance data for all cancers, particularly those that are very rare, we asked the panelists to discuss the conditions by which real-world evidence to support clinical validation may be acceptable.

We asked that they comment on what data collection elements might be needed in this in order to capture accurate real-world data and evidence and whether it is acceptable to use this data to validate rare cancers to expand upon the per cancer assessment and expand upon the testing interval and the clinical utility, such as gathering data for state shift studies.

We also ask the Panel to consider what post-market studies may be appropriate in this space in addition to real-world evidence. So that is all that we have. We have a packed day, and we look forward to the insight we're going to obtain from the Panel for today's meeting and I'd like to thank them in advance and express our appreciation for their time today.

We look forward to their valuable insights into the clinical validation and studies needed to support multi-cancer detection tests, and welcome to everyone else who was able to join us today. Thank you.

Open Public Hearing

Dr. Gallagher: Thank you. Dr. Roscoe and Dr. Stenzel. We will proceed with the open public hearing portion of the meeting. Public attendees are given an opportunity to address the panel to present data, information, or views relevant to the meeting agenda. Ms. Nalls will read the open public hearing disclosure process statement.

Ms. Nalls: Both the Food and Drug Administration (FDA) and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is

important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Dr. Gallagher: Thank you, Ms. Nalls. FDA has received 12 requests. Each speaker will be given five minutes to speak. We'll begin with our prerecorded presentations. The first speaker is Dr. Joshua Offman.

Dr. Ofman: Hello, I'm Josh Ofman, a physician and the president of GRAIL. We are losing the war on cancer, largely because we're finding most cancers too late. Over 70% of cancer deaths occur due to cancers we are not screening for at all. The status quo for cancer screening is simply unacceptable. And more single cancer screening is not the answer.

First, we don't get to choose the cancer we get. Second, these single cancer screens will accumulate false positives in individuals, they will never be cost-effective for the more uncommon deadly cancers, and the number of false positives will simply overwhelm the delivery system. MCD technologies require a complete rethinking of the way we screen for cancer and how to evaluate these technologies. GRAIL's technology measures abnormally methylated DNA, a hallmark of cancer, through a simple blood test. And it represents a shared cancer signal across more than 50 different cancer types.

We've rigorously trained machine learning classifiers to recognize and classify this signal, and it can detect a broad range of deadly cancers. This signal is rarely seen in people without cancer, making it highly specific and gives the test a single, very low false positive rate. The ability to predict the signal origin is essential to guide the targeted diagnostic workup. An optimal MCD test should not contribute to over diagnosis of indolent cancers, and they are a complement, not a replacement for standard of care, single cancer screens.

So, how should we measure their benefits? With a shared cancer signal, performance must be based on aggregate measures, not one cancer at a time. The positive predictive value and the cancer yield are the most important clinical and public health measures. Observed reduction in late-stage cancer incidence is a really important intermediate endpoint and actually is a prerequisite for a mortality finding.

A mortality study will require hundreds of thousands of participants, followed for over a decade to weed out, and as recommended by experts, there are rigorous ways of modeling potential mortality impacts based on the stage of diagnosis.

GRAIL has been developing multi-cancer detection technologies since 2016, and we've thought deeply about the best ways to study and evaluate them. We've consulted extensively with world experts in genomics, machine learning, population science, and trial design as part of our 300,000-person clinical program.

This program includes a fully enrolled, randomized clinical trial of over 140,000 individuals, leveraging important endpoints that we believe comprehensively capture the clinical impact of MCD tests. Aggregate measures of performance and clinical validity are the most important for MCD tests. Lung cancer screening in high-risk smokers offers a great example.

Take a look at the box on the left to illustrate the point. We can screen high-risk smokers

with a single cancer test, and when you look only for lung cancer, you can do so with high sensitivity, but you end up with low positive predictive value and a relatively low yield for cancer. In contrast, when you use an MCD test, you may have lower aggregate sensitivity, but you have a much higher positive predictive value and five times higher yield in cancer detection.

From a public health perspective, this is a much better outcome than screening for a single cancer. And since we don't get to pick the cancer we get, if you look at the box on the right, you can see in the NLST trial for high-risk lung cancer, the risk of lung cancer was actually lower than the risk of non-lung cancer across all of the different smoking levels.

It reminds me that when I got my colonoscopy a few years ago, I was actually more than ten times more likely to be diagnosed with some other cancer other than colon cancer. But I was only looking for colon cancer. So, to summarize, for MCD tests, performance and clinical outcomes need to be evaluated in aggregate, not one cancer at a time.

The shared cancer signal optimizes a high specificity and low false positive rate and with highly accurate signal origin prediction to guide a directed and efficient diagnostic evaluation. Positive predictive value and the cancer yield are the most important aggregate measures of the public health and clinical impact of MCD tests.

A reduction in late-stage cancer incidents and sophisticated mortality modeling, as we are doing in the NHS-Galleri trial, is the best approach to ensure appropriate access to technology that is rapidly evolving. We should be screening individuals for many cancers in addition to screening for individual cancers. Thank you very much.

Ms. Raoof: My name is Sana Raoof, and I'm a practicing physician in the Department of Radiation Oncology at Memorial Sloan Kettering Cancer Center. I'm also an active consultant to GRAIL, Exact Sciences, and Verily. Today, I'd like to propose consideration of a clinically

relevant endpoint to make an early assessment on the value of molecular cancer screening tests.

The endpoint that I'm proposing is receipt of curative intent treatment. I'm going to take a step back and explain what I mean by this. We all understand that, for the most part, solid tumors begin as a single cell that expands into a localized mass, may ultimately involve lymph nodes, at which point we call it regionally advanced, and finally, may spread through bladder lymphatics to distant metastatic sites.

And somewhere along this continuum, we lose the ability to cure that cancer. If a patient is diagnosed with a metastatic solid cancer, the quarterback of their care will be a medical oncologist who can offer them a variety of exciting treatments ranging from targeted therapies to immunotherapies. But with very very few exceptions, these systemic treatments do not have the potential to cure an advanced solid tumor.

On the other hand, if a patient is diagnosed with a local or local, regionally advanced cancer, they're referred to someone like me, a radiation oncologist, or to a surgeon who would provide them, rather than a systemic treatment, a localized treatment with the attempt to remove or kill every single cancer cell in some confined area.

And so today, the only way that we have in general of curing a solid cancer is catching it early enough that they can get some sort of curative intent treatment like surgery or radiation. Now, of course, we lack randomized trials in most types of cancer to help us quantify the value of detection at stage 1 versus 2 versus 3 versus 4.

But what we do have for sure is abundant clinical intuition that a patient's prognosis largely depends on the type of treatment that they're offered. For example, imagine trying to start a trial in a thoracic oncology clinic where we offer patients randomization for their stage one lung adenocarcinoma either to a definitive surgery this week, or we'll monitor with scans for a

few years until the lung cancer has spread to brain or bones or liver and at that point, we'll offer them our best drugs.

Of course, this trial would be considered exceedingly immoral, and no oncologist would enroll a single patient on this trial. Whether or not we have an RCT to prove it, we know that it would be a complete disservice to the patients that are in the watch and wait arm. And the reason we feel that way is that we know in our bones as oncologists that if a patient is diagnosed early and qualifies for curative interventions, then you must give them the curative intervention with the chance of actually beating the cancer.

In order to try to quantify the sentiment a little bit more rigorously, a few statisticians and I did an analysis that was published in Cancer Epidemiology in June of 2023. In this analysis, we looked at about a dozen types of solid tumors for which the gold standard curative treatment is surgery.

We looked backwards in the SEER database at how patients did if they received surgery or if they didn't, and we tried to control for obvious founding factors like patient comorbidities. And what we've found, not surprisingly, is that for all of the types of cancer we looked at, if a patient received surgery, they had a much greater chance of living at least 12 years, and 12-year overall survival is roughly equivalent to lifetime cure for about 95% of cases of solid tumors. There's a variety of confounders that plague any retrospective analysis like this, no question. But the general point that we tried to make with this study is that, of course, if a patient is offered a definitive treatment and gets it, they have a greater chance of being cured than a patient who cannot get that curative intervention.

This endpoint of receipt of curative intervention is something that can be measured very early on because those curative treatments are given very shortly after a cancer diagnosis. As a

physician, I think it's particularly important in the post-COVID era to look for these sorts of earlier assessments, for example, in order to make conditional decisions about MCEDs, because we see patients coming into the clinic with later and later stages of diagnosis because of a delay or a lack of cancer screening and primary care since 2020. This is a trend that is particularly common in disadvantaged populations and minority communities. And so, in this spirit, I propose consideration of this early endpoint.

Mr. Royse: Hello, my name is Roger Royse. I'm a cancer patient, and I'd like to thank you for this opportunity to present my experience with multi-cancer early detection to the FDA Advisory Committee on November 29, 2023.

First of all, want you to know that without multi-cancer early detection, I would not be here right now. I would not be alive right now. I want to say it again because I want to make sure you get it. Without multi-cancer early detection, I would be dead now.

I was diagnosed with pancreatic cancer 18 months ago. I've had six months of chemotherapy and surgery. I'm currently no evidence of disease 18 months out from diagnosis and a year out from surgery.

That would not be the case if I had not caught this early. And that's one thing that all my doctors agree on: that this particular cancer would have been silent and would have had no symptoms or signs that I would have been able to pick up on until the very late stages. So I might have had a month, maybe a couple of months left if I had not caught this early if I had let it go, or if I had waited for symptoms.

Clearly, early detection saved my life. I first read about the Galleri test by GRAIL in a book in April of 2022, early April, and I immediately contacted my primary care physician and asked that they prescribe that test for me.

He didn't do it. He refused. He said it was unnecessary testing because I had no signs or symptoms, wasn't covered by insurance, wasn't FDA-approved for diagnostics, and, plus, he wasn't that familiar with it. So, I went and found a different doctor in Palo Alto who at least acknowledged that there was such a test and that these tests do work, but still refused to prescribe it.

I don't know why. I assume because it's not FDA-approved. It took me until the end of June to find a doctor that would prescribe this test so that I could get it. And the test fairly immediately came back with a signal for pancreatic cancer. The next day, I bought my own private MRI because, again, I can't get a doctor to prescribe it; I have no symptoms, and that MRI disclosed a mass on my pancreas.

Based on that evidence, I was able to get into a major medical institution. They did a CT, a scan, and a biopsy, and they confirmed the diagnosis. Within a couple of weeks, I was on chemotherapy and in treatment. None of that would have happened without early detection. That's what I'm trying to drive home to you today.

Now, I lost two or three months because the FDA hasn't approved this, and in pancreatic cancer, two or three months could be the difference between life or death. It might be the difference between my life or death. I don't know yet. We have to wait and see whether I caught it early enough.

I do know that it was super simple. It was very easy. But yet, it's still not an approved therapy that insurance will cover because of that, a lot of patients just won't get it. They're reluctant to get it. I know I've spread the word to everybody I know, and $1,000 for a test or $2,500 for a scan that's beyond what most people in this country are willing to pay. And it's unfortunate because it puts them at very high risk of having a deadly cancer and not knowing

about it.

Now, why hasn't the FDA approved this? I was curious about this. I reached out to the US Preventative Services Task Force, which advises and makes recommendations on which early screening tests to adopt.

I asked them about pancreatic cancer. They have twice now recommended against early screening for pancreatic cancer for asymptomatic individuals, people like me that had no signs. Not only that, I had a sonogram before my test that didn't disclose any problems. Okay, so my sonogram was wrong, making it even more difficult for me to get this test.

According to the US Preventative Services Task Force, pancreatic cancer screening tests are, and I quote, because they sent this to me in writing, invasive, cause pain, and sometimes lead to unnecessary and risky treatment. My Galleri liquid biopsy test took ten minutes; they came to my office, and I did not even stop working. It was not invasive, it didn't cause pain, and it didn't lead to any unnecessary or risky treatment. It led to an MRI and a CT that confirmed the diagnosis.

Unfortunately, the US Preventative Task Force Services data and their conclusions are based on 2019 data, four years old. That's what they're basing their conclusions on in informing the FDA.

I'm here to tell you that 2019 data is way out of date. It's not even close to what's in the market now and, what's available and what can be done. So again, I'm Roger Royce, pancreatic cancer patient. I'm free of disease because I caught this cancer early through a liquid biopsy test followed up by an MRI.

I really want to encourage the FDA to quickly adopt whatever rules it needs to approve these tests so that they can gain insurance coverage and become immediately more broadly

accessible to patients. And I can tell you that delay is costing lives. That's 100% certain. The longer the FDA delays on this, the more people are going to die unnecessarily from preventable cancers. Thank you.

Ms. Caro: Thank you. Hi, my name is Valerie Caro. I have no disclosures. This is my story. Just last year in 2022, I read the Tony Robbins book, Life Force. The book explains the newest breakthroughs in health technology that help maximize your energy and strength, prevent disease, and extend your health span. And who doesn't want that?

It was in this book that I was introduced to the MCED test. I was feeling great. But the thought of testing for 50 types of cancers with one blood draw was too tempting to pass up. I figured I would take the test every year to stay ahead of cancer. And by the way, cancer does not run in my family.

I went to two different doctors locally who weren't familiar with this new technology, and neither one would prescribe me the test. On my third try, I ended up reaching out to a tele-health doctor to confirm the prescription. I took the test that was mailed to me, and about a week and a half later received the results of the test via phone call from two tele-medicine doctors. I was informed that there were two cancer signals detected in my blood.

One was for breast cancer, and the other was for gallbladder or pancreas. I had recently completed my yearly mammogram, so I figured that was fine, but at the doctor's recommendation had an MRI for my chest and abdomen. The chest MRI came back clear, as expected, and the radiologist mentioned that although he didn't see cancer in my abdomen, my gallbladder was filled with more stones than he'd ever seen.

He said it looked angry, and it should come out soon. I took the radiologist's advice and scheduled gallbladder removal surgery within the month. I really wasn't concerned because my

mother and brother have both had their gallbladders removed without incident. I had a normal surgery and was recovering the next day at home when we got the call about the pathology results from my doctor.

He let us know that there was, in fact, a four-and-a-half-centimeter cancerous tumor in my gallbladder and that my gallbladder was basically kissing my liver. Obviously, we were shocked but thankful to have it removed. As you can imagine, the next month was a whirlwind: learning about cancer, interviewing doctors, scheduling consultations, learning the intricacies of health insurance, and preparing for the next phase of my care.

We spoke to teams from NIH, Mayo Clinic, and MD Anderson and decided on a team who are also scientists with TGen in Arizona. I had a second surgery at the City of Hope in California to create margins for my gallbladder surgery and check for any additional cancer in my abdomen. The surgery was a huge success, and the next step was six months of chemotherapy, just as insurance.

I was healthy and in such good shape that I was able to take Xeloda, a pill form of chemo. In May of this year, I was finished with the chemo and assured my doctors that it was no offense, but I was finished with these shenanigans and was happy to only see them once in a while for the next couple of years.

I'm thrilled to report that last week, I had my six-month follow-up, and I'm cancer-free. It's crazy to imagine what the conversation would have been if we were all just meeting this year. From what I've been told by every doctor I've spoken with, I'm extremely lucky to have found the cancer when I did.

They say no one ever catches it at that stage without symptoms except by a fluke. This was no fluke. This MCED test is the future of healthcare. I can honestly say to you that the

Galleri test saved my life. As I look back at the last year, I'm in awe of how fast my surgery, follow-up, chemo, and recovery happened.

I imagine that if this cancer had spread in me, the cost to my family, Blue Cross Blue Shield, and my care team would have been astronomical. I'm so grateful for this technology, and I'm now honored to share my story with you. Today, I'm an active 55-year-old, enjoying my life with family and friends, looking forward to maintaining my healthy lifestyle, and continued contribution in sharing that early detection really does save lives.

Thank you so much for the opportunity to share my story. You're all on the cutting edge of modern health care. I'm honored to be part of this journey with you. Thank you.

Dr. Gallagher: Thank you. We have eight presenters speaking live this morning. The first speaker is Alberto Gutierrez. Dr. Gutierrez, you may begin your presentation.

Mr. Veizis: We see your slides. Yep, full screen. Good.

Dr. Gutierrez: Thank you. I first want to thank the FDA for the opportunity to present in the public part of this meeting. And I'd like to thank the panel members for their willingness to give FDA their expertise in this important area. I want to start by saying that we actually support the development of multi-cancer detection tests. We believe there's a great need and there's a great promise for this test. And we understand that following the current evidentiary and study designs that have been developed for single cancer screening tests is not practical and we need to explore new ways to move forward. But we are concerned that we get right the evidentiary threshold that is needed both for approval of this test and for follow up reimbursement decisions.

We have been following the community discussion in this area, and my presentation and Dr. Putcha's will pull out certain threads that we believe need to be discussed and need to be presented.

I do want to begin by saying that both of us bring not only our current experiences as consultants, but I actually spent 25 years at the FDA and Dr. Putcha is an expert in reimbursement, so we bring that to the table too. But I think, like many of you in the panel and everybody who's participating in this, screening tests are in some ways different than what the agency usually sees in that all of us are patients in one way or another, and most of us have participated in screening and some of us had actually probably been touched by cancer even closer. In my case, two members of my family have died of cancer. They were both actually originally cancer survivors in that they had cancers that were found by screening tests and treated appropriately. Unfortunately, and somewhat unusually, both of them later on came out with primary cancers of all the cancers that were not screened. So it's clear to us what the benefit of screening for such cancers would be, and it's clear to us what the need is in this. I must say that my sister also had many years of multiple false results in her breast in her mammograms, and that led to over treatment in many ways, so I'm also quite aware of the dangers of overtreatment in the screening area.

Some people have talked about cancer screening multi-detection cancer tests as a single intended use and talked about possible aggregate performance for the different tests. But I do want to stress that, as the agency has pointed out, evaluating tests is needed to understand what the intended use is, and multi-cancer screen tests do not have a single intended use. And that's because many of the cancers are quite different. They have different benefit-risk profiles. They have different intended-use populations. Each cancer has a different prevalence, and the biological profile is very different. So a single aggregate score or single aggregate evaluation is not very helpful to either the agencies that are making the decision as to whether the benefits outweighs the risks or even to particular doctors or patients that need to make decisions as to

what to do with a positive result or what is the probability of a false result and what makes sense for that particular patient.

I think the agency is quite used to dealing with tests that have multiple indications for use; the cancer panels come to mind. It is clear that doing what they typically do, that is, evaluating different studies for each of the intended uses, would be quite burdensome here. So, designing a single study that can actually support multiple intended uses, I think, will be the right way to go here, but there are many challenges with doing so, particularly when the risks of the tests are so different. Things like whether you have a prescreen or a screen that is there? Is this test going to feed into a screenable standard of care test? Or is this a test that is for those test that are not screenable?

And it's a question as to how you design the study and how you design the test that can actually perform appropriately in each of those scenarios.

Dr. Gallagher: Excuse me, Dr. Gutierrez, you only have a few seconds left.

Dr. Gutierrez: Okay, I do want to touch quickly on whether, for rare cancers, one can actually use only the case-control part of the studies, and there is some data that shows that, and as FDA said, over-performance is problematic when you do case-control studies.

Finally, and the second slide goes to that, I do want to say that because it is not realistic to get tissue-pathology-based confirmation of truth, one is going to have to design a study in which there is a pre-specified period of time for specimen collection. And I think that is important.

We do think that it is possible to design cohort studies that will establish clinical truth, and this can be done in one single study, but it's going to be important to pre-specify your goals for each of the cancers, and it's going to be quite a complex study. I want to thank you for your

time, and Dr. Putcha will deal with some of the other issues.

Dr. Gallagher: Thank you. And now it is Robert Smith's time.

Dr. Smith: All right. Everything. Oh, let's see. Sorry. That's the last slide. So we don't want that one.

Mr. Veizis: We still don't see your slides.

Dr. Smith: Yeah, I know somebody let me just get them to the beginning. Okay, they're all good.

Mr. Veizis: No, not yet. You need to hit the share button.

Dr. Smith: I'm sorry.

Mr. Veizis: There you go. Something's loading, and now you need to share your PowerPoint.

Dr. Stenzel: You will likely have to stop sharing. And then, when you share, select the file that you want to show. I see your presentation now. Good. Full screen.

Dr. Smith: Hey, finally. Are we ready to go then?

Mr. Veizis: You're a minute into it.

Dr. Smith: Yes. Good. I'm not seeing how I can. Actually, let's see if this changes my slide. Does that change the slide?

Dr. Gallagher: It did, keep going.

Mr. Veizis: Yes.

Dr. Smith: OK. All right. Good. I'll try to do it this way. Good morning. I'm sorry this went so well in the rehearsal, but my name is Robert Smith. I am a cancer epidemiologist. I'm the senior vice president of cancer screening at the ACS, and I lead the ACS Center for cancer screening and early cancer detection research. We are responsible for developing the American Cancer Society's cancer screening guidelines. So this is of great interest to us; not only the evaluation issues but everything that goes into evaluating a cancer screening guideline.

I want to emphasize, as others have, that the burden of cancer in the US is high. It's the leading cause of death from all causes before the age of 85. It's the leading cause of premature mortality from all causes of death. The numbers are enormous and staggering, and as other groups have emphasized, we are challenged to make the best use of the cancer screening tests that we have in our armamentarium, but the majority of cancer deaths in men and women are among cancers for which we do not have a cancer screening test or a strategy.

We oftentimes emphasize that most cancers do better when they're found early. That is indeed true. We want to guard against these biases of assuming that earlier detection will always lead to a reduction in mortality. But in fact, you're not going to get a reduction in mortality if you don't get a stage shift. And the promise of reducing the stage of diagnosis from principally distant and advanced regional disease to more favorable stages, even if they were predominantly localized, could ultimately result in saving a great many lives.

The potential for these tests is even actually beyond our conventional thinking since we typically focus on single cancer screening tests. But the potential for simultaneous multi organ detection, a test that would include all cancers, single medium modality efficient, potentially cost-saving; all of that really is a modern game changer in the new direction that we have in precision medicine. But I also want to emphasize that in our lifetimes, there is actually no potential or very low potential to add to single cancer screening tests one at a time. The cost would be enormous. The time would be enormous. It hasn't happened yet. And because these cancers are rare, it would be unlikely to happen.

So, given that the panel is primarily interested in benefits and safety and efficacy, we wanted to emphasize that the goal of cancer screening for single cancers or multiple cancers is to reduce the incidence rate of advanced disease. That's what cancer screening does.

And in this respect, we think that the primary Endpoint for MCED should be the aggregate incidence rate of advanced cancers for cancers included in that test. There would be any number of ways to do this, especially in an intention-to-treat analysis. You can also focus on the aggregate death rate for the cancers included in the MCED. Based on experience to date, if we did see a reduction in advanced disease, it would be expected to be followed by a reduction in mortality and in morbidity.

And from a design standpoint, it seems quite reasonable that a focus on individual cancers would require possible sample sizes. If you look at the distribution of the incidence of any of these cancers, it's more significant in some and really quite small in others. But it would be very difficult to do, and it would be at odds with the design of a multi-cancer early detection test. It does not mean that we shouldn't be interested in how MCEDs perform at the level of individual cancers, but these are secondary endpoints, in our opinion. And to better understand test performance, the natural history of disease, and for research and development purposes.

Dr. Gallagher: You have only a few seconds left, please.

Dr. Smith: Okay, with respect to harm, we do want to measure conventional outcomes, and especially want to measure whether the care pathways that exist are being followed. I think this is of critical importance. Concerns about anxiety have really been overstressed for all of the conventional cancer screening tests. The data do not show any lasting effects, but it doesn't mean we shouldn't be trying to minimize anxiety, and we can do that with better communication. The possibility of some overdiagnosis is real, but again, it's extremely difficult to evaluate, and it's only going to be able to be evaluated in the long term.

The possibility that adults would forgo conventional screening tests is also a concern, but I think it is largely an unexpected one. But, organizations like the American Cancer Society and

referring clinicians would be obliged and advised to strongly emphasize that these tests are not a substitute for conventional screening tests.

I want to thank the panel on behalf of the American Cancer Society committee for the opportunity to provide testimony on this important issue. And thank you. And sorry for the mix-up at the beginning.

Dr. Gallagher: Thank you. And now we'll hear from Dax Kurbegov.

Dr. Kurbegov: Thank you. I appreciate you saying my last name so well. Let me share.

Mr. Veizis: We see your presentation.

Dr. Kurbegov: Thank you. Good morning. I'm Dr. Dax Kurbegov, Vice President, Physician in Chief at Sarah Cannon. I'm a medical oncologist by training. I'm honored to provide these remarks on behalf of our organization. In terms of disclosure, Sarah Cannon has participated in a number of sponsored trials via sponsors, including Braille, Harbinger, Freenome, and others. I want to be clear that I received no direct funding, nor is my compensation tied to participation in those studies.

HCA healthcare is one of the nation's largest providers of healthcare services, with more than 182 acute care facilities in more than 2,000 sites of care overall. We are, similarly, one of the nation's largest providers of cancer care services with more than 130,000 new patients engaged each year, more than 1,500 stem cell transplants conducted annually, and more than 1,000 patients receiving radiation therapy each day. We also have a substantial body of experience with MCED or multi-cancer early detection, with more than 25,000 patients enrolled in studies ranging from preclinical to development slash validation to return results to patient studies.

We, therefore, are well-positioned to articulate the community's perspective on these

issues. I think we understand the urgency we've heard that well-articulated today. I think the one point that I would call out here that maybe we haven't heard as clearly is that large health systems like HCA Healthcare are increasingly sophisticated and able to identify populations of individuals who are at risk for a variety of cancers based on genetic, familial, or other identifiable risk back.

I just remind the panel that this magnifies the evolving chasm between our ability to identify those who are at risk and to offer them appropriate screening or management options. Current modeling suggests that MCEDs potentially afford us the opportunity to save more than 100,000 lives per year.

MCED screening tests are distinguished from one test one cancer tests, both by the breadth of the cancers they detect, as well as by the nature of the cancers they detect. While MCED tests can detect traditionally screened for malignancies like breast, colon, and cervical, they're uniquely positioned to identify a range of highly lethal cancers, like pancreas, biliary, ovarian, and lung, by virtue of this shared cancer signal. We should, therefore, avoid the pitfalls associated with treating MCED platforms in the same manner as traditional screening tools. And we should be especially wary about over emphasizing single tumor performance comparisons as a basis for assessing MCED screening impact more broadly.

And while we recognize that mortality, or at least cancer-specific mortality, is an important and top-of-mind endpoint, we would argue against placing too much emphasis on this singular target. It is likely that such studies would be challenging to execute. And takes so long to read out that the technology would be out of date before the results became available.

We, therefore, would urge this FDA panel to consider alternate endpoints that would likely provide more timely and actionable insights. Foremost amongst these would be AJCC

stage-related endpoints. AJCC group stages are defined based on differential outcomes and continue to evolve to better discriminate amongst prognostic groups.

Shifting populations of individuals from advanced stage 3, 4 cancers to stage 1, 2 cancers would necessarily translate into an improvement in outcomes. The published literature today is both promising and remarkably consistent with regard to test performance in age-based risk populations. As noted earlier, large community-based systems are ideal testing grounds for screening strategies targeted at large, diverse populations.

As testing becomes commercially available, Sarah Cannon is making a concerted effort not to dictate adoption but rather to invest in education, outreach, and infrastructure to support the inevitable community uptake of such testing and to generate insights based on that experience.

Our clinical experience suggests that implementation is feasible in the community setting and is characterized by acceptable timelines for diagnostic resolution, the rare need for invasive testing in false positive cases, no serious complications associated with any case of a positive signal, and regular identification of early-stage disease in asymptomatic individuals eligible for curative intent therapy.

In conclusion, MCED platforms represent a promising new paradigm to address a critical unmet need. Study endpoints should recognize the unique nature of MCED testing grounded on a shared cancer signal and should embrace endpoints, appropriate surrogate endpoints for cancer-specific mortality that allow for timely and actionable insight.

And finally, community health systems like ours are likely to play a major role in the failure or success of population screening programs and, therefore, should be central participants in both study design and execution. I thank the panel for their time and their effort on this issue.

Dr. Gallagher: Thank you very much. And now we will hear from Mylynda Massart.

Dr. Massart: Good morning, everyone. My name is Mylynda Massart. And before I begin, I would like to disclose that I am on the Speaker's Bureau for GRAIL. However, today, I'm speaking on my own behalf, and I am not representing any specific organization. I'm a Ph.D. molecular biologist and, a board-certified family medicine physician at UPMC and an associate professor at the University of Pittsburgh, where I started a primary care precision medicine clinic in 2019.

I teach in the medical school and research the clinical implementation of genomics, and I am one of the coinvestigators for all of us in the state of Pennsylvania. While I bring both an understanding of the genomic technology behind multi-cancer detection and the critical need to expand cancer screening on the front lines of primary care, today, I will leave the science for my esteemed colleagues from around the country, and instead, I would like to tell you my why for supporting the introduction of multi-cancer detection in my clinic and to educate my colleagues around the country about MCED technology.

I have spent over five years in the National Health Service Corps in rural Idaho and another five years as medical director of an underserved clinic in the Hill District of Pittsburgh. I have also been a hospice medical director for my entire career. In these years, caring for rural underserved patients and those in hospice, I have seen the ravages of late-stage cancer diagnosis on patients, families, and their communities. I also had cancer at age 46 and have seen the value of genomic technology firsthand applied to my own care for risk stratification and the need for only surgery versus chemotherapy and radiation. There is a clear and urgent need for clinically validated tools that enable the detection of more cancer types at earlier stages when patients are asymptomatic that can be accessed as easily as a blood draw from rural America to the hearts of

our inner cities through primary care screening.

Since I started practicing medicine, I have had so many patients ask me why there is not a blood test that can screen for all cancers? I know that cancer lives in the fear of each one of our hearts. We have all been touched by cancer in our families and, our patients, and ourselves. Now that we do have a blood test, I have introduced that option for adding MCED to routine cancer screening for my patients, as I believe they should all know and have access to cutting-edge, potentially lifesaving genomic technology.

Unfortunately, the bulk of my patients cannot afford this screening test until it is covered, like other cancer screening tests. As a clinician, it amazes me that after years of sending patients through diagnostic odysseys for false positive mammograms or PSA screens and advocating heavily for patients to complete their four or five available cancer screenings, that there is now a potential point-of-care screen that could help catch the 70% of cancers, we have not been able to screen for previously, including the dreaded pancreatic and ovarian cancers that most often manifest with symptoms only weeks before death.

Furthermore, this screen has a positive predictive value of over 40%, which means far fewer diagnostic odysseys and less false positives for my patients. I know that many are worried that the opposite will be the case, and we will not know how to find and diagnose these cancers, but the technology guides the answer with the methylation fingerprint of the cell-free tumor DNA.

The field of oncology may need to adopt and grow with the opportunity to now diagnose and treat certain cancers that we have rarely had the experience to catch so early. While we have gold standards for single organ testing with our current guidelines, achieving these is already a major challenge for primary care providers.

The time and barriers to accessing routine screening are immense. We need to evolve into aggregate screening, such as MCED, to avoid adding additional single-organ screens for each type of cancer that would only further prevent effective public health screening strategies.

My patients who have had the ability to access MCED screening have found great value thus far. My patients who cannot afford MCED are eagerly awaiting news that it will be equitably available for everyone, especially my African American patients, who bear the largest burden of delayed cancer diagnosis and mortality rates. My one recommendation is that any and all studies must reach the patients most in need without delaying access to this emerging technology. I personally see my oncologist for follow-up every year, and he orders tubes of blood work and chest X-rays to monitor for recurrence. I restate every year that by the time something shows up on these tests, it will actually be too late. So, I have also started using MCED to supplement my own screening.

I am a mom of three, and I want to catch cancer as early as possible to provide the best likelihood of successful treatment and survival. And as a physician, I want to be able to do the same for all of my patients as well.

So this is my why. There is only one way forward to understand and advance the science. If we wait for perfection, how many more cancers will we miss? How many more family, friends, and patients will we lose? In our collective battle against cancer, we must deploy all the tools we have to prevent cancer, shift to early detection of cancer, and improve cancer treatments, and MCED is one critical part of this pathway to success. I will conclude with a brief statement from one of my patients just seen earlier this month.

Dear Dr. Massart, as someone whose contemporaries have passed away in their young 50s due to various cancers, I actively sought testing to detect any cancer traces in my own body.

It was not inexpensive, to be sure, but given my commitment to well-being and preventative care, I decided the cost was well worth it. I was lucky to have this option.

Having received the results and consulted with both my primary care physician and genetics experts, I am grateful to know better how to care for my own health, which impacts not only me but my entire family.

Because I bore witness to the pain and suffering of my friends and family, it strikes me as obvious that if we're generally committed to patient well-being and preventative care and to avoiding the enormous cost of treatment after diagnosis, we should ensure that multi-cancer early detection is covered by health insurance. It's a no-brainer, and it will save lives and money.

Thank you.

Dr. Gallagher: Thank you. Okay, and now we'll hear from Tomasz Beer.

Dr. Beer: Good morning. My name is Tom Beer. I'm a practicing medical oncologist at Oregon Health and Science University and serve as chief medical officer for multi-cancer early detection at Exact Sciences. I'd like to thank the committee very much for the opportunity to offer comments on behalf of Exact Sciences. My current disclosure is employment and stock ownership in Exact Sciences.

We're all here today because successful screening programs reduce mortality and morbidity from cancer, yet the benefits of screening are limited to a handful of cancers, with the majority of cancer deaths caused by cancers without guideline-recommended screening options. Beyond the most common cancers, the prevalence of each individual cancer is likely too low to design, evaluate, and implement effective screening tests for the general population, one cancer at a time.

The opportunity we see lies in searching for these cancers collectively rather than

individually by developing multi-cancer screening tests that take advantage of the aggregate prevalence of the cancers they're designed to detect. To extend screening through multi-cancer tests, we need to measure performance across aggregate cancer types and not on a cancer-by-cancer basis.

This approach would more closely match the public health need and would align with the design of multi-cancer tests. People, after all, seek to be protected from as much of their cancer risk as possible and cannot anticipate the type of cancer they may face. The clinical and scientific community has historically organized its thinking on a cancer-by-cancer basis, but considerable heterogeneity of outcomes is a feature within any individual cancer type as well as across cancer types, and this approach merits reconsideration to fully center the public health need of today and to match the technological possibility before us. A cancer-by-cancer approach would evaluate multi-cancer tests as though they were a collection of single cancer screening tests squeezed into a single blood analysis. This would substantially limit their potential. A cancer-by-cancer approach would necessarily leave behind many less common cancer types that, taken together, are responsible for considerable harm to humanity.

We see test efficacy measured by test performance demonstrated in a prospective randomized controlled trial, reflective of the diversity of the US population. We see safety assessment of multi-cancer tests primarily focused on the direct consequences of the test, the diagnostic workup that follows, and the burden related to false positive results.

We foresee a number of innovative strategies to demonstrate the clinical utility of these tests, with some elements of the clinical utility requiring longer follow-up than the assessment of efficacy and safety that would be expected to lead to regulatory approval. These clinical utility assessments will inform patients, their physicians, guideline makers, and payers.

At the same time, we're convinced that a cancer-specific mortality requirement for clinical utility would be a significant impediment to progress in this promising field. Finally, and these comments do not appear on this slide but are provided in our written submission, I'd like to comment on the diagnostic resolution strategy.

We believe it is critically important at this time to avoid being prescriptive about the methods used to resolve a positive multi-cancer test result. Some have proposed relying on a molecular signal that is suggestive of the organ of origin of a suspected cancer, so-called TOO. Our prospective clinical trial experience from some 10,000 participants demonstrated reliable tumor localization and false positive test resolution with an imaging-focused strategy. Our modeling analyses of diagnostic burden strongly suggest that an imaging-based strategy is likely to prove safe, efficient, and less burdensome than other strategies. We believe it would be premature to take a position on the optimal approach to the diagnostic resolution of a positive multicancer test result.

Thank you very much for the opportunity to share our views, and we look forward to the committee deliberations.

Dr. Gallagher: Thank you. And next up is Ruth Etzioni.

Dr. Etzioni: Good morning. Can I confirm that my audio is adequate, please?

Mr. Veizis: : Your audio is good. Yes. Thank you.

Dr. Etzioni: Thank you.

Mr. Veizis: And we can see your slides.

Dr. Etzioni: Great. Thank you. My name is Ruth Atzioni. I'm a biostatistician and cancer modeler at the Fred Hutch Cancer Center in Seattle. And I've worked on methods for the evaluation of cancer screening tests for over 30 years. Today, I want to talk about urgency. There

is a lot of urgency on this topic of multi-cancer early detection; urgency to approve urgency to make these tests accessible in the scientific literature in the media, and in the submissions to this panel. But the fact of the matter is that it is a formidable challenge to properly evaluate a cancer screening test for diagnostic performance for safety and for efficacy. And that is why the standard pipeline for assuring that the balance of benefit to harm is sustainable is multiphasic and takes many years to complete.

The volume of tests now demanding regulatory and policy approval is unprecedented. We are truly at an unprecedented moment in the history of cancer early detection research. And there's immense pressure to expedite evaluation and make the tests broadly accessible. But we've learned from experience that a cancer screening test that looks promising may ultimately turn out to be disappointing. For example, we've learned that a test can advance diagnosis and even seem to improve survival from diagnosis without extending cancer-specific life expectancy due to lead time, length bias, and overdiagnosis.

We've learned that we can greatly increase the number of screen-detected cancers without making a dent in disease-specific mortality due to overdiagnosis. We've learned that we can achieve an excellent positive predictive value by making a test very conservative and reducing the chance of early detection and ultimately reducing efficacy.

We've learned that we can make tests highly accessible but that people who are concerned about downstream costs of further testing and treatment will not use them. And we've learned, most recently with the UKCTOCS trial of ovarian cancer screening in the UK, that a test with seemingly highly favorable sensitivity can fail to show a mortality benefit in a well-controlled randomized trial.

And this is because cancer screening is not a standard diagnostic test. There is a huge gap

between performance and outcomes, and the gap is different for each cancer and depends on natural history and, ultimately, the opportunity presented by each cancer for early detection and interception, which may be very narrow for some cancers. As multi-cancer early detection becomes mature, we're being asked, and the panel is being asked today, to consider whether what the standard should be and whether the standard should be different for performance and for the design of studies. And make no mistake. These are enormous questions because they represent a major shift for the field and a departure from established hard-won standards designed to ensure that we only approve tests and recommend tests that will save lives.

At this moment, my message to the panel is that the real urgency is that the field is being asked to create a new action plan for early cancer detection. We need to agree on new evidence standards for and changes to the evaluation pipeline. For example, will we accept late-stage incidents as an end point in screening trials? Will we be able to retain rigor and make sure that we adhere to the standards, the high standards, the justifiably high standards that we've had historically?

This will require creating collaborations across regulatory, academic, and policy spheres. We all need to work together on this. We all need to become scholars of early detection, develop awareness of the complexities involved, and know that it is not enough to detect.

Detection does not always imply public health benefit. And we need to, most importantly, resist urgency in favor of validity while working to improve efficiency. This is happening on multiple fronts at the National Cancer Institute, in academic departments in the UK, and in the companies, and we need to work together to resist the urgency so that we can retain our standards going forward. Thank you.

Dr. Gallagher: Thank you very much. And next is Girish Putcha.

Dr. Putcha: You see my screen?

Mr. Veizis: Yes, we do.

Dr. Putcha: So first, good morning and thank you for this opportunity. My name is Girish Putcha. I'm a molecular genetic pathologist by training. Here are our disclosures, which Alberto has previously shared, but the opinions expressed here are our own.

So, as Alberto indicated, cancer is not one disease but many. So, cumulative performance measures alone are insufficient to determine whether MCD tests are safe and effective. Similarly, the detection of cancer is not actionable without localization information to guide the subsequent workup, so the accuracy of TOO information must be understood to determine safety and effectiveness. If such information is not provided by the MCD test itself, we urge the Agency to consider the test as part of a system that includes the downstream modality that provides such TOO information.

We believe that both cumulative and per-cancer analyses should be performed because a focus solely on cumulative metrics can obscure poor performance in certain cancers, especially when as much as 70 to 80% of the PPV of such tests is attributable to USPSTF, AB cancers, and prostate.

One proposal we submit for your consideration is whether one should adopt a tiered approach for MCD test claims like that used for tumor profiling NGS tests. For example, level 1 claims would be reserved for cancers for which screening has accepted clinical utility in the intended use population and pre-specified statistically significant CV endpoints. Level 2 would include cancers with pre-specified statistically significant CV endpoints but no accepted CU in the intended use population. And finally, Level 3 would include those cancers with only analytical claims.

In addition, one could group cancers to improve statistical power. Two approaches that may have some practical appeal are to group cancers based on follow-up diagnostic procedures or the clinical specialty to which a test-positive individual would be referred.

Next, regarding the concept of early detection, various groups seem to be coalescing around a shared definition of early as a localized cancer amenable to local intervention for curative intent. Using such a definition, clinically impactful early detection is different for different cancers a fact we all know and is shown here for what the authors call the cure fraction, but is also true for other outcome measures.

And finally, we notice others have that the detection of cancer, early or otherwise, is a measure of clinical validity, not utility. Like so many others, we too have been personally affected by cancer and sincerely want to see the promise of these tests realized, so we propose the following principles.

First, clinical validation must be done in the intended use population. Second, one must pre-specify and statistically power not just cumulative endpoints but also those for specific cancers for which one seeks to make clinical claims, Levels 1 and 2 in our proposed tier approach.

Third, as a practical matter, clinical truth likely must be based on the diagnosis of cancer with a pre-specified time after sample collection. And finally, enrichment strategies, such as the enrollment of elevated but not high-risk populations, should be allowed, but the target number or percentage of cancers from this group should be pre-specified to mitigate bias.

Next, clinical utility and surrogate endpoints. To our knowledge, no test granted a screening claim by the FDA to date has performed an interventional study for premarket authorization, but the risk-benefit of MCD tests may be fundamentally different and, therefore, require a different

approach.

Various surrogate endpoints have been proposed, but the fidelity of these surrogates and hard endpoints can vary greatly by cancer type to the point of non-existence. So, at a minimum, we need more transparency and consistency in how these endpoints are defined. That said, we also believe that a focus on only overall mortality misses some very real benefits that come with accurate early detection.

Next, just as for CV, one can and should consider cumulative and per-cancer analyses for establishing CU. However, we also believe that if one is going to lower the evidentiary bar for market authorization, one must also be willing and able to enforce the timely and rigorous completion of post-market commitments.

This leads to some final thoughts on CU. First, as with CV, CU must be done in the intended use population. Second, especially if USPSTF AB cancers are included, we believe that single-arm studies and historical controls are inadequate, so one must randomize the standard of care versus the MCD test and assess both the surrogate and hard endpoints like those listed here and in the previous slide, potentially using real-world data.

Finally, the menu of potential CUN points is fairly clear. The real challenge is where we draw the line for pre-market approval versus post-market commitment. Thank you.

Dr. Gallagher: Thank you very much. And our last public speaker for today is Gary Puckrein.

Mr. Puckrein: Good morning and thank you so much for this opportunity to present. The National Minority Equality Forum has not received any support for this for this presentation. I want to talk to you about these MCEDs from the lens of equity, and I'm going to use the African-American population as a reference point. But you should understand that we think the value of these MCEDs goes beyond the African-American community. So, African Americans

have the highest level of incidence of cancer of any population in the United States. There are about 1.2 million African-Americans in the Medicare and Medicaid program that are being treated for cancer. In most instances, African-Americans are being diagnosed late for cancer, they are not in the clinical trials, they're not getting advanced therapies, and their survival rates are poor.

On top of that, because of public policy, they live in carcinogenic environments; you can look at Flint, Michigan; Cashmere Gardens in Houston, Texas; Cancer Alley in New Orleans; I could go on. And what we see right now with these MCEDs is a real opportunity to stage shift these communities, to move them from late-stage diagnosis of cancer to early-stage diagnosis of cancer.

And the problem with this cancer inequity, and that's what I'm really describing to you, is that it's all been set up by public powers. The literature in the Medicare and Medicaid program about access to advanced care of for minority and underserved populations is quite explicit of that they're not getting the care of that they deserve; what you've also heard this morning is that affluent people are getting these tests. They can afford to go out of the out of pocket. If you look at the African-American and Hispanic community, for example, a third of them are on Medicaid; if you look at the Medicaid population generally, a third of the US population is getting their health care through Medicaid; 69 million Americans are getting their health care through Medicare. And the point of pointing that out is because that 169 million Americans are not going to get these MCED tests anytime soon because they're not reimbursable.

So what we're looking at is an expansion in the inequities in cancer care because the affluent are going to get their cancers diagnosed early, and poor people are going to walk around with metastatic cancer. That's what you're really talking about. So we want a sense of urgency

about this in the same way that we had urgency for COVID; we learned how to fly the plane while we were building it, and we would urge that you learn how to fly the plane and build it.

We need this technology in our communities right now. And we need FDA to not contribute to further inequities in cancer care, but to really make a concerted effort to make sure that these technologies are available to underserved communities.

If you do not do that, what you've already heard is that the inequities in cancer care are going to expand. And we think we have a great opportunity here to change the paradigm. When we look at these MCEDs, what we see is the beginning of us writing the last chapter on the war on cancer. This is what it looks like.

And what we have to do here is figure out how to get these new technologies into underserved communities. Because if we do not do that, we're going to have public policy contributing to the inequities that it has been doing historically.

So we urge this group to think about it very carefully because the decisions you make are going to affect millions and millions of Americans and expose them to continuing risk for cancer, and we urge you to take that into consideration. Thank you so much.

Dr. Gallagher: Thank you to all of our public speakers. We only have a few moments left in this time block. So I'm wondering if any of our panel members have any questions, maybe we can fit in maybe one or two questions to our public speakers. If panel members have questions, please make sure to hit the raise hand button. Karen Rue, your hand is raised. Yes, ma'am.

Ms. Rue: For the gentleman that talked about preference for imaging over a blood study, it's interesting because I recently had a friend; he's been in and out of the hospital, he's in his 60s, a couple times in the past year for a variety of things, surgical and medical, has had a couple different X-rays done in various places of his body, but just was recently diagnosed in the past

two months with metastatic renal cell carcinoma that is already metastasized to his brain. His brain was his primary surgery site. All his lab work was normal. He was asymptomatic until about two weeks before he ended up with this surgery. And in going back through all of his previous X-rays, it just never happened to X-ray the right spot where the tumors were growing, and they told him that he probably had the tumor on his kidney, which obviously is a primary site growing for eight to nine years. So, I have a question just in the discussion of that and in this particular case.

Dr. Beer: Was that directed to me? Should I respond?

Ms. Rue: I think yes, if you spoke about your preference for imaging.

Dr. Beer: Sure. So, first at all, hearing that story is heartbreaking, and of course, it's hard to comment on what transpired with a particular person and the imaging they got. I think there's a variety of ways to localize and rule in and rule out the presence of cancer. And my comments were really centered on the notion that there are a variety of approaches under study, and we need to learn about which ones will perform the best. We happen to think that a thoughtful and thorough imaging approach provides the shortest path to diagnostic resolution available, and would that be considered as folks discuss approaches to diagnostic resolution.

Dr. Gallagher: And Mitch Gail, your hand is raised.

Dr. Gail: Yes, the first talk was about the GRAIL system, which I understand is a system that detects any cancer, and the claim was made that it has very good performance characteristics. And suppose a GRAIL test is positive. How do you prove, how do you determine whether the person really did have a disease if you're testing for any kind of cancer? Operationally, what do you mean by the state of the patient? What standard tests do you have to apply to determine that there is a cancer present or not? If a GRAIL test is negative, how do you prove that there is no

cancer present using available technology? So, the claims of good performance are tied up with the methods that we operationally use to determine the state of a patient~~,~~. Whether there's any cancer present or not is very hard to assess operationally, and I'd like to hear some discussion of that.

Mr. Royse: I can tell you my experience on that because I found my cancer through the GRAIL test, and I received a report that showed signals, it did not say cancers. You have a very strong signal for pancreatic cancer, so you should follow up. So, it didn't say you had one of 50 different cancers. It was very specific and actually identified four, pancreatic and then some, gallbladder, stomach, esophagus, which were lesser signals, and based on that, I had an MRI done, but a full body MRI, but they knew pretty clearly what they were looking for. So that was my experience with it.

Dr. Gallagher: Maybe we'll take the two more comments, and then we'll take a break. So, the next hand that was raised belongs to Ruth Etzioni.

Ms. Etzioni: Thank you. I can't answer the question, but I just want to make the point that Dr. Gail, you said that the speaker showed favorable performance. So, the question when someone shows you performance is you need to ask what study, kind of study did this come from? And what is the metric? The main favorable performance metric that was shown was positive predictive value. And the speaker said that is the key measure of clinical utility and that was from a prospective screening study. And we all know the limitations of positive predictive value and that we can make positive predictive value.

Dr. Gallagher: And she's gone off-screen. The other person who still had a hand raised was Roger Royse.

Mr. Royse: No, I've offered my comment.

Dr. Gallagher: OK. Thank you. In that case I will now pronounce the open public hearing to be officially closed. So, thank you to everyone. And we will now take a five-minute break. It's now 11 o'clock Eastern time, and we will be back in five minutes. Thank you very much.

Clarifying Questions to FDA

Dr. Gallagher: Welcome back, everybody. It is now 11:07, and we're going to begin again. So, resuming our panel meeting. So, we're about to move into topic number one. So, I'm wondering, first, if anyone on the panel has any brief clarifying questions that they would like to ask of the FDA. Dr. Gail, your hand is raised.

Dr. Gail: Yes, the term MCD, when we say MCD, do we just mean a global test for any cancer, or do we mean some kind of combination of a global test for any cancer plus a TOO? In other words, if the global test is positive, then we subsequently perform a TOO to find out where the cancer originates, and so we could either have just a global test with no localization, a global test, which is followed by localization if the global test is positive, and a third option would be a global test and a tumor of origin test regardless of the results of the initial global test.

Dr. Castle: So, first of all, it's not a global test. Every test has a panel that detects a certain number of cancers, and then each test has a proposed strategy for how to manage the positives, and then there's the clinical diagnostic pathway, which I think we're talking later about what to do with that information. So, the TOO is a probability score of where the algorithm thinks the cancer is, and one of the challenges is if you don't find cancer at the highest probability, how far down do you go in probability scores before you say we can't find cancer and what does that mean in terms of follow up and care when you don't find the cancer. And then there are other tests that are basically saying do, full body imaging, like the Exact Science test, and they've all made their arguments one way or the other.

I think this is why many of the questions that were raised by the FDA are exactly the reason why the NCI is proposing a multi-arm randomized control trial to evaluate these technologies and not just for their mortality benefit but also all these other questions.

Do people adhere to standard of care screening? What's the diagnostic pathway? What's the best practices for diagnostic pathways? And so on. Almost verbatim, every question that the FDA laid out is exactly the questions that we laid out two years ago when we stood up our clinical trials team to develop a randomized control trial.

Dr. Gail: I just wanted to clarify the terminology because some people, like the GRAIL person, was talking about MCD as a test. It's positive if any cancer is present, but I'm not going to tell you where it is.

Dr. Castle: No. Their tests then gives you a probability score where they think the cancer is. It comes as a whole. It's not a second test.

Dr. Gail: OK.

Dr. Gallagher: Okay, so I want to make sure that Dr. Stenzel has a chance to answer the question because I know he started to answer the question. So, I want to make sure that he gets to have his input as well.

Dr. Stenzel: Yeah, first of all, the FDA is open to different ways of doing this, and in our definition, it's really two or more cancers detected with the test. There could be some technologies that have a more limited scope and don't necessarily have the potential to detect any cancer. And then, as far as determining where the cancer is with a positive signal, there are some technologies that have this separate TOO assay. Some, and I'm not speaking to any specific, I'm just talking about the possibilities, could have something built-in or that you could have a positive result and not know from the test itself where the tumor is, and then do imaging,

for example, to localize the tumor. So, hopefully, that addresses your questions.

Dr. Gail: The only thing is that from a statistical point of view, there are very different combinations here.

Dr. Gallagher: I think as we get through the big questions, the long list of questions that were being asked, I think we'll get into some of those differences. Dr. Carroll, you had a question.

Dr. Carroll: Just a quick question. I just wanted to be sure I understood from the FDA and you, Dr. Gallagher, what the specific goals of our meeting are. Because when I heard the speakers, is it trial design, test characteristics? When I heard some of the speakers, I think they're expecting something from us, which is a little bit different than the intended meeting. So, is a trial design, test characteristics, is that we are here to deliberate about? [indiscernible – Audio cutting out]

Dr. Stenzel: We have three topical areas, and we have slide decks that may have been provide to all the folks ahead of time, and there are specific questions on each of the slide decks for each topic area. And the overall meeting discussion, no, it says that we're interested in any important features of task design and important questions about test performance and the benefits and risks. So those are the broad topics. There's a hand up.

Dr. Gallagher: Yes. Deneen Hesser, your hand is raised. Would you like to ask your question?

Ms. Hesser: Yes. Can anyone tell me have any of the MCED developers have been given breakthrough status so far by the FDA? And if so, were they given any particular guidance as to what you might be looking for?

Dr. Stenzel: So, I think this gives me a good opportunity to talk about a number of things briefly here at this point in the meeting, and first of all, on breakthrough designation, that is an active program. We encourage it. And the FDA, when it makes a determination that something is a breakthrough, does not make that public, but companies are allowed to make that public. And

there are some in this space who have made that breakthrough status public. I can't be any more specific than that without giving away company confidential information, but I do want to review briefly at a high level what the FDA process is.

We take review of applications very seriously, and when we receive an application for a new test, we assign the specific experts in our office who, have been trained and have the experience to be able to best evaluate that test. Then, under law, we are required to do that review in a timely manner, and for each type of submission, there is an FDA day number that we're held to, and for the fiscal year 23 data, which is the most recent complete data, our office, the Office of In Vitro Diagnostics exceeded all of the goals set out in law. So, we're very pleased with that performance. We make it an effort that when we have an application, then we do a timely review.

We are also required to do the least burdensome review. So, the easiest pathway to an FDA authorization is the one that we look for, and that's the overall goal. I do want to say that the FDA, in this technology area, multi-cancer detection, is very open to using aggregate the cancer detection along with specificity and PPV to make an overall benefit-risk analysis. Some of these tumors are very rare, and to get enough cancers for each type that the test may detect and require that before making a decision would be pretty extreme. So, we do invite you, if you haven't already, to come to talk to us about your test and through the free program, the pre-submission program, and if you would like to apply for a breakthrough status, that is also open to you as well. Thank you for the opportunity to share those thoughts.

Dr. Gallagher: Okay, and it looks like Dr. Lipkowitz has a question.

Dr. Lipkowitz: This is Stan Lipkowitz from NCI. So, just a question in the approval of drugs, there are approvals, which are accelerated approvals, which, for lack of a better term, are

provisional. But the idea is there's approval based on a surrogate marker, for example, pathologic complete response in breast cancer, followed by the requirement for additional data demonstrating clinical benefit beyond the initial approval with the expectation of withdrawal of the drug and if it doesn't meet the requirements.

And there have been a number of cases where the drugs were approved, for example, even on progression-free survival, but because they didn't have an overall survival benefit, eventually, the approvals were withdrawn. The question is, for devices or for these sorts of tests, do you have a similar mechanism? Because I think one of the issues we're wrestling with here is what is the bar to allow these to get out into the public space and what should be the bar? And again, that may be reflected in some sort of similar mechanism.

Dr. Stenzel: Yes, thank you. For FDA authorization, we don't have that exact program that drugs and biologics have. However, we have the breakthrough designation program. And if you are designated as meeting that designation, we do accelerated reviews. We try to do those reviews in less time than is required than is set out in law for those types of applications.

Topic One: Clinical Study Design Considerations for FDA Submissions

Dr. Gallagher: Thank you very much. At this time, we're going to focus our discussion on topic one. Panel members, copies of the questions were in the panel packs that were sent to you earlier. I would ask that each panel member identify him or herself each time he or she speaks to facilitate the transcription. AV there, you got there faster than me because you're already showing the first question. Thank you. This is the topic. Go ahead, FDA.

Question 1

The first clinical design trial question that we have to discuss is what are critical study design

considerations when planning an MCD clinical validation with respect to these things: What are the advantages and disadvantages of different study designs? Type of clinical trial–Is a control arm necessary? Size and enrollment strategies? What considerations need to be given for data subjects from non-US sites? Appropriate age for using an MCD, and how should high risk patients be defined for an MCD, and is it acceptable to enrich with high-risk patients?

So, let's start our conversation with that idea. What are the critical study design considerations when planning to clinically validate an MCD? Okay, I see that Mary Margaret Kemeny has raised her hand. OK.

Dr. Kemeny: I think one of the things that is vitally important and doesn't happen in most of these studies is that minority and low socioeconomic populations are included and differentiated because what happens is in a lot of these studies is that it's all our, more affluent white population and, in the minority population, they may have cancers already and also higher stages of cancer. So, it might be a whole different picture. Serving a minority population in New York City, I can tell you that most of the cancers that we see are in higher stages already. So, it has to be a concerted effort to make sure that there is a good percentage of minority groups in each of the studies.

Dr. Gallagher: Thank you. And now we're, the next hand is Philip Castle.

Dr. Castle: Hi. I'm Phil Castle. I'm at the US National Cancer Institute. I'm going to shoot the first shot across the bow here and say that we believe that mortality has to be the end point, cancer-specific mortality, and here's why.

First, the reason for doing cancer screening and early detection is either the reduction of incidence or cancer-related mortality. That's why we do screening. And for many cancers, there is not a proven surrogate endpoint that has been shown to correlate with mortality benefit. And I

think the example that Ruth Ezioni provided about UKCTOCS, which showed an early advanced-stage reduction for ovarian cancer that ultimately did not lead to a mortality benefit, is a perfect example of why a reduction in advanced-stage cancer for a particular cancer type may not actually provide a mortality benefit and may lead to a false finding. Keep in mind that these tests, when we say sensitivity and specificity, you have to clarify what stage you're talking about. I think if you dug through the literature as we have, they are somewhat sensitive, imperfectly sensitive, but better sensitivity for late-stage cancer, which is not the point of using these tests.

And that the tests only have very low sensitivity for early-stage cancer and also, keep in mind that they have tried, and I think this is a flawed approach to then say well, those few cancers that we found earlier represent a mortality reduction. And here's the problem with that argument.

First of all, reducing those advanced stages, it's not at random; it's not a random sample of the advanced stage moving to the early stage. So you don't know if they are more lethal or less lethal, and then you're comparing them to incidentalomas like pancreatic cancer, which for stage 1 are not representative of all stage 1 pancreatic cancer if you could find them, right?

So when you look at SEER, and you say, stage 1 pancreatic cancer is 80%—I don't know what the number is; I'm just, I'm making up a number here—those are not representative stage 1 pancreatic cancers. Those are the ones that are slow growing that were accidentally found through other imaging technologies, for example. So, you can't make any inferences. You have to actually show that there's a direct relationship, a causal relationship, between that reduction in late-stage cancer—or advanced-stage cancer is probably a better term—and mortality.

Once you've shown that, then you can build off of that, and then you can accelerate the

field. But until you've proven those surrogates, you can't, and with all due respect to those cancer patients—and those are great and tragic stories both—these trials are not going to not going to show pancreatic-specific benefits or ovarian-specific benefits because the trials are going to be driven by lung, colorectal, and prostate, which are the most common cancers.

We've done all the modeling on this. You're not even going to be able to say this is going to save lives related to pancreatic cancer or ovarian cancer; its statistically not possible, at least in the early trials. So for all those reasons, we strongly feel that mortality is the only certain endpoint that truly represents a benefit.

The other thing to keep in mind, just to put it in perspective, it was interesting that one of the speakers said, well, if we implemented these tests, there would be 100,000 lives saved, which, of course they can't really validate. They're making inferences. But let's go ahead and say that's true. What if people stop getting colorectal cancer or cervix cancer, which not only prevents mortality but prevents incident cases. So, if you just look, if they stop doing colorectal cancer, if people stop doing colorectal cancer because they got MCED testing, it would actually reverse the effects. I mean, cervix alone screening probably prevents 25,000 cases of related deaths a year, and colorectal has got to be ten times that.

So if people stop getting colorectal cancer because they got the MCED, you'd actually see an increase in cancer-specific mortality in those arms. The final point I want to make is that not all MCEDs are equal, and not just from a performance and potential lifesaving benefit, but also that the different MCEDs target different cancers and may be appropriate for different subsets of the population, which nobody's really talking about at the moment.

So, for all these reasons, we need to do an unbiased evaluation of these technologies, but the companies need to have their feet held to the fire and really have mortality endpoints. And I

recognize that slows progress, but we've seen too many things that have gone out the door, without true validation, and actually end up hurting people, and nobody would think about doing this and doing a similar thing with a drug in a healthy population.

Like, here's a drug; come back in ten years and tell us whether this is, this worked for you. We would never do that. So why are we even considering such a thing for a screening test? Which obviously, the screening test is an in vitro diagnostic, but the follow-up care is invasive and really has to be considered in that context.

And so, for all those reasons I don't think sensitivity and specificity are the metrics here of importance for validation of these tests. And I'll leave off there and I realize my viewpoint is quite extreme. I'm sure there will be some pushback from others on this, and I welcome the discussion.

Dr. Gallagher: OK. And I'm going to ask Karen Rue.

Ms. Rue: I have three comments. One as far as the age of the population, I feel personally pediatrics has a lot of background in that. The pediatric population definitely needs to be concluded, but as a subset because some of their cancers are totally different. A lot of that population group, especially the younger of them, are seen more frequently and probably have more testing done that would show up some incidents of cancers as opposed to the adults, so that may skew the adult population. I'm not a statistician, but just from practice.

The targeted population, I have a question on that because recently, last year, in one of my regular exams, I was asked, you want to participate in a cancer survey study? I said sure, and I filled out a questionnaire. I have a scattering of cancer in my family background, so I thought this is good because I would be eligible, and that would be good.

Then, I was told I didn't qualify. I was given no reason. I don't know what the test was.

So they really need to work with the population, whatever it is to make sure they're better informed. And as far as follow up in how far we're going to follow these people up and how do we follow them up as a suggestion and it wouldn't catch everybody, but most of the cancer centers large and small have tumor boards, and that's part of a national organization. And if there was a database, they could maybe connect with that to make sure we have fewer people falling out of follow-up. That's my comments.

Dr. Gallagher: OK. And Mitch Gail, you're up next.

Dr. Gail: Thank you. I'd like to follow up a little bit on what Phil was saying about the end point. Of course, the overall aim is to reduce mortality, and I agree with that being an ideal end point and for that, we do need randomized trials, and the question is, what would a comparative group be? And it might be a standard of care screening versus, let's say, MCED-type screening, but that's going to be very difficult to carry out it. It should be carried out, but there could potentially be some preliminary studies to say is this MCED promising enough to even warrant introducing it into this very expensive long-term mortality reduction study. And I thought I heard someone from the FDA say that we can approve something even though we don't know it's going to have a long-term public health benefit. It just has to be promising at the early stage. And we can let it out, go out there, and before it's been proven to have a long-term public health benefit.

So, one could ask some preliminary questions: What is a promising MCED? And even that is a difficult question to approach. Suppose you wanted to define the sensitivity of an MCED and by MCED, I'm using the term as an MCED is positive if it says any cancer is present for the moment, that's my definition. How can I determine whether any cancer is present? How can I estimate the sensitivity if I don't know? I have to have a definition of any cancer is present an operational definition based on standard methodology. And this gets a little bit to the distinction

between case-control studies and a study in a target population.

In a case-control study, we know who has cancer, and we can see what the sensitivity of this MCED might have been to pick up a particular type of cancer, but in the general population, target population, you don't know who has the prevalent cancer. Unless you do a series of screening tests and pick it up, that would be your ground truth evidence of cancer being present, and among those people, you want to see what proportion of the MCEDs were positive.

What I'm saying is it's very hard in a target population without an operational definition of what I mean by any cancer present to evaluate even sensitivity or an even probably more problematic specificity of an MCED. But those issues have to be grappled with even to get preliminary evidence that an MCED is useful. Then, you go to the clinical trial for proof of actual public health benefits.

Dr. Gallagher: Okay, so I see that Dr. Stenzel has raised his hand. I'm thinking that based on when he did that, he might have response to something that was said earlier.

Dr. Stenzel: Yeah, I just want to clarify following Dr. Gail's comments that for IVD devices in vitro diagnostic tests, we don't have a preliminary approval program. We do have the breakthrough program, which is not an authorization of the test. It's simply a recognition that the technology may have promise, and it allows for an accelerated review. But the review is still the same standard in the end that we would do for any other test. The standard is the same. The review time could be shorter. That's all. Thank you.

Dr. Gallagher: Thank you. And Carla Ballman, you were next.

Dr. Ballman: Hi. Yes. Thank you. This is Carla Ballman. And I just want to say, I do agree with Dr. Castle and Dr. Gail's points. I do think that mortality has to be sort of the endpoint, or we're going to be in a situation that's going to be prostate cancer magnified.

We're still trying to figure out today who has indolent cancer and who doesn't. And my main point was to go back to the first panelists. I do agree that there has to be sort of a look at underserved populations because a lot of the tests are saying we're going to get to those underserved populations.

And my concern is that, yes, they can get the test, but will they do the necessary follow-up in the case of a positive test? Because I think the trials do need to track that because even if it's paid by the trial, they still might not do it just due to the time necessary that they would lose, like from work and so forth, and may not have the coverage available. So, I do agree that, I really encourage that it be looked at across a representative population.

Dr. Gallagher: Thank you. Rebecca Perkins.

Dr. Perkins: Thank you. I'm going to express the alternative viewpoint. I'm concerned about mortality being the only endpoint that is looked at. Obviously, it's an important endpoint, but if you have to wait for people to die, I think that may take too long.

And also, there's so many other steps that happen along the way. People may survive on palliative cancer treatment for years but with no intent to cure, and we know the cancer will eventually take their lives, but it may be outside of the time period of the trial, or other things may come along that may alter their cancer course, but they have been suffering for many years with advanced cancer. This is especially true currently in the lung cancer space, where many people are on palliative chemotherapy for years when there is no chance of cure. So I thought the presenter who said using a cancer diagnosis at which point in time the patient can have treatment with curative intent is a really interesting and potentially very important endpoint because then we can say that this early diagnosis had a benefit because the patient was told that they could be cured as opposed to they could not be cured.

I also wanted to just talk a little bit about the concerns of people either not doing other screening tests or safety net populations not following up. So, in the space where I think this has been the most true is in the HPV vaccination and cervical cancer space. People were concerned that if patients got their HPV vaccines, they wouldn't be screened for cervical cancer. And in fact, we see that patients who got their HPV vaccines are more likely to be screened for cervical cancer. So I think, in general, people who are going to run and get this test are people who are worried about cancer, and they're probably not going to forego their other cancer screening tests. So, I don't think, that may be a concern, but I think it hasn't really been borne out by the data, and it probably shouldn't be elevated to a potential negative impact of these tests because it hasn't been shown in other settings.

And in terms of safety net populations. I do work in an FQHC and have done a fair bit of work in this area. And what we see in terms of patients attending colposcopy after a positive cervical cancer screening test is that if you provide a patient navigator, you can actually have higher attendance rates at your colposcopy than you do for the patients who are white and affluent and didn't get a navigator.

It's very important to provide support for the safety net populations, but without the support, you may see differences that you could overcome with patient navigators or their support, and to say the test isn't worth doing because these patients didn't come seems to be throwing out the baby with the bathwater. Whereas really, there are ways to make sure that patients and safety net settings receive the appropriate standard of care with adequate insurance coverage and patient navigation. Thank you.

Dr. Gallagher: Thank you. And Edward, you're next. We're not hearing you. Please unmute yourself.

Dr. Bujold: Thank you. I've been in an independent primary care practice in the same location for 40 years and have always been looking for screening tests, whether it be for coronary artery disease and sudden death or from cancers.

And as I've listened to the discussions through the morning, I keep coming back to screening for prostate cancer. And how, when that test, the PSA test first came out, it was designed for people looking for recurrent cancer, and it was a great test for that. It continues to be a great test for that. And then someone got the right idea, we should use this as a screening test for prostate cancer, and it's not really a good screening test for prostate cancer. And yet, we use it all the time. And occasionally there are adverse events that happen when we do the test, even though we've looked at informed consent and all those things.

And a certain as a physician, there are always cases that stick out in your mind over the course of years. And one that has always stuck out in my mind was a 75-year-old white male that had a PSA test done and was elevated. He had a biopsy done, started having fevers on the table, on the operating room table, and ended up getting septic and spent a month in a hospital with multi-organ failure and almost died, and his biopsy report was benign. There are risks to doing these things, and I'm in favor of any tests if properly vetted, that can screen and pick up cancers. In the last three years, during our annual wellness exams, we've looked at people that are high risk for lung cancer and do these CT screens and have picked up five or six early lung cancers. And it's probably saved people's lives. These are things that we'd love to do, but we need to make sure that the tests are vetted and, the designs are well-controlled, and the right populations are used, et cetera. But there are risks involved in doing these tests.

Dr. Gallagher: Thank you. Daniel Swerdlow.

Dr. Swerdlow: Hi, Daniel Swerdlow, the radiologist from Georgetown. I like the idea of

mortality being an endpoint, but it was phrased as cancer-specific mortality. And then I get a little confused when you have a test that maybe that turns positive, and it's one of these ten cancers. And maybe cancer A is at 80% likelihood, and cancer B is 60%, and then cancer J is 1%, and you start the workup, and at some point, you decide that the likelihood of the low probability cancer isn't worth the risk, cost, etc. of making the diagnosis.

So which cancer is it that is going to be the mortality end point, then? Is it all of them? I think that's where we need to be. If you get cancer and die of it after having a screening test, be positive or negative. I think that has to be factored in because I'll also point out these are the ones that screening test misses. So, I would advocate all cancer screening deaths as opposed to a specific one that you would have to pick as the most likely.

Dr. Gallagher: Okay, thank you. And Nathan Winslow, your turn.

Mr. Winslow: Yeah, just continuing with the theme around the end-point discussion. I would offer that the idea of mortality, I think, is one where there would be some concerns, I think, from the part of industry in terms of the feasibility of those types of studies, the size and the longitudinal duration of those, and the impact that could obviously have on some of the innovation that we'd be talking about. And I would suggest that there's a holistic way to look at benefit-risk. And I think that's ultimately what we're trying to do here.

I've heard mentioned healthcare equity, and the fact that this can bring more to underserved populations, for example, increased compliance with existing screening methods, because we've talked about this being complementary. I just offer, when we look at the various ways to see the benefit-risk of these tests, that we don't simply look at the gold standard for what could be the clinical endpoint.

But there's other ways to get at that. And also consider what could also be delaying something

that could be very beneficial to broad parts of the population, and if we do have studies that go many years that we are delaying the introduction of a technology that, again, we would want to have a positive benefit-risk. But that's something that we could feasibly prove.

Dr. Gallagher: Thank you. And again, I see Dr. Stenzel's hand raised, so we'll let him address whatever, and then I'm going to ask AV to pull up the questions again.

Dr. Stenzel: Yeah, there there's a lot of discussion about using mortality as an end point for this type of submission to the FDA. And for this type of submission a standalone IVD test not linked to other things like therapy, we, under law, can look at analytical validity and clinical validity. When you get into mortality, you do get into clinical utility, which is not in our tools to use for this type of submission, whereas I do realize the overall goal is to reduce mortality. For this type of submission to our Office of In Vitro Diagnostics, we do not assess mortality as an endpoint.

I would also like to add, though, that we do take into consideration all the benefits versus all the risks. This analysis is performed by our medical officers and is an important element of our review. There may be small benefits and big risks, that would be an inverted ratio. There might be equal benefits and risks, and that would be in the unity of one. And there might be a slight or a huge magnitude of benefit and a small amount of risk. So, we do get the opportunity to review that in the submission. So, we do take into account potentially all the potential risks here. So I just wanted to add that what's in our purview, what we can do with these kind of submissions, just to clarify that.

Dr. Gallagher: Thank you. Okay, and I think if we can have the question pulled back up, please, by AV. Thank you. Now, we want to consider defining how early detection should be defined for the MCD test and discuss the data and considerations necessary to support an early cancer detection claim. I know there are more questions to come; we had a few hands that were still

raised, so we'll take them in order, adding this to that clinical trial kind of thing. Carla Bellman, you were next.

Dr. Ballman: Yeah, I guess we're talking about that new question now, and I think early, it cannot be something like, and this was my comment before, is if the end point would be whether or not someone could have early intervention, that's just as saying if we detect more stage one or stage two, which we know a lot of that would be indolent. So I don't think that is a good end point.

And it's interesting that mortality can't be an endpoint when we're asked what an endpoint should be. I'm not sure how else you would show benefit and do the cost-benefit risk ratio because, because, well if you say it's detecting a lot more late-stage disease, again, if it doesn't translate into any sort of benefit and all these people are being treated aggressively, how are you going to be able to capture that in terms of your risk-benefit analysis?

Dr. Gallagher: OK

Dr. Stenzel: If I could clarify, I think there's a need for potentially clarifying what we consider benefit in this type of submission. So, it would be an accurate test; what is the sensitivity? Is the sensitivity a benefit? And what is the specificity? And, of course, specificity is related to positive predictive value. The higher the specificity, the higher the positive predictive value and understanding what the positive predictive value is. You could have, potentially have an extremely high positive predictive value. And then, you wouldn't have a lot of potentially off-target risks; people who don't have cancer and are undergoing invasive procedures or radiological imaging that may have certain exposures. Or you may have a very low positive predictive value, and for each cancer detected, there might be an extreme amount of potential risk to patients who don't have cancer to be able to find those cancers. So those are the kinds of

things that we look at in the benefit-risk calculation.

Dr. Gallagher: Thank you. OK. Philip Castle.

Dr. Castle: Tim, sorry, I apologize for pushing on this because it's such a critical issue that I feel like we have to keep after this. You're talking about the positive predictive value for cancers, but how do you know that those cancers are clinically relevant cancers?

If you detect a lot of indolent cancers, then you would have a great positive predictive value and no population benefit. And I feel that this is the struggle. Particularly when you hear these individual case reports that these interventions are population level, and they have to show some population benefit and the two benefits I'm aware of, one of which is not in play here, which is a reduction of incident cancer, like cervix and colorectal in this case, and one is early detection, but early detection of what? Okay, so it has to be early detection of clinically relevant disease, and that clinically relevant disease has to be linked to mortality.

And the problem is, with all due respect, is that for many of these cancers and, again, bring back the example of ovarian cancer, we don't know what that is. And those were for very general screening tests like imaging or CA 125. Now you're talking about a very biologically specific test, which, in fairness, could be more correlated with mortality, or it could be less correlated with mortality. We don't know. So, when you say benefit, finding cancer itself is not a benefit. Okay, finding stage 1 or 2 or 3, does the outcome for the patient improve, and specifically, is there survival because of that, which is why we do cancer screening. If that's not why we're doing cancer screening, then I should get out of the business because I don't know what I'm doing, to be honest.

Dr. Stenzel: Yeah, if I could respond to that. We can only do what we're legally allowed to do. And we simply aren't legally allowed to go for this type of submission to go into clinical utility

assessments. Is it an accurate test? Does it accurately detect cancer or not? That's our role. There are others, insurers, CMS, who can look at clinical utility. But we play our part in this ecosystem, and that is, is the test accurate? Does it have analytical and clinical validity? And, if the risks in our medical officers' opinions outweigh, based on data, outweigh the benefits, we can deny an authorization.

Dr. Castle: I think the authorization should, has to, because you're asking the public to some degree to understand the difference between the detection of cancer and mortality benefit. And as we've learned from COVID, the population is not that savvy about risk. In fact, most scientists are not that savvy about risk, not this panel. My experience is people don't really understand risk. They think about relative risk and not absolute risks and things like that. But then, if the indication is you can detect cancer, it should also carry the indication. It also should say that we don't know if that actually helps you in terms of mortality benefit because you don't. To just say that it detects cancer, we could come up with a test that detects indolent prostate cancer, nobody [...]

Question 2

Dr. Gallagher: I want to focus on something a little different because this particular question is asking us about the early detection question, and I think, with the previous question, we had some of the conversations that you're having now, so I'd like us to move on to what would be early cancer detection, how that might be able to be identified.

Dr. Castle: But how do you disentangle this calling? Because it's the same thing. It's the natural history of the disease.

Dr. Gallagher: So my question related to this question would be, you'd require, it would require, probably several clinical trials to get to the point of being able to say whatever test we're talking

about actually detects this earlier than most people used to get it detected, right? If it's usually detected when it's stage 3, and it's now detected when it's stage 1, then it's early. If it's not detected until then anyway, then it's not early detection. So, I don't know that early detection would; I don't know how you would classify otherwise.

Dr. Stenzel: I want to, again, respond to Dr. Castle. I understand what you're saying, and in a perfect world, that's all there. But, as far as our legal authorities, it's been determined we can't go there for this type of submission. It would require a change in our authorities before we could use mortality as an endpoint for this type of submission. So it perhaps would be unofficial to go on to other topics here, we still have a lot of questions.

Dr. Gallagher: Try to move us forward. Yeah. So, Mary Margaret, your hand's been up for a while.

Dr. Kemeny: All right. We need to use stage, not mortality, or stage, or intent for curative treatment because mortality is out of the question. Especially in today's new, we're getting new drugs every few minutes, basically, for cancer.

I'm a practicing surgical oncologist and director of the Cancer Center. Like for lung cancer, with the new drugs, people with stage 4 lung cancer can now live for years. You can't use mortality, but the stage is very important, and the stage is the way we, as practicing oncologists, treat cancer. We treat stages 1, 2, 3, and 4 differently. And it's very important for a person to have early-stage cancer because the kind of number of treatments available to those people, the lower morbidity available, is much greater than for the stage three and four cancers.

So, we want these tests to show us if there's cancer present when people are asymptomatic and not showing up with any other tests. And that could hopefully lead to earlier detection of cancers. And that's what we need to have.

Dr. Stenzel: And I think question three gets to that, and talking about stage shift.

Question 3

Dr. Gallagher: All right, so we want to go to question three, because that's the next where we're headed in our conversation. AV could put up the next question. Thank you. Aggregating multiple cancers into one study has its advantages, but the benefit or risk is likely unique to each cancer. Please discuss the benefits and limitations of a single aggregated study, and given the various differences across cancers, shed rates, natural history, variety, histologies, all those kinds of things, should physicians be informed of per cancer performance? One set of questions. Another set of questions for consideration is please discuss what aggregate and per cancer validation for MCDs would entail, including things like the minimum number of positive cancer cases for each cancer, minimum sensitivity for early stage, and minimum sensitivity for each cancer. Mitch Gail, your hand was up next.

Dr. Gail: Yeah, thank you. To the previous question, I guess one answer that we heard was a stage shift toward early stages as evidence of early detection, and somebody has said that it is a necessary condition to translate into a mortality result but not a sufficient condition. Another possible definition would be detecting tumors that would not have been detected through routine screening. So, I just wanted to make those two comments regarding the previous question.

Tim has mentioned that he would like to get back to sensitivity and specificity. And I'd just like to just show one slide and just try to reiterate something that I've said before, but I wanted to make sure that I'm saying it clearly. Do you mind do you mind, can I share a screen at this point?

Dr. Gallagher: Okay, so AV, I think you have to stop sharing so that they can do that.

Dr. Gail: Thank you. Okay, and here I'm trying to... Can you see these, not yet? Pardon, you can or cannot?

Dr. Gallagher: Cannot.

Dr. Gail: Oh, it's on my screen,

Dr. Gallagher: So you have to hit share screen?

Dr. Gail: Yeah, I did that. But here, I got a share screen.

Dr. Stenzel: So, if you shared it.

Dr. Gail: Oh, I'm sorry. Yeah, there we go. There we go. Can you see it now?

Dr. Gallagher: Yes.

Dr. Gail: OK. And we were familiar with testing for a single a single cancer type. We could have a global test that tests for any cancer but doesn't tell you where it is. We could test for case-specific cancers, each with their own combination of what we might call MCD and tumor of origin, or we could do a global test, and only if it's positive do we try to figure out where it's coming from.

And each of these three types of MCD tests has different statistical characteristics. But one thing that they all share is that if you want to compute positive predictive value or sensitivity or specificity, you need to know what the true state of the patient is.

For an MCD test, which is just a test that says there's a cancer there, that's positive. Or the MCD test says there's no cancer there. How do you know which of those conditions actually exist? And that has to be defined operationally by standard tests that you could apply to everyone. If I want the positive predictive value of a positive MCD test, I have to go through a set of clinical operational procedures to determine if there is any cancer present. If I just do just one procedure, I'm going to underestimate the positive predictive value. If I do very extensive

testing, I'll get higher and higher positive predictive values, and the same concepts apply to sensitivity and to specificity. So one of the difficulties of an MCD test that just says there's cancer present is how do you know what the true state of the patient is based on accepted ways of diagnosing any cancer? That's an essential problem of all MCD tests.

The tests that test for case-specific cancers have a multiple comparisons problem, and they tend to have more false positives. Tests like B or D that have to have a positive MCD global test first before trying to figure out where it is; if you do that, those control the false positive rate a little bit better because you can adjust the threshold for the global test to make sure that it doesn't have too many false positives.

But a point that I wanted to make to the FDA and to the rest of the panel is that you might want to consider precisely what you mean by an MCD test when you're defining the various criteria for evaluation, even such simple things as trying to determine sensitivity and specificity. And if the MCD test is a test for any old cancer, you've got to operationally define how you're going to test for any old cancer using conventional methods. And this has to do with the aggregate; there is a concern about aggregate. I'll stop sharing now, but this has to do with what we mean by an aggregate test that Colleen is trying to get us to talk about. How can we talk about an aggregate test if we don't even know what it means to use classical methods to define any old cancer?

Dr. Gallagher: So you're using the phrase, any old cancer, and I'm imagining that someday somebody might get to go, oh, all cancers share this one marker. But at the same time, I'm thinking it might be a long time to get to that particular point. So it might be that these are multiple tests; one test detects multiple things, and if I heard Dr. Stenzel correctly earlier today, he mentioned that it means two or more cancers. So it could be a couple of things combined and

not be any old cancer, but be specific to looking for a set of specific cancers.

Dr. Gail: Yeah, but the GRAIL test was for any old cancer, up to 50 cancers.

Dr. Gallagher: OK. Carla Ballman, you were next.

Dr. Ballman: Yeah, thank you. This is Carla Ballman, and I was going back to your question three if I can remember, and I don't have it pulled up, but...

Dr. Gallagher: Hey, we can ask AV to pull it back up.

Dr. Ballman: And, I think it talked about aggregating into one study has its advantages, and I don't know if there's a better question to comment this on, but in my opinion, I think if there's an established test out there that's being used, that before the indication can go into the multiple tests, it has to have better performance characteristics than the standalone test. Now, I'm not saying they can't test for it, and if they find it, they can go ahead, and obviously, the person would get a workup for it, but I don't think it should be on the indication if it doesn't outperform the current standalone standard of care test.

Dr. Gallagher: Okay, and Debra Schrag, you're next.

Dr. Schrag: Hi, thanks for the opportunity to comment. This is a really tricky set of issues, and it feels like we're now between Scylla and Charybdis. On the one hand, we all understand the validity of mortality is an end and how critical that is, and we don't know this is a public health intervention. And we don't want to we don't want to wreak real harm on the public and [...]

Dr. Gallagher: Hey, it seems like Deborah has actually frozen on her screen. Dr. Stenzel, did you want to comment?

Dr. Stenzel: Yeah, while she reconnects. I always wonder, is it me that's frozen, or is it the speaker? I did want to respond to Dr. Gail's comment or question about how you know what ground truth is. And that is one of the questions we have in the series of questions today.

And I'll just throw out there that one idea is to monitor a patient after a negative result in the clinical study or in the case of a positive result, you're going to try to find the tumor. If you can't find it, then that would be a false positive. But in the case of negatives, you could use time. And monitoring the patient, you also could compare to any other tests that are done contemporaneously with this test, any standard care tests, any other sort of screening programs, any other reasons it could be fortuitous, they get an ultrasound for something else, and they find something.

So, with time as a factor, I think we have a specific question later on: what's the right amount of time to be able to assess in the best way possible without being overly onerous in the studies, to assess what ground truth is. Thanks.

Dr. Gallagher: Thank you. All right. Let's move on to question number four. OK. If per cancer evaluation gets recommended for those cancers with alternative recommended screening tests, how should the evaluation of the test for cancers with current screening methods be assessed? Should performance be compared to recommended screening, and then asking us to discuss the risks of having an MCD test that does not perform as well as the alternative screening methods? And if the MCD performance is significantly lower for a particular cancer, with all well-established alternative screening methods, should that cancer type be contraindicated for the test, though able to be reported if positive? And Stanley Lipkowitz, your hand's raised first.

Dr. Lipkowitz: Yeah, this may be the first time. Stan Lipkowitz from NCI. So, just to address this, I think the idea of doing one study and then answering all the questions is really compelling and all that, but I think this points to where the problem would come up because you really need a concurrent control where you have everybody getting their standard screening for colon cancer or for breast cancer, for cervical cancer, with or without this test.

So, it needs a randomized control because all of these questions are very important. Should you do the MCD test if, mammography is going to turn out to be much better than doing it, and the MCD might discourage somebody from getting their mammogram when that's the better test.

So, I think the only way to answer that question is a randomized controlled study. And even if the metric in that test is which one detects cancers at a better rate, again, the problem you're going to run into, and this addresses some of the comments that Tim just made, is that the sensitivity of these MCD tests is going to increase with time. But, even with the current sensitivity, it's quite conceivable that you'll have a positive test. The patient, in fact, may have cancer, but you can't detect it by imaging. And the current standard of care as a medical oncologist is you image patients and biopsy something to make a diagnosis of cancer. So a positive MCD test with a negative biopsy and imaging or negative imaging and no biopsy doesn't necessarily mean they're free and clear. It means you can't detect a cancer that you can meaningfully intervene on, so there are a lot of open questions about this.

I do agree with Dr Castle that, at the end of the day, it's clinical benefit that matters. And so it's going to be mortality or overall survival at a fixed time point since even in metastatic disease, we sometimes do well. But I do feel that you would have to do a separate or defined study that randomizes the recommended screening with recommended screening plus MCD, and as I heard from the speakers earlier, most of them were recommending that this was not meant to replace the standard of care screening.

Dr. Gallagher: Okay, and I don't see anyone else wanting to comment on this particular question. Nathan Winslow.

Mr. Winslow: Yeah, I would just add that I think it really goes back to the intended use. When we look at this question, and I think, as noted by the previous comment, or a lot of these tests out

there are intended to be complimentary. And when we think about other benefit risks, these are non-invasive tests. Whereas a standard of care could be, quite invasive. It could increase test compliance of those subsequent tests if they're complementary. Those are things I think that we'd want to take into consideration when looking at do you compare to current methods and standards and apply those to these MCD tests if, in fact, they're intended to be complementary, for example.

Dr. Gallagher: Thank you. And Peter Carroll.

Dr. Carroll: I think Dr. Castle just answered my question on trial design, and it was whether it was MCD plus standard of care versus standard of care or MCD versus standard of care. And I think you're mentioning it will be the MCD plus standard of care versus standard of care. Is that correct? Dr. Castle?

Dr. Castle: Yeah, we cannot not offer a standard of care, and we would measure whether people are adherent to a standard of care because of the issues that are raised. Yeah, we have to offer now one of the challenges, of course, as you can imagine that over time, there may be reticence to go to the standard care arm, and we're now wondering, we have a pilot study called Vanguard, which many of you may have heard of which will launch next year, which is looking at several of these multi-cancer detection tests, two or three.

Can we randomize? If we can't randomize the standard of care, then we have to think about an alternative trial design to do that, but regardless of the design, we would be measuring adherence to a standard of care and particularly important for cervix and colorectal, not to the exclusion of the other ones, but because those actually prevent cancer even a tradeoff of early detection versus prevention of cancer is especially concerning, I should say. So anyway, the point of the trial is to address many of the topics that were raised in our, will be raised in the rest

of the panel.

Dr. Gallagher: Thank you, we'll move on to question number five; two more questions to go gang in this topic. OK. What are the critical data collection and assessments needed to address potential bias? Please discuss the data elements that should be collected to address comorbidities for aggregated and per-cancer performance, as well as how should comorbidities and other conditions, which may lead to false positive results, be addressed in aggregate and per-cancer things such as cirrhosis, emphysema, inflammatory bowel disease, diabetes, smoking, obesity, and other diseases. OK. And, Karen Rue you – no, Mitch Gail, your hand is raised.

Dr. Gail: OK. It depends on the kind of study you're doing, but if you're doing these preliminary studies to try to see if it's a promising test, not the definitive clinical trial that Phil has been talking about, you want to make sure, ideally, you would have a sample from the target population, and you would have defined operationally what the ground truth is for that population. And then you would, you would see how the MCD performs compared to that ground truth. Now. Sometimes, though you, you don't have that. You do have case-control samples of various stages of the disease. You want to see, as Phil was saying, what the sensitivity of the MCD is over the spectrum of positive cases, depending on the stage of disease, and you'd like to also have data on the specificity not only in sort of healthy target population controls but also in people who have various comorbidities.

So those are some of the issues, and I think people have mentioned that there's a danger of using the case-control type data of overestimating the performance of the test compared to what it would have been if you had taken samples from the target population because sometimes the cases that you get in your case-control study are more flagrant or in some ways they've been detected as cases through methods that are not necessarily consistent with the methods that you

would use to define cases if you took a sample from the target population. So, those are some of the threats to unbiased estimates of sensitivity and specificity.

Dr. Gallagher: OK. Thank you. Other comments on this question? I don't see any, so we'll move on to question number 6. Should specificity be calculated on a per-cancer basis?

Dr. Gail: I think it definitely should excuse me, Mitch Gail. Sorry.

Dr. Gallagher: OK. And I see that Dr. Roscoe has raised her hand, so I'll let her say what she wants to say.

Dr. Roscoe: I just wanted to clarify that this request about the specificity on a per-cancer basis is tied to that issue of evaluating the comorbidities as well because the specificity of the assay for various cancers will be impacted greatly by those factors that are related to a specific cancer, such as cirrhosis for liver or diabetes in pancreas. So, I just wanted to let the group know that these two questions are related.

Dr. Gallagher: Thank you. And Carla Ballman, your hand was raised next.

Dr. Ballman: Yeah, I would say that it may not have to be the overall sort of thing that it's being evaluated on, but it would be useful information to have the specificity on a per-cancer basis.

Dr. Gallagher: All right. And Dr. Roscoe, your hand is raised again. OK. All right. Then, what I'd like to do is summarize a little bit about what we talked about in this block of things and make sure that Dr. Stenzel and the team have gotten what they need from us on it.

So, for the first question, there was a strong feeling in two directions. One was certainly that the mortality endpoint be strongly used for this and the other was that staging be included somehow so that there was a way to deal with the practical use by the physicians as well as the general idea of using the mortality endpoint score. The other aspect related to this was that minority inclusion was expected. And then the idea of pediatrics came up, and between the

comments that were made out loud verbally as well as in the chat, I think there's a notation that we think that while these tests have thus far been looking at adult populations that, perhaps separate things could be done for the pediatric population because there are ways that cancer acts, acts differently in children than it does in adults. But we don't want to leave the children out because there are so many children who do get cancer. Dr. Stenzel, do you need more on number one?

Dr. Stenzel: Apologies, I was trying to find the unmute button as I'm scanning the questions as well.

Dr. Gallagher: So the one on study design considerations when planning the clinical validation.

Dr. Stenzel: So the screen is showing question six, so it might be good to if the AV person can scroll back to, I think, slide number two for these questions… Yeah, that one.

I think we're good on this one. I think I'm going to have some follow-ups for one or two of the others.

Dr. Gallagher: OK. Very good. To question number two, please define how early detection should be defined. And here, we attached the idea of early to some kind of clinical relevance so that it would fit. There was some discussion, at least, about that clinical relevance being related to staging and how that might be used. Was there an intent to treat those kinds of things related to that question? That's really all that was said there. Did you need something else from us on that?

Dr. Stenzel: Not at this time. Thank you.

Dr. Gallagher: OK. And number three, one of our big long questions. Okay, so this is on the aggregate multiple cancers. And so basically, some kind of comparison between the current standard test and the MCD test and trying to find out if there was a way, talking about trying to

find out if there was a way to make sure the MCD test was better than some aspect of the detection so that we're looking at what would come next so that it would have to be the same or better than the current standard test.

And then there was also an element in there about possibly narrowing to groups of cancers so that when looking at the results of these kinds of tests, the clinical study design, maybe these things could be grouped into what kinds of cancers, similar organs, those kinds of things. And let's see if I can pull it up in the chat because it made a whole lot more sense there. It's not there now. Sorry, it's out of my chat at the moment. But it was related to that idea that perhaps there would be a way to design the study so that the types of cancers could be grouped together if that was at all possible. Nothing was really said about the minimum or maximum number for the determinations.

Dr. Stenzel: Yeah, so I think I do have two follow-up questions for the panel on this. One is for the four or five cancers that do have more standard-of-care screening. How important is it to assess the performance of an MCD submission to the standard of care? I think it was mentioned by one of the panelists that in order to have a claim for that specific cancer, I think the comment was that it should match or exceed the standard of care to be able to have a specific claim. You may have a claim that says overall, you can accurately detect cancer, but there may be sub-claims based on potentially performance cancer by cancer. So I think a little bit more input on comparison to standard of care for the four or five that have a standard of care.

Although one category of lung cancer is a high-risk population rather than a normal-risk population. A lot of the submissions that are coming in for MCDs may have just a normal-risk population rather than high-risk. So, the lung may be an outlier, and only if perhaps enrichment technologies are used to enrich for lower abundance cancer, maybe for lung cancer or others, to

get a little bit more data on a per cancer type. That's an additional question we had. But I think a comparison of the standard of care and a little bit more input on that would be helpful.

Dr. Gallagher: OK. Philip Castle, your hand was raised first.

Dr. Castle: Tim raises an interesting question. We actually went through this process of modeling this to say, what if we selected for smokers, and it turns out to be not a very efficient way of doing it because of the number of smokers that you would find, you'd end up doing a lot of screening to find people to get that smaller population and the return on investment's not great. But lung cancer is an interesting dilemma, I would say, Tim, because there's so little uptake of lung cancer screening right now. So the question I think back to you is. If this test increases the detection of lung cancer, hopefully, for mortality benefit, I'm not going to harp on that. Even if it's less sensitive, right? But because people are more willing to do it there may be, may cross over, if you will. It may not be as an effective test; it may be, may not be as efficacious, but it may be more effective, right? If you get my meaning. So that's something that you need to consider. For the other ones, there's really three or two possibilities. One, it could be a claim of a replacement. Let's take colorectal cancer as an easy one to talk about. So, for colorectal could be a replacement. But again, keep in mind that the main benefit of colorectal cancer is actually the prevention of colorectal cancer. It's not early detection. It's two-thirds of the mortality benefit is really the prevention of colorectal cancer.

So you'd have to show in some way that would be a very high bar for a company. Now, it could be they could claim an adjunctive use where adding this to routine care increases the detection of early colorectal cancer. But I think they would be hard-pressed to show the same benefit because of that prevention benefit. So let's see, breast cancer, but these tests right now are not performing particularly well for breast cancer. So it's a bit of a slippery slope, but I'll let

other people chime in on this good question.

Dr. Gallagher: OK. And Mary Margaret Kemeny, you were next.

Dr. Kemeny: I think that these tests are saying that there may be cancer present. They're not saying anything about what to do about it. And you, so comparing these with the standard of care like mammography or colonoscopy, you cannot take away the standard of care at this time. That's not what these tests are doing. These tests are saying there's a high probability of X cancer. And so, the cancers that we have tests for. Yeah, sure. We'd like to know if this test is positive. If this test is positive for breast cancer. Yeah, then the person will be sent for a mammography if they haven't had their mammography already. If lung cancer, they've said they're sent for a low dose cat scan. There are things to do for those cancers. For the other cancers, you have to look for them. But to say that you would take away the standard of care because of these tests, no, I would not be for that at all.

Dr. Stenzel: Yeah, I don't think anybody's saying that.

Dr. Gallagher: OK. And Mitch Gail, you were next.

Dr. Gail: You were talking about comparing with the standard, right? And I think the Cologuard example that was presented earlier today is a really interesting case because the data showed that Cologuard was performing better than FIT. Suppose FIT was the standard and Cologuard was the new kid on the block. You would have shown that Cologuard was performing better than the standard, but why could you show that? You could only show that because there was an even better test called colonoscopy that could be used to evaluate both FIT and Cologuard. So if the only thing that we have right now, let's say, for detecting breast cancer is mammography as a routine screening test, then the MCD test is going to be compared against mammography, but you can't show that it's better or worse than mammography because if mammography is the

operational gold standard. Unless you have a better test, you can't really compare MCD versus the current the current procedure, just as you couldn't compare Cologuard against FIT unless you had a colonoscopy in the background to decide which what was the true state.

Dr. Gallagher: Okay, Deborah Schrag, you're next.

Dr. Schrag: Yeah, hi; hopefully, I don't have technical difficulties this time. I feel like we've seen this movie before, and we're dancing around the issue of the distinction between efficacy and effectiveness. So we have screening tests, and colonoscopy is a great example that, when appropriately implemented is terrific because it's a screening test that also prevents polyps, which is the cancer precursor. We know from a recent randomized trial that. When you offer population-level colonoscopy screening, not everyone wants to engage in it. And that's where the drop-off between the theoretical efficacy and the actual effectiveness comes into play.

As we develop these technologies, these really exciting technologies, we have to really be clear about looking at both efficacy and effectiveness and distinguishing between the two. We can get really excited about a technology if there's efficacy. And, but we also have to look at the effectiveness, but I don't think we want to [...] if there are MCD tests that engage large members of a population that is currently unscreened or folks who are left behind. We know that current lung cancer screening, colorectal cancer screening, lung cancer leaves a tremendous number of people behind, and colonoscopy and mammography have a last mile problem where we still have, I don't know, up 10 to 20% of people who are recalcitrant and appropriate, but remain unscreened.

If these tests are more palatable to the public, that has to be considered as an advantage of engaging people in participation in screening for cancer.

Dr. Stenzel: Yeah, I would say that's one of the benefits that might accrue from something that is

picked up by more people. So the net benefit compared to, say, colonoscopy or CT scan for lung cancer is, can you detect the same amount of cancers in a population, given normal behavior, versus an ivory tower really pure study that forces everybody to do everything you do a direct comparison. So the goal is to detect more, maybe to detect more cancers in the population and that could be a benefit.

Dr. Schrag: Can I just want to make one other comment, which is that, and I guess this harkens back to a previous question. I think that the feasibility of operationalizing a metric, which is this is a cancer that doctors say we can cure. I think that is going to be too subject to interpretation and a very difficult standard to operationalize.

I agree with fellow panelists who said that stage-specific metrics are imperfect because not all stage 2 cancers mean the same thing, and you can have over-diagnosed stage 2 cancers for sure. But I do think that there are national and international standards that are staged for cancer staging that are specific to cancer type and histology. And I think that's much more likely to be feasible for implementation at a broad scale as a surrogate intermediate marker before cancer mortality, which we all know is the ultimate valid endpoint for cancer screening studies, but I think that stating that this is a potentially curable cancer is too subjective and the stage is imperfect, but a more feasible, reliable surrogate.

Dr. Gallagher: Okay, we'll take a couple more comments and then move on to the next question. Stanley Lipkowitz.

Dr. Lipkowitz: Yes. Stan Lipkowitz from NCI. Just to come, it's not this question per se, but something that was just brought up by Tim is that one of the issues is that the uptake of screening isn't perfect especially the CT and lung; I think it was 10 or 15% of total patients. So, a metric that has to be rolled into these MCD studies is the uptake of the workup that comes after it

because the workup after it is invasive in most cases. I think you can't ignore that. To say these tests are great because it's just a blood test and everyone's going to get them, you still have the downstream problem of, but then everybody has to get worked up.

I think as you look at these tests, that has to be incorporated into the evaluation. On a study, it may mandate: Phil, I don't know if your study mandates the workup and dictates what the workup is and funds it, but in the real world, these tests will be gotten, and then many patients won't go for the workup. I think that has to be incorporated as a metric of how well the test works because if you get the test and it's not responded to by the patient, I think or, or there are populations where it's not responded to, that's not a problem the FDA can fix, but that's a problem that has to be addressed as well.

Dr. Gallagher: Okay, and Philip Castle.

Dr. Stenzel: Dr. Castle, did you have a comment? He may have been lost to the call.

Dr. Gallagher: He seems to have disappeared.

Dr. Stenzel: Okay, and then if there's not any other comments on that question, I just wanted to follow up on the last question before we move on to probably a break and then come back to topic two is the questions under the second bullet here.

If we do a per-cancer validation, what is the minimum number of positive cancers per cancer that we would want to see? And we use enrichment. And what should be the sensitivity? And in order maybe to say I have a claim for that specific cancer and, and this would depend perhaps on whether it's a cancer that has a standard of care versus one that doesn't have a standard of care screen.

Any thoughts on the pancreas? How many pancreatic tumors should we request in order to make an assessment of, say, sensitivity? At least to be able to report that out, if indeed, it's

important to do a per-cancer evaluation for those that have enough minimum positives.

I think it goes without question that if any of these tests are approved, that, if there's a really rare cancer that, and it's just too rare to even show up in a large study, if it, for example, and it pops up as positive that, that should, that result should be acted on, it should be followed up on and not ignored.

Dr. Gallagher: OK. And Mitch Gail has his hand up. If you're talking, we're not hearing you; you got to unmute yourself.

Dr. Gail: Yeah, you could say, how many people do I need to have a certain precision on the estimated sensitivity, right? Not how many cancers do I have to observe, but how many people do I have to have studied in order to get a certain precision on the sensitivity.

And as just an example, if you took 100 people, and if the sensitivity was 0.7, you would have a precision of plus or minus. That's the 95% confidence interval, plus or minus 0.09 on 0.7. If you had 500 people, I think the confidence interval would be something like plus or minus 0.04.

So, the part of the answer to this question is how precisely do you want to estimate the sensitivity? I think a more difficult question, especially for MCD tests, is, how am I going to define somebody who in the target population has prevalent cancer of some type or another? Because those are the people that you would like to see whether the MCD test picked it up. But, the operational definition of this person in the target population has some kind of cancer. That's the real bugaboo.

Dr. Stenzel: Yeah, I agree. And yes, the larger the N, the more accurate the assessment of test performance. Wasn't asking for a threshold for super accurate versus you just getting a pretty good idea. I think if there's no more comments, I think we've gone well into our lunch break. And I want to thank the panel and the chair for this great discussion on topic 1.

Dr. Gallagher: Yes, as you can tell, we're not a quiet group. We have lots to say, which is a good thing, but we do want to stay on time. So we're going to break for lunch, and we will come back at 1.15 Eastern Standard Time. For those of us on Central Time, it's going to be 12.15, because I know I'm on Central Time, and I heard a couple other people say that. So we'll see each other then. Thank you.

Topic Two: Use of Tissue Origin (TOO)

Dr. Gallagher: It's now 1:19 Eastern Standard Time, and I'm calling this meeting to resume the meeting for the Molecular and Clinical Genetics Panel. And we're going to move on to topic number two of our discussion, which relates to the use of tissue of origin assays, or TOO, to help identify tumor location versus other methods and patient workup considerations following positive results and follow-up for patients with negative results. If we can look at those on that topic, and I ask anyone on the panel if they have any brief clarifying questions for the FDA before we start.

Okay, I didn't see anything, so we will go to the first question.

Question 1

When an MCD test identifies a cancer signal, a tissue of origin, TOO assay provides a starting point for follow-up to identify the tumor source. Which methods, either clinical and or laboratory, are acceptable to determine the possible TOO of a cancer signal detected by an MCD test? What are the risks of using CT or PET CT scans for repeated testing? And what is an acceptable clinical performance of a TOO test either as a diagnostic component of the original MCD assay or as a standalone test?

Now open for our discussion. Mary Margaret Kemeny, you're up next.

Dr. Kemeny: I want some clarification here of what I don't understand. First of all, different

cancers have different tests. So what are they asking exactly? What laboratory tests? What are they talking about?

Dr. Stenzel: Yeah, sure. So happy to address that question. So TOOs are part of some of the MCD Tests and some have them, some may not. And if they have them, you get a positive signal for cancer detected somewhere in the body or not. If you have a positive signal, then some of the developers have developed a follow-on test that basically says, yes, you had a positive result, and it's either this tumor type, or this tissue, or it could be a small set of possibilities based on some signature that they're looking at. If you're screening for any cancer anywhere in the body, one of the big questions in this technology is, how do you find that tumor, especially if it's a small tumor? And, if there is a tissue or tumor of origin part of the assay, then it certainly perhaps can help if it's performing well enough versus, say, if you want to do a PET CT scanning of most or all of the body rather than a standalone or an associated test. If developers of MCD technology want to do a TOO, then that will be part of the package that we receive, and we would evaluate that part for its performance as well.

Obviously, you might have a cancer detection test that does very well, but the TOO part might not do well enough, and that may not be able to be authorized. So that's what this pertains to.

Dr. Kemeny: But I still don't understand because, like for instance, a PET scan, they're very good for melanomas, may not be so good for GYN cancer. How can you say that the test is authorizing the TOO. The TOO is a standalone test.

Dr. Stenzel: No, if a developer of an MCD assay says we want to resolve where the tumor is using our own TOO test, it would be part of the FDA submission package. And we would look at its performance separately from whether or not cancer is active and accurately detected.

So cancer, yes or no, is that accurate? And then, if cancer is positive for those developers that have an associated test as part of their FDA package that says, we think it's pancreas then we would want to know how good it is at saying how accurate it is saying, yes, it's pancreas or no, it's not pancreas.

I hope that helps it. It may be the same or different genetic markers, depending on how they assess the tumor. And there are numerous different approaches to MCDs. And it's difficult to generalize. Some MCD developers appear to not have a TOO component, and they would potentially rely on imaging to localize the tumor.

Dr. Gallagher: Okay, Stanley Lipkowitz.

Dr. Lipkowitz: So again, thanks for that clarification because I had the same question. So you're not asking about the follow-on scanning that would happen with a positive test. You're asking if there's a molecular component that says this is cancer X, Y, or Z. I think that if they have a molecular test that's either incorporated or standalone in addition to their test, I think all of the same metrics that we've discussed for the other tests become valid, which is sensitivity, specificity, positive and negative predictive value. I don't see how it's any different from trying any test.

The issue will be that all patients will have subsequent, usually image-guided unless you're thinking of a melanoma that might be peripheral, but almost all of this is leading towards imaging. I would argue that if you have a TOO that says this patient has pancreatic cancer, it certainly would be reasonable, to begin with some sort of imaging that would at least concentrate in that area, but I think then to really prove the specificity and sensitivity of this test, you would have to do a more complete imaging because if the pancreas is negative, you need to know they don't know that this didn't detect a lung cancer and you just misclassified it. I would think that to

really define the benefit of a TOO, you'd need both the dedicated imaging that the TOO might indicate, but you'd need more broad imaging, especially if that's negative, to prove that your signal didn't come from another cancer. I guess if it's positive, it's less of an issue, but I think you would need some sort of global imaging.

Dr. Gallagher: Mary Margaret, your hand is still raised. Nope. OK. Then we'll call on Daneen Hesser.

Ms. Hesser: I would like to be very interested in an MCD that had a TOO attached to it as a patient from a patient perspective. I would be less reticent and less enthusiastic about one that didn't give us a point to start exploring. My concern comes from, access to rural communities to underserved communities. If there isn't a TOO attached to it, and maybe even a nice waterfall plot that tells us where we should look for a second, third, it is very hard to get PET scans scheduled in rural communities where that community center or academic center doesn't have a regular standing PET scan. So, that delays diagnosis even further. I think in underserved communities and senior communities now, with so many seniors shifting toward MA insurance coverage, it's going to be less likely that you can get a PET scan for an asymptomatic patient when you don't know where you're starting. I'd be leaning toward a lot more interest in an accompanying TOO.

Dr. Gallagher: Okay, Daniel Swerdlow.

Dr. Swerdlow: Yeah, it's Swerdlow from Georgetown. I'm the imager, so I guess this is where I come in a lot. I guess I would have some questions about a TOO that's incorporated as a follow-up to the blood test. If it's another blood test and what is it, is that going to be some established thing that we know about, like for the pancreas, the CA 99, or whatever, I don't keep up on all the tumor markers.

As well, but we know an AFP doesn't work very well for liver cancer, et cetera, et cetera. How, and this is a new territory where it's not really now quite a screening test because there's already now a positive test, but we're not exactly following up a tumor to look for tumor response and potential recurrence either.

So we don't know the performance, even if it's something we know about a test that's already existed. And if they're new tests, then they completely have to be validated. From the imaging point of view, a whole lot of issues get raised. I did some Google searching just to try to get some numbers because we've talked about rural settings and stuff.

And your point about PET in the rural environment is very valid. All comers, there's roughly one PET scanner per 100,000 in the United States. But they're not evenly distributed by a long shot. Almost all of them are going to be in larger population centers. And especially along the coast, and there's going to be many empty states in the middle that don't have a whole lot of PET, and somebody's going to have to drive hundreds of miles for it.

The other thing about a PET is, yeah, its whole body, but it doesn't find everything. We had an anecdote earlier today about a person who had undiagnosed renal cell carcinoma that's terrible for renal cells. It's also terrible for the prostate and a whole lot of other things. And, generally speaking, below seven or eight millimeters, it's not going to find stuff.

It's also bad in the brain. And there may be some very active things that it can detect less than seven to eight millimeters, but that's roughly its threshold. If these tests are really that good that they're catching stuff really early, PET isn't always the be-all and end-all. Another point that was buried in the paperwork that we got was should we have other countries involved in this? So that immediately raised alarm bells to me. If we have a problem with PET access in this country, it's not going to be better elsewhere. So I looked at what does Canada have? So we have

a PET for every hundred thousand. Canada has one PET for every million, and I don't know what the wait lists are to get a PET in Canada, but I bet it's a long time.

CT is much better in terms of access. There's 42 CT scanners per million people in the US. They're pretty ubiquitous here. It's not too hard to get in, but then it's not going to be as good at a lot of things as MR and PET. And then, we're going to start talking about radiation and whether or not you need to give IV contrast with contrast reactions. Kidney failure is not really an issue anymore, but so we have to think about radiating the population.

There are certain things it's really good at; we've talked about lung cancer screening. You can get by with very low-dose CTs and screen for lung cancer very well. I think there we can start to discount the radiation dose to a significant degree. But if you want to go find that pancreas cancer, you need a nice IV contrast bolus and a really good scan.

And other tests may be better. That's separate from actually getting a tissue diagnosis after that. This stuff gets tricky, really hard, especially if you're talking about trying to provide service to underserved populations. They're not going to have access to this. It's got to get paid for in some way. I would hope that this would all be paid for by the companies and their trial data, but eventually, it's got to come out into the real world, and then cost becomes an issue. I'm very sensitive to what happened with the CT colonography, which was an excellent screening test.

There's been a lot of studies that showed essentially it worked as well as colonoscopy. It's also been shown that simply if every physician in the country who's trained to do colonoscopy did nothing but colonoscopy all day, we still couldn't screen everybody who needs to be screened. We're only getting 50 to 60% of the population screened for colon cancer, and that was before we lowered the age to 45.

And the US Preventative Services Task Force basically gave it a failing mark, mostly, I think, on the basis of politics, and they were concerned about costs from incidental findings and papers that have largely debunked that. When I've had incidental findings, they're usually pretty helpful. I've found lung cancers and kidney cancers and aortic aneurysms and things that are useful to find. So there's a lot of issues in this and radiology is not going to solve them and it's going to create some more issues too. And that all has to be taken into account because there's going to be incidental things that you have to read very carefully and it's going to be hard to get a universal way to interpret these.

When I read a CT colonography, if I see gallstones, I mention them, but I don't recommend an ultrasound because it adds cost to the screening test, which ruins it. I only try to work up things I think are really probably bad. But not everybody's who's going to be reading these CTs, if they become ubiquitous, are going to read it like that. They're going to order extra tests, and I can see this: the cost is skyrocketing quickly.

Dr. Gallagher: Dr. Stenzel, did you want to reply?

Dr. Stenzel: Yeah, a couple things. Probably, PET alone won't do it. CT or PET CT might be okay. But, if a developer is going to say our test can detect cancer, they're going to have to find it. So they're going to have to probably find a decent method to do it, and the thinking is it's either CT or PET CT after you get a positive signal with or without, associated with the tumor of origin assay. The tumor of origin assay can either be built into the original detection component of the test, or it could be a separate component of their test. When they get a positive result, then they would do an analysis. It wouldn't be a separate blood draw; it wouldn't be sent anywhere else. They would do it. And the FDA would assess how well the test does at detecting cancer, how well it does to if it has a TOO, and how well it does to localize that.

To know how well it does, you're going to have to find the tumor. So if it says it's pancreas, but it's really lung, then it's good to know that, and maybe their TOO needs to be refined in some way. But excellent points. Otherwise, I think I covered what I wanted to say about that. Thanks.

Dr. Gallagher: Ok. The next person with their hand up is Rebecca Perkins.

Dr. Perkins: Hi, I'm Rebecca Perkins from Boston University. I just wanted to echo the importance of having tissue of origin to help people start to figure out where the tumor might be. if there is one. I think, especially if you think about this probably isn't a once-in-a-lifetime test. Is it once a year? Is it once every three years? Is it once every five years? If you have people getting a full body CT or PET CT scan every year or every three years or every five years for a positive finding, that becomes pretty quickly a very significant radiation dose and also a financial toxicity.

So I think having a place to start is really critical, and I would be concerned about the practical implementation of a test that just said, there's cancer somewhere in your body. Good luck.

Dr. Gallagher: To add to that comment, I know that working so closely with cancer patients that someone even suspecting that they have cancer and having to wait a couple of weeks to get an answer can drive them a little crazy because it's so stressful. So, I think the more that can be found in the test itself, the more helpful it will be rather than creating more fear as well as creating other things that have, that may or may not be actionable in the future. Peter Carroll.

Dr. Carroll: Hey, I just wanted to comment that I agree completely, and also in Pathfinder, the Galleri test did reasonably well on tissue of origin. I think they localized it in 88% of patients.

Now, obviously, once they localized the cancer, they didn't do all the other tests to see if they missed anything, but it actually performed very well.

And one thing Dr. Berry did not mention in his presentation and in his letter was the exact imaging scheme. He argues strongly that tissue of origin should not be a requirement, but what was not stated is what would be the diagnostic testing, which would flow from a test which was agnostic to the type of cancer. Because I think that's going to be very important.

Dr. Gallagher: And Mitchell Gail

Dr. Gail: You could create a panel of different cancers from different sites. And the panel might have the same proportion of the different cancer sites as you might expect in the target population. This is a kind of … and then, of course, then you can see how well the classification by the TOO corresponds to what this panel actually contained, so you can get misclassification rates.

But that's a little bit akin to case-control. We know these cancers, and we know their sites and everything. And then, we compose the panel. And then we test the TOO. If you had a sample from the target population, you could use a set of standard screening tests to decide if any of them had cancer, and if so, which, what their site was, because these standard screening tests are going to be site-specific. And then, you could cross-classify the standard screening test results against the TOO and see what the rates of concordance are. But those are things you could do to assess the reliability of the TOO component.

Dr. Gallagher: And Daniel Swedlow, your hand is still raised. Did you want to continue your comment?

Dr. Swerdlow: Yes. So, even if the test is perfect and they have a TOO test as a follow-up that is perfect at identifying the organ of origin, they're still going to need imaging to get staged to decide where they are. So, there's no getting around the imaging and other things that we do to stage a cancer.

Yeah, the TOO is great if it supplies it. I think that would be a big help because it would narrow it down, but we still need to figure out where is this thing? Is it operable or not? So, we just can't get around that.

Dr. Gallagher: OK. Thank you. And Karen Rue.

Ms. Rue: The only other thing I wanted to ask about was they talked about what to do with follow-up with negative patients and ask about the feasibility of having people that are negative have been beyond some kind of registry and ask them to report if sometime in the next X amount of years if they ended up with a cancer diagnosis that they would report back.

Dr. Gallagher: Thank you. Dr. Stenzel, did you get the information that you needed from this group?

Dr. Stenzel: Can we pull that slide deck back that one slide back up just briefly?

Dr. Gallagher: Sure, question number one in topic two. Thank you.

Dr. Stenzel: Yes. I think we would like to get more specifics around how accurate does the TOO needs to be. There was one mention of a study that showed an accuracy for one TOO of 88% getting it right. And/or the accuracy of imaging if there isn't a TOO, we'd like to understand what the panel believes would be an acceptable threshold. What does the panel say, that the FDA can entertain as far as what our expectations might be.

Dr. Gallagher: Thank you. Mary Margaret Kemeny. Your hand is raised.

Dr. Kemeny: Again, in clinical practice accuracy. For instance, someone has liver metastasis. You do a biopsy. The biopsy can only tell you it's an adenocarcinoma. It's a hepatoma. It doesn't tell you necessarily where it comes from. Sometimes, you can say it looks like it could be gastric, it could be pancreatic, but that's even a tissue.

An invasive test for diagnosis doesn't give you that kind of accuracy. I don't think we

can ask too much of these tests. But we can say, they can say, I imagine some of the tests that are available now, it looks like a GI adenocarcinoma. Could be pancreas, could be gastric. So, they can say things like that, but I don't know that they could pinpoint the organ. If they could, I'd like to be using it right now in my clinical practice.

Dr. Stenzel: One of the panelists mentioned that one of the tests at least reported in the literature was 88% accurate in identifying the organ. And again. The question before the panel is, does it need to happen?

Dr. Kemeny: Here's some cancers that you, for instance, melanoma; there's some cancers you can identify with some biologic tests, but others you can't.

Dr. Stenzel: Again, referencing the one test that was mentioned by panelists today, it does have, at least for the cancers that it says it can detect, it does have a TOO associated with it that in that study, it was reported to be 88% accurate. So even when there's a melanoma or whatever, that, that was the assessment. So obviously, it was not accurate in 12% of the cases, and the FDA would appreciate what the threshold of accuracy of either a TOO or imaging should be at finding the tumor, not necessarily classifying the tumor by subtype. In the lung, whether it's a large cell or small cell that would require something else, and sometimes, or it may have some tests that may have the accuracy. So, it's in the lung, and it's a small cell, or it's in the lung, and it's a large cell. So anyway, thanks.

Dr. Castle: So, I wanted to say something about the 88%. I can't remember, that it's been a while since I've read the article, but it has to be 88 or whatever. We really have to talk about the asymptomatic because many of those studies; those early studies, had a mix of symptomatic and asymptomatic populations, and really, the point is you have to look at what's actually being assessed. How did they, even in those cross-sectional? Oh, somebody corrected me; it's

asymptomatic. I should say it differently because some of those cancers were already found essentially.

The question is, what is the accuracy in the intended use population's intended use, which is it's not a cross-sectional study? It's, you come in, people are walking in the door, and how does it perform? And those sorts of cross-sectional studies always raised a flag with me in terms of how they actually identified those cases because it wasn't a random sample of the population, to be sure. The question is, what's the alternative? I guess what is the standard of care otherwise? And that, is there is the TOO better than what would be the standard of care? But it's, there is, it really is no standard of care. There really is no benchmark. It's like the question of how frequently should we screen these tests?

We don't have any data, and we have one test with more data because, but each test is going to be different. And it's going to depend on which test, which cancers they're going after, and I don't know that you can have a uniform recommendation.

Dr. Gallagher: Thank you. Deneen Hesser.

Ms. Hesser: My question is really directed to Dr. Stenzel. Is it possible if an application comes to the FDA that, for an MCED that does have a TOO attached to it and you need to know more about the validity of that tool, can that be added into a PMA and looked at afterward and, can they be given some guidance as to what you want to see in the future?

Dr. Stenzel: So, PMA pre-market authorization submissions, which is the category these tests would come in under, we do have the ability to ask for a post-market study. We may have enough information to authorize the test, but there may be open questions. Maybe because the sample size for some tumors might be too small or something like that. But yes, we absolutely can ask the company as part of the process to do a post-approval study; it's PAS for short, and

then they would go off and do that after they get their authorization, and then we would get collect data later, and assess that data.

Dr. Gallagher: Okay, thank you. Thank you for correcting me on PAS. So, I don't know how much help that was to try to get more specificity or not.

Dr. Stenzel: I asked everyone the way I could, thank you. One of the reasons to hold this panel is we're still really in the early days with this technology, and so we're trying to gather, not just evidence from the literature and other ways for us to know these things but to ask a larger community through having a panel like yourselves, allowing open comment to help us, accelerate our decision-making process when we do get an application going forward so that, we can assess the technology as quickly as possible and make a decision as quickly as possible. Great. Thank you. And I've received word from the team that some of these questions that we've answered a little bit in other ways, so we are able to move on to the second question in the group. Thank you.

Question 2

Dr. Gallagher: So, if an MCD test does not have a TOO component of the original MCD assay, which is some of what we were just talking about, what are the acceptable diagnostic alternatives to determine the tissue of origin? I think we've mentioned some of those, but if people want to add to that.

Okay, I'm not hearing anything. I'm assuming that we're still going with most of the time. We're talking about trying to image something. Oh, wait. I see Mitchell Gale has his hand up.

Dr. Gail: Just a comment that if an MCD test is positive, and we don't know how to assess the tissue of origin, then we really don't know how to determine whether it's a false positive or not.

We don't know what the positive is; if we can't answer this question, we don't have a positive predictive value. If we can't answer this question, we can't decide what the sensitivity of the test is, and we can't even talk of the negative predictive value or the specificity. We have to be able to answer this question to know what the true state of the patient is.

Dr. Stenzel: I would agree. We're talking about trying to identify more cancers. So, let's just say an MCD test was able to detect a cancer. But, the clinicians can't find it, but it's still there. Technically, in an FDA world, that's a false positive, but realistically, it's a cancer that isn't yet found.And if it's indolent, you may never find it. But if it is aggressive or malignant and grows, eventually, you will find it. Really, to make this technology really work, you want to be able to localize where the tumor is and find it so that you can have the greatest benefit.

Dr. Gallagher: Carla Ballman, your hand is raised.

Dr. Ballman: Yeah, I don't think I know if I have much to add, but I guess my question is, as I think was alluded to. It might be that these tests are much more sensitive than what our current sort of finding of cancer is like. They're finding things we can't even imagine. And so could there be a specified follow-up period for both the test positives and test negatives to make sure that within that period they remain, they become true positives because they did find something or were a little bit more assured that perhaps it's a negative.

Dr. Stenzel: The FDA would be very open to that study design. Likely, negative patients would have to be followed at some defined period rather than exposing a negative patient to a PET CT, a full body PET CT. The safer approach is to wait a period of time and ask a question later in the panel's discussion;, we'll ask the panel, what is the appropriate time that the FDA should expect to monitor for tumors and test negative patients. Thank you.

Dr. Gallagher: Stanley Lipkowitz.

Dr. Lipkowitz: Stanley Lipkowitz from NCI. Yeah, so just to make the point again, and I think Dr. Swerdlow was absolutely right. At the end of the day, there's going to be imaging to find the tumor. And I think as people come to the FDA with the study done but to plan studies, they should have a plan for how this will go.

It can't be haphazard. I think it has to be pre-specified that patients who have a positive test will undergo it. And then have an imaging plan or a workup plan. I think that would have to be part of the mix of any study. Now, it could be if the TOO was part of the test that we'll first look for evidence of the specified tumor. Not finding that, we'll look more broadly, but it would have to be there. There would also have to be statistics associated then with that would be considered reasonable efficacy of that part of the study. So, I think, I'm not a statistician, but I would think that all of this would have to be incorporated into the study on the front end.

I don't particularly like a model where you say we're going to do the MCD, and then we're going to let the patient go back to their doctor to have a workup because I think that adds such a variable to any study that you would do. So, it would really have to be specified, I think, in the study in a reasonable way. You can allow some alternatives where there are reasonable alternatives, but I think it would have to be specified.

Dr. Stenzel: And really, test developers, if there is a cancer, they want to find it. They don't want to not find it. Having a good follow-up method…

Dr. Lipkowitz: True, but as you've heard, so, for example, with an asymptomatic patient with a positive test, some imaging will be hard to get. So, it'd have to be pre-specified. And actually, how it's going to be paid for would have to be included in the study. Obviously, eventually, if this is a validated methodology, insurance will pay for it, but in the short term, I think that has to be part of the plan, and it can't be left vague. I think it has to be very specific.

Dr. Gallagher: And I would agree with that as well as looking at part of the safety factors for things. It's if someone is in a rural area or an underserved area and something is found in the MCD. For those follow-up tests, they may not be able to get them otherwise because of distance or whatever. So, some part of the planning for those for the clinical trials that go with those would have to involve how to get someone to and from some place and pay for that as well.

I know there are several cancer trials that require patients to travel to and from cancer centers, and they might have to stay overnight, things like that. And sometimes those are paid for, sometimes they're not, but I think that is part of the efficacy of the trial, but also the safety of the patients who would undergo such a test and have a positive response; they would need something possibly. So, I think that would have to be built into the study as well. Daniel Swerdlow, your hand is raised again. Go for it.

Dr. Swerdlow: Yeah, I'd like to take that a little further. In addition to it being part of any study protocol to establish the efficacy of the test. I think if anything ever gets approved, the referring or the physician ordered the blood test and is dealing with this positive result and talking to a patient needs to be provided with a workup algorithm that is specific to that test result. Because my experience is that there's an awful lot of clinicians out there who really don't understand imaging and are often ordering the wrong test or unnecessary tests, a lot. And this is all new ground, and everybody is going to be struggling with what's the way to go. There needs to be a well-defined pathway for the workup of these positive tests that is based on the likelihood of any particular test, so that people have some idea of what to do.

Dr. Gallagher: Thank you. And Philip Castle, your hand is raised as well.

Dr. Castle: Thank you. To Daniel's point, because it's such a new area, the NCI has an entire working group just focused, and this is both intramural and extramural scientists, a working

group on what we call the diagnostic odyssey. What should, even for our trial, what should we be recommending or what might be the best practice given that we don't actually know, right? We don't know if you get a positive test and it says Cancer X, and we've never had that before; what do you do with that information? Where do they go? How do you make sure they don't fall through the cracks of a fragmented healthcare system?

Particularly if you're going to be on a trial perspective and certainly in an implementation perspective you want this to be widely available to all populations that have get care in very different ways. So, I think that having that worked up, and that is part of any screening test; there's the test, and then there's the screening, right? The test is the IVD. The screening is the completion of care from recruitment to completing the diagnostic follow up in any treatment of cancer. And we shouldn't have to say that in this day and age, but we still do have to remind people that the test is only part of the of the whole process. It's a small part. It's actually the easiest part. But in terms of the TOO versus not and stuff, part of it is presumably that the TOO would ultimately reduce the harms of those follow-ups. How do you quantify that when there's really no comparison is a little unclear to me. But it is the fundamental principle here that the TOO would avert full body scans and things like that.

And I guess that would be the comparison, and maybe that's what somebody needs to do: how good is the TOO versus the full body scan. I'm just thinking out loud. I haven't thought all the way through that, but that's where I think it would be going if you wanted to prove that the TOO actually offered a population benefit. That it would reduce exposure to radiation or whatever things that would come with a full body scan versus a targeted and would you find cancer sooner and with a less invasive procedures, something like that.

Dr. Gallagher: Thank you. And Edward Bujold, you're next. Unmute yourself, please.

Dr. Bujold: I would like to just reiterate a comment that Dr. Swerdlow made. You know, In the primary care setting, particularly in rural areas, it may be a little hard to believe, but when you have one of these tests come out as a new test, it's generally 10 to 15 years before it actually gets to the place where people in the primary care center are using it, much less understanding it. And I think it'd be very important because I would envision the primary care force ordering a lot of these tests, and it would be very important to have guidelines set up. I frequently call my radiology colleagues when I'm not quite sure what tests I should order. And it's very valuable information for me because they know a lot more about imaging and its pros and cons than I do. But I can see just a whole Pandora's box opened up about people ordering tests inappropriately, and they're costly, and here you order a test that really wasn't the right test, and so I think it's really important to nail that all down if you can before, you go too far down this rabbit hole.

Dr. Gallagher: Thank you. And Mary Margaret Kemeny, you're next.

Dr. Kemeny: A lot of what we're talking about is fixing the whole medical system as it is. And we're not going to be able to do that here. For instance, let me just say I'm in a city hospital in New York City. There was one PET scanner in my hospital for all 11 public hospitals. The PET scans are not available to people without insurance. So, you can't just say you, you're going to do PET scans on everybody that has a positive test if they could even get the test to begin with. That's the first thing. The second thing is, I just want to point out to the FDA that delaying these tests from coming into the market, obviously they, need to be good tests, and all these things have to be looked at, but it hurts the underserved the most. Because these people are the ones that cannot afford these tests in any way, shape, or form right now. Whereas the people if the tests are made somewhat reasonable enough, even maybe a few hundred dollars, a lot of people can get it, but the underserved can't. So, we have to keep that in mind. We have to keep

those people in mind because these people have been underserved and will continue to be underserved if there's a lag in these tests coming into the market.

Dr. Stenzel: Yeah, we're wanting to accelerate the access through events like this, and as I mentioned earlier, we're exceeding all of our under-law requirements for FDA time of review in fiscal year 23, and we appear to be carrying that forward as well.

So, part of the question is, and I think we need to move to the last question in this topic pretty soon as well: if not CT or PET CT, what should be the imaging modality? The FDA is interested in diverse populations, both geographically and in the underserved and as well as ethnic groups.

If not CT or PET CT, then what are the imaging modalities or other modalities that could be used to localize the tumor? Because, again, if whether or not there's TOO, you need to find the tumor. And so, how are you going to find the tumor if the test detects it?

Dr. Gallagher: Thank you for that. I see Deborah Schrag's hand is up at the moment.

Dr. Schrag: Yeah, so I just want to say this is a really critical topic because finding the tumor is so important. I don't think that we are going to get to one answer here: PET CT or CT. Part of my day job is treating gastrointestinal cancers, and we work up the metastatic tumors, or they're often metastatic of unknown primary origin, and to Dr. Swerdlow's earlier point, we have to use CT, whereas colleagues in other areas prefer PET CT, so there's variation, and it depends, and CT and PET CT are good for different things. But really, what we need to use is clinical common sense, and I think that developers of this powerful technology can really assist both through developing good TOO tests but also through providing frameworks that provide guidance to primary care physicians, particularly those practicing in underserved areas, and often these days we're talking about generalists, family physicians, APPs, people who are working in minute clinics because there are different factors. Some of those factors are endogenous to the test. But

some are endogenous to the patient. So, if you have one of these tests in somebody with red hair and freckles, you're going to be thinking melanoma or somebody who works out in the sun and who's a farmer with heavy sun exposure. So, they're individual patient factors that are going to influence the workup. And I think the educational tools that come along with this technology are going to be really powerful. And we go, we jump straight to imaging. But we also need a history of obesity, sun exposure, and some of the basic risk factors that will point to clues because the image tests you order for renal cell and melanoma, as previously mentioned, are so different, and many clinicians know that, and some will need a refresher.

Dr. Gallagher: Thank you. And Daniel Swerdlow.

Dr. Swerdlow: As far as alternatives to the high-end, expensive imaging modalities, it's going to be really tough. Decades ago, we tried to do chest X-rays on smokers to screen for lung cancer, and it failed miserably. Then we reinvented the wheel with CT, and CT is better. It works. And that's been shown. Ultrasound is used as a screening test in high-risk populations for HCC, people who have hepatitis. And it works reasonably well. It's not fabulous, but it does work, and it's the best we got right now. MRI is just not practical for the number of people out there with hepatitis.

Ultrasound fails pretty badly when people start getting heavy, which is a big problem. X-rays aren't really going to cut it. So, we're left with our expensive stuff. And it's not likely to get cheaper to do this stuff, and if the demand goes up, we can bring the price down in terms of that, but people have to buy more scanners, and you have to have enough radiologists to read them, and there aren't enough, just like there aren't enough GI docs to do colonoscopy out there. There are simply not enough doctors for the rate of population growth, and we're not training them enough. It gets very systemic very fast. There's not going to be cheap imaging ways to work up

most of this stuff with any technology we have now. The only way we can keep the cost down is if the MCDs and their associated TOOs can narrow it down enough that we can do a short and efficient workup and, most of the time, quickly get to the answer.

But if you try and do a whole-body MR, which has been in the news lately, or a whole-body PET or a whole-body CT scan, by definition, not for PEPA, for the other two, by definition, you're not going to image any one thing very well. So, A, you might miss a lot of stuff, and B, even if you find it, you still really haven't answered the question of whether this is going to be resectable or not.

Yeah, okay, I can see there's a pancreatic cancer. And I can see where it is, but I can't really tell if it's encased in the superior mesenteric vein and if it's inoperable or not. And it really comes down to a few millimeters of tumor here or there, and you need a really good quality CT or MRI that's dedicated to staging pancreatic cancer to do that. It's just not going to be an easy answer to all of that.

Question 3

Dr. Gallagher: Okay, thank you very much. We're going to move to our third question in this segment. And. So, if our AV colleagues would pull that up. Thank you. So, this is the time when we look at what is the clinical truth for tests without other methods and for tests with other methods.

Let's consider that. I know that we've mentioned several different types of imaging and what MCEDs are whatever, but I think we need to take a few moments to look at this question. So, how should truth be obtained for test negatives? And for those without alternative methods, is there a minimum follow-up period, and should a second test be taken at the end of a follow-up period, by, for example, one year, two years, three years, a time frame?

One of the questions that had come up that had been made earlier was that, for example, CT and PET, getting those over and over again might possibly be too much radiation for people. So, I think just think about those kinds of things as we are looking at this question. Rebecca Perkins, your hand went up first.

Dr. Perkins: Hi, this is Rebecca Perkins. I'm from Boston University. And just to make sure I'm answering the right question. For test negatives, you mean someone who is negative on the initial blood test, so there is no sign of cancer on that initial test and how do we make sure it wasn't a false negative?

Dr. Stenzel: That's correct.

Dr. Perkins: OK. Thank you.

Dr. Stenzel: Many of the reports in the literature on MCD tests right now show that it doesn't detect all cancers and I think Dr. Castle mentioned that as well earlier. And so how do you know how do you know it's a false negative if you don't do some sort of assessment?

Dr. Perkins: I was thinking that you would want to make sure in these trials that all of your patients were getting all of the other recommended screenings so that you could see if it's missing breast and colon and prostate and cervix and all of the other ones, and lung, and all of the things that we actually can screen for. And other than that, I think it's just a matter of monitoring over a certain period of time to see if any cancer becomes detectable. And for a lot of these cancers would become detectable at an advanced stage that you would hope would have been picked up at an early stage where it could have been treated and potentially cured because, as we talked about earlier, if it's detected at a very late stage by the blood test, then you may not have done anyone any favors.

Dr. Stenzel: Yeah. If they monitor the negatives over time and they find a tumor, then at the time

the tumor is found, then they'll do an assessment of where the tumor is, what the origin was, and at the time of diagnosis, what the stage was, right? It doesn't mean that was the stage at which the false negative occurred. It's just the stage at which the cancer is detected clinically.

Dr. Perkins: But you would hope, if we want these MCDs to be effective, then we would want them to pick it up at earlier stages. So, I would call it a false negative, if someone had a negative MCD and then the next year they had stage four pancreatic cancer, I would say there's a good chance that was a false negative MCD test.

Dr. Stenzel: And that's difficult to assess, right? If it's stage four, then probably a year prior, it should have been there. Yes, if it's stage one, if you detect it, if you say the follow-up is three years rather than one year, and you detect stage one tumor at three years, maybe that was not a false negative. And that's why the FDA is asking for what is, what is the proper time period between the original MCD test and the study for negatives what period of time is the optimal period of time to assess whether that is a false negative result or not.

Dr. Gallagher: Philip Castle.

Dr. Castle: Yeah, I think Rebecca hit on some of this. It's time, but it's also going to be organ-specific. It's going to be the natural history, which we don't understand. This is why we need to do the trial. This is why I've expressed my concern. It's not just the mortality benefit or not, but all of it, in terms of bringing it into the public without all the data, knowing what a negative result means, and the next question is, what's the interval of screening after that?

But, also to your point, Tim the traditional way to adjust for this is to do the statistical way is to do a verification bias adjustment, right? So, you send some of the negatives to whatever the workup is. But that's not going to happen in this context. You're not going to do a verification bias-adjusted clinical performance, I don't think. And particularly if it's TOO because there's no

TOO to incorporate, right? Because it's a negative. So then, are you doing full body? So, I don't know that you can uh, do a verification adjusted analysis.

I think it's really going to require time, and then you're going to have to make some sort of modeling approach to whether this was more likely. I'm using the term likely with emphasis here because it'll be a span. The early ones. I agree, particularly if they're late-stage and likely to be missed prevalent diseases. The ones later at a lower stage are likely to be truly incident. And it's going to be different for each cancer type. So, what we've seen in the natural history of pancreatic cancer is our ability to find anything the year before you're completely normal negative, and then you show up with stage four.

Now, did they have? Stage one, the year before, we don't know because we haven't had the ability to look at it. It's really complicated. It's going to be really organ-specific, and our ability to find it and diagnose it is also going to influence our understanding of that natural history and whether it's false negative or true negative, and what's the time frame. Sorry, I don't have answers. I have more questions than answers.

Dr. Gallagher: Okay, and Mary Margaret Kemeny.

Dr. Kemeny: I think, time obviously is one way of doing it, but it may take a lot of time. But I would think one of the ways is to do the test on a cohort of patients with known cancer and some of the early-stage cancers to see if there are false negatives in those groups because that would be one way of doing it. And, also possibly repeat the test just to make sure there isn't a mistake in the test also. But I certainly don't think you could work up false negatives. That would be just too time-consuming, and I don't think we'll give you enough answers.

Dr. Gallagher: Thank you. Does anyone have any comments about how often the test should be done? Stanley Lipkowitz.

Dr. Lipkowitz: I guess my only comment would be we have no data that, and I think Phil has said this a number of times, I have no way of making a judgment on that should you screen people once a year, which is frightening to think about, you could wind up with CTs every year, once every three years, I don't know how we even begin to give that number.

I would just be pulling it out of something if I gave it to you. I don't know if anyone else has a better feeling for it, but I just don't know how we come to that number.

Dr. Gallagher: Okay, Peter Carroll.

Dr. Carroll: I'm in total agreement. We don't know the latency for so many of these cancers. We do know them for a few cancers, prostate and breast, but we don't know the latency period well for pancreatic and other types of cancer. So, I agree. I would probably err on the side of yearly, but we just have no idea how we would estimate latency for cancers we know nothing about.

Dr. Gallagher: Thank you. And our last comment on this question, Mary Margaret Kemeny.

Dr. Kemeny: I agree with the other two, but yearly seems like it would be a good way of doing it at this point.

Dr. Gallagher: Ok. Thank you everyone. I think it's time for us to take a break for the moment. And I'm thinking we should probably make it a 10-minute break at most. So, if everyone could be back, it is now 2:20. So come back in 10 minutes. Thank you.

Topic Three: Benefit/Risk Considerations

Dr. Gallagher: It's now 2:30 and I would like to resume the panel meeting. So, we're going to begin with topic number three, on the benefit-risk considerations including post market study considerations. Please note that there are 11 questions to this topic, so we're going to look at this and I'm reminding everyone that we need to identify ourselves each time we speak to help with the transcription.

Question 1

Let's show the first question. Thank you. FDA must be able to support that the probable benefits of a test are greater than the probable risks, to determine the test is safe and effective. Please discuss the following. What is critical to determining benefit? How should we weigh the benefit of potential screenings of more patients? What performance is necessary for overall performance to make this determination? What is minimum specificity, minimum sensitivity, and what are the risks of false negatives and false positives? Does anyone want to begin our conversation on this topic? Mitchell Gail.

Dr. Gail: I think that this really gets back to some of the issues that Phil raised earlier. To show that the probable benefits of the test are greater than the probable risk, you really need to know what the ultimate effect of what doing the test is going to be. And that means knowing, if you get a positive test, you have to know what the plausible interventions would be and how effective they are, given the positive test result, for a range of cancers. And, really, the best way to obtain data of that type is probably the randomized trial that Phil was talking about earlier, with mortality as an endpoint. And really things like minimum specificity, minimum sensitivity: we've seen how hard it is even to define these, for an MCD, because of the operational difficulty of defining the true state of the patient. And again, the risks of false negatives and false positives depend very much on the specific cancer, the nature of the follow-up for a false positive, and the availability of damage from an intervention to a false positive. If you have a false negative, one of the potential downsides might be that you would fail to use a conventional test which would have detected the cancer. And so, I think that this is a very difficult question. But ultimately, you really need trial data against an alternative screening strategy to determine whether there is a benefit.

Dr. Gallagher: Thank you. Dr. Stenzel.

Dr. Stenzel: Yes. There's another kind of analysis that the FDA does, because we never have complete information. There's never going to be a perfect test, and we have to make decisions in a relatively timely way. So, we do an uncertainty analysis. So, what do we know? What do we not know? How big is the uncertainty level? And how does that fit into the overall probable benefit versus probable risk?

Dr. Gail: I'd just like to make one more comment; a little bit more positive comment. Suppose we're going to use the MCD test because it's cheap and widely accepted. But we're only going to use it: let's suppose that we're trying to improve coverage of colorectal cancer screening, but we use a little blood test. If the blood test is positive, we do it. And it also has a TOO that also indicates colon cancer. Then that's a very specific application. It's really to broaden the coverage of what are already pretty good standard tests. And we would know how to follow up that result very easily, because we know how to evaluate somebody that's at high risk for colorectal cancer. That's a very different use of MCD tests, as more or less a preliminary screen, when tied to a TOO for a specific cancer. And in that setting, we could evaluate risk and benefits quite easily. It's just that when you try to do a global MCD test, you get into all these problems that we were talking about earlier, and it makes it very hard to assess risk and benefit.

Dr. Stenzel: It would be good to hear from the panel, what are their beliefs, opinions on the risks and how severe a false positive or a false negative.

Dr. Gallagher: This is Colleen Callagher, and I'm relating this to the, I mentioned before, the fear that patients have. I think that a false negative is actually more difficult to handle than a false positive. Because a false positive, you're going to follow up on that, you're going to, you're going to see something, and you're going to follow up, and you're going to get an answer. A false

negative, the person may, of course, continue to have the cancer, if they have cancer, continue to develop it, and those kinds of things, which is much riskier to their overall health. But, in terms of fear, it's bad either way. A false positive or negative is never good for a patient to have to experience, so we would want to reduce those as much as possible. Mary Margaret Kemeny, your hand was raised.

Dr. Kemeny: It's very hard to say what the risks are for false positive, because it depends on what it's saying, where the cancer is, and what tests have to be done. Again, some tests are more invasive than others. If it's just a question of a CAT scan, then that's not that invasive. Obviously, it has some risks. But doing a more invasive test is much more risky, like for instance when there's a lung mass, and then if you have to do a lung biopsy, that is already much more invasive and much riskier. It's very hard to make that kind of a judgment.

Dr. Stenzel: You see some of the difficulty of our job.

Dr. Kemeny: Absolutely. It's very complicated.

Dr. Gallagher: Karen Rue.

Ms. Rue: As everybody's talking, it makes me wonder. We already currently have, in our cancer screening tests, false positive and false negatives, that we handle, and some of them are more invasive than others. We have false positive mammograms and you go in and have a biopsy done and it's still negative. So that is not something that we're not currently doing already, and it varies depending on what you're finding. It's colonoscopies, you go in and you take out stuff and some of it's negative, even after you've seen it. So that's not a new thing in doing screening tests.

Dr. Gallagher: Thank you. Deneen Hesser.

Ms. Hesser: And from a patient advocacy perspective, I don't have a problem with well-

educated patients. And there's a caveat to that: making a decision as to what their acceptable risk level is. I would be a proponent of a health care professional training program that coaches physicians, nurse practitioners in what should be discussed with the patient, setting realistic patient expectations before the test is done. Explaining to them the risks of false positives, false negatives. And then letting the patient share in that decision as to what their risk level is. So, I think you can mitigate some of that false positive, false negative data.

Question 2

Dr. Gallagher: Thank you. Now, if we can have A/V pull up question number two.

Dr. Stenzel: We may be able to skip question two, because I think we have had some discussion.

Dr. Gallagher: We did talk a little about this, but what is the definition of early stage, and what supportive data is needed for a test to be defined as an early-stage detection test? Does anyone want to add anything to what they said earlier? Stanley Lipkowitz.

Dr. Lipkowitz: Stanley Lipkowitz, yeah. So, I think that, unfortunately, there's not going to be one size fits all. I think, in breast cancer, we consider stage 1, 2, and many patients with stage 3 as curable. To me, those are all early stage, but that varies by cancer as to what is the risk and the curability of the patient, and the benefit to the patient. I think that would almost have to be defined on a cancer-by-cancer basis, in terms of what is the approach, in each cancer, to patients with a given stage. In most cancers stage one is likely to be curable. When you get to stage two and three, that varies tremendously. If you look at pancreatic cancer, as an example, the fall off; there is some cure in stage one, of about 40 or 50 percent I think is the number that I've seen/ And again, yeah. I think that's going to vary from cancer to cancer.

Question 3

Dr. Gallagher: Thank you. Alright, let's move on to question number three. Should MCD test developers pre-specify a fixed specificity to support a low false positive rate? Dr. Stanley Lipkowitz your hand is still raised. I'm not sure if you wanted to speak to this question or not.

Dr. Lipkowitz: No, just forgot to put it down.

Dr. Gallagher: Okay, that's fine.

Dr. Gail: I think that there has to be some criteria, yes. Because you could have an MCV test that says everybody has cancer, and it's going to have a very high sensitivity, and now you just have to find the cancer. But that would have a very low specificity, right? So, you have to have some reasonable criteria for avoiding false positives. And the only question is, how do you know that the person was truly negative when the test gave a false positive? And that all depends on the workups that we've been talking about earlier. So yeah, it's tough, but unless we know that these tests, MCD tests, with very high probability do not give false positive results, we're going to create an avalanche of useless medical procedures.

Dr. Gallagher: Rebecca Perkins.

Dr. Perkins: In one of the preliminary talks, the person said that in the health system they had screened 1600 patients. 14 were positive, 11 had been worked up, and there were five false positives, six cancers, three of which were early stage. So, that would be a number needed to screen of about one per 500. Is that generally around the performance of these tests, or was that just one off the cuff number?

Dr. Stenzel: I think what you're asking, first of all, is what is the incident cancer rate in an average risk population? And I don't have that at the tip of my tongue. And then, what percentage of those incident cancers does the MCD detect at what stage? The percent positive

detection in a study is probably somewhere, and it's going to vary depending on the risk categories of the study. But if it's entirely low risk, it may be well below one percent. So, we're not talking about detecting a ton of cancers. And the higher the specificity, so, if the specificity is well over 99%, then that tells you the false positive rate. And if a test is more than 99 percent specific, then that false positive rate is less than one percent.

Dr. Kemeny: You used the number 99 percent specific and I think it might, in answer to this question: if you know some idea of the prevalence of the cancers you're detecting in the target population, specificities like 99 percent might be needed to get good positive predictive values. So, that may give you some idea of what kind of specificities are required; typically very high.

Dr. Stenzel: Yes, I would agree. To maintain a high predictive value in a low-risk population when you're screening a lot of people, you do need a very specific test.

Question 4

Dr. Gallagher: Okay. Can we move on to question number four? Or does anyone have anything else they want to add to question number three? Okay, we'll move on to four. So, please describe the anticipated follow-up for a positive result in terms of diagnosis, number of procedures, and repeat testing.

Dr. Stenzel: So, we haven't discussed this before, but it would be good to understand from the panelists who have expertise in the area, of what would the diagnostic path be after a positive result? And how difficult would it be? A little more granularity perhaps. But I know we talked a lot about this, and that it's not one size fits all, and not all technologies are as good as others.

Dr. Gallagher: Mary Margaret Kemeny.

Dr. Kemeny: As was mentioned before, and in clinical practice, like if a woman has a positive mammogram, she wants like it out the next day. It's like, people get very upset when they think

they have cancer, and they want it to be worked up as soon as possible. So, we're not talking about a long period of time. If somebody has a positive test, and the patient knows about the positive test, it needs to be worked up as quickly as possible, usually meaning weeks to months, but not longer than usually two months.

Dr. Perkins: What if somebody just says to you, I think you have a cancer? What do you do?

Dr. Kemeny: What do you mean by somebody?

Dr. Perkins: Somebody has just gotten their MCD result test and it says, I think you have a cancer.

Dr. Kemeny: If you're the doctor, if they are asking me that and this is a test that is a legitimized test by the FDA, then I would say the test shows that there's a high probability you have cancer, so we need to look for it, or we need to do such and such. And then, yes, obviously it's up to the patient, as to what they want. But, in general, as I can tell you, patients are usually very eager to have it proven that they don't have cancer. If they do, they want something done about it.

Dr. Perkins: Yeah, but, in this question that we're being asked is, what would you recommend to that patient, how much testing and everything?

Dr. Gallagher: Oh, Peter Carroll.

Dr. Carroll: That question, I think, it depends on whether they're symptomatic, asymptomatic, or do they have risk factors. If it was a chronic smoker, you might lead with lung CT. The problem is, if you have an asymptomatic patient with no risk factors, no family history, then I think you're really in trouble. That's why I think tissue of origin makes it much easier. So, I think if you have someone who's got no risk factors, they don't have tissue of origin, no germline results, then you're in for a big workup. I don't know if it's body seat, body MR, or, you might

screen for the common cancers first. So, you'll ask them whether or not they've had a standard of care. Can I make one additional comment on the question that was asked earlier real quickly?

Dr. Gallagher: Certainly.

Dr. Carroll: The one point, that, when you look for stage shift per cancer, the problem is that the prevalence rate of these cancers are going to be low, and the benefits may be an accumulative avoidance of cancer. So even in Pathfinder, I think it was 1.6 percent positive. I think they had five breast cancers. I think it was, I don't know, two pancreatic or esophageal. So. the number in each study is going to be low. I don't know that you can do a per-cancer estimate on stage shift, and you might argue for this operational definition, of a global shift in cancers, because of the relatively low prevalence of a lot of these cancers. I don't know if I made that clear enough.

Dr. Gallagher: Thank you.

Dr. Stenzel: To me you did.

Dr. Gallagher: And that's what counts. You guys are the ones that got to understand it, right? Okay. Rebecca Perkins.

Dr. Perkins: I think this underscores the importance of having the tissue of origin in the test, and also someone earlier alluded to having the follow-up protocols be part of the... I don’t know if part of the FDA approval, but certainly part of the way it's rolled out to clinicians, so we'll know if the test is positive. Hopefully, you have tissue of origin, and then you do XYZ for that. And if you don't have tissue of origin, then you do all the recommended screenings and a full body MRI or whatever it is. But it should be very standardized, so there's not very much guessing, and hopefully should be part of the way the trials are designed. Although they may be designed to have more workup than you'd want to do in clinical practice. But, if they're getting CTs and MRIs of their entire bodies, and then they find out that 85 percent of the time it's the

abdominal CT that shows you whatever it is, then maybe you start with that in clinical practice.

Dr. Stenzel: Yes, and the FDA has flexibility in the language. So, if there's a method of imaging that's applied overall in a study, but we see that the more focused imaging might be beneficial, we don't have to make such a strong recommendation that that whole body PET CT is needed.

Dr. Gallagher: Alright, thank you. Deborah Schrag, your hand's up.

Dr. Schrag: Yeah, so I just want to say that I think that there's a lot we can learn from history, because even though these technologies are new and exciting, there are a lot of analogies to existing screening technologies, and I just want to focus for a second on cervical cancer screening. Women all over the world get an abnormal screening test and then, let's just take the United States, there are approaches to working up an abnormal pap smear. It could be cone biopsy, or colposcopy, it could be repeating the pap. It depends on risk factors, but there are algorithms that have been developed, there are teaching tools, there's educational materials. Women who find that they have an abnormal pap smear get really anxious. But because partnerships with organizations, there's the ACS, but that's only one, the American College of OBGYN, many organizations have developed companion tools to help primary care physicians, OBGYNs, family physicians, APPs, cope with what it means to be told that you have a positive pap smear, and help work those up, which sometimes includes waiting and repeating the test. It's going to be an analogous process here, where it's not just the test and the TOO companion that may accompany it, it's the suite of communication tools to help physicians and patients act on the information. And I think having industry partners really develop the companion, support teaching tools is going to be critical, and make the power of the technology even greater.

Dr. Gallagher: Thank you.

Dr. Stenzel: Thank you, I think that addresses that question, if you want to move on.

Question 5

Dr. Gallagher: Very good. We will then move on to number five. AV folks, we'll see number five please. Thank you. What is the anticipated frequency physicians would order an MCD test? Does this depend on having received a positive or negative result?

Dr. Stenzel: If you've previously received a positive result, but you couldn't find the tumor, does it make sense to test again at one year? And then, as far as a more standard screening program, if you're negative and have any incident and cancer in between, what are the thoughts about how frequently this test should be used?

Dr. Gallagher: Thank you for the clarification.

Dr. Perkins: I think we covered this earlier. There's really no data. Ideally you would, the follow-up of a positive versus negative would be different, if there's significant risk reduction, or significant risk stratification of the test. But also keep in mind that these have been set to be very specific. Population reduction and cancer risk, or the differences, may not be as great. My opinion is that these tests are much more like a diagnostic, in terms of the way they've set the cut point, than other screening tests. And the example going back to cervix, we screen with HPV, not because it's immediately more sensitive, but because the rule out allows you to extend the screening interval, and then you have to do a secondary test to decide whether they need immediate colposcopy or follow up. So it's actually a three-tiered risk stratification, which I've mentioned to the companies. They haven't really bought into this idea that you could have a lower and higher threshold. But I don't think we have enough data to make a recommendation of how frequent. We need the data to drive the evidence. It’s not the other way around.

Dr. Stenzel: This question, I just want to clarify, is in the benefit risk topic area. Let's just take it as a given that we're not going to have a large enough study to answer all of the questions that we would all like to have, and when something comes into the FDA and we have to make a decision. So, there are mitigating things that we can do. For example, if there was a positive test result and they did a full body workup and they couldn't find it, there's a residual risk, right? That there could still be a tumor, and they just haven't found it. What can the FDA do, in the course of the authorization, to mitigate that risk? So, one of those could be to say follow up testing at one year.

Dr. Lipkowitz: I agree with that. I agree that in the positive realm, having a yearly follow-up essentially until you get resolution. The signal goes away, you find the cancer, makes a lot of sense. I think the harder question is, if you're negative, do you extend the screening interval? That would ultimately be the ideal and I suspect what would happen is if you did the trial with one year interval, whether they were positive or negative, or whatever interval, pick one. You would find the first round you get many more, the positive predictive value of clinically relevant disease would be the highest. Then the next time you did it, it would be fewer actual clinically relevant findings. You'd have more false positives. And then you'd say that seems like too many false positives.

So we should extend that screening interval for the negatives, something like that. I think you're going to have to inch your way out. Because we just don't have enough data. Or you say, I'm going to do one year interval for the positives and two years for the negatives until we have evidence otherwise, that would suggest shortening or lengthening intervals. I think you have to put a stake in the ground and do something. And then, unfortunately, you're going to find out whether that was a good guess or not. I don't see how you do otherwise. I think it's reasonable to

assume that if you're positive on the whole, you're at higher risk than if you're negative.

Dr. Stenzel: Let's say though that you're negative. and then the overall study shows that the overall sensitivity is, let's say, below 50%. So, we know that if the test is used out there, it will miss more than 50 percent of the tumors. And part of the benefit risk situation is, what do we recommend? So, I think what you're saying melds more into the practice of medicine and what are the professional guidelines, once we know more about the technology. But one of the challenges that the FDA has is, when we make an authorization, it's a legal authorization, and unless there's harm or something wrong with the test, we can't go back and change it. It's just really difficult. So, we have to build in, when we make a decision, the potential upsides and downsides, and mitigate risks in the best way we can, with the knowledge we have at that time.

Dr. Perkins: But your harms, so you have two different types of harms, right? You have the harms of missing cancer. And you have the harms of all the procedures and people that don't have cancer. How do you weigh that? I think, ultimately, what's going to happen is you're going to pick an interval. One year, two years, whatever it's going to be, because we just don't have any information. And I think Stanley said this well before, you put the stake in the ground and then you evaluate. And I suspect you'll find that the second round among the first-round negatives, it's going to be much less beneficial because you've already screened out the things you already might find, and the likelihood of a lot of incident stuff occurring in a year is probably really low.

Dr. Gallagher: Okay, I'm going to call on Mitchell Gail, because he's had his hand up for a while.

Dr. Gail: Yeah, I agree with the fact that if you've screened once, then you've called out the prevalent cancers to a certain degree, and therefore a second screen following will have a lower yield. And, my only thought is that, yeah, for example, with colorectal cancer, if you have a

negative colonoscopy with no adenomas then you can lengthen out your period to the next colonoscopy. But, if you're talking about detecting any cancer, I think the incidence rate of any cancer is very age dependent.

And the frequency of screens will depend on that incidence rate. So age is going to be an important factor in determining the frequency of testing for any cancer. There's been a lot of work, that I don't know in any detail, about screening frequencies, but they do depend on the incidence rate.

Dr. Gallagher: Thank you. Rebecca Perkins.

Dr. Perkins: Is this something that the FDA could ask for in the trials? Because I'm imagining they're multiyear trials, and if you ask them to screen every year, and then they find that in the first year they found a lot, and the second year they found the same amount, or they didn't find any new stuff until the third or fourth year, wouldn't that be very helpful information to have?

Dr. Stenzel: Yes. But we have to be reasonable in our expectations for clinical trial design. We heard plenty of folks today mention that they want access to FDA-approved tests as soon as possible. So, our job is really finding the right balance between risk and benefit, and waiting for complete information isn’t really necessarily the best thing.

Dr. Gallagher: This is Colleen Gallagher. I think, one of the other aspects that is important, even if someone is asymptomatic and they're going to get this test, if they have comorbidities that are more likely, then maybe that time frame for the retest should be moved up compared to those who do not have comorbidities or other things that align to people who generally have that cancer. So, just something else to add to the mix, in terms of age. I think sometimes we have to look at the comorbidities as well. Thank you. Mitchell Gail, you still have your hand up. Did you have more to say?

Dr. Gail: I'm sorry. I'll take my hand down. Sorry.

Dr. Gallagher: It's okay. I just want to make sure you get your chance. Okay, Karen Rue.

Ms. Rue: Just along with comorbidities, obviously, if any family history, all those things need to be taken into factor when determining frequency of testing, I would think.

Dr. Gallagher: Other comments to this particular question? Dr. Stenzel, was that enough for you, or did you need more for that question?

Dr. Stenzel: I think it's enough. Thank you.

Question 6

Dr. Gallagher: Okay, then we'll move on to number six. AV folks, let's look at the next question. Thank you. What are the harms from unresolved positive results, and are there risk mitigation strategies? Mary Margaret Kemeny, your hand is raised.

Dr. Kemeny: First, of all the positive results, if it's a very small tumor, you may not be able to find it when you look. So you may have to wait for time, for it to show itself. Even the PET scans and d even CAT scans, if it's less than one centimeter, or less than five millimeters, you're not going to see it. I don't know how you can answer what are the harms from unresolved positives PET. Yes, you're going to have to continue to follow that patient in some way.

Dr. Stenzel: And the second part of that question is how to mitigate the risks, and we talked a little bit about this in the last question. For example, lets just say a test gets approved by the FDA and just say that overall sensitivity is less than 50 percent. When a patient gets a positive result, and they can't find it, that there might be a nagging feeling there. And so, how do patients, you said patients want to know, they want to find if it's a positive result, they want to find it. So how do you how do you mitigate that situation?

Dr. Kemeny: Again, in the clinical situation, you have to work with the patient. Explain the

situation to them and then find out what they want to do to find out whether this test is correct or not correct. And if you're talking about 50%, that's really not too high. So they have 50 percent of a chance of not having it.

Dr. Stenzel: I'm sorry, I threw in sensitivity there. We're really talking about specificity in this question.

Dr. Kemeny: Okay, but so, you have to work with the patient as far as that's concerned. And when you're talking about tests like this, risk, you may be over-emphasizing risk. Because when we talk about risks, in clinical trials, often it's giving new drugs or stuff like that. We're talking about actual harm that may come to them. Here, it's just a question, is the test accurate? Are you going to find the cancer earlier? Eventually, if they have cancer, it's going to present itself. The risk is a little bit, it's a different kind of risk. There is emotional risk, of course, if it's positive. If you say it's positive, and then they think they have cancer, and they don't have it, yes, there's an emotional risk. But, I think it's a different type of risk than actually giving a drug or something.

Dr. Gallagher: Thank you. Karla Ballman.

Dr. Ballman: Yeah, we did talk about the risk of all the extra testing that they'll have to go through, and they'll have to go through the gamut and still not have an answer. And I don't think we should minimize what the patient anxiety level would be, even though it might be a different risk. In cancer trials, we measure patient-reported outcomes and quality of life a lot, and that has a big impact. To mitigate it, I don't know what the FDA can do other than, as what we talked about, like what follow-up should be for positive tests, to try to give assurance that this truly is a false positive. And we talked about some of those already.

Dr. Gallagher: Thank you. Edward Bujold.

Dr. Bujold: Yeah, I think this is all about communication with the patient and shared decision

making, and some upfront before the test is done, talking about, these aren't perfect tests. Although I will say I have a few patients that are the 'worried well', and there isn't anything you're going to ever do to take that worry from them, if you say that we've got a positive test for cancer here, they probably won't sleep again until that's resolved. But it's all about communication, I think, that point. It is all emotional versus… it's not something physical. But don't discount how emotional it can be, because it can be very emotional for some people.

Dr. Gallagher: Yes sir.

Ms. Hesser : I think that Karla had just touched on the quality-of-life component to this, and we really, as a group, have not talked about the importance of these applications coming to the FDA, hopefully, with a quality-of-life tool having been studied in the information that comes to you. Looking at the impact of false positive and false negatives, on those patients, would be an important part, not just the psychological burden that it may have, but what is the patient's satisfaction with the results of the tests. Did they understand that, what was their satisfaction with their communication with their health care providers. So it'd be really nice to see some of those tools incorporated early on.

Dr. Gallagher: Thank you. Daniel Swerdlow.

Dr. Swerdlow: This brings up, to mind, a lot of the issues that happened when lung cancer screening with CT got off the ground. One of the smaller community hospitals, as part of our medical system that I was associated with, they were a gung-ho to get lung cancer screening going, despite pretty low smoking incidents in that population. And they were saying, oh, we got to do this, we got to do this, hurry up, and the administration was breathing down their necks and says, yeah, I can do the scan. It doesn't take a fancy scanner to do this. Who do I report the results to? And who's going to talk to the patient about what these results mean when we find

these little three- and four-millimeter nodules in smokers, and how likely they are to be cancers, and how we're going to follow this, which was met by all these blank stares, and 'oh, we never really thought of that part'. And that's the really important part of all this. So, this we're talking about as being a much broader screening program across the population, than this lung cancer screening, where we have trained nurse practitioners and pulmonologists who've gone through education on how to talk to these patients about what these three- and four-millimeter nodules mean and how likely they are to be cancer and why we're not whacking them all out immediately, because that's the patient featured reaction. If there's not a lot of back-up about, with robust statistics, and what this all means and how do we do this, and what happens if we can't find it? How often is this test positive when the tumor is really tiny? And we're not going to find it yet, but we're going to keep following this until it presents itself or the test stops being positive, it's going to be a mess. And there needs a lot of information made available to the people who are going to have to talk to these patients. And it is going to be that broadly done, the way we're talking about here. That's going to the primary caregivers, the primary care docs, the nurse practitioners that are increasingly seeing these patients. They're going to have to be educated with a lot of literature, and really get it, and then be able to then take that and explain it to the patient in lay terms. This is a big deal and it's really hard to do, and the lung cancer screening is just a tip of the iceberg compared to what this is going to be.

Dr. Stenzel: Yeah, thank you. What was the specificity, and probably specificity of low dose CT, for lung cancer screening depends on what you call a positive and what you follow up.

Dr. Swerdlow: Yeah. It's all these nodules and then there's an involved LI-RADS score of likelihood. Obviously if you have something that's been growing quickly, because we do these every year on people, and you have a one-centimeter mass with speculation, yeah, it's probably

going to be a cancer. But the overwhelming majority of the stuff we find are these two, three, four-millimeter nodules, which rarely turn into anything. They're almost always benign. If you count those, the specificity is poor, and then we have this LI-RADS scoring system, so the low numbers, the ones and twos, are pretty low specificity. When you get to the fours, now they're pretty high specificity. We're assigning a risk concern, and those come with recommendations that have been made by the experts in this, about how do we handle this. A lot of this one-year follow-up and then sometimes it's big enough now and then we ought to do a PET and see if it's there, or do some tissue sampling. A sort of stratified thing, but we don't know what these tests, how small a tumor it is that they're actually detecting.

Dr. Stenzel: Right, but if we're talking about specificity and positive predictive value, since at least some of the test developers are setting a very high specificity, so, definitely we can define a false positive rate. And then, depending on the prevalence of cancer, you can define the positive predictive values. We have tried to poll the panel here on what specificity needs to be, what positive predictive value needs to be, because that is my recollection of the studies on low dose CT for lung cancer, that you had to not worry about smaller nodules, otherwise you would be following up a lot of things. Other than if you might monitor them over time. Thanks.

Dr. Swerdlow: Yeah. But the real question here, is it a false positive if the tumor shows up three years later because it was truly microscopic when the test detected it and our imaging isn't going to cut it until it has a chance to grow. Not really a false positive, it's just beyond the rest of our technology at this point.

Dr. Gallagher: Thank you. Deborah Schrag.

Dr. Schrag: Yes. I believe the question was about risks and risk mitigation strategies, and I think that based on my experience, one of the key risk mitigation strategies is setting

expectations clearly up front. Patients are smart, but they need to be empowered with good, clear information. If you set expectations at the beginning that, if this test is positive, if this test is negative, here's what will happen, and what needs to happen, you need to continue routine cancer screening and that's critically important. That has to be part of the package, as well as lifestyle behavioral modification recommendations. If the test is positive, we are not going to drop everything and get you a full body workup and an appointment within five hours. That won't happen. It can't happen. We have to set realistic expectations that should be within a couple of months this will get worked up. And if people don't think that they would undergo the workup, or wouldn't want to undergo the workup, then the testing probably wasn't appropriate to begin with. So, I think the main risk mitigation strategy is clarifying expectations right up front. A big risk is crowd out, and what I mean by crowd out is if you're busy chasing pulmonary nodules or these tests, or I mean we've seen this movie before, with lung cancer screening as, I think I'm agreeing with Dr. Swerdlow's comments. And we've learned a lot from those experiences. We have patients with new diagnosis of lung cancer who are waiting for imaging and to get in to be seen. And we've got incredible workforce pressure to add on patients at eight, nine o'clock, particularly in underserved, I work in a non-physician-shortage area, but it's terrible in rural parts of the country in an underserved area, people who already have cancers can't get into be seen. And we have to make sure that people who are identified as a result of this screening, are seen within a reasonable time frame, but don't crowd out those who are symptomatic and need to be seen urgently. And that's all about balance, but it's tricky.

Dr. Gallagher: Thank you. Edward Bujold. Edward Bujold, your hand is up. Did you want to say something?

Dr. Bujold: No, no.

Dr. Gallagher: Okay. Just making sure. We want to make sure everybody with a hand up gets to say something. Alright. Dr. Stenzel, did you need more on that question, for risk mitigation strategies?

Dr. Stenzel: No, I think that's good.

Dr. Gallagher: Okay.

Dr. Stenzel: Next question.

Question 7

Dr. Gallagher: Sure. We will now move on to question number seven. What are risks and harms from over diagnosis, and are there potential risk mitigation strategies? So, I would like you to clarify for me, Dr. Stenzel, what is meant by over diagnosis?

Dr. Stenzel: So, I think there's two areas of over diagnosis. One is, as was mentioned for low dose CT for lung cancer, you were finding things that were not cancer. And so then you're working up something that's not cancer. And the other thing is that you're finding indolent tumors. And they may not progress to anything of importance. So, are we going to find a lot of indolent cancer. So, think about the prostate cancer screening program. And we really need a great prostate cancer screening program. Because a lot of people die of prostate cancer still, every year.

Dr. Gallagher: Thank you. Mary Margaret Kemeny.

Dr. Kemeny: I think, haven't we answered this question already? This test is not going to solve some of the problems of cancer screening. We can't always make the diagnosis, and we certainly don't know what to do with some cancers when we do make the diagnosis in a population, for instance, prostate cancer in 80 year olds. We don't know those things. So these tests are not going to be answering those questions. And we shouldn't ask them to answer those questions.

Dr. Gallagher: Thank you. Mitchell Gail.

Dr. Gail: There are many people here that are qualified to answer this, than I am, but, obviously if one kind of overdiagnosis has just been mentioned is that it's not a cancer, but the other kind is it is a cancer that would not have killed you during your normal lifetime. And if you left it alone, it would leave you alone. There's a lot of argument about what percentage of screened cancers fall into that category, but whatever percentage it is, there will be follow up for them. They will probably have interventions, maybe surgery. There'll be all the complications and costs of managing a cancer that didn't need to be managed.

Dr. Gallagher: Thank you. Peter Carroll.

Dr. Carroll: This is a real problem for prostate cancer. And we found two things. One, we had to let people know ahead of time of the risk of our over diagnosis, before they were screened. Because I think telling a patient they may have cancer afterwards is more challenging. Two, we found that we had to modify testing significantly. And I think for these tests, we have to understand that may be the case. So now we don't screen primarily by PSA, but by ancillary test of specificity. So it wouldn't surprise me that these tests may be modified for some cancers that are most at risk for overdiagnosis, with time.

Dr. Gallagher: And don’t forget the other part of the question is about other potential risk mitigation strategies. So add that in, if you've got them.

Dr. Carroll: I think, again, you have to tell patients of the risk of diagnosis up front. I think once you do that, before they're screened, it becomes a much easier discussion to have, rather than have the patient go down to be screened, find a cancer, and then try and tell them you don't have to worry about it. So when we have this conversation to begin with and let them know that we have ancillary tests that will tell us whether or not this tumor is one that puts them at risk, I

think is very helpful.

Dr. Gallagher: Okay. So I think part of that means that we would encourage saying, this test determines whether you may or may not have cancer. Not that you do or you don't. You know, that distinction, to know that we have to do something further based on what we learned, or something like that. Even in the package inserts, the education that goes to clinicians, whatever.

Dr. Carroll: So we have to… de-link diagnosis with treatment. So you can tell a patient they may have a cancer, but whether or not they need to be treated for it is a separate conversation based on additional factors.

Dr. Gallagher: Great. Thank you.

Dr. Stenzel: And the FDA is asking some of these questions, anticipating some of the challenges clinically. And if there's something that we can put, for example, in the package insert, as Dr. Gallagher said, that could help the downstream process here, then the FDA is open to hearing what the panel thinks. And so, what we call labeling is the instructions in the package insert for the test, that ordering physician clinicians should be familiar with, and patients might want to look at it as well, so that they understand there may be patient materials as well. So those are some of the possible mitigations. Thanks.

Dr. Gallagher: Okay. And Rebecca Perkins, you're next.

Dr. Perkins: I'm an OBGYN and I was just thinking this may be somewhat analogous to the genetic testing that we do in pregnant women and for fetal anomalies. And there's a requirement usually to have the patient have a session with the genetic counselor to go through all of the pros and cons of testing. Do they want to get tested? What are the tests mean? Blah, blah, blah. So then, by the time they decide to get the test, they have a very good understanding, expectation of what it would be. And so maybe something like that. And it's really nearly impossible to get any

sort of genetic test without seeing a genetic counselor. So maybe something like that could be baked into how these tests are packaged, just so people have realistic expectations before they decide to move forward with the testing.

Dr. Gallagher: Thank you. Karla Ballman.

Dr. Ballman: Yeah, this is Karla Ballman. I'm not sure, I don't know if we know what the indolent cancer rate is going to be. So I don't know how you're going to mitigate that. Because the only way of really getting some sort of handle on it is by having mortality as an endpoint, which is not in the purview of your organization. Other than just saying on the indication that cancers that are detected may not have needed to be treated, unless it's other information from somewhere. I just don't know what else can be done.

Dr. Gallagher: Thank you. Philip Castle.

Dr. Castle: Yes. Phil Castle from the NCI. I don't think we know what, I mean, this again comes back to several points. Which cancers are clinically relevant, those that are going to ultimately kill the patient, those that are not, for many of these cancers we don't have that natural history. Prostate is one of few that, if you had a MCED test that pointed to prostate and you went through it and you found a low grade, a low risk, I think is the current terminology, then you would know that's a surveillance situation. If you found a DCIS of the breast, you would also probably watch and wait. But for the other ones, because we haven't had any screening, it's circular. We haven't had screening tests. We don't know the natural history. We haven't found all the, what we say in the cervix world, warts and all, of screening, and being able to unfortunately go through the process of saying, oh this is something we really need to treat. This is something we don't need to treat. Again, going to the cervix world, we used to call CIN2 and CIN3 together.

And it's very clear that those are different entities carrying very different risk. And now we watch CIN2, particularly in young women, because of the harms associated with treating, in terms of reproductive health. For being able to differentiate indolent versus not, it comes right back to the mortality versus not. You can't disentangle this, I'm sorry, I wish we could. If I had the answer, I promise I would share, widely, because, even like we can't, even PRS doesn't differentiate between prostate cancer that is clinically relevant versus indolent disease. So, we don't really have biomarkers. The division of cancer prevention is sponsoring a lot of research to try to identify markers that would differentiate between indolent and high-risk disease, but we're not there yet. I don't know if, retrospectively, the companies can look at which things on their panels were positive. Because, remember, it's multiple markers. It's not one marker. Whether they could then adjust their algorithm to say, to pull out, to avoid causing some of these, finding these indolent. I think some of the companies, in the early iterations of these tests, were finding a lot of chip. And so, they made some adjustments in their algorithm to find less chip because that wasn't particularly useful. So same thing, I think over time, they could take some of the data from trials, look back at what they found, what they not, and then disentangle their algorithm a little bit and say, if we changed our cut point we would eliminate these indolent disease. But you have to do the trial and find the indolent disease for these ones for which we've never had a screening test. It's an iterative process, it's an organic process. It's kind of like all AI, right?

We continually learn, and adjust, that's the only way. And I think somebody else made this point earlier, that not so good screening tests lead to a better screening test. It's much harder to go from zero to one than it is to go from one to two, because once you have a predicate test, things get a whole lot easier. What's important and what's not.

Dr. Gallagher: Thank you. Daniel Swerdlow.

Dr. Swerdlow: Daniel Swerdlow, radiology from Georgetown. I think, I agree with what Dr. Castle said, we really don't have any way of predicting which ones are indolent and which ones are not. But the very nature of doing screening means that we're going to find indolent tumors. And when I think about the indolent tumors, it's everything we screen, it's prostate, it's breast. And I do a lot of thyroid work, and it's really a solution in search of a problem. We're finding a lot of thyroid cancer out there nowadays. We're doing an awful lot of thyroid cancer surgery, and the death rate from thyroid cancer hasn't changed since 1980. So we're really accomplishing nothing.

The South Koreans wrote an article that was in the New England Journal a few years ago, where the government started paying internists to do ultrasound screening in their offices and the thyroid cancer rate exploded. It's the number one cancer in South Korea. The complication rate from the thyroidectomies was large. It was eight or nine percent. And I don't mean hypothyroidism, vocal cord paralysis, and things like that. We're not accomplishing anything, and we essentially have a de facto thyroid cancer screening program. And I'm seeing people referred for mammograms and CT colonography and thyroid ultrasounds who are in their late 80s. So in the absence of having a way of predicting which ones are going to be indolent, I think what we need, we have these bottom age cutoffs of when people need to start screening, but we really need top ends, as people start to approach their life expectancy, where we got to stop screening.

Dr. Gallagher: Okay. Thank you. We'll take two more comments and then we're going to move to our next question. Edward Bujold.

Dr. Bujold: Yeah, I think the FDA would do well to look at the entire landscape of cancer screening for prostate cancer. There were so many mistakes made, and so many people had,

particularly for indolent cancers and people that were over the age of 70, there were so many people who had procedures done that didn't need to have them done. And we could have easily watched and waited. And I can't tell you how many hours I've spent having discussions with elderly males in regards to, you might be opening up this Pandora's box. And when I think about a blood test for any kind of cancer, we were talking just about one cancer, which was hopefully fairly simple, and we never did get that right and we still probably haven't gotten it right. And we're potentially opening up this Pandora's box for all sorts of problems. So, it's a scary path we're all walking down here.

Dr. Gallagher: Thank you. And Mary Margaret Kemeny, you're the last speaker on this topic.

Dr. Kemeny: I just want to correct a few of the things that have been said here. One by Dr. Castle. First of all, DCIS we still treat, so we do not watch and wait on that. Second of all, cervix cancer is one of those cancers that is so problematic for like surgical oncologists, GYN oncologists, because we know that cervix cancer could be wiped out entirely if everybody did pap smears or other tests. And in my population, in the underserved in New York City, we still see advanced cervical cancers and young women dying from cervical cancers, because they didn't get pap smears. And it kills me as much as it kills them. And then the last thing is, confusing breast cancer and thyroid cancer. Thyroid cancer is not the same as breast cancer.

Breast cancer still kills like 40,000 women a year in the United States. You can't say that we shouldn't screen with breast cancer because the thyroid cancer screening program doesn't work. It's two different, we're mixing up two different kinds of cancers. And by the way, breast cancer in the elderly is the same as breast cancer in the younger women, as far as killing people. And so whether or not we should screen the elderly, that's a whole other question. Because, as I do a lot of cancer in the elderly work, and the population of the United States now is going to be

over a million people are going to be over a hundred years old. So people are living longer. So, an 80-year-old may live to be a hundred. Should they get, mammograms? That's a whole question that we're going to have to answer, but it's not a slam dunk that at 80 we should stop mammograms.

Question 8

Dr. Gallagher: Okay. Thank you very much. We're going to move on. We've got several more questions. So we're going to skip one of them and try to fit in the rest of them that are really important. So, we want to look at number eight. Does anyone want to comment on the significance of time to diagnosis from getting the test?

Dr. Stenzel: Yeah, I'll just clarify this, so we've covered this a little bit, but it's asking in a different way. You have a positive result, and how soon do you find that, and what is the significance of that time lag in our evaluation of these tests?

Dr. Gallagher: Okay, I see two hands raised. Philip Castle? Nope. Edward Bujold? Nope, they have nothing to say.

Dr. Bujold: Stale hand. Sorry.

Dr. Gallagher: That’s alright. If there are no comments because we have, oh, there's one.

Dr. Schrag: I think the reason there are no comments is it's a second-order issue. In other words, we've discussed the key issues and this is just a second-order issue. Obviously, it shouldn't be five years. It also doesn't need to be five minutes.

Question 9

Dr. Gallagher: Okay, then we're going to move on to question number 9.

Dr. Castle: Can I add one point to this, with Deborah? But I think one of the big issues, time to diagnosis and getting diagnosis is a health disparities issue, a major order. Part of this is

making sure, and I know you know this Deborah, I'm just trying to...

Dr. Schrag: I completely agree with you a hundred percent and I think it's important. In other words, we shouldn't be doing screening tests if we can't then work them up. In fact, that's... there an ethical violation. We shouldn't, I don't know, back in the day…

Dr. Castle: It's not screening.

Dr. Schrag: Exactly.

Dr. Castle: Screening is the whole care. And the test is just part of that. And we have to, when we say screening, we shouldn't even have to qualify that. But we still do because people focus on the test, which is, as I said earlier, is the easy part. But making sure people are linked to care is critical and so that's going to be a big determinant of time to diagnosis is, where they're getting their care, even, and that's going to be influenced by so many different things. Like, issues of persistent poverty or morality are going to really make a big, how are these, you could get these tests out to rural areas through the mail, let's say, you could collect a small amount, and keep in mind that right now you need a lot of blood for many of these tests. So that doesn't make it so easy, but, let's say, sometime in the future, you could do it with a drop of blood, and I don't know that's any time soon. But even then, if you live three or four hours away from the clinic that's going to provide the next level of care, they may not come. So, there's some real issues on time of diagnosis that are related to health equity.

Question 10

Dr. Gallagher: Thank you. So let's move on to question number 10. So AV folks, let's see number 10. Under what conditions is the use of real-world evidence to report clinical validation of an MCD test acceptable? Expand upon per cancer assessments, validate rare cancers, evaluate reduction in cancer stages and or stage shift, and/or establish a valid interval for testing.

Dr. Stenzel: So, let me just explain what real-world data or real-world evidence is, at least as the FDA views it. So this is outside of a standard clinical study. But there would be some parameters around data. It might be something that was a post approval study. It might be something that a company might use to improve their test after they get it authorized and come back in with something. But it's data collected in more standard practice. The FDA likes to know that data is good. That it's correct and valuable for a regulatory decision.

Dr. Gallagher: So this is Colleen Gallagher, and I guess I'm thinking about this a little bit like running a tumor board or something. You have to have a place to collect the data. So I would expect that the companies would want to collect data on their product, how it worked over time. And I think they could be asked to do some of that. But based on that real world experience, just following up, if their test has been used, kind of thing, rather than saying they're in a clinical trial, after a period, after the trials over and it's on the market. So I'm wondering if there's a way to create some kind of portal where this kind of thing could be reported, about what's going on. Especially for the rare cancers, I think, because those are ones that people only track them when they get them, and I don't know if people are going to use this test for that or not. I don't know. The companies might say, it might work for that, but I don't know if people are going to want to get tested for that. It's a little tough. But I think that, looking at the when, in terms of what stage the cancer is in when it's found, might be a key important factor to how, not just the effectiveness of the test, because I think that's not as effective as they would want it to be. But I think it would be effective in helping clinicians in design of treatment plans. So I think it has some additional elements to it that may be helpful to patients overall. Mitchell Gail.

Dr. Gail: Yeah, I guess it depends on what kind of questions you want to answer. If you wanted to determine the prevalence of certain diseases that could be detected by standard

screening procedures, in a target population, you might get decent prevalence estimates based on those criteria, from real world evidence. If you wanted to try to estimate sensitivity and specificity, and positive predictive value and things like that, you'd have to know, as we've been discussing, a lot about how the ground truth is being established for these patients. And that might be very difficult in a so-called real-world evidence setting. Certainly, I would not rely on real-world evidence to determine that an MCD program versus standard screening, reduced mortality, because the people who, well there you need randomization. Because the people who volunteer for this kind of special screening are not necessarily representative of the target population.

Dr. Gallagher: Nathan Winslow.

Mr. Winslow: Yeah, I just want to cite, I think it was the Friends of Cancer that submitted some white paper on the use of rural evidence, and there is, from a development perspective and post market, there are questions that rural data might be able to answer actually. Even better, some of them that have been discussed today. So something I would encourage as we consider how these are developed, where perhaps in the post market setting, or even in the development setting, like a control arm, for example, if there was a need for a comparison in that regard, where you could envision the use of real-world data. Properly designed studies of course. As you mentioned, Tim, you would need to make sure that prospectively or retrospectively that those are appropriately designed. But there is a role potentially for rural evidence when it comes to these tests, particularly with the sizes of the studies that we're talking about.

Dr. Stenzel: And our center has guidance on the use of it. And we do encourage it when appropriate.

Dr. Gallagher: Karla Ballman.

Dr. Ballman: Yeah, I just want to say I agree with what Mitch… this is Karla Ballman. I agree with what Mitch has said. I think there are some questions that it can be used for, and it depends upon the question, but it cannot be used for mortality. We know, just even in clinical trials, even if patients match what the eligibility criteria are, patients that decide to go on a clinical trial are very different from those that decide not to go on, even if they have the same eligibility criteria, and patients do better on clinical trials. I just think that people that are going to opt for the test are different. Even if you have measures that show that they're not different, you're not going to collect all the variables that are necessary to be evaluated, to show that the two groups are the same.

Dr. Gallagher: Yeah, I'm not seeing anyone else's hands up. Dr. Stenzel, did you need more on that question?

Question 11

Dr. Stenzel: No, I think that's good. And I think the next question, you can pop it up if you want, but I think we covered that as well. We broke out the questions maybe a little bit too finely. Some of them we might be able to lump, but this has to do with what are the considerations around use of it. So I think we had…

Dr. Gallagher: What considerations are critical when allowing the use of real-world evidence to support the aforementioned? Okay, I'm not seeing anybody's hands up. So, I'm going to suggest that this time we take a five-minute break so that we can get back to our schedule a little better. So, we'll see everybody in five minutes.

Panel Summations

Dr. Gallagher: It is now 3:55 and I would like to resume the panel meeting. At this time, I would ask our representatives, Karen Rue, our consumer representative, Nathan Winslow, our industry

representative, and Deneen Hesser, our patient representative, if they have any additional comments. Karen Rue, the floor is yours. She doesn't seem to be sitting at her camera, so I'll move on. I think we'll ask Mr. Winslow to go first.

Mr. Winslow: Yeah, maybe just to summarize a few points on behalf of industry. I would say that universally we're excited about the opportunity that this brings. There's obviously a lot of discussion that's occurred, a lot of things that are new that'll have impact on the delivery of healthcare. And so these are things that we're, I think taking very seriously, and multiple discussions that sponsors are happening with FDA. And in that regard, I think it's important that we are thinking about this differently, in terms of how we would deliver this from a development and as well as an execution standpoint. And so what's required from an evidence generation perspective may not look the same as what a single test might look like, for example. I think that was brought up earlier this morning. And then consider what can be done pre-market and give us the level of evidence we need to justify that we do have an appropriate benefit risk. And where can we answer some of these questions post-market too, that I think will be important for people who are getting the test and needing answers sooner than later. So that's probably just a general summary from our side. Thank you.

Dr. Gallagher: Thank you. And Deneen Hesser, you're next.

Ms. Hesser: I very much appreciate the many opportunities I've had today to represent the patient population, and future patients. If there was one priority item that I would like to carry as a banner for this meeting, it would be that whatever comes to the FDA, whatever future studies are proposed, I would really like to see traditionally underrepresented populations in those studies. African Americans, the Latino communities, native Americans, seniors, and the underserved populations. So, if that can be prioritized, hopefully that too will help mitigate or

bring to fruition, in the future, some coverage and better access to the diagnostics that are going to be needed.

Dr. Gallagher: Thank you very much. And Karen Rue.

Ms. Rue: A couple things. I agree with Ms. Hesser and some of the statements, and also the other part is, we talked about the endpoint being mortality or staging, and I just have known too many people being in clinical practice, it's like if you give them the option that they get 10 more years, to me, that for them, that's a very valid endpoint also, rather than just mortality. And also, again, the pediatric population. And again, if we could include some component while we're doing all this, if it comes to fruition. Again, educating people on the importance of their cancer screening test, whether it be the current ones or whatever this offers, because we just need to get that. Because they're not as effective as they could be, because people aren't getting them. And there's access to so many of them, even in the underserved communities now. Thank you and I appreciate the opportunity.

Dr. Gallagher: Thank you. And of course, we want to hear from our panelists, what they would like to add to any comments that they've already made today. I'm going to call you all out to say something. So I'm going to go across my screen and whoever's listed there is who's going to get to speak first. Mary Margaret Kemeny, you're the first person on my screen.

Dr. Kemeny: One thing we haven't talked about is cost, of anything. I, again, being at a minority-based hospital in New York City, what the underserved have generally gotten or not gotten is very important to me, and that they get the same kind of opportunities as people who have insurance and… It is very important to me. So I think we have to keep that in mind, all the way around. From, the clinical trials need to include, and they can't just open them up, and then say oh we didn't get enough. They have to have a predetermined minority population in the

clinical trials. Like 20% or 40%, whatever, and that has to be reached. And also to remember about the financial burden, in the future, about this testing, and whether this is going to be covered by Medicare, Medicaid. I think these things need to just be kept in mind.

Dr. Gallagher: Okay. Thank you. And Daniel Swerdlow, you're next on my screen.

Dr. Swerdlow: Yeah, I want to echo Dr. Kemeny's thoughts on cost. As a survivor of the CT colonography wars that went on, last decade, where, essentially a valid test that was fairly reasonable for cost wound up not getting approved by the U.S. preventative services task force, when there's a very large segment of the population unscreened for colon cancer. Enlighten me as to how some of this works. The potential for these screening tests is fabulous. But so are the costs. I just don't know how we're going to do all the imaging that will be engendered by these positive tests. If this comes, it's going to break the bank. And there simply aren't enough scanners around to do the job, in many areas, especially the populations that Dr. Kemeny just talked about, native Americans, rural, going to have a really hard time doing their follow-ups. And then, what's the benefit of getting the blood test if we can't do anything about it? I, having survived that, I just have a hard time imagining that the preventative services task force with the costs involved, is going to recommend this stuff, because something else is going to have to give out of out of the pot that pays for Medicare and Medicaid. And I don't know what that's going to be. I'm very concerned about that. And it doesn't really matter how cheap the blood test is, because that's not the problem. I think somebody's going to have to figure out a way around that, and I don't see an easy answer.

Dr. Gallagher: Thank you. Deborah Schrag.

Dr. Schrag: Yeah, so I think we've touched on many key issues, and the disparities, I wholeheartedly agree with. I just want to focus on a couple points that I think maybe got short

shrift earlier in the day. And one has to do with the development strategy. We heard very powerfully, from some patients, about the urgency and eagerness to accelerate development of this technology. But at the same time, we also understand the population wide risks, and chaos, and havoc, that could ensue if we are excessively trigger happy. And it's really trying to find that right balance, that's so terribly tricky. I think that, because a screening test requires very large populations, and the event rate, thank goodness cancer is not that common, even among adults. Thank goodness. It requires very large populations of patients. Screening in cancer survivors is a different undertaking, for second malignancies, but the event rate is much higher, and those individuals tend to be plugged into care. And there are smarter statisticians on this panel who can weigh in on this topic, but I think that if we use populations that are high risk, whether because they've already had a diagnosis of cancer. So we have tens, if not hundreds of thousands, of cancer survivors in this country, and they are highly motivated, have a pretty good understanding of the healthcare system, are plugged into research, and are representative of all backgrounds, races, geographies, nationalities, ethnicities. I think we can engage that population in evaluating these technologies, because the event rate is high. And if they don't work there, they're unlikely to work when moved more proximally, into a true average risk population. So I think as a development strategy, we should exploit the higher event rate in cured cancer survivors, as a strategic approach to accelerate development.

Dr. Gallagher: Thank you. And Philip Castle.

Dr. Castle: I don't really have much to add. I think I've spoken my piece many times today. I do want to agree with Deborah's comment on the cancer survivors. Twenty percent (20%) of all incident cancers occur in cancer survivors. One other point I want to come back to, I touched on it briefly, is these tests are different. They're not, and they don't diagnose cancer. They identify

people at risk of cancer, but they have different profiles. They have different target cancers, and the intended use population also have different cancer risks associated with them. So it's not just one size fits all.

And part of what we're trying to do, and what needs to be done, is deciding which test is best for which person. And that has a number of different parameters associated with it. So, it's not just a plus/minus, and it's not just all cancers. For example, if you were a BRCA carrier, and you're a woman, you want something that's going to find breast, ovarian, and pancreatic cancer, for sure. If it didn't, then why wouldn't you pick another test that actually was more appropriate, more targeted, to that risk? If there's an MCED that does a better job of covering cancers related to smoking, and you have a smoker, you'd want to pick that test. Those are very simplistic examples and I'm not going to call out a particular technology here. I'm just saying that it's not as simple or straightforward in doing what's best for the population, which I think we all want to see happen. It takes some careful thinking and consideration. So I'll stop there. Thank you, and thanks for including me.

Dr. Gallagher: Thank you. Mitchell Gail.

Dr. Gail: Thanks. One thing that occurred to me is that the MCD tests, there are two motivations for them. One, to pick up cancers that are not currently being screened for, and two, possibly to cover those cancers that are being screened for, but for which the uptake of the screening is insufficient. And I think that there are a lot of problems that we've discussed today, about screening for all cancers, and including the ones that are not being routinely screened for now. But there are about five cancers I think we saw listed that are currently being screened for, but the uptake of screening is not that great. And I think there's an opportunity here if we had MCD tests with a tumor of origin complement.

So, if we had MCD tests with tumor of origin content tuned just to those five cancers that we're already screening for. And if those MCD tests with the TOO were cheap and blood-based, so that a large number of people would take them, they could be used as a prescreening device. If they were positive, then that person who normally wasn't in routine screening for these five cancers, would have a signal that they should go and have their regular screen. That might increase the uptake for regular screening, already validated screening. And it might be a very cost-effective way of broadening that coverage, because the blood tests presumably are an easy test, an attractive test, people might be used to that. And it might be offering the incentive people need to go into bona fide screening for the five cancers that we know we can do something about. So I think that's an opportunity for the use of a MCD with tumor of origin complement, that does not require these vast workups that we've been talking about. It only requires that a person who's positive there go get their routine accepted screening for those five cancers. So that's just a possibility. I know it's not the philosophy that engendered the MCDs, which is to catch all the cancers, but it might be a cheap way of improving uptake for the screening tests that we know work.

Dr. Gallagher: Thank you. Now we'll hear from Edward Bujold.

Dr. Bujold: I'll just highlight a couple of things that have already been said. I had worked in a rural area for 40 years, and it's hard for most people to believe this, we have a lot of people that basically live on social security and $50 is something they can't afford in any given month. And, in addition to that, transportation is an issue. I'm an hour and a half from Charlotte, where we can get a lot of wonderful things done, but, it's an hour and a half too far for a lot of people that are in the practice that I serve. I also wonder, I've always wondered why we develop these tests, they're going to be very expensive, and the insurance industry, third party payers, Medicaid, Medicare,

and the pharmaceutical companies, they're not brought into these discussions.

They're always, we develop the test and then we start ordering them, and they get turned down. And it represents a tremendous burden to us, as physicians, trying to get these things approved or not approved. And it's just, it seems like everybody ought to be in the same bucket, working together, to figure out a cost-effective way to do these things that we've been talking about. It just seems backwards to me. The other thing I've thought about through the day is the companies that are developing these MCD tests, if they're going to do this right and include people of color, the elderly, children, those that can't afford to test, I don't know if they realize how much money they're going to have to spend in clinical trials and things. I hope they're up to the task.

Dr. Gallagher: Thank you. Stanley Lipkowitz.

Dr. Lipkowitz: Like others, I think I want to thank you all for inviting me to be part of this committee, and it's been a very interesting day. And I wanted to start with just some general comments, because I think as we've gone through and critiqued or made comments, it comes across as we're angry or something at the tests and the way they're being developed. I, and I think most of us, think that these tests have tremendous potential, and I think tremendous potential with a minimally invasive test to expand the access to care. So I don't think that's a question.

The question is to do it right. And I think, so that's why there's been so much discussion about trial design. And I think we've had examples, I think PSA is the best example, as you brought up, Dr. Bujold, of something that we still argue about, whether it should even be done. And so, I think this is something where we have to do it right on the front end. So I do think that's important. And I do think, as a clinician, that the end of all of this is not stage migration.

It's not, did a patient get surgery? It's, did we improve outcomes? And I think that's the big picture. And I know that's not what you guys in this venue are going to regulate, but I think that's an important thing to keep up the eye on. That the trials ultimately have to be, even if they're using a surrogate, that they have to be powered to look at those other endpoints. Because it's going to be hard to repeat these once the tests are out there, it's going to be hard to pull them back. So I would say that it's very important to make sure that clinical outcomes are really the, they are the gold standard, and I think that they need to be included in these tests.

Dr. Gallagher: Thank you, Peter Carroll.

Dr. Carroll: Just a quick word about PSA. We know what to do with PSA. Just people are not following the guidelines, so that's the problem. But we have good guidelines. Again, I was very happy to be part of the panel. I learned a great deal. I do think it's got to be applied to a broad, diverse, average risk population, and do include some higher risk populations. I'm very intrigued about the idea of this bespoke MCD test. You could do that based on symptoms risk factors like smoking. I do think that it's got to be a test that looks at a broad range of cancers, not just common cancers, because I think the benefit to this is likely in these uncommon, low prevalent cancers that are currently not being detected, if there's going to be a benefit. I think in the near term, you are going to have to look at something like a stage shift, decrease in advanced disease. I think I very much support the NCI's perspective on a decrease in mortality, but I don't think the tests could be done… that would take many years.

The last thing I think we have to acknowledge is that technology's going to evolve very rapidly on this. There's a lot of AI in these algorithms, and I think we have to be open to that, and I would ask the companies, to some extent, how often they'll be updating their tests based on information they get going forward. Because I don't think the tests they have now will be likely

the tests we'll see in three to five years.

Dr. Gallagher: Thank you. And Karla Ballman.

Dr. Ballman: Yes, this is Karla Ballman. I also am grateful to have been on the panel. I have learned a lot. I am very enthusiastic about these tests. I just, as others have said, and I echo what all the others ahead of me had said, that, I just think that there has to be some careful thoughts put in so that we aren't in a situation where we're doing more treatment than what we need to do, though I know that we can't do that within the purview of this particular NCI group or FDA group. I do think, and we didn't talk about it per se, but I do think that the idea of having real high specificity, I don't think any specificity under 99% should be considered. I'm a bit, really, sensitivity of only 50%, I think that's quite low. But again, if it isn't a cancer that doesn't have a screening test, that does give something. So, I think that has to be taken into account, that if there's currently no screening tests whatsoever then maybe a sensitivity of 50 percent's okay. But I really don't have anything else to say other than what I've said before, and I do endorse what the previous panelists have said.

Dr. Gallagher: Thank you. And Rebecca Perkins.

Dr. Perkins: I want to echo the other panelists and say thank you so much for including me, and I've learned so much today. It's such an interesting field. I do think it has tremendous potential to revolutionize cancer diagnosis and treatment, but it also brings up a tremendous amount of complexity and new questions. Some things that we talked about that I just wanted to elevate in this summary, was the idea of doing pre-test counseling to promote realistic expectations for patients to decide whether they want to go through with the testing, and what would be expected with a positive and negative test result, and what that means. I think a lot of us express the opinion that having the tissue of origin information within the test was incredibly

important so the patient would then know how to have targeted follow-up testing, which is both important for managing expectations, finding cancers, not having incredible financial toxicity, and not overwhelming our radiology system.

We talked about needing clear guidelines for positive results, what tests should be ordered and in what order. If you have a tissue of origin, and it points to maybe one of the screenable cancers, maybe that would be first, then followed by something else. But I think that can't be something that each clinician has to figure out with a positive test. It needs to be really clear in whatever messaging is put out as these tests are approved. And then, there's so many unanswered questions, and this will be, we think that, people are really wanting this test, and it's going to be a big moneymaker for the companies developing the test, possibly having a post-marketing registry where all participants are enrolled. It's really not an option. Everybody's enrolled in these post-marketing registries. And then we can look at the questions that we can't answer right now, likewhat should the interval be for repeating after a negative test, after a positive test with a negative workup? And what about longer term outcomes including secondary cancers, morbidity, and mortality?

Dr. Gallagher: Thank you. So my opinions, my expert opinions, from the meeting today are, first of all, thank you very much. I think it has been a very interesting day and I appreciate everyone respecting each other and giving good thought to all the questions that were provided to us. I guess what I think of screening, I think of screening more as a public health event, than the diagnosis and treatment of a person who is found to have a disease. And so, I know for lots of our discussion today, we jumped through to the - what happens to the person who gets a positive or a negative to the person for that diagnosis and treatment portion. But I guess for myself, I just keep going back to how would this also affect the general public health of the country if we had

testing that would be able to determine whether or not a person was likely to have a cancer, based on what we learned from that blood test.

And I think it, it might overwhelm some systems within our system, but it also might prevent some things from happening, that are happening now that shouldn't. So hopefully it would level out over time. It's not something that I think we could get through quickly, with being overwhelmed in those things. But I think that, when we shifted from the screening portion to the actual, what we would have to do next, I think having a test or set of tests, that also includes the TOO, becomes really important whenever that's possible. Because that then helps those next steps not be as drastic, in the sense of we may not have to do five diagnostics things, maybe we only have to do one or two. Those kinds of things. So I think that will make a difference to this, and certainly to the person who is given that information, but also to the system itself, and how we can provide.

I think that the high-risk kinds of cancers, or people who are at high risk, are the kinds of things that we would hope for these tests to do, at least I would, at the beginning. Because so often people who are at high risk are the underserved. And so I think having some additional tools that would be less cumbersome upon them, would be of benefit. And I have to chuckle at talking about being an hour and a half away from something. I live in Houston, everything's an hour and a half away. So, you can live in a rural area or a big city and it can still not be as accessible as you would want it to be. So I think that's another key element.

When I think about what are the risks, I think we've named several of them. And, for me, I'm an ethicist by trade, and so I see people who are in a crisis. They've just gotten information and they don't know what decisions to make and where to go, and maybe they're given three possible treatment plans, and they don't know what to do. I come at this also very much thinking

about those patients, who would be given this information about ‘oh this was a test result’. And that's where I think the education of the practitioners who would be giving the tests or ordering the tests and giving that information back is so essential. I know I've been part of other FDA panels where the education aspect has become a vital part of the process of utilizing whatever the device is or whatever. So I think this is another place where that becomes important.

So I think that we have to look at this from start to finish. It's not just the mechanics of, does the test do what we think it does, it's where does the test fit within the scope of our healthcare system and caring for our public? So maybe my view's a little bit different in that way than I come at the screening portion from that particular vantage point. So I will stop there. So we've done our round robin. So at this time, what I'm going to do, is ask the FDA to be prepared so that we can hear their summations and comments and clarifications. Dr. Stenzel.

Dr. Stenzel: Well, first of all, thank you, to everybody who's part of the panel and everybody who's dialed in to watch this. And I'll say more thanks later, but I did want to make a couple of clarifications about what's in the wheelhouse of the FDA and what's not. So there has been a very robust and wide-ranging discussion today, and lots of important things. We were listening to the things that, well we're listening to everything, but we're focused on the things that are in the FDA's wheelhouse. So I know there's mention of reimbursement and that's not in what FDA's wheelhouse. However, that's decided by CMS and payers. But we do have a program, and we do have a relationship with CMS, a close one, and if a test developer wants to invite CMS to their meetings with the FDA, and/or many other payers have signed up for this program as well,the test developers are welcome to invite them to the discussions that they're having with the FDA, so that everything can be discussed at the same time. Not just FDA approval, but also reimbursement. That is a very important program, and there are test developers who take

advantage of that. And we do encourage it, because we know that if it's a good test and people want it, they want there to be reimbursement. And whereas reimbursement is not in our wheelhouse, we have partners who are welcome to work with us. And it's up to the test developer to make those invitations. But, so I'll go through my thanks, and then I'll leave a little time, I'll definitely leave time for Dr. Roscoe, if you want to make any comments too.

First of all, Dr. Gallagher, thank you for chairing this panel. You told me that this is the first time you've chaired a panel that we've been on, more than 10, I forget, 14, 15 panels before. As far as chairing your first panel, you did a great job. Thank you. And I do want to, again, thank all of the panelists. I want to thank all of the public speakers. I want to thank, on the panel, our consumer rep, our patient rep, and our industry rep for being here. Your input is very important as well. I want to thank everybody, especially patients and patient advocates, who have dialed into this meeting. I hope you found this meeting informative and helpful. The FDA is interested in authorizing new cancer tests that are going to help save lives. This is all about finding the best way to do that. And the best ways to do that include doing it as quickly as we can. And with that, I think I'll turn it over to Dr. Roscoe in case you have any remarks to make.

Dr. Roscoe: Are you turning it over to me, Tim? I didn't hear you really well.

Dr. Stenzel: Yes, I am.

Dr. Roscoe: Okay. Okay.

Dr. Stenzel: You were essential.

Dr. Roscoe: I'll say a few things. So I think this is really exciting and interesting that we're in this era of medical breakthroughs in cancer, and that we're all witnessing and experiencing what's probably going to be looked at in 200 years in retrospect, as similar to the Industrial Revolution. It's just a revolution in diagnostics, thanks to all of the technological advances. And so we have

to have the FDA find a way to promote this and understand the benefit and the risks with this particular diagnostic test. And the questions today were really around trying to understand, how can we support this type of test, given that we all really understand the benefits. It will detect more cancer. It might improve compliance with cancer detection. But also all of the risks. So a lot of the questions were designed to gain information about what the risks are, whether we could help establish best practices with study designs, whether we could mitigate some of these risks through study designs. We certainly heard you loud and clear about some of these topics with TOO.

And, finally, one of the things, and also I want to just say that I also heard very loud and clear that communication is going to be the most important mitigator here. Helping the patients and the physicians understand the limitations of this test, and what is likely to be the patient experience. And that is the role of the FDA. And some of the questions were designed to help us understand that. And so we do have the authority to help generate physician and patient labeling, which will definitely be something that we'll look at. We understand that physicians such as yourselves are really taxed for time, when you're up in the front line with all of your patients and you have to get through so many patients in the day, and you have a lot of other responsibilities that are pressing on you. So, we may look outside the box for different types of risk mitigation measures that help minimize some of that effort that would be your responsibility. Maybe, we could work with test developers to develop videos that have opt-in procedures. We've done things like this before with genetic testing. So, definitely communication is going to be key here so that everyone understands what the limitations are, as well as the benefits moving forward.

And things will always get better. Things will always continue to improve and hopefully as generations come, everyone will experience the benefit from these types of tests. So, I think

that's just all I want to say. And to also echo Dr. Stenzel's appreciation for your time. It was definitely a long day, a ton of topics. You were extremely helpful in providing valuable information to us. I also would like to thank my FDA colleagues in the background who did a lot of work to get this in place and to get this program, this advisory panel set up. There was a ton of moving parts in the background, and a lot of challenges that we had to navigate along the way.

So thank you to them as well. And thank you, Dr. Gallagher. You did an excellent job chairing this and I really appreciate your time.

Dr. Stenzel: Thank you Donna and I echo thanks to our FDA team who are behind the scenes supporting all of these efforts. And I just want to talk about next steps. We have all the public comments now. We have, in the form of a transcript that will be generated very quickly, we have all of your comments. And we will be pouring over these in detail, and using them to help make the very best decisions going forward. So thank you.

Adjournment

Dr. Gallagher: Thank you everyone. At this time, I'm giving one last chance to our panelists to add any more comments before we prepare to close out the day. Any more burning issues? I'm not seeing any hands.

Okay, I want to thank the FDA panel, the open public hearing speakers. I want to thank our AV crew, and I want to thank the FDA people who are behind the scenes. There are several of them. Some that I've encountered in preparation for the meeting and others who've been done months of preparation even before that.

And I also want to thank the developers, who have brought new thoughts and new methods to the world in which we live. So we're grateful for all of those. So at this time, I'm going to say that the meeting of the molecular and clinical genetics panel is adjourned. Thank

you all.