SUMMARY MINUTES

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MOLECULAR AND CLINICAL GENETICS PANEL MEETING

CANCER SCREENING DEVICES

November 29, 2023
9:00 a.m. EST

Attendees

Temporary Voting Chairperson
Colleen M. Gallagher, Ph.D.
Sr. Counselor, Bioethics & Health Policy,
Department of Ethics
Chief Medical Executive
The University of Texas MD Anderson Cancer Center
Houston, TX

Voting Members
Philip E. Castle, Ph.D., M.P.H.
Director
Division of Cancer Prevention
Senior Investigator, Division of Cancer Epidemiology and Genetics
US National Cancer Institute
Rockville, MD

Edward J. Bujold, M.D.
Family Medicine
Granite Falls Family Medical Care Center
Granite Falls, NC

Peter R. Carroll, M.D., M.P.H.
Professor of Urology
Department of Urology
University of California San Francisco
San Francisco, CA

Temporary Non-Voting Members
Mitchell Gail, M.D., Ph.D.
Senior Investigator
Biostatistics Branch
National Cancer Institute
National Institutes of Health
Rockville, MD

Daniel R. Swerdlow, M.D., FSRU
Professor
Department of Radiology
MedStar Health
Washington, D.C.

Deb Schrag, M.D., M.P.H.
George Bosl Chair

Department of Medicine
Memorial Sloan Kettering
New York, NY

Stanley Lipkowitz, M.D., Ph.D.
Chief and Senior Investigator
National Cancer Institute
National Institutes of Health
Bethesda, MD

Rebecca B. Perkins, M.D., M.Sc.
Professor of Obstetrics and Gynecology
Boston University Chobanian and Avedisian School of Medicine/Boston Medical Center
Boston, MA

Karla V. Ballman, Ph.D.
Consultant, Division of Clinical Trials & Biostatistics
Professor of Biostatistics, Mayo Clinic College of Medicine and Science
Associate Director of Quantitative Health Sciences, Mayo Clinic Comprehensive Cancer Center
Director, MCCCC Biostatistics Shared Resource
Rochester, MN

Mary Margaret Kemeny, M.D.
Surgeon
New York Health and Hospitals Corporation
Queens, NY

Industry Representative
Nathan Winslow
Global Head
Global Regulatory Affairs
Roche Diagnostics
San Anselmo, CA

Consumer Representative
Karen Rue, RN-BC, M.B.A.
Board Certified Gerontology Nurse
Aging Life Care Professional®
Owner Hailind Consulting LLC

Patient Representative
Deneen Hesser, MSHSA, RN
Patient Representative
Chicago, IL

FDA Participants

Timothy Stenzel, MD, PhD
Office Director
CDRH/OPEQ/OHTVII, FDA - Silver Spring, MD

Donna Roscoe, Ph.D.
Division Director
CDRH/OPEQ/OHTVII/DMGP, FDA - Silver Spring, MD

Designated Federal Officer
Candace Nalls,
FDA - Silver Spring, MD

CALL TO ORDER

Dr. Colleen Gallagher, senior counselor for bioethics and health policy at the University of Texas MD Anderson Cancer Center, chaired a meeting of the Molecular and Clinical Genetics Panel. The meeting aimed to discuss and provide recommendations on the design of multi-cancer detection (MCD) in vitro diagnostic devices or tests. The agenda included considerations for potential study designs and outcomes that could inform the assessment of the benefits and risks associated with MCD screening tests. **Dr. Gallagher** emphasized that the discussion and recommendations from the meeting would contribute to future regulatory efforts by the FDA for these innovative tests. The meeting was a non-voting session.

PANEL INTRODUCTIONS

Dr. Colleen Gallagher, the chairperson, introduced attendees and requested attendees state their area of expertise, position, and affiliation. The panelists introduced themselves as follows: **Dr. Philip Castle**: Director of the Division of Cancer Prevention and Senior Investigator in the Division of Cancer Epidemiology and Genetics at the US National Cancer Institute, specializing in cancer prevention and screening. **Dr. Peter Carroll**: Professor of urology at UCSF and a member of the Cancer Center, focusing on the early detection of prostate cancer and its treatment. **Dr. Mitchell Gail**: Medical statistician in the Division of Cancer Epidemiology and Genetics at the National Cancer Institute, serving as a senior investigator. **Dr. Daniel Swerdlow**: Professor of radiology at Georgetown University, specializing in abdominal imaging and running the CT colonography program for colorectal cancer screening. **Dr. Deb Schrag**: Medical oncologist, gastrointestinal medical oncologist, and health services researcher, serving as the chair of the Department of Medicine at Memorial Sloan Kettering. **Dr. Stanley Lipkowitz**: Chief of the Women's Malignancies Branch at the National Cancer Institute, with expertise in the treatment and management of breast cancer patients. **Dr. Rebecca Perkins**: Professor of obstetrics and gynecology at Boston University and Boston Medical Center, involved in cervical cancer screening and management guidelines. **Dr. Carla Ballman**: Professor of biostatistics at Mayo Clinic, also serving as an associate director of quantitative health sciences for the cancer center at Mayo, specializing in clinical trial design. **Dr. Mary Margaret Kemeny**: Professor of surgery at Mount Sinai Medical School, a surgical oncologist,

and the director of the Queens Cancer Center. **Nathan Winslow:** Industry representative for the panel and global head of regulatory affairs with Roche Diagnostics. **Deneen Hesser**: Patient representative, two-time cancer survivor, and oncology nurse affiliated with the National Cancer Institute Center for Strategic Scientific Initiatives. **Dr. Timothy Stenzel**: Director of the Office of In vitro Diagnostics at the FDA, a molecular pathologist with extensive experience in laboratory medicine in cancer. **Dr. Donna Roscoe**: Acting Division Director for the Division of Molecular Genetics and Pathology in the Office of In Vitro Diagnostics at the FDA, responsible for reviewing tests seeking marketization. **Karen Rue**: Owner of Halen Consulting and consumer representative with expertise in women's and children's health and geriatrics. **Dr. Edward Bujold**: Primary care physician in Western North Carolina, representing the American Academy of Family Practice

CONFLICT OF INTEREST STATEMENT

Ms. Candace Nalls, in her role as the representative of the Food and Drug Administration (FDA), opened the Molecular and Clinical Genetics Panel meeting. She informed the participants that the meeting was convened under the authority of the Federal Advisory Committee Act (FACA) of 1972. **Ms. Nalls** provided information on the Panel's compliance with Federal ethics and conflict-of-interest laws, including the fact that the FDA had determined that the members and consultants were in compliance. She explained that waivers under 18 U.S.C. §208 could be granted by the FDA when the agency's need for an individual's services outweighed their potential financial conflict of interest.

The agenda for the meeting included discussions and recommendations on the design of multi-cancer detection (MCD) in vitro diagnostic devices, study designs, and outcomes related to the assessment of the benefits and risks of MCD screening tests. **Ms. Nalls** emphasized that no conflict-of-interest waivers had been issued based on the financial interests reported by the Panel members and consultants. **Mr. Nathan Winslow** was identified as the industry representative from Roche Diagnostic Solutions, and **Dr. Colleen Gallagher** was noted as the Chairperson for the meeting.

Ms. Nalls reminded participants to exclude themselves from discussions involving products or firms for which they had a personal or imputed financial interest. She encouraged participants to disclose any financial relationships with relevant firms. **Dr. Stanley Lipkowitz** was announced as a Temporary Non-Voting Member for the duration of the meeting, with disclosure of his role as a consultant to the Oncologic Drugs Advisory Committee.

Ms. Nalls concluded with general announcements, including the request for participants to identify themselves when speaking and providing contact information for press inquiries. The meeting was then turned over to **Dr. Colleen Gallagher**, who invited **Dr. Timothy Stenzel** to give opening remarks.

WELCOME: DR. TIMOTHY STENZEL

Dr. Timothy Stenzel, Director of the Office of In vitro Diagnostics at the FDA, expressed gratitude to **Ms. Candace Nalls**, **Dr. Colleen Gallagher**, the distinguished panelists, speakers, and the audience for participating in the meeting. **Dr. Stenzel** highlighted the careful selection of a diverse range of experts, including those from primary care to specialized oncology professionals and patient advocates.

Acknowledging a gap in the panel concerning pathologists and laboratory medicine experts, **Dr. Stenzel** encouraged professionals and the public to submit comments to the docket for the meeting. He emphasized the importance of today's topic, focusing on the widespread identification of cancers across various types and early intervention for potential therapeutic cures.

FDA PRESENTATION

Dr. Colleen Gallagher opened the meeting, introducing the FDA's presentation on in vitro diagnostic multi-cancer detection tests.

Dr. Timothy Stenzel, director of the Office of In Vitro Diagnostics at the FDA, then welcomed participants, highlighting the importance of the meeting on multi-cancer detection tests. **Dr. Stenzel** discussed the FDA's mission to advance and protect public health, emphasizing the agency's focus on cancer outcomes improvement. He mentioned the Oncology Center of Excellence and health equity initiatives. Noting that two million cancers are expected to be diagnosed in the U.S. that year, **Dr. Stenzel** highlighted the impact of screening programs on lowering mortality rates for certain cancers, though challenges remain for cancers lacking screening programs.

He provided insights into routine screening programs in the U.S., covering approximately 30% of incident cancers, with significant contributions from colorectal, cervical, breast, lung, and prostate cancer screenings. **Dr. Stenzel** outlined current preventative screening methods for various cancers, such as mammography for breast cancer, stool-based tests and colonoscopy for colorectal cancer, HPV tests and Pap tests for cervical cancer, low-dose CT scans for lung cancer, and the PSA test for prostate cancer. He then introduced **Dr. Donna Roscoe**.

Dr. Colleen **Gallagher** opened the meeting, introducing the FDA's presentation on in vitro diagnostic multi-cancer detection tests. She reminded public observers that while the meeting is open for observation, public attendees may not participate unless specifically requested by the Panel chair. **Dr. Timothy Stenzel**, director of the Office of In Vitro Diagnostics at the FDA.

Dr. Donna Roscoe provided an in-depth overview of the FDA's approach to reviewing diagnostic tests for cancer screening, emphasizing the agency's historical focus on single cancer tests. The review process involves a thorough examination of the intended use statement, covering aspects such as analyte identification, technology, target population, and associated limitations. Analytical and clinical validation studies, conducted in large, diverse trials, play a crucial role in assessing test performance.

Dr. Roscoe highlighted the significance of evaluating tests in subjects with comorbidities, she discussed key considerations, including sensitivity, specificity, and positive predictive value (PPV), especially for rare diseases. The FDA assesses whether a test provides a reasonable assurance of safety and effectiveness, considering benefits against risks, and may employ risk mitigation strategies.

Dr. Roscoe sought the panel's input on clinical study design considerations, including study size, enrollment strategies, and the need for evidence of per-cancer performance. Questions

encompassed comparisons with existing screening methods, historical biomarkers, and balancing benefits and risks for MCEDs.

The subsequent topics addressed confounding variables, non-malignant comorbidities, cancer-specific risk factors, and appropriate follow-up for positive MCED results. **Dr. Roscoe** concluded by expressing gratitude and anticipating a productive discussion on clinical validation and studies needed for MCEDs.

Dr. Gallagher expressed gratitude to **Dr. Roscoe** and **Dr. Stenzel** and passed the presentation to Ms. Nall to read the open public hearing disclosure process statement.

Ms. Nalls began by emphasizing the shared commitment to transparency between the Food and Drug Administration (FDA) and the public during the open public hearing session of the advisory committee meeting. Speakers were encouraged to disclose any financial relationships with companies or groups affected by the meeting's topic. This disclosure could include financial support for travel, lodging, or related expenses provided by such entities. Speakers were also given the option to declare the absence of such financial relationships without any consequence to their eligibility to speak.

Dr. Gallagher acknowledged Ms. Nalls' statement, mentioning that the FDA had received twelve requests for public speaking. Each speaker was allocated five minutes for their presentation, starting with prerecorded presentations. The initial speaker was **Dr. Joshua Ofman**.

Dr. Ofman, the president of GRAIL, presented insights on the need for a paradigm shift in cancer screening due to the current challenges in detecting cancers at advanced stages. He stated GRAIL's MCD technology, measuring abnormally methylated DNA through a blood test, showed promise in detecting various deadly cancers with high specificity and a low false positive rate. **Dr. Ofman** stressed the importance of evaluating MCD test benefits through aggregate measures, focusing on positive predictive value, cancer yield, reduction in late-stage cancer incidence, and mortality modeling.

Dr. Sana Rauf, a practicing physician at Memorial Sloan Kettering Cancer Center, proposed a novel clinically relevant endpoint for assessing the value of molecular cancer screening tests and receipt of curative intent treatment. **Dr. Rauf** highlighted the ethical challenges of conducting randomized trials to quantify the value of early detection but stressed the intuitive understanding among oncologists about the importance of curative interventions for improving patient outcomes. She presented an analysis supporting the correlation between curative interventions and improved long-term survival, suggesting this endpoint as a valuable measure for assessing the impact of screening tests.

Mr. Roger Royse, a cancer patient, shared his experience with multi-cancer early detection. He expressed gratitude for the opportunity to present his case and underscored that without multi-cancer early detection, he would not be alive today. **Mr. Royse** was diagnosed with pancreatic cancer 18 months prior, and early detection played a crucial role in his survival. He recounted his struggle to obtain the Galleri test by GRAIL, Despite the hurdles, **Mr. Royse**

emphasized that the Galleri test detected a signal for pancreatic cancer, prompting further diagnostic imaging that confirmed the mass on his pancreas.

Mr. Royse highlighted the simplicity and efficacy of the Galleri test, conducted through a liquid biopsy, contrasting it with outdated recommendations from the US Preventive Services Task Force. **Mr. Royse** urged the FDA to expedite the approval of multi-cancer detection tests, enabling insurance coverage and broader accessibility to save lives promptly.

Ms. Valerie Caro expressed her gratitude for the opportunity to share her experience, after learning about the Multi-Cancer Early Detection (MCED) test, which could screen for fifty types of cancers with a single blood draw. Despite not having a family history of cancer, she decided to take the test annually. The test revealed signals for breast cancer and gallbladder or pancreas issues. While the chest MRI came back clear, an issue with her gallbladder was identified, prompting surgery. Unexpectedly, a cancerous tumor in her gallbladder was discovered during the procedure, emphasizing the importance of the MCED test.

Ms. Caro shared the subsequent whirlwind of activities, including consultations with various medical teams, surgeries, chemotherapy, and navigating health insurance intricacies. She completed chemotherapy and in her six-month follow-up, received the news that she was cancer-free. **Ms. Caro** credited the MCED test, specifically the Galleri test, with saving her life, and emphasized that it is the future of healthcare.

Dr. Gutierrez expressed gratitude for the opportunity to present to the FDA Advisory Committee meeting. He conveyed the FDA's support for developing multi-cancer detection tests and emphasized the need to establish an appropriate evidentiary threshold for test approval and subsequent reimbursement decisions. Dr. Gutierrez highlighted the unique challenges of evaluating multi-cancer screening tests.

He underscored the impracticality of a single aggregate evaluation for multi-cancer tests due to these differences and advocated for the design of a single study supporting multiple intended uses. **Dr. Gutierrez** discussed the necessity of pre-specifying a timeframe for specimen collection, emphasizing the complexity of designing cohort studies to establish clinical truth for each cancer. He concluded by expressing appreciation for the time.

Dr. Robert Smith, presented on behalf of the American Cancer Society. He emphasized the significant burden of cancer in the U.S. and the challenges posed by the lack of effective screening for many cancers. **Dr. Smith** highlighted the potential of multi-cancer early detection (MCED) tests to shift the stage of diagnosis and potentially save lives, particularly for cancers without existing screening strategies. He stressed that reducing the incidence rate of advanced cancers should be the primary endpoint for MCED, as it aligns with the goal of cancer screening. **Dr. Smith** recommended measuring conventional outcomes and ensuring that existing care pathways are followed. He expressed concern about adults forgoing conventional screening tests due to reliance on MCED and advised strong communication from organizations and clinicians to clarify MCED's role as a supplement, not a substitute.

Dr. Dax Kurbegov, Vice President, Physician in Chief at Sarah Cannon, spoke on behalf of the organization, emphasizing the capability of large health systems like HCA Healthcare to identify populations at risk for various cancers based on genetic, familial, or other risk factors.

Sarah Cannon, with extensive experience in multi-cancer early detection (MCED), has enrolled over 25,000 patients in studies ranging from preclinical to development and validation.

Dr. Kurbegov highlighted the potential of MCEDs to save over 100,000 lives annually by detecting a broad range of cancers, including highly lethal ones like pancreatic, biliary, ovarian, and lung cancers. He urged the FDA panel to consider alternative endpoints, such as AJCC stage-related endpoints, providing more timely and actionable insights than cancer-specific mortality. **Dr. Kurbegov** recommended avoiding an overemphasis on single tumor performance comparisons and acknowledged the challenges of conducting studies solely focused on cancer-specific mortality.

Dr. Mylynda Massart, a molecular biologist and family medicine physician at UPMC, presented her independent perspective on multi-cancer early detection (MCED) during an FDA Advisory Committee meeting. Despite her association with GRAIL, she emphasized her independent stance. Drawing on her experiences in rural healthcare and as a cancer survivor, **Dr. Massart** underscored the urgent need for clinically validated tools like MCED to detect various cancers at early, asymptomatic stages. She highlighted the impact of late-stage cancer diagnoses, Dr. Massart introduced MCED in her clinic to provide cutting-edge genomic technology to her patients, acknowledging the financial barrier for many until insurance coverage is available. She emphasized the value of MCED in detecting cancers, especially those with few early symptoms, and reducing false positives compared to traditional screening methods.

Dr. Massart supported the transition to aggregate screening like MCED to address time and access barriers associated with routine single-organ screenings. Sharing positive experiences of her patients with MCED, she advocated for equitable availability, particularly for African American patients facing higher mortality rates due to delayed cancer diagnoses.

Dr. Tom Beer, Chief Medical Officer for multi-cancer early detection at Exact Sciences, emphasized the primary goal of reducing cancer mortality and morbidity through successful screening programs. He acknowledged the limitations of current screening benefits, which are applicable to only a few cancers, leaving a majority with no guideline-recommended screening options. Dr. Beer proposed the development of multi-cancer screening tests that collectively search for cancers, leveraging their aggregate prevalence.

Dr. Beer suggested measuring the performance of multi-cancer tests across aggregate cancer types rather than evaluating each cancer individually. He argued that this approach aligns better with public health needs and the design of multi-cancer tests, emphasizing the importance of considering outcomes' heterogeneity within and across individual cancer types.

Dr. Beer proposed evaluating test efficacy through prospective randomized controlled trials reflecting the diversity of the US population. While expressing concern about imposing a cancer-specific mortality requirement for clinical utility, considering it a significant impediment to progress, he stressed the need for flexibility in diagnostic resolution strategies for positive multi-cancer test results and discouraged being prescriptive about specific methods at this time.

Dr. Ruth Etzioni, a biostatistician and cancer modeler at the Fred Hutch Cancer Center, highlighted the urgency and challenges in evaluating multi-cancer early detection tests. She emphasized the difficulty in assessing diagnostic performance, safety, and efficacy, given the unprecedented volume of tests seeking approval. While acknowledging the sense of urgency, **Dr. Etzioni** cautioned against potential disappointments based on past experiences with promising

tests. She underscored the complexity of cancer screening, emphasizing the variability in test performance and outcomes for different cancers. **Dr. Etzioni** urged collaboration across regulatory, academic, and policy sectors to establish new evidence standards and changes to the evaluation pipeline. She raised critical questions about endpoint acceptance and the maintenance of rigorous standards in screening trials. **Dr. Etzioni** called for collective efforts to create a new action plan for early cancer detection, prioritizing validity over urgency while seeking to improve efficiency.

Dr. Girish Putcha, a molecular genetic pathologist, discussed considerations for multi-cancer early detection (MCD) tests and proposed a tiered evaluation approach. He emphasized the complexity of cancer and suggested a tiered system for MCD test claims, similar to tumor profiling next-generation sequencing. **Dr. Putcha** recognized varying definitions of clinically impactful early detection for different cancers, emphasizing that early detection is a measure of clinical validity, not utility. He outlined principles such as the importance of clinical validation in the intended use population, pre-specification and statistical powering of endpoints, and consideration of clinical truth based on diagnosis within a specified time. **Dr. Putcha** stressed the need for transparency and consistency in defining endpoints, cautioning against focusing solely on overall mortality and advocating for a rigorous approach, including randomizing standard care versus MCD tests, assessing both surrogate and hard endpoints, and potentially using real-world data.

Mr. Puckrein, representing the National Minority Equality Forum, emphasized the importance of equity in multi-cancer early detection (MCED) tests, particularly for the African-American population. He highlighted the significant cancer burden faced by African Americans, including high incidence rates, challenges in late-stage diagnoses, limited access to clinical trials, and poor survival rates. **Mr. Puckrein** saw MCEDs as an opportunity to address cancer disparities by enabling early-stage diagnoses, especially in underserved communities. However, he expressed concern that existing inequities influenced by public policy could be exacerbated if MCEDs are not made accessible to all populations. Urging a sense of urgency, **Mr. Puckrein** called for the FDA to actively work against further disparities in cancer care and ensure that MCED technologies are available to all communities, preventing the widening of existing gaps.

Ms. Rue shared a personal story about a friend in his sixties who, despite undergoing various medical procedures and X-rays over the past year, was recently diagnosed with metastatic renal cell carcinoma that had spread to his brain. In response, Dr. Beer expressed empathy for **Ms. Rue's** friend's situation and acknowledged the challenges in individual cases. He highlighted different methods for localizing and detecting cancer, emphasizing the need to study and determine the most effective approaches. **Dr. Beer** suggested that a comprehensive imaging approach might offer a quick path to diagnostic resolution and recommended considering various methods in discussions about diagnostic strategies.

Dr. Gail expressed concerns about the GRAIL system, questioning the challenges in confirming the presence or absence of cancer and the standards for operational assessment. He raised issues about proving disease existence when the GRAIL test is positive and the process of demonstrating cancer absence when the test is negative. He called for a discussion on the operational methods used to determine a patient's cancer status. In response, Mr. Royse shared

his positive experience with the GRAIL test, noting that the report provided specific information about potential cancer types, leading to further investigation through a full-body MRI. **Ms. Etzioni** emphasized the importance of scrutinizing performance metrics in context, particularly focusing on positive predictive value (PPV) and its limitations.

The open public hearing was officially closed by **Dr. Gallagher**, and a five-minute break was announced. After the break, the meeting resumed, and **Dr. Gallagher** welcomed everyone back, indicating that they were about to move into topic number one. **Dr. Gail** had the first question.

Dr. Gail sought clarification on the term Multi-Cancer Detection (MCD) and its scope, presenting three options: a global test with no localization, a global test followed by localization if positive, or a global test combined with a Tumor of Origin (TOO) test regardless of the initial result. **Dr. Castle** clarified that MCD is a panel detecting a specific number of cancers, each with a strategy for managing positives. TOO provides a probability score for the cancer's location, but challenges arise in setting probability thresholds and determining follow-up care when cancer is not found. The FDA's questions align with the National Cancer Institute's trial, evaluating mortality benefits, adherence, diagnostic pathways, and best practices. Tests like GRAIL provide a probability score, not a separate second test. **Dr. Stenzel** clarified the FDA's openness to different MCD approaches, defining it as detecting two or more cancers, with variation in cancer location determination among technologies, potentially involving a separate assay or imaging after a positive result.

Dr. Carroll sought clarification on the specific goals of the meeting, questioning whether the focus is on trial design and test characteristics, and he sought clarification on the intended scope of their discussions. **Dr. Stenzel** responded by clarifying that the meeting has three topical areas, each with specific questions outlined in the slide decks. The overall discussion is aimed at exploring important features of trial design, questions about test performance, and consideration of the benefits and risks associated with multi-cancer early detection.

Ms. Hesser asked about whether any multi-cancer early detection (MCED) developers have been granted breakthrough status by the FDA and if there were specific guidance provided regarding what the FDA is looking for in such cases. **Dr. Stenzel** responded by stating the FDA's approach to breakthrough designation for multi-cancer early detection (MCED) tests..

Dr. Stan Lipkowitz from NCI raised a question comparing the approval process for drugs, which includes accelerated approvals based on surrogate markers, to the process for devices or tests like multi-cancer early detection (MCED). He inquired whether there is a similar mechanism for provisional approval of MCED tests based on certain criteria, with subsequent data required to demonstrate clinical benefit beyond the initial approval. The question aimed to explore the appropriate bar for allowing MCED tests into the public space and whether there are mechanisms for adjustments or withdrawals based on additional evidence. **Dr. Stenzel** clarified that while the FDA doesn't have an exact program like accelerated approvals for drugs and biologics, they do have the breakthrough designation program. For tests designated as breakthroughs, the FDA accelerates the review process, aiming to complete the reviews in less time than required by law for those types of applications.

SESSION ONE PANEL DELIBERATIONS
QUESTION ONE

Dr. Gallagher posed question 1 to the panel, discussing the advantages and disadvantages of different study designs for multi-cancer detection (MCD) tests. He inquired about the necessity of a control arm, the optimal size and enrollment strategies, and considerations for data subjects from non-US sites. Additionally, he addressed defining high-risk patients for MCD and whether it is acceptable to enrich studies with high-risk individuals.

Dr. Kemeny emphasized the importance of including minority and low socioeconomic populations in MCD studies, expressing concern that many studies predominantly focus on more affluent white populations. She stressed the need for a concerted effort to ensure representative percentages of minority groups in these studies, considering that minority populations may already have higher cancer stages at diagnosis.

Dr. Castle advocated for cancer-specific mortality as the primary endpoint for MCD clinical validation. He argued against relying solely on surrogate endpoints, such as reductions in advanced-stage cancer, without demonstrated correlations with mortality benefits. **Dr. Castle** highlighted the limitations of inferring benefits for specific cancers from trials dominated by more common cancers and emphasized the importance of an unbiased evaluation with mortality endpoints. He expressed concern about potential harm caused by insufficiently validated tests, emphasizing the need for a careful assessment of each technology, considering different target cancers and populations.

Ms. Rue addressed several points during the discussion on multi-cancer detection (MCD) studies. She emphasized the inclusion of the pediatric population in MCD studies due to differences in cancer types and higher testing frequency in younger individuals. **Ms. Rue** highlighted the importance of addressing issues related to the targeted population and advocated for better communication and information for the population being studied. Drawing from personal experience, she suggested leveraging tumor boards and a national database to improve follow-up and reduce the number of individuals lost to follow-up after testing.

Dr. Gail stressed the significance of considering mortality reduction as the ideal endpoint for MCD studies, acknowledging the challenges of conducting randomized trials. He proposed preliminary studies to assess the potential of MCD before committing to long-term mortality reduction trials. **Dr. Gail** raised questions about determining the sensitivity of an MCD, especially in a target population where the prevalence of cancer is unknown. He highlighted the challenges of evaluating sensitivity and specificity without a clear operational definition of "any cancer present" in a target population, emphasizing the need for grappling with these issues to gather preliminary evidence.

Dr. Stenzel clarified that there is no preliminary approval program for in vitro diagnostic (IVD) devices. She mentioned the breakthrough program, which doesn't authorize the test but recognizes the technology's potential, allowing for an accelerated review. However, she

emphasized that the standard for review remains the same, with the potential for a shorter review time.

Dr. Ballman expressed agreement with the points made by **Dr. Castle** and **Dr. Gail** regarding mortality as the endpoint for evaluation. She also raised concerns about follow-up in underserved populations, emphasizing the importance of tracking and assessing whether individuals in those populations who test positive are receiving necessary follow-up care.

Dr. Perkins presented an alternative viewpoint, expressing concerns about relying solely on mortality as an endpoint, emphasizing the potential delays in waiting for people to die. She suggested considering early diagnosis as an important endpoint, especially if it enables treatment with curative intent. **Dr. Perkins** also discussed concerns about people forgoing other screening tests and safety net populations not following up, highlighting the need for patient navigation and support to overcome these challenges.

Dr. Bujold shared insights from his experience in primary care, drawing parallels to the PSA test for prostate cancer screening. He emphasized the importance of properly vetting tests, considering well-controlled designs, and using the right populations. **Dr. Bujold** acknowledged potential risks associated with screening tests and highlighted a case involving sepsis and multi-organ failure after a biopsy, underscoring the need for careful consideration in implementing new screening methods.

Dr. Swerdlow expressed support for mortality as an endpoint but raised concerns about the specificity of cancer-specific mortality. He highlighted the complexity when a positive test indicates varying likelihoods for different cancers, leading to a subsequent workup. **Dr. Swerdlow** suggested considering all cancer screening deaths, regardless of specific cancer types, as the endpoint to account for cases where screening tests may miss certain cancers.

Mr. Winslow expressed concerns about the feasibility of mortality as an endpoint due to the size and duration of studies, emphasizing the potential impact on innovation. He suggested taking a holistic approach to assess benefit-risk, considering factors like healthcare equity and increased compliance with existing screening methods. **Mr. Winslow** urged not to solely focus on the gold standard clinical endpoint but to explore alternative ways of evaluating benefits and risks to avoid unnecessary delays in introducing potentially beneficial technologies.

Dr. Stenzel clarified that for standalone in vitro diagnostic (IVD) tests not linked to other therapies, the FDA primarily assesses analytical and clinical validity, not mortality as an endpoint, as it falls into the realm of clinical utility, which is not considered for this type of submission. However, he emphasized that the FDA thoroughly evaluates overall benefits versus risks, considering various scenarios.

Dr. Ballman expressed concern about using early intervention as an endpoint, emphasizing that detecting more stage one or stage two cancers does not necessarily indicate a meaningful benefit. She also questioned how one could demonstrate the cost-benefit ratio without mortality as an endpoint, highlighting the challenges of assessing the impact of aggressive treatment without clear evidence of survival benefits.

Dr. Stenzel highlighted the need to clarify what constitutes a benefit in the context of the submission. He emphasized the importance of assessing sensitivity, specificity, and positive predictive value as key factors in the benefit-risk calculation. **Dr. Stenzel** pointed out that a higher positive predictive value could minimize off-target risks, while a lower positive predictive value might pose increased risks to patients without cancer.

Dr. Castle expressed concern about the importance of distinguishing clinically relevant cancers when assessing positive predictive value. He emphasized the need for early detection to be linked specifically to clinically relevant diseases associated with improved patient outcomes, particularly survival. **Dr. Castle** highlighted the uncertainty around whether biologically specific tests would genuinely correlate with mortality, underlining the essential purpose of cancer screening in improving patient survival outcomes.

Dr. Stenzel clarified the FDA's legal constraints focusing on analytical and clinical validity. The assessment of clinical utility, including the impact on patient outcomes, falls under the purview of other entities such as insurers and CMS.

Dr. Castle emphasized the need for clear communication in authorizations, suggesting that if a test is authorized for detecting cancer, it should also include a statement conveying the uncertainty regarding whether this detection leads to a mortality benefit. He highlighted the importance of public understanding of the distinction between cancer detection and proven mortality benefit.

QUESTION TWO

Dr. Gallagher redirected the discussion to the topic of early cancer detection, emphasizing the need to explore how it can be defined and identified. This shift was made in response to the ongoing discussions regarding the challenges and nuances associated with endpoints like mortality and the distinction between cancer detection and mortality benefit.

Dr. Gallagher raised a question about the classification of early cancer detection, suggesting that to determine if a test truly enables early detection, multiple clinical trials may be necessary. She highlighted the importance of understanding when cancer is typically detected (e.g., stage 3) and how a new test could shift that detection to an earlier stage (e.g., stage 1) to qualify as early detection.

Dr. Stenzel responded to **Dr. Castle's** comments stating, based on existing legal authorities, the FDA cannot use mortality as an endpoint for this type of submission. He noted that any changes in this regard would require alterations to the FDA's authorities.

Dr. Kemeny stressed the importance of considering cancer stage rather than mortality as an endpoint. She highlighted the significance of early cancer detection, especially with the advancements in new drugs that can extend the lives of individuals with advanced-stage cancer.

QUESTION THREE

The discussion for question three revolved around the aggregation of multiple cancers into one study for MCD (Multiple Cancer Detection) validation. **Dr. Gallagher** initiated the conversation, prompting exploration of the benefits and limitations of a single aggregated study, considering the unique characteristics of each cancer. The question arose whether physicians should be informed of per-cancer performance. **Dr. Gail** addressed the previous question, proposing two definitions for early detection and emphasized the challenges of defining operational criteria for MCD tests. He presented three types of MCD tests and discussed statistical challenges, particularly in determining the true state of the patient.

Dr. Gail urged careful consideration of the definition of an MCD test by the FDA and the panel, especially in aggregate testing. **Dr. Gallagher** envisions the possibility of identifying a shared marker for all cancers in the future. **Dr. Ballman** suggested that new indications for multiple tests should outperform existing standalone standard-of-care tests. **Dr. Schrag** emphasized the challenge of validating mortality as an endpoint and stressed the importance of understanding interventions' impact on public health. **Dr. Stenzel** responded to **Dr. Gail's** question about determining the ground truth in MCD tests, suggesting using time as a factor in monitoring patients after negative results over a specific period. This approach aims to assess ground truth without being overly burdensome in clinical studies.

QUESTION FOUR

Dr. Gallagher shifted the discussion to Question four, focusing on the evaluation of MCD tests for cancers with current screening methods. The question raised considerations about comparing MCD test performance to recommended screening, discussing the risks of MCD tests performing poorly compared to alternative screening methods, and whether a specific cancer type should be contraindicated for the test if its performance is significantly lower than established alternatives. **Dr. Lipkowitz** emphasized the need for a randomized controlled study to address these questions, particularly comparing MCD tests to standard screening practices. He stressed the importance of factors such as sensitivity and clinical benefit and suggested a concurrent control group undergoing standard screening to assess the effectiveness of MCD tests. **Dr. Lipkowitz** also acknowledged challenges in interpreting positive MCD test results when traditional imaging methods fail to detect cancer.

Mr. Winslow underscored the intended complementary use of MCD tests, emphasizing their role in enhancing existing screening practices rather than replacing them. He suggested evaluating benefits and risks by comparing MCD tests with current methods, considering factors like invasiveness and test compliance. **Dr. Carroll** sought clarification on the trial design, specifically whether it involved comparing MCD plus standard of care versus standard of care alone. **Dr. Castle** confirmed that the comparison would indeed be between MCD plus standard of care and standard of care alone.

Dr. Castle highlighted the necessity of offering a standard of care in the trial design and discussed challenges related to potential reticence towards standard care over time. He mentioned the Vanguard pilot study aimed at exploring multi-cancer detection tests, emphasizing the importance of measuring adherence to standard care, especially for cancers like cervix and colorectal, where prevention is crucial. The trial is designed to address various topics raised in the panel discussion.

QUESTION FIVE

Question 5 focused on addressing potential bias in data collection and assessments. The discussion had delved into the critical data elements necessary to evaluate aggregated and per-cancer performance, taking comorbidities into account. Participants explored how conditions like cirrhosis, emphysema, inflammatory bowel disease, diabetes, smoking, obesity, and others could influence false positive results, discussing how these factors should be considered in both aggregate and per-cancer evaluations.

In addressing potential bias, **Dr. Gail** had highlighted the importance of having samples from the target population with a well-defined operational ground truth. He had emphasized the need to assess MCD performance in comparison to this ground truth. In cases where only case-control samples were available, he had suggested examining sensitivity across the spectrum of positive cases, considering the different stages of the disease. **Dr. Gail** had also mentioned the potential danger of using case-control data, cautioning that it might lead to overestimating test performance due to the detection methods used and the nature of the cases included.

QUESTION SIX

Dr. Gallagher proceeded to Question six, focusing on whether specificity should be calculated on a per-cancer basis. **Dr. Roscoe** highlighted the connection between evaluating specificity on a per-cancer basis and considering the impact of comorbidities on the performance of multi-cancer detection tests. The discussion emphasized how specific factors for each cancer type, such as cirrhosis for liver cancer or diabetes for pancreatic cancer, could influence the specificity of the assay. **Dr. Ballman** commented on the value of having specificity information on a per-cancer basis, even though the overall evaluation may not necessarily depend on it.

Dr. Stenzel had two follow-up questions. The first was about assessing the performance of MCD submissions for cancers with standard-of-care screening. The panel discussed how crucial it was to compare MCD test performance to the standard of care for these cancers, considering whether MCD claims for specific cancers should match or exceed the standard of care to be accepted.

The second question focused on lung cancer as a potential outlier due to its high-risk population. **Dr. Stenzel** inquired about the potential need for enrichment technologies to enhance data on lower abundance cancers, especially for lung cancer. **Dr. Castle** responded, explaining the challenges in screening for lung cancer, particularly in the context of low uptake. He suggested that even if a lung cancer detection test is less sensitive, it might still be more effective due to increased willingness for participation.

Dr. Kemeny emphasized that multi-cancer detection tests indicate the potential presence of cancer but don't provide guidance on what to do. **Dr. Gail** highlighted the importance of having a superior test as a reference when comparing new tests with existing standards, emphasizing the challenge in accurately assessing the performance of multi-cancer detection tests without a better reference. **Dr. Schrag** emphasized the distinction between efficacy and effectiveness, urging consideration of both aspects in the development of screening tests. She stressed the need for tests that engage a large portion of the population, aligning with typical behavior patterns.

Dr. Stenzel discussed the potential benefit of screening tests in reaching more people and detecting cancers in a real-world scenario compared to more invasive methods. **Dr. Schrag** expressed reservations about operationalizing a metric based on the notion of a cancer being potentially curable, suggesting the use of national and international standards for cancer staging as a feasible surrogate intermediate marker. **Dr. Lipkowitz** emphasized the importance of considering the downstream impact of MCD tests, particularly the uptake of follow-up workup procedures. He suggested evaluating effectiveness by incorporating metrics related to patient response and adherence to recommended workup.

Dr. Stenzel sought input on the minimum number of positive cancers per specific cancer type needed for per-cancer validation and what sensitivity should be considered acceptable. The discussion focused on the challenges posed by rare cancers and the importance of actionable follow-up for positive results. **Dr. Gail** suggested considering the precision of estimated sensitivity based on the number of people studied, emphasizing the complexity of operationalizing the definition of individuals with prevalent cancer in the target population for MCD tests. **Dr. Stenzel** expressed agreement on the importance of a larger sample size for a more accurate assessment of test performance. The panel acknowledged the active discussion, announcing a lunch break and indicating the planned time for the session's continuation.

Topic Two: Use of Tissue Origin (TOO)

The meeting resumed, and **Dr. Gallagher** introduced the second topic for discussion, focusing on the use of tissue of origin assays (TOO) in identifying tumor location compared to other methods. She invites panel members to pose any brief clarifying questions for the FDA before delving into the topic.

QUESTION ONE

Question one centered on the follow-up process after an MCD test identifies a cancer signal, specifically exploring the use of tissue of origin assays (TOO). The panel discussed acceptable methods, both clinical and laboratory, for determining the possible tissue of origin for a detected cancer signal. Risks associated with using CT or PET CT scans for repeated testing were considered, along with acceptable clinical performance criteria for a TOO test, whether integrated into the original MCD assay or as a standalone test.

Dr. Kemeny sought clarification on specific laboratory tests discussed, emphasizing the variability in tests for different cancers and requesting more details. **Dr. Stenzel** clarified that some MCD tests incorporate TOO assays designed to identify the specific tissue or tumor type when a positive signal for cancer is detected. The discussion also involved considering alternative methods, such as PET CT scans, for follow-up testing.

Dr. Lipkowitz emphasized that if an MCD developer incorporates a molecular TOO test, the same metrics as other tests become relevant. He suggested that targeted imaging in the area indicated by TOO would be reasonable for follow-up. **Ms. Hesser** expressed a strong interest in MCDs that include a TOO component from a patient perspective, especially in underserved communities where access to PET scans can be challenging.

Dr. Swerdlow raised concerns about the incorporation of a TOO component, questioning whether it is another blood test and emphasizing the need for validation, especially for new tests. **Dr. Stenzel** clarified that developers need to find an effective method, likely involving CT or PET CT, to locate the detected cancer, and the TOO assay can be integrated or exist as a separate component. Dr. Perkins emphasized the importance of having a tissue of origin to help patients determine where the tumor might be and raised concerns about frequent full-body scans. **Dr. Gallagher** highlighted the psychological impact of waiting for cancer test results and the importance of providing more information within the test itself.

Dr. Carroll mentioned the Galleri test achieving reasonable performance in localizing the tissue of origin in the Pathfinder study. **Dr. Gail** suggested a method to assess the reliability of the TOO component, proposing a panel of different cancers for misclassification rate determination. **Dr. Swerdlow** emphasized the inevitability of requiring imaging even with a perfect TOO test, stressing the necessity of additional procedures to determine the location of the cancer.

Ms. Rue raised the question of follow-up for patients with negative results and suggested establishing a registry for ongoing monitoring.

Dr. Stenzel sought specifics on the required accuracy of TOO tests and the panel's perspective on the acceptable threshold for accuracy in imaging without TOO. **Dr. Stenzel** reiterated the need for clarity on the acceptable threshold of accuracy, whether for TOO or imaging, in locating the tumor without necessarily classifying it by subtype. **Dr. Castle** emphasized the importance of considering the asymptomatic population when evaluating reported accuracy and raised concerns about the lack of a standard of care for comparison.

Ms. Hesser inquired about the possibility of adding TOO into a pre-market approval (PMA) and evaluating its validity afterward, seeking guidance from the FDA**. Dr. Stenzel** explained the FDA's ability to request a post-market study (PAS) for PMA submissions, allowing ongoing assessment and understanding of the technology.

QUESTION TWO

Dr. Gallagher posed the second question regarding acceptable diagnostic alternatives for determining the tissue of origin when an MCD (Multi-Cancer Early Detection) test lacks a TOO (tissue of origin) component. **Dr. Gail** stressed the importance of knowing the tissue of origin for assessing the accuracy of the test, with **Dr. Stenzel** concurring and highlighting the practical benefits of localizing the tumor. **Dr. Ballman** raised concerns about test sensitivity, proposing a specified follow-up period for both positive and negative results. **Dr. Stenzel** expressed openness to this study design, emphasizing the importance of defining a follow-up period for negative patients.

Dr. Lipkowitz emphasized the need for a well-planned approach for follow-up studies, including a pre-specified plan for positive test results. **Dr. Lipkowitz** emphasized the need for pre-specification in studies involving asymptomatic patients. **Dr. Gallagher** highlighted safety factors and logistical challenges, suggesting provisions for transportation and accommodation,

especially for those with positive responses. **Dr. Swerdlow** stressed the need for a well-defined pathway for positive results and specific guidance for physicians ordering the test.

Dr. Castle emphasized addressing the diagnostic journey with a comprehensive approach, considering recruitment, diagnostic follow-up, and cancer treatment. The potential benefits of the TOO component in reducing harms and providing targeted information were highlighted. **Dr. Bujold** stressed the importance of clear guidelines and education for primary care practitioners, especially in rural areas, to avoid inappropriate test ordering and unnecessary costs.

Dr. Schrag acknowledged the complexity of finding a singular imaging solution, emphasizing the importance of clinical common sense and the role of developers in providing guidance frameworks for primary care physicians. **Dr. Swerdlow** addressed the challenge of finding alternatives to high-end imaging modalities, pointing out the effectiveness of ultrasound in specific populations but cautioning against whole-body imaging methods for cost-effectiveness.

QUESTION THREE

Dr. Gallagher introduced the third question, focusing on establishing clinical truth for tests without alternative methods and those with alternative methods. She asked the panel to consider determining truth for test negatives and whether a minimum follow-up period is necessary. The discussion included the idea of a second test after a specified follow-up period, considering concerns about excessive radiation from repeated CT and PET scans. **Dr. Perkins** sought clarification on "test negatives" and discussed the challenge of confirming true negatives, especially in the context of false negatives in Multi-Cancer Detection (MCD) tests. Dr. Stenzel and Dr. Perkins emphasized the importance of monitoring patients over time and conducting recommended screenings to identify any missed cancers.

Dr. Castle acknowledged the complexity of determining the accuracy of MCD tests, emphasizing organ-specific considerations and the need to understand the natural history of different cancers. He expressed concerns about verification bias-adjusted analysis, particularly for MCD tests without Tumor of Origin (TOO) information and stressed the need for time and modeling approaches. Dr. Kemeny suggested using a cohort of patients with known cancer to assess false negatives over time and recommended repeating the test to rule out errors, expressing practical concerns about individually working up false negatives.

Topic Three: Benefit/Risk Considerations

QUESTION ONE

During the discussion on benefit-risk considerations, **Dr. Gail** emphasized the importance of knowing the ultimate effect of the test, especially with positive results, requiring data from randomized trials with mortality as an endpoint. **Dr. Stenzel** mentioned the need for an uncertainty analysis due to the lack of perfect tests and the importance of assessing risks and benefits. **Dr. Gallagher** highlighted the challenges posed by false negatives, particularly in handling patient fear. The panel acknowledged the difficulty in assessing the risks of false positives and false negatives, with considerations for the invasiveness of follow-up tests..

QUESTION TWO

In discussing the definition of early stage for cancer detection tests, **Dr. Lipkowitz** emphasized the lack of a one-size-fits-all definition and suggested that it should be determined on a cancer-by-cancer basis. He pointed out the variability in the curability of different cancer stages, providing examples such as breast cancer where stages 1, 2, and many cases of stage 3 are considered curable. **Dr. Lipkowitz** stated the importance of considering the risk, curability, and benefit for patients with different cancer stages.

QUESTION THREE

In response to the question of whether MCD (Multi-Cancer Early Detection) test developers should pre-specify a fixed specificity to support a low false positive rate, **Dr. Kemeny,** and **Dr. Stenzel** emphasized the importance of having specific criteria to avoid false positives. **Dr. Kemeny** suggested that high specificity, such as 99 percent, might be needed to achieve good positive predictive values, especially considering the prevalence of the cancers being detected in the target population. **Dr. Stenzel** supported this notion, stating that maintaining a high predictive value in a low-risk population requires a very specific test. The discussion also touched on the incident cancer rate in an average-risk population and the need to understand the prevalence of the cancers being detected by the MCD tests.

QUESTION FOUR

The panel discussed the anticipated follow-up for a positive MCD test result in terms of diagnosis, number of procedures, and repeat testing. **Dr. Kemeny** emphasized the importance of quick follow-up, ideally within weeks to months, particularly for asymptomatic patients. **Dr. Carroll** highlighted the significance of considering whether patients are symptomatic, asymptomatic, or have risk factors when determining the diagnostic path. **Dr. Perkins** stressed the need for standardized follow-up protocols, especially if the test includes information about the tissue of origin and recommended that these protocols be part of the FDA approval process. **Dr. Schrag** drew parallels with cervical cancer screening and suggested that industry partners should play a role in developing companion tools and educational materials to support physicians and patients in understanding and acting on MCD test results.

QUESTION FIVE

The discussion on question number five centered on the anticipated frequency physicians would order an MCD test and whether it depends on receiving a positive or negative result. The panel acknowledged the lack of data on this aspect and emphasized the need for further research.

Dr. Perkins highlighted the importance of evaluating the frequency of testing during clinical trials and suggested that the FDA could request this information in trial designs. The panel also discussed the challenges of setting screening intervals, especially in the absence of comprehensive data, and emphasized the importance of considering age, comorbidities, and family history in determining the frequency of testing. The discussion emphasized the need for a balanced approach that takes into account the potential benefits and harms of testing.

QUESTION SIX

The discussion on question number six focused on the harms from unresolved positive results in MCD testing and potential risk mitigation strategies. The panel highlighted several challenges, including the difficulty of detecting very small tumors and the emotional burden on patients who receive positive results. The importance of communication and shared decision-making with patients was emphasized, and the need for clear expectations regarding the follow-up process was stressed. Quality-of-life components, including patient-reported outcomes, were mentioned as crucial aspects to consider in assessing the impact of false positives and false negatives. The discussion also touched upon the potential risk of crowding out resources for symptomatic patients in the healthcare system. Overall, the panel acknowledged the complexity of addressing these issues and emphasized the importance of a balanced approach to risk mitigation.

QUESTION SEVEN

In the discussion on question number seven, the focus was on the risks and harms associated with overdiagnosis in cancer screening, along with potential risk mitigation strategies. Overdiagnosis was defined in two ways: finding things that are not cancer and detecting indolent tumors that may not progress to a clinically significant stage.
Several participants highlighted the challenges of distinguishing between indolent and clinically relevant cancers.

Panelists suggested that informing patients about the potential for overdiagnosis and discussing ancillary tests for specificity could help manage expectations.
The discussion also touched on the difficulty of predicting which cancers are indolent and which are clinically relevant, emphasizing the importance of ongoing research and the iterative nature of refining screening tests. Participants acknowledged the complexities and uncertainties in addressing overdiagnosis, particularly in the absence of a clear understanding of the natural history of various cancers and the need to consider top age cutoffs for screening, especially as individuals approach their life expectancy. The experience of other cancer screening programs, such as thyroid cancer screening in South Korea, was cited as a cautionary example of potential harms associated with widespread screening.

QUESTION EIGHT

The panel discussed question number eight, focusing on the significance of the time to diagnosis after receiving a positive result from a cancer screening test. **Dr. Stenzel** clarified that the question is essentially asking about the time lag between receiving a positive result and the subsequent diagnosis, and whether this time frame has any implications for evaluating the effectiveness of the tests.

Dr. Schrag then offered a brief comment, stating that the time to diagnosis is a second-order issue. The panel had previously discussed key issues, and the time to diagnosis is considered less critical. **Dr. Schrag** mentioned that while it shouldn't take five years, it also doesn't need to be as short as five minutes.

QUESTION NINE

During the discussion of question number 9, **Dr. Swerdlow** raised a point about the significance of time to diagnosis and its association with health disparities and **Dr. Schrag** expressed full agreement. **Dr. Swerdlow** highlighted that screening is not just about the test itself; it's part of a broader continuum of care. He stressed the importance of ensuring that individuals who undergo screening tests are effectively linked to further care.

Dr. Schrag added that conducting screening tests without a clear pathway for follow-up care is an ethical violation. **Dr. Swerdlow** reiterated the need to consider issues related to health equity and access to care, pointing out that even if screening tests are made accessible, challenges such as geographical distance, persistent poverty, and other factors can impact the timely diagnosis and subsequent care for individuals in underserved or rural areas.

QUESTION TEN

During the discussion of question number 10, the focus was on the conditions under which the use of real-world evidence for reporting clinical validation of a multi-cancer detection (MCD) test would be acceptable. **Dr. Stenzel** clarified that real-world evidence refers to data collected outside of standard clinical studies, often in a post-approval or practice setting. **Dr. Gallagher** expressed the need for a systematic way to collect real-world data on the performance of MCD tests over time. He suggested the creation of a portal where companies could report real-world experiences with their tests.

Dr. Gallagher highlighted the importance of tracking rare cancers and assessing at what stage the cancer is detected, as this information could contribute to the design of effective treatment plans. **Dr. Gail** emphasized the limitations of real-world evidence in estimating sensitivity, specificity, and positive predictive value, especially in the absence of clear criteria for establishing the ground truth for patients. He cautioned against relying on real-world evidence to determine the reduction in mortality, as individuals volunteering for special screenings may not be representative of the target population.

Dr. Stenzel added that the FDA encourages the use of real-world evidence when appropriate, and **Karla Ballman** supported the view that real-world evidence cannot be used to assess mortality outcomes due to the inherent differences between individuals opting for testing and those who do not.

QUESTION ELEVEN

During the discussion of question number 11, which focused on the considerations around using real-world evidence to support clinical validation of MCD tests, **Dr. Stenzel** suggested that the questions might have been broken down too finely, and some could be combined.

Panel Summations

Mr. Winslow summarized on behalf of the industry, expressing excitement about the opportunities presented by MCD tests. He highlighted the importance of considering the unique aspects of MCD tests in terms of development, execution, and evidence generation. He emphasized the need to explore different approaches to evidence generation, both pre-market and

post-market, to ensure an appropriate benefit-risk profile. Overall, he acknowledged the ongoing discussions and collaborations with the FDA on these matters.

Ms. Hesser expressed appreciation for the opportunity to represent the patient population during the meeting. She emphasized the importance of including traditionally underrepresented populations in future studies and clinical trials related to MCD tests. **Ms. Hesser** specifically mentioned the inclusion of African Americans, Latino communities, Native Americans, seniors, and underserved populations.

Ms. Rue echoed the importance of considering additional endpoints beyond mortality, emphasizing that some individuals may value the option of gaining additional years of life. She also reiterated the significance of addressing cancer screening in the pediatric population. **Ms. Rue** suggested including an educational component to raise awareness about the importance of cancer screening tests, both existing ones and potential future options, to improve overall effectiveness. She expressed gratitude for the opportunity to contribute to the discussion.

Dr. Kemeny emphasized the importance of considering the cost aspect in discussions, particularly in the context of minority-based hospitals and underserved populations. She stressed the need for clinical trials to proactively include a predetermined percentage of minority populations, ensuring representation in research. **Dr. Kemeny** also highlighted the significance of addressing the financial burden associated with testing in the future, including considerations about coverage by Medicare and Medicaid.

Dr. Swerdlow echoed **Dr. Kemeny's** concerns about the cost associated with screening tests. Drawing from the experience of the CT colonography discussions, he expressed apprehension about the potential financial burden of widespread implementation of screening tests, especially in the context of limited resources and the challenges of follow-up imaging. **Dr. Swerdlow** emphasized the importance of considering the overall impact on healthcare budgets, particularly with regard to Medicare and Medicaid, and raised concerns about the feasibility of recommendations from the U.S. Preventive Services Task Force given the potential strain on resources.

Dr. Schrag emphasized the need to find a balanced approach in the development strategy for cancer screening technologies. Acknowledging the urgency expressed by patients for accelerated development, they also highlighted the potential risks and chaos associated with overly hasty implementation. The suggestion was to consider cancer survivors as a population for screening tests, as they have a higher event rate, are motivated, engaged in healthcare, and represent diverse backgrounds.

Dr. Castle emphasized the importance of recognizing the differences among various cancer screening tests. He highlighted that these tests do not diagnose cancer but identify individuals at risk, each with different profiles, target cancers, and associated risks. **Dr. Castle** stressed the need to tailor the choice of a screening test to an individual's specific risk factors, considering parameters such as genetic predispositions or lifestyle factors like smoking. The message was that a one-size-fits-all approach is not suitable, and careful consideration is required to determine which test is best for each person

Dr. Gail suggested that Multi-Cancer Early Detection (MCD) tests could serve two key motivations: detecting cancers not currently screened for and addressing the low uptake of screening for certain cancers. He proposed focusing MCD tests on the five cancers that are already screened for but have low screening uptake. These tests, if cheap, blood-based, and with tumor-of-origin content specific to these five cancers, could act as prescreening tools. Individuals testing positive with MCD tests could then be encouraged to undergo regular screening for those specific cancers.

Dr. Bujold emphasized the challenges faced by individuals in rural areas, particularly the financial constraints and transportation issues. He questioned the current approach of developing tests without involving insurance companies, third-party payers, Medicaid, Medicare, and pharmaceutical companies in discussions. **Dr. Bujold** suggested a collaborative effort involving all stakeholders to find a cost-effective solution. Additionally, he expressed concern about the financial burden on companies developing MCD tests, urging them to recognize the costs associated with including diverse populations in clinical trials.

Dr. Lipkowitz expressed gratitude for the opportunity to be part of the committee and acknowledged the tremendous potential of MCD tests in expanding access to care with minimally invasive methods. He clarified that the critiques and comments made during the discussion were not indicative of anger but rather a focus on ensuring the proper development of these tests. **Dr. Lipkowitz** emphasized the importance of trial design, using the example of PSA, and stressed the need to do it right from the beginning.

Dr. Carroll shared insights about PSA, stating that there are good guidelines in place, but the challenge lies in people not following them. He expressed satisfaction with being part of the panel and emphasized the importance of applying MCD tests to a broad, diverse, average-risk population while also including some higher-risk populations. He stressed the need for a test that examines a broad range of cancers, with potential benefits in uncommon, low-prevalent cancers that are currently undetected. **Dr. Carroll** also supported the NCI's perspective on a decrease in mortality but acknowledged that achieving this would take many years. Lastly, he highlighted the rapid evolution of technology in these tests, especially with the incorporation of AI in algorithms, and urged companies to be open to updating tests based on emerging information over the next few years.

Dr. Ballman expressed gratitude for being part of the panel and conveyed her enthusiasm about the MCD tests. She echoed the sentiments of previous speakers, emphasizing the need for careful consideration to avoid excessive treatment. While acknowledging the limitations within the purview of the NCI and FDA, **Dr. Ballman** highlighted the importance of high specificity, suggesting that any specificity below 99% should not be considered. She expressed concerns about a sensitivity of only 50%, considering it quite low, but noted that it might be acceptable for cancers without existing screening tests. **Dr. Ballman** concluded by endorsing the remarks made by previous panelists.

Dr. Perkins expressed gratitude for being included in the panel and highlighted the tremendous potential of MCD tests in revolutionizing cancer diagnosis and treatment. She

emphasized the complexity and new questions arising in the field. Key points included the importance of pre-test counseling to set realistic patient expectations for positive and negative results, the significance of including tissue of origin information in the test for targeted follow-up testing, and the need for clear guidelines on ordering tests following positive results. Dr. Perkins also emphasized the importance of addressing unanswered questions through post-marketing registries, including considerations for repeating tests after negative results and assessing longer-term outcomes such as secondary cancers, morbidity, and mortality.

Dr. Gallagher expressed gratitude for the insightful discussions during the meeting and shared her expert opinions. She emphasized the importance of viewing screening as a public health event that could have a significant impact on the general public health of the country. **Dr. Gallagher** highlighted the potential of testing to identify individuals at high risk, particularly those who are underserved and may benefit from less cumbersome tools. She stressed the importance of including tissue of origin information in the tests to streamline the next steps in the diagnostic process. As an ethicist. She encouraged a comprehensive approach to evaluating the role of tests within the healthcare system. The meeting concluded with a request for FDA summations, comments, and clarifications.

Dr. Stenzel expressed gratitude to the panelists and participants, clarifying the FDA's role and mentioning the agency's focus on aspects within its jurisdiction. He highlighted the FDA's collaboration with CMS for reimbursement discussions and encouraged test developers to involve payers in meetings. **Dr. Stenzel** thanked **Dr. Gallagher** for chairing the panel, acknowledged the valuable contributions of panelists, public speakers, and representatives, and expressed appreciation for the attendees, especially patients and advocates.

Dr. Roscoe shared her excitement about the era of medical breakthroughs in cancer diagnostics and emphasized the FDA's role in understanding the benefits and risks of new diagnostic tests. He mentioned the importance of communication to mitigate risks and informed about the FDA's authority to generate physician and patient labeling. **Dr. Roscoe** expressed the FDA's commitment to considering innovative approaches and thanked the panelists and FDA colleagues for their contributions.

Adjournment

Dr. Gallagher expressed gratitude to the panelists, open public hearing speakers, AV crew, FDA staff, and test developers for their contributions to the meeting. She acknowledged the extensive preparation efforts by FDA personnel and concluded the meeting of the molecular and clinical genetics panel, thanking everyone for their participation.

I approve the minutes of this meeting as recorded in this summary.

Colleen M. Gallagher, Ph. D..
Chairperson

Summary Prepared By:

Jennifer Solis
Translation Excellence
3300 South Parker Road, Suite 200
Aurora, CO 80014
(720-325-0459)
September 25, 2023

I certify that I attended this meeting on November 29, 2023 and that these minutes accurately reflect what transpired

Candace J. Nalls -S
Digitally signed by Candace J. Nalls -S
Date: 2023.12.15 10:03:46 -05'00'

Candace Nalls
Designated Federal Officer