THE 2022 EARLY DETECTION OF CANCER CONFERENCE REPORT

OCTOBER 18-20
PORTLAND,
OREGON
USA

OHSU
KNIGHT CANCER Institute
CANARY CENTER AT STANFORD
CANCER RESEARCH UK


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The 2022 Early Detection of Cancer Conference

Early detection: one of the most powerful ways to improve cancer survival

Improving the early detection of lethal cancers is fundamental to treating patients more effectively. Cancer Research UK, the OHSU Knight Cancer Institute, and the Canary Center at Stanford are collaborating to accelerate progress with efforts to overcome research barriers such as the lack of cohorts of sufficient size, unavailability of clinical samples and limited understanding of the biology of early cancer. The Early Detection of Cancer Conference is part of this collaboration. Nearly 400 attendees from academia, industry, policy and government gathered in Portland, Oregon, from 18-20 October 2022, for the seventh meeting in the series.

Scientific program chairs leading the conference were **Shelley Barton, Ph.D.,** OHSU Knight Cancer Institute, **George Hanna, Ph.D.**, Imperial College London, and **Tanya Stoyanova, Ph.D.**, Stanford University.

Keynote: Population and tumor heterogeneity in cancer genome science

Social inequality is a driver of disparities in cancer incidence and survival, but genetic ancestry also plays a role. **John Carpten, Ph.D.**, at the USC Norris Comprehensive Cancer Center is a pioneer in investigating the biology behind disparities in cancer outcomes among populations. His keynote highlighted work on triple negative breast cancer, an aggressive subtype that disproportionately affects Black women and contributes to racial disparities in breast cancer mortality. Carpten presented data from novel spatial transcriptomic technologies revealing that proportions of tumor and immune cell types were different in triple negative breast cancers from Black and White subjects. Specifically, genes indicative of cells in a hypoxic state were enriched in tumors from Black subjects, and these hypoxic cells tend to be distanced from immune cell populations. With a deeper understanding of these and other differences in tumor biology across racial ethnic groups, Carpten said it should be possible to better detect and treat those cancers.

Session 1: From models to mechanisms to humans

Topic chairs: Simon Leedham, Ph.D., University of Oxford, and Victor Velculescu, M.D., Ph.D., Johns Hopkins University

Breast cancer is frequently diagnosed as ductal carcinoma in situ (DCIS), which may or may not progress to invasive cancer. **Jos Jonkers, Ph.D.**, from Netherlands Cancer Institute, described how his lab is using animal models to seek ways to distinguish indolent lesions from potentially hazardous ones. They are using intraductal injections of patient-derived DCIS cells to generate mouse PDX models of DCIS, and intraductal injections of lentiviruses encoding DCIS driver genes to

generate genetically engineered rat models of DCIS. They've identified a number of risk factors for the progression of DCIS to invasive cancer, such as the growth pattern of the lesion, high copy number aberrations, and combinations of particular driver genes.

Sabine Tejpar, M.D., Ph.D., from KU Leuven, and others have identified a group of human colorectal cancers (iCMS3) that account for up to half of human tumors. Tumor development in this group is different from the classical model in which colorectal cancer evolves from a polyp following a sequential mutational model (that starts with loss of the tumor suppressor APC, with subsequent mutations in KRAS, TP53 and SMAD4). She gave an update on work to understand this large but previously unrecognized subpopulation of cancers.

Clonal hematopoiesis of indeterminant potential (CHIP) predisposes people to develop blood cancers. **Ryan Schenck, Ph.D.,** from Stanford University, described a machine learning method to diagnose CHIP without DNA sequencing**.** The method uses fluctuating CpG sites to serve as a fluctuating methylation clock (FMC) to uncover stem cell dynamics. Analyses combining FMCs with mutation data can infer the induction time of somatic mutational events and their aggressiveness and expansion rates (aggressive clonal expansions bring a high risk of malignant progression). Used with gene sequencing, the method may provide risk stratification from a single blood draw.

Victor Velculescu, M.D., Ph.D., from Johns Hopkins University, and colleagues are analyzing the pattern of DNA fragments found circulating in blood to detect cancers. Cell-free DNA fragmentation profiles are altered in cancer, and the pattern reflects changes in chromatin structure. Two clinical trials are underway to determine the ability of the blood-based screening technology to detect lung cancer accurately and reliably. Velculescu, CEO and founder of a company developing the technology, made the case that DNA fragmentation gives a stronger signal and is cost-effective compared with liquid biopsy approaches based on sequencing.

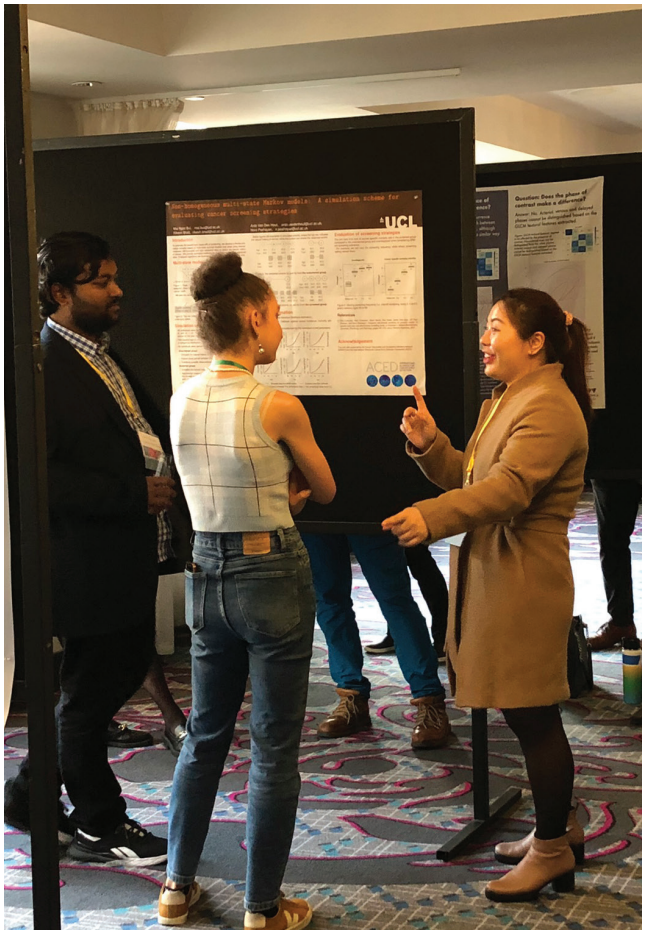
Challenges and future directions:

- Researchers need to further develop models of cancer progression that reflect biological mechanisms in patients. This will require access to early tumor tissue from patients and, ideally, matched longitudinally collected blood samples to look for changes over time that reflect cancer progression.
- Datasets and models must follow FAIR principles to be findable, accessible, interoperable, and reusable by the research community.
- Biologists and mathematical modelers should collaborate to drive interdisciplinary approaches across the cancer research ecosystem.

Lightning talks

Gladys Poon from the University of Cambridge, described efforts to learn from clonal trees reconstructed from single-cell sequencing of 2,000 hematopoietic stem cells. Development of AML required single cell to acquire 3-4 driver events, preleukemic dynamics appeared to be highly variable; parallel evolution occurred in some cases where AML almost evolved multiple times in the same individual but showed a simpler linear evolution pattern in others. Stanford University's

Shiqin Liu, M.D., Ph.D., showed data on the potential for using Trop2 shed in urine as a biomarker for high-risk prostate cancer. Trop2 is a transmembrane glycoprotein that is differentially expressed in many cancers.



Panel: How should we evaluate Multi Cancer Early Detection (MCED) Tests?

Moderator: Michelle Le Beau, Ph.D., Cancer Prevention and Research Institute of Texas

Allan Hackshaw, M.Sc., Ph.D., director CRUK Cancer Trials Centre at University College London, pointed out that after decades of research, reliable screening tests exist for only four cancer types, highlighting the role for MCED. Key to this will be validating that MCED tests have a high diagnostic yield, very low false positive rate, reduce late-stage incidence, and reduce mortality. **Jeffrey Venstrom, M.D.,** from GRAIL, said that in his company's premier study of their MCED technology in the UK's health service, NHS Galleri, the primary objective is a significant reduction in the absolute numbers of stage III & IV cancers diagnosed in the intervention versus the control arm. Cancer-specific mortality will be assessed during trial follow-up. He said the company's MCED trials are also measuring patient reported outcomes, and seeking ways to more fully include populations historically underserved by cancer screening. **Anne Mackie, MBBS,** Director of Screening for Public Health England, said evaluations must show MCEDs do more good than harm when used in systematic population health screening programs, and that they can do that at a reasonable cost. Even after successful clinical trials, **Minetta Liu, M.D.,** from Mayo Clinic said much work will be needed to successfully deploy MCED in clinical practice. Novel workflows will be needed to not overburden primary care providers and to assure that systems are in place for patients to receive support from detection, to diagnosis, and treatment.

Session 2: Emerging technologies for early detection and precision diagnosis

Topic chairs: Robert West, M.D., Ph.D., Stanford University, and Thuy Ngo, Ph.D., OHSU Knight Cancer Institute

Thuy Ngo, Ph.D., from the OHSU Knight Cancer Institute, reported on the diagnostic potential of profiling cell-free RNA in blood. The RNA biomarkers can distinguish multiple myeloma blood samples from non-cancer samples, and multiple myeloma from its pre-malignant condition. And they are also able to distinguish liver cancer from non-cancer and liver cancer from cirrhosis. The level of the cell-free RNA biomarkers displays a gradual transition from non-cancerous states through to pre-cancerous conditions and cancer. A clinical trial is testing whether cell-free RNA profiling can be used to stratify patients with suspected pancreatic cancer before they undergo endoscopic ultrasound.

Rapid, simple, and inexpensive point-of-care assays are the goals of technologies under development by **Brian Cunningham, Ph.D.**, at the University of Illinois. One is a digital-readout diagnostic that uses microRNA-activated nanoparticle-photonic crystal hybrid coupling for highly selective and sensitive detection of microRNAs. Another, a target recycling amplification process, which requires no enzymes, is done at room temperature in a single step in 10-20 minutes. The limit of detection is two orders of magnitude lower than PCR.

Robert West, M.D., Ph.D., from Stanford University, and colleagues are using spatial analysis of RNA, DNA and proteins to find a way to classify DCIS lesions for their risk of progressing to invasive cancer. They used multiplexed ion beam imaging by time of flight (MIBI-TOF) and multiplex antibody staining to identify features of tumor microenvironment structure that are predictive of invasive relapse.

MRI scans often fail to detect early-stage prostate cancers, but they also generate many false positive findings. Stanford University's **Mirabela Rusu, Ph.D.**, is taking pathology data and mapping it onto matching MRI imaging to make it more reliable. They are using the correlated data to train machine learning models to automatically localize prostate cancers on MRI scans, and to distinguish idle vs. aggressive prostate cancers.

Challenges and future directions:

- Digitization of images allows for others, including machines, to ask questions of pathology and radiology data; the results of these 'digital' pathologists/radiologists can be compared to the real thing with the potential to improve workload and optimize detection.
- It will be important to bridge the knowledge from basic molecular assays, genomics and imaging. One way is to include people across disciplines during the planning of clinical studies to make sure to capture the most informative data.
- With the ability to detect cancers at earlier and earlier stages, new measures will be needed to determine if lesions are clinically significant or not. The follow-up needed could be many years.
- It's possible that some cancers only acquire high risk phenotypes at later stages as they progress, which would make them impossible to detect at the early stage.
- Much work remains to understand the biology of early lesions and the interventions that will be appropriate for treating early lesions.
- Liquid biopsy approaches would benefit from a better understanding of how the signal detected in blood relates to the changing biology within early cancer cells.
- Increasingly sensitive liquid biopsy methods may be able to detect cancers too small to locate with existing imaging modalities, posing a conundrum.

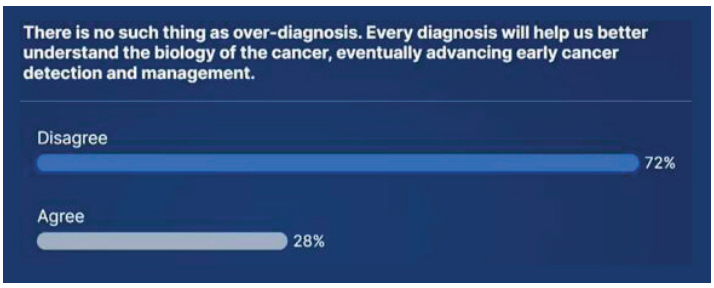
Lightning talks

Jie Wang, Ph.D., from Stanford University, presented a strategy for the rapid formation of functional biorobots composed of live cardiomyocytes. They can be used to for controlled actuation of a soft skeleton and pumping of microparticles, making them useful for cellular manipulation in tissue engineering, for example. **Travis Moore, Ph.D.,** and colleagues at OHSU developed a way to detect copy number variation using single-cell ATAC-seq less susceptible to noise and outliers than other single-cell methods.

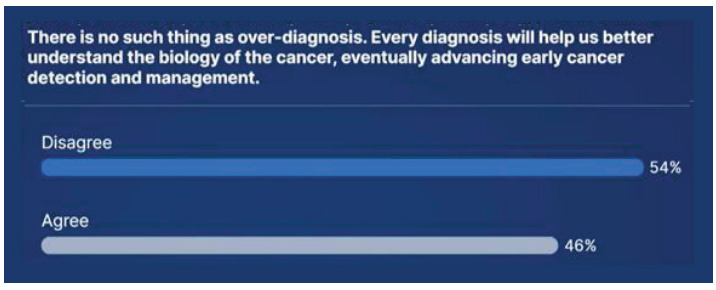
Great debate 1: There is no such thing as over-diagnosis. Every diagnosis will help us better understand the biology of the cancer, eventually advancing early cancer detection and management.

Eithne Costello, Ph.D., from the University of Liverpool, made the case for no such thing as over-diagnosis. She argued that the problem isn't overdiagnosis but misdiagnosis; that we need identify which cancers are harmless and which are harmful. The main thing is to balance the benefit vs. the risk, she said, to make the trade-offs clear to the public, and give individuals the choice about what to do with diagnostic information.

Arguing the contrary, **Nora Pashayan, Ph.D.**, from University College London, asserted that overdiagnosis is inevitable in any cancer screening program. Overdiagnosis occurs in two ways: when tumors are indolent, or when a person's life expectancy means they die of other causes before their cancer progresses. In both cases, there is no benefit, but all harm, including the distress of the diagnosis, comorbidities of treatment, cost to the individual, and wasting of resources.



PRE-debate



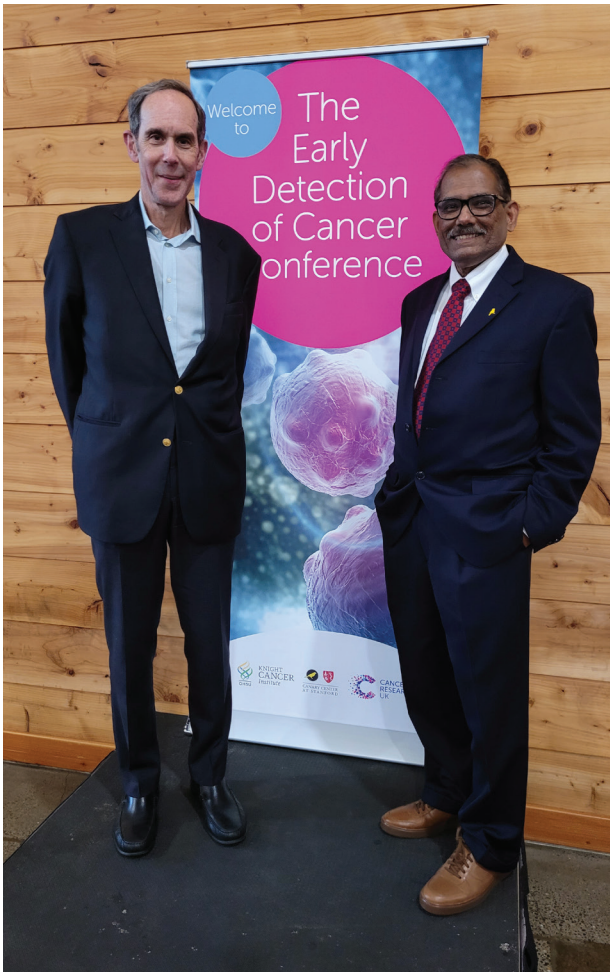
POST-debate

Keynote panel: A funding agency perspective on early detection

Karen Knudsen, M.B.A., Ph.D., CEO American Cancer Society, highlighted some of the payoffs of cancer research, including a 32% decline in cancer mortality from 1991-2019. Ongoing disparities, however, make clear that advances have only benefitted some. Knudsen outlined some of the advocacy work by ACS to improve access, such as state laws mandating coverage for biomarker testing in FDA-approved oncology treatment regimens. Now the organization is lobbying for federal legislation to create a path to coverage for multi-cancer early detection tests that gain FDA approval.

An important role for the National Cancer Institute is validating early detection tests, determining their clinical utility and who would benefit from which tests, said **Phil Castle, Ph.D., M.P.H.,** director of the Division of Cancer Prevention at the National Cancer Institute. Castle noted that none of the many technologies available have been shown to reduce cancer mortality yet, nor have potential harms been quantified. His division is proposing a randomized platform clinical trial comparing a number of early detection tests to the standard of care.

Catherine Elliott, M.D., M.Phil., director of research & partnerships at Cancer Research UK, said critical roles for her agency are accelerating the adoption of evidence-based interventions. CRUK's Early Detection and Diagnosis of Cancer Roadmap calls for the significant investment in diagnostic equipment and technologies, along with NHS staff, to support new ways of working to make it possible to diagnose more cancers at an earlier stage. It also endorses efforts to ensure early detection and diagnosis is delivered ethically, equitably and transparently with extensive involvement with patients and the public.



Don Listwin Award for Outstanding Contribution to Cancer Early Detection

Sudhir Srivastava, Ph.D., M.P.H. is known for establishing a number of transformative programs on translational research on cancer screening, early detection, risk assessment and enabling technologies. He championed the creation of the Early Detection Research Network, a flagship program at the National Cancer Institute that has begun translating biomarkers into clinical tests for early detection. He was honored with the 2022 Don Listwin Award, established to recognize a sustained contribution to, or singular achievement in, the cancer early detection field. The award is named in honor of the founder and chairman of The Canary Foundation. Srivastava is senior scientific officer and chief of the Cancer Biomarkers Research Branch in the NCI Division of Cancer Prevention.

Session 3: Microbiological risk factors for early detection

Topic chairs: Xin Lu, F.Med.Sci., Ludwig Institute for Cancer Research, and Zhenzhen Zhang, Ph.D., M.P.H., OHSU Knight Cancer Institute

It's increasingly clear that microbes inhabiting the human body can be complicit in cancer growth, acting through the host's immune system or by other means. **Zhenzhen Zhang, Ph.D., M.P.H.**, and colleagues at the OHSU Knight Cancer Institute have research underway seeking to detect gut microbiome differences between treatment-naïve breast cancer cases and controls. A pilot study has identified three potential microbial biomarkers associated with breast cancer risk.

Curtis Huttenhower, Ph.D., from the Harvard T.H. Chan School of Public Health, focused on the gut microbiome and colorectal cancer. Metagenomic analyses of later stage colorectal cancers have revealed many detailed changes in the gut microbiome that occur with cancer progression. A study enrolling people with Lynch syndrome made it possible to look at earlier stage colorectal cancer, and observed shifts in the microbiome that closely paralleled the later stage patterns. But the changes are difficult to detect, so less than ideal for screening or diagnostic purposes.

Diet affects colorectal cancer-associated microbial ecosystems, and **Emma Allen-Vercoe, Ph.D.**, and colleagues at the University of Guelph are using a "robogut" – colon biopsy cells grown in a bioreactor set to mimic conditions of colonic lumen – as a laboratory model to study those effects. Her talk was presented via pre-recorded video. Among the findings: potential oncomicrobes, when seen, are almost always more abundant under high protein conditions. And the source of the protein, animal or vegetable, may matter for some microbial species; animal protein seems to favor the growth of bacterial strains associated with the development of colorectal cancer.

Gabe Kwong, Ph.D., from Georgia Institute of Technology and Emory School of Medicine described efforts to engineer biomarkers, such as protease activity sensors conjugated to PD1 antibodies for the monitoring of anti-tumor responses to immune checkpoint therapy. During treatment, the sensors are cleaved by proteases, releasing reporters that filter into urine. After urine collection, cleaved reporters are quantified by mass spectrometry according to a mass barcode. In more recent work, his lab is using cytotoxic T cell activity as an early biomarker of response to immunotherapy.

Challenges and future directions:

- Better laboratory models of pre-invasive cancer are needed to give direction to research in this area.
- When introducing new early detection methods, it will be important to choose a first clinical application very carefully to maximize the chance to demonstrate its potential.
- Animal models will be key to validate the assumed causal relationships between candidate biomarkers and disease.
- Computational-biology identified biomarkers of the microbiome will require more stringent validation.
- Changes in the microbiome can be both a cause and a consequence of disease; studies of the role of microbes in cancer should account for that.
- The role of fungi and viruses in cancer remains less explored than that of bacteria and is deserving of more research.
- The full range of cancer-causing pathogens remains unknown and open for future discovery.

Lightning talks

Danielle Brasino, Ph.D., from the OHSU Knight Cancer Institute, previewed a new organ-on-chip platform to study the relationship between gut microbes and distal tumors. The design aims to improve biological relevance with cell-line based cultures growing in three dimensions to simulate the gut lumen on one chip that is connected to another chip simulating the tumor. Imperial College London Ph.D. candidate **Michael Fadel** presented study results with a non-invasive breath test for colorectal cancer. Breath samples are captured in tubes and transferred to a lab for analysis of volatile organic compounds. In the Colorectal Breath Analysis 1 (COBRA1) study, which took samples from about 1,400 patients on the day of colonoscopy or surgery, the test accuracy showed an AUC of 0.87 overall.

Panel: What can we learn from trials that return unexpected results on mortality benefit from early detection biomarkers/tests?

Moderator: Peter Johnson, M.D., University of Southampton

Screening colonoscopy showed no significant impact on colorectal cancer mortality or all-cause mortality in the NordICC Study, a perplexing result. **Ernest Hawk, M.D., M.P.H.**, from the University of Texas MD Anderson Cancer Center, detailed a number of revealing factors to interpret the results, including insufficient uptake of screening (42% received colonoscopy), too short of follow-up, insufficient quality of colonoscopy, and lower than expected rates of colorectal cancer in the cohort.

Consultant **Christine Berg, M.D.**, retired from the National Cancer Institute, dug into confusing results of three major prostate cancer PSA screening trials: ERSPC, PLCO, and CAP. Low compliance stood out in CAP, with only 34% in the intervention arm getting tested. Rate of biopsy for a positive test stood out in PLCO, wherein only 35% ended up having a biopsy, versus 85-86% in the two other studies. Berg said the data show that PSA screening lowers prostate cancer mortality. The question is how to improve the benefit/harm ratio.

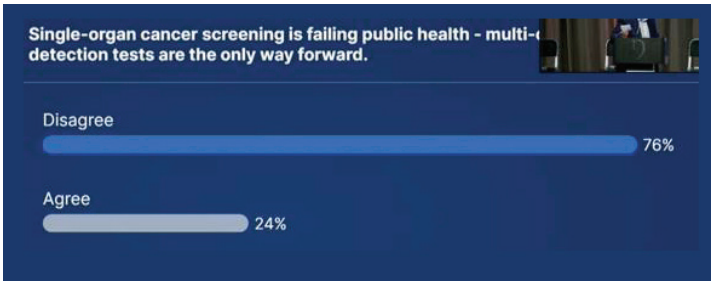
UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) found no difference in deaths between the screening arm and control arm. But **Usha Menon, M.D.**, from University College London, said the study is yielding valuable insights. Screening tests will need to detect ovarian cancers earlier in their development than in UKCTOCS, for example. Because small lesions are missed by current imaging, Menon said there is an urgent need for more sensitive second line tests. Citing evidence of less than ideal therapy delivered to subjects in UKCTOCS, Menon said screening trials need to pay more attention to treatment.

Great Debate 2: Single-organ cancer screening is failing public health – Multi-cancer early detection tests are the only way forward

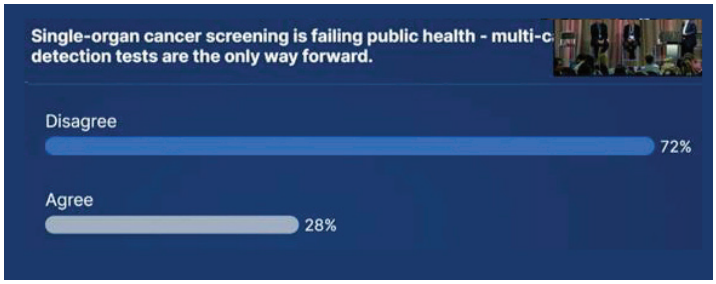
Given that cancer remains a leading cause of death worldwide, and more than 70% of all incident cancers have no standard-of-care screening test, **Paul Limburg, M.D., M.P.H**., of Exact Sciences, said, yes, single-organ cancer screening is failing. MCED tests combined with routine screening methods may expand the range of detectable cancers. Using a blood draw to obtain test samples, they could expand access too screening for underserved populations.

Taking the con position, **Bob Steele**, from the University of Dundee, posed three arguments: 1) The effect of early detection on mortality is unknown, and it's possible that screening is merely lengthening the interval between diagnosis and death. 2) With MCED, false positives are going to be more difficult to resolve, leaving patients to diagnostic odyssey. 3) Circulating markers are unlikely to detect premalignant disease, unlike screening for cervical cancer and colorectal cancer.

Going into the debate, about 75% of the audience disagreed with the proposition, and few minds were changed, with 74% disagreeing after.



PRE-debate



POST-debate

Lightning talks

University of Oxford mathematician **Joshua Bull, Ph.D.**, is developing spatial analysis tools that more fully capture the information available in multiplex medical images. Bull noted that many existing tools used to analyze multiplex images are suboptimal because they have been adopted from other fields. **Elinor Nemlander,** a doctoral student at Karolinska Institute, described her project developing tools to help find patients in primary care who are most at risk of developing cancer. She's analyzing questionnaires from patients with suspected lung cancer using machine learning to find possible combinations of symptoms and findings that can predict lung cancer in never-smokers.

Session 4: What is needed for an earlier cancer detection test to have clinical impact?

Topic chairs: Tom Beer, M.D., Exact Sciences Corp., and Rebecca Fitzgerald, M.D., University of Cambridge

Sharmila Anandasabapathy, M.D., at Baylor College of Medicine, described efforts to develop practical, effective endoscopy tools for use in low-resource settings. Her team's portable, battery-operated, high-resolution microendoscope costs less than $3,500 and makes subcellular resolution images. In a clinical trial in northern China and the U.S., the device improved the accuracy of screening for esophageal squamous cell neoplasia. When deployed in community-based clinics, however, specificity was much lower, she said, a performance issue that may be solved by incorporating an AI decision aid.

Hormuzd Katki, Ph.D., from the National Cancer Institute, delved into the challenge of translating clinical trial findings on the risks and benefits of cancer screening to make them applicable to wider populations. For example, the NLST trial of computed tomography screening for lung cancer showed a 20% reduction in lung cancer death, but subjects at lowest risk may have had no mortality benefit from screening. How to select candidates for screening? Katki described a "life-gained" approach, using a model for individualized life-years gained from screening.

A target product profile, or TPP, is a planning document that systematically sets out the characteristics of a new product that are needed to fill an unmet clinical need. **Larry Kessler, Sc.D.**, from the University of Washington, described how TPPs could help advance multi-cancer early detection tests and avoid pitfalls encountered in existing cancer screening tests. TPPs explicitly incorporate patient, clinician, industry, regulatory and health system input. They define parameters of success, giving developers tangible targets.

Cancer biomarker research is tremendously inefficient. **Chris Peters, Ph.D.**, from Imperial College London, brought the data: over the years, researchers have published papers on more than 2,100 prognostic biomarkers for breast cancer. Only 24 have made it into clinical use, a success rate around 1%. For colon cancer diagnostic biomarkers, the success rate was 0.12%. Aiming to improve efficiency, Peters and his team developed a biomarker toolkit, a sort of a scoring system to help decide how likely a biomarker is to succeed. It lists over 120 attributes that are beneficial in creating a robust biomarker. Peters said it can help researchers focus on the types of studies needed to prove clinical usefulness, and perhaps rescue stalled biomarkers that have potential but were not developed in the right way.

Challenges and future directions:

- When choosing the threshold for which patients to screen for cancer, it is critical to account for not only the benefits of screening but also the harms.
- The benefits and harms of screening in a real population will probably differ from those in clinical trials, so trials should be designed to deliver results that help define the populations most likely to benefit from screening.
- Researchers need better guidance from regulators on the use of real-world evidence.
- The impact of early detection screening tests on patient quality of life deserves more study.
- To make biomarker development more efficient, the field should coordinate efforts with consortia and specialist centers, rather than leaving it to the current individualistic approach. For example, cooperating groups could validate multiple biomarkers in the same patient cohort.
- Current incentives for publishing and securing grants can dissuade researchers from embarking on the kind of studies needed to advance biomarkers to the clinic.

Save the date

The 2023 Early Detection of Cancer Conference takes place 10-12 October, Central Hall Westminster, London, hosted by Cancer Research UK.

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