THE EARLY DETECTION OF CANCER CONFERENCE 2021

earlydetectionresearch.com

#EDx21

CANCER RESEARCH UK

OHSU KNIGHT CANCER Institute

CANARY CENTER AT STANFORD

EARLY DETECTION

ONE OF THE MOST POWERFUL WAYS TO IMPROVE CANCER SURVIVAL

The Early Detection of Cancer Conference is designed to stimulate creative thinking, build relationships across the globe, and assess the state of the field. Nearly 500 scientists, students, industry and policy leaders gathered online from 6–8 October 2021, for the sixth meeting in the series organized by Cancer Research UK, the OHSU Knight Cancer Institute and the Canary Center at Stanford University.

The conference is part of a long-term commitment to invest in early detection research, to understand the biology behind early-stage cancers, find new detection and screening methods, and enhance uptake and accuracy of screening.

The scientific program chairs leading this year's virtual event were **Andrew Flewitt, Ph.D., (University of Cambridge), Beverly Emerson, Ph.D., (OHSU Knight Cancer Institute) and Alice Fan, M.D., (Stanford University).**

ANDREW FLEWITT

BEVERLY EMERSON

ALICE FAN

KEYNOTE

This year's conference began with a motivating discussion on the impact and importance of early detection research. A longtime science writer with Cancer Research UK, **Henry Scowcroft** gained a shattering new perspective on cancer when his partner Zarah was diagnosed with a stage IV carcinoma of the bladder at age 36. Scowcroft's **recently published memoir** of the caregiving experience is interspersed with details of his science-minded effort to understand the disease that took his partner's life. In the keynote talk, Scowcroft said he was driven to create something that would help others facing cancer, particularly those not privileged with medical knowledge and expert contacts. Caring for Zarah sensitized him to the burden of tests and treatments on cancer patients. He exhorted researchers to always include a focus on making a difference to the lived experience of people with cancer.

HENRY SCOWCROFT

SESSION 1

WHEN AND WHERE DETECTION MATTERS: 'THE TIPPING POINT'

Chaired by Christina Curtis, Ph.D., Stanford University

Cells with cancer-associated mutations become increasingly common with advancing age, but few ever give rise to invasive tumors. Why not? **Phil Jones, Ph.D.**, at the Wellcome Sanger Institute, showed how emerging tumors can be driven to extinction by competing clonal populations of cells. In studies using mouse esophageal epithelium as a model, it was this competition that eliminated incipient tumors, not immune defenses. With deeper understanding, Jones said it could be possible to manipulate this competition of clones to stop early cancer from developing.

Irene Ghobrial, M.D., from Dana-Farber Cancer Institute, also focused on precursor states, asking whether well-timed interventions can stop the advance to multiple myeloma, an incurable blood cell cancer. Ghobrial is principal investigator of the PROMISE Study, the first to screen healthy people at risk for precursor conditions of multiple myeloma, including monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma. The study aims to uncover why some patients progress to myeloma and others do not – and inform the development of screening and preventive treatment strategies. In earlier work, her group identified genetic alterations in smoldering multiple myeloma that could distinguish patients at high risk of progression to multiple myeloma.

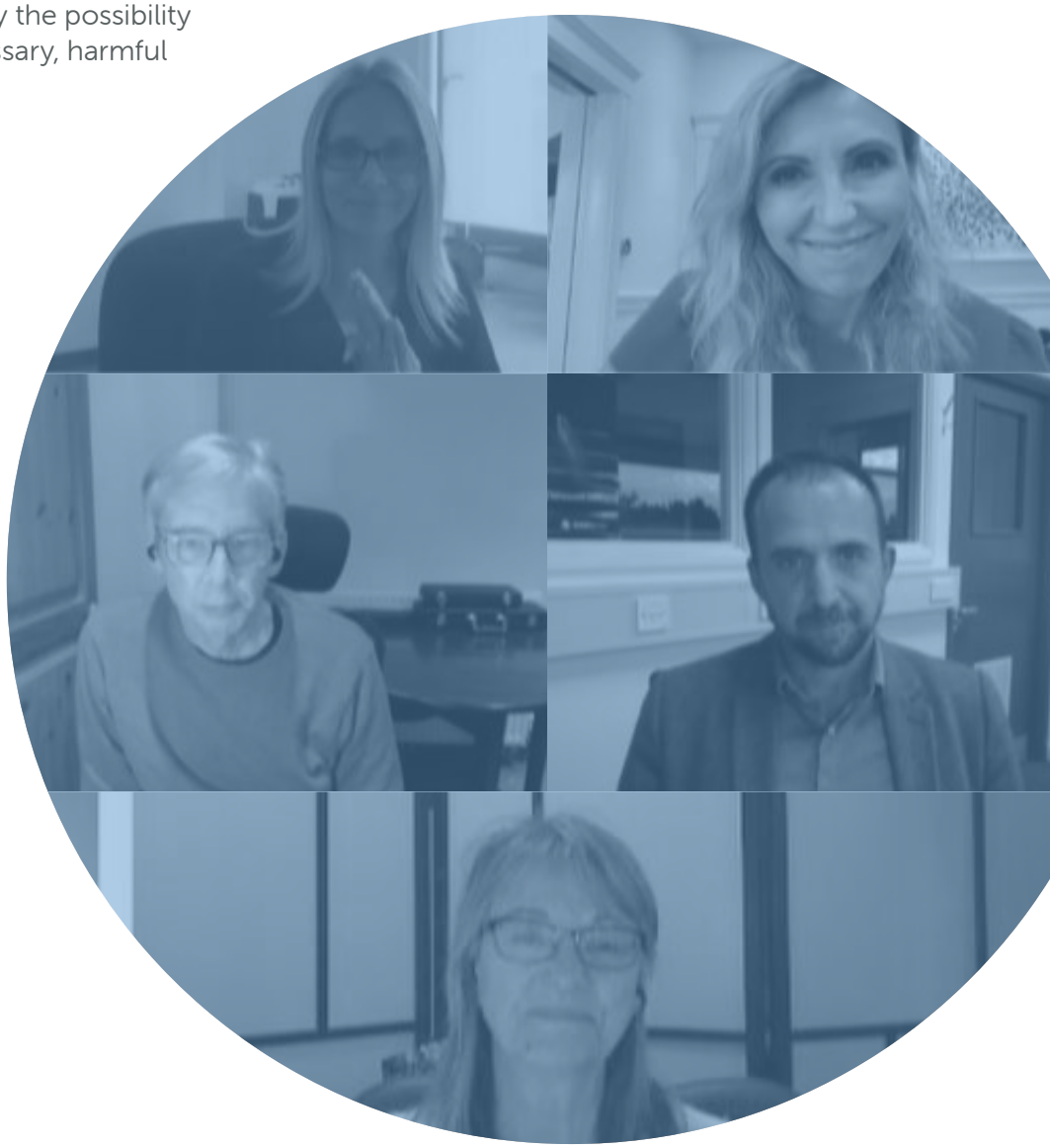
Breast cancers that emerge in young women within a few years after pregnancy are strikingly more dangerous. **Pepper Schedin, Ph.D.**, with the OHSU Knight Cancer Institute, detailed how tumor cells are shaped by the postpartum environment to become more prone to metastasis. At the end of lactation, 80–90% of milk-secreting cells undergo programmed cell death, in a process called mammary gland involution. The early phase of gland involution resembles an acute inflammatory response that subsides and is followed by an immune response similar to what happens during wound healing. Proximity to a recent pregnancy makes breast cancers more lethal in part through immune suppression, Schedin and colleagues found, and in postpartum breast cancers, estrogen receptor status does not adequately delineate risk of metastasis. Mammary gland involution should be an informative model for studying how factors outside of tumor cells drive cancer development, which provides another potential area for cancer detection.

In a lightning talk, **Daniel Muñoz-Espin, Ph.D.**, from the University of Cambridge, explained how targeting senescent cells could be a way to prevent non-small cell lung cancer progression in people presenting with multifocal primary lesions in their lungs. Such lesions pose a treatment conundrum: most will progress to invasive cancer and there is no good way to stop them. Muñoz said accumulation of senescent cells is a common feature. In a mouse model, drug ablation of senescent cells decreased lung tumor burden and increased survival. In some of the mice, the treatment prevented cancer initiation.

CHALLENGES AND FUTURE DIRECTIONS BROUGHT OUT IN THE DISCUSSION

Session 1 explored cancer "tipping points," such as whether or not a cancer arises from mutated cell clones; whether the precursor disease state MGUS progresses to the full-blown malignancy of multiple myeloma; and whether an in situ tumor changes based on intrinsic environmental signals to become an aggressive, invasive cancer. The changes between these states remain a fundamental challenge of cancer detection and point to many open questions for research.

- Choosing the most appropriate therapy for early lesions is complicated by the possibility of overdiagnosis and unnecessary, harmful intervention.
- Is it possible to detect lesions when it is too early to intervene?
- Clinicians will need better risk stratification to select those likely to benefit from therapy.
- Risk stratification approaches need to account not only for tumor factors, but host factors.
- The field needs to establish more targeted, precision interventions for early lesions.



GREAT DEBATE

BLOOD IS THE ONLY DETECTION MEDIUM THAT MATTERS

Minetta Liu, M.D., from Mayo Clinic, made the case for blood – an unpopular position going into the debate with the audience poll showing more than 90% disagreeing. Liu pointed out that existing modalities only screen for a few types of cancer. And some, like colonoscopy, are significantly invasive. Staying on schedule with all the separate screening tests is cumbersome for practitioners and, more importantly, burdensome for patients. Blood-based screening, in contrast, involves a point-of-care blood draw to screen for multiple cancers at once. Results so far suggest blood-based tests are pretty good at identifying the tissue of tumor origin to guide follow-up. Liu gave a whirlwind review of data from several companies readying multicancer, early-detection blood test for broad use, an indicator of the potential for rapid changes in screening practices.

Arguing the contrary, **Mark Emberton, M.D.**, from University College London, asserted that blood tests will only ever serve as a triage tool for selecting patients for more informative imaging tests. He said imaging more reliably delivers consistent results while blood test findings can vary considerably from day to day. He said imaging captures a range of attributes – location, volume, morphology, and more – that can't be derived from a blood test. And imaging, he said, seems to land at a point in tumor development when cancers have the clear potential to become dangerous, while blood tests might detect too many indolent, non-threatening cases invisible on imaging scans.

In the end, Liu swayed 19% to side with her while support for Emberton's position dropped to 81%.

DON LISTWIN AWARD FOR OUTSTANDING CONTRIBUTION TO CANCER EARLY DETECTION

Rebecca Fitzgerald, M.D., is internationally recognized for her research into the prevention and detection of esophageal cancers, including the development of the Cytosponge, a cell-collecting device on a string that patients can swallow instead of undergoing an endoscopy. Fitzgerald and her team have published work showing the device can increase by 10-fold the identification of Barrett's esophagus — a precursor to esophageal cancer — compared to standard of care. She was honored with this year's 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 Don Listwin, founder and chairman of The Canary Foundation. Fitzgerald is the interim director of the MRC Cancer Unit, Hutchison-MRC Research Centre, professor of cancer prevention, and a clinician scientist leading research in the early detection of cancer for the University of Cambridge and the Cancer Research UK Alliance for Cancer Early Detection.

SESSION 2

HOW TO DETECT: EMERGING TECHNOLOGIES FOR UNDERSTANDING SIGNALS OVER TIME

Chaired by Billy Boyle, CEO, Owlstone Medical

Stanford University's **Shan Xiang Wang, Ph.D.**, highlighted the advantages of giant magnetoresistive sensors, or GMR, to look for cancer mutations in circulating DNA, such as EGFR in lung cancer. GMR is more sensitive than fluorescent PCR assays – and less costly, he said. And GMR can show response to therapy within two weeks, while CT imaging can take two months or more. Wang's team is also using GMR to find methylated DNA targets in the blood as a way to detect liver cancer in patients with liver cirrhosis, which produces methylation signatures that are difficult to distinguish from cancer.

In a lightning talk, **Hannah Brewer, Ph.D.**, from Imperial College London, gave an update on the Cancer Loyalty Card Study, which is tracking changes in purchases that could signal early signs of ovarian cancer. Her team has recruited 117 women diagnosed with ovarian cancer (cases) and 420 women without ovarian cancer (controls). Comparison of loyalty card data of cases and controls has revealed an increase in purchases of pain and indigestion medications prior to diagnosis, suggesting it might be feasible to use such data to prompt medical screening.

Can smartphones and wearables help triage the use of expensive and more invasive tools for cancer early detection? **Stephen Friend, M.D., Ph.D.**, from Oxford University, described studies underway with the nonprofit 4YouandMe. Researchers will collect semi-continuous measurements via smartphone, smart ring and smart wristwatch. They will retrospectively analyze relative changes of multi-modal data streams among those who did and did not demonstrate new tumor growth.

Most ovarian cancers are detected dangerously late. **Daniel Heller, Ph.D.**, at Memorial Sloan Kettering Cancer Center, has developed sensors that can be placed inside the uterine cavity, like an IUD, to detect protein biomarkers of ovarian cancer that take too long to show up in blood. In mouse models of ovarian cancer, the carbon nanotube based optical sensors were stable for at least a month after implantation and reliably detected HE4 protein.

CHALLENGES AND FUTURE DIRECTIONS BROUGHT OUT IN THE DISCUSSION

The second session highlighted technologies and approaches to monitor signals over time, seeking deviations from an individual's "normal" state, which is a powerful way to detect changes that could indicate cancer. While longitudinal sampling is not without challenges, it has the potential to provide personalized health trajectories and signal when deviation happens.

- It will be worth spending more time seeking to understand what information people are willing to share for population-based early detection efforts. At the same time, the field needs to understand how to explain to people how their data will be used.
- When rates of false positive results are high and positive predictive value is low, early detection technologies can be optimized by targeting populations at risk, that is, with cancer prevalence sufficiently high.
- The most benefit may be gained from having multiple measures, not just one technology or assay.

GREAT DEBATE

EMERGENT PROPERTIES OF THE ECOSYSTEM ARE HOW WE'LL UNDERSTAND CANCER; A FOCUS ON A SINGLE CANCER CELL'S BIOLOGY IS MISGUIDED

Single cells can't tell the story without the context of what's going on around them, asserted **Aaron Grossberg, M.D., Ph.D.,** from OHSU Knight Cancer Institute. Organisms have evolved to respond to localized threats in ways that change systemic physiology, he said. Given that the probability of a positive finding in cancer screening is very low, even if cancer is present, he said that bio-amplification of the signal across physiological systems like the immune system may be an essential process for detecting cancer. And knowing the prevalence of cancer-associated mutations in non-cancerous tissues, the state of single cells may be misleading without also knowing the state of the microenvironment.

Peter Kuhn, Ph.D., from the University of Southern California, countered that the single cell holds the necessary information to signal a cancer, you just need to find the right cell, the needle in the haystack. It is not necessarily the cell that is a cancer cell, it could be a non-cancer cell that is indicative of the cancer, he added.

Kuhn changed a few minds; before the debate 75% agreed with Grossberg and 25% disagreed. After, 72% agreed and 28% disagreed.

SESSION 3

EARLY DETECTION IN THE REAL WORLD

Chaired by Robert A. Smith, Ph.D., American Cancer Society

Stacey Fedewa, Ph.D., from the American Cancer Society, contrasted cancer screening among women in the United Kingdom, which provides healthcare to all permanent residents, and the United States, where many go uninsured and cancer screening is opportunistic and not organized with coordinated outreach. But in both countries, only about 4 in 10 women were up to date on cervical, breast and colorectal screenings, and 1 in 10 women in both countries said they received no cancer screening.

Livia Giordano, M.D., Ph.D., from Centro di Riferimento per l"Epidemiologia e la Prevenzione Oncologica, made clear the challenges of communication in cancer screening efforts. It is essential to maximize informed choice to participate but also informed choice not to participate in screening, just as it is essential to minimize disinformed participation in addition to minimizing involuntary non-participation. While it's important to convey knowledge that informs risk perception to help people make choices that fit their values, Giordano said information is not enough. Communicators must consider emotions and trust.

In the real world, the introduction of new technologies can create new health disparities, pointed out **Robert Winn, M.D.**, of VCU Massey Cancer Center. Winn introduced a concept of ZNA – where an individual lives, their zip code, has an impact on their health. He traced the history of Richmond, Virginia, to illustrate how generations of societal policies have marginalized populations to create health disparities, from segregationist real estate practices, to the concentration of polluting industries in poor neighborhoods. For too long, he said, medicine has avoided directly addressing the social determinants of health.

The day concluded with a lightning talk on a rapid diagnostic service presented by **Spencer Robinson**, from York and Scarborough Teaching Hospitals NHS Foundation Trust. The service aims to give a single point of access to diagnosis for all patients who have serious nonspecific symptoms. General practitioners refer patients to rapid diagnostic centers where a triage clinician determines those who will receive a default workup including a CT scan and a trans-nasal endoscopy. Robinson said 336 referrals have resulted in 27 cancer diagnoses, including, in order of prevalence, metastases of unknown origin, pancreatic tumors, gynecologic cancers and lymphomas.

CHALLENGES AND FUTURE DIRECTIONS BROUGHT OUT IN THE DISCUSSION

Session 3 covered the breadth of challenges faced when implementing early detection tests and technologies in populations both with and without symptoms. Unfortunately, even the best screening tests face issues with adoption, and performance is affected not only by individual behaviors and risks, but also by broader societal challenges and inequalities.

- With isolated promotion of single screening tests, health systems are missing the opportunity to provide a more comprehensive and coordinated screening for multiple cancers.
- Early detection strategies need to recognize and find ways to overcome the inequities in current cancer screening efforts. In every health system, many people who would choose to undergo cancer screening if informed and given access are denied those opportunities.

SESSION 4

MODELS AND SYSTEMS TO INFORM DETECTION

Chaired by Joan S. Brugge, Ph.D., Harvard Medical School

Harvard University's **Benjamin Ebert, M.D., Ph.D.**, is finding ways to understand the risk of cancer in people with somatic mutations in blood cells, which are extraordinarily common. Access to hundreds of thousands of exomes from peripheral blood is making it possible to trace the path from clonal hematopoesis of indeterminate potential to life-threatening cancer, and to identify events that signal escalating risk. Abnormal blood count is one such event.

Hans Clevers, M.D., Ph.D., at the Hubrecht Institute, detailed the first patient-derived organoid model for cervical cancer, developed in his lab by Kadi Lohmussaar, Ph.D. Ordinary Pap sampling provides enough starting material to grow either healthy organoids or cervical cancer tumoroids. The organoids reproduce gene expression patterns of the organ, as the tumoroids mimic the mutations, gene expression and histology of patient tumors.

Cancer associated fibroblasts, or CAFs, play a role in malignant initiation and progression. **Thea Tlsty, Ph.D.**, from the University of California San Francisco, detailed efforts using bioengineered culture systems to reveal CAF signaling pathways that could be targeted for therapy or early detection. In an air-liquid interface culture system, bronchial epithelial cells grown alongside CAFs acquire squamous characteristics. Adding stress signaling triggers high-grade neoplasia. The next step will be to reproduce the development of full-on cancer.

The session closed with a lighting talk by **Carolyn Schutt Ibsen, Ph.D.**, from the OHSU Knight Cancer Institute. Her team has developed a way to simulate, in an *in vitro* 3D model, the localized oncogene expression found in early-stage cancers. The system uses lipid-monolayer gas-core microbubbles containing plasmid DNA. Directed ultrasound releases the plasmid DNA from the microbubbles so that only cells in the ultrasound focal zone are transfected.

CHALLENGES AND FUTURE DIRECTIONS BROUGHT OUT IN THE DISCUSSION

The final session explored recent developments in understanding the early biology of cancers using model systems. Models allow researchers to manipulate and mimic mechanisms that lead to the development of cancers, providing new information on potential targets for early detection and even cancer interception.

- Understanding mechanisms will inform development of more effective early detection methods.
- As technologies enable the detection of smaller and smaller lesions, the field will need to find ways to determine which merit intervention.
- At present, it remains impossible to predict which early lesions are likely to progress, and the mechanisms that lead to progression are unclear.
- Are there genetic alterations or changes in the microenvironment that indicate likelihood to progress?
- Ostensibly normal cells harbor many oncogenic mutations. What mechanisms break down to allow mutant cells to proliferate abnormally?

PANEL DISCUSSION

WHAT DO WE DO ONCE WE DETECT EARLY?

Existing cancer therapies have largely been developed to treat advanced tumors. This panel of experts discussed the new therapeutic strategies that will be needed for people diagnosed with very early cancers or pre-cancerous lesions to ensure that early detection does translate into better outcomes for patients. Chair **Charles Swanton, Ph.D.**, from the Francis Crick Institute/ UCL, highlighted a daunting challenge: advances in early detection are revealing that some early-stage cancers can be as deadly as later stage disease. More research and discussion of appropriate adjuvant therapies for early cancers is needed, especially if detected cancers are more likely to have already seeded metastatic cells and require monitoring for residual disease. **Tom Beer, M.D.**, at the OHSU Knight Cancer Institute, noted encouraging data suggesting that multi-cancer early detection blood tests might be better at detecting aggressive disease than indolent. It is now time to further develop what the clinical evaluation looks like following a positive multi-cancer detection test to ensure that survival rates improve, not just an increase in overtreatment and lead time bias.

Susan Galbraith, M.D., Ph.D., from AstraZeneca, highlighted the need for well tolerated therapies for patients diagnosed with early-stage disease. **Avi Spira, M.D.**, with Johnson & Johnson said localized delivery of drugs could be one way to minimize toxicity. Early disease may be easier to stop with targeted therapy drugs as its genomics are less complex. **Usha Menon, M.D.**, University College London, expressed hope for linking screening trials with treatment trials; subjects found to have early disease could be randomized to trials of various treatments.

All agreed that understanding the biology of early stage and pre-malignant disease will be critical to finding therapeutic targets for treating early cancers and intercepting pre-malignant disease with less toxic treatments.

CHARLES SWANTON

TOM BEER

SUSAN GALBRAITH

AVI SPIRA

USHA MENON

GREAT DEBATE

IT'S TIME TO GIVE UP ON HUMAN HYPOTHESIS-DRIVEN RESEARCH; MASSIVE, MULTIMODAL DATA MINED BY AI IS THE ONLY WAY WE'LL TRULY UNRAVEL THE COMPLEXITY OF CANCER EARLY DETECTION

Relying on hypothesis-driven research is like wandering through an infinite jungle hoping to stumble on the correct path, asserted **Bissan Al-Lazikani, Ph.D.**, a professor at MD Anderson Cancer Center. Early detection faces a signal-to-noise ratio problem, she said, that can only be solved by machine. She pointed to the development of BRAF inhibitors. BRAF emerged as a worthwhile target from computational analysis of massive amounts of DNA sequencing data, not from a scientist's hypothesis about that particular signaling pathway.

Xin Lu, FRS, F.Med. Sci., with Ludwig Cancer Research and the Oxford Centre for Early Cancer Detection, countered that AI-generated results lack meaning if they can't be explained by a scientific hypothesis. A machine learning algorithm may find complex patterns linked to early cancer, but without a hypothesis to explain them, it's impossible to validate the truth, Lu said. And AI requires a starting point and training data to learn from, which Lu said requires a human-generated hypothesis about the way the world works.

Going in, 82% of the audience sided with Lu, and 18% with Al-Lazikani. After the debate, Lu's support dropped to 54% and 46% agreed with Al-Lazikani, the largest post-debate shift seen during the conference.

REGISTER YOUR INTEREST FOR 2022

ACKNOWLEDGEMENTS

SCIENTIFIC PROGRAM CHAIRS

Andrew Flewitt
Ph.D., University of Cambridge

Beverly Emerson
Ph.D., OHSU Knight Cancer Institute

Alice Fan
M.D., Stanford University)

SCIENTIFIC TOPIC LEADS

Christina Curtis
Ph.D., Stanford University

Billy Boyle
CEO, Owlstone Medical,

Robert A. Smith
Ph.D., American Cancer Society

Joan S. Brugge
Ph.D., Harvard Medical School

Charles Swanton
Ph.D., Francis Crick Institute/UCL

CONFERENCE ORGANIZERS

CANCER RESEARCH UK

Alexis Webb, Ph.D.

David Crosby, Ph.D.

Aurora Callaghan

Naomi Gallimore

Emily Steer

OHSU KNIGHT CANCER INSTITUTE

Stephanie Torres

CANARY CENTER AT STANFORD

Katie Pontius

Ryan Spitler, Ph.D.

Ashley Williams

This report was authored by science writer Joe Rojas-Burke.