THE 2020 EARLY DETECTION OF CANCER CONFERENCE REPORT

CANCER RESEARCH UK

OHSU KNIGHT CANCER Institute

CANARY CENTER AT STANFORD

ADVANCING THE EARLY DETECTION OF LETHAL CANCERS IS FUNDAMENTAL TO TREATING PATIENTS MORE EFFECTIVELY

One of the most important factors in cancer survival is diagnosis at an early stage. Screening and diagnostic tests that detect the early events of cancer make it possible to intervene and stop tumors from progressing. Rapidly advancing technologies are now able to glean significant information from the cells, nucleic acids and proteins released by tumors and abnormally growing tissues. Major hurdles, however, stand in the way of translating new findings into clinical application. The Early Detection of Cancer Conference is part of a long-term commitment to meet these challenges and accelerate progress.

More than 600 scientists and clinicians gathered online from 6–8 October 2020, for the fifth conference in an ongoing series organized by Cancer Research UK, the OHSU Knight Cancer Institute and the Canary Center at Stanford. Scientific program chairs leading this year's virtual event were **Rosalind Eeles, Ph.D. (The Institute of Cancer Research), Paul Spellman, Ph.D. (OHSU Knight Cancer Institute),** and **H. Tom Soh, Ph.D. (Stanford).**

Rosalind Eeles

Paul Spellman

H. Tom Soh

SESSION 1: WINDOWS OF OPPORTUNITY FOR EARLY DETECTION

Chaired by Sam Janes M.B.B.S, Ph.D. (University College London) and Pepper Schedin, Ph.D. (OHSU)

Caroline Dive, Ph.D., (University of Manchester) presented an update on efforts to improve lung cancer screening by combining CT imaging with a liquid biopsy. Her team at the Cancer Research UK Manchester Institute is running an observational cohort study to test whether blood biomarkers can detect lung cancer recurrence earlier than standard of care clinical surveillance. The field has no shortage of potential biomarkers to choose from, including: circulating tumor cells, tumor DNA, RNA, and tumor-educated platelets. Progress, Dive said, will hinge on a deeper understanding of early disease biology and pre-clinical models that more accurately represent the early stages of cancer.

To that end, **Anton Berns, Ph.D., (Netherlands Cancer Institute)** highlighted the promise of autochthonous tumor models, that is, tumors induced in lab animals, in which it is possible to study early tumor formation in the presence of an intact immune system. With such models, researchers can switch particular oncogenes and tumor-suppressor genes on or off in a given tissue and compare cancer development. Berns said his team's mouse models closely recapitulate the phenotype of human cancers including small cell lung cancer, and may help identify specific early biomarkers of dangerous tumors.

Challenges and future directions brought out in the panel discussion:

- Of the many potential biomarkers, are there any particular ones that the field should focus on? Will it be better to integrate across multiple marker types?
- After a long latency, tumors often show explosive growth in autochthonous models; this poses a challenge for early detection of human tumors with comparable development trajectories. Will it be possible to differentiate latent but dangerous tumors from indolent, non-threatening ones?
- Not only will improved animal models be needed, but also a deeper understanding of the limits of specific models and how experimental findings using them translate to human tumors.
- New training opportunities to prepare the next generation of early detection researchers will be pivotal to maintaining progress.

LIGHTING TALKS, ROUND 1

Quick takes from the authors of selected posters

Naoki Oshimori, Ph.D., (OHSU Knight Cancer Institute) described how a mouse model of squamous cell carcinoma enabled his team's discovery of a signaling loop between tumor-initiating cells and nearby non-cancer cells that generates the microenvironmental niche that is required for invasive progression and drug resistance. **Jennifer Munkley, Ph.D., (Newcastle University Biosciences Institute)** gave an update on the GlycoScore blood test for prostate cancer, which looks for specific glycans (sugars that attach to proteins, lipids, and other glycans on cells). Tested in more than 600 patient samples, a three-glycan test distinguished between benign tissue and prostate cancer with high sensitivity and specificity, she said.

Emerging opportunities for early detection reflecting on COVID-19 – Panel discussion

The COVID-19 pandemic, as in all of medicine, poses severe challenges for cancer screening. Despite this, participants in a special panel discussion called out opportunities the pandemic has created for early detection and diagnosis. When it became unfeasible for patients to visit the clinic for melanoma screening, **Sancy Leachman, M.D., Ph.D., (OHSU Knight Cancer Institute)** and colleagues came up with an alternative: dermatoscopes that attach to a mobile phone, which high-risk patients can borrow and transmit images of suspicious lesions. It has become a permanent option for rural patients and those who can't easily travel.

For patients with worrying symptoms, such as severe heartburn or trouble swallowing, that call for endoscopy, **Rebecca Fitzgerald, M.D., (Cambridge University, MRC Cancer Unit)** said her center began cautiously testing an alternative diagnostic method: the Cytosponge, a small mesh sponge within a soluble gelatin capsule that is swallowed and retrieved to collect esophageal cells.

Kevin Monahan, M.B. B.S, Ph.D., (St. Marks Hospital) said his team learned the cost of halting colonoscopy procedures on missed diagnoses and is working to safely maintain the service for symptomatic patients even if a pandemic second wave hits hard.

Jackilen Shannon, Ph.D., (OHSU Knight Cancer Institute) said the pandemic has brought worldwide attention to long entrenched inequalities and health disparities, perhaps enough to drive much-needed policy changes and enduring efforts to reach underserved populations who would benefit the most from a shift to earlier cancer detection and diagnosis.

SESSION 2: LEVERAGING RISK STRATIFICATION FOR EARLY DETECTION

Chaired by Professor Timothy Rebbeck, Ph.D. (Harvard University) and Fiona Walter, M.D. (University of Cambridge)

To maximize benefits and minimize potential harms, cancer screening frequency should be matched to an individual's risk of getting cancer. Colorectal cancer screening illustrates the challenge: many people do not receive screening often enough while others undergo too much screening. **Jon Emery, M.B. B.S., D.Phil., (University of Melbourne)** described efforts to use genetic testing to help patients make informed decisions on colorectal cancer screening. He said it's looking feasible to start to implement genetic risk stratification to determine screening intervals in the general practice setting. In the future, insights will be more tailored to individuals with decision support tools that include risk factors such as diet, smoking, screening history, and medication use.

Julia Hipsley-Cox, M.B. B.S., M.D., (University of Oxford) and colleagues are drawing upon the UK health system's deep and detailed patient records to develop risk stratification algorithms to target cancer screening resources to people at highest risk and most likely to benefit from interventions. Qcancer, a 10-year risk algorithm, can be run via an online risk calculator (available at qcancer.org/10yr together with the open source software for download). Hipsley-Cox and her team have developed other risk-stratification tools that are integrated into electronic medical record systems.

Challenges and future directions brought out in the panel discussion:

- The development of reliable risk prediction models depends on access to high-quality and relevant data; more such data are needed.
- Existing data sets may not be representative of the people targeted for cancer screening. Often, for example, data sets don't reflect the genetic diversity of a population.
- Risk stratification models should always be calibrated to the locality of the population of interest.
- The field needs to consider the implementation of early detection in low-resource settings, where there may not be infrastructure for rolling out screening programs and providing follow-up treatment in the same way it is done in high-resource settings.

LIGHTING TALKS, ROUND 2

Quick takes from the authors of selected posters

Rebecca Landy, Ph.D., (National Cancer Institute) noted a huge disparity in lung cancer screening guidelines: only 32% of African Americans who develop lung cancer would have been eligible for CT screening, compared with 56% of white people. She showed how an individualized risk calculator (the LYFS-CT model) can effectively eliminate this disparity.

Tom Callender, Ph.D., (University College London) presented findings on the impact of MRI prior to biopsy on age-based and risk-tailored screening for prostate cancer. This approach reduced biopsies by 33% and offered an 8% reduction in detection of clinically insignificant cancers and a 2% increase in the detection of significant ones.

SESSION 3: THE FUTURE OF DESIGNING AND DELIVERING EARLY DETECTION TRIALS

Chaired by Christine Berg, M.D. (National Institutes of Health) and Peter Sasieni, Ph.D. (King's College London)

More evidence is needed to establish risk-tailored cancer screening as a standard of care, but getting that evidence won't be easy. **Hilary Robbins, Ph.D.**, a scientist with the International Agency for Research on Cancer, gave examples from lung cancer and breast cancer screening trials. The Yorkshire Lung Screening Trial and the International Lung Screen Trial are prospectively comparing the performance of U.S. Preventative Services Task Force criteria with promising multivariable models [PLCOM2012 and LLP (V.2)] for identifying individuals at high risk of lung cancer. For breast cancer screening, MyPeBS is a randomized trial that will compare a risk-stratified screening strategy with standard screening in terms of the incidence of breast cancer (stage 2 and higher) within four years. Robbins noted that classic randomized clinical trials may not be the best way forward for developing new early detection approaches; they require very large numbers of subjects and take many years to achieve measurable results. The technology used, and the questions asked may become obsolete before the trial is complete.

A cancer blood test developed by GRAIL, Inc., is being evaluated for its ability to detect more than 20 types of cancer and predict tissue of tumor origin. **GRAIL Vice President of Clinical Development, Eric Fung, M.D., Ph.D.**, highlighted the clinical studies that have led the company to focus on DNA methylation patterns for its multi-cancer early detection test undergoing a multicenter clinical trial due for completion in early 2021. Fung said the sensitivity of the assay increases as a function of cancer stage. He said it preferentially detects dangerous cancers, which would be helpful to limit overdiagnosis, that is, detection of indolent tumors not destined to cause harm. The company is factoring in ways to make the assay readily deployable in primary care clinical workflows.

Challenges and future directions brought out in the panel discussion:

- Trial-within-cohort, or TwiC, studies collect data on the exposures and outcomes of a group of patients, offering a way to conduct multiple randomized trials with usual care comparators. The design could be used for cancer early detection.
- Policy makers such as the U.S. Preventive Services Task Force have rejected risk-tailored cancer screening. Will it be possible to produce the level of clinical trial evidence for early detection strategies that such groups are demanding?
- Are there meaningful surrogate endpoints (in place of mortality) that could be used in clinical trials of risk-stratified selection algorithms?
- Governments and health agencies may need to reconceptualize their approach to assessing risk-based screening in terms of what needs to be achieved by a screening program and what kind of evidence should be used to judge its effectiveness.

LIGHTING TALKS, ROUND 3

Quick takes from the authors of selected posters

Amelie Lutz, M.D., (Stanford University) is developing an ultrasound guided molecular imaging method for detecting ovarian cancer using microbubbles filled with contrast agents that target tumor angiogenesis. She highlighted that one of the challenges of these early clinical translational studies is linking the radiological results with the pathological components of tumor specimens.

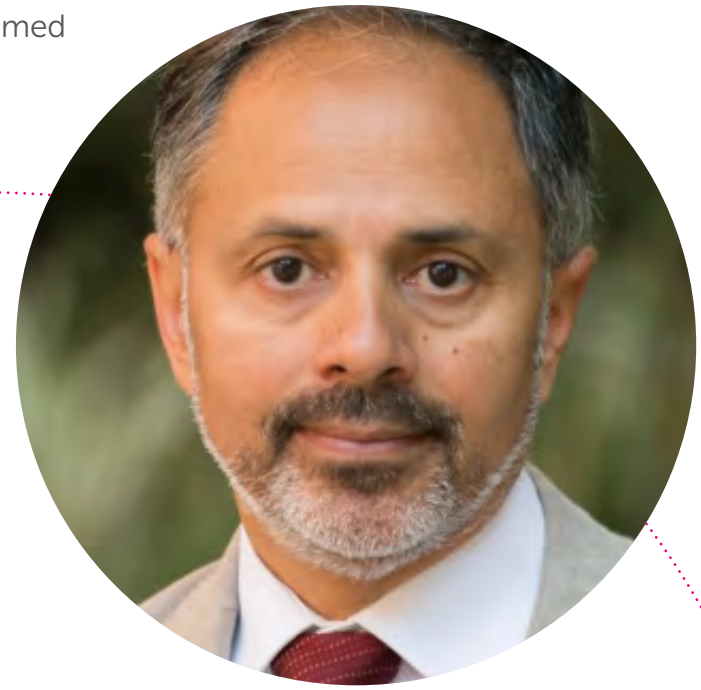
Stefano Avanzini, Ph.D., (Stanford University) is using mathematical models to estimate the size tumors must reach to become detectable by assays that measure tumor DNA circulating in blood. For lung cancer, he estimates a median tumor detection size of 2cm, which is 43% smaller than the median size of diagnosed cancers in the SEER database.

Keynote address: Dinah S. Singer

Dinah S. Singer, Ph.D., is deputy director for scientific strategy and development at the National Cancer Institute (NCI). Her talk began with a rundown of the NCI's response to the COVID-19 pandemic, from virus-focused research initiatives to the ways the agency is flexing to support grantees. Turning to the overarching themes in early detection, Singer highlighted the need to define the molecular, cellular and morphological basis of transition points from normal to pre-cancerous to cancerous states. This understanding of the 'seed' must be complemented by understanding the pre-cancer microenvironment that promotes transitions. She concluded with an overview of the cancer early detection programs the agency has underway, such as the Early Detection Research Network (now focusing on AI and machine learning to integrate omic data to find biomarkers), and The Human Tumor Atlas Network (HTAN), a massive effort to map the complex ecosystems of cancer — and pave the way for advances in prevention, early detection and treatment.

Don Listwin Award for Outstanding Contribution to Cancer Early Detection

Sanjiv Sam Gambhir, M.D., Ph.D., was an internationally recognized pioneer in molecular imaging who dedicated his career to developing methods of early disease detection. The director of the Canary Center at Stanford died of cancer on July 18, 2020. He was honored with the Don Listwin Award in a ceremony with heartfelt and moving remembrances from **Utkan Demirci, Ph.D., (Stanford University)** and **Iain Foulkes, Ph.D., (Cancer Research UK)**. The Don Listwin Award was established last year 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.



SESSION 4: MAKING THE MOST OF BIG DATA – ARTIFICIAL INTELLIGENCE AND EARLY DETECTION

Chaired by Sharon Hori, Ph.D. (Stanford University) and David Wedge, Ph.D. (University of Oxford)

From Google Health, **Lily Peng, M.D., Ph.D., and Sunny Jansen, Ph.D.**, expounded on three overlooked requirements for building successful AI models: data of high quality, not just quantity; human-centered usability, not just model accuracy; and cost-effectiveness, not just excellent performance. They noted that there is a gap between expectations and reality when it comes to what AI can achieve, as translating AI models into healthcare is often more challenging than it seems.

THERE IS A GAP BETWEEN EXPECTATIONS AND REALITY WHEN IT COMES TO WHAT AI CAN ACHIEVE, AS TRANSLATING AI MODELS INTO HEALTHCARE IS OFTEN MORE CHALLENGING THAN IT SEEMS.

AI systems are becoming adept at reading radiology images and pathology slides to correctly classify lesions as cancer or benign. Stanford University's **Parag Mallick, Ph.D.**, explained how tools such as saliency mapping are making it possible to understand how the machines reach their conclusions — building confidence and potentially revealing biological insights. He also showed examples of AI tools for biomarker discovery that extract and create knowledge from massive, unstructured data sets.

Challenges and future directions brought out in the panel discussion:

- Rapidly advancing technology will make it possible to detect increasingly minute lesions. But uncertainty persists about how to differentiate those that are dangerous from those that are not. This could worsen the problem of overdiagnosis if AI algorithms can't distinguish between the two.
- AI algorithms used for medical decision-making need to be transparent and clinicians need to understand how algorithms make distinctions. Is an open source requirement justified, or would that stifle commercial development?
- Is there a problem with treating a radiologist or pathologist's cancer/no cancer call as ground truth? How will you get beyond that, to exceed human ability to spot the smallest lesions and assess their significance?
- What is the best way to establish the ground truth of the performance of AI algorithms used for cancer early detection? Typically, researchers measure the incidence of pathologically confirmed cancers in the screened population at a given point in time after the screening event.
- For researchers who want to begin applying AI and machine learning in their investigations, several open source tools are available. Jansen suggested these as starters: ai.google/education, tensorflow.org/tutorials and developers.google.com/machine-learning/crash-course

LIGHTING TALKS, ROUND 4

Quick takes from the authors of selected posters

Freya Woods, a doctoral student at **Swansea University**, showed how AI can improve the sensitivity and specificity of cancer detection by Raman spectroscopy, which her group is developing as a triage tool in the diagnosis of colorectal cancer.

Rawen Kader, M.B. B.S., and colleagues at **University College London** have developed a neural network to assist real time decision-making during colonoscopy by classifying polyps as pre-cancerous or not, with a randomized clinical trial in the offing.

GREAT DEBATES

This year's conference featured two spirited discussions between expert speakers tackling provocative statements about the challenges of early detection. The debates were friendly, light-hearted and fun conversations where we asked our speakers to take firm positions for or against the statements, noting that their own personal views might not be so black and white.

Is stratification based on germline risk a required component for any early detection strategy, or will we need other ways to ensure we find early tumors?

Gareth Evans, M.D., (University of Manchester) made the case that it must be part of any detection strategy, noting that polygenic risk scores robustly predict risk for several common cancers and can be used to fit the frequency of screening to a person's risk of getting cancer. **Cristian Tomasetti, Ph.D., (Johns Hopkins University)** argued that, while genomic risk stratification is useful for some cancer types, many others have no known inherited factors. He asserted that the development of affordable and minimally invasive multi-cancer blood tests will reduce the need for genetic risk stratification. Before the debate, 60% of meeting attendees agreed with Evans, and 40% agreed with Tomasetti. The ratio shifted to 50:50 after.

Do we require randomised controlled trials with cancer-specific mortality endpoints for all new early detection approaches and technologies or should we be pushing for other ways to validate discoveries and get them to patients faster?

Harry De Koning, M.D., Ph.D., (Erasmus University Medical Centre) pointed to the conflicting findings of clinical trials of the utility of screening methods such as PSA for prostate cancer to make the affirmative case. **Steve Skates, Ph.D., (Harvard University)** asserted that requiring such evidence unnecessarily delays the use of early detection advances, and costs too much, when there are faster and less costly trial endpoints, such as reduction in late-stage diagnoses. In the poll of meeting attendees, agreement with De Koning dropped from 32% pre-debate to 20% after, with many more deciding that it's too prohibitive for progress in early detection to require randomized trials showing mortality benefit.

Access to videos from the conference are available to all registered attendees: earlydetectionresearch.com/conference-recordings

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Scientific program chairs:
Rosalind Eeles, Ph.D.,
The Institute of Cancer Research
Paul T. Spellman, Ph.D.,
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Hyongsok Tom Soh, Ph.D., Stanford University

Scientific topic leads:
Sam Janes, M.B.B.S, Ph.D.,
University College London
Pepper Schedin, Ph.D.,
OHSU Knight Cancer Institute
Timothy Rebbeck, Ph.D.,
Harvard TH Chan School of Public Health,
Dana Farber Cancer Institute
Fiona Walter, M.D., University of Cambridge
Peter Sasieni, Ph.D., King's College London
Christine Berg, M.D.,
National Institutes of Health
David Wedge, Ph.D.,
University of Oxford, Big Data Institute
Sharon Hori, Ph.D.,
The Canary Center at Stanford

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

CONFERENCE ORGANIZERS

Cancer Research UK:
Alexis Webb, Ph.D.
David Crosby, Ph.D.
Aurora Callaghan
Naomi Gallimore

OHSU Knight Cancer Institute:
Stephanie Torres

Canary Center at Stanford:
Katie Pontius
Ryan Spitler, Ph.D.
Ashley Williams