The 2019
Early Detection of Cancer Conference Report

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Frances C. Arrillaga Alumni Center
Stanford, California, USA

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

Advancing the early detection of lethal cancers is fundamental to treating patients more effectively. But the path forward is not easy to see. It will require multi-disciplinary collaborations, long-term studies to establish clinical effectiveness, and entirely new approaches to tackling disease. The Early Detection of Cancer Conference is part of a long-term commitment to meet these challenges and accelerate progress.

More than 300 scientists from multiple disciplines met at Stanford University in California, Sept. 24-26, 2019, for the fourth conference in an ongoing series organized by Cancer Research UK, the OHSU Knight Cancer Institute, and the Canary Center at Stanford. The conference is designed to stimulate creative thinking by attendees, build relationships across the globe, and assess the state of the art in the early detection field.

Integrative Early Detection through Multiple Technologies

Chairs: Gordon Mills, M.D., Ph.D., OHSU Knight Cancer Institute; Tony Ng, M.D., Ph.D., King's College London

A major challenge for the early detection of cancer is to achieve sufficient sensitivity and specificity to enable broad screening without worsening the problem of overdiagnosis. Some tumors and tumor-like growths are unable to advance swiftly enough to become life-threatening during a human lifespan, but existing screening tests can't tell the difference. The integration of multiple signal types, such as biomarker tests combined with imaging, will likely be necessary to understand which lesions are consequential and require treatment. This session explored scientific and technological barriers to implementing integrative early detection, and new opportunities to overcome them. Improved understanding of the biology of early cancer promises to enable the integration of signals from cancer metabolism, circulating nucleic acids, imaging, and other studies towards accurate early cancer detection, using rapidly advancing technologies such as wearable devices and implants.

Session co-chair **Gordon Mills, M.D., Ph.D.,** from the OHSU Knight Cancer Institute set the stage with a rundown of some unavoidable complications. Biomarkers and screening methods must be exceedingly sensitive and specific, he said, but not too expensive for patients and payers, while also being profitable enough for companies and investors to back. He stressed the need for multi-modal approaches and more academic collaboration with industry.

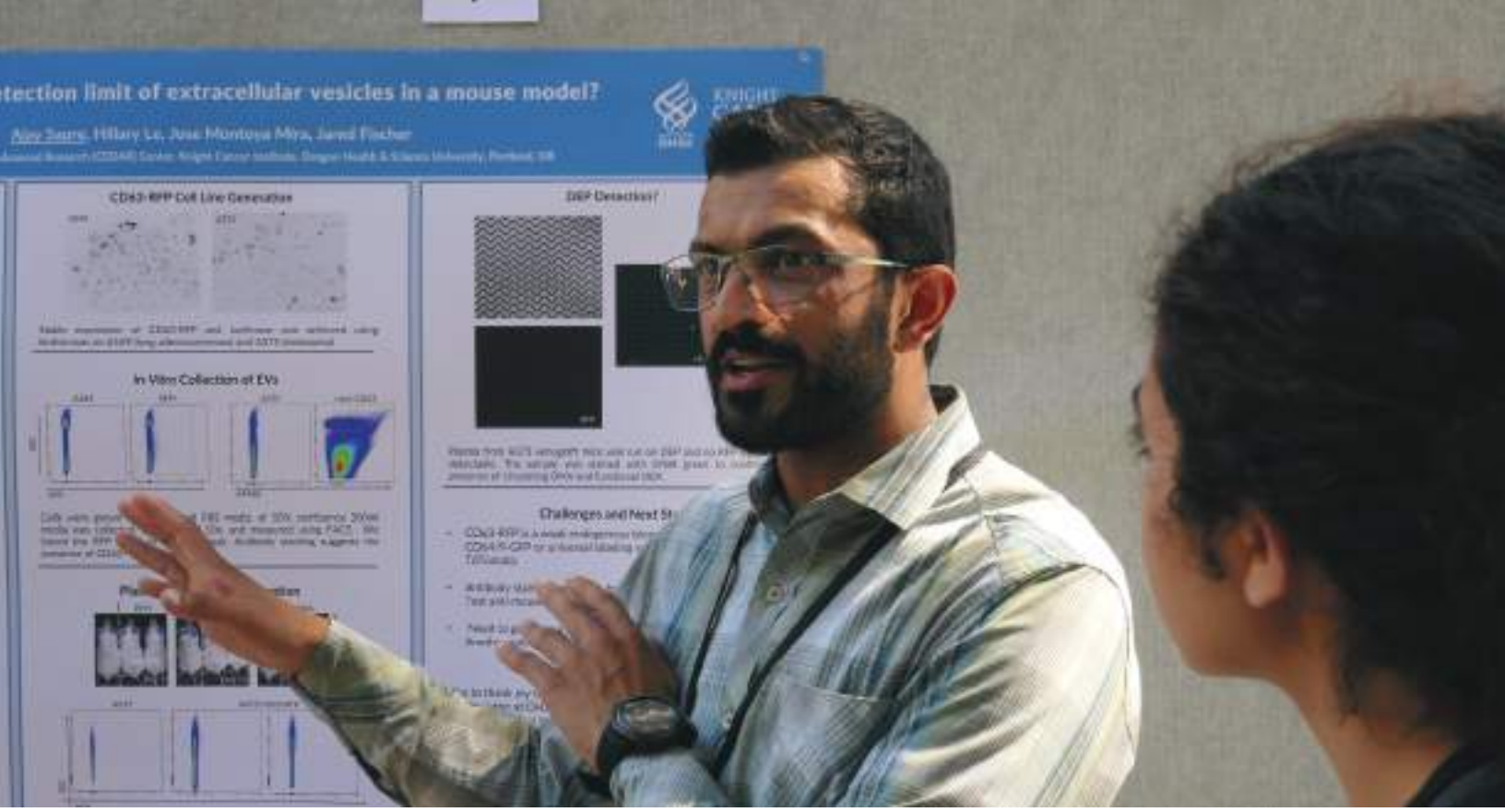
Victor Velculescu, M.D., Ph.D., described how his group at Johns Hopkins Kimmel Cancer Center, is going beyond sequencing of cell-free DNA in blood by looking at patterns in the fragmentation of the DNA. Fragmentation profiles reflect the jumbled packaging of cancer genomes. Because fragmentation profiles vary by tumor type, it may be used to identify the likely tissue of origin of a suspected cancer. By detecting many types of alterations simultaneously, this approach also has the potential to increase the sensitivity of liquid biopsy approaches.

From drops of blood, it's possible now to simultaneously measure hundreds of metabolites. **Jason Locasale, Ph.D.,** and colleagues at Duke University School of Medicine are doing so to investigate the disruption of mitochondrial metabolism in cancer cells. His group is using this to better predict drug response and to explore the influence of nutrition in the development of cancer.

Session co-chair **Tony Ng, M.D., Ph.D.**, of King's College London, concluded the session with a look at the potential of combining technologies for early detection. For example, measures of tumor hypoxia combined with the status of oncogenic receptor signaling may improve the specificity of early detection. Magnetic resonance elastography combined with innate lymphoid profiling may help identify cancers that are likely to spread. Imaging exosomes in blood samples and measuring immune changes may detect cancer recurrence early following treatment. Signals from these newly developed tools could be integrated using machine learning strategies to produce new multi-modal detection algorithms.

Challenges and future directions brought out in the panel discussion:

- As new early detection tests and technologies develop, the field must consider under what circumstances the test will apply. What is the test for? Is it for a high-risk group or the wider population? Is the test intended to be a triage test or a confirmatory diagnostic? These considerations will help to define whether a multimodal, integrated approach is required, and what its performance characteristics should be.
- What counts as early detection? Should the field focus on detecting pre-malignant lesions? Should it set sights on getting more cancers diagnosed at stage 1 or 2 rather than stage 3 or 4? Should the field encompass efforts to detect cancer recurrence?
- Integrating modalities is likely to increase sensitivity due to a wider coverage of indices, but could potentially decrease specificity by inadvertently including markers of general ill health.
- In some cases, the optimal and most-cost effective approach might be a system of sequential rather than integrated tests, analogous to Pap screening for cervical cancer, a sensitive but low specificity test used to identify patients that merit the more definitive colposcopy and biopsy.
- The field needs better models to evaluate tests which are designed to work over time to track changes within individuals, rather than single timepoint, yes/no measures.
- To establish specificity in early detection, it will be important to validate not only a sufficiently high number of cases and controls.
- Even if the field achieves the sensitivity and specificity needed to detect early, lethal cancers, it remains largely unknown if they will prove curable with existing therapies.
- Can cell-free DNA fragmentation differentiate between lung cancer and lung fibrosis or other diseases? Is there a cancer-specific pattern? Fragmentation differs by tumor type; what is the biological reason for this?
- What biological factors influence the release of DNA from different cancer sites and why does test accuracy vary so dramatically between cancer sites. Some cancers release more cell-free DNA than others and not only due to the size of the tumor. It's not clear why. Structure features, cell death and renewal, infiltrating immune cells and vascularity might be influencing factors.



Lightning talks, round 1

Quick takes from the authors of selected posters at the meeting

Elise Robinson, a Stanford biomedical engineering doctoral student, described her work exploring the use of extracellular vesicles to deliver PET imaging tags to reveal the location of early tumors. The system is designed to work with a probe that detects cancer specifically and secrete a biomarker.

People born with Li-Fraumeni syndrome face a significant lifetime risk of developing a wide spectrum of early-onset cancers. **Sangeetha Paramathas, Ph.D.,** at the University of Toronto and The Hospital for Sick Children, presented findings on circulating tumor DNA for use in cancer surveillance in Li-Fraumeni syndrome.

Rakesh Bam, Ph.D., a Stanford research scientist, is developing microbubble contrast agents for ultrasound imaging that use antibodies to target the hB7-H3 protein associated with breast tumors. He described efforts to more selectively identify dangerous tumors.

Cell surface carbohydrates called glycans are often aberrantly expressed or found at atypical levels in cancer. **Emma Scott, Ph.D.,** a research associate at Newcastle University, reported on the potential to exploit glycans as biomarkers for prostate cancer, and the potential to identify aggressive tumors and avoid overtreatment of indolent disease.

En-Chi Hsu, Ph.D., from the Department of Radiology at Stanford, found that Trop2 drives aggressive prostate cancer via PARP1 and that the level of this biomarker is prognostic of prostate cancer recurrence. Trop2 could be a minimally invasive biomarker with the capability to identify aggressive prostate cancers earlier than existing methods.

Walid Khaled, Ph.D., and his lab at University of Cambridge are looking at tumor initiation at the single cell level. Using a mouse model, they demonstrated that aberrant differentiation is an initiating step and that repression of oncogene Bcl11a might lead to reversion of this phenotype.

Prognostic Early Detection: How Can We Differentiate Indolent from Progressive Cancers when Looking at Early or Pre-Cancerous Lesions in Different Tissues?

Chairs: Denise Aberle, M.D., UCLA; Tanya Stoyanova, Ph.D., Canary Center at Stanford

Distinguishing indolent from aggressive cancer remains a key challenge for the field of early cancer detection. To accurately discern which patients require intervention and not just surveillance, we must understand the hallmarks of early cancer transformation in different tissue types. It may be possible to identify predictive biomarkers by building a systems-level understanding of early disease through combining model systems, longitudinal population studies, and novel molecular and data analysis approaches. This session focused on lessons learned from previous and ongoing surveillance studies and how these findings could be applied across different organ sites.

James Brooks, M.D., from Stanford University pointed out that each tumor type is going to present unique challenges and opportunities for early detection. For those cancers such as prostate tumors where the majority tend to advance slowly, finding ways to avoid overdiagnosis and overtreatment is a top priority. For cancer types advancing more aggressively, such as lung cancer, it will be important to develop ultrasensitive assays and to find practical ways to monitor more continuously to enable detection at earlier stages.

The key for all tumor types, Brooks said, will be gaining a much deeper understanding of the biology of precursor lesions. That will require more committed investing in projects such as assembling large cohorts for longitudinal tracking and establishing tissue banks with healthy controls needed for early detection research.

The Canary Prostate Active Surveillance Study (PASS) is good example. It's a multi-center study enlisting men who have chosen active surveillance to manage their prostate cancer. **Daniel Lin, M.D.,** from the University of Washington, said about a third of men in the study have had moderate-appearing cancers advance. The investigators are testing a variety of biomarkers for their ability to predict which cases will become aggressive.

Ductal carcinoma in situ, or DCIS, poses a similar dilemma, explained **Jelle Wesseling, M.D., Ph.D.**, from the Netherlands Cancer Institute. DCIS has become a very common diagnosis in the era of mammography screening. Not all DCIS lesions are capable of advancing to life-threatening breast cancer, but there is no sure way to identify those that are. Thus, almost all women with DCIS receive treatment as if they had invasive disease. Wesseling emphasized the need for multidisciplinary collaboration, and for bringing together findings in genomics, the tumor microenvironment, imaging, and model systems to build better risk prediction models to avoid the burden of treating harmless DCIS.

Concluding the day, **Sam Janes, M.D., Ph.D.**, from University College London, presented findings on carcinoma in situ lesions in the lungs. Up to 30% of such lesions regress, while about 50% progress to invasive lung cancer. Janes described how it is possible to predict progression using genomic, epigenomic or transcriptomic data, and how immune system surveillance likely accounts for regression of CIS lesions. Janes' group found intriguing evidence that quitting smoking allows the airways to repopulate with cells that no longer show the smoker's heavy mutational burden. The researchers compared airway epithelial cells grown as clones from 800 current and former smokers.

Challenges and future directions brought out in the panel discussion:

• Validating early detection technologies will require large-scale prospective cohorts and randomized controlled trials that will take considerable time and effort, but can and must be done.
• In addition to randomized clinical trials, which may take a decade or longer, the field should plan for large, retrospective cohort studies that can provide some answers in a shorter time frame.
• Investigators also will need access to more extensive repositories of tissue with detailed clinical data – including control tissue from people with no cancer to compare with early cancer.
• If there are biomarkers capable of distinguishing dangerous lesions from those that are unlikely to progress, they will probably be tumor specific. That is, what marks a progressive lesion in lung cancer is unlikely to mark progressive lesion in the breast or prostate cancer.
• Studies to date have not included enough subjects from racial and ethnic populations in which cancer risks are higher and outcomes worse than the predominantly white, European-ancestry populations that are better represented in the research.

Signals from Beyond the Tumor: Role of Tumor Microenvironment and Immune System in Early Cancer Detection

Chairs: Mark Davis, Ph.D., Stanford University; Amanda Lund, Ph.D., OHSU

Understanding the tumor microenvironment has potential for not only immune-based treatments, but also for understanding cancer initiation and progression, and developing new early detection tools. Signals from non-cancer cells such as leukocytes, T-cells, platelets, and stromal cells have potential as biomarkers and may provide clues that indicate the presence of cancer at the earliest stages. This session explored how the properties of the 'soil' provided by the microenvironment and immune system can influence the 'seed' of the cancer cell and how that translates to its potential for progression. Presenters considered how these mechanisms might be exploited for early detection and treatment.

Kicking off the morning, **Jennifer Wargo, M.D., M.M.Sc.,** from MD Anderson Cancer Center highlighted the combined roles of the immune system and microbes in tumor development and response to therapy. Her group has identified gut microbiome signatures with potential to predict which patients will respond to treatment with checkpoint inhibitors. The question remains how such signatures could be exploited to for cancer early detection.

Using a fluorescent imaging technology called CODEX, **Garry Nolan, Ph.D.,** at Stanford University and colleagues have been able to define a neighborhood-like organization of cancer cells and infiltrating immune cells. The structure of these neighborhoods is more fragmented and less organized in tumors that don't respond well to treatment. Examining this level of organization could yield insights into mechanisms of disease progression and potentially how the immune system responds to early cancerous changes.

Washington University's **Sheila Stewart, Ph.D**., detailed the many influences of senescent cells in cancer development and noted the potential for early detection and therapeutic targeting. Senescent cells pump out tumor-promoting factors, direct the localization of immune cells, and foster an immunosuppressive microenvironment. Signals from these senescent cells and the associated stromal environment are ripe for exploration and exploitation as early detection biomarkers.

Differences in the specificity of T cells might help explain why early cancers progress in some individuals but not others. **Mark Davis, Ph.D.**, and colleagues at Stanford University are pursuing that question using methods they have developed to derive T-cell specificity from raw sequence data. By applying a systems level approach to immune cell heterogeneity, Davis hopes to uncover early cancer biomarkers.

Challenges and future directions brought out in the panel discussion:

- The role of the microbiome in tumor development is only beginning to be understood, but offers opportunities for early detection.
- New technologies are making it possible to see all of the players in cancer development, including the metabolites mediating between cancer cells and their microenvironment.
- Progress using new methods and technologies hinges on access to more tissue samples from early tumors and pre-cancerous lesions in which to discover the biology of early cancer and seek biomarkers capable of predicting lesions likely to advance and become dangerous.
- Treatments aimed at early lesions may need to target not only incipient tumor cells but also the microenvironment of immune and stromal cells.

Lightning talks, round 2

Quick takes from the authors of selected posters at the meeting

Women with benign breast disease make up a large proportion of those who will be diagnosed with breast cancer. **Jonine Figueroa, Ph.D., M.P.H.**, from the University of Edinburgh presented her work exploring histopathologic features of tissue from women with benign breast disease and their future risk of developing breast cancer.

Carrie Shemanko, Ph.D., at the University of Calgary shared work from the Breast Cancer to Bone Metastasis Research Program, which is examining 500 patient samples and data to identify prolactin receptor signatures as biomarkers for early detection of bone cancer metastasis risk in breast cancer.

From the University of Cambridge, **John Lizhe Zhuang, Ph.D.,** presented his work exploring the complexity of immune cells in esophageal adenocarcinoma and its precancerous states. Using immunohistochemistry and clustering approaches, he hopes to identify different immune cell profiles between normal, Barrett's esophagus, and dysplastic disease.

A novel family of contrast agents for optical coherence tomography has been developed using gold nanobipyramids. Research associate **Peng Si, Ph.D.,** from Stanford showed the potential for these agents for high-resolution mapping to aid in cancer screening and diagnosis.

Late Breaking Results: TRACERx Study

The TRACERx (TRAcking Cancer Evolution through therapy (Rx)) lung study is a multi-million-pound research project taking place over nine years, aiming to transform the understanding of non-small cell lung cancer and take a practical step towards an era of precision medicine. The study seeks to uncover mechanisms of cancer evolution by analyzing the intratumor heterogeneity in lung cancers from approximately 850 patients and tracking its evolutionary trajectory from diagnosis through to relapse. At £14 million, it's the biggest single investment in lung cancer research by Cancer Research UK, and the start of a strategic UK-wide focus on the disease. **Charles Swanton, M.D., Ph.D.,** from The Francis Crick Institute gave an update on TracerX results using circulating tumor DNA for early detection of lung cancer recurrence after surgery. Swanton described progress in the effort to increase lead times by expanding the number of gene variants in the individualized panels derived from each patient's primary tumor. The idea is to detect minimum residual disease early, before the emergence of drug-resistant clones, when treatment may be capable of halting tumor growth. The study will also explore ctDNA-based prognostication and whether it may be used to spare low-risk patients from the toxicity of unnecessary adjuvant therapy.

Integrative Susceptibility for Early Detection: How Can We Go Beyond Traditional Risk Factors, Integrating Across Measures, to Better Select Populations at Higher Risk of Cancer?
Session Chairs: Antonis Antoniou, Ph.D., University of Cambridge; James Ford, M.D., Stanford University

Which individuals are most susceptible to cancer? Answers to this central question are emerging from the integration of germline susceptibility mutations, phenotypic measurements, and environmental and other pathogenic exposures. This session explored the potential to study these factors and learn from them in high-risk populations, to derive insights that may underpin future approaches for earlier detection of cancer. Important questions include how we define high risk and how we might utilize high-risk cohorts for the discovery and validation of early detection markers and technologies.

Stanford's **Allison Kurian, M.D., M.Sc**., noted advances in genetic risk stratification for targeted cancer screening, but also some pitfalls, such as the frequency of finding variants of uncertain significance, which occurs more often in some minority populations and has the potential to spur unnecessary interventions. The key to successful integrative risk prediction is to find the right intervention for the right patient at the right time.

Paul Pharoah, M.D., Ph.D., from the University of Cambridge, charted in detail the increasing reliability of polygenic models of cancer risk that incorporate lifestyle and other traditional risk factors and have potential to improve greatly the cost-effectiveness of screening. Dr. Pharoah's work points to the benefits of a risk-adaptive model as the future of breast cancer screening.

From the Netherlands Cancer Institute, **Gerrit Meijer, M.D., Ph.D.**, pointed out that since most polyps will not become cancer, it's important to focus on what drives the polyps that do progress. Current stool-based screening tests not only have suboptimal sensitivity for detecting polyps but also can't distinguish those at high risk of progressing from those at lower risk. He described a colorectal cancer early detection project in which researchers compared new protein markers in stool samples, in combination with traditional FIT screening, from cases and controls to create a more accurate risk profile that can be used for the early detection of high-risk polyps and colorectal cancer. Plans are underway to validate the panel in a prospective study with 10,000 people run via the Dutch government screening program.

Concluding the session, **Suzette Delaloge, M.D., M.Sc.**, from the Gustave Roussy Institute brought some eye-opening perspective to targeted versus mass screening and prevention. When targeted by genetic risk, both screening and prevention are more likely to produce measurable survival benefits with acceptable risk-benefit ratios. At the same time, she said, policy makers need to keep in mind that most cancers occur in people not at high risk, and that cancer screening efforts should not be blind to non-cancer health risks.

Challenges and future directions brought out in the panel discussion:
• Many critical questions remain unresolved: When does a lesion actually become cancer? What defines lesions that progress? What level of intervention is appropriate for premalignant lesions?
• Genetic risk scoring will improve with deeper knowledge of the multitude of genes involved. In breast cancer, for example, more than a third of the genetic component of risk remains unexplained and there may be thousands of risk variants yet to be discovered.
• Genetic testing laboratories remain inconsistent in calling pathogenic variants, an unresolved issue that must be taken into account in studies of cancer susceptibility and risk scoring.
• Biomarkers could be more effective than trying to accurately collect the necessary, relevant exposure data.

Special Presentation: Artificial Intelligence / Machine Learning Challenges and Opportunities for Early Detection – Jim Brase, Deputy Associate Director for Computation, Lawrence Livermore National Laboratory

Few technologies have been subject to as much hype as artificial intelligence. Jim Brase, who leads large-scale computing for life science, biosecurity, and nuclear security at LLNL, clarified the capabilities and limits of machine learning. His talk for non-experts focused on supervised algorithms, in which the model learns from a training set of data with given outcomes and then makes predictions for new data with unknown outcomes. "Overfitting" is an ever-present vulnerability; all data sets have noise and models made to fit their training data too closely capture too much noise. Machine learning algorithms are fragile; small changes in the input often cause large errors. They have a black box problem; why the model makes a given prediction may be inexplicable, especially with more complex models. And uncertainty in predictions is hard to quantify. Some of these limits are mitigated by reducing the complexity of the model and feeding it more data. Unlike human minds, machine learning algorithms can't learn from a few examples, they need voluminous data. When given an appropriate task, machine learning can massively accelerate—discovery. Brase gave the example of a machine learning framework for small molecule drug design, which took 16 hours to do what would have taken more than a year by traditional means.

Fostering a Translational Mentality in Early Detection Research

Chairs: Ruth Etzioni, Ph.D., Fred Hutchinson Cancer Research Center; George Hanna, Ph.D., Imperial College London

To move early cancer detection discovery and translational research towards patient and population impact, we must create a framework that considers health economics and health system implementation. To this end, a better understanding of the characteristics of successfully translated technologies and approaches can provide learning opportunities that can be applied to future work. Innovations in the early detection space should be made affordable and accessible to underserved and high-risk populations. This session focused on how to work with the groups required for translation –industry, regulators, government, and economists among others – to ensure that new detection technologies can be translated to market and implemented in our health care systems.

Fiona Walter, M.D., from University of Cambridge, highlighted the role of primary care in cancer early detection; in the UK about 67% of cancer diagnoses start with a report of symptoms to a general practitioner while only about 6% are detected by screening. Walter co-leads CanTest, an international team investigating ways of developing and implementing new and improved cancer diagnostic tests for the primary care setting.

Cervical cancer screening has been saving lives for decades. **Philip Castle, Ph.D.,** from the Albert Einstein College of Medicine reminded us that a disorganized health system can stymie progress. Most women in the U.S., for example, do not receive appropriate screening levels. Many are subjected to too much screening while others receive none at all, and there is approximately a three-fold difference in cervical cancer mortality across U.S. regions. This points to health inequalities in early cancer detection, even for an established screening modality like cervical smears. Self-collection of these samples is a solution that serves harder to reach populations and leads to an increase in screening uptake.

Stanford University's **Douglas Owens, M.D.**, chairs the U.S. Preventive Services Task Force and he demystified how that panel makes its influential recommendations, balancing the magnitude of potential benefits and the certainty (often lacking) of estimates of the benefit versus harm. If a test is going to detect a cancer, then there needs to be an effective treatment available in order to evaluate the benefits and harms of diagnosis, and its effect on morbidity and mortality.

Julie Barnes, Ph.D., with the company Abcodia, related the difficulties of establishing a screening method for ovarian cancer. Using samples from the UKCTOCs program, the world's largest ovarian cancer screening trial with 200,000 women participating in a 15-year multi-arm follow-up, Abcodia developed the ROCA test for ovarian cancer detection. It uses a woman's age, menopausal status, risk status and serial blood measurements of CA-125 over time to produce a score that indicates her likelihood of having ovarian cancer. In the UK FOCSS Phase II study of high-risk population, ROCA-based multimodal screening every 4 months, alongside reminders of the effectiveness of risk-reducing salpingo-oophorectomy, was associated with lower high-volume disease, and a high zero residual disease rate after surgery compared with women from the same cohort in whom cancer was diagnosed more than one year after screening ended. It remains unknown whether the screening strategy can improve survival.

Challenges and future directions brought out in the panel discussion:

- Many nonscientific factors came to bear on whether science gets translated. It will be important to envision the obstacles and the setting that any translational project aims to serve.
- Early detection modalities may require different analyses than the types currently performed by regulators and technology assessment agencies. Developer of early detection diagnostics need a shorter path for regulatory approval and payer acceptance.
- Surrogate measures that reliably predict clinical benefit are needed to speed translation of early detection technology. Stage shift is a candidate, that is, an increase in early stage diagnosis coupled with a decrease in late stage diagnoses.
- Advances in early detection have the potential to worsen disparities if marginalized populations are denied access. Global procurement programs, comparable to those developed for vaccines, could help make early detection technologies available in low-resource settings.
- The USPSTF and American Cancer Society often differ in their screening recommendations. How should primary care providers and the public decide which guidelines to follow?
- Two out of three cancers are identified through general practitioners, and prevalence of cancer in this group is perhaps 1%. Shouldn't early detection focus on diagnostics for this group of patients? What kind of tests are practical for use in the primary care setting? Are we making adequate use of the existing options? Helping GPs to triage patients safely and effectively should be paramount.

Lightning talks, round 3

Quick takes from the authors of selected posters at the meeting

Shreya Deshmukh, a doctoral student in bioengineering at Stanford, shared work on magnetic levitation and cell-phone based imaging without electricity to measure multiple parameters from blood cells in low- and middle-income countries.

Health economic evidence presented by **Ewan Gray, Ph. D.**, a research fellow at the University of Manchester, suggested that breast cancer screening in low-risk women may not be cost effective and that enhanced screening for high risk women could be a better use of resources.

Research at Queen Mary University of London led by **Belinda Nedjai, Ph.D.,** asked if self-testing is a possible alternative modality for cervical cancer screening. Work showed that most women testing positive for grade 3 cervical intraepithelial neoplasia (CIN3) can be identified using a novel methylation classifier with vaginal and urine samples with an AUC of 0.78.

Don Listwin Award for Outstanding Contribution to Cancer Early Detection

The Don Listwin Award recognizes 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 Canary Foundation, and he was the inaugural recipient in 2019. Listwin became personally involved in cancer early detection after his mother's death from ovarian cancer. With the Canary Foundation, he has supported research at numerous research institutions and ignited interest in cancer early detection. He formed teams of researchers from various disciplines to tackle the problem of detecting cancer at an early and more treatable stage. In 2009, he partnered with Stanford University to establish the Canary Center at Stanford – the first center in the world dedicated to cancer early detection.

Final Discussion

Facilitators: Sharon Pitteri, Ph.D., Canary Center at Stanford; Ashok Venkitaraman, M.D., Ph.D., University of Cambridge; Bree Mitchell, Ph.D., OHSU Knight Cancer Institute

In a wrap-up final session, participants reconsidered some of the gaps in knowledge and barriers to progress that surfaced during the meeting, and raised many questions across the breadth of topics covered at the conference:

Multi-modal detection

- Multi-modal, multi-analyte testing is a potential way to overcome current limits of detection. Is there a way to define a relation between the quantity of a biomarker and the stage of disease?
- Will it be feasible to use mass spectrometry as a clinical tool for early detection?
- With multi-modal testing, are we developing impractically expensive strategies? Or will research methods provide proof-of-principle for approaches that can be refined and optimized for cost-effectiveness?
- Machine learning could be a powerful tool for advancing early detection, but not until we have more high-quality data to compare early cancer and control samples.
- What will be the best way to implement multi-model testing?
- How do we deal with poorly vascularized tumors at the early stages for detection (if we are relying on serum-based detection assays)?
- Should we collect multiple different sample types from the same patient rather than many separate cohorts? Should we establish large-scale cohorts across multiple cancers instead of each laboratory and research program focusing on its cancer of interest?

Risk Stratification and Prognosis

- What are the prospects for cohort studies that recruit people with multiple cancer types, or at risk for multiple cancer types, to follow longitudinally?
- Differentiating indolent from progressive cancers remains a critical challenge, but the field needs to carefully define what these terms mean. What is clinically actionable? And how do we classify between indolent and progressive as that would be cancer dependent?

• Vested interests make it difficult to compare risk models and biomarker panels head-to-head. How can the field overcome this hurdle, given the heterogeneity of cancers and patients and the need for longitudinal sampling. Are we exponentially increasing costs by using multiple technologies?

Signals for the Microenvironment

• Are there tumor specific changes we can identify, or will it always be complicated by normal stress response? Are the signals the same? Is there information to be gained from the interaction between cancer and immune cells, not just either one alone? Host and microenvironment will eventually become risk factors. How do we integrate those?

• How can longitudinal, human experiments be designed to be informative about the tumor microenvironment and immune response in early disease to understand how we can use the biology for biomarkers or targets for interception? What questions should we be asking?

• The "neighborhood" organization of cancer and non-cancer cells in the tumor microenvironment may be informative for early detection. But studying it in tissue will be challenging. Are there signatures in the blood that would be more accessible for research and clinical testing?

• The field should not overlook the implementation of early detection tests, as made clear in the case of CT screening for lung cancer, a test proven to reduce mortality that is still not implemented widely.
• In the development of early detection technologies, should health economic modelling and human factors be included at an early stage to ensure that science is clinically viable? Would it be too inhibiting to consider economics in the beginning, or is it impractical to ignore the economics?
• Symptomatic patients account for a high proportion of cancer detection. How can we encourage and direct research toward triage tests in patients with non-cancer specific symptoms?
• Do we need to be involving other disciplines such as social sciences and psychology?

Save the date:

The fifth Early Detection of Cancer Conference takes place virtually on Oct. 6-8, 2020.

Acknowledgements

Scientific program chairs

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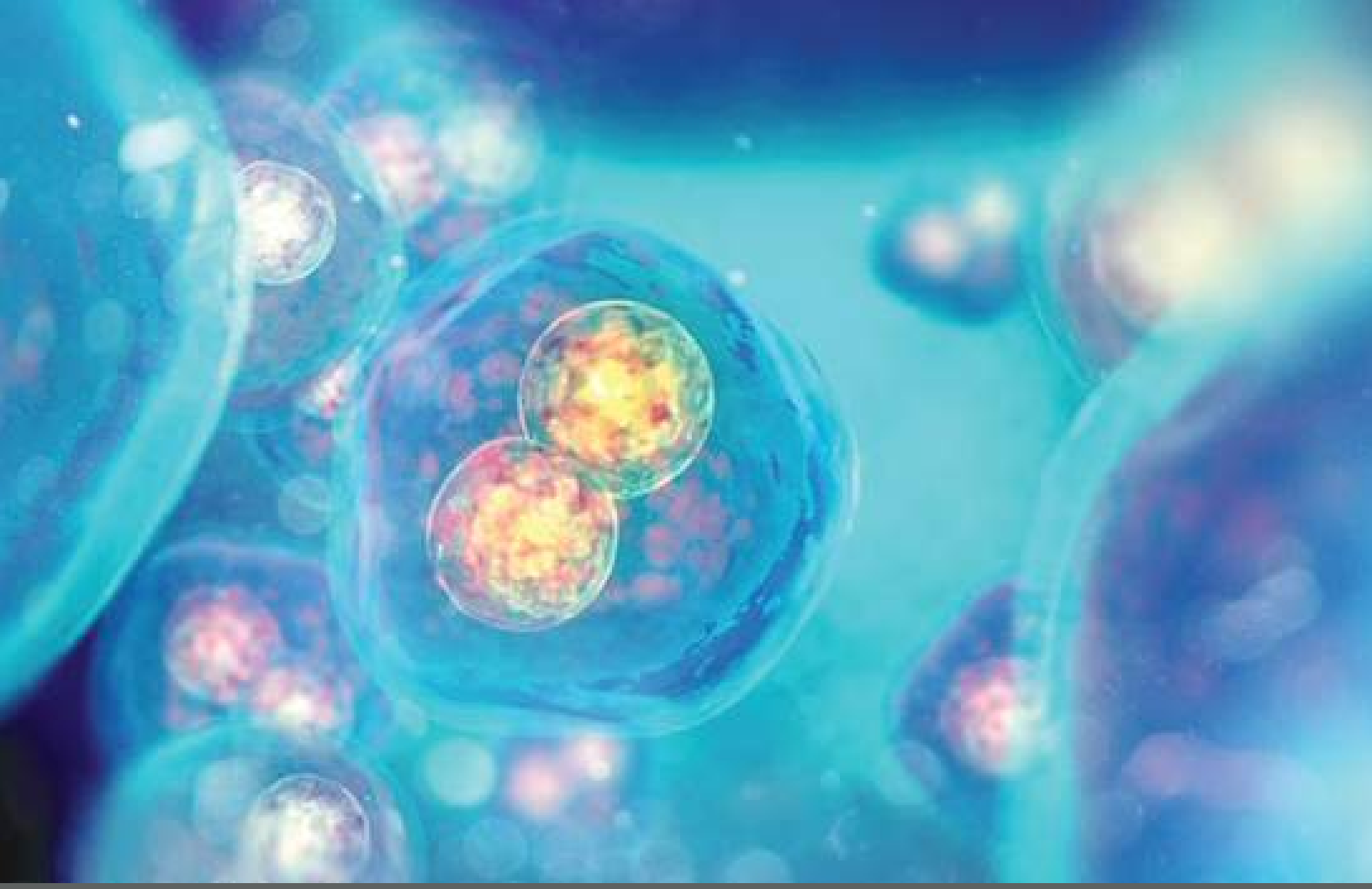

Save the date:
October 6-8, 2020
A virtual event

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