PERSPECTIVE

BLOODPAC: Collaborating to chart a path towards blood-based screening for early cancer detection

Earlier detection of cancer enables intervention when it is more likely to be treatable and curable, resulting in improved patient outcomes, such as the reduction of morbidity and mortality. Analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results data revealed that cancers diagnosed after distant metastasis represent ~18% of all diagnoses and close to half of all deaths.[1] Reducing the proportion of cancers diagnosed at late stages is therefore important.

BACKGROUND

Currently, guideline-recommended cancer screening programs vary in convenience, invasiveness, accuracy, adherence, and effectiveness. For example, cervical cancer screening with the Pap test has dramatically reduced mortality from cervical cancer among US women, from 5.55 deaths per 100,000 in 1975 to 2.16 deaths per 100,000 in 2019.[2] More recently, the incorporation of molecular human papillomavirus testing increased sensitivity for detection of cervical cancer and allowed for less frequent screening. In contrast, the use of prostate-specific antigen-based tests to screen for prostate cancer has led to challenges related to overdiagnosis and overtreatment without improving overall mortality in a statistically significant manner.[3]

Recent advances in the understanding of tumor biology and technological innovations in genomics and molecular profiling are enabling development of cancer-associated biomarkers in blood. Analytes of interest include circulating tumor cells, circulating tumor DNA, exosomes, microRNA, proteins, and tumor educated platelets. All have the potential to enable earlier detection of single or multiple cancer types through analysis of a blood sample.

Whereas the US Preventive Services Task Force has recommended screening the general population for some

cancer types, such as breast and colorectal, for years,[4] such screening is not recommended for most cancer types. Blood-based tests, including multi-cancer early detection (MCED) tests, have recently emerged to address this unmet need in cancer screening. Based on lessons learned from existing screening efforts, such tests will require clinical evidence development frameworks that address the tension between proximal (e.g., sensitivity and specificity) and distal (e.g., cancer-specific or overall mortality) end points.[5]

In the journey from bench to bedside, developers of liquid biopsy technologies need to navigate a host of challenges. The BLOODPAC Consortium was launched on October 17, 2016, as a commitment to the White House Cancer Moonshot to help overcome these challenges and accelerate the development, validation, and clinical use of liquid biopsy tests to better inform medical decisions and improve cancer patient care and outcomes. Consortium members, including diverse stakeholders from industry, academia, government and non-profits, coalesced around a central understanding that no single entity could establish the "infrastructure" needed to bring safe and effective technologies to patients faster. Only a multi-stakeholder collaboration could develop consensus standards and best practices in evidence development necessary to enable clinical implementation of liquid biopsies.

Drawing on the consortium's deep multidisciplinary expertise, BLOODPAC has tackled key challenges in the broader liquid biopsy field, addressing critical questions, such as standards for analytical validation and data sharing in genomic testing.[6] Today, BLOODPAC consists of over 60 collaborators who recognize that developing frameworks for evidence generation and aggregating data to support those frameworks are two fundamental requirements for success. The consortium's unique and growing footprint in the liquid biopsy landscape signals the success of BLOODPAC in anticipating and addressing the needs of stakeholders. By fostering a culture in which experts can leave their competitive interests at the door and focus on common needs and goals, BLOODPAC has helped to broaden awareness and implementation of

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recommended standards and guidelines, and thereby enabled the appropriate clinical utilization of safe and effective liquid biopsies.

So, why now in 2022, is BLOODPAC focusing on developing standards that can support rigorous evaluation of blood-based screening for early cancer detection? Recent and rapid technological developments in biomarker assays (e.g., next generation sequencing) and data analysis (e.g., artificial intelligence/machine learning) have enabled disruptive approaches to blood-based cancer screening. Furthermore, these innovations are occurring in the context of (1) lessons learned from the COVID-19 pandemic regarding the impact of molecular diagnostics on population health, and (2) renewed focus on ensuring equitable and timely access to healthcare advances. With this publication, BLOODPAC aims to chart both the opportunities and challenges ahead for the clinical use of blood-based tests for screening and early detection in cancer. This emerging field requires stakeholders to align on potential solutions to these challenges and to create standards and frameworks to facilitate the robust and responsible development, validation, and implementation of blood-based cancer screening tests.

CHALLENGES AND OPPORTUNITIES

Although blood-based tests for early cancer detection could materially advance the existing cancer screening paradigm, there remain a number of unsolved challenges. Table 1 describes the challenges and opportunities presented by this new class of tests. In bringing these forward, BLOODPAC seeks to identify areas of focus for the consortium to work with stakeholders to provide evidence-based guidelines and frameworks to help resolve these challenges and, ultimately, advance the field. By working collaboratively to help enable a future in which blood-based screening and early cancer detection can become commonplace, the BLOODPAC Screening and Early Detection Working group seeks to facilitate the implementation of evidence-based screening modalities for cancers with and without effective population screening today.

FUTURE DIRECTION FROM THE BLOODPAC CONSORTIUM AND EARLY DETECTION WORKING GROUP

Following the global COVID-19 pandemic, we are at a reflective time as a society and as a healthcare industry. In many ways, the pandemic disrupted our healthcare system and exposed both the barriers and opportunities that exist in cancer care – including the opportunity to harness the power and promise behind new approaches, such as blood-based screening for early cancer detection. It also demonstrated the importance of a public health approach to major health challenges, such as cancer.

A blood-based test can make screening and early detection of cancer more accessible and convenient due to the ability of samples to be collected in the setting where individuals typically receive care. This can augment efforts to provide access to cancer screening for people in medically underserved communities. As the use of blood-based tests is increasingly integrated into the cancer care continuum (i.e., cancer detection, diagnosis, treatment, and surveillance), it is important to address the complexities and challenges of these tests to ensure that the potential benefits are quantifiable, with risks clearly elucidated and appropriately mitigated.

No single entity can overcome all these challenges. Multi-stakeholder collaboration is critical to advancing this field, and as an established consortium, BLOODPAC has launched the screening and early detection working group to support efforts related to (1) standards and framework development; (2) education; and (3) access and care coordination. These efforts will help a variety of audiences, including supporting the development of safe and effective cancer screening tests by test developers; improving consistency and transparency in regulatory and payer evaluations of these tests; and accurately communicating with patients and providers about their benefits and risks in an effort to accelerate equitable access to these tests for the benefit of society at large. This work will also coordinate with and complement that of others, such as the National Cancer Institute, Cancer Research UK, Friends of Cancer Research, and the MCED Consortium.

The BLOODPAC Consortium's mission is to accelerate the development, validation, and accessibility of liquid biopsy tests to improve the outcomes of patients with cancer. The vision of the BLOODPAC Screening and Early Detection Working Group includes (1) thinking creatively about how best to evaluate the impact of early detection strategies on morbidity and mortality resulting from rare and currently unscreened cancers; (2) engaging providers and patients in understanding and mitigating the barriers to implementation of blood-based cancer screening tests and provide recommendations for an equitable, resilient, and sustainable healthcare ecosystem that benefits people; and (3) engaging and collaborating with regulatory agencies to generate post-market evidence to support the safety and effectiveness of blood-based cancer screening tests in real-world use.

Specific goals of the BLOODPAC Screening and Early Detection Working Group will be to (1) develop and socialize a lexicon of standard terms for blood-based assays for the screening and early detection of cancer; (2) develop

TABLE 1 Examples of challenges and opportunities for screening and early cancer detection tests

What is the challenge or opportunity?	Where are we today?	What could a future state be?
How do we fully realize the population health benefit from cancer screening in the United States?	• Even though four cancer types (colorectal, breast, lung, and cervical) are recommended for screening in asymptomatic individuals, adherence is poor and inconsistent, limiting the population benefit of such screening. • Most cancers lack established screening paradigms and are often detected after patients become symptomatic.	• Noninvasive blood-based screening to enable easier access to cancer screening, for both cancers with and without existing screening recommendations. • Earlier detection of cancer to enable the development of innovative treatment strategies and reduce cancer-specific mortality.
How do we tackle the complex and heterogeneous biology of cancer and the technological challenges of blood-based cancer signals?	• Low tumor volumes in early-stage cancers can make detection more difficult. • Organ-confined cancers may release few signals into blood.	• Technological innovations enable other multi-modal technologies, like epigenomics, fragmentomics, proteomics, and low-pass whole genome sequencing. • Combining multi-modal detection technologies with new data analysis methods, including AI/ML, increases the accuracy of blood-based tests.
How do we enable timely access to novel technologies within a robust regulatory framework?	• Technological advances and evidence generation can outpace the regulatory review process and sometimes even require new regulatory paradigms.	• Regulatory innovation and clear guidance documents support novel and flexible study designs and facilitate approval of safe and effective tests. • BLOODPAC frameworks help standardize approaches and facilitate safe and effective, yet more flexible, innovation.
How do we generate robust clinical evidence to support the validity and utility of blood-based cancer screening tests?	• Traditional randomized clinical trials to demonstrate clinical utility in an "average" or "elevated" risk population are lengthy, operationally challenging, and expensive. • The size of a trial to demonstrate clinical utility for low incidence cancers can become impractical. • Different terminology and measures of benefit/harm are used for different cancer types.	• New approaches to randomized clinical trials to support the approval and adoption of new tests for early cancer detection. • Real-world evidence and pragmatic clinical trial designs to reduce the burden of large-scale clinical validation and clinical utility studies. • A more consistent lexicon and standardized measures across all cancer screening and early detection efforts to align evaluation of benefit/harm in clinical trials.
What are appropriate comparators for blood-based tests in clinical trials?	• Defining a "true negative" in the absence of pathological confirmation for a blood-based cancer screening test can be challenging.	• Robust follow-up methods to better understand the natural histories of different cancers and to assess the truth of a negative test over time.
How do we ensure the new tests do not exacerbate health disparities?	• Novelty can exacerbate distrust of health care, and clear communication by providers is needed to foster trust and acceptance by individuals eligible for screening. • Slow and inconsistent insurance coverage can exacerbate disparities.	• Blood draws can reduce barriers to access, such as transportation insecurity and geography (e.g., rural vs. urban), and may be more acceptable to underserved communities when compared to more invasive or inconvenient conventional screening approaches (e.g., colonoscopy, CT screening for lung cancer, or mammography). • Extra emphasis on reaching people in underserved populations with community interventions that facilitate low-cost blood-based testing.
How do we ensure that these tests can achieve broad insurance coverage and reimbursement?	• Traditional approaches to technology assessment and health outcome assessment can be lengthy and expensive. • Tests have different intended uses, making clear frameworks challenging.	• Consistent and transparent paths to reimbursement for cancer screening tests, including MCEDs, such as the framework provided by the Center for Medicare Services' recent national coverage determination for blood-based screening in colorectal cancer. • Stakeholder collaboration to create consistent and transparent approaches to evidence generation to support coverage and reimbursement.

Abbreviations: AI, artificial intelligence; CT, computed tomography; MCED, multi-cancer early detection; ML, machine learning.

consensus frameworks that address the tension between proximal (e.g., sensitivity and specificity) and distal (e.g., cancer-specific or overall mortality) end points; and (3) recommend best practices for demonstrating the clinical validity and utility of blood-based early cancer detection tests.

opinions and the authors do not have any particular or specific conflict with the work described in this paper, beyond those just enumerated.

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