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POSITION PAPER

Lexicon for blood-based early detection and screening: BLOODPAC consensus document

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Abstract

In the United States, 2.0 million new cancer cases and around 600,000 cancer deaths are estimated to occur in 2024. Early detection gives cancer patients the best chance for treatment success. Currently, cancer screening in the general population is recommended for a limited set of cancers; as a result, most cancer types are not regularly screened. Thus, in recent years, we have seen a wave of novel, non-invasive, single- and multi-cancer detection tests (SCD and MCD), promising detection of cancer signals prior to the onset of symptoms and/or clinical diagnosis. To accelerate the development, access, and adoption of these tests, the Blood Profiling Atlas in Cancer (BLOODPAC) Consortium, a collaborative infrastructure for developing standards and best practices, established the Early Detection & Screening (ED&S) Working Group. The early detection space is in need of consensus around definitions for SCD and MCD tests that harmonize terminology across diverse stakeholders, thereby reducing communication barriers and ultimately advancing the discipline. To this end, the ED&S Working Group compiled a lexicon of terms, chosen based on perceived importance, frequency of use, lack of clarity, and unique challenges in the context of SCD and MCD tests. This lexicon was submitted to the FDA for their feedback, which was incorporated. In this work, we present the first installment of the lexicon, consisting of 14 primary terms, that will be part of an online dictionary and provide a foundation for future projects of BLOODPAC's ED&S Working Group.

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INTRODUCTION

In the United States alone, 2.0 million new cancer cases and over 600,000 cancer deaths are estimated to occur in 2024.[1] With advancements in screening and treatment strategies, trends in the incidence and mortality rates of cancer have steadily declined over the years; however, this has slowed or even reversed for some cancer types in recent years.[1] In the United States, screening in the general population is recommended for a limited number of more prevalent cancer types, such as colorectal,[2] breast,[3] lung,[4] and cervical[5] cancers. However, existing screening strategies for these cancer types have limitations. For example, mammography screening for breast cancer has a high false positive rate leading many patients to unnecessary follow-up procedures.[6] Low-dose computed tomography (LDCT) screening for lung cancer has been plagued with accessibility[7] issues. Both LDCT and colonoscopy suffer from low adherence due to the time-consuming and invasive nature of the procedures.[8,9] Together these barriers mean that less than 100% of eligible cancers are being detected through screening. Moreover, most cancer types are not currently covered by screening recommendations in the general population. Therefore, a substantial unmet need exists, with a significant opportunity for developing and implementing novel cancer screening and early detection strategies to improve cancer patient outcomes.

EARLY CANCER DETECTION TESTS AND THE NEED FOR A STANDARDIZED LEXICON

In recent years, there has been an emergence of non-invasive blood-based single-cancer detection (SCD) and multi-cancer detection (MCD) tests that leverage innovative biomarkers for screening and early detection of cancer. These tests often utilize next-generation sequencing and machine learning algorithms to identify novel cancer signals. The promise of these technologies lies in their ability to detect cancer signals prior to symptom onset and/or clinical diagnosis,[10–12] when treatment may be more effective and/or cancer mitigation strategies may be implemented.[13]

Recently, the Early Detection & Screening (ED&S) Working Group of the Blood Profiling Atlas in Cancer (BLOODPAC) Consortium,[14,15] a collective effort across public, industry, academia, and regulatory agencies, focused on developing shared best practices on liquid biopsy and outlined key challenges and opportunities for SCD and MCD tests.[16] The Working Group identified the need for a collaborative infrastructure and best practices for the development, validation, and implementation of these new tests. However, prior to establishing the standards for clinical validation or other evidence generation, it became clear that the community was not using common terminology to describe key concepts.[16,17] For example, community members were using different words for the same concept or the same word for different concepts (e.g., screening, early detection, and diagnosis). Similarly, what constitutes "early stage" cancer was unclear, as were the meanings of terms such as "average" and "elevated" risk, especially in the context of MCD tests. It became clear that confusion existed among different stakeholders, including test developers, healthcare providers, patients, biopharmaceutical developers, regulators, and payers, all of whom are critical to the appropriate development and clinical implementation of these tests. Without clear and consistent definitions, the group realized that it would be impossible to address more complex challenges, such as developing best practice guidelines for validating and using these tests.

As more tests are designed, developed, and commercialized, a standardized lexicon can help ensure the accurate and consistent use of terminology by stakeholders,[18] which can facilitate alignment in different settings, such as intended use statements in regulatory authorizations and coverage policies among payers. Additionally, a standardized lexicon would support the development of future consensus frameworks to address both clinical validity (e.g., sensitivity and specificity) and utility (e.g., cancer-specific mortality)[16] as tests emerge in clinical practice. To our knowledge, no other consortia have compiled a standardized lexicon for SCD and MCD testing.

DEVELOPMENT OF A STANDARDIZED LEXICON

In late 2021, the ED&S Working Group generated a lexicon of 153 terms (Table S1) that were nominated by members including all terms and related terms suggested. Over time, this expansive lexicon was condensed to 14 primary terms (with synonymous terms) based on several criteria, most notably perceived importance, frequency of use, lack of clarity among stakeholders, and unique challenges in the context of SCD and MCD tests. The terms were then assigned for review to individual Working Group members who used various sources, including but not limited to the National Cancer Institute's Dictionary of Cancer Terms and Thesaurus[18] and recommendations from professional societies and other organizations (e.g., the Friends of Cancer[19]). Members subsequently shared proposed definitions, which were

reviewed and discussed with the full membership, and revised until consensus was achieved. For terms where consensus was not achieved, different viewpoints are summarized below to facilitate continued discussion and progress. As such, this work represents the first installment of a lexicon that is intended to grow and evolve with the field.

The lexicon was submitted to the FDA in late 2023 for review and feedback through the agency's pre-submission program. The FDA's comments were integrated into the document and further reviewed by the College of American Pathologists' (CAP's) Preanalytics for Precision Medicine Project team and the Association for Molecular Pathology (AMP). The final lexicon of terms is presented in Table 1.

TERMS REQUIRING FURTHER EXPLORATION

As with any multi-stakeholder effort, Working Group members expressed nuanced and disparate opinions about the meaning of terms included in the lexicon. These opinions reflected their expertise and experience, as well as their backgrounds and roles as test developers, patient advocates, healthcare providers, academic researchers, biopharmaceutical developers, regulators, and payers. From the original list of 153 terms (Table S1), there were a few key terms that Working Group members felt were critical for the field to understand but had significant debate and for which full consensus was not achieved. Outlined below is an overview of these terms: true negative, true positive, false negative, false positive, and stage shift. It is the intent of the Working Group to continue to engage the broader community on the definitions of those terms and report on the outcomes of those discussions in the online lexicon and/or subsequent manuscripts.

True negative, true positive, false negative, false positive

In the context of MCD, the terms "true negative, true positive, false negative, and false positive results" elicited some debate, due in part to different approaches being taken by MCD test developers. For example, MCD tests may provide results that indicate (1) that a "cancer signal" has been detected and (2) the one or two most likely organs of origin for that signal referred to elsewhere in the lexicon as the "tissue of origin" (TOO). Whether a test reports one or both results can affect what is considered a true or false result. More specifically, for a test that reports 1 but not 2, a "false positive (FP) result" occurs when the test is positive in an individual who does not have any cancer type(s) that the test purports to detect, and a "true positive (TP) result" occurs when the test is positive in an individual who has any of the cancer type(s) that the test purports to detect. Similarly, a "false negative (FN) result" occurs when the test is negative in an individual who has any cancer type(s) that the test purports to detect, and a "true negative (TN) result" occurs when the test is negative in an individual who lacks all cancer type(s) that the test purports to detect. Debate focused on how to address the concepts of TP, TN, FP, and FN when a test reports both 1 and 2. Some posited that if an assay reports the TOO as, for example, breast or lung when it is actually colorectal, then it should be considered an FP result for breast and lung and an FN result for colorectal, while others suggested that this unfairly penalized tests that include TOO on their test reports since the presence of cancer was correctly detected and reported even if the TOO was reported incorrectly. This can be exacerbated when considering symptomatic versus asymptomatic detection. An alternative position advocated by others was to calculate two sets of numbers for TP, TN, FP, and FN, one based on the detection of any cancer and a second that addressed the situation described above related to the accuracy of the TOO result. A variation of this approach was to report TP/TN/FP/FN rates for "cancer" as defined by all cancer type(s) that the test purports to detect, and a separate measure of TOO accuracy.

Stage shift

An additional term requiring further deliberation is "stage shift." Our current definition for this term is "a consequence of implementing a new cancer screening test within a population that results in decreased 'late stage' incidence and increased 'early stage' incidence for the cancer type(s) included in the test." Debate centered on a few nuances: (1) whether the terms "decreased" and "increased" refer to absolute and/or relative changes and (2) whether "decreased late-stage incidence" is sufficient or "increased early-stage incidence" is also required. With respect to the first topic, opinions were expressed in favor of both absolute and relative changes, relative only and absolute only. Similarly, on the second topic, some were concerned about the prospect of encouraging overdiagnosis by including "increased early-stage incidence" in the definition, while others responded by asking why "decreased late-stage incidence" would not necessarily be accompanied by "increased early-stage incidence," whether absolute or relative. Finally, current staging definitions do not include molecular measures which will add complexity to how we will consider these terms in the future.

TABLE 1 BLOODPAC early detection and screening lexicon of terms.

BLOODPAC primary term	Alternate terms	Definition
Average risk		"Average risk" describes a population with risk that is comparable to the general population after consideration of age and sex. When applied to individuals and specific cancer type(s), "average risk" means that the individual has no known attributes, such as an exposure history, a family history, or a medical history that puts him/her at a greater or lesser risk for that specific cancer type(s) than the typical person of their age (and sex, when relevant)
Cancer detection		In the context of cancer screening and early detection, identification of a cancer-associated signal requires diagnostic testing for confirmation of the presence and type of cancer. (Contrast with other clinical applications of "cancer detection," such as minimal/molecular residual disease. Also, see definitions of "cancer screening" and "diagnosis.")
Cancer detection rate		The number of true positives divided by the total number of screening tests over a given test interval for the specific cancer type(s) that the test purports to detect. Test developers should clarify the number of screening rounds and the test interval when calculating the cancer detection rate
Cancer screening		Testing for cancer in an individual with no signs or symptoms of cancer at the time the test is performed, regardless of risk. (Contrast with definition of "diagnosis.")
Cancer type		For current single- and multi-cancer detection tests, the organ or tissue in which the cancer initially forms. For example, lung cancer forms in the lung, and breast cancer forms in the breast. Future tests may provide additional information, such as cell type and mutational status, relevant to the subsequent diagnostic workup and management of the patient. Multiple well-established classification schemes (e.g., ICD-O-3) exist for more precise definition or standardization of cancer types. Test developers should clarify which specific scheme was used
Diagnosis		Confirmation of the presence of cancer, most commonly based on tissue pathology. (Contrast with definition of "cancer screening.")
Early detection of cancer	Early cancer detection, cancer early detection, and early detection	Detection of a cancer-associated signal at an early stage for that specific cancer type. (Also see definition of "early stage" and "cancer detection.")
Early stage		For solid tumors, specific tumor–node–metastasis (TNM) stage varies by cancer type but is generally a localized (confined to primary tumor site) cancer amenable to local intervention for curative intent. Since multiple well-established staging systems exist, test developers should clarify which staging system was used. The converse of "late stage."
Elevated risk		"Elevated risk" describes a population with risk that is greater than the general population after consideration of age and sex. When applied to individuals and specific cancer type(s), "elevated risk" refers to an individual with known attributes, such as an exposure history, a family history, or a medical history, that puts him/her at a greater risk for that cancer type(s) than the typical person of their age (and sex, when relevant). Note that the term "elevated risk" is preferred to "high risk" because it is a relative, not an absolute, characterization of an individual's risk. For example, one can be at "elevated risk" for a specific cancer type, but the absolute risk for that cancer type may still be very low
Late stage		For solid tumors, specific tumor–node–metastasis (TNM) stage varies by cancer type, but is generally a cancer that has spread regionally or distantly and is NOT amenable to local intervention for curative intent. Since multiple, well-established staging systems exist, test developers should clarify which staging system was used. The converse of "early stage."

TABLE 1 (Continued)

BLOODPAC primary term	Alternate terms	Definition
Liquid biopsy		In the context of cancer, a test that detects a cancer-associated signal in a body fluid sample (e.g., blood, urine, or saliva) that may be used for multiple applications (e.g., treatment selection, disease monitoring, and cancer screening). For cancer screening specifically, this word can be misconstrued to indicate a cancer diagnosis, and BLOODPAC, therefore, recommends the use of a more precise term, such as single-cancer or multi-cancer detection test, to avoid confusion with biopsy performed after diagnosis
Multi-cancer detection (MCD) test	Multi-cancer early detection (MCED) test, multi-cancer screening test, multi-cancer screening, and early detection (MSED) test	Any test that purports to screen simultaneously for two or more cancer types using a biological specimen (e.g., blood). (Also see definitions of "cancer screening" and "diagnosis.")
Single-cancer detection (SCD) test	Single-cancer early detection (SCED) test, single-cancer screening test, single-cancer screening, and early detection (SSED) test	Any test that purports to screen for a single cancer type using a biological specimen (e.g., blood). (Also see definitions of "cancer screening" and "diagnosis.")
Tissue of origin	Cancer signal origin, tumor tissue of origin, and primary malignant neoplasm	A result reported on some tests that indicates or predicts the most likely origin(s) for a cancer signal that has been detected. Identification of the tissue of origin may be based on various approaches, such as molecular analyses or imaging, and is used to guide the subsequent diagnostic workup to confirm the presence and type of cancer

CONCLUDING REMARKS

Innovations in the development, validation, and implementation of non-invasive tests for the screening and early detection of cancer are occurring quickly, challenging the ecosystem of stakeholders to define and unify their terminology and reconcile their different viewpoints. It is critical that these stakeholders pause to establish a shared understanding and standardized lexicon. To that end, BLOODPAC's ED&S Working Group developed the lexicon presented herein.

While this lexicon is focused on cancer early detection and screening, it is part of a broader effort being undertaken by BLOODPAC for multiple applications of cancer liquid biopsies, also including (for example) molecular residual disease detection and monitoring. As such, the terms included in this and other lexicons from BLOODPAC will be part of an online dictionary (https://www.bloodpac.org/) that will be updated periodically to reflect our evolving understanding and new advances in the field. For example, even though the lexicon currently includes definitions for "average" and "elevated" risk, a recent special session at the 2024 American Association for Cancer Research's annual meeting co-hosted by BLOODPAC highlights that our understanding of "risk" in the context of SCD and MCD tests continues to evolve and requires continued elucidation. Although that discussion did not change our definitions, we plan to publish a commentary on the nuances of these terms, including comments from the discussion at the AACR session. Moreover, as part of our next workstream on clinical validity, we will work to achieve consensus on terms related to the clinical validation of SCD and MCD tests. Furthermore, we recognize that these definitions may not align with those used by other organizations, thus warranting ongoing conversations and continued refinement of the lexicon to reach full alignment within the community.

Finally, the development of a standardized lexicon represents an important first step towards working together as a community and is a prerequisite to enable future work streams for BLOODPAC's ED&S Working Group. In particular, future areas of focus for the Working Group include the development of recommendations for demonstrating the clinical validity and utility of SCD and MCD tests.

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CONFLICT OF INTEREST STATEMENT

Christina A. Clarke is an employee at GRAIL and stockholder at ILMN; Breeana Mitchell is an employee and stockholder at Natera; Girish Putcha is a former employee and equity holder at Freenome; Emma Alme is an employee and shareholder at Guardant Health; Peter Bach is an employee and shareholder at DELFI Diagnostics; Jonathan P. Beer is a shareholder of Bristol Myers Squibb, Novartis and Vertex; Tomasz M. Beer is an employee and shareholder at Exact Sciences and shareholder at Salarius Pharmaceuticals, Osteologic, Osheru; consultant/advisor at Arvinas, AstraZeneca, Sanofi, and GlaxoSmithKline; research funding: Alliance Foundation Trials, Astellas, Adela, Bayer, DELFI Diagnostics, Freenome, and GRAIL, Inc.; Michelle A. Beidelschies is an employee and shareholder at Exact Sciences, consultant/advisor at Cleveland HeartLab, Inc., Patent No. 20110269150 issued; Nancy Krunic is an employee at Novartis; Kathryn Lang is an employee at Freenome; Jerry S.H. Lee is an employee at Ellison Institute, LLC, and equity holder at AtlasXomics, LLC, and miRoncol, LLC; David E. Morgenstern is an employee and shareholder at DELFI Diagnostics and a shareholder at Roche Diagnostics; Victoria M. Raymond is an employee at Guardant Health; Stephanie A. Sanchez is an employee and stockholder at Natera; and Ryan Serra is an employee and stockholder at Quest Diagnostics, and stockholder at Exact Sciences and Illumina. The authors worked together collaboratively to develop consensus opinions and the authors do not have any particular or specific conflict with the work described in this paper, beyond those enumerated in the conflict of interest statement.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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