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# Establishing a Common Lexicon for Circulating Tumor DNA Analysis and Molecular Residual Disease: Insights From the BLOODPAC Consortium

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**Keywords:** ctDNA | liquid biopsy | MRD

## ABSTRACT

The use of a liquid biopsy to assess molecular residual disease (MRD) of solid tumors holds significant promise for improving outcomes for patients with cancer. Liquid biopsies are a minimally invasive approach for the identification of circulating tumor biomarkers through a simple blood sample. Assays capable of detecting MRD through analysis of circulating tumor DNA (ctDNA) are rapidly evolving for clinical study applications and therapeutic interventions. To address these opportunities, BLOODPAC—a multi-disciplinary consortium representing stakeholders from public, industry, academia, and regulatory agencies—formulated a lexicon that provides a shared framework and clear definitions using liquid biopsies for solid tumor MRD with an emphasis on ctDNA detection. The terms in the lexicon are categorized under general MRD, ctDNA testing methodologies, reporting results, and acquisition timepoints, including examples of current and potential clinical use cases for MRD tests. The overall goal is to provide a unified language and approaches to solid tumor MRD to advance applications of these technologies, allow data aggregation to strengthen future evidence, and facilitate regulatory approvals, leading to the use of liquid biopsy as an early endpoint in clinical trials. We believe that a common set of terminology and methods for solid tumor MRD can improve understanding and appropriate use of testing, accelerate clinical development, and improve outcomes for cancer patients.

Andrew G. Hadd and Angela Silvestro: Co-first authors.

## 1 | Introduction

The use of liquid biopsy for the analysis of cancer biomarkers is improving the ability to monitor cancer progression, to predict response to therapy, and to innovate clinical trial designs. Liquid biopsies offer the advantage of being minimally invasive; therefore, they can be performed more frequently than tissue biopsies. This characteristic allows for the continual monitoring of the molecular status of the disease over time and provides insights into the progression and characterization of the molecular drivers of particular cancers [1, 2]. The presence of subclinical micrometastatic disease biomarkers, which are not detected by standard imaging techniques, can be detected using highly sensitive liquid biopsy molecular residual disease (MRD) assays such as next-generation sequencing tests [3]. Detection of MRD in liquid biopsies relies on the analysis of tumor-derived DNA fragments released into the bloodstream or other body fluids, namely, circulating tumor DNA (ctDNA) [4]. Analysis of ctDNA as cancer-specific DNA markers (e.g., mutations, copy number variation, epigenetic patterns, fragment size, etc) represents the presence and relative abundance of the originating cancer tissue. The detection of ctDNA also provides information about different aspects of cancer treatment, for example, determining response to neoadjuvant therapy applied prior to surgery, monitoring of molecular relapse during surveillance, or indications of response to therapy in the metastatic setting [5]. Compared to standard biopsy and imaging techniques, the advantages of liquid biopsy for ctDNA analysis are driving innovations in cancer care [6, 7]. As the field of liquid biopsy for ctDNA analysis is rapidly expanding, there is an increasing need to standardize terminology in the field.

The Blood Profiling Atlas in Cancer (BLOODPAC) Consortium was launched on October 17, 2016, to accelerate the development, validation, and implementation of blood-based liquid biopsy tests with the overall goal of improving the outcomes of patients with cancer. The consortium created a collaborative infrastructure that enables sharing of information, development of standards, and best practices among various sectors—public, industry, academia, and regulatory agencies. The lexicon is designed to assist a diverse group of stakeholders across technology manufacturers, clinical testing, pharmaceutical companies, payors, and regulatory authorities to align on terminology and language to accelerate access to liquid biopsy for MRD and use as an early endpoint in clinical trials.

The lexicon terms focus on development, accessibility, analytical validation, and clinical validation of ctDNA-based MRD for solid tumors. We describe concepts, relevant terms, and examples within four specific categories: (i) general terminology, (ii) methods for the detection of MRD, (iii) reporting results, and (iv) clinical acquisition timepoints. General terminology addresses use of molecular versus minimal residual disease and factors that affect MRD analysis. An overview of methods and reporting results provides context for key technologies in this field and guidelines for comparing results from longitudinal testing. Standardization in clinical acquisition timepoints can help with interpretation of results and meta-analysis between different clinical trials. This lexicon expands on and complements other publications, such as BEST (Biomarkers, EndpointS and other Tools) published by the National Institutes of Health [8] and "Circulating Tumor DNA in Development of Therapies for Cancer: An Evidentiary Roadmap to an Early Endpoint for Regulatory Decision-Making" published by Friends of Cancer Research [9]. These efforts at creating an MRD lexicon also address the challenge of difficulty with terminology, which is identified by Febbo et al. [10] as a potential barrier to ctDNA testing implementation and access.

BLOODPAC's members, representative of diagnostic developers, academia, pharmaceutical industry and regulatory bodies, aligned on and reviewed these terms and definitions. The diversity in stakeholder expertise reinforces the practical utility of this lexicon, which the group supports as a foundation to address the needs of the broader community utilizing liquid biopsy for ctDNA analysis. The lexicon was submitted to the FDA in late 2023 for review and feedback through the agency's presubmission program. The FDA's comments were integrated into the document and the manuscript was 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 here (Table 1).

## 2 | General Terminology for MRD

We include a set of general terms to align on a framework for the components of liquid biopsy for MRD testing. Solid tumors present different cancer-associated biomarkers in the blood for which the detection depends on a number of factors, including type of cancer, stage, location, and response to therapy [11]. Therefore, the choice of "molecular" residual disease instead of "minimal" residual disease for liquid biopsy of solid tumors is intentional. Minimal residual disease is historically linked with the lowest quantifiable presence of anatomic disease below a visually interpretable method; e.g., imaging or cell counting for chronic myelogenous leukemia (CML). Unlike CML, for which the signature biomarker of bcr-abl references the disease, solid tumors may have varying levels of biomarkers based on the specific cancer, stage, or other factors [12]. In these cases, the absence of a solid-tumor biomarker in the blood does not necessarily mean the cancer is absent. Therefore, we use molecular as an indication of the biomarker of disease instead of the disease itself. This approach is consistent with terminology adopted by the European Society for Medical Oncology (ESMO) [13], FDA draft guidance on the use of circulating tumor DNA [14], and Friends of Cancer Research [9].

The use of liquid biopsy is not limited to the MRD setting of post-curative intent therapy surveillance monitoring. Serial measurements of ctDNA may also be applied to the determination of neoadjuvant treatment response, adjuvant therapy response, and detection of molecular response, molecular recurrence, or molecular markers of resistance in the metastatic setting. These techniques and associated terms are shown in Figure 1. A recent publication highlighted the interpretation of ctDNA results and provided general recommendations on the clinical utility of ctDNA in different treatment settings [11]. Other studies have focused on the current and future clinical utility of ctDNA in specific cancer types, including breast cancer [15] and gastrointestinal (GI) cancer [16]. Clinical applications can vary across

**TABLE 1** | BLOODPAC MRD liquid biopsy lexicon of terms.

| BLOODPAC primary term | Alternate terms | Definition |
|---|---|---|
| Cancer shed (ctDNA shed) | ctDNA shedding | The release of circulating tumor DNA (ctDNA) from tumor cells into the bloodstream or into other bodily fluids through the processes of secretion, apoptosis or necrosis. ctDNA shed rates may vary based on cancer stage, histology, cancer biology, type, vascularity, growth, size, treatment type, treatment status, and location of the tumor among other factors |
| Circulating tumor DNA (ctDNA) | | Tumor-derived DNA fragments released into the bloodstream through extracellular vesicles or tumor cell apoptosis or necrosis |
| Clonal hematopoiesis of indeterminate potential (CHIP) | | The presence of clonally expanded genetic variants in the blood from hematopoietic stem cells (HSCs) or other early blood cell progenitors independent of malignancy. CHIP mutations can be confounding factors in ctDNA testing. The use of matched normal sequencing information or bioinformatic filtering using databases of common CHIP polymorphisms are some methods in use to reduce the influence of CHIP on false positive calls for MRD |
| Mutation copies per mL | | The number of DNA fragments containing the mutation of interest divided by the volume of plasma |
| ctDNA clearance | | The change in ctDNA status from detected to not detected as a function of tumor biology or response to treatment |
| ctDNA detection | | The identification of a biomarker or pattern of biomarkers associated with circulating tumor DNA above a validated threshold |
| ctDNA dynamics | ctDNA kinetics | The change or the rate of change in the relative abundance of ctDNA as a function of serial measurements and/or the response of a solid tumor to treatment |
| ctDNA fraction | | The proportion of cell-free DNA derived from tumor cells compared to cell-free DNA derived from "normal" cells (mainly of hematopoietic origin) present in a liquid biopsy sample in reference to a specific marker (or set of markers) |
| ctDNA methylation fraction | | A methylation-based quantification of the circulating tumor allele fraction and estimate of ctDNA abundance |
| Fold change | | The difference of ctDNA levels expressed as a multiple or percentage between two values. Because of biological factors, method precision and analysis of values near the detection limit, this parameter should be used cautiously |
| Lead time | | The difference in time between the first positive ctDNA result and subsequent clinical or radiologic evidence of disease recurrence or progression |

(Continues)

**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) |
| Mean tumor molecules per mL (MTM/mL) | | The mean of tumor molecules per milliliter of plasma calculated from the mean ctDNA VAF multiplied by the number of cfDNA molecules (as mass of cfDNA in ng divided by 0.0033 ng/haploid copy) and divided by the volume of plasma in mL |
| Molecular persistence | | The observation of a steady-state presence or fluctuating low levels of ctDNA above and below the limit of detection in serial timepoints during/after cancer treatment, such as surgery, systemic therapy, or locoregional treatment (i.e., radiation therapy) |
| Molecular progression | | The increase of a tumor-derived circulating biomarker in response to cancer treatment. It is determined through serial assessments of circulating analyte levels during the course of treatment or follow-up. Whereas molecular recurrence defines situations of a circulating analyte such as ctDNA becoming detectable after an undetected status, molecular progression refers to the analyte increasing in quantity following a previously detected status |
| Molecular recurrence | | The detection of a tumor-derived circulating analyte, such as ctDNA, after an undetected ctDNA status. Molecular recurrence may be observed prior to radiographic imaging or other clinical recurrence signals |
| Molecular residual disease (MRD) | Minimal residual disease, measurable residual disease | The subclinical presence of a cancer-associated biomarker indicating a high risk of recurrence which cannot be detected by standard imaging techniques |
| Molecular response | Molecular remission | The reduction of a tumor-derived circulating biomarker in response to cancer treatment. It is determined through serial assessments of circulating analyte levels during the course of treatment. Molecular response can encompass a complete reduction (from detected to undetected analyte levels, i.e., clearance) or partial reduction according to pre-specified criteria |
| Molecular residual disease (MRD) assay | | A method for determining the presence of cancer-associated biomarkers from liquid biopsies that are associated with a remnant or recurrence of residual disease following curative intent |

(Continues)

**TABLE 1** | (Continued)

| BLOODPAC primary term | Alternate terms | Definition |
|---|---|---|
| Molecular Surveillance Monitoring | | Testing to detect the presence or recurrence of cancer as early as possible after completion of curative intent therapy. Surveillance may also refer to longitudinal monitoring for return of disease after a patient with metastatic disease has achieved clinical no evidence of disease (NED) status and is no longer receiving active treatment |
| Multi-omic marker panel | Multi-modal marker panel | The analysis of more than one group of biomarkers identified within a classification of common elements such as proteins, methylation, DNA or RNA variants within a liquid biopsy sample. For instance, an MRD assay which detects both somatic mutations and DNA methylation or somatic mutations and proteins would qualify as multi-omic |
| Parts per million (ppm) | | Expression of VAF as counts of biomarker sequencing reads divided by background reads multiplied by a million |
| Qualitative assay | | A type of assay that reports only two categorical responses for the presence of a cancer-derived biomarker, e.g., "ctDNA positive/negative" or "ctDNA detected/not detected" |
| Quantitative assay | | An assay that measures and reports a value for the target biomarker proportional to the number of mutant molecules, concentration (e.g., MTM/mL or mean tumor molecules per volume of plasma), or VAF |
| Semi-quantitative assay | | An assay for which absolute or relative levels of a residual disease biomarker are binned into distinct categories. Semi-quantitative categories may be useful in comparing patients for which relative biomarker levels vary within the assay method or clinical context |
| Single-omic assay | | An assay format that is based on a single analyte (e.g. DNA mutations, RNA, or protein). For example, a ctDNA assay which detects only somatic mutations would be considered single-omic |
| Surveillance samples | | Liquid biopsies collected at predefined intervals after curative intent treatment. These samples are used to infer the molecular absence, persistence, remission or recurrence of cancer over time |
| Tumor-informed ctDNA assay | Bespoke assay | An assay format that defines a set of specific variants to test in cfDNA based on the sequence analysis of a patient's tumor tissue |
| Tumor-agnostic ctDNA assay | Tumor naive, tumor-independent, tissue-free | An assay format that relies on directly testing a blood sample for the presence or absence of a pre-specified set or panel of cancer-associated biomarkers based on prior knowledge of the tumor or population-level data applicable to the tumor type, without the need for characterizing the tumor tissue |

(Continues)

**TABLE 1** | (Continued)

| BLOODPAC primary term | Alternate terms | Definition |
|---|---|---|
| Variant allele frequency (VAF) | | The ratio of the number of times a particular variant allele is observed in a sample to the total number of alleles observed at that locus in the same sample. VAF can be averaged across multiple variants for a sample level and is most commonly expressed as a fraction, a percent, or as parts per million (PPM) |

cancer types and use cases. Understanding how multiple factors, such as tumor shed, can affect the detection of ctDNA is important. Low shedding of ctDNA due to tumor origin, aggressiveness, or response to treatment may lead to a negative ctDNA result, even if a tumor is present.

## 3 | Approaches to ctDNA Assay Development for MRD Detection

Current methods for ctDNA detection show promise in identifying cancer recurrence earlier than conventional clinical or radiological approaches. The terms in this MRD assay section include tumor-informed, tumor-agnostic, single-omic, and multi-omic methods. Tumor-informed ctDNA tests leverage sequencing of DNA derived from the patient's tumor tissue to define specific targets for analysis [9, 14]. These targets are sourced from either creation of a personalized ctDNA assay based on the tissue profile or bioinformatically selecting specific variants detected on a predefined panel. This type of MRD test is specific to each patient, as the patient's tumor informs the alterations being measured by the test. Tumor-agnostic tests, also referred to as tumor-naive, tissue-naive, or tissue-free tests, rely on a fixed panel [9, 14]. These tests may utilize prior knowledge of the tumor alterations or methylation patterns, population-level data applicable to the tumor type, or, in some cases, data from pretreatment plasma sequencing. This approach mitigates the need for access to or analysis of the tumor tissue from the patient. Current approaches to tumor-informed and tumor-agnostic panels are single-omic methods focused on the detection of variation in DNA [13]. These techniques are expanding into methylation, fragment length distribution, and protein analysis for multi-omic approaches [17–19].

## 4 | Reporting Terms in MRD Testing

Key challenges for liquid biopsy for ctDNA are the biological variation of ctDNA and cfDNA levels and the high degree of sensitivity required for MRD detection. Terms in this section distinguish between types of liquid biopsy assays and common terminology to describe ctDNA detection. Qualitative assays report binary outcomes for ctDNA as "positive/negative" or "detected/not detected." Quantitative assays use various units of measurement including mean tumor molecules per mL (MTM/mL), variant allele frequency (VAF), mutant allele frequency (MAF), tumor methylation fraction (TMeF), tumor fraction or, similar to qPCR, in mutant copies per mL. Given the low VAFs associated with MRD, an alternative approach is to express the tumor allele fraction in parts per million (ppm). An important consideration in the reporting of results is that negative, or not detected, outcomes are relative to the analyte. A negative test result does not definitively indicate the absence of cancer.

## 5 | Sample Acquisition Timepoints for MRD

This section includes terms related to the role of unified nomenclature for acquisition and analysis of liquid biopsy samples and implications of ctDNA levels during treatment. Specificity in describing the naming of sample acquisition timepoints relative to the patient journey will be critical to allow for data aggregation in this emerging field. This shift will allow for continued generation of stronger clinical evidence, which we hope will ultimately lead to the use of ctDNA as an early endpoint in clinical trials and accelerated development of cancer treatments. Using specific terms overcomes limitations inherent in the use of relative time points such as "baseline" or "landmark". While a baseline sample typically refers to a chronologically obtained "first" ctDNA result, depending on the use case being evaluated, a baseline sample could be obtained anywhere along the treatment or monitoring continuum. In addition, depending on limitations of sample collection protocol, certain samples may be inaccessible, making it difficult to compare studies corresponding to a presurgical, pretreatment timepoint. There are similar difficulties associating landmarks with a timepoint that is relative to milestones along a cancer patient's journey, instead of a landmark analysis, which has a specific statistical connotation. A landmark timepoint may be relative to surgery or a specific line of treatment, which must be further defined. However, landmark analysis is an important concept when used statistically to account for the fact that patients must have lived for a certain period to be included in the survival analysis. Because the initiation of testing will vary between studies and patients, it is important to overtly define the timing of the first blood draw (e.g., at diagnosis before initiation of any therapy, presurgical in the absence of neoadjuvant therapy, post-curative intent therapy, etc). Therefore, BLOODPAC recommends that sample acquisition timepoints represent combinations of phase, surgery, and therapeutic intervention, such as pretreatment, presurgical or postsurgical, preadjuvant therapy, as shown in Figure 1.

Sampling over time provides an informative profile of disease. Changes over time can be described in terms of ctDNA dynamics, where magnitude, direction, and rate of change can be important indicators of disease progression [20]. ctDNA clearance is a term increasingly used to describe a change from detectable to not detectable levels of ctDNA. Fold change may be used to

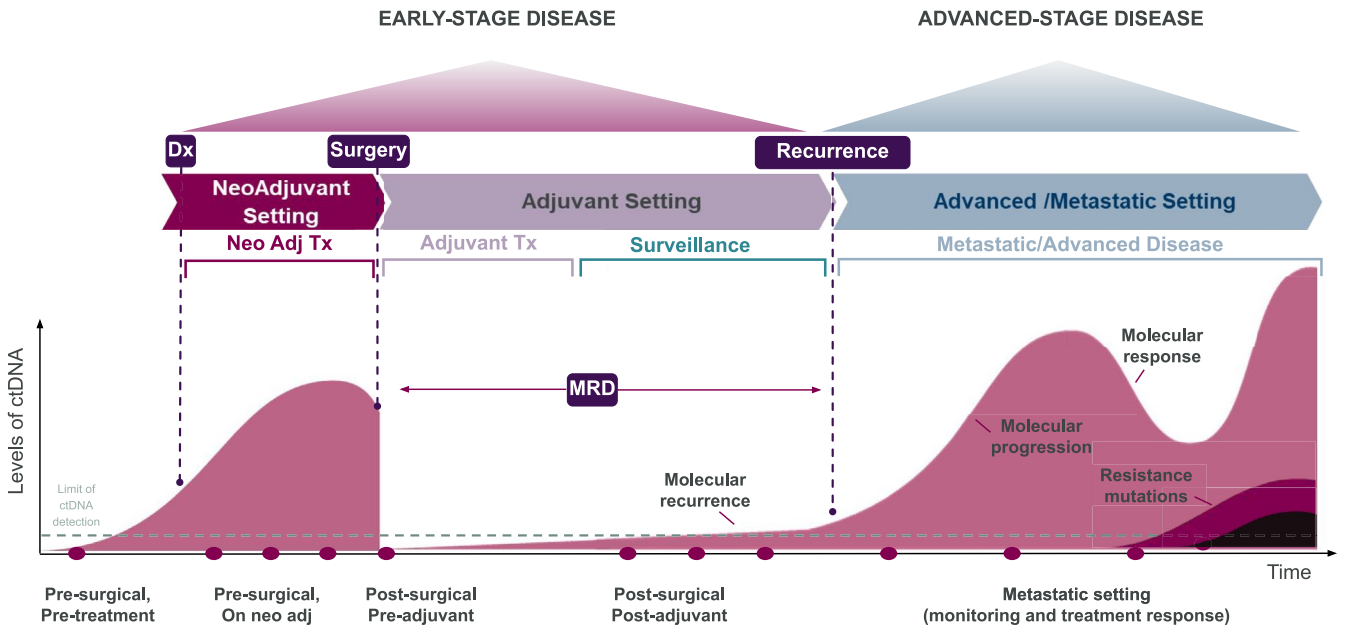


**FIGURE 1** | Applications of liquid biopsy for ctDNA analysis applied along a continuum of patient status, treatment stage, and response. Response curves of levels of ctDNA, y-axis, are presented at different stages of disease and treatment over time with regards to acquisition timepoints. Pretreatment in the neoadjuvant setting guides effective presurgical therapies; postsurgical ctDNA status is used for MRD surveillance; and molecular assessment in advanced-stage settings determines treatment efficacy or response.

compare quantitative results from two timepoints; however, the magnitude of this change may be exaggerated due to biological variability and assay precision at low input levels. Sampling over time may reveal molecular recurrence of disease; however, trends must take into account assay reproducibility as well as tumor and host biological changes over time, requiring clinical correlation. On the other hand, molecular persistence describes a steady-state presence of ctDNA that may have a low but relatively stable level of ctDNA across serial timepoints. Surveillance samples, corresponding to blood collections at predefined intervals after curative intent treatment, can be used to assess molecular absence, persistence, remission, or recurrence of cancer over time. These samples can be further specified by treatment status and relationship to curative intent to improve meta-analysis between studies.

## 6 | Outlook for Clinical Study Use Cases for ctDNA and MRD Detection

Agreement and use of common terminology in MRD provide a foundation for expanding applications of MRD in clinical studies. MRD assays and reporting terminology can reinforce the suitability of a particular method for different applications and comparisons of qualitative or quantitative metrics. A shift from the use of baseline or landmark as relative time points to more specific descriptors can help standardize trial design and facilitate comparisons between studies. We briefly highlight aspects of current and potential applications of liquid biopsy MRD in different clinical contexts while first acknowledging the ethical considerations and equity concerns associated with implementing liquid biopsy technologies in cancer care. Although these issues fall outside the scope of this work, they have been extensively addressed by others. In a recent publication, De Carli et al. [21] provided a framework for ethical considerations at the patient-oncologist, clinical practice, and societal levels when utilizing ctDNA to detect MRD in patients. Febbo et al. [10] recently outlined recommendations for equitable and widespread implementation of liquid biopsy as part of BLOODPAC's efforts to enhance patient access. The liquid biopsy MRD use cases below are not intended as a comprehensive review but as examples of current and potential impacts on the field of MRD for solid tumors.

A growing utility of solid tumor MRD is patient monitoring and therapy adaptation. Liquid biopsy for molecular surveillance can help indicate the return of disease after a patient with metastatic disease had previously both clinical no evidence of disease (NED) status and molecular remission. The detection of ctDNA after curative intent therapy helps to identify disease recurrence or risk of recurrence ahead of current methods [22]. The presence or increasing quantities of MRD could result in a shift in monitoring or a change in therapy decision. Conversely, the absence of ctDNA could be used to reduce surveillance or influence consideration of a "drug holiday." Notably, the ctDNA threshold for any prognostic claim should be supported by clinical endpoints and clinically significant outcome data in the intended disease setting [23].

The detection of levels of ctDNA has the potential to improve clinical study designs and measures through patient enrichment, selection, and/or stratification [11]. Patient enrichment refers to obtaining adequate numbers of patients at a specified treatment decision point to satisfy clinical trial designs. The presence of ctDNA identifies patients who are more likely to benefit from a given therapy. In a de-escalation trial design, lack of ctDNA detection may help select for patients most likely not needing therapy. Using ctDNA for patient selection trials can trigger changes in surveillance strategy, therapy, or eligibility for a novel agent/regimen in a clinical trial. For example, patients positive for

ctDNA and a known therapeutic marker could be selected for targeted therapies [24]. Finally, randomization within clinical trial arms can be facilitated by adjusting for ctDNA results in statistical analyses. Recent examples support the importance of accounting for ctDNA status as an important clinical co-factor of tumor status or recurrence [25]. In combination, there are multiple options for effective incorporation of ctDNA status within trial designs as current and future applications of liquid biopsy.

A primary goal of the BLOODPAC MRD Working Group is to support the use of liquid biopsy as an early endpoint indicator in clinical trials. Liquid biopsy MRD offers clinical trial alternatives that can shape multiple designs in patient cohorts, response monitoring, and ultimately, as a surrogate to support drug approval in the early-stage cancer setting. Although not currently clinically validated for use as an early endpoint, application of liquid biopsy could help bring new interventions and therapeutics more quickly to those in need. This lexicon is intended as a stepping stone in that process with intent to support harmonization of terminology, meta-analysis between different trials, and regulatory pathways for approval.

The members of the BLOODPAC consortium endorse this lexicon as a tool for the community in support of access to liquid biopsy for MRD and improved health outcomes for patients with cancer. It is the intent of this lexicon to encourage data sharing and a unified messaging to patients and the public for applications of liquid biopsy. We intend the lexicon to help avoid misuse or misunderstandings of ctDNA technology. Furthermore, the FDA and other regulatory agencies will benefit from this resource as they evaluate submissions and conduct approvals within a common framework.


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### Conflicts of Interest

Andrew G. Hadd is an employee and owner of Natera Stock; Angela Silvestro is an employee and owner of stock at GSK; Jonathan Baden is an employee of BMS and holds equity in BMS and J&J; Christina Bormann Chung is an employee of GRAIL and owner of stock in GRAIL, Guardant Health & Roche; Ben Brown is an employee and owner of stock options at Adela Bio; Fernando Cruz-Guilloty is an employee and owner of Johnson and Johnson Stock; Gregory Jones is an employee and owner of stock at Neogenomics; Cheng-Ho Jimmy Lin is an employee of Freenome and owner of stock in Natera and Freenome; Daniel Norton is an employee and owner of stock options at Personalis; Melanie R. Palomares holds equity and is an employee of Exact Sciences; Carol Pena is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co. Inc., Rahway, NJ, USA, and holds equity at Merck & Co. Inc., Rahway, NJ, USA; Thereasa Rich is an employee and stockholder at Guardant Health; Angel Rodriguez is an employee and owner of Natera Stock; Diana Merino Vega is an employee and owner of stock options at AstraZeneca. All other authors declare no competing interests for this work.

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