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Recommended Clinical Context and Patient Context Data Elements for Liquid Biopsy Data Submitted to Data Repositories and Data Commons

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ABSTRACT

In 2020, BLOODPAC recommended 11 pre-analytical minimal technical data elements for collection and submission of liquid biopsy data to public databases. This article expands on that work by recommending 22 clinical context and 10 patient context data elements. These elements, essential for liquid biopsy data submitted to repositories like the BLOODPAC Data Commons, cover tumor characteristics, disease progression, and patient demographics, supporting biomarker validation, research, and clinical trials.

Robert L. Grossman and Jake Vinson are Co-First Authors.

Disclaimer: The work described here was done through the BLOODPAC Consortium, which is a not-for-profit consortium consisting of members from industry, academia, not-for-profits, and US Government agencies, including companies that sell liquid biopsy assays, companies that use liquid biopsy assays as companion diagnostics, organizations that do research related to liquid biopsies, organizations that conduct clinical trials involving liquid biopsies, and agencies that develop policies and procedures related to liquid biopsies. In addition, some of the authors are employed by companies in the liquid biopsy field, have stock in companies in the liquid biopsy field, or consult with companies in the liquid biopsy field. 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 section.

1 | Background

BLOODPAC is a consortium of over 60 organizations whose common mission is to accelerate the development, validation, and accessibility of liquid biopsy assays to improve the outcomes of patients with cancer. Through a consortium consensus process, BLOODPAC recommended 11 preanalytical attributes [1] (Table 1) that should be collected for liquid assay studies in general and, in particular, for liquid assay studies that contribute data to the BLOODPAC Data Commons [2] or to other data platforms or repositories that share research data supporting liquid biopsy research. In this article, we extend this work and recommend 22 clinical context data elements and 10 patient context data elements (Figure 1).

Standardized data collection is essential for ensuring consistency, comparability, and interoperability across studies in the liquid biopsy field. By delineating key variables, the BLOODPAC MTDE effort facilitates robust data integration, enabling more meaningful cross-study analyses and accelerating advancements in liquid biopsy research.

The recommended clinical and patient context data elements are intended for applications such as liquid biopsy biomarker validation and research studies, including clinical trials, but not for routine clinical care. To optimize the utility of liquid biopsy testing, assays and instruments must be integrated into the clinical parameters that define the current standard of care. As liquid biopsy continues to evolve as an adjunct or potential replacement for imaging, it is crucial to align liquid biopsy testing data with the clinical context variables that physicians use to evaluate patient response and disease prognosis.

Patient testing involving the detection of circulating tumor DNA (ctDNA), as well as other analytes including RNA and proteins has been examined using numerous assays and instrument platforms for more than a decade. Liquid biopsy testing—if related to key clinical variables—can be properly positioned to address the major questions of modern clinical oncology. Important questions to this end include: Did the patient's tumor completely resolve with intervention (surgery, radiation, therapeutic)? Did the disease progress? If the cancer resists treatment, how is it now different? Where is the patient in the journey and which next course of interventions will have the best chances to extend life while minimizing suffering, debilitating side effects, and co-morbidities?

2 | Clinical Context Data Elements for Liquid Biopsies

In this section, we provide an overview of the 22 required or recommended clinical context data elements (Table 1).

To optimize the utility of liquid biopsy testing, assays and instruments must be associated with the clinical parameters that define the current standard of care. New standards of care involving liquid biopsy testing results must refer to the clinical variables from which physicians evaluate patient response and disease prognosis.

Currently, many of the answers to the aforementioned challenges in molecular oncology are provided by radiology/imaging using Response Evaluation Criteria in Solid Tumors (RECIST) criteria [3]: (1) complete response, (2) partial response, (3) stable disease, (4) progressive disease, (5) inevaluable for response due to: (a) early death due to malignant disease, (b) early death due to toxicity, (c) early death due to another cause, (d) unknown, not accessible, or insufficient data. To position liquid biopsy testing and consider it as an adjunct or replacement for imaging, BLOODPAC suggests embedding liquid biopsy testing data to correlate results with 22 patient clinical context variables. The 22 variables are either required or recommended to be included with data submitted to BLOODPAC data commons to assess the advantages/limitations of certain tests and technologies, and how certain biomarkers relate to patient trial stratification, disease burden, residual disease, surveillance, therapy response, resistance, progression, and overall survival.

The first 8 clinical context data elements include the tumor type, stage, grade, when the cancer was first diagnosed, and whether clinicopathological sampling and imaging show evidence of metastatic disease. These 8 data elements provide the basic contextual framework with which to map a liquid biopsy test result onto the patient's disease and to assess the accuracy of the test result to map onto the disease state, as determined by standard of care tumor tissue biopsy and imaging.

An additional 3 data elements are included to determine whether the patient's primary tumor is still present (intact) at the time of blood testing, whether imaging was performed at this time, and whether tumor size and volume are ascertained, and whether there is indication of progressive disease using standard of care assessment.

There are a number of data elements in Table 1 that link a liquid biopsy test result with the timing of medicinal treatment and surgical procedures. These include the treatment type, name, line of treatment, and duration, as well as dates since last treatment. With respect to surgical interventions, there are 3 data elements that focus on type of surgery, date of surgery, and notably, whether there was a complete resection with clean margins. There are also multiple data elements that are concerned with determining the identity of actionable biomarkers examined in the tumor that was surgically removed, any visual or other indicators other than liquid biopsy results for suspicion of residual disease after surgery, and the timing of liquid biopsy testing results with respect to other indicators of residual disease, progressive disease, and evidence of metastases.

The integration of liquid biopsy testing in clinical studies and trials has provided key information about the options and efficacy of surgery and medicinal treatments, has advanced the characterization of optimal and durable responders to novel treatments, and has provided early warnings on resistance to treatment. For the biopharma industry, liquid biopsy testing is accelerating patient stratification to find the patients that might benefit the most from novel therapies, regardless of whether the patient is in the early stage of malignancy, shows evidence of minimal residual disease postsurgery, is resisting treatment, is in remission, or has entered a phase of rapid tumor growth and metastasis.

TABLE 1 | List and description of the pre-analytical, clinical context, and patient context data elements.

#	Data element	BLOODPAC term	Type	Description	Required *Note that all elements that are not required are recommended*
Pre-analytical data elements					
1	Blood collection tube type	Blood_tube_type	Controlled vocabulary from: • EDTA • CellSave • Streck • Acid citrate dextrose (ACD) • Not applicable	The kind of tube used to collect the sample(s) taken from a biological entity for testing, diagnostic, propagation, treatment, or research purposes	X
2	Sample composition	Composition	Controlled vocabulary from: • Clinical • Derived or contrived cell line • Buccal cells • Buffy coat • Bone marrow components • Bone marrow components, NOS • Control analyte • Circulating tumor cell (CTC)	Sample type describing the cellular composition of the sample, as specified from a controlled vocabulary, containing clinical, contrived, and other terms	X
3	Shipping temperature	Shipping_ temperature	Float	The temperature, in centigrade, at which the biospecimen was kept while it was being transported from the procurement site to its processing destination	X
4	Blood fractionalization method	Blood_ fractionation_ method	String	The name or description of the method used to obtain the blood fraction sample. (e.g., Ficoll Method, Novartis Protocol #001, 2000 g centrifuge at 4°C with gentle deceleration). Alternatively, if you have provided a detailed protocol, enter its file_name here	X
5	Time to fractionation	Hours_to_ fractionation_ upper, hours_to_ fractionation_ lower	• Float • Unknown • Not applicable	The upper/lower limit on the amount of time, in hours, between the sample collection and the fractionation into its components. If the exact time is known, make this value equal to that of the lower limit. If the time is completely unknown, enter Unknown. If no fractionation was performed on this sample, enter not applicable	X
6	Analyte isolation method	Analyte_ isolation_ method	String	The name or general description of the method used to isolate the analyte. Alternatively, if you have provided a protocol, put the file_name here	X

(Continues)

TABLE 1 | (Continued)

#	Data element	BLOODPAC term	Type	Description	Required *Note that all elements that are not required are recommended*
7	Time to freezer	Hours_to_freezer_upper, hours_to_freezer_lower	• Float • Unknown • Not applicable	The upper/lower limit on the amount of time, in hours, that it took between the sample being fractionated and the aliquot being frozen or otherwise preserved. If the exact time is known, make this value equal to that of the lower limit. If the time is completely unknown, enter Unknown. If no fractionation was performed on this sample, enter not applicable	X
8	Storage temperature	Storage_temperature	Float	The temperature, in centigrade, at which the aliquot was preserved and/or stored	X
9	Concentration: cellular concentration or molecular concentration	Molecular_concentration or cellular_concentration	Float	If the analyte is a molecule (e.g., DNA or RNA), report the observed concentration in nanograms per microliter (for molecular concentration). If the measurement is a cell count, then this is reported as cells per microliter	X
10	Assay method	Assay_method	Controlled vocabulary from: • Targeted sequencing • Copy number analysis	General name or description of the method used to characterize the analyte	X
11	Time to assay	Days_to_assay	Integer	The amount of time, in days, between the date used for index and the assay used to address this analyte	X
Clinical context data elements					
Administrative					
i	Subject ID	SUBJECTID	String	A unique identifier for the study participant. This identifier is required, but format is not restricted in any way	X
ii.	Index event	INDEX	String	Describes the Index Event, which is used as a temporal anchor for all temporal data within the dataset	X
iii.	Duration from sample collection	SAMPCOLL	Integer	The duration (in days) from the sample collection date to the date of the index event *This field is only required if the Index Event is NOT the Sample Collection. If a different event is represented as the index event, the duration from that date to the sample* collection date is required*	Conditional*
Diagnostic details					
1	Cancer type/diagnosis	CANTYPE	String	Include specific histopathology information	X

(Continues)

TABLE 1 | (Continued)

#	Data element	BLOODPAC term	Type	Description	Required *Note that all elements that are not required are recommended*
2	Cancer stage/ diagnosis	STAGE	String	Include specific TNM staging vocabulary	X
3	Cancer staging system (if applicable)	STAGESYS	String	Identification of the staging system used to measure the cancers' status and progression	X
4	Cancer grade	GRADE	• Grade 0 • Grade 1 • Grade 2 • Grade 3 • Grade 4	Associated cancer grade (e.g., 0, 1, 2, 3, 4)	X
5	Cancer grading system (if applicable)	GRADESYS	String	Identification of the staging system used to determine cancer grades	X
6	Duration from initial diagnosis	DXDUR	Integer	The duration (in days) from the initial diagnosis to the date of the index event	X
7	Is the primary tumor clinically detectable by standard-of-care at time of sample collection? Y/N	TUDETSOC	Boolean	Indicates whether the tumor is detectable by the standard of care (i.e., sample collection, imaging, exam), at the time of sample collection	X
Disease status and response					
8	Metastatic disease at time of study enrollment? Y/N	METDXENR	Boolean	Indication of whether the disease is metastatic at the moment the participant is enrolled	X
9	Site of metastasis if applicable	METLOC	String	The location of the metastatic disease, when applicable	
10	Duration from metastatic diagnosis	METDUR	Integer	The duration (in days) from the metastatic diagnosis to the date of the index event	
11	Is the disease progressing?	PROGDX	Boolean	Indication of progressive disease, qualified according to RECIST or other standard-of-care criteria	
12	Duration between the sample collection and confirmation of disease progression	PROGDUR	Integer	The duration (in days) from the confirmation of disease progression to the date of the index event	
13	Molecular alterations in tumor tissue results Y/N	MOLALT	Boolean	Indication of a molecular alteration(s) within the tumor tissue results	
14	Is there evidence of molecular residual disease? Y/N	MOLRESDX	Boolean	Indicates evidence of residual disease based on molecular findings	

(Continues)

TABLE 1 | (Continued)

#	Data element	BLOODPAC term	Type	Description	Required *Note that all elements that are not required are recommended*
Treatment					
15	Treatment type at time of sample collection	RXTYPE	• Adjuvant • Neoadjuvant • No treatment	Describes the type of treatment the participant was undergoing at the time of the sample collection	
16	Treatment drug name, other non-drug treatment (e.g., radiation)	RXNAME	String	The treatment or drug name	
17	Duration from treatment/last treatment date	RXDUR	Integer	The duration (in days) from the last treatment date to the date of the index event	
18	Line of treatment for metastatic disease (if applicable)	METINTNUM	Integer	The total number of unique systemic medical interventions, including the current intervention, in treating metastatic disease	
19	Was there a surgery or invasive procedure?	SURGPROC	Boolean	Indicates whether surgery or an invasive procedure was performed	
20	Was there a complete surgical resection with clear margins?	SURGCLMRG	Boolean	Indicates a surgical resection was completed resulting in clear margins	
21	Is disease progression subsequent to treatment? (If applicable) Y/N	PROGDXRX	Boolean	Indicates whether disease progression was observed or diagnosed after treatment	
22	Duration from last surgery	SURGDUR	String	The duration (in days) from the last surgery to the date of the index event	
Patient context data elements					
Demographics					
1	Year of birth	BRTHYR	Integer	The participant's year of birth (with an upper limit of 89 years ago)	X
2	Race	RACE	Array • American Indian or Alaska native • Asian • Black or African American • Native Hawaiian or other pacific islander • White • Other	The self-reported race of the participant	X
3	Ethnicity	ETHNICITY	String	The self-reported ethnicity of the participant	X

(Continues)

TABLE 1 | (Continued)

#	Data element	BLOODPAC term	Type	Description	Required *Note that all elements that are not required are recommended*
4	Sex assigned at birth	SEX	• Female • Male • Intersex	The sex or gender of the participant assigned at birth	X
5	Self-identified gender	GENDER	• Female • Female-to-Male Transsexual • Intersex • Male • Male-to-female transsexual • Other	The sex or gender assignment preferred by the participant	
Biospecimen collection					
6	Fasting status	FASTSTAT	Integer	The number of hours from the last time the participant had a meal	
Medical history					
7	Patient BMI	BMI	Number	The participant's body mass index (BMI)	X
8	Tobacco smoking status	SMOKSTAT	• Current reformed smoker, duration not specified • Current reformed smoker for ≤15 years. • Current reformed smoker for >15 years. • Current smoker • Lifelong non-smoker • Smoker at diagnosis • Smoking history not documented	Captures the participants's tobacco use	X
9	Tobacco smoker pack years	SMOKPKYR	Integer	Quantifies the participant's smoking status using pack years	
10	Medical history term*	MEDHX	String	Comorbidities for which the participant has been clinically diagnosed	

Note: The pre-analytical data elements listed correspond to those initially published in 2020 [1]. To these minimum technical data elements, the BLOODPAC RDE Working Group has added clinical and patient data elements, as shown in this table. These elements are designated as either required or recommended. The numbering does not indicate prioritization but rather reflects the sequence in which these elements may be collected during the sample or information collection process, as illustrated in Figure 1.

*If the comorbidity data provided for a single study participant includes more than one medical condition or if additional data elements related to the comorbidity are provided (e.g., duration of the medical condition), an additional table will be required to accurately capture this information. For more details, see the Multiple Data Instances examples found in the supplemental documentation.

The promise of liquid biopsy testing has entered a very exciting second decade; however, a key challenge is to relate a liquid biopsy test result, or several of them in succession, in clinical contexts to best illustrate the most robust indicator of how well therapies work, whether the disease has been eliminated, whether a response is durable, or whether the disease is progressing.

The 22 clinical variables below represent a concise set of criteria to evaluate the type, timing, and extent of a patient's disease to best assess where the patient is in their journey, whether surgical removal of the tumor is effective, and which medicines are the best to use at what dose and for how long to optimize survival and progression-free survival.

3 | Patient Context Data Elements for Liquid Biopsies

In this section, we provide an overview of the 10 required or recommended patient context data elements. For the full list, see Table 1.

In addition to the clinical context data elements discussed above, and as important for an accurate assessment and interpretation of liquid biopsy assays' aim to improve the outcomes of patients with cancer, BLOODPAC identified demographic traits of patients that are to be submitted concurrently to the data commons.

This list of patient context data elements includes information that is readily available, well defined, and provides insights into disease detection and health outcomes. As such, results from the reported data may be influenced by these variables. These elements include age, ethnicity, race, BMI, fasting status, smoking habits, sex at birth, gender-affirming hormone therapy, and comorbidities and can directly influence liquid biopsy detection and analyte concentrations [4–9].

Six of these data elements are required for submission to the BLOODPAC data commons: year of birth (capped at 89 years old), ethnicity, race, BMI, tobacco smoker (yes/no), and sex at birth. Several of these data elements may not be collected or are unknown for a particular data set, and these are listed as recommended rather than required. These are fasting status, tobacco amount, self-identified gender, and clinically validated comorbidities. Elements were excluded if they were believed to place too great a burden for data collection or if there was not an unambiguous method of reporting the data.

Note that patient context data elements, such as age, ethnicity, race, sex at birth, and self-identified gender, are associated with health disparities and can impact patient outcomes [10].

4 | BLOODPAC'S Process for Defining Recommended Data Elements

The not-for-profit BLOODPAC consortium is organized into working groups, and the Recommended Data Element (RDE) Working Group meets virtually every other week and in person two times a year. The data elements were established and classified as recommended or required using an expert consensus process, consistent with the prior establishment of pre-analytical and analytical data element recommendations [1].

The process of defining standardized data elements for liquid biopsy studies has evolved through iterative engagement with the FDA. Initial discussions with the FDA in 2017 identified approximately 150 candidate data elements, which were systematically refined and categorized, culminating in the recommendation of 11 pre-analytical minimal technical data elements (MTDEs) in 2020 to support standardized data collection and submission.

Building on this foundation, the present study expands these efforts by defining 22 clinical context and 10 patient context data elements, two additional categories that emerged from continued discussions with the FDA. This refinement process, initiated in 2019, involved a multi-year review with input from clinicians, diagnostic manufacturers, researchers, and pharmacists who took into account the impact of these variables on assay performance and clinical outcomes. To ensure regulatory

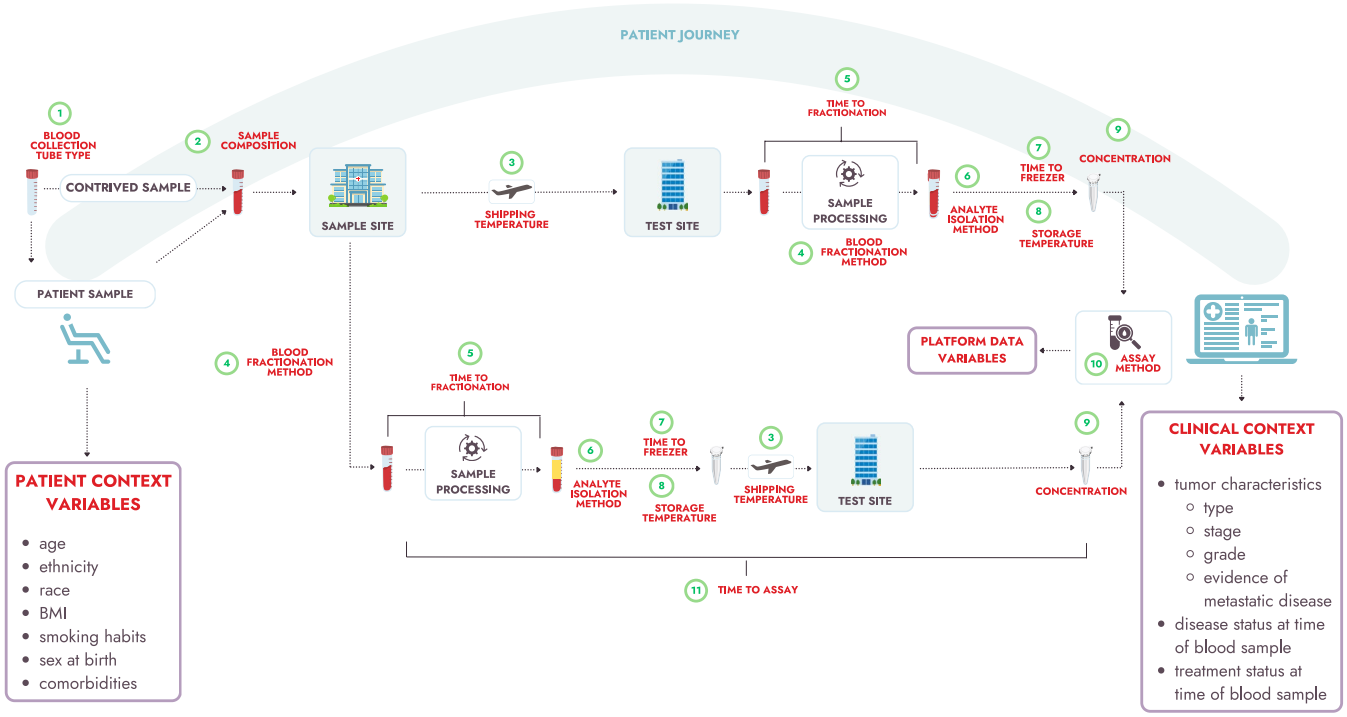

FIGURE 1 | Graphical workflow view of the pre-analytical [1], Patient and Clinical Context recommended data elements, with elements grouped together to simplify the figure.

alignment, BLOODPAC engaged in two FDA pre-submissions (2021 and 2023), incorporating feedback on the inclusion, classification, and integration of these data elements into liquid biopsy research and biomarker validation frameworks and data collection and system integration.

Additionally, to align with standardized terminology, the RDE Working Group mapped each clinical data element to CDISC's Clinical Data Acquisition Standards Harmonization (CDASH) framework. Given the complexity of CDASH, an intermediary CDASH "Lite" term was introduced to consolidate multiple CDASH terms into a single, more interpretable label. The Supporting Information (Standard Terminology Table) provides the full mapping, demonstrating that compliance with established standards can be achieved by linking program-specific terminology to existing frameworks rather than creating entirely new terms.

5 | Conclusion

Prior work from the BLOODPAC consortium identified 11 preanalytical data elements [1]. In the current manuscript, we add 22 clinical context data elements and 10 patient context data elements. These data elements are required or recommended to contribute data to the BLOODPAC Data Commons [2], but we also suggest that these data elements should be collected for liquid assay studies in general. Generation of these preanalytical, clinical context, and patient context data elements brought together diverse practices from diagnostic and pharmaceutical companies, regulatory bodies, academic groups, and other organizations. This represents a key initial step toward harmonization and standardization. As we have done for the preanalytical variables, we will monitor the inclusion and completeness of these clinical and patient context data elements for data sets contributed to the BLOODPAC Data Commons as well as the incorporation of these data elements into future best practice recommendations, standards, or guidelines. These data elements will also be revisited on a regular basis to ensure they keep up with a rapidly changing field. Ultimately, harmonization efforts can support the generation of standardized data sets to facilitate regulatory review, shorten the time to bring clinically useful diagnostics to market, and hopefully improve the care of patients with cancer.

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Conflicts of Interest

John Hu is an employee and stockholder of Exact Sciences, John Lyle is an employee and stockholder of Personalis, Jean-Francois Martini is an employee and stockholder of Pfizer Inc., and Lauren Saunders is an employee and stockholder of Ceres Nanosciences. All other authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.