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International liquid biopsy standardization alliance white paper

Dana Connors [a], Jeff Allen [b], J.D. Alvarez [c], Jennifer Boyle [d], Massimo Cristofanilli [e], Carolyn Hiller [c], Susan Keating [f], Gary Kelloff [g], Lauren Leiman [h], Robert McCormack [i], Diana Merino [b], Emily Morgan [a], Klaus Pantel [j], Christian Rolfo [k,*], Maria Jose Serrano [l], A. Pia Sanzone [d], Thomas Schlange [m], Caroline Sigman [f], Mark Stewart [b]

[a] Foundation for the National Institutes of Health, United States
[b] Friends of Cancer Research, United States
[c] Medical Device Innovation Consortium, United States
[d] National Institute for Biological Standards and Control (NIBSC), UK
[e] Northwestern Medicine, International Society of Liquid Biopsy (ISLB), United States
[f] CCS Associates, Inc., United States
[g] Biomarkers Consortium Cancer Steering Committee, United States
[h] BloodPAC, United States
[i] FNIH ctDNA QCM Project, United States
[j] European Liquid Biopsy Society, Germany
[k] University of Maryland Medical Center, International Society of Liquid Biopsy (ISLB), United States
[l] Centro GENyO, International Society of Liquid Biopsy (ISLB), United States
[m] Cancer-ID, Czech Republic

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ABSTRACT

The promise of precision medicine as a model to customize health care to the individual patient is heavily dependent upon new genetic tools to classify and characterize diseases and their hosts. Liquid biopsies serve as a safe alternative to solid biopsies and are thus a useful and critical component to fully realizing personalized medicine. The International Liquid Biopsy Standardization Alliance (ILSA) comprises organizations and foundations that recognize the importance of working towards the global use of liquid biopsy in oncology practice to support clinical decision making and regulatory considerations and seek to promote it in their communities. This manuscript provides an overview of the independent liquid biopsy- and standardization-based programs engaged with ILSA, their objectives and progress to date, and the tools and resources each is developing to contribute to the field. It also describes the unique areas of effort as well as synergy found within the group.

1. Introduction

The promise of precision medicine as a model to customize health care to the individual patient is heavily dependent upon new genetic tools to classify and characterize diseases and their hosts. To accomplish these goals with traditional tumor sampling, invasive procedures to obtain genetic material would necessarily increase to provide enough material to accurately capture and describe genomic variations and their phenotypes. Liquid biopsies serve as a safe alternative to solid biopsies (Ma et al., 2020) and are thus a useful and critical component to fully realizing personalized medicine (Rolfo et al., 2020; Heitzer et al., 2019; Keller and Pantel, 2019; Pantel et al., 2019). Liquid biopsy may include tumor-derived nucleic acid such as circulating tumor DNA (ctDNA), circulating tumor RNA (ctRNA), circulating tumor microRNA (ctmiRNA), RNA or DNA from exosomes, and circulating tumor cells (CTC) collected from peripheral blood, which can be obtained non-invasively through a simple venipuncture (Anfossi et al., 2018; Kalluri et al., 2020). This material is now being used to identify actionable mutations for targeted therapy and through their less invasive nature can be utilized to monitor therapy response serially and screen for early detection of disease (Keller and Pantel, 2019; Russo et al., 2019).

* Corresponding author at: Thoracic Oncology Department and Early Phase Clinical Trials Section, School of Medicine, Maryland University, 22 South Greene Street, Baltimore, MD, 21201, United States.
E-mail address: christian.rolfo@umm.edu (C. Rolfo).

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Clinical oncology is being transformed with the adoption of next-generation sequencing (NGS-) based diagnostics. This new technology can enable the rapid identification of potentially significant genetic variations across the human genome, and the results are increasingly being used to determine the best course of treatment for oncology patients (MacConaill, 2013). Ensuring that these patients receive accurate results is imperative given that a false negative or false positive result could cause a patient to be diverted from a more beneficial therapeutic option, assigned to the wrong arm of a clinical trial, or unnecessarily subjected to adverse drug effects. However, lack of agreed-upon, well-characterized and community-validated reference samples and data benchmarks creates a potential challenge for the efficient development of these critical tests and for understanding their results (Normanno et al., 2013; Lampignano et al., 2020).

The International Liquid Biopsy Standardization Alliance (ILSA) comprises organizations and foundations that recognize the importance of working towards the global use of liquid biopsy in oncology practice to support clinical decision making and regulatory considerations and seek to promote it in their communities. Multiple efforts have joined together under the auspices of the ILSA group to share the scope of their work, discuss lessons learned, and disseminate the tools and data they have developed as a coordinated effort. The group recognizes that a preponderance of technologies and pursuits in the field of liquid biopsy has the potential to confound the field and obscure important progress. As an alliance, the ILSA partners have found strong value in the exercise of information exchange through in-person meetings and teleconferences, as well as the dissemination of their collective efforts. This manuscript is a further step to inform the scientific community about the formation of the collaborative group and the availability of resources (Fig. 1).

This manuscript provides an overview of the independent liquid biopsy- and standardization-based programs engaged with ILSA, their objectives and progress to date, and the tools and resources each is developing to contribute to the field. It also describes the unique areas of effort as well as synergy found within the group. Collaborative opportunities, tools, and resources the group desires to make available are also shared for interested researchers and clinicians.

2. Overview of liquid biopsy efforts

The **BloodPAC** (Anon, 2020a) mandate is to accelerate the development and validation of liquid biopsy assays to improve the outcomes of patients with cancer. To do this the group developed a collaborative infrastructure that enables sharing of information between stakeholders in the public, industry, academia, and regulatory sectors. There are currently six active BloodPAC Working Groups. The Data Experience Working Group will determine how data are aggregated, reviewed, and processed. The Pre-analytical Variables Working Group identified and created 11 Minimal Technical Data Elements (MTDEs) from the critical variables required for new studies submitted into the Data Commons. The Analytical Variables Working Group focuses on developing analytical protocols, while the Patient Context Variables Working Group identified 5 critical required MTDEs and an additional 11 suggested MTDEs. The Reimbursement Working Group will discuss their developing project plan to address reimbursement for liquid biopsy assays at the annual meeting of American Society of Clinical Oncology (ASCO). The JFDI Working Group, which leads the effort, has increased to 10 members aligned to develop a framework for evidence generation to bring liquid biopsy into routine clinical practice.

The BloodPAC consortium recognizes data sharing and evidence generation as the two fundamental requirements for success and is pursuing them through two dedicated workstreams:

- To create a BloodPAC Data Commons to serve the community at large for all liquid biopsy stakeholders; and to
- Align around a framework for evidence generation to bring liquid biopsy into routine clinical practice.

The University Medical Center Hamburg-Eppendorf established a novel EU consortium called the **European Liquid Biopsy Society (ELBS)** (Anon, 2020b) which aims to become the leading hub for liquid biopsy research in Europe with the key goal to translate liquid biopsy assays into clinical practice for the benefit of patients. 40 European Institutions from academia and private industry attended the kickoff meeting in 2019 in Hamburg, and the number of candidate institutions has increased to 97 within one year, demonstrating the enormous interest in the ELBS consortium, which also welcomes non-EU members. ELBS will replace the public-private partnership CANCER-ID (Anon, 2020c), a five-year Innovative Medicines Initiative (IMI) (Anon, 2020d) consortium, which came to an end in 2019. In the course of its activities, CANCER-ID published best-practice protocols and the results of ring studies based on the implementation of harmonized protocols and standard materials (Kalluri et al., 2020; Kloten et al., 2019). The results are the basis for implementation of liquid biopsy protocols in ongoing clinical studies which are evaluating the predictive value and clinical utility of CTC and ctDNA assays in patients treated with immune

Fig. 1. Member organizations of ILSA perform synergistic functions from pre-analytical variables analysis to clinical utility activities to bring the promise of globally standardized and evaluable precision medicine to clinical practice.

checkpoint inhibitors (Hofman et al., 2019).

ELBS is an institutional network (not individual membership organizations) with the following goals, which build upon and extend the CANCER-ID objectives:

- Foster the introduction of liquid biopsy into clinical trials and practice;
- Support liquid biopsy research (CTCs, ctDNA, cell-free microRNA (cfMiRNA), extracellular vesicles (EVs), platelets, proteins, etc.);
- Provide a partner for regulatory agencies, health care providers and patient advocacy groups;
- Encourage interactions between academia and industry;
- Develop guidelines and provide training in liquid biopsy for medical scientists;
- Disseminate knowledge about liquid biopsy to the medical community through regular symposia, publications, and press releases;
- Increase European visibility as a leading hub for liquid biopsy research;
- Outreach to non-EU networks of liquid biopsy research (in the US, Asia, and Australia).

The main aim of the **International Society of Liquid Biopsy (ISLB)** (Anon, 2020e) is to introduce recommendations to develop reliable and sustainable diagnostics and prognostics tools using liquid biopsies that will benefit patient health management and wellness. Founded in 2017, the ISLB was created considering that: technologies evolve day by day, and the concept of liquid biopsy requires continuous attention and research to provide patient and community benefit; there is a growing worldwide effort under way that combines the knowledge and motivation of clinicians, biotech companies, and the pharmaceutical industry, all considered essential in the development of this field; there is an urgent need to establish criteria and provide guidelines for the design, development, and validation studies necessary before clinical application can be made with confidence; an opportunity exists today to coordinate efforts and strategies between key players through communication and collaboration to establish research priorities and avoid overlap of efforts that simply delay the implementation of these technologies; and there is a fundamental need to support collaboration with all professionals and colleagues around the world to ensure the ability to translate the benefits of liquid biopsy to all communities irrespective of social and economic status, providing them access to both research and clinical application of these new technologies.

Based on these considerations the ISLB was created to provide a forum for the exchange of ideas and to represent the efforts of stakeholders and professionals interested and active in this field. The group maintains and supports regular multisectoral meetings to better understand global advances and existing problems of implementation and to respond to the needs of patients, health systems, and laboratory services. The group also works to assess and advise on existing technologies and their suitability for clinical practice and implementation, improvements that can be made, and the practical benefits that will accrue, and promote and facilitate initial and ongoing training of experts and professionals interested in the development of liquid biopsies. ISLB collaborates with other professional societies, associations, and groups with similar objectives to support researchers, clinicians, and laboratories across the world, including developing countries where economic difficulties may limit early access to these technologies.

To enable the ISLB to act as an ethical conversation point for stakeholders in the emerging liquid biopsy field, the group ensures communications regarding progress are made on a global basis and in a timely manner, and encourage where possible the standardization of procedures when translating research into clinical diagnostic protocols. The ISLB places no limits on those who wish to join and has created membership categories for individuals, institutions, and corporations. Undergraduate and post-graduate medical and biology and genetics students are encouraged to join or participate. The group has created a series of supervisory committees and plans to develop key regional supporting committees over time.

The ISLB encourages conversations about liquid biopsies to help advance patient care by creating and delivering world class workshops, symposia and conferences in Europe, North America, Asia and South America. In the future, it is expected ISLB will create members' only sections of the ISLB website, as well as access and contact points for non-members, such as the public, media, and health care providers, as well as those with a specialist interest in liquid biopsies. The ISLB hopes to stimulate an active and continuous flow of interest, ideas, and information between members, as well as interested non-members, and to act as an important reference site for health care professionals and governments.

The **Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium (BC)** is a public-private biomedical research partnership that endeavors to discover, develop and seek regulatory approval for biomarkers to support new drug development, preventative medicine and medical diagnostics. The organization works to combine the forces of the public and private sectors in working groups and project teams to accelerate the development of biomarker-based technologies, medicines and therapies for prevention, early detection, diagnosis and treatment of disease. The **ctDNA Quality Control Materials Project** (Anon, 2020f) is an approved collaboration of the BC which gathered multiple private sector, government agency, academic, and not-for-profit partners together to characterize Quality Control Materials (QCMs) and demonstrate their comparable performance to ctDNA and their suitability to establish performance characteristics for NGS assays already in use.

An initial liquid biopsy working group of the BC Cancer Steering Committee, which included members from ASCO, the Association for Molecular Pathology, the College of American Pathologists, the National Institute of Standards and Technology, and regulatory representatives among multiple other stakeholders, identified 14 common and clinically relevant, and actionable variants across the four variant classes to establish a workflow. The project team has conducted a phase 1 performance evaluation of reference materials from three commercial manufacturers, which include these variants. The team will soon launch a phase 2 contrived sample functional characterization (commutability) study in coordination with input from the U.S. Food and Drug Administration (FDA) and the other project stakeholders to determine if the QCMs perform similarly to clinical specimens. During phase 3 a clinical pilot will engage multiple external laboratories across four continents to further evaluate the QCMs in their daily runs and alongside clinical samples for additive performance information.

The manufacturers of the reference materials will be provided final data from these assays that may be used in submission for regulatory approval of standardized QCMs that can be used in laboratories across multiple assay types to accurately identify variant allele fractions of the original 14 clinically relevant variants. Together, the project team hopes to define a cost-effective, practical approach for the validation of ctDNA QCMs that includes a demonstration of commutability and which could serve as a "roadmap" for other groups in the future.

Friends of Cancer Research (Friends) (Anon, 2020g) is an advocacy organization that drives collaboration among partners from every healthcare sector to power advances in science, policy, and regulation that speed life-saving treatments to patients. Friends has been instrumental in the creation and implementation of policies ensuring patients receive the best treatments in the fastest and safest way possible. **ctDNA to MONItor Treatment Response (ctMoniTR) Project** (Anon, 2020h) is a pilot project involving several key pharmaceutical stakeholders with the objective to harmonize the use of ctDNA to evaluate or monitor patient response, and to better answer the pressing question: Do changes in ctDNA levels accurately reflect the therapeutic effect of cancer therapies? The hypothesis under which this project operates is that broad changes in ctDNA levels can detect tumor response to cancer therapies, including immune checkpoint inhibitors, targeted therapies and

chemotherapy.

The project has a multi-step approach including Step 1: the study of ctDNA as a monitoring tool in previously collected trial data from a subset of trials (e.g. NSCLC treated with ICI), and Step 2: the study of ctDNA as a monitoring tool in prospectively collected trial data from various types of advanced cancer and therapies (e.g. immune checkpoint inhibitors (ICIs), tyrosine kinase inhibitors, chemotherapy). Step 1 will assess the feasibility of investigating the directionality of change in ctDNA levels from baseline and investigate its association with patient response by looking at a smaller cohort of studies with a specific indication. Results from Step 1 will inform Step 2, which will investigate the ability of ctDNA to detect early therapeutic response in clinical trials for different indications and different treatments that share a uniform plasma and data collection methodology.

The ctMoniTR project will seek to promote a harmonized advancement of the field of liquid biopsies and to facilitate evidence development that will generate the necessary foundation for regulatory evaluation of ctDNA as a monitoring tool and early predictor of treatment response. As such, it will propose several key methodological and knowledge questions and define what type of data will be needed to respond to these relevant questions. Moreover, the project will seek to align plasma collection methodologies, and suggests uniform approaches for reporting relative directional changes in ctDNA using NGS panels.

The Japanese bio-Measurement and Analysis Consortium (JMAC) (Anon, 2020i) is an industrial group established in 2007 to support biotechnology with international standardization activities. The International Organization for Standardization (ISO) activity of JMAC is continuously expanding to cover clinical laboratory (TC 212), food (TC 34), biotechnology (TC 276), and nanotechnology (TC 229). In parallel to the ISO activities, JMAC participates in several research project including miRNA cancer biomarker discovery project and a central nervous system biomarker discovery project pursuing liquid biopsy technologies. JMAC drafted the standards document "Molecular biomarker analysis - general definitions and requirements for microarray detection of specific nucleic acid sequences." Member companies of JMAC benefit from the latest updated information in the biotech industry through these activities and the group is open to new members.

The **Medical Device Innovation Consortium (MDIC)** (Anon, 2020j) is a public-private partnership created in 2012 to advance medical device regulatory science for patient benefit. MDIC brings together representatives of the government, industry, not-for-profit and patient organizations to improve processes for the development, assessment and review of new medical technologies.

MDIC aims to identify and pursue projects that will improve diagnostic testing and product development using novel regulatory science approaches developed through collaboration among MDIC stakeholders. Providing a predictable path for innovation will help patients benefit through quicker access to more cost-effective advanced diagnostic technologies in less time. One focus of this work is the establishment of a public-private partnership to guide the development of reference samples that can be used to develop and validate NGS-based oncologic tests.

Currently, many test developers, including commercial manufacturers and clinical laboratories, are developing their own contrived samples and sample mixes for validation of oncology tests since well-characterized and agreed-upon oncology samples/reference materials do not exist. This makes it difficult to efficiently develop or compare tests and methodologies. Reference samples that can be used to more efficiently develop and assess the various components of an NGS test are needed to ensure confidence in the results being provided by different NGS clinical tests.

The objective of the MDIC's Somatic Reference Samples (SRS) initiative is to guide the development of reference samples that can be used to develop and validate NGS-based oncologic tests, with the focus on solid tumors. These samples are to be properly consented, widely shareable reference samples to be made available to the public and scalably produced in order to enable efficient development and improve the accuracy, reliability and transparency of tissue-based oncology tests. These samples will be quality checked and validated, made available in varying forms (e.g., cells, DNA/RNA, formalin-fixed paraffin-embedded tissue [FFPE]), represent the majority of potential variations and allele fractions of interest (e.g., ploidy, fusions, large/small indels, copy number variations (CNVs), homopolymeric regions), and represent tumor/normal matched pairs. The output of the effort will be shared broadly with the community, with the intent to have any reference samples developed through this effort scaled for commercial distribution.

A cross-functional working group is developing processes for identifying and acquiring appropriately consented tumor/normal matched samples containing variants of interest, consistent production of materials at scale to facilitate public availability in various formats, sequencing data integration and consensus call determination to develop high-confidence truth sets, and long-term maintenance of reference samples and accessibility of data sets. The ultimate goal is to pilot the production of several high priority NGS reference samples for the oncology community. When the project outputs are validated and characterized, they will be made widely available to allow for scale up, production, and broad public accessibility by interested commercial entities.

The **National Institute for Biological Standards and Control (NIBSC, UK)** (Anon, 2020k) is a World Health Organization (WHO) International Laboratory for Biological Standards and is the world's primary producer of WHO International Standards. These highest order reference materials, which are typically prepared as a single homogeneous batch of several thousand ampoules intended to last many years, serve to harmonize the measurement of biological activity in internationally agreed units through traceability to a single common standard; they are not intended for routine use, but rather as calibrators of assays and secondary standards, which in turn may be used as assay run controls. Their use enables comparability between laboratories and methods, towards improved public health via accurate and sensitive measurement in ensuring the quality of biological medicines, diagnostic testing, and therapeutic response in patients worldwide. All NIBSC-produced WHO standards are provided on a non-for-profit basis to facilitate global availability.

NIBSC has endorsement from the WHO Expert Committee on Biological Standardization to generate the WHO 1st International Standards for ctDNA. The intention is to first produce ctDNA standards for the most frequent clinically-associated variants in EGFR, including p.L858R, p.T790M, and exon 19 deletions, with the aim to subsequently address other solid tumor-associated gene variants as their utility in liquid biopsy analyses increases (Rolfo et al., 2018). These standards should ideally capture and allow harmonization of the multiple variables associated with ctDNA measurement, including variant percentage, DNA fragment size(s), ctDNA yield, and gene copy numbers. They should also demonstrate excellent stability since International Standards are typically prepared as a single homogeneous batch of several thousand ampoules intended to last many years.

Commutability, i.e. comparability to real clinical samples, is also a critical component of these standards, since they should perform equally well in laboratory assays and are appropriate for in vitro diagnostic use worldwide. NIBSC is currently assessing the performance of several matrices with various cell-line derived fragmented DNAs to determine the optimal format for the standards, while cross-referencing to patient ctDNA materials. Co-incident with this program, NIBSC is also developing genomic DNA standards for EFGR variants from the same source cell lines; this is intended to facilitate the alignment of both liquid and solid tumor biopsy and aid the transition to a non-invasive diagnostic approach. The establishment of these standards must coincide with standardized protocols for sample collection and preparation, testing, analysis, and reporting, towards a fully harmonized liquid biopsy approach.

3. Synergy and unique areas of development

The ILSA partners described above came together due to a similar objective: to bring about the ubiquitous and meritorious use of liquid biopsy in oncology practice to support clinical decision making and regulatory considerations and to obviate the need for invasive solid tumor biopsies. Given the overlapping interests of the members, at its first meeting participants were surprised to find that the efforts are largely non-duplicative. In fact, the efforts noted here are synergistic and cover the spectrum of need to bring liquid biopsy into routine clinical application.

As outlined above, the BloodPAC effort and Cancer-ID/ELBS Consortium are working from U.S. and European perspectives to develop pre-analytical variables considering laboratory handling and patient contact. Both consortia have published reviews outlining developments in liquid biopsy (Pantel et al., 2019c; Alix-Panabieres, 2020). They have also considered downstream use of the materials to establish naming convention and appropriate standards for collection and data coordination.

The FNIH Biomarkers Consortium ctDNA QCM and MDIC SRS projects dovetail with these pre-analytical development steps to provide examples, roadmaps, and initial efforts at reference material development. These groups have noted that they seek to provide U.S. laboratories with reference materials for an initial set of variants across the variant classes and multiple diseases and clinically relevant applications, while leaving room for further material development and improvement upon the processes they establish.

The ELBS and Friends of Cancer Research ctMoniTR Project are taking the next steps to develop ring studies in Europe and clinical trials in the United States, respectively, that will utilize established standardized methods to devise clinical collection standards for downstream implementation and to make the case for clinical utility in practice. ELBS and ILBS participants have collaborated to publish an international expert consensus paper on the clinical use of CTCs in breast cancer (Cristofanilli et al., 2019). The ILBS and MDIC's SRS initiative will build upon these early steps to support the use of liquid biopsy in research and clinical trials in countries around the world, while JMAC and NIBSC provide the infrastructure needed for laboratories to collaborate and build complementary data sets.

Among the multiple stakeholders participating in each of the listed projects are academic partners, private sector organizations and industry, government agencies and patient advocacy. FDA and the European Medicines Agency (EMA) regulatory representatives have also been supportive of the efforts and are interested to provide their support to discuss and develop liquid biopsies for use in clinical research and drug development.

4. Collaborative opportunities

A consistent theme from the collaborative discussions of the ILSA group is the continued communication of ongoing efforts. To that end, ILSA has committed to building a central repository for information sharing hosted by the BloodPAC Data Commons. The platform will share links to each organization to help researchers and clinicians recognize existing collaboration and avoid duplicative work.

Future development of the repository is planned to host protocols, white papers that highlight best practices, relevant policies for different countries and regions, and eventually de-identified data sets from studies that can be utilized in continued research.

The groups are interested in sharing the outputs of their projects as well. The FNIH Biomarkers Consortium ctDNA QCM project team will work with reference material manufacturers to qualify their materials with the FDA and eventually disseminate them for real-world-use ctDNA testing in the field. At the same time, the SRS initiative seeks to guide the development of reference samples used to validate NGS-based oncologic tests with an initial focus on solid tumors. Both groups are seeking to produce properly consented, widely shareable reference samples to be made available to the public and scalably produced in order to enable efficient development and improve the accuracy, reliability and transparency of blood- and tissue-based oncology tests. Developed materials from these projects will represent the majority of potential variations and allele fractions of interest (e.g., ploidy, fusions, indels, CNVs), and will be shared broadly with the community. The teams within ILSA have the opportunity to share beset practices to ensure that reference samples developed through their efforts can be scaled for commercial distribution.

In developing the WHO 1st International Standards for ctDNA, NIBSC must likewise ensure materials are well suited for their intended purpose in harmonizing ctDNA measurement across laboratories, assays, and secondary standards. It is thus imperative that the groups seek input from liquid biopsy community members worldwide. ILSA serves as a connection point and open market for commercial vendors, clinical centers, diagnostic laboratories, and other consortia, and welcomes further engagement. Given that participants benefit from and seek global agreement for the assignment of values and standards, they recognize the need for continued education and collaboration towards global alignment of measurement.

5. Resources for the field

As a first step to support the larger field, the ILSA partners have proactively linked partner efforts on their websites to promote and disseminate their work (Anon, 2020l). Each effort has also provided descriptive information to include on a central repository including contact information, organizational descriptions, website listings, and links to additional references and collaborative groups (Anon, 2020m). The ILSA partners are identified in a matrix form to provide interested parties with easily accessible and relevant information.

As a second step, the ILSA group is working to translate the current alliance into a recognized Collaborative Community in which the FDA can participate and provide supportive regulatory perspective (Anon, 2020n). The EMA is also active with the group and sees it as a forum in which their unique regulatory perspective can be shared as well, facilitating future coordinated efforts in this field to more precisely refine and describe pathways for qualification of standards and assays. The group provides a forum to ensure standards organizations are frequently engaged with to discuss regulatory pathways and are able to share insights and recommendations with their own networks.

In the future, the group aspires to build a database with various tiers of information that can be accessed by other efforts wishing to partner with one or multiple of the members of ILSA. First tier of information will provide simple descriptions of each effort and contact information. Second tier of information will include publications, white papers, and standard operating procedures from the various groups, diving into detail on their specific efforts. This information will serve both as an educational resource for the liquid biopsy community, as well as a way for other efforts to replicate different aspects of the liquid biopsy development pipeline for which the members of ILSA have developed lessons learned and best practices. Finally, a third tier of information the ILSA group envisions is a data resource with the original data from the experiments being conducted by each endeavor. This resource could then be used to further refine clinical use of liquid biopsy, standards development, and best practices.

6. Call to action

The ILSA group would like to invite additional members of the liquid biopsy field to join their efforts to synergize the science being conducted in this space. ILSA members wish to create a comprehensive repository of resources, lessons learned, and best practices in the liquid biopsy space in order to harmonize the disparate efforts that continue to hinder progress toward liquid biopsy achieving the status of full "clinical

utility" in the many contexts of use in which it is being used (Merker et al., 2018).

Eventually, ILSA would like to develop a uniform end-to-end process identified from pre-analytic capture through technology/assay validation to clinical collection and analysis. The group would then hope to promote the use of this process to allow for standardized data capture for liquid biopsy to build the necessary level of evidence required to have multiple contexts of use qualified by the FDA for clinical implementation.

Declaration of Competing Interest

Dr. Rolfo reports speaker bureau for MSD and AstraZeneca; advisory board role for ARCHER, Inivata, Merck Serono; consultant role for Mylan and Oncopass; supported research grant from Lung Cancer Research Foundation-Pfizer; research support from Guardant Health and Biomark inc. Dr. Cristofanilli reports consultant role for Foundation Medicine, Lilly, Pfizer, Cytodyn. Dr Serrano reports consultant role for Astellas. The other authors do not report any conflict of interest.

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