Proposed Framework for Leveraging a Distributed Pan-cancer Profiling IVD as a Companion Diagnostic for Oncology Targeted Molecular Therapies

WHITE PAPER: ONCOLOGY CDX STRATEGY

Introduction

In August 2024, a distributed (kitted), pan-cancer profiling in vitro diagnostic (IVD) was FDA-approved for tumor tissue: the Illumina TruSight™ Oncology Comprehensive IVD (FDA PMA Database, P230011). Now that this IVD is commercially available to molecular diagnostic laboratories in both the US and EU (CE-IVD), this IVD could be potentially leveraged as a companion diagnostic (CDx) for oncology targeted molecular therapies, given the recent FDA CDx reclassification announcement (January 31, 2024) stating most CDx IVDs will be reclassified from Class III (Premarket Approval [PMA] regulatory path) to Class II (De Novo Request or 510[k] regulatory path).

The intended use in the FDA PMA Database (P230011) and associated company press release (Illumina 2024) includes:

- Detecting variants in 517 genes using nucleic acids extracted from formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples from cancer patients with solid malignant neoplasms using the Illumina® NextSeq™ 550Dx instrument
- Detecting single nucleotide variants, multi-nucleotide variants, insertions, and deletions from DNA, and fusions in 24 genes and splice variants in one gene from RNA
- Reporting Tumor Mutational Burden (TMB) score
- CDx claims for VITRAKVI® (larotrectinib) and RETEVMO® (selpercatinib)
- Tumor profiling information for use by qualified health care professionals

Having access to a globally, distributed, pan-cancer profiling IVD provides more biomarker testing and CDx IVD options to Biopharma developing Oncology Targeted Molecular Therapies. CDx development adds significant costs to oncology therapeutic development and often extends clinical trial timelines. This is especially burdensome to small Biopharma with lower budgets, shorter timelines, fewer clinical operations and translational medicine personnel, higher risks, and more pressure due to smaller pipelines.

This white paper proposes a potential framework for leveraging a distributed (kitted), pan-cancer profiling IVD for EU and US clinical trials and for the commercial EU and US CDx IVD considering the recent FDA IVD reclassification announcement (January 31, 2024), FDA Final LDT rule (May 6, 2024), EU IVDR (May 26, 2022) and EMA CDx marketing authorization regulations. This framework may be helpful for Biopharma developing targeted oncology molecular therapies for a molecular biomarker that is accurately and precisely detected by a FDA-authorized, CE-IVD tumor profiling IVD.

The proposed framework may reduce oncology therapeutic development burden, costs, and timelines to maximize access to targeted oncology molecular therapies for all patients afflicted with cancer through high quality tumor profiling in a regulatory compliant manner during investigational and commerical phases.

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Maximizing Cancer Patient Access to Molecular Biomarker Testing

Decentralized biomarker testing (i.e., testing in many molecular diagnostic laboratories versus in one single molecular diagnostics laboratory) increases cancer patient access to approved molecularly targeting therapies and clinical trial opportunities (**Figure One**). As highlighted in the recent *"Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies"* FDA Draft Guidance (June 2024), certain populations are frequently underrepresented in biomedical research even when they bear a disproportionate burden for certain conditions or diseases relative to their proportional representation in the general population based on race, ethnicity, sex, and age group. A representative intended use population should be enrolled into oncology clinical trials to improve the generalizability of results across the intended cancer patient population, improve understanding of cancer and the therapeutic product, and inform the safe and effective use of the therapeutic product for all oncology patients across all geographies, socioeconomic backgrounds, and care settings (e.g., local, community, and major oncology centers). Biomarker testing should be readily accessible to all patients afflicted with cancer, and the American Cancer Society (July 2024) is diligently campaigning to mandate biomarker testing in all US states to improve cancer outcomes. Without adequate access to biomarker testing, advances in precision medicine could increase existing disparities in cancer outcomes by race, ethnicity, income, age group, and geography.

An accurate, precise and robust distributed (kitted), pan-cancer profiling IVD that can be run in any molecular diagnostics laboratory should enable more cancer patients to be molecularly profiled in a shorter turnaround time (essential for advanced cancer patients), and hopefully in the long-term a smaller cost per test versus using a send out test when there is adequate global biomarker testing

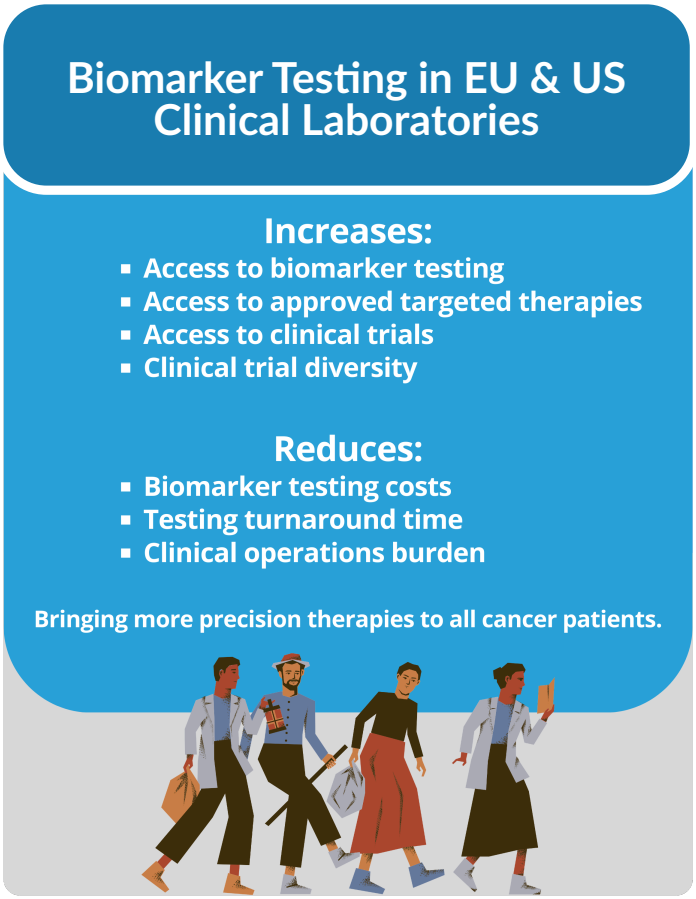


Figure 1: Decentralizing Biomarker Testing Increases Access to Precision Therapies & Improves Clinical Trial Diversity

adoption to reduce time lags between batching and greater cost reductions. Using an IVD kit is less regulatory burden for the clinical laboratory, i.e., no marketing submission or additional regulatory compliance is required when using an un-modified, FDA-authorized IVD (FDA Final LDT Rule). In addition, using a comprehensive molecular profiling IVD with both DNA and RNA-based detection of biomarkers ensures maximal detection of clinically actionable molecular biomarkers, for example, RNA-based Next Generation Sequencing (NGS) is more sensitive for fusion detection. A hybrid capture NGS approach also enables detection of de novo molecular aberrations. It is critical for the Biopharma Translational Medicine Team to evaluate the test methodology for sensitive and specific detection of the biomarker(s).

Biopharma Clinical Trial Eligibility Testing Options

If maximal patient access is important to ensure that the oncology clinical trial meets its enrollment goals in a timely manner (e.g., rare biomarkers [low prevalence], rare indications, small clinical trial budget, etc.), it may be beneficial to leverage local laboratory testing (i.e., US CLIA LDTs and EU in-house testing) and both tissue-based and liquid ctDNA testing (tissue biopsy acquisition can be challenging and tissue testing has a longer turnaround time). Example global clinical trial protocol inclusion criterion for this scenario is:

Tumors must harbor <BIOMARKER> confirmed by the site's local or preferred tissue or ctDNA testing platform in a laboratory compliant with National provisions.

This enables local laboratory testing for global clinical trial eligibility. Using "National provisions" means that the Sponsor will comply with all national provisions, which is important in the EU where individual countries may have different regulatory requirements and expectations. It is helpful to use globally appropriate inclusion criteria to mitigate the need for country-specific clinical protocols, which is burdensome for Clinical Operations. It is also critical that the Translational Medicine team consider the expected performance of local laboratory testing for detecting the specific biomarker(s) to ensure that the rates of false positives and false negatives are low to avoid both slowing down enrollment and enrolling an incorrect intent to treat population.

Alternatively, it may be beneficial to restrict clinical trial eligibility testing to laboratories that are only using one FDA-authorized, CE-IVD tumor profiling IVD (e.g., TruSight™ Oncology Comprehensive IVD). The reasons for this strategy may include: (1) concerns with local laboratory testing performance for detecting the specific biomarker(s), (2) the want for harmonized global biomarker data for the intent to treat population, and (3) a potentially easier CDx regulatory path, which will be discussed in a later section. Example global clinical trial protocol inclusion criterion for this scenario is:

Tumors must harbor <BIOMARKER> confirmed by an FDA-authorized or CE-IVD tumor profiling IVD in a laboratory compliant with National provisions.

These two approaches are detailed in **Figure Two** along with potential advantages, disadvantages, and regulatory considerations. Both approaches (Option Three) can also be applied, which may be optimal to maximize patient access while reducing overall regulatory, clinical operations, and translational medicine burden. Of note, CLIA tumor profiling LDTs, EU in-house tumor profiling tests, and the Illumina TruSight™ Oncology Comprehensive tumor profiling IVD are all available for clinical trial eligibility use either in molecular diagnostic clinical laboratories or at Contract Research Organizations (CROs) with no additional assay development costs and no CDx provider partnership agreement required. For option one, Biopharma will have costs associated with sample banking and collecting the necessary test information and for option two, there would be costs associated with supporting laboratories in setting up the IVD testing for the clinical trial if not existing. Global commercial uptake of the recently approved Illumina TruSight™ Oncology Comprehensive IVD would be expected to increase over time, especially as it would reduce regulatory burden for molecular diagnostics laboratories if this test is used (FDA Final LDT rule and EU IVDR).

When Biopharma has decided on the optimal approach for the clinical trial, it is critical to ensure that adequate detail is included in the US Investigational New Drug (IND) and EU Clinical Trial Application (CTA). In the US, a study risk determination (SRD) in accordance with FDA Draft Guidance *"Investigational IVDs Used in Clinical Investigations of Therapeutic Products"* (FDA Guidance, December 2017) can be submitted to the

IND independently by Biopharma through the streamlined pathway providing responses to four questions based on their specific clinical protocol, i.e., study design, specific biomarker(s), and cancer patient population:

1. Will use of the results from an investigational IVD lead to some study subjects foregoing or delaying a treatment that is known to be effective?

2. Will use of the results from an investigational IVD expose study subjects to safety risks (e.g., adverse events from the investigational therapeutic product) that exceed the risks encountered with the control arm therapy or non-trial standard of care?

3. Is it likely, based on existing knowledge about the relationship between the biomarker and the investigational therapeutic product, that incorrect results from the investigational IVD would present a potential for serious risk to study subjects?

4. Does use of the investigational IVD require invasive sampling that is not part of standard of care?

If the responses are all "no," then the biomarker eligibility testing is likely to be a Nonsignificant Risk (NSR) and an Investigational Device Exemption (IDE) submission is not required to be sent to CDRH (FDA) prior to the clinical trial, which will reduce clinical trial costs and timelines. Biopharma must still comply with the abbreviated requirements in 21 CFR 812.2(b) of the IDE regulation for a NSR study. The device must be labeled in accordance with 21 CFR 812.5; institutional review board (IRB) approval must be obtained for the study; each investigator must obtain informed consent from each subject under the investigator's care; must comply with the monitoring requirements of 21 CFR 812.46; must maintain records required under 21 CFR 812.140(b)(4) and (5) and must file the reports required under 21 CFR 812.150(b)(1) through (3) and (5) through (10); and ensure that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and file the reports required under 21 CFR 812.150(a)(1), (2), (5) and (7). Under the abbreviated IDE requirements, a sponsor must also comply with the prohibitions against promotion and other practices as identified in 21 CFR 812.7. The sponsor, investigator, or any person acting for or on behalf of the sponsor or investigator is prohibited from promoting or test marketing the investigational device; commercializing the device by charging a price greater than that necessary to recover the cost of manufacture, research, development, and handling; unduly prolonging the investigation; and representing the investigational device as being safe or effective for the purposes for which it is being investigated. By May 6, 2026 in accordance with the Final LDT Rule, CLIA laboratories are required to comply with investigational requirements, which will hopefully alleviate some of this burden from the Biopharma Sponsor in the future.

In the EU, an IVD that has CE-marking for the intended purpose or an "In-house IVD," defined as an IVD manufactured and used within the same health institution as outlined in IVDR Article 5 (5) and "health institution" as defined in IVDR Article 2 (29) can be used for clinical trial eligibility (interventional use). Using either approach can be aligned with regulators at EU Scientific Advice meetings and/or during the approval of clinical trial applications (CTAs) with provision of testing approach and associated rationale. The CE-IVD tumor profiling intended use can be included in EU CTA documentation to inform EU regulators that the test is appropriate for the molecular profiling of patients with solid malignant neoplasms, which is the targeted patient population for an oncology clinical trial. The use of a CE-IVD test or an in-house testing approach for clinical trial eligibility is preferred over the submission of a performance evaluation application (PEA) to the National Competent Authority (NCA), given the extremely long review times of over 200 days as noted in the recent COMBINE CTR-IVDR-MDR Report, (European Union 2024) and the additional costs associated with preparation and submission of PEAs to each EU country, and responding to requests for information, which frequently differ between

regulators. The PEA process is burdensome for oncology trials, especially when the target population is patients with advanced cancer and no available standard of care. The CE-IVD TruSight™ Oncology Comprehensive tumor profiling test run in EU molecular diagnostic laboratories or in-house tumor profiling testing are options available to Biopharma, and the aforementioned inclusion criteria cover each approach depending on what is preferred for the specific clinical trial.

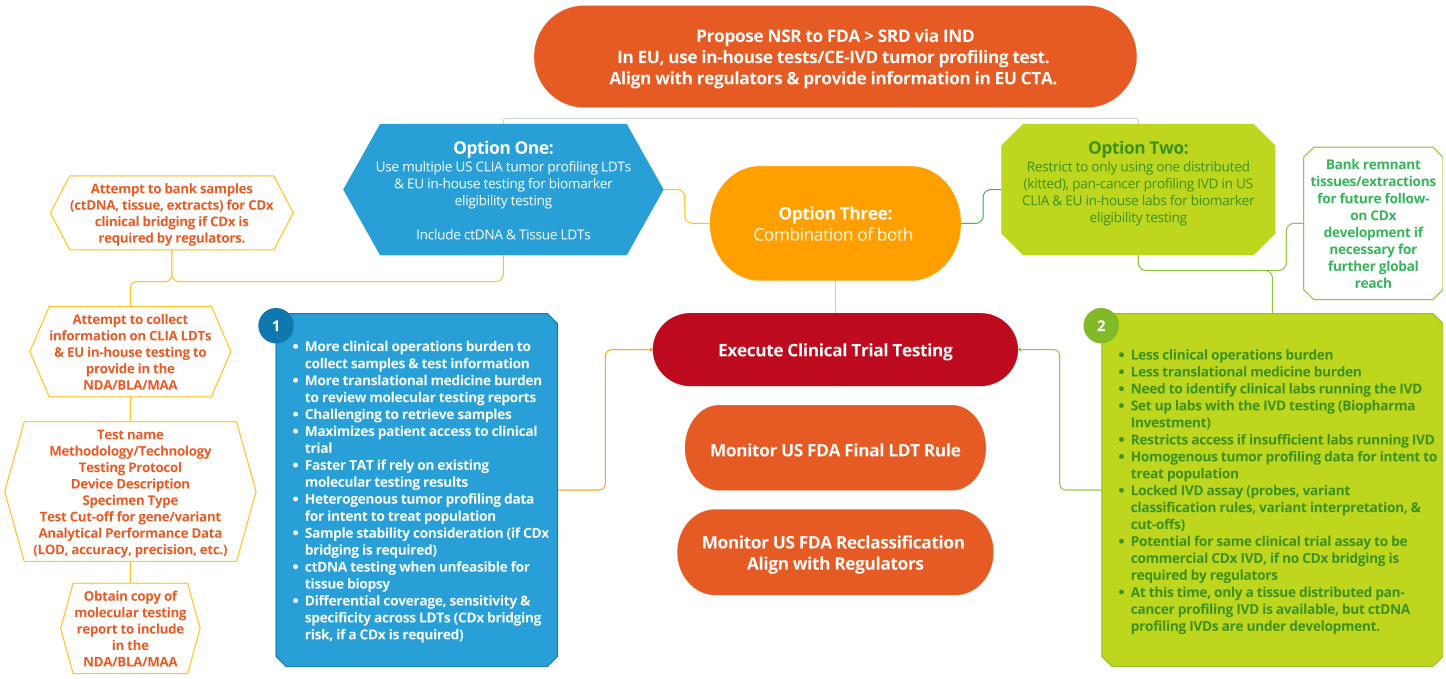
It can be advantageous to utilize the same clinical trial eligibility test to globally harmonize biomarker data and leverage all the data for global regulatory submissions (supporting regulatory convergence). Using the same locked IVD across geographies makes it easier for global regulators to consider regulatory recognition and reliance for marketing authorizations. This white paper specifically focuses on EU and US; however, other countries often recognize US IVD and EU CE-IVD products, and the use of these approved EU and US products can be aligned on with regulators in other countries to maximize the potential acceptance of the global harmonized molecular biomarker data and a harmonized tumor profiling approach for the therapy.

Biopharma can implement global clinical trial biomarker testing using the available options discussed and outlined in **Figure Two** to reduce costs and timelines while maximizing cancer patient access to life-saving therapies and increase clinical trial diversity.

The next consideration is the approach for the commerical CDx IVD, which will require alignment with regulators to understand the **specific CDx requirement for the oncology targeted molecular therapy.**

It is important to align with regulators prior to signing any agreements with CDx providers to avoid over-investment, additional burdens that could extend timelines, and large CDx contract termination fees. With the recent FDA approval of a distributed pan-cancer profiling IVD, and given both the recent CDx reclassification announcement and FDA Final LDT rule, it is important to consider all available CDx options and align with the regulators on the CDx requirements and regulatory path.

Figure 2: Biopharma Clinical Trial Molecular Profiling Options



Regulatory Considerations for a Companion Diagnostic for an Oncology Targeted Molecular Therapy for Solid Tumors

A CDx product provides information that is essential for the safe and effective use of a corresponding drug or biological product; it is used to identify patients who are most likely to benefit from a particular therapeutic product, identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product, or to monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness. As discussed in the FDA Guidance *"Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product,"* FDA may decide to approve a therapeutic product even if a CDx IVD is not yet approved, granted a de novo request or cleared when the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory available therapy exists and the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an IVD companion diagnostic with marketing authorization. This happens in oncology, especially in the case of advanced cancer and therapies approved as later-line. Thus, a CDx is a potential regulatory requirement for an oncology therapy and the need for a CDx is determined by regulators during the therapeutic product review process. Thus, it is critical to align with regulators on the CDx strategy to confirm that a CDx is required and to ensure that the Biopharma Sponsor is taking the least burdensome approach.

The European Medicines Agency (EMA) released *"Frequently asked questions on medicinal products development and assessment involving companion diagnostic (CDx)"* (December 6, 2023), which mentions that there is no legal requirement that the evaluation of the medicinal product and the device certification take place in parallel, and there are no mandatory simultaneous reviews. Sufficient documentation on the biomarker assay(s) should be provided to support the robustness of the clinical data generated to support the medicine. The Summary of Product Characteristics (SmPC) states that the biomarker "should be assessed by a CE-marked IVD with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used." Thus, a validated test is an option for an EU-authorized therapy, and it is important to confirm if a CDx is an EU regulatory requirement for the oncology therapy marketing authorization.

Figure Three provides a framework for CDx regulatory alignment and includes options based on: (1) the availability of a distributed pan-cancer profiling IVD for any molecular diagnostics laboratory to use, (2) the recent CDx reclassification announcement that most CDx IVDs will be reclassified as Class II by November 2027, and (3) the final FDA LDT rule, which effectively requires CLIA LDTs and NYS-CLEP tests to become single-site FDA-authorized IVDs by May 2028. This proposed framework could potentially reduce oncology therapeutic development costs, free up Biopharma resources, and accelerate market entry timelines while in parallel, potentially relieving burden on regulators through a reduction in the number of CDx marketing submissions that need to be reviewed and overall streamlining the oncology CDx process depending on the biomarker(s) and therapeutic context of use. This frees up investment for Biopharma to invest in new precision medicine approaches and new biomarker testing technology to identify the appropriate patients for their therapies.

Figure 3: CDx IVD Strategy

Conclusions

The proposed pragmatic framework in this white paper provides potential options for Biopharma developing oncology targeted molecular therapies in solid tumor indications to consider for their CDx strategy given:

- availability of a distributed pan-cancer profiling IVD for any EU and US molecular diagnostic laboratory to use to test solid tumor tissue specimens
- need to maximize cancer patient access to biomarker testing to identify life-saving therapies and clinical trial options
- need to increase clinical trial diversity to ensure cancer patients from all geographies, socioeconomic backgrounds, and care settings are represented in clinical trials and have access to life-saving therapies and clinical trial options
- recent FDA CDx reclassification announcement that most CDx IVDs will be reclassified as Class II IVDs, reducing CDx regulatory burden
- recent final FDA LDT rule, which effectively requires LDTs to become single-site FDA-authorized IVDs, increasing the regulatory burden for LDTs transitioning them into FDA-regulated tests
- potential for regulatory recognition and reliance of US IVD and EU CE-IVD products in other global territories to apply a harmonized global biomarker testing approach in clinical trials and a global CDx strategy to support regulatory convergence

The options for clinical trial biomarker eligibility testing (**Figure Two**) and the commercial CDx (**Figure Three**) proposed in this framework may enable Biopharma to get their therapies to patients afflicted with cancer faster, reducing costs and timelines while ensuring high quality tumor profiling testing is used in a regulatory compliant manner to identify the appropriate intent to treat population. A limitation of the Illumina TruSight™ Oncology Comprehensive tumor profiling IVD is that it is only approved for tissue testing, and tissue biopsies can often be challenging to obtain from advanced cancer patients. Tissue testing has a longer turnaround time as compared to ctDNA testing. Hopefully, a global (US IVD and CE-IVD) ctDNA distributed, pan-cancer profiling IVD also becomes commercially available for cancer patients soon. In the meantime, local laboratory testing can be leveraged to ensure cancer patients who are unable to provide tissue biopsies do not miss access to life-saving oncology therapies and clinical trial opportunities (**Figure Two**). The CDx reclassification may enable a ctDNA-based IVD to get to market faster via the De Novo Request or 510(k) submission pathway; IVD developers should engage FDA on what validation data would be required for a De Novo Request or a 510(k) for a ctDNA-based tumor profiling IVD, if there is an appropriate predicate for comparison. There is a high unmet need for a ctDNA distributed, pan-cancer profiling IVD for cancer patients to maximize access to oncology therapies and clinical trials, and reduce turnaround times to ensure patients receive treatment faster. ctDNA is a complementary tool to tissue tumor profiling and is capable of quickly identifying clinically actionable biomarkers for cancer patients; however, there are differences in coverage and sensitivity for certain biomarkers. For example, fusions (RNA-based detection is optimal), and ctDNA testing may not be appropriate for certain biomarkers, e.g., tumor loss of heterozygosity biomarkers, etc. No diagnostic test or technology is optimal for every biomarker and it is important to evaluate in the context of the biomarker.

Emerging CDx Development in Non-Oncology and Novel, Complex CDx Approaches

Given the:

- adoption of precision medicine approaches for non-oncology, e.g., CDx development for alcohol use disorder, chronic diseases, inflammatory bowel disease, neurodegenerative diseases, septic shock, etc., presents unique CDx challenges given the complex disease heterogeneity, differing risk benefit profiles, and often smaller budgets.

- development of complex genomic and transcriptomic-based CDx approaches, e.g., unique, multi-biomarker, predictive signatures based on RNA expression profiles, combinations of DNA aberrations, combination of DNA and RNA-based signatures, etc.

- development of novel CDx biomarker approaches, e.g., cfRNA, circulating tumor cells, digital pathology, epigenetics, fragmentomics, glycoproteins, metabolomics, methylation, phosphoproteins, proteomics, multiomics, novel tumor biomarkers, AI/ML-informed algorithms, etc.

- Emergence of novel technologies for CDx, e.g., single-cell approaches, multi-parameter flow cytometry, spatial proteomics, etc.

There is a definite need to streamline CDx development and regulatory burden wherever possible. Biopharma can then use their budget and resource savings to support the development of novel precision medicine approaches to understand the underlying biology of the diseases they are developing therapies for and to understand how to best stratify and/or select patients to identify those who will (companion Dx) or are most likely (complementary Dx) to benefit from the precision therapy. Streamlining CDx where possible frees up investment to evaluate novel precision medicine approaches and enables Biopharma to invest in novel CDx approaches (new technology, new predictive and prognostic signatures, etc.). Diagnostic companies struggle with investment and often rely on Biopharma to support their product development.

The proposed framework for the oncology targeted molecular therapy case study described in this white paper is an appropriate use case in the opinion of Boudicca Dx., LLC.

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Version 2.0. September 10, 2024. Correction to Figure 3 & typographical errors in text.

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