ORIGINAL ARTICLE

In vitro diagnostic tests: Ensuring test accuracy and patient safety when used as companion diagnostics

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ABSTRACT

Risks associated with drugs and treatments are a key concern in clinical investigations of therapeutics. There is a keen attention to side effects and adverse events included in critical safety documentation presented in regulatory submissions for new drugs. Likewise, Companion Diagnostic (CDx) technology is subject to rigorous regulated research and testing because of the risk associated with a false test result that could affect clinical decisions and treatment. The rigor of testing imposed by the regulatory path to clearance or approval is intended to ensure an assay is reliable when performance criteria are defined by a fixed set of these variables so that there is the least risk of false test results. The clinical validation of these assays is especially important when the test result is used to manage therapeutic decisions for patients. The same patients that expect a clinician to use reliable diagnostics to recommend treatment may also be recruited to participate in CDx clinical investigations. This educational review of CDx product development, regulations, and clinical investigations involving human subjects is important to: (1) Clinicians who rely on the test results to manage patient care; (2) Patients who trust these test results are informing the clinician, and (3) Hospital administrators who oversee human subjects safety and data intergrity for clinical investigations in the personalized medicine space.

Key Words: In vitro diagnostic, Companion diagnostic, Clinical performance

1. INTRODUCTION

Testing tumor genetics has enabled clinicians to match genomic alterations with the most current scientific literature and receive information about agents with predictive clinical benefit (or lack of benefit). This field of research has accelerated the application of genomic technologies in other areas and more than half of the personalized therapies the FDA approved in 2020 are intended to treat diseases other than cancer. Diagnostics are key to facilitating interventions at earlier stages of disease and targeting treatments to optimize the patient benefit.

In our earnest desires to bring testing answers and therapeutic options to patients, there is also an obligation to ensure a CDx is an accurate and reliable testing assay that generates current and meaningful data to aid the clinician in therapeutic decision making with those patients. CDx product development and the relative clinical investigations as described are highly complex with intentional controls that protect human subjects and ultimately patients. When considering this subject matter and what is at stake:

- Clinicians who rely on biomarker test results to manage patient care will weigh the risk/value of a fully

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regulated CDx test option against other tests that may not be subject to the same rigor.
- CDx product development and clinical investigations are part of a heavily regulated research obligation to protect human subjects and preserve the integrity of the data.

There is an added complexity to research and clinical trials that evaluate the safety and efficacy of both an in vitro diagnostic (IVD) and a drug or other therapeutic intervention. In some cases, a therapeutic may be tested and approved as safe and effective in blocking specific biomarker variants that can be tested on any technology or platform. Many therapies targeting a specific biomarker have been proven safe and effective using simple, low risk laboratory developed tests (LDTs) performed in a CLIA (Clinical Laboratory Improvement Amendments) certified laboratory. In other cases, an IVD and therapeutic may be tested contemporaneously resulting in a clearance or approval limited to very specific labeling for each product. Product claims for both the IVD and the therapeutic are important to analyze risks associated with each product and define appropriate scientific objectives for a clinical study.

1.1 Complexity of companion diagnostic clinical investigations

A companion IVD is often a molecular diagnostic and can require very specific sample preparation, high-tech instrumentation and software, and ultimately influences therapeutic choices and clinical outcomes for patients. It is important that when these devices are used to direct care they generate reliable information to manage risks potentially associated with inaccurate test results. A CDx can be used as an investigational assay in the same clinical study that determines safety and efficacy of a specific therapeutic product. This creates a complex clinical investigation that must demonstrate the IVD can safely and reliably identify a biomarker or a target that is ultimately an indication for a therapeutic that is being tested in the same study for safety and treatment efficacy. Regulatory obligations as well as the implementation considerations for these complex investigations underscores obligations to protect patients, preserve the integrity of the data, and facilitate efficient and compliant implementation of the clinical investigation toward a favorable research outcome.

1.2 The therapeutic

Drugs are the most likely to come to mind in the context of therapeutics, yet therapeutics can also include antibodies, cell therapies, therapeutic vaccines and other treatment modalities such as radiation therapy. FDA regulations for drugs fall within the scope of 21 CFR § 312 also known as the investigational new drug or IND regulations. This is the unique drug regulation consistent with the spirit of 21 CFR § 812 commonly referred to as the investigational device exemption or IDE regulations for investigational devices. Both of these regulations establish the rules that permit drug and device distribution for the purposes of clinical investigations. Drug development most often follows phases of experiments and data collection:

- Phase I – Drug administration in a small number of healthy volunteers (20-80) to establish safety in humans and a range of safe dosing (pharmacokinetics (PK) and pharmacodynamics (PD)).
- Phase II – Drug administration to a larger group (100-300) of subjects who have the targeted disease to determine dosage efficacy in the disease population and common side effects.
- Phase III – Drug administration in a large number of subjects (1,000+) to confirm earlier efficacy results, and capture adverse event occurrence in a larger population over a longer period of time and support a risk/benefit profile and labeling parameters.[1]

If clinical trial outcomes are favorable, all of the data is reported in a New Drug Application (NDA) and submitted for FDA review. Once the NDA is approved and the drug is available, Phase IV studies looking at the broad use of the drug in the general population may be appropriate to understand effects in unique populations and gather long-term safety and efficacy data.

1.3 The technology

In Vitro Diagnostics are regulated by the Food and Drug Administration (FDA) as medical devices and classified into Class I, II, III, according to the level of control necessary to assure safety and effectiveness of the device. The intended use of the device as well as indications for use determines the device classification and the type of premarketing submission/application required for FDA clearance or approval to market.

All medical devices including IVDs are classified into one of three risk classifications (these classifications are adapted for application to IVDs):

- Class I IVDs: Low risk tests/assays/instruments that do not require pre-market approval (PMA) or 510k clearance and are usually specific to a single analyte. These IVDs have minimal potential for harm and typically measure antibodies, receptor proteins, ligands, nucleic acid sequences.

- Class II IVDs: Medium risk test/assays/instruments that are cleared using the 510(k) or de novo reclassification process. The IVD may be proven substantially equivalent to a legally marketed (predicate) device often called a comparator product and/or to another diagnostic ground truth such as a biopsy result. IVDs with specific sample collection devices, reagents, equipment and/or instruments for automation such as RNA collection, stabilization and purification for molecular testing are usually medium risk and require special controls such as performance standards, post-market surveillance, and special labeling in addition to general controls to assure safety and efficacy.
- Class III: Significant risk IVDs that are approved by the PMA process, analogous to a New Drug Application. These tend to be assays used alone without additional corresponding clinical, lab or imaging data to determine a treatment course. In these cases, a false positive or false negative test result could cause erroneous clinical decisions associated with poor clinical outcomes for patients.[2]

1.4 The specimen

While medical devices work on or in a subject, IVD products are used to collect, prepare or examine specimens after they are removed from the body. They include reagents, instruments, and systems intended to aid in the diagnoses of diseases or determine a state of health.[3] Specimens or samples are critical to IVD clinical investigations. Some assays may require a prospective sample collection if/when the biospecimen requires specific collection equipment, prep, reagents, fixative and/or processing steps prior to running the test on an investigational instrument. Alternatively, the clinical investigation may permit the use of leftover or residual specimens after routine care testing such as blood or tissue biopsy samples. Ultimately, a clinical investigation must consider the sample characterization expected for the commercial application of the IVD and either mimic those characteristics (sample type, target population, collection, prep, stability for transport, time to testing, storage considerations, etc.) or provide a reasonable explanation for any deviations. For example, it may be acceptable to contrive samples for an investigation when the prevalence of samples for a specific disease or condition is very low.

2. COMPANION DIAGNOSTICS

Early "single test" technology such as immunohistochemistry (IHC/protein expression) and genetic tests used to identify molecular biomarkers preceded the more advanced technologies like next-generation sequencing (NGS) which is now the preferred technology used to generate large DNA/RNA sequencing data sets. As new targeted therapies are developed, pharmaceutical industries and clinical laboratories are eager to adopt new high-throughput IVD platforms yet are challenged by FDA requirements to demonstrate the reliability as well as the clinical utility of the test in selecting therapeutic products that favorably impact patient outcomes.

2.1 Definition

A companion diagnostic (CDx) is a medical device, often an in vitro diagnostic (IVD) test designed to provide information that is essential for the safe and effective use of a corresponding drug or biological product.[4] Until recently, most US FDA approved companion diagnostics are a correlation of "one drug/one biomarker". However, sophisticated, high-throughput NGS assays generate molecular and proteomic data potentially associated with multiple targeted therapy options.[5]

Companion diagnostics can be developed after a drug is marketed, or could be co-developed alongside an investigational drug through clinical trials. Contemporaneous FDA approval of an IVD and therapeutic product involves very specific study scientific endpoints in a well-defined target population. An example of this kind of required evidence is demonstrated in the product instructions for use and final product labeling:

- Cobas RT-PCR 4800 BRAF V600 Mutation Test for ... detection of the BRAFV600E mutation... and aid in selecting melanoma patients for treatment with vemurafenib.[6]
- Zelboraf™ (Vemurafinib) is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test.[7]

A number of targeted therapies are approved for specific types of cancer with an appropriate molecular aberration and do not require a specific technology or test platform in the labeling. In many of these cases, the IVDs used to detect the biomarker are simple, low risk laboratory developed tests performed in a laboratory certified in accordance with the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

2.2 Next generation sequencing (NGS)

Many IVD products measure only single or a few markers such that multiple samples and tests are needed for full evaluation of a patient's status. Alternatively, NGS is a combination of high throughput instrumentation, reagents, computational analysis, informatics and variant interpretation. The platform can typically deliver over three billion

bases in the human genome and identify millions of genetic variants in a test with a very small sample requirement.[5] This analytical power has key advantages in, for example, companion diagnostics used in cancer therapy or infectious disease where an ever-increasing number of mutations or pathogens have value in drug and biomarker associations. A rapid sequencing rate minimizes the delay in an effective diagnosis and initiation of effective treatment.

NGS describes a number of different modern sequencing technologies that allow for swift and inexpensive DNA and RNA testing compared to early low volume Sanger sequencing. NGS platforms perform interrogation of millions of little fragments of DNA in parallel. These little fragments are pieced together using bioinformatics analyses by mapping the individual reads to the human reference genome. The three billion bases in the human genome are sequenced multiple times respectively, providing high depth in the delivery of accurate data and shedding more light on unexpected DNA variation.

There are four steps in NGS testing, namely DNA extraction, library prep, DNA sequencing, and bioinformatics. An instrument/device reads the DNA and provides a sequence of bases. The sequences from patient samples are then compared to known references.[8] NGS allows researchers to deeply sequence target regions, rapidly sequence whole genomes, and study the human microbiome. RNA sequencing (RNA-Seq) is used to discover novel RNA variants and splice sites, or quantify mRNAs for gene expression analysis. NGS can be used to identify novel pathogens and analyze epigenetic factors such as genome-wide DNA methylation and DNA-protein interactions.

2.2.1 *Efficiency*

In molecular diagnostics, surveying for more than a handful of hotspot mutations by traditional methods can be laborious and requires precious sample from a limited supply. Traditional molecular testing (laboratory analysis of genes, proteins, etc.), when performed in sequence requires more sample and testing one biomarker at a given time extends the wait time to get results. NGS screens samples for multiple genes at the same time, eliminating the serial testing approach and generating a volume of biomarker detection results in a few days. This rapid turnaround time (TAT) facilitates treatment planning for patients.

Traditional CDx tests require more tissue than NGS assays. There is a limit to how many sections a diagnostic tumor specimen block can yield enough tumor for analysis. Likewise, needle biopsies yield very little material for testing. When sample is limited and tests are not multiplexed; separate slides are usually required for different immunohistochemical (IHC)-, ribonucleic acid (RNA)-, or deoxyribonucleic acid (DNA)-based tests. Liquid biopsy is a measure of circulating tumor cells, circulationg cell-free DNA, or microbial cell-free DNA to assess tumor or infection status/risk and may evolve to a standard that makes available sample less of a challenge given blood is not as limited as tumor tissue.

2.2.2 *Risks*

With the transition to NGS platforms to generate large amounts of molecular test results, the FDA has suggested there are added risks to patients. A therapeutic effective against a target biomarker considered key in one cancer may not be an effective drug choice for a different cancer with the same biomarker in the presence of other confounding mutations. (Example: Patients with colorectal cancer whose tumor expresses the epidermal growth factor receptor (EGFR) are usually resistant to anti-EGFR therapy if the tumor also harbors mutations in KRAS or NRAS[9]).

FDA also acknowledges risks associated with variability between laboratories, instruments, test platforms and variant interpretation. Foundation Medicine has FDA clearance of their NGS IVD for detection of molecular aberrations in 324 genes with relevant approved targeted therapies (see Table 1). In this case, the biomarker target is already supported by clinical evidence in the literature and/or along with the favorable drug effect on the target resulting in better clinical outcomes. The NGS product has been cleared by FDA as a reliable oncology panel, somatic or germline variant detection system.[10]

Variants of unknown significance (VUS) may be buried in large amounts of NGS molecular data. These biomarkers have inadequate scientific evidence of correlation to a therapeutic product. Clinicians can become confused about the impact of VUS on clinical decision-making. In a clinical investigation, however, a VUS may actually be the target biomarker in a CDx study with a correlating scientific endpoint.

Highly sensitive genetic information may also present itself in NGS molecular data. When testing includes gene mutations, there is a risk of incidental findings such as a mutation known to be a predisposition for a genetic disease not related to a specific clinical indication for testing. This newly discovered predisposition to a genetic disease may require genetic counseling for the patient and their family members. Other biomarkers of heredity may call into question paternity and pose additional ethical quandaries.

Table 1. FoundationOne CDx NGS test indications for use[11]

Disease	Target	Therapy
Non-Small Cell Lung Cancer (NSCLC)	• EGFR exon 19 deletions and EGFR exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), or Tarceva® (erlotinib)
	• EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	• ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	• BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
Melanoma	• BRAF V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	• BRAF V600E and V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib)
Breast Cancer	• ERBB2 (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab-emtansine), or Perjeta® (pertuzumab)
Colorectal Cancer	• KRAS wild-type (absence of variants in codons 12 and 13)	Erbitux® (cetuximab)
	• KRAS wild-type (absence of variants in exons 2, 3, and 4) and NRAS wild type (absence of variants in exons 2, 3, and 4)	Vectibix® (panitumumab)
Ovarian Cancer	• BRCA1/2 alterations	Lynparza® (olaparib), or Rubraca® (rucaparib)
Other solid tumors	• Genomic alterations and biomarkers including microsatellite instability (MSI) and tumor mutational burden (TMB) across 300+ genes with median depth of coverage of 500X	

3. PRODUCT DEVELOPMENT

IVDs and especially NGS platforms can be a powerful approach to diagnosis especially when applied to CDx in the clinical laboratory. Clinical validation of these products requires quality sampling and testing controls incorporating secure sample tracking through multi-step prep processing and NGS workflow including complex drug/biomarker algorithms and bioinformatics. Study designs may vary depending on assay intended use. For example, an assay may detect a specific biomarker used to: 1) select subjects for participation in a treatment, 2) stratify subjects into treatment groups, 3) determine dosing or monitor the treatment effect, or 4) exclude subjects from a treatment. Clinical study design is a consideration of use case and user requirements, target population for the clinical study, IVD scientific endpoints, and operational workflow to optimize study implementation.

3.1 Co-development and regulatory agencies

For all FDA submissions, the safety and effectiveness of the IVD must be demonstrated through analytical and clinical validation studies. Research involving the therapeutic must comply with investigational drug regulations in 21 CFR § 312; and research involving the technology must comply with the investigational device regulations in 21 CFR § 812. Three centers within the FDA could be important in study planning especially if/when seeking contemporaneous clearance/approval of both the CDx and the therapeutic:

- CBER: Center for Biologics Evaluation and Research
- CDER: Center for Drug Evaluation and Research
- CDRH: Center for Devices and Radiological Health

When a clinical trial is properly designed to establish the safety and effectiveness of a therapeutic product in a population based on measurement or detection of a marker, the results of the clinical trial can also be used to establish the clinical validity of the IVD companion diagnostic. A series of FDA presubmissions may require interactions between the assay developer and CDRH separate from interactions between the pharmaceutical partner and CBER/CDER to establish the critical device performance criteria and safety and efficacy parameters for the therapeutic. Ultimately, these agencies are likely to collaborate on a pivotal study design supporting clinical safety and efficacy of both the technol-

ogy/assay and the therapeutic for the intended use and target population.

Alternatively, when a therapeutic is already known/marketed as safe and effective for a target population (i.e. specific disease and biomarker), it may be sufficient to demonstrate an assay can reliably detect the biomarker in support of a CDx claim (only CDRH).

3.2 IVD test performance

FDA requires analytical and clinical validation studies as evidence of assay (the entire test system from sample collection to preparation through test result) safety and effectiveness. Analytical studies ensure the test can correctly and reliably measure a particular target of interest (i.e. analyte, bacterial antigen, pathogen) under controlled conditions by trained scientists. Clinical validation studies evaluate whether the test can accurately identify a particular disease or tumor biomarker associated with a specific treatment. Depending on the IVD intended use, the test may aid the clinician to select patients for treatment, monitor treatment response, or determine when to stop and/or restart treatment.

3.2.1 *IVD pre-clinical testing*

FDA cautions manufacturers to ensure the IVD product is "market-ready" before introducing it in a pivotal clinical investigation. Product development should conform to design controls in 21 CFR § 820.30. Analytical test methods establish performance attributes such as precision, sensitivity and stability. These metrics are given numerical specifications that are subsequently documented as design inputs. The Clinical Laboratory Standards Institute (CLSI) publishes consensus-based guidelines used by the global laboratory community to ensure laboratory testing for quality, safety and effectiveness. The International Conference on Harmonization (ICH) also offers guidance on validation of analytical methods.[12] Examples of pre-clinical testing requirements are noted in Table 2.

Table 2. Examples of analytical and pre-clinical testing for IVDs

Analytical & Bench Testing (examples)	Applicable Standard	Purpose
Precision	CLSI EP12-A2	Measures qualitative test performance (series of measurements on the same sample for repeatability (same operating conditions), precision (different days/operators/equipment) and reproducibility (between labs)
Interference	CLSI EP07-A2	Ensures no factors interfere with test results
LOD	CLSI EP17-A	Establishes linear range of enumeration at which the lowest amount of an analyte can be detected
Electrical Safety	IEC 61010	Assures device electrical safety
Shipping and Packaging • Device • Samples	ASTM 4169	Assures packaging sufficient to protect against mechanical shock
EMC	IEC61326	Assures device function within specified ranges of electro-magnetic exposure
Usability	IEC 62366-1	Test if users can follow the user manual and operate the device correctly
Sample Characterization	None	Assures processing, fixation, storage, shipping conditions, do not impact test result

Assay results determine a medical decision point. A qualitative assay may have a positive or negative decision point. A quantative assay result may be a number or a numerical range (analytical measurement range or AMR with linearity measuring test results as directly proportional to the concentration of an analyte) medical decision point. Alternatively, the decision point at which the assay changes patient treatment may be a combination of quantitative and qualitative performance criteria. Regardless, the testing must consider sources of variability in assay reliability (sample characterization, controls, calibrators, instrument performance and patient factors). Design verification is the proof that specifications have been, and will be met consistently as part of quality manufacturing. FDA recommends a full product analytical validation to evaluate critical performance parameters and establish "clinical readiness" including the following:

- Analytical Sensitivity (the frequency of false negatives) or Limit of Detection (LOD)
- In Use Stability
- Assay Robustness
- Exclusivity (Analytical Specificity)

- Inclusivity (Analytical Reactivity)
- Co-Infections
- Interfering Substances
- Carry Over
- Sample Stability

3.2.2 *IVD human factors and usability studies*

Risk assessment is a critical step in product development. When risk analysis points to the possibility of serious harm if users miss sample-processing steps or perform testing tasks incorrectly, the test manufacturer is obligated to human factors/usability engineering risk mitigations. Usability engineering may focus on displays and controls on a user interface and consider product design that minimizes potential for user errors.[13] Separate from human factors engineering during product design, FDA looks for clinical data collected in well-controled clinical studies using the IVD the same way, by the same user, on the same target population as intended in the commercial setting after device clearance/approval.

3.2.3 *IVD clinical performance studies*

The validity of an IVD CDx is determined by the ability of the test result to support conclusions made about the therapeutic efficacy when the medical decision cut off is used in the clinincal investigation. An IDE is required to introduce investigational devices into interstate commerce for clinical performance research if the device is considered significant risk (SR). In most cases, an IVD clinical investigation may be nonsignificant risk (NSR) because sample collection is noninvasive, clinical care is at the discretion of the clinician, and the test result is not used to manage patient care. Regulations have evolved to include the term "interventional" to describe studies using an investigational test result to make clinical care decisions.[14] These clinical investigations and the relative informed consent must consider risks associated with false negative and false positive test results and the impact on the scientific endpoints. FDA defers to the IRB to determine if those risks are significant (SR) and warrant an IDE to conduct an interventional IVD clinical investigation.

In the case of CDx intended use, the IVD research is potentially considered SR because inaccurate IVD results could lead to treatment error and an approved IDE may be required to conduct the study. Using an investigational test to direct clinical care triggers a number of key regulatory points regarding disclosure of investigational IVD test results in an interventional IVD study:

(1) The Health and Human Services (HHS) and FDA regulations (45 CFR § 46 and 21 CFR §§ 50 and 56, respectively) are silent regarding the return of individual investigational laboratory results to research subjects.

(2) FDA may require IDEs for a broader set of clinical investigations and it is unclear under such IDEs whether IVD research test results may be communicated to subjects.

(3) CLIA prohibits research labs from providing test results to patients generated by non-CLIA-certified labs when those results are provided for treatment purposes.

(4) CMS forbids any communication of test results to patients from non-CLIA-certified labs.

(5) HIPAA requires patient access to results that are part of their designated record set, however the Office of Civil Rights (OCR) has not provided guidance on how to interpret the term "designated record set" in the context of return of results from non-CLIA research labs.[15]

Regarding number two, note that the Institutional Review Board (IRB) serves as the FDA surrogate in device risk determinations. NSR device studies do not require an Investigational Device Exemption (IDE) application, however SR devices intended for research must have an IDE from the FDA before distribution. Sponsors may make an initial NSR determination based on the potential low risk of harm to the subject from participation in the study including the risks associated with the use of the device. If the IRB disagrees and determines by their risk/benefit assessment that the research is of significant risk, the Sponsor must notify the FDA of the IRB determination within 5 working days and submit an IDE application before commencing the study. SR research reviewed by the IRB should include evidence of an IDE# from the FDA prior to approval to ensure agency awareness and appropriate regulatory oversight.

When there is an intent to disclose the investigational test result and use it to direct clinical care, the protocol and informed consent should include an explanation of how a potentially false result will impact the subjects. The IRB will consider this risk to subjects in the determination of a NSR vs. SR study that would require an IDE.

4. BRIDGING STUDIES

When a test other than the clinical trial assay (CTA) is used for a therapeutic clinical investigation, there may be an opportunity to demonstrate the performance characteristics of the CTA are very similar to the assay used in the therapeutic clinical trial. The same specimens from subjects who were tested in the therapeutic clinical investigation are ideally retested with the CTA and used to assess comparative performance with the IVD CDx used in the trial. "A re-analysis of the primary outcome data should be made according to the final test results with the retest sample set in order to assure that any reclassification that occurs does not alter conclusions

about the safety and efficacy of the therapeutic product in the selected population... additional analytical validation may be requested" in the event of discordant test results.[4]

5. Conclusions

Risks associated with drugs and treatments are a key concern in clinical investigations of therapeutics. There is a keen attention to side effects and adverse events included in critical safety documentation presented in regulatory submissions for new drugs. Likewise, CDx technology is subject to rigorous regulated research and testing because of the risk associated with a false test result that could affect clinical decisions and treatment. Analyzing the reliability of clinical diagnostic products is a critical measure of safety. There are clear product development obligations that ensure an assay can detect an analyte and report a test result with precision. Repeatable and reliable target detection is dependent on any number of variables including technology platform, computational bioinformatics (NGS analyte interpretation), timing, quality and quantity of the biospecimen sampling and handling, tumor molecular composition, microbial virulence and processing controls (fixation, DNA/RNA extraction). The rigor of testing imposed by the regulatory path to clearance or approval is intended to ensure an assay is reliable when performance criteria are defined by a fixed set of these variables so that there is the least risk of false test results. The clinical validation of these assays is especially important when the test result is used to manage targeted therapeutic treatment decisions.

Laboratories, scientists and device manufacturers are moving technology forward in most cases faster than the clinical evidence can be collated into professional practice guidelines. This presents challenges to clinicians who may struggle to keep up with the growing library of evidence behind the laboratory reports generated by complex instruments and assays that combine test results with bioinformatics. Clinicians expect reliable test results, biomaker correlations and therapeutic recommendations when using a companion diagnostic (CDx) to manage therapeutic decisions for patients. The same patients that expect a clinician to use reliable diagnostics to recommend treatment may also be recruited to participate in CDx clinical investigations. These subjects must understand the test result in the clinical study is investigational and has not yet been proven reliable. As such the subject needs to be informed of the risks associated with a false test result and how that test result drives clinician decisions around an investigational therapeutic for participants in the clinical investigation. Hospitals and institutions who enroll subjects into CDx clinical trials should have a research infrastructure to support human subject protection, data integrity and personalized medicine services such as genetic counseling. Given all of the complexities, participating in these clinical studies and managing personalized medicine services should be a thoughtful consideration of compliance obligations as well as clinician and patient support services.

Conflicts of Interest Disclosure

The authors declare they have no conflicts of interest.

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