FRIENDS of CANCER RESEARCH

A Friends of Cancer Research Whitepaper

DATA GENERATION (AND REVIEW CONSIDERATIONS) FOR USE OF A COMPANION DIAGNOSTIC FOR A GROUP OF ONCOLOGY THERAPEUTIC PRODUCTS

OBJECTIVE

Friends of Cancer Research (*Friends*) convened a working group to explore evidentiary standards that could be useful in supporting a determination that an IVD companion diagnostic (CDx) device is appropriate for use with a class of therapeutic products, rather than with one or more specific products within the class.[1] This whitepaper constructs a framework within which the evidentiary standards necessary to establish confidence in the safe and effective use of a CDx to direct treatment of a specific group or class of therapeutic products, rather than specific individual products, may be considered for the benefit of patients to provide increased information regarding therapeutic options from a single test. This framework is intended to define categories, informed by technical and biologic considerations, where a approval of or expansion of a CDx label to include use in directing treatment with a specific group or class of oncology therapeutic products may be associated with different evidentiary requirements for class/group labeling considerations.

BACKGROUND

An increasingly detailed understanding of the genetic basis and molecular heterogeneity of cancer has driven the development of targeted therapies and associated companion diagnostic tests that have provided significant benefit to patients. These advances in precision medicine have given rise to approvals of subsequent same-in-class therapeutic products each of which are, most often, paired with a different companion diagnostic test. The benefits of multiple therapeutic options offered by approvals of same-in-class therapeutic products, such as the EGFR and PARP inhibitors, may in part be compounded by added complexity in CDx development as well as clinical testing workflows and practice, inadvertently introducing obstacles to access.

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ABOUT FRIENDS OF CANCER RESEARCH

Friends of Cancer Research drives collaboration among partners from every healthcare sector to power advances in science, policy, and regulation that speed life-saving treatments to patients.

A unique characteristic of certain targeted therapies is their reliance on the detection of a biomarker using a specific companion diagnostic test as an aid to identify the patient population most likely to benefit from that therapeutic. A CDx is the regulatory title given to tests approved that are essential to the use of a specific drug or biologic based on the detection of a biomarker. When a diagnostic test is approved as a CDx, its intended use in identifying patients who are appropriate for treatment with a specific therapeutic agent (including the name of the therapeutic), which is typically supported by results demonstrating an acceptable benefit-risk profile of the therapeutic agent used to treat patients identified using the CDx, is described in the CDx test label. Conversely, the indication statement of the corresponding drug or biologic label describes the requirement to test for the relevant biomarker using an approved test without naming the specific test. The Center for Devices and Radiologic Health (CDRH) typically considers companion diagnostics to be high-risk devices (Class 3) requiring pre-market approval, due to the potential for life-altering adverse events associated with incorrect test results. The clinical utility of a companion diagnostic is most often determined in the context of the test informing use of a single targeted therapy. However, more recently there have been approvals of multi-marker, panel-based CDx tests that can inform the use of multiple therapeutic products across multiple tumor types.[2,3,4]

In the Guidance for Industry and Food and Drug Administration (FDA) Staff on In Vitro Companion Diagnostic Devices, the concept of more broadly labeling an IVD companion diagnostic device that would enable use with a class of therapeutic products was introduced:

> The labeling for an in vitro diagnostic device is required to specify the intended use of the diagnostic device (21 CFR 809.10(a)(2)). Therefore, an IVD companion diagnostic device that is intended for use with a therapeutic product must specify the therapeutic product(s) for which it has been approved or cleared for use. In some cases, if evidence is sufficient to conclude that the IVD companion diagnostic device is appropriate for use with a class of therapeutic products, the intended use/indications for use should name the therapeutic class, rather than each specific product within the class.

Additional guidance pertaining to the definition of a class of therapeutic products or elaboration on the evidence that would be sufficient to support expanding a CDx label to reference a class of therapeutic products was not provided. Therefore, a draft Guidance was issued in December 2018 on Developing and Labeling In Vitro Companion Diagnostic Devices for a Specific Group or Class of Oncology Therapeutic Products – Guidance for Industry. Included among the important considerations regarding broader labeling was further definition of a class or group of therapeutic products, which would be "Approved for the same indication, including the same mutation(s) and the same disease for which clinical evidence has been developed with at least one device for the same specimen type for each therapeutic product."[5]

Development of a new targeted therapeutic agent within a potential drug class requires the identification and treatment of patients within the same indication using a test for the same or a biologically

highly related biomarker. However, the new or next generation "same-in-class" (e.g. targeting the same enzyme) therapeutic agent may be intentionally designed to overcome limitations (e.g. resistance mechanisms) associated with the previously approved same-in-class drug that has become established as the standard of care. Use of the new same-in-class drug subsequent to treatment with the approved same-in-class drug eliminates the need to utilize a companion diagnostic test to identify patients for treatment with the new drug given that patients have already been identified to direct the earlier line of treatment with the approved same-in-class drug. Rather, patients are enrolled based on their prior treatment. For example, five drugs are currently approved for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) that is determined to be anaplastic lymphoma kinase (*ALK*)-positive, but due to differences in the line of therapy for which the drug was approved, differences in the requirement for an FDA-approved test differ across these drugs. Drugs that are used subsequent to treatment with a prior (e.g. first-line) same-in-class therapeutic agent do not directly rely on an approved test "as an aid in identifying patients eligible for treatment" but rather take advantage of the existing standard of care established by same-in-class agents, with associated companion diagnostic tests, previously approved as an earlier line of treatment.

Further, given the limitations of tumor tissue availability, testing with multiple CDx for the same biomarker in order to enable treatment with specific or different *ALK* inhibitors may not be feasible. Similarly, serial or parallel application of the multiple single-analyte CDx tests now relevant for the optimal management of NSCLC is challenging and, in some cases, impractical to implement or unfeasible due to tissue availability. In addition, subsequent testing companies that come to market with a test for *ALK* could encounter problems, for example with accessing clinical trial tissue samples, with expansion of their label indication to include all drugs.

The FDA published draft guidance in December 2018 to inform the development and labeling of companion diagnostics for indication with multiple therapeutic products across a group or class of therapeutic products and final guidance is pending.[5] The draft guidance provides an important first step to advancing the use of group labeling for companion diagnostics, but further discussions are needed in order to address the issues outlined in this whitepaper. For example, the draft guidance refers to diagnostic devices for the identification of specific EGFR mutations in tumors of patients with NSCLC. Five different FDA-approved therapeutic products are indicated for patients with NSCLC whose tumors have EGFR mutations – deletions in exon 19 or base-substitution mutations in exon 21 (excluding the T780M and other resistance mutations). In many of these cases, the CDx may only have been clinically validated with one of the therapeutic products in the class. Prior FDA guidance documents[5,6] address how a CDx may seek approval for additional drugs in the same class beyond the agent for which it was originally approved. The guidance suggests how thorough analytical validation of the biomarker including cut-offs for the specific indication, and potentially clinical experience of the diagnostic with at least two therapeutic products can help broaden the labeling of the companion diagnostic for multiple therapeutic products that are in the same class.

The current whitepaper will consider case studies for three biomarkers, EGFR, *ALK*, and *BRCA*/HRD, to 1) define categories of biomarkers based upon biological and technical complexity, 2) explore how FDA's draft guidance could be implemented for simple or moderately technical biomarkers, and 3) begin to develop a common solution on how to establish a shared definition and evidentiary standard for high complexity biomarkers.

The formulation of a scientific evidentiary standard will be helpful to stakeholders as follows:

a. **Industry** – make for efficient diagnostic development by providing a clear, consistent understanding of the types of validation studies required.
b. **FDA** – help align various definitions of the "same" biomarker CDx and help FDA evaluate the safety and efficacy of the drug and diagnostic more efficiently.
c. **Physicians** – communicate information about new and exciting targeted therapies to physicians using 'simplicity in labeling'. This will be of enormous help to them as they manage their patients.
d. **Patients** – who seek streamlined and efficient access to both innovative life-changing therapies and to high-quality diagnostic tests that are critical in directing their safe and effective use.

A Framework for Companion Diagnostic Group Labeling

A framework to inform group labeling for companion diagnostics requires accurate classification (**Table 1**). Diagnostic tiers should be stratified by complexity of the principle of operation/technology, the biology of the drug target and diagnostic biomarker, including an understanding of mechanism of action, and the test's clinical application. This framework is predicated on the assumption that a group of therapeutic products can be appropriately defined, as described in the draft guidance (a specific group or class of oncology therapeutic products are those approved for the same indications, including the same mutation(s) and the same disease for which clinical evidence has been developed with at least one device for the same specimen type for each therapeutic product).

Classification Schema

Tier A companion diagnostics would include tests designed to identify biomarkers that are technically or biologically "simple", such as SNVs or indels associated with dominant driver oncogenes, where measurement of the biomarker in the intent-to-test population demonstrates a distribution that is largely bimodal, supporting a binary (positive vs negative) readout in which classification is not highly sensitive to the cut-point. In this Tier, group labeling would be based upon other tests targeting the same analyte (for example, a nucleic acid change), using the same technology, and from the same matrix. We propose the creation of a regulatory pathway for review and approval of Tier A biomarkers primarily on the basis of analytical and clinical validation, including assessment of clinical concordance, and demonstration of non-inferiority, with at least one other approved assay measuring the same analyte. **Tier B** companion diagnostics would represent a slightly more complicated or "moderate" biological and technical complexity and/or require a higher level of evidence to support group labeling and may include tests using the same or different platform technologies. An example of a Tier B CDx may be detection of a gene fusion event that defines a biologically distinct subgroup within a given indication, which can involve a variety of upstream partners, or assays that require a high degree of clinical interpretation (for example, a test that involves pathogenicity assessment of a germline variant). Lastly, **Tier C** companion diagnostics would represent the most technical tests, such as algorithmically determined biomarkers and/or require a high level of evidence to support group labeling where different platform technologies or matrices are used, or the algorithms are so unique to each test that a "group" labeling may not be feasible for Tier C biomarkers. Examples here include assignment of homologous recombination deficiency (HRD) scores or tumor mutation burden as a continuous variable each based on next-generation sequencing.

Table 1 outlines a rough framework of how a test might qualify for each tier based upon a general pattern of characteristics and provides examples of those characteristics. Placement in a tier is dependent upon the biologic and technical considerations of the test itself but also the diversity that exists between tests within a group label. A test would not have to meet all the listed characteristics to be placed in a tier. For example, the currently FDA approved CDx for EGFR are FFPE tumor tissue specific and are placed under Tier A here. However, if an NGS-based EGFR CDx were developed for cell-free DNA (cfDNA) isolated from plasma, this difference in matrix used by the test would merit placement in Tier C for the type of evidence needed to support a label expansion to a group label where other tests within the group use FFPE. Further, a detailed understanding of the mechanism of action of the indicated class of therapeutic products and the interaction between the therapeutic product and the biomarker would contribute to consideration of whether tests evaluating different matrices or utilizing distinctly different platform technologies would warrant placing the test in a different tier.[5,6]

Table 1: Categories Relevant to Consideration of Evidentiary Requirements for Class-Based Companion Diagnostic Test Labeling

Tier	Complexity[1]	Example					Type of evidence to support Dx label expansion to a specific group or class of therapeutic products[2]
		Rx	Alteration Type	Dx Analyte	Dx Platform	Dx Matrix	
A	Low	EGFR TKI	Simple: SNVs, indels	Single gene (e.g. EGFR) or small # of genes (e.g. BRCA1 & BRCA2)	NGS	FFPE tumor tissue	Concordance[4] with approved test(s)
B	Moderate	ALK TKI	Moderate: Gene fusion, low # fusion partners	ALK gene fusions	IHC; FISH; NGS	FFPE tumor tissue	Concordance[4] with approved test(s); additional supporting evidence and rationale
C	High	PARPi	Complex: Many variants, some may be unknown (e.g. tumor suppressor mutants; fusions with many partners)	HRD[3]	NGS	FFPE tumor tissue; plasma	Concordance[4] with approved test(s) along with additional supporting evidence and rationale; prospective design of the test/test algorithm (e.g. cut-off) to optimize concordance with established tests may be necessary; if acceptance criteria cannot be met, test-specific association with clinical outcome is needed and a class-specific label would not be feasible

Footnotes:

[1] Referring to the Dx target (specific analyte), the test platform technology and the biospecimen matrix (see Table 2), all considered within the context of the biology of the drug and Dx target and associated understanding of the drug class mechanism of action

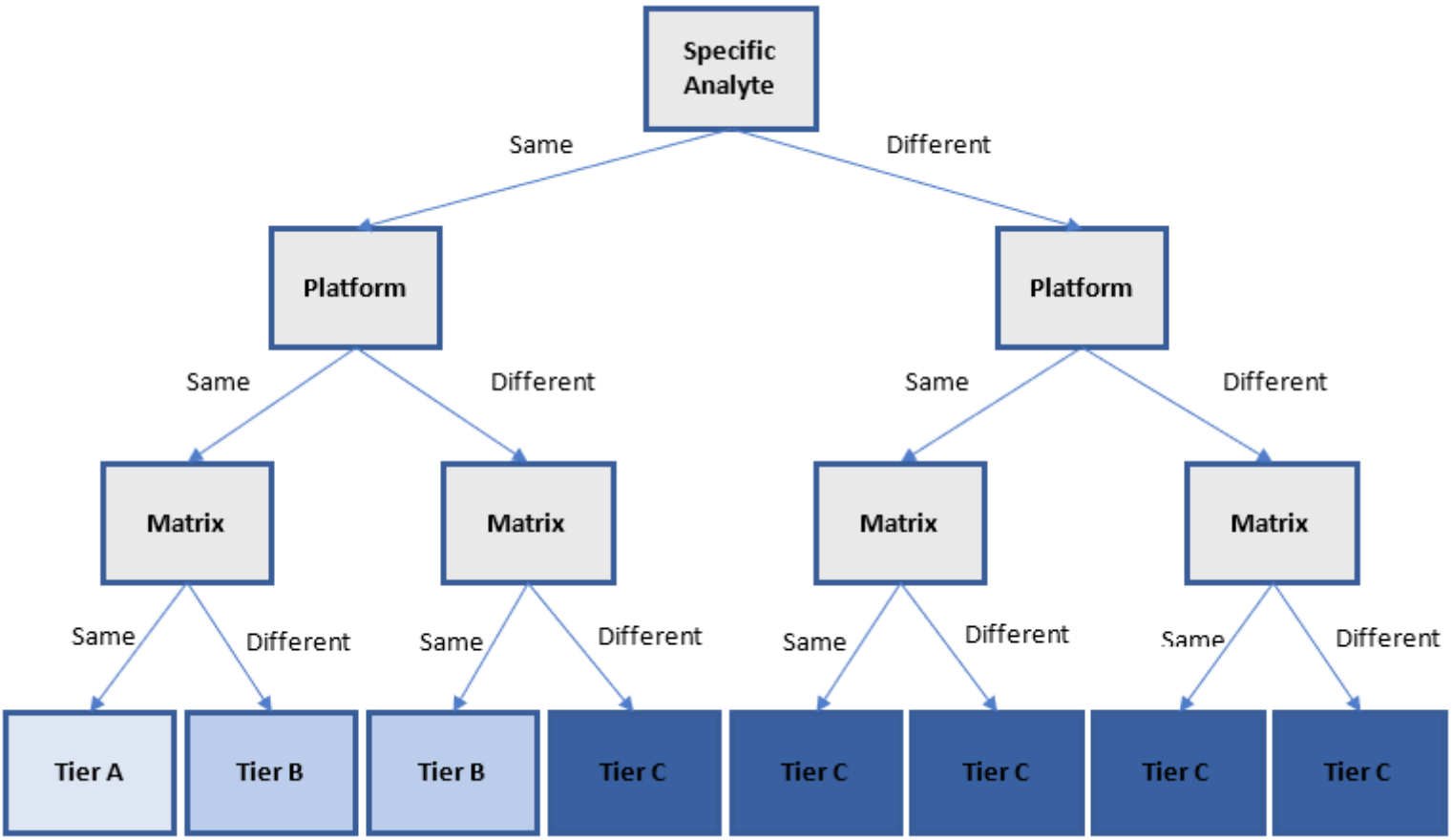
[2] Predicated on appropriate consideration of the key factors relevant to drug class Dx labeling (see below; group or class definition, MOA and biomarker-drug interaction, clinical experience, analytical validity, clinical validity)

[3] HRD, homologous repair deficient; this term is intended to refer to a biologically defined state (i.e. "BRCAness") that can be variably measured using different types of assays that may employ different platform technologies, bioinformatic pipelines, biospecimen matrices, etc.

[4] Acceptance criteria for PPA and NPA are defined on a case-by-case basis informed by prevalence of biomarker-positive subgroup within the intent-to-test population and the benefit-risk profile of the class

Note: In all cases, as per draft FDA guidance, sponsors are encouraged to engage in discussions with FDA (CBER, CDRH, or CDER), in coordination with the Oncology Center of Excellence, early in the development or consideration of possible class-based labeling of a companion diagnostic test

Figure 1: Decision Tree for Tier Placement



Challenges to Address and Evidence to Support Label Expansion by Category

In its draft guidance, FDA outlines five specific factors companion diagnostic developers should consider when deciding to pursue a broader labeling claim:

1. **Group or class definition.** Whether there is a specific group or class of oncology therapeutic products that can be defined (according to the indication, mutation(s), or disease listed in the therapeutic product's label) for which a companion diagnostic will identify an appropriate patient population for potential treatment.
2. **Understanding of MOA and biomarker-therapeutic interaction.** Whether there is a detailed understanding of a) the mechanism of action of the specific group or class of oncology therapeutic products being considered for use with the companion diagnostic and b) the interaction between the therapeutic products and the biomarker(s), at the mutation level, detected by the companion diagnostic.
3. **Sufficient clinical experience.** Whether there is sufficient clinical experience with at least two therapeutic products for the same biomarker-informed indications.
4. **Demonstration of analytical validity.** Whether analytical validity of the companion diagnostic has been demonstrated across the range of biomarkers that inform the indication.
5. **Demonstration of clinical validity.** Whether clinical validity of the companion diagnostic has been demonstrated with the therapeutic products in the disease of interest.

The below case studies seek to apply the framework outlined above with this guidance to development of a companion diagnostic test where a group label is pursued. By application to examples of companion diagnostic tests used to detect biomarkers representing each tier in **Table 1**, this whitepaper will outline the variables that could be used to provide assurance of drug efficacy across a drug class when indicated by a CDx with a group label across increasingly technical and biological complexity of biomarkers.

CASE STUDY 1: APPLICATION OF TIER A TO EGFR MUTATIONS

According to the categorization schema in Table 1, CDx currently used to identify patients with EGFR-positive NSCLC as an aid in directing treatment with specific members of the class of therapeutic products that inhibit the EGFR receptor tyrosine kinase fit the characteristics designed for Tier A CDx. The biomarker measured by EGFR CDx tests is a specific nucleotide deletion in exon 19 and specific SNVs in exon 21 of the EGFR gene, and the tests utilized to identify these alterations all evaluate the same analyte derived from the same biospecimen matrix. In addition, the alterations represent reasonably well-understood oncogenic driver mutations. The FDA's draft guidance identified EGFR as a case study to illustrate the thought process that would identify appropriate companion diagnostics for group labeling and demonstration of evidence to support a group label.[4]

Group or class definition

As noted in FDA's draft guidance:

> In this example, the oncology community would be better served by a companion diagnostic that detects EGFR exon 19 deletions or exon 21 (L858R) substitution mutations indicated for "identifying patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and are suitable for treatment with a tyrosine kinase inhibitor approved by FDA for that indication." This could enable greater flexibility for clinicians in choosing the most appropriate therapeutic product based on a patient's biomarker status.[5]

Understanding of MOA and biomarker-therapeutic interaction

As noted in FDA's draft guidance:

> EGFR exon 19 deletions and exon 21 (L858R) substitution mutations are known to upregulate EGFR phosphorylation and respond to treatment with tyrosine kinase inhibitors of EGFR based on functional studies. Many mutations in EGFR exon 20 are tyrosine kinase inhibitor resistant, so these mutations would be excluded from this group or class.[5]

Sufficient clinical experience

As noted in FDA's draft guidance:

> Afatinib, erlotinib, gefitinib, osimertinib, and dacomitinib are all indicated for the treatment of patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, so they will fall under one specific group or class (tyrosine kinase inhibitor indicated for the treatment of patients with NSCLC whose tumors have EGFR mutation exon 19 deletions or exon 21 (L858R) substitution mutations). Also it would not be appropriate to include therapeutic products in this specific group or class that only target resistant mutations, such as EGFR T790M and C797S, for which there may not be sufficient or consistent clinical experience.[5]

Demonstration of Analytical and Clinical Validity

The FDA guidance discusses considerations for demonstration of analytical and clinical validity as it applies to group labeling, although it does not provide an EGFR example for demonstration of analytical and clinical validity. For the discussion in this whitepaper, CDx tests that evaluate these nucleotide mutations are appropriately considered within Tier A because, unlike Tier B/C CDx tests, Tier A CDx tests do not require the identification of a complex rearrangement, do not evaluate different analytes that are directly or indirectly linked to the specific gene alterations, do not require a complex algorithm, and are often analytically

validated by comparing to bi-directional sequencing as the gold standard. Although the guidance does mention use of a reference test to detect false results and consideration of discordance between technologies, examples are needed to address the many outstanding questions, some of which are outlined in the **Discussion Questions** section below.

CASE STUDY 2: APPLICATION OF TIER B TO CDX ESTABLISHING *ALK* STATUS

Group or Class Definition and Understanding of MOA and Biomarker-therapeutic Interaction

Anaplastic Lymphoma Kinase (*ALK*) inhibitors belong to a class of compounds called Tyrosine Kinase inhibitors (TKI). These therapeutic products have proven effective in patients with metastatic NCSLC that is determined to be ALK-positive, reflecting the presence of a rearrangement in the *ALK* gene that functions as an oncogenic driver. During the past eight years, there have been five *ALK* inhibitors developed and approved, representing three generations of therapeutic products - crizotinib (first-generation), ceritinib, alectinib and brigatinib (second generation), and lorlatinib (third generation) - with additional drugs in development.

In general, subsequent generations of *ALK* inhibitors are designed to overcome limitations in potency, selectivity, brain penetrance, and mechanisms of resistance involving mutations within the *ALK* catalytic domain[6]. Studies have shown that patients can develop resistance to *ALK* inhibitors over time and that these mutations can represent a biomarker of response in previously treated patients.[7] Studies continue to shed light on the extent to which the various *ALK* inhibitors differ from each other in terms of mechanisms of resistance.

Sufficient Clinical Experience

The sequential development and approval, over a period of time, of next-generation *ALK* inhibitors using different CDx tests establishes increasing clinical experience and evidence demonstrating the clinical utility of an established class of therapeutic products in patient populations identified by different CDx tests. As mentioned previously, two of the five *ALK* inhibitors currently approved by the FDA for the treatment of patients with *ALK*-positive metastatic NSCLC do not further specify "as detected by an FDA approved test" because these two drugs were approved as 2nd line or 3rd line and greater treatments for patients who progressed on or may be intolerant to another *ALK* inhibitor that was previously approved as a first line treatment. While the safe and effective use of all of these drugs ultimately requires identifying patients with metastatic NSCLC whose tumors are *ALK*-positive as detected using an approved test, those drugs that are used subsequent to treatment with a prior (e.g. first-line) same-in-class therapeutic agent take advantage of the existing standard of care established by these previously approved same-in-class agents and their companion diagnostics.

There are presently three CDx tests approved by the FDA to identify patients with *ALK*-positive NSCLC appropriate for treatment with specific *ALK* inhibitors. Of particular note, each of the three approved tests measures distinctly different analytes (chromosomal DNA, protein, DNA sequence) using completely different platform technologies (FISH, IHC, NGS). These CDx tests therefore are best considered as Tier B tests, as additional evidence and supporting rationale would be necessary to support the expansion of any one test

with a class label.

Demonstration of Analytical and Clinical Validity

There are several technologies that have been developed to detect *ALK* rearrangements including IHC, fluorescent in-situ hybridization (FISH), and NGS. Because the analytical validity of each test and test platform is reviewed in the context of a single trial, the level of cross-platform divergence is unknown. The sensitivity of each of these tests varies, and interpretation of clinical data derived from the use of these different methods should be performed carefully.[8] Inconsistent results have been observed in the analysis of *ALK* rearrangements in NSCLC.[9] Core datasets and/or standard assays should be developed to facilitate harmonization of test sensitivity and analytical validity across tests within a test group. A recent study on *ALK* testing trends and patterns using Flatiron Health electronic health record-derived database reviewed results over 6 years for patients diagnosed with Stage IIIB or IV NSCLC. Average *ALK* testing rates increased over time from 32.4% in 2011 to 62.1% in 2016 and showed that FISH was the most common *ALK* testing method and may help understand relative performance of the various testing methods.[10] Harmonization efforts have been undertaken by comparing IHC testing methods across multiple centers and laboratories leading to standardized methods and interpretation criteria.[11]

In addition to each *ALK* diagnostic being required to demonstrate clinical validity in the context of the therapeutic for which it is a companion, for NGS based testing the FDA has required that the NGS panel test, for example, FoundationOneCDx, demonstrate clinical concordance to previously FDA-approved IHC/FISH tests.[12] While it is helpful to compare the performance of the NGS test with the IHC/FISH tests, if the various *ALK* therapies slightly vary in their mechanisms of action, one wonders if there should be an expectation of clinical concordance between the various diagnostics. In such cases, the same-in-class diagnostics category may have to be considered more carefully.

CASE STUDY 3: APPLICATION OF TIER C TO HOMOLOGOUS REPAIR DEFICIENCY AND SIMILAR TESTS

Poly (ADP-ribose) polymerases (PARP) have shown true promise in early clinical studies due to reported activity in *BRCA*-associated cancers. As a drug class, PARP inhibitors have had their greatest impact on the treatment of women with epithelial ovarian cancers (EOC). PARP inhibition exploits this cancer vulnerability by further disrupting DNA repair, thus leading to genomic catastrophe. Early clinical data demonstrated the effectiveness of PARP inhibition in women with recurrent EOC harboring *BRCA*1/2 mutations and those with platinum-sensitive recurrences. Three PARP inhibitors (olaparib, niraparib, and rucaparib) are now approved for use in women with recurrent EOC.[13]

These new therapeutics have demonstrated clinical use variously in treatment and maintenance settings, and more clinical trials are underway to expand use of this new generation of medicines.[14] Olaparib, Rucaparib, and Niraparib have all been approved with the requirement of a companion diagnostic, for certain indications. They are summarized in a recent FDA presentation.[15] These drugs have shown differential activity in patients with *BRCA* mutations or whose cancers demonstrate *BRCA* mutations or genomic scar-

ring resulting from homologous repair deficiency (HRD) of a variety of origins, including mutations, deletions, loss of heterozygosity (LOH), miRNA and DNA methylation.

Various diagnostic tests to detect *BRCA* or HRD have been approved: Myriad BRACAnalysisDx, Myriad myChoice, FoundationFocusCDxbrca and FoundationOneCDx. It is important to consider here that some of the tests only interrogate germline mutations in *BRCA* while others also detect tumor-derived mutations. Even with the approved diagnostics, there may be potential variation with the way homologous repair deficiency is defined (also referred to as genomic instability). In the case of one NGS panel, the HRD is represented by BRCA mutations and genomic score-based alteration called loss of heterozygosity (LOH).[16] This contrasts with another NGS-based diagnostic where *BRCA* mutations are supplemented by three algorithmic-score based alterations, namely telomere allelic imbalance (TAI), large-scale state transitions (LST) in addition to LOH.[17] Furthermore, recently a direct-to-consumer testing device has also secured FDA approval for detecting *BRCA* mutations, albeit not as a companion diagnostic to prescribe therapeutic, leading a prominent researcher in the field to worry that there may be insufficient testing of the *BRCA* pathological mutation with this test.[18]

BRCA certainly is gaining importance as a window into the tumorigenic process due to its role as a tumor suppressor, but there are even more genes implicated in the repair pathway that also seem to play a role. In addition to *BRCA*1/2, there are variously 15 or 17 other genes referred to as HRR pathway (homologous recombination and repair), where alterations in those genes are also being studied for response to PARPi therapies. The next iteration of Myriad's diagnostic named myChoicePlus will have an additional 90 genes compared to the original version.[19]

While these are exciting advances, the community will have to come together to define, classify, and harmonize these diagnostic devices as they are all likely going to apply to the same class of therapies, namely PARP inhibitor therapies. HRD or PARPi diagnostic devices, for lack of a better term, are sufficiently complex in their differences and nuances, that the average community physician may not be commensurate in understanding how each of them may detect slightly different tumor genotypes resulting in differences in clinical outcomes for the therapeutic.

Potential Implications for Clinical Trial Design

As FDA and industry consider these questions and other concepts to facilitate CDx development, the resulting policies and their implications need to be considered in the broader clinical context. For example, current CDx development pathways and regulations can impact the flow of patients onto clinical trials because current regulatory guidance may favor enrollment strategies that utilize prospective patient selection on the basis of an investigational device exemption (IDE) that will eventually form the basis of the CDx. By comparison, enrollment strategies that utilize locally obtained testing performed outside of the auspices of the clinical trial for the purpose of enrollment, with storage of samples tested by the local lab test for retrospective bridging testing is currently permitted, primarily where the biomarker is very rare, but this approach may not be favored. This "retrospective approach" can also be associated with challenging-to-meet downstream requirements such as collection of negative samples to be tested by the most prevalent local lab test used for eligibility determination.

Enrollment strategies that utilize prospective central confirmation via an IDE (if needed) for eligibility determination may result in duplication of testing if patients known to harbor the relevant biomarker are re-tested. This could create several concerns including duplication of testing, exhaustion of tissue sometimes requiring repeat invasive procedures to obtain more material necessary for central testing, and delays in patient enrollment during which the tissue is sent, accessioned, tested and results returned. These potential barriers to clinical trial participation, and the evidence they generate, should be carefully weighed against the potential benefits of this approach from an assay validation perspective.

Given these considerations, both regulators and sponsors may need to consider whether retrospective confirmation and enrollment of patients based on local testing could be sufficient to reduce the potential of duplicative testing and how to clearly articulate retrospective pathways that might be used for patient enrollment.

WHITEPAPER DISCUSSION QUESTIONS

- How should a same-in-class drug be defined in the context of a CDx group label?
    - What is the minimum number of drugs needed for creation of a group label?
    - How should variability in efficacy between drugs within a class be addressed?
- How can parity in measurement between tests within a test group be maintained?
    - Can tests be awarded a group label based upon comparison to a reference test?
    - How should harmonization of measurement between technologies be achieved?
    - What if harmonization cannot be obtained as newer technology is more accurate and provides for more efficient use of tissue (NGS)?
- When demonstrating analytical and clinical validity with reference to a comparator test, what characteristics should be considered when choosing the comparator test?
    - Should the first-in-kind or first approved test be the de facto comparator for all tests within a group label?
    - For example, in the case of EGFR, the Cobas[20] may be the reference diagnostic to harmonize to, but for BRAF[21], Biomerieux test may be the better reference diagnostic to harmonize to instead of Cobas. Examples of successful harmonization efforts exist, such as for validation of blood glucose monitors in which a standardized enzyme-based assay was used to establish a set range of performance values that all tests are required to meet. Further, the *Friends* TMB Harmonization project is an example of a molecular biomarker harmonization effort in which the use of NCI's The Cancer Genome Atlast (TCGA) data, cell lines, and clinical samples were used to help define and establish analytical performance thresholds.[22,23]
    - Should clinical trial data demonstrating validity be required for the comparator test?
    - Due to limited access to quality banked samples, are there alternate approaches that can be used?
- How should concordance be demonstrated for a pan-tumor indication?
    - Does concordance have to be demonstrated within each separate tumor type or is across a number of tumor types acceptable?
    - How many tumor types would be necessary?
- Are there situations when "unacceptable concordance" is acceptable?

    - Example: Qiagen PIK3CA testing in cfDNA only detects ~60% of mutations that are detected in tumor samples indicating cfDNA testing will miss many patients eligible for the targeted therapy, alpelisib. However, cfDNA testing is much more convenient than tumor testing, providing some benefit/reason for testing with this matrix. Further, the test label recommends repeat testing of tumor sample if the cfDNA result is negative.
- What type and level of data can be used to compensate for missing efficacy data?
- Are there cases where retrospective RWE could support widening a CDx label to a different drug in the same class (e.g. retrospective survey of outcomes based on which test was used before prescribing a given drug, showing similar outcomes)?
- Is there a role for non-invasive monitoring of treatment response in the adjuvant setting (i.e. ctDNA monitoring)? Would this enhance the identification of patients who respond to treatment vs. patients who never achieved a benefit?

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