

FDA Public Workshop on Next Generation Sequencing-Based Oncology Panels

The information and questions contained in this document are not binding and do not create new requirements or expectations for affected parties, nor is this document meant to convey FDA's recommended approaches or guidance. Rather, the information contained in this document offers background and the basis for discussions at the Public Workshop.

Background

A number of oncology therapeutic products have been approved with corresponding companion diagnostics (Ref. 1). To date, approved companion diagnostic assays assess a single analyte or pre-specified mutations associated with therapeutic response; however, next generation sequencing (NGS) technology can interrogate a patient's tumor specimen for numerous biomarkers concurrently, introducing challenges to the current companion diagnostic regulatory paradigm. Additionally, NGS tumor panels are increasingly employed for use in oncology applications because the technology can be used to screen a cancer patient's specimen for many relevant mutations simultaneously.

In the past submissions that have obtained favorable outcomes for these types of devices have included both analytical and clinical information. FDA is holding this public workshop primarily to obtain and solicit input from external stakeholders on approaches to (1) establish analytical performance characteristics of NGS-based oncology panels that include variants intended to be used as companion diagnostics as well as other variants that may be used for alternative therapeutic management of patients who have already been considered for all appropriate therapies and (2) produce the clinical information that is needed to support follow-on companion diagnostic devices (companion diagnostic devices not associated with the original clinical trial that supported approval of the corresponding drug). The Agency is requesting public input on strategies for establishing performance characteristics for NGS-based oncology panels for rare variants across tumor types, claims for follow-on companion diagnostic, and post-approval assay modifications. Discussion topics at the upcoming public workshop include the potential general intended use of such panels; considerations for pre-analytical and quality metric approaches; challenges in analytical validation and the potential for development of a flexible regulatory

approach for post-approval assay modifications; and the evidence needed for clinical and follow-on companion diagnostic claims.

Scope

The scope of the upcoming public workshop and the discussion questions included in this document are limited to targeted NGS-based oncology panels for human genomic DNA/RNA that are intended to be used as companion diagnostic devices for the clinical management of previously diagnosed oncology patients, and for alternative therapeutic management for patients who have already been considered for all appropriate therapies. Clinical indications that are not within the scope of the upcoming public workshop or the discussion questions below include use of oncology panels for cancer monitoring, cancer risk assessment, cancer screening, and standalone clinical diagnosis. The discussion will also not address circulating tumor DNA testing devices.

Please consider and provide input at the upcoming public workshop or in writing to the docket on the following discussion questions.

Intended Use of NGS-based Oncology Panels

The intended use statement below is intended to be a starting point for discussion on what an appropriate intended use statement might be for a targeted NGS-based oncology panel. FDA is seeking stakeholder input and comments on this intended use statement's format and content and would like to discuss any comments or concerns about this intended use statement at the upcoming public workshop.

The [device name] is a qualitative in vitro diagnostic test that uses high throughput parallel sequencing technology intended to detect sequence variations using the [instrument name]. The [device name] is indicated as an aid in characterizing sequence variations in [xx genes] on [DNA and/or RNA] isolated from [specimen type] specimens.

The device is also indicated as a companion diagnostic to aid in selecting oncology patients for treatment with the targeted therapies listed in Table 1 below in accordance with the approved therapeutic product labeling.

Table 1

Gene	Variant Status	Tissue Types	Targeted Therapies
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Results other than those listed in Table 1 are only indicated for use in patients who have already been considered for all appropriate therapies (including the ones listed in Table 1). Safe and effective use has not been established for selecting therapy using this device for the variants in the associated tissue types not listed in Table 1. Analytical performance has been established for the variants listed in Table 2 below.

Table 2

Gene	Variants	Sample Type (e.g., FFPE, fresh frozen)	Tissue Type (e.g., lung, skin)	LoD (based on LoD and reproducibility data)
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The device is not indicated to be used for standalone diagnostic purposes, screening, monitoring, risk assessment, or prognosis.

Question for discussion regarding intended use statements:

- 1. Does the general intended use statement proposed above capture the necessary elements to enable correct use and interpretation of an NGS-based oncology panel by expected end-users?*

Pre-analytical and Quality Metric Approaches

Variations in sample preparation and processing can have large effects on the outcome of any nucleic acid-based test. In the past FDA has required that clinical specimens from all tissue types specified in the intended use statement of the device be individually validated. Additionally, successful submissions have demonstrated that any critical processing parameters, such as specimen processing times, acquisition methods (e.g., fine needle biopsy, core needle biopsy, or surgical biopsy), tumor content (e.g., micro- or macro-dissection), and/or preparation (e.g., formalin fixed paraffin embedded [FFPE] or fresh frozen tissue) were suitable to achieve the expected device performance. However, it is not clear that information about each processing parameter across each tissue type is needed to support the claims of NGS-based oncology panels

intended to be used across all tissue of origin. Therefore, FDA is seeking input on whether there are suitable pre-analytical tests, representative sets of sample types, and QC-metrics that may be used instead of requiring all sample types and processing parameters to be assessed to demonstrate robustness for a particular NGS-based oncology panel. For purposes of this document, specimen type could be used to describe either the tissue of origin (e.g., lung cancer or melanoma), the tissue preparation process (e.g., FFPE or fresh frozen), or the nature of the nucleic acid analyte examined (e.g., DNA or RNA). In each instance below these distinctions will be noted.

Questions for discussion regarding pre-analytical and quality metric approaches to validate specific sample claims:

- 1. Are there pre-analytical steps that are most critical for NGS-based oncology panel performance?*
- 2. Are there tumor types that are more challenging for NGS-based oncology panels (e.g., brain, pancreas, etc.) and in what processing contexts (e.g., fresh frozen vs. FFPE)?*
- 3. What could be the appropriate level of validation needed to support both FFPE and fresh frozen tissue claims? For instance, should performance of the NGS-based oncology panel be validated with matched clinical samples, differently prepared cell cultures (e.g., cell cultures frozen or embedded to closely mimic how clinical samples are treated), or some other way?*
- 4. Are there differences in pre-analytical validation that should be expected when specimens are RNA versus DNA?*
- 5. Should differences in tumor cellularity be accounted for in pre-analytical quality control parameters? If so, how should these differences be addressed?*
- 6. Are there specific concerns that should be addressed for FFPE-based specimens (consider variables such as fixation times, types of formalin, fixative pH, likelihood of deamination due to variant genomic context)?*

7. *When there are modifications in pre-analytical parameters (e.g., specimen processing, etc.) are there conditions under which there should be a comparison of assay output (e.g., run the assay from start to finish with samples representing the new pre-analytical parameters) versus conditions under which demonstration that critical quality control metrics are met (e.g., ensure the critical controls metrics such as nucleic acid purity, quantity, and amplifiability are still acceptable) would be sufficient?*
8. *Is there a specific level of validation that would be appropriate in order to add or modify specimen types (tissue source and/or tissue sample processing) for an already legally marketed NGS-based oncology panel?*
9. *Should critical quality metrics be established that apply to all NGS-based oncopanels and, if so, how can it be ensured that the proposed critical quality metrics are suitable to preserve assay performance?*

Analytical Validation and Bioinformatics

Establishing analytical validity of in vitro diagnostic assays is essential to demonstrating a reasonable assurance of safety and effectiveness. With the understanding that NGS-based oncology panels report on variants over a spectrum of clinical validity, from variants of uncertain significance, to variants with companion diagnostic indications linked to specific therapies, the FDA is seeking input on the appropriate level of analytical validity that should be demonstrated for variants included on NGS-based oncology panels.

Questions for discussion regarding analytical validation approaches to NGS-based oncology panels:

1. *Is there a level of clinical importance for a variant that should warrant individual analytical validation of a variant reported by a NGS-based oncology panel?*

2. *Should the number of variants being reported by an NGS-based oncology panel determine whether a representative variant approach to analytical validation is acceptable? If not, are there other validation approaches that should be considered?*
3. *Are there parameters (e.g., variant type, variant size, local sequence context, global sequence context, other) that are most important to capture in a representative variant set? Are there differences in sequencing platform that would impact selection of a representative variant set?*
4. *In addition to validating individual assay steps, are there “best methods” to demonstrate the analytical validity of the complete assay system, starting with sample acquisition through the report generation?*
5. *Once analytical validity has been satisfactorily established for a specific set of variants, are there requirements or controls that should be in place to add, subtract, or substitute variants from the panel? For example, if an NGS-based oncology panel included a 3 base pair deletion, and a 3 base pair deletion was included in the representative variant panel, would it be appropriate for the manufacturer swap in a new 3 base pair deletion variant without any additional analytical validation?*
6. *Should the types of variants (single nucleotide variants (SNVs), indels, translocations, amplifications, etc.), size of variants (small indels vs large deletions, etc.), local sequence contexts (GC-rich, homopolymeric, etc.) and global sequence contexts (pseudogenes, etc.) included in an NGS-based oncology panel inform the appropriate analytical validation strategy? If so, are there particular validation strategies that are best-suited to establishing analytical performance of the NGS-based oncopanel?*
7. *Should commutability studies be conducted in order to infer the performance of the assay on clinical samples from data obtained in cell lines or plasmids?*
8. *Are there valid approaches to distinguish somatic versus germline variants? For example, would software approaches based on allelic frequency difference be sufficient or would matched tumor/normal tissue comparisons be needed?*

9. *Are there best approaches for defining assay sensitivity and specificity in a way that accurately reflects assay performance for NGS-based oncology panels?*
10. *Is it useful or practical to consider establishing an approved modification protocol to add or subtract variants from the panel without additional FDA premarket review? If so, are there key criteria that should be included in this modification protocol?*
11. *Are there risk-based strategies can be employed by FDA and manufacturers to determine when bioinformatics pipeline changes have significant potential to impact assay performance?*

Clinical and Follow-on Companion Diagnostic Claims

In an NGS-based oncology panel test, gene/variant(s) that are intended to guide therapy with a corresponding therapeutic for a specified indication will be considered to be a companion diagnostic (Ref. 2). In accordance with the companion diagnostic guidance (Ref. 2), the clinical claim should be stated in the intended use statement of an NGS-based oncology panel assay. The types of companion diagnostic claims for such gene/variant(s) could be categorized into either traditional/first-of-a-kind or follow-on companion diagnostics.

FDA anticipates that NGS-based oncology panel tests may also include claims for non-companion diagnostic gene(s)/variant(s). The possible rationale for reporting these non-companion diagnostic biomarkers on an NGS-based oncology panel may include both clinical and analytical relevance (such as biomarkers for disease prognosis). FDA is seeking input on the appropriate level of clinical evidence that should be provided to provide a reasonable assurance of safety and effectiveness for both follow-on companion diagnostic claims and other clinical claims.

Questions for discussion regarding clinical evidence and follow-on companion diagnostic claims:

1. *Are there key considerations for evidence that would or would not be sufficient for providing a reasonable assurance of safety and effectiveness for a follow-on companion*

diagnostic claim? Please consider the evaluation of differences in assay performance using procured specimens from the original therapeutic trial, procured specimens to mirror the therapeutic patient population, or other specimen types (e.g., the companion diagnostic used FFPE but the NGS panel utilizes fresh frozen tissue).

2. *Are there appropriate expectations for routine reporting of variants without established companion diagnostic claims? Please consider variants with comparable analytical performance to similar variants with established companion diagnostic claims, the availability of targeted agents to patients, and other means of establishing assay clinical performance.*
3. *Are there disclaimers that should be considered around issues of panel comprehensiveness? Please consider cases of absent or inadequate coverage of genes/variants with associated therapeutics or disease states, absent or inadequate coverage of known hotspots, and other variations in panel composition that could potentially impact assay interpretation.*
4. *Is there a specific level of clinical evidence that should be provided in order to move a variant from Table 2 to Table 1 of the proposed general intended use above when new targeted therapeutics are approved?*

References:

1. FDA website on companion diagnostics: <http://www.fda.gov/companiondiagnostics>
2. FDA companion diagnostic guidance: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>