Biomarker Report Harmonization Meeting Summary

Meeting convened on

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LUNGevity Foundation

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Executive Summary

Precision medicine, including targeted therapies and immunotherapy, now have wide application across multiple cancer types with the potential to deliver better outcomes for thousands of cancer patients. These advancements are possible thanks to improvements in diagnostic technology, particularly next-generation sequencing platforms, that allow for in-depth analysis of a cancer patient's biospecimen (e.g. solid tissue, body fluid, and/or blood) to identify molecular alterations that are causing the growth of the patient's cancer.

While advancements in care are incredibly valuable to patients, there are potential barriers to prescribing the correct targeted treatment or immunotherapy. These barriers include tissue quantity, turn around time for the testing results, and interpretation of the results. To date, most studies have focused heavily on how to overcome barriers related to obtaining the tumor biomarker testing results in the first place. However, less focus has been placed on the barriers that health care providers encounter in interpreting the complicated tumor biomarker reports once the test has been completed. Some of the challenges providers may encounter in reviewing the biomarker report include:

- Inconsistent nomenclature for mutations in results reports that cannot be missed (mutations with FDA-approved indications)
- Inconsistent level of evidence associated with a given variant with a given drug outside of NCCN guidelines and DA approvals
- Lengthy results reports which many providers, particularly those at the community level, don't have time or expertise to review completely
- Inconsistent and complex reporting structure across reports

How a provider navigates these challenges could make a difference in the patient's treatment decisions and outcomes. In order to discuss these critical barriers, LUNGevity Foundation, under the leadership of Dr. Christine Lovly, MD, PhD, convened a meeting on December 8, 2021 with community and academic center oncologists, testing companies and laboratories, regulatory agencies, and professional societies. The goal was to consider barriers for report interpretation; establish consensus on harmonization of vocabulary; and discuss best practices in report generation and upkeep.

To highlight some of the most pressing issues, leading thoracic medical oncologists presented four case studies on challenges with report interpretability to clearly highlight how next generation sequencing (NGS) reporting lacks clarity and on complex variant naming in reports, which may result in confusion on how a variant is interpreted, and with treatment selection. Additionally, attendees discussed the results from a pre-meeting survey on barriers for interpretative report generation and upkeep (labs/testing companies' feedback) and their interpretability (oncologists' feedback). The FDA also shared its perspective on results reporting.

Following a robust and dynamic dialogue on challenges with harmonizing aspects of the reports, participants voiced a shared interest in improving reports' interpretability to ensure patients are matched to the most appropriate treatment. Participants agreed that it is important to harmonize biomarker testing reporting as the field has become more complex and will be advancing even more in the future with the addition of testing for genomic signatures, genetic germline mutations, and other complex biomarkers. The clinical experts treating patients, and the testing companies and laboratories that develop advanced ways of delivering

detailed information about the patient's individual cancer type need to come to consensus on how to collectively address the challenges. Testing companies and laboratories require a focus on delivering up to date, critical information identified by their proprietary assay, while oncologists need the most salient information to make the most accurate treatment selection for their patient. Seeking a balance between these two forces will require a common and deep-rooted commitment to discussion and collaboration. Given the imperative to collaborate on this important gap in clinical care, attendees identified these four areas for further investigation:

- Clarification of nomenclature for all mutations, especially those that cannot be missed (mutations with FDA-approved indications)
- Establishing a minimum level of evidence required to associate a given variant with a given drug, outside of NCCN guidelines and FDA approvals
- Shortening the length of the report
- Refining the reporting structure of the first page of the report (for non-FDA-approved assays)

LUNGevity will work with attendees to identify the top opportunities for collective action, and partner with professional societies such as the Association for Molecular Pathology and/or the FDA to lead or provide feedback on issues that may already have multi stakeholder workstreams in progress.

It is not enough to promote biomarker testing for lung cancer patients. Even if 100% biomarker testing was achieved for lung cancer patients, this does not guarantee that precision medicine will be delivered. We need to focus attention onto best practices for report generation and interpretation, so that test results are both clearly communicated to the ordering physicians and correctly interpreted by clinicians to ensure appropriate biomarker-driven care is prescribed or patients are appropriately directed to a clinical trial. LUNGevity encourages oncologists, testing companies/laboratories, professional societies, and regulatory agencies that participated in the meeting, and those who may not have participated but have an interest in being involved, to stay engaged and committed to coming to consensus on how to address these results reports interpretability barriers for the improvement of lung cancer patient care.

Overview

On December 8, 2020, LUNGevity Foundation convened a multi-stakeholder group to discuss the need to streamline the variant calling and clinical terminology, as well harmonize the actual way mutation data (biomarker data) is being presented across different reports from different companies for lung cancer patients. This two-hour virtual meeting brought together 40 key stakeholders, including leaders in thoracic medical oncology, professional society leaders, diagnostic company officials, and regulatory experts to discuss challenges and opportunities for clearly communicating information stemming from tumor biomarker testing.

There was consensus from all participants that the complexity of reporting tumor biomarker testing presents challenges for all stakeholders: clinicians, testing companies, regulatory agencies, and patients. There was shared interest in harmonizing aspects of these reports to the greatest extent possible in order to support delivery of care and informed shared decision making between providers and patients in evaluating treatment options. The meeting yielded alignment that this effort is necessary to ensure delivery of appropriate care based on proper interpretation of biomarker testing.

Background & Meeting Objectives

Biomarker testing has become increasingly important for prognostication and guiding therapeutic decision-making for lung cancer.[1,2] Knowledge about molecular sub-types and understanding of novel biomarkers is expanding dramatically, increasing the complexity of information generated by these tests.[2,3] For example, the p.L858R mutation in the *EGFR* gene may be described as either the c. nomenclature (based on the DNA sequence) or the p. nomenclature (based on the resultant protein level change) – as per the Association for Molecular Pathology (AMP), the American Society of Clinical Oncology (ASCO), and the College of American Pathologists (CAP) Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer.[4] However, clinicians are typically most interested in the p. nomenclature:

- DNA nomenclature: - c.2573T>G (Substitution, position 2573, T➞G)
- p. Nomenclature: p.L858R (Substitution - Missense, position 858, L➞R)

The nomenclature and variant calling are even more complex than the simple example above, as an increasing number of complex rearrangements (rearrangement involving more than two chromosomes), splice site mutations, and large indels (insertions/deletions) are being detected in tumors. For example, c.3028+3A>G or c.3025_3027GAA>G are both classified by different testing companies as *MET* Exon 14 skipping mutations.

The multiplicity of testing platforms creates further complications and variations among test reports. While the lung cancer community continues to make progress toward the goal of ensuring that lung cancer patients receive evidence-based biomarker testing, patients will not benefit fully from this effort if providers struggle to comprehend results reports.

Launching a dialogue toward systematically unifying and harmonizing clinical biomarker reports to best serve the oncology community, the meeting focused on lung cancer as a case study within precision medicine. The objectives of the meeting were to:

- Consider barriers for interpretive report generation and upkeep
- Establish consensus on harmonization of vocabulary, and
- Discuss best practices in report generation and content curation

The Appendix includes:

- Meeting agenda
- List of meeting attendees
- Meeting slides

FDA Perspective

Dr. Reena Philip (Center for Devices and Radiological Health [CDRH], FDA) noted that harmonization in biomarker reporting is key to the success of precision medicine. CDRH regulates medical devices, including in vitro diagnostic tests, based on their risks and benefits. In describing the various requirements for submission of data to the FDA, Dr. Philip emphasized that while diagnostic sponsors provide analytical validation data for both companion diagnostic and tumor profiling claims, the depth of data needed for each claim varies. She reviewed the three levels of evidence required for tissue-based Next Generation Sequencing (NGS) oncology panels.

- **Level 1: Companion Diagnostics** which are prescriptive for a specific therapeutic
- **Level 2: Cancer Mutations with Evidence of Clinical Significance**, based on professional guidelines
- **Level 3: Cancer Mutations with Potential Clinical Significance**, based on literature or mechanistic rationale for inclusion in panel

Categories 2 and 3 are not conclusive or prescriptive for therapeutic use.

In the case of liquid biopsy tests, there are additional categories that are distinct from the solid tissue-based tumor biomarker testing categories. **Category 2-4 are not conclusive or prescriptive for specific therapeutic(s)**

- **Category 1**: A companion diagnostic (CDx) that is prescriptive for specific therapeutic(s)
- **Category 2**: Strong evidence of clinical significance from other FDA-approved liquid biopsy CDx
- **Category 3A**: Evidence of clinical significance presented by tissue-based FDA-approved CDx(s) or professional guidelines and includes blood to tissue concordance
- **Category 3B**: Evidence of clinical significance presented by tissue-based FDA-approved CDx(s) or professional guidelines
- **Category 4**: Evidence from peer-reviewed publications for genes/variants in tissue, variant information from well-curated public databases, or in-vitro preclinical models

Dr. Philip described various aspects of laboratory testing reporting relating to these types of diagnostic tests, noting that there are FDA approved elements of a report, a "page one" which will include FDA indications reviewed by the FDA, and a "professional services page" or "page two" which may include information on relevant clinical trials and is not reviewed by the FDA.

Four case studies presented by oncologists to describe the landscape of reports

To highlight some of the most pressing issues, leading thoracic medical oncologists presented four patient case studies. Participants then discussed the challenges, considered potential solutions, and identified opportunities to streamline and harmonize reports in similar circumstances moving forward.

The four cases highlight issues within two major categories. The first relates to lack of clarity in the reporting on a particular NGS test, which is a problem because the physician needs to know how to interpret the report to direct therapy for the patient. Ultimately, it is critical to ensure that every patient with a mutation appropriate for a specific therapy is offered that treatment. The second category relates to the very large data sets within NGS reports, within which there are often multiple variants or confusion in the variants that are reported.

Case Study #1: This case highlights the differences between variant calling on an interpretive report and clinical nomenclature and illustrates potential confusion which may arise regarding how a variant is reported.

Brief Summary: A 60-year-old male presented with progressive dyspnea on exertion x 6 months and was diagnosed with stage 4 lung adenocarcinoma. Biomarker testing results were positive for an *EGFR* c. 2237-2255del Ins T mutation in exon 19. Plan per the patient's oncologist was to initiate chemotherapy. Patient was admitted to local hospital for hypoxia, transferred to tertiary care center for higher level of care. Oncology consulted during the admission and results of the molecular testing were noted. After discharge, the patient was started on osimertinib with partial response ongoing for greater than 1 year.

The challenge that this case highlights: The biomarker testing results for this patient included the c. nomenclature and the p. nomenclature for the variant detected but *did not explicitly state that the EGFR variant detected (c. 2237-2255del Ins T) was an exon 19 deletion*. As a result, there was some confusion from the ordering clinician's perspective regarding the significance of this variant. There were questions about how to interpret the nomenclature in the framework of known actionable *EGFR* mutations that respond to approved TKIs.

The proposed solution: There are >10 different genomic variants, encompassing complex insertions and deletions, leading to what is called "*EGFR* exon 19 deletion" in the clinic. Ultimately, if the c. nomenclature is included in the report, and participants agreed it should be, then 'bins' or 'categories' of genomic changes

which lead to an actionable variant (such as *EGFR* exon 19 deletion, *EGFR* exon 20 insertion, *MET* exon 14 skipping variants) should be made and the specific name of the bin (i.e., '*EGFR* exon 19 deletion') should be included to provide clarity to the treating physician. This situation occurs in lung cancer because the terms used to describe the genomic variant on the DNA level and the terms used to describe the genomic variant in the clinic are not always the same. Ideally, when possible, the name of the bin for a companion diagnostic variant should match the wording used in the drug labeling for the associated drug(s) with language that as close as possible to that in relevant drug labels (such as "ALK fusion-positive").

Case Study #2: This case highlights the need to harmonize nomenclature on biomarker testing reports and provide support for clinicians in understanding the report.

Brief Summary: A 30-year-old female presented with cough and fatigue and was diagnosed with stage 4 lung adenocarcinoma. Biomarker testing reports called a complex rearrangement at chromosome 2p, including *ALK*. The clinician was uncertain if this complex rearrangement represented a clinically actionable *ALK* fusion in the patient's tumor or not. The clinician had previously seen reports which stated "*EML4-ALK* fusion" or "TFG-*ALK* fusion", and the clinician had experience treating those patients with ALK TKIs which are FDA approved. However, for this report in question, it was unclear if the variant calling ('complex rearrangement in *ALK*') was therapeutically actionable. And the clinician was uncertain who to turn to for support / discussion.

The challenge(s) that this case highlights:

1) The need to harmonize nomenclature on biomarker testing reports: With *ALK* rearrangements, there is heterogeneity in the reporting. Nomenclature used in the reports may include: "*ALK* rearrangement present", "*ALK* gene fusion present", "*EML4-ALK* rearrangement present". These variations in reporting may unintentionally create confusion and ambiguity for making appropriate treatment decisions. This same challenge exists for other therapeutically actionable kinase fusions, such as *ROS1, RET,* and *NTRK*.

2) The need for clinicians to have assistance in real time to help understand the biomarker test result.

3) The need for clinicians to understand what analyte is sequenced (DNA, RNA).

The proposed solution: Given that the treating physician, who is an expert in lung cancer molecular subtypes, struggled with this case, it raises the question of how best to transmit information to a clinician who may not be as familiar with the nuanced details of *ALK* (or any genomic variant). This case highlights the ambiguity that may be inherent to reporting complex tumor NGS data and the critical need for physicians/providers to be able to review the report with a colleague (for example, at molecular tumor board) or with a representative from the testing company – in as close to real time as possible - to clarify the report and determine appropriate next steps for the patient based on the result. In addition, it would be helpful for the reports to state whether a gene rearrangement is in frame and whether the entire kinase domain is included or not.

Lastly, reports that come from the same institution or company should be reconciled so that potentially confusing or discordant results can be resolved or explained in the report.

Case Study #3: This case highlights issues with terminology for some mutations that cause confusion among providers and difficulty in explaining complexity to patients.

Brief Summary: A 76-year-old female never smoker Stage IV- Right lung mass, mediastinal lymph nodes, palpable chest wall metastasis and a nape of neck nodule. Clinically, the patient was told that she likely had breast cancer before any tissue biopsies were completed. She underwent biopsy of both the lung mass and chest wall metastasis. The patient's tumor was found to harbor an *EGFR* exon 19 deletion mutation identified through tissue testing and a concomitant *ERBB2* mutation (p.S310F) (**note**: *ERBB2* gene encodes HER2 protein) found through ctDNA testing (but not tissue testing). Though the patient had initially been diagnosed with *triple negative breast cancer* before this additional testing suggested that, in fact, she had *lung* cancer. It was difficult for the clinician to discuss the biomarker report with the patient because she had been told initially that her tumor was HER2 negative, and now she was being told she had a specific *HER2* mutation that was neither the *HER2* exon 20 insertion nor a *HER2* amplification. This led the patient to question the lung cancer diagnosis (given that people often hear HER2 associated with breast cancer) and created complications for communicating with the patient and making therapeutic decisions.

The challenge(s) that this case highlights: This case highlights issues with terminology for some mutations that may be associated with multiple tumor types originating in different tissues and treatments, causing confusion among providers and difficulty in explaining complexity to patients.

The proposed solution: This case underscores that not all HER2 variants are the same and therefore treatment decisions are not the same in all HER2 cases. Some providers who are not as focused on the granularity of biomarker testing may see HER2 on a biomarker report and immediately make a treatment decision, before drilling down to the variant specific level and ensure that amplification is not conflated with different insertion deletion mutations or point mutations outside the kinase domain. It would be helpful to communicate on a report what certain variants are NOT.

Case Study #4: This case highlights challenges that arise with co-occurring mutations in patients who have complex molecular profiles.

Brief Summary: A 70-year-old male former smoker was diagnosed with Stage IV lung adenocarcinoma, with metastatic disease involving the pleura (pleural based masses), lymph nodes (mediastinal and cervical), and bones (ribs, sternum, and spine). Tumor and liquid biopsies were ordered, with different results:

1) Liquid: *KRAS* p.G13D, *KRAS* p.G12V, four different *TP53* variants, and *BRCA2* (50%)
2) Tumor tissue: *KRAS* p.G12V, *KEAP1, STK11, NOTCH1, ARID1A*, *CDKN2A*, high TMB, PD-L1 TPS 2%

There were also numerous VUS reported: *KDM5C, AGO1, CBLC, KEL, CSF1R, APOB, PIK3CG, HGF, ITNF1A, HDAC2, PHOX2B, ELF3, FANCM, DYNC2H1, RECQL4, INPP4B, ABCC3, MPL*.

The challenge(s) that this case highlights: This case focused on co-occurring mutations and involved a patient with a tremendously complex molecular profile that included a significant volume of mutations. Major challenges in this case were how to prioritize treatment(s) when multiple potential options are available, how to think about co-occurring alterations (for example, *KRAS*/*STK11*), how to put the VUSs in context, and when to send a patient for genetic counseling, given the *BRCA2* mutation, which was present at 50% variant allele frequency.

The proposed solution: Clinicians need access in real time to experts who can assist in report interpretation. It would be helpful to have a statement on if/when a patient should be referred to genetic counseling because of a possible germline deleterious variant. It would be helpful to know when 'normal' tissue from the patient was sequenced to clarify germline status. The reporting of dual mutations that have concurrent implications for therapy selection is something that clinicians struggle with and is not necessarily clearly transmitted on current reports, but how to fix this issue was not immediately apparent.

Pre-Meeting Survey Results

Survey of Clinicians

To identify key issues of concern and opportunities for progress, LUNGevity surveyed a diverse group of oncologists (N=8) representing different training, practice settings, practice sizes, and practice demographics. The clinicians were asked to:

- List barriers they face in reading and interpreting biomarker reports
- Suggest solutions and describe major changes that should be made to how reports are formatted, portrayed, or described

Perceived barriers and solutions identified in the survey are described in Table 1.

Table 1: Perceived Barriers in Reading and Interpreting Biomarker Reports

Perceived Barrier(s)	Example(s)	Proposed Solution(s)
Inconsistences in variant calling Sources of inconsistencies may be derived from: 1. Reporting differences (c./p.). 2. Nomenclature differences between the actual genomic variant and how	***EGFR* exon 19 deletion variants** Multiple genomic changes involving complex insertions and deletions lead to what is referred to as "EGFR exon 19 deletion" in the clinic. Different reports from different companies may / may not	▪ Distill down the multiple different genomic variants that can lead to what clinicians consider to be the therapy for the actual variant. In addition to the correct genomic name, consistently add in parenthesis the common vernacular. ▪ Make sure that the FDA-approved biomarkers are listed first. When a

the genomic variant is referred to in the clinic.	include a combination of the following: ▪ The c. nomenclature ▪ The p. nomenclature ▪ The more colloquial yet more clinically common nomenclature "EGFR Exon 19 deletion" variant.	mutation is not detected, make sure that is explicitly stated.
Lack of clarity around what type of alterations within a given gene match to an FDA approved therapy within a given tumor type. A perceived common misunderstanding amongst the community was that some providers do not always understand that different genomic variants (e.g., missense mutations, rearrangements, etc.) may occur within a given gene and that only certain variants have approval status.	***NTRK alterations*** *NTRK1* rearrangements vs. *NTRK1* missense mutation	The report needs to be very specific and say if the variant detected has an FDA approved drug or not – as well as the converse. For example, if *NTRK1* missense mutation detected – this is not an FDA approved indication.
Possible over-reporting of therapies based on variant reported Biomarker reports often list "potential" therapies based on approvals in other indications. This can lead to difficult discussions between patients and their treating clinicians to explain why an off-label drug is not being prescribed even when it shows up on a report.	***Listing treatments for NRAS mutations such as NRAS* p.Q61R** *NRAS* mutations have been described in cutaneous melanoma. Drugs targeting these mutations in melanoma are often listed in lung reports.	Clearly articulate the levels of evidence used to tie a particular mutation to a particular drug. Linking to professional guidelines (such as NCCN or ASCO) will help clinicians with decision-making and support transparency with patients who will have access to their reports.
Use of the headings of "actionable" or "biologically relevant" to define variants These terms are confusing as the meaning of these categories is not always clear to clinicians based on the information within the report.	***KRAS* p.G12C *and STK11/LKB1* p.G242V *co-occurring mutations.*** *KRAS* p.G12C is actionable through an FDA-approved drug or a clinical trial; *STK11*/LKB1 p.G242V is not actionable but	Need for clear articulation of levels of evidence and linking to major guidelines (ASCO, NCCN, etc.).

	biologically relevant because it confers resistance to immunotherapy.	
Reporting of possible germline variants While currently not actionable in lung cancer, reports often note presence of germline variants.	***EGFR mutations*** p.T790M germline versus tumor-specific mutations	While the topic is complex, a good starting place is to use information from the ASCO/AMP/CAP guidelines.[4]
Lack of clarity on relevant clinical trials	Not a focus of the LUNGevity meeting because it is a highly complex issue and is being addressed by several major groups at a national level.	

Survey of Diagnostic Company Representatives

As a companion to the clinician survey, LUNGevity also engaged representatives from 12 diagnostic companies (with 100% response) to solicit their perspectives on barriers and solutions. Diagnostic companies included reference laboratories and test manufacturers. Most respondents currently conduct testing on tissue and blood (plasma) samples. One of the participating companies specialized in genetic testing for inherited mutations (germline testing).

Respondents all cited similar goals including creating up-to-date, current, and clinically relevant reports that facilitate excellent patient care and provide superior customer satisfaction. All noted access to multidisciplinary teams to curate information that is updated on a regular basis, but the frequency with which information is updated varied across companies (ranging from continually, to weekly, to quarterly to approximately twice a year).

Areas of difference among the companies included the following:

Differences in report generation	a) Frameworks used to determine therapeutic actionability and biological relevance b) How frequently information is updated c) How information is tied to the level of evidence (there are various approaches for evaluating levels of evidence, though most incorporate the FDA-tiered classification system in some way and some also rely on NCCN, AMP and other professional society classifications) d) If/how clinical trials are annotated (those who provide clinical trial information in their reports pull information from clinicaltrials.gov or a similar source, relying on a third-party vendor to collect and curate trials, and incorporating manual edits/updates to trials) Updating clinical trial data in reports happens at a varied pace

	across companies (updated “daily” or “every few weeks”)
Differences in report layout/architecture	a) How different genomic variants are classified b) How they educate their staff c) Who the report is geared for or the report’s “reading” level

Taking into consideration all of the different components and efforts that are required for generating biomarker testing results reports, all company respondents noted that it is a time-and-resource-intensive process. A majority said they use in-house teams to curate the information though some rely on a third-party vendor or publicly available information. Additionally, they stated a reliance on a variety of resources including literature/data reviews, database mining, consulting with disease experts, machine-learning algorithms, and advanced analytics/validated reporting software. All companies surveyed have systems in place to support oncologists in interpreting biomarker testing results reports. These systems include phone call and email access to medical support teams, Medical Science Liaison (MSL) support and virtual tumor boards.

Diagnostic companies review multiple sources for generating the levels of evidence to accompany their reports, including peer-reviewed published clinical data, prescribing information for an FDA-approved therapy, companion diagnostic inserts, consensus guidelines, retrospective cohort studies, pre-clinical case reports, and internal expert review (among PhD-level scientists, molecular pathologists, lab directors, oncologists, and genetic counselors).

Diagnostic company representatives cited the following **barriers to updating and customizing reports**:

- Meeting customer needs: “All oncologists are different and require different types of reports.”
- Keeping content in the reports current and relevant (recognizing liability issues for the company).
- Operational challenges of performing a daily review of new variants.
- Taking complex information and making it digestible and user-friendly for an audience encompassing a wide variety of healthcare providers.
- Challenge of providing relevant information without having access to patient’s clinical data/history (including diagnostic information, line of treatment, prior treatments that have failed etc.).
- Challenge of providing clear information without being prescriptive.

Summary of Key Discussion Themes

With the four case studies, survey results, and FDA perspectives as a backdrop, participants identified and discussed key barriers and opportunities for harmonization of reporting. In addition to the “live” discussion, comments were captured via the chat function and through a white boarding application (Jam Board).

Discussion themes included:

Key Content Elements in the Report

- Clearly state that the test has or has not adequately assessed the variants that have FDA-approved treatments.
- Harmonize approach to ensure that all reports prioritize and clearly transmit all FDA approvals and make sure there are no missing variants that have a clear FDA indication.
- Address levels of evidence and cite guidelines or published reports.
- Reports should include the c. and the p., as well as the specific alteration vernacular.
- For **blood-based biomarker testing** (also known as circulating tumor DNA or liquid biopsy), there should be a large disclaimer. If the test results are "negative" for actionable biomarkers, it should state that no alterations were found. The provider should understand that this does not mean that the patient does not have actionable biomarkers. Rather, the test did not identify genetic alterations, and the provider should continue other forms of testing, such as tissue-based biomarker testing, as the patient may not have a DNA-shedding tumor (among other possibilities).
- Review ***Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists***, issued in 2017.[4]

Address Growing Complexity of Our Understanding of Biomarkers and Lung Cancer Biology

- It is important to scale biomarker testing results reporting as the field has become more complex with the advent of immunology biomarker testing and complex transcriptomic profiling. Reporting in lung cancer will need to address genomic signatures, germline variants, clonal hematopoiesis, and multiple different data elements.
- It is necessary to drill down to the variant-specific level and avoid conflating amplification with different insertion deletion mutations or point mutations outside the kinase domain for relevant biomarkers.
- The field needs to determine how to collectively address unexpected data and unexpected findings, including actionable variants that have never been reported on in this specific cancer type. Additionally, there may be data that was not requested but might prove useful, such as VAF data to assess the possibility of germline transmission or development of sub-clonal resistance.
- Give consideration to the difficulty of upgrading a database of 30,000 reported variants, variant descriptions, and interpretations, to even a slight modification of reporting standards

Provide Information that Is Understandable by a Variety of Providers from Different Practice Settings

- Reports must be available and user-friendly for a range of providers. The understanding of different genomic variants within genes is not immediately obvious given the complexity of possible alterations.
- Reports should support portability. This refers to the need for the report to be interpreted by the initial physician (perhaps a community oncologist) and then maybe presented to a tertiary care center for a

second opinion or transfer of care where additional detail may be needed. Additionally, it needs to include all the relevant data for quality control and review by an insurance company or a legal team.

Support Real-Time Medical Decision-Making

- Most clinicians are assessing these reports at the point of care just moments before they are about to meet with the patient. The urgency of real-time decision-making requires the reports to provide relevant information to the provider so they can determine what they need to do to treat the patient. It is important to summarize pertinent negatives, as well as clearly actionable positive findings on the front page.

Address Accessibility of Information in the Report

- Reports are often faxed from one office to another. As a result, color charts that convey important information may no longer be legible for the provider often due to limitations in EHR displays of data, tables, and color coding.
- The length of these reports is challenging. Upfront information should address key questions like whether there is a classic mutation and a particular drug that is likely to work. For atypical cases, provide more detail but keep it as straightforward as possible.

Provide Support to Clinicians in Interpreting Reports

- Companies should continue to offer opportunities for clinicians to contact diagnostic companies to review and discuss complex reports to address confusion and uncertainty, such as those related to clarification of ambiguous results or help with understanding the variants. For example, some companies have developed a successful Molecular Tumor Board to help providers interpret differing "inconsistencies" in biomarker testing results reports. To the extent possible, questions regarding the assay or its interpretation should converge on a single resource (i.e., third party annotation services should be avoided)

Address Information Need Among Patients

- Providers want to offer options, but there are times when options that appear in a report may not be good options for the patient. For example, patients may become confused by reading their reports and seeing reference to certain genes they recognize. They also may have questions about potential off-label therapy options included in the report that their provider is not recommending.
- Patients may be asking about the implications for their cancer care and their families, beyond prognostication for a specific germline variant. While this may currently not be pertinent for lung cancer, this issue will become more common as hereditary components of lung cancer and associated biomarkers are discovered.

Next Steps

As immediate next steps from the meeting, participants agreed to continue engaging on these issues, with consensus that this type of dialogue is critical to advancing the harmonization effort. Participants have

completed surveys on areas of the discussion for ongoing engagement. The feedback from the surveys will help organizers determine next steps. By continuing to collaborate on this issue, oncologists, diagnostic companies, professional societies, regulatory experts, and patient advocates acknowledge that there are opportunities to improve the reporting-out of the patient's biomarker testing results. It is not enough to promote that non-small cell lung cancer patients receive comprehensive biomarker testing. Test results need to be both clearly communicated to the ordering physician and correctly interpreted by clinicians to ensure appropriate biomarker-driven therapeutics are considered for patients when indicated and/or when assessing potential eligibility for an appropriate clinical trial. Meeting organizers will develop a manuscript stemming from the meeting to summarize major points from the discussion and the oncologist and diagnostic company survey results, as well as an action plan for moving forward.

Post-Meeting Survey

A post-meeting survey was sent to all attendees to prioritize short-term action items that the meeting participants are willing to undertake. Eight diagnostic companies, 7 oncologists, and 4 key opinion leaders participated in the survey.

Action items prioritized on a scale of 1 to 5 where 1 = highest priority and 5 = least priority are as follows:

Action Item	Priority Score
Shortening the length of the report	**2.2**
Refining the reporting structure of first page of a report from a non-companion diagnostic test	**2.3**
Clarification of nomenclature for mutations that cannot be missed (mutations with FDA-approved indications). Example, all exon 20 insertions in EGFR named as EGFR Exon 20 insertions, all exon 19 deletions in EGFR named as EGFR Exon 19 deletions, all MET exon 14 skipping mutations named as MET Exon 14 skipping mutations, etc.	**2.2**
Establish the minimum level of evidence required to associate a given variant with a given drug, outside of NCCN guidelines and FDA approvals	**3.6**

Items not covered in the list above included the following (responses captured as open-ended text responses):

1. I worry that some of the action items above--in an effort to simplify and clarify the information contained in a molecular profiling report--may stifle or limit innovation as well. We are learning all the time...and to limit the potential associations (target and drug) or to limit the length the report containing information may suppress the "bleeding edges" of discoveries in this arena.
2. Many of the items above are to be addressed by AMP in 2021 as part of our guideline update process, however we would like to continue to engage with this stakeholder group to help provide feedback to improve those efforts.

3. Rare Lung Cancers and new targetable mutations or gene-re-arrangements. Multiple co-mutations. Follow up reports need to be linked together
4. Being clear what test was performed. Were all alterations for which FDA approved treatments are available tested and what is the likely that the test is false negative.
5. Updating AMP/CAP/ASCO guidance for clinical significance to include immune markers/signatures (PD-L1, TMB, MSI)
6. Increasing the granularity regarding types of alterations shown on the report, e.g., fusion vs. mutation vs. amplification.
7. The discussion focused on cannot miss that includes approved therapies. This maybe nuanced but where would FDA breakthrough and fastback designations fit into this paradigm? These are certainly important for an unmet need, but it may/may not have made it to guidelines yet.

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Appendix A: Participants List

Medical Oncologists

Clinician	Affiliation	Title
Christine M. Lovly, MD, PhD (meeting chair)	Vanderbilt University Medical Center / Vanderbilt Ingram Cancer Center	Associate Professor of Medicine, Division of Hematology-Oncology Ingram Associate Professor of Cancer Research Co-Leader, Translational Research and Interventional Oncology Program Group Leader, Basic and Translational Research, Division of Hematology-Oncology
Lyudmila A. Bazhenova, MD	UC San Diego Moores Cancer Center	Clinical Professor of Medicine Lung Cancer Unit Leader Director of the Hematology Oncology training program
Shirish Gadgeel, MD	Henry Ford Cancer Institute/Henry Ford Hospital	Chief of Division of Hematology and Oncology Associate Director of Patient Experience and Clinical Care
Justin Gainor, MD	Massachusetts General Hospital	Director of the Center for Thoracic Cancers Director of Targeted Immunotherapy in the Henri and Belinda Termeer Center for Targeted Therapies Co-Leader of the DF/HCC Lung Cancer Program
Jhanelle Gray, MD	Moffitt Cancer Center/ University of South Florida Morsani College of Medicine	Department Chair, Program Leader & Senior Member for Thoracic Oncology at the Moffitt Cancer Center (MCC) Co-Leader of the Cancer Center Support Grant Molecular Medicine Program and Professor in the Department of Oncologic Sciences
Melissa Johnson, MD	Sarah Cannon Research Institute	Associate Director, Lung Cancer Research Program
Nagla Karim, MD	Medical College of Georgia-Augusta-Georgia	Professor of Hematology/Oncology Director of the Thoracic Oncology and Phase I Programs
Philip Lammers, MD	Baptist Cancer Center, Memphis, TN	Chief of Medical Oncology
Kathryn Mileham, MD, FACP	Atrium Health's Levine Cancer Institute	Chief of the Section of Thoracic Medical Oncology Associate Professor
Greg Riely, MD, PhD	Memorial Sloan Kettering Cancer Center	Vice Chair, Clinical Research, Department of Medicine
Alexander Spira, MD	Virginia Cancer Specialists (VCS) Research Institute	Director of the Virginia Cancer Specialists (VCS) Research Institute and Phase I Trial Program

Regulatory Experts

Leader	Affiliation	Title
Reena Philip, PhD	CDRD, FDA	Director in the Division of Molecular Genetics and Pathology in the Office of In Vitro Diagnostic Devices and Radiological Health
Harpreet Singh, MD	OCE, FDA	Director of the Division of Oncology 2 in the Office of Oncology Diseases Acting Associate Director for Cancer in Older Adults and Special Populations in the Oncology Center of Excellence
Julia Beaver, MD	OCE, FDA	Chief of Medical Oncology in the Oncology Center of Excellence and the Deputy Director (acting) in the Office of Oncologic Diseases

Key Opinion Leaders from Professional Societies

Leader	Affiliation	Title
Murry Wynes, PhD	International Association for the Study of Lung Cancer (IASLC)	Director of Scientific Affairs
Robyn Temple-Smolkin, MBA, PhD	Association for Molecular Pathology (AMP)	Director of Clinical and Scientific Affairs
Jason Rosenbaum, MD	Association for Molecular Pathology (AMP)	Assistant Professor, Department of Pathology and Laboratory Medicine, University of Pennsylvania Director of the Molecular Genetic Pathology (MGP) Fellowship Program Medical Director for Solid Oncology Diagnostics at the Penn Center for Personalized Diagnostics

Diagnostic Company Leaders:

Company	Contact	Title
Caris Life Sciences	Rebecca Feldman-Moreno, PhD	Senior Director of Biomarker and Drug Intelligence
Foundation Medicine	Prasanth Reddy, MD, MPH	VP of Medical Affairs
Guardant	Becky Nagy, PhD	VP, Medical Affairs
Illumina	Carolyn Dumond	Senior Manager, Global Patient Advocacy
	Kevin Keegan, MBA	Senior Director, Clinical Oncology Marketing
	Dave Eberhard, MD, PhD	Sr. Medical Affairs Director, Oncology
OmniSeq (Integrated Oncology)	Mary Nesline, MS	SVP, Clinical Evidence Development
NeoGenomics	Gina Wallar, PhD	Senior Vice President, Clinical Services Sales
Myriad Genetics, Inc.	Brian Strike, MS, CGC	Oncology Medical Affairs Manager – Western U.S.
PGDx	Maura Kadan, RN, MSN, OCN	Director of Clinical Education and Outreach

Quest Diagnostics	Yuri Fesko, MD	Chief Clinical Officer and Strategic Alliances
Resolution Biosciences	Mark Li	President and CEO
Tempus	Leslie Pierce, MBA	Director, Strategic Partnerships
	Michael Axelson, MD	VP, Clinical and External Research
	Tim Taxter, MD	Senior Medical Director
	Ameen Salahudeen, MD, PhD	Scientific Director
Thermo Fisher	Jody Courtney McIntyre, Ph.D.	Associate Director, Oncology Product Management, Clinical Sequencing Division
	Amy Carroll, PhD	Medical Affairs Director, North America, Clinical NGS and Oncology Division, Life Sciences Solutions
	Santhoshi Bandla, MS, PhD	
	Nitesh Patel, MS	Associate Director, Product Management, Clinical Sequencing Division (CSD)
LabCorp Inc.	Stephanie Carter	Oncology Testing Specialist