In 48 Hours

A Case Study Series from inVibe Labs

inVibe

Oncologists' Current Perceptions and Utilization of Biomarker Testing for Newly-Diagnosed Non-Small Cell Lung Cancer Patients

A Qualitative Case Study Utilizing an Automated Voice-Response Research Platform in a Complex Subject Area

Research Background

With the possible exception of breast cancer, biomarker testing is more established in non-small cell lung cancer (NSCLC) than in other oncology indications. If you believe that NSCLC biomarker testing is fully standardized, you would be wrong. Our survey respondents taught us that we are only at the end of the beginning of standardization for NSCLC biomarker testing.

Research Approach

inVibe fielded an open-ended, eight-question survey in just 48 hours with 12 academic and community oncologists who treat an average of 40 NSCLC patients per month. The specific study objective was:

To understand how oncologists currently perceive and utilize biomarker testing for newly diagnosed non-small cell lung cancer patients.

Research Methodology

Qualified physicians were sent a text message to their mobile phone, which provided a link to the background of the research and a preview of the eight open-ended questions. Upon reviewing the information, a simple 'tap' on their phone enabled them to call in to inVibe's secure, automated interview phone line, where they listened to a recording and answered each question simply by speaking. Upon completing the survey, the audio files were validated, transcribed, and analyzed.*

*The validation process includes monitoring for adverse events and personally identifiable information.

Biomarker Testing for NSQ-NSCLC Patients

For the newly diagnosed non-squamous cell (NSQ) NSCLC subset, the same core tests are used among survey participants. All study respondents said that they test for PD-L1 (not PD-1) protein levels as well as for the common EGFR and ALK gene mutations. They also test for ROS1 mutations, although these are found in only one percent of all lung cancer patients. Why test for these biomarkers? Because identification enables patients to benefit from FDA-approved targeted treatment.

"There is ample data suggesting that patients with certain mutations will benefit more from directed targeted therapy than they will from chemotherapy."

Outside of these core tests, biomarker testing for NSQ-NSCLC patients is highly variable:

- About half the participants, aware of the June 2017 FDA approval of dabrafenib plus trametinib for metastatic patients with the BRAF V600 mutation, include BRAF testing up-front
- Many participants test patients for the T790M EGFR mutation at least when it is time for second-line therapy
- Several oncologists, especially those from academic centers, order extensive "next generation" sequencing in-house (e.g., Memorial Sloan Kettering's MSK-Impact) or from Foundation Medicine or Guardant. Resultant profiling of up to 400 or more genes gives additional guidance on second-line treatment and identifies patients that may be appropriate for current clinical trials involving new biomarkers. However, most still have not bought into next generation testing
- One quarter of the participants specify KRAS testing. Although there is no FDA-approved treatment for this common mutation, they hope to find open clinical trials for their patients

"I order NGS, which is Next Gen Sequencing ... We can decide if the patient is eligible for the clinical trial or not."

- One oncologist tests for HER2 protein overexpression, since he prescribes trastuzumab (Herceptin) off-label for HER2-positive patients if reimbursement is not an issue

Biomarker-driven Treatment for NSQ-NSCLC Patients

Treatment for non-squamous, non-small cell lung cancer patients is multifaceted and evolving. In our voice study, participants told us they prescribe the following:

- gefitinib (Iressa), erlotinib (Tarceva), and afatinib (Gilotrif) for EGFR positive
- osimertinib (Tagrisso) for T790M EGFR positive
- crizotinib (Xalkori) and alectinib (Alecensa) for ALK positive
- crizotinib (Xalkori) for ROS1 positive
- dabrafenib (Tafinlar) and trametinib (Mekinst) for BRAF V600E positive
- chemotherapy plus or minus platinum or pembrolizumab plus pemetrexed and carboplatin for patients without mutations

It is interesting to note that although treatment was not the specific focus of this study, there was no mention of ceritinib (Zykadia) or brigatinib (Alunbrig) for the treatment of ALK-positive patients.

If results for ALK, EGFR, and ROS1 biomarkers are all negative, participants turn next to PD-L1 biomarker testing results for guidance. With high PD-L1 tumor expression, participants prescribe pembrolizumab (Keytruda) immunotherapy for newly diagnosed patients. If PD-L1 expression is low or zero, they commonly use chemotherapy plus platinum first-line and immunotherapy, either pembrolizumab (Keytruda) or atezolizumab (Tecentriq) given every three weeks and less often nivolumab (Opdivo) given every two weeks, for refractory patients. Only two participants said they use pembrolizumab (Keytruda) plus pemetrexed (Alimta) and carboplatin based upon the FDA's May 2017 approval for new patients regardless of whether or not their tumors express PD-L1.

Biomarker Testing for SQ-NSCLC Patients

Fewer biomarker tests are used to direct squamous cell (SQ) NSCLC treatment than NSQ. All survey participants order PD-L1 testing as described above. SQ patients who have never smoked or have mixed SQ and NSQ histology, however, also receive EGFR mutation tests.

"I don't necessarily order testing for squamous non-small cell lung cancer. If I do, I'll often restrict it to perhaps next generation sequencing alone, which can often find the other markers."

Testing variations implemented by a few participants for SQ-NSCLC include:

- Next generation sequencing as described above to give additional guidance on second-line treatment and identify patients that may be appropriate for current clinical trials involving new biomarkers
- ALK and ROS1 testing as a policy to perform the same mutational testing for all lung cancer patients, especially since they are relatively easy to order
- Sometimes excluding PD-L1 testing, since they say that first-line standard of treatment is platinum plus paclitaxel (Abraxane)

Biomarker-driven Treatment for SQ-NSCLC Patients

SQ-NSCLC patients receive the same treatment as NSQ-NSCLC patients who are positive to mutational tests or PD-L1 tests or neither.

"If there is no driver, then the decision is made based on PD-L1 status. High expressors of PD-L1 would receive presumably monotherapy first line. Low expressors or negative PD-L1 expression, if they have non-squamous cell histology, will be offered carboplatin, pemetrexed, and pembrolizumab. Squamous cell patients will be offered chemotherapy."

Challenges and Needed Improvements

As reported above, biomarker testing is fairly established although not fully standardized in NSCLC. Ordering and reporting are routine, and standard testing generally is reimbursed. So, what are the challenges and improvements needed in NSCLC biomarker testing?

Survey participants suggested several approaches:

Time related

While a few participants are satisfied with the turnaround time for testing, most are not. Patients sometimes must start treatment before testing results become available, or suffer disease progression with a decline in function.

An ever-expanding number of non-squamous biomarker tests makes it challenging to obtain a short turnaround time (e.g., < 2 weeks).

"Waiting for the test in a symptomatic patient is not always appropriate, so sometimes I'm forced to start chemotherapy while I'm waiting for biomarker testing."

Some, but not all, facilities have implemented reflexive testing (i.e., an automatic request to the pathologist to implement biomarker testing at the time of diagnosis), so that results are available during the initial appointment with the treating oncologist.

Correct testing

There may be a delay or sub-optimal treatment if community-based oncologists or pathologists do not order the correct tests.

For non-academic centers, finding a reliable, standardized testing vendor is important, so that treatment is optimized in patients.

Mutational and PD-L1 testing

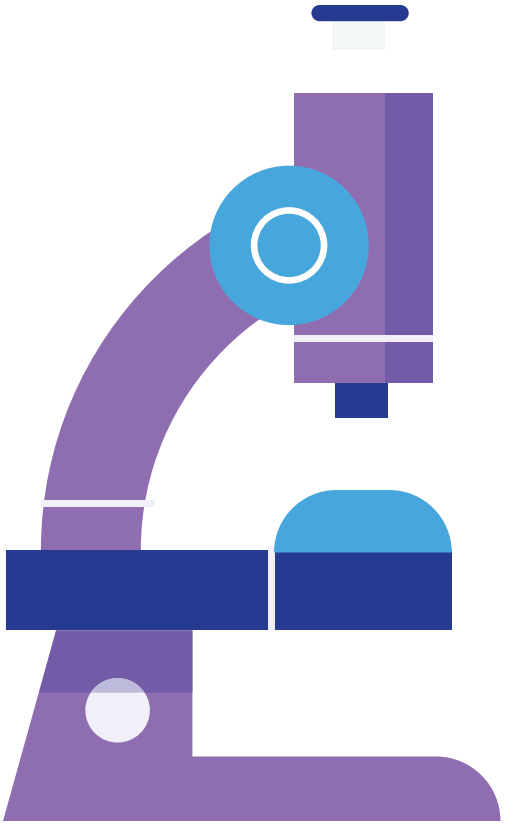
PD-L1 testing is poor at predicting the success of immunotherapies. Reported PD-L1 levels are dependent upon the assay, antibody, and platform that is used; observer variability between pathologists; the tissue sample that was taken; the time of the tissue sample; the position of the tissue sample; and other variables. Incorporation and understanding of other biomarkers or tumor mutation burdens as a factor in the immunotherapy treatment decision may prove helpful.

EGFR and T790M tests, which are based upon circulating DNA, can be done with plasma or tissue biopsy methods. Both are well established and becoming the standard of care. BRAF testing is reliable as well.

"PD-L1 expression, in contrast with the other more molecular biomarkers, is not as predictive of a good efficacy as we would like it to be."

Other mutational tests are good but less standardized. ALK testing, for example, can be accomplished via fluorescence in situ hybridization (FISH) or immunohistochemistry (IHC) methods. Participants don't know which is best and they are concerned with false-positive and false-negative results. An RNA-based platform to look for fusion events with ALK, ROS1, and other mutations may offer improvement.

"For the ALK we use the FISH test and we'd like to convert to the IHC test. I think there's concern about false positive as well as false negatives with the FISH test."



Tissue vs. liquid-based testing

Tissue for testing may be limited due to underlying lung conditions (e.g., COPD) or methodology (i.e., fine needle assay biopsy). Also, biopsy may not be feasible, especially in second- or later-line disease due to risk of pneumothorax in elderly patients, quality-of-life issues, or patient choice. Supplying enough tissue is difficult if different biomarker tests are done at different laboratories.

It would be helpful if testing for all biomarkers was plasma-based, which does not require tissue sampling. To date, however, most plasma-based tests have poor sensitivity, which requires improvement to gain acceptance.

Numerous genomic abnormalities associated with NSCLC are yet to be translated to the clinic. Many are identified through gene sequencing, which is expensive and not widely available.

Future Research

On occasion, a second round of qualitative research may help to answer questions that become apparent from the first iteration or questions that are extensions of the subject area. A second round of inVibe qualitative research could address the following topics, among others you might suggest:

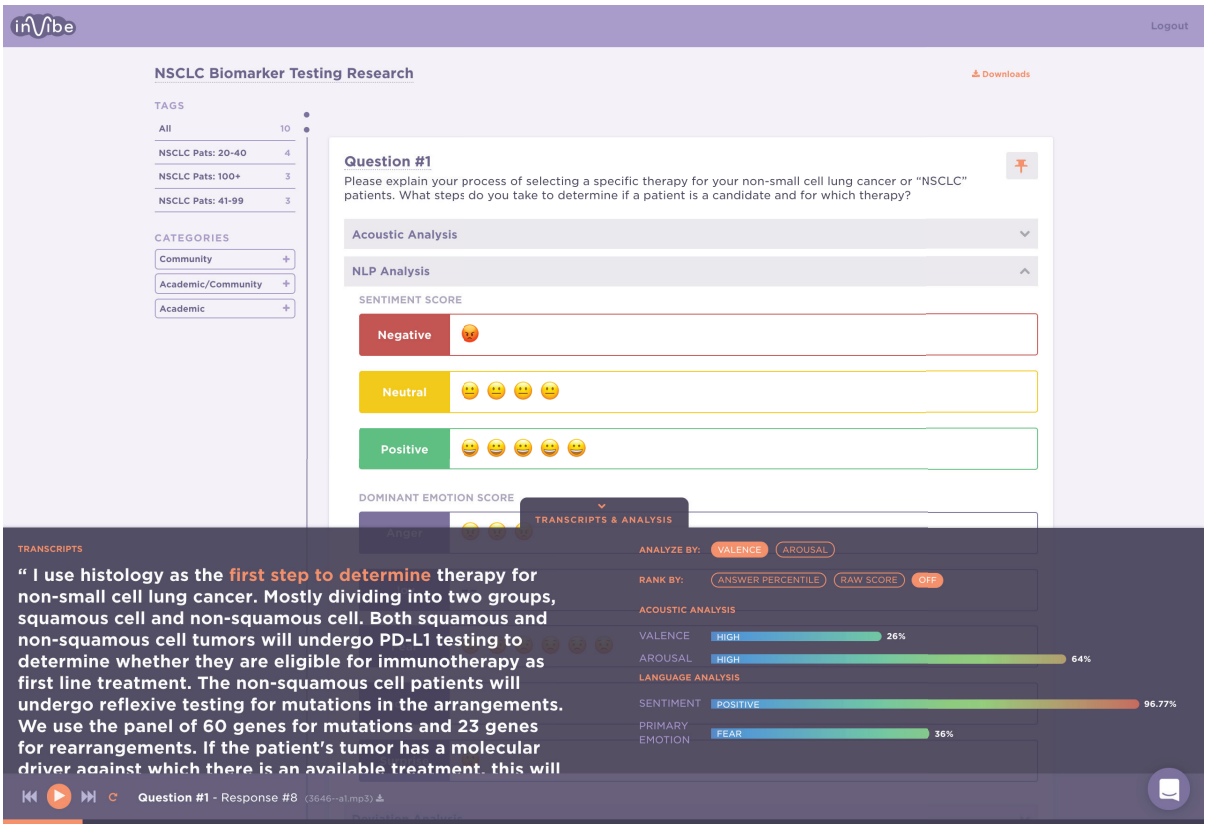
- Given current and future FDA approvals, how will oncologists use each of the immunotherapies?
- What is the future of next-generation sequencing, and what practical information does it provide? Will it become part of the standard of care?
- Why are individual oncologists specifying testing and treatment that differ somewhat from NCCN guidelines?

Such research could be accomplished easily and effectively by similar methodology with either selected first-round participants or with a new group of respondents.

"The greatest challenge is not only to develop drugs for the rare molecular-defined subtypes, but to have easier and more widely available testing panels that can be added to existing technology, rather than requiring the purchase of any machine."

Final Thoughts

We have shared a whitepaper summary of our findings, but what we actually deliver to our clients is even more informative, interactive, and actionable. Along with an easy-to-interpret Excel matrix of findings (transcripts of the respondents' voice recordings), we also provide a dashboard (see screen capture below), which allows clients to follow along with the audio responses from each participant as it provides language- and speech-based emotional analytics to help bring more color to each of the responses. Although our real-time emotion analytics overlay is still in early beta, the initial findings from thousands of minutes of analysis have yielded promising results. If you are interested in seeing the emotion analytics associated with this study, please contact us.



If you are interested in seeing how our quick-turn research methodologies can support your business research goals, please call or e-mail info@inVibe.co for an in-person or Web demonstration of inVibe's qualitative and quantitative research methodology with built-in emotion analytics.

inVibe — Benefits and Limitations: The Unbiased Perspective of an Outside Research Consultant

We asked a 30-year veteran of the market research industry to provide their candid feedback about the inVibe platform based on their experience utilizing it for this research project. The following is a high level overview of their observations.

Most quick-turnaround qualitative research methodologies provide only low-quality, superficial analysis. Consequently, you receive little, if any, understanding of the underlying emotional context of the findings. The opposite is true for inVibe's quick-turnaround digital voice-response methodology, which combines in-depth audio responses with sophisticated emotional analytics.

Benefits

- Platform is designed for any therapeutic area and audience type
- Remarkably in-depth, robust responses that convey confidence in findings
- Extensive, reliable findings obtained very quickly (under 48 hours) and inexpensively (a fraction of the cost of live interviews or a focus group)
- Responses are complementary; one participant's responses build upon the responses of others
- Most respondents provide in-depth answers; some provide more top-line summarized responses. It is helpful to have this balance, as it allows findings to be put in context
- The succinct nature of the questions keeps the responses focused and clear
- Structured delivery of typically "unstructured" data allows for powerful analytics
- Ability to deliver same-day mixed methods studies (this study focused exclusively on inVibe's voice-response methodology)

Limitations

- Cannot ask follow-up questions; for example, to further explore a surprising response
  - However, inVibe has the ability to recontact the same respondents to ask additional questions through a follow-up voice-response survey or a phone consult (think of it as an audition before spending 45-60 minutes on the phone with someone)
- Cannot clarify questions in real-time if respondent misunderstood
- Cannot easily test one physician's thinking vs. another's, although follow-up conference calls with multiple physicians can be arranged

Conclusion

inVibe's high-speed, automated voice-response research platform can be an extremely effective solution for conducting high-quality, in-depth research in complex subject areas with difficult-to-reach stakeholders, in just a few days.

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