NEED FOR CONSISTENT LANGUAGE AROUND BIOMARKER TESTING IN THE DIAGNOSIS AND TREATMENT OF LUNG CANCER

A white paper by LUNGevity Foundation

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ACKNOWLEDGMENTS

The authors are deeply indebted to the lung cancer survivor community for taking the time to share their perspectives on this topic.

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INTRODUCTION

Lung cancer treatment options have expanded significantly in the past decade, beginning with the increased understanding of specific gene mutations that drive or enable growth of the cancer. These mutations include ALK, EGFR, BRAF, ROS1, and others. The testing to identify these mutations is the first step in determining if a patient can benefit from the targeted therapies currently approved or in development in clinical trials.

In addition to these targeted therapies, in 2015 the first immunotherapies were approved for lung cancer, with many more in clinical development. Efforts to identify the patient population that is most likely to respond have focused on using PD-1 and PD-L1 as biomarkers. Because often only limited amounts of tumor tissue are available for testing, the decision was made to include testing for all biomarkers in this research.

Despite the enthusiasm around the potential of using targeted therapy in the treatment of lung cancer, evidence suggests that not all eligible patients are benefiting from targeted therapy, due in part to lack of tumor testing. [Lynch et al, Genetics in Medicine, 2013] Recognizing the complexity of the issue, as a first step we sought to understand how information around this testing is being communicated through public sources and to what end. The ultimate goal is to develop consensus on consistent terminology to describe the testing used to help choose lung cancer treatments for individual patients, as it is used in patient communications.

To help assess whether inconsistent communications could be a contributor to the suboptimal rates of testing for biomarkers related to lung cancer treatment, LUNGevity commissioned an audit. The focus was the online communications of organizations that were actively communicating on the topic of testing. In addition, people living with lung cancer were interviewed. The audit established that there is tremendous diversity within and across different stakeholders in testing and lung cancer patient care, as well as resultant confusion within the patient/survivor community as to whether they were tested at all or had “the right test” and how to effectively advocate for their own care.

The resulting report was shared with advocacy organizations (lung cancer-specific and general, as well as breast cancer) and pharmaceutical and biotech companies with relevant products on the market or in final development. Following initial outreach, a meeting of these stakeholders was held in September 2015 in Denver, CO, to come to some agreement on terminology.

This white paper reviews findings and recommendations of the audit, as well as the discussion by the subset of stakeholders who met in person.

COMMUNICATIONS AUDIT APPROACH

In early 2015 Edge Research was tasked with researching and analyzing how a cross section of organizations is talking about molecular testing and its use in the diagnosis and treatment of lung cancer. The primary goals were to:

- Identify and inventory the various terms being used to reference molecular tumor testing;
- Identify the audiences organizations are addressing, i.e., Who is talking to patients and who is talking to the medical community?;
- Catalog the message and calls to action, to identify any differences in the way the many organizations with a stake and interest in molecular testing and/or targeted therapy are communicating; and
- Finally, identify the implications of these differences for patient and medical community understanding, and application of, molecular testing for lung cancer.

The 28 organizations in the audit included general cancer organizations, lung cancer advocacy groups, government and general health sites, pharmaceutical and biotech companies (including patient-focused microsites), and testing companies. In addition, in-depth interviews were conducted with 15 lung cancer patients to gain insights into their understanding and experiences with molecular testing and related procedures and therapies.

Terms Inventoried

- Molecular testing
- Molecular diagnostics
- Biomarker testing
- Molecular pathways
- Personalized medicine
- Genetic testing and/or genetic diagnostic
- Mutation testing/mutation profiling
- Targeted therapies

MAJOR AUDIT FINDINGS

Over 9,000 (9,379) mentions of eight different terms to reference molecular testing and targeted therapy were inventoried, and the use of numerous other terms to reference this type of testing was uncovered. Search terms used by sector, as well as additional terms discovered, are included in Appendix 1.

The findings highlight important considerations for the lung cancer and general cancer communities.

1. Content on cancer testing is dominated by the term “genetic testing.” The use of this term in reference to testing for genetic mutations or the biomarkers for targeted therapies is confusing. Patients tell us that genetic testing is looking for hereditary indicators. When they hear it, they wonder if they could have inherited their lung

cancer. Patients caution that language and terms that distinguish molecular testing from genetic testing for hereditary cancer is important.

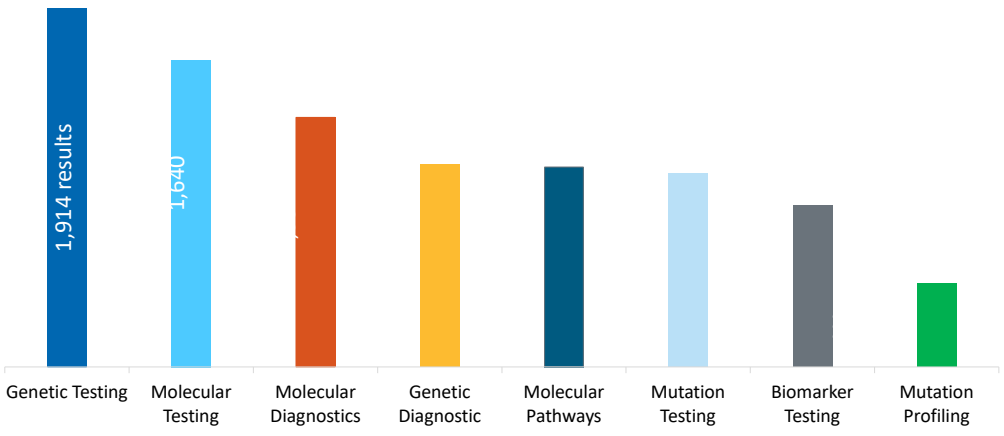
2. By far the greatest amount of content on molecular testing that is directed to patients comes from lung cancer advocacy groups. While many terms are used to refer to molecular testing, there is an effort to relate terms to one another and to define them as they are used. The patient advocacy groups tend to focus on the terms "molecular testing," "testing for genetic mutations," and "testing for biomarkers." Among patients, the organic phrase seems to be "get your tumor tested."

3. Of particular concern is that as the audit moved beyond patient advocacy communications to the terms used by the industries developing the tests and the targeted therapies, there is very little consistency in terminology. Even more terms are introduced, and terms are used with and without clear definitions. Sources use different terms to speak to different audiences–one set for the medical community and a different set for the patient. This lack of consistency has clear implications: If pharmaceutical and testing companies are talking to doctors about "genomic profiling" but patients are hearing about "molecular testing" from support groups, it sets the stage for unclear communication in the critical doctor-patient relationship.

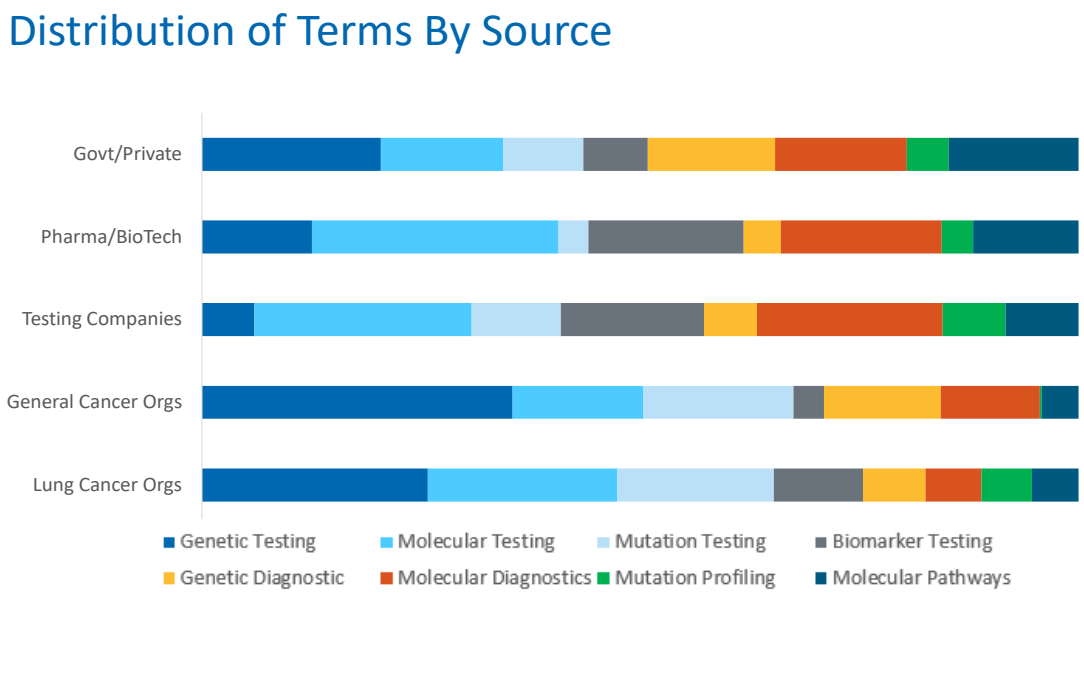
Key Findings

1. Patient confusion created by use of term "genetic testing"
2. Overall, there are too many terms, inconsistently used
3. Divisions between terms used to talk to health care practitioners and those used to talk to patients setting up a communications gap
4. No clear or consistent call to action for testing – who, when and why
5. Lack of information in the clinical setting means learning about and understanding of testing is often left to word-of-mouth

Many Terms, None That Dominate



Graph: website search results



4. There is a significant range in how molecular testing is framed, what it means for the patient, and the calls to action around it. Lung cancer patient advocacy groups tended to have a more unified voice around a strong call to action to patients to push for this type of testing without condition. In other words, they often advocated testing at the outset of diagnosis or before standard care had been shown ineffective. The more general cancer groups are more likely to say “Ask your doctor.” On the testing and pharma industry side, there is also a call to establish molecular testing as a new standard of care. Some also advocate to establish tissue sampling protocols that allow for the expansion of the number and type of mutations for which the tumor can be tested. Lung cancer patients who know about molecular testing tell us they strongly urge all the patients they meet to get tested.

5. When it comes to what the testing is looking for, there is heavy emphasis on mutations linked to existing FDA-approved targeted therapies. The most commonly cited are the EGFR and ALK mutations and related inhibitor drugs. While these are the tests covered by insurance, a risk here is that less informed doctors may not order tests for other mutations being studied in clinical trials.

6. Further, patients tell us that doctors do not always discuss clinical trials with them. This raises important questions about when and why patients should be tested: solely to be matched to treatments that are FDA-approved, or to find all possible options for treatment when the current standard of care is not working?

7. Despite the volume of information about targeted therapies and the use of molecular testing to identify patient candidates, this information is not necessarily reaching patients. In fact, learning about this critical step in diagnosis and treatment can easily be hit or miss. Information is not easy to find at many of the treatment sites. and patients tell us they hear about it through word-of-mouth.

8. Patients flag that there is little information about mutation testing available or given to them in the clinical setting–the very place where they get most of their information about their cancer and their treatment. Explanations given to patients about testing by members of their medical team vary widely.

Finally, new terms were emerging during the research. In the time it took to conduct the audit, some sources shifted language. Most apparent is a shift from "personalized medicine" to "precision medicine" and the emergence of "comprehensive genomic profiling." Notably, discussions about testing for biomarkers to estimate immune checkpoint efficacy increased, specifically PD-1 and PD-L1.

STAKEHOLDER DISCUSSION HIGHLIGHTS

Twenty-one representatives of 11 different advocacy and pharmaceutical/biotech companies attended a meeting, which coincided with the World Congress on Lung Cancer, to come to some agreement on terminology. A complete list of attendees can be found in Appendix 2.

While each organization that communicates around lung cancer and testing has worked internally to select logical terminology for testing, there has been no discussion across organizations. This is typical of evolving fields. This meeting on September 7th in Denver, CO, provided the opportunity to discuss the different options and logic guiding a choice for consistent, broad implementation.

All agreed on the importance of a more unified voice and message to help the medical community and patients, at a minimum, achieve common understanding about the use and potential impact of molecular testing and targeted therapies.

Biomarker testing was the strong favorite, as it integrates the concept of "biology" of the tumor and is more inclusive than "molecular testing," now that PD-L1 testing is also a consideration. **Molecular testing** was favored by a smaller subset, although they also agreed to use of biomarker testing. All of the other terms that were audited or "discovered" during the audit were dismissed for various reasons.

A suggested definition was also developed: Biomarker testing uses samples of a person's cancer. The samples are taken by biopsy or surgery. A biomarker test looks at the cancer's unique biological makeup. This information can be used to help choose treatments for a person's specific lung cancer.

Other key points of agreement included:

The most prevalent term also creates greatest confusion: "Genetic testing" carries implication of a heritable disease to the majority of lay people. The word "genetic" was originally used for patients who have rare genetic disorders and for the BRCA gene related to increased risk for breast cancer.

- All agreed that "genetic testing" should NOT be used in the context of lung cancer biomarker or molecular testing. Industry participants stated willingness to change this language in their pipeline descriptions and labels.

The goal of increasing rates of testing to at least guideline levels is to empower patients and help them make the best treatment decisions for their specific lung cancer. All attendees pointed out that patients involved with advocacy groups are often more "educated and informed," so that the patient feedback from the audit may reflect better knowledge than in the general community and the situation is likely even worse than assessed. Also, it was noted that rates of testing in community versus large academic institutional settings differ. The big challenge is to reach and make an impact on the 85% of patients treated in a community setting, where testing is less likely to take place, based on other research studies.

As the number and type of tests entering the lung cancer space increases, clearly indicating goals of testing is key. Both advocacy and industry stakeholders have used the phrase "Get your tumor tested." However, we have to be clear about "what" we are looking for when advocating testing. It could be the type of lung cancer by histology, druggable mutations, PD-L1 status, or something else down the road.

Also, the difference between "understand your tumor" versus "understand your tumor type" needs to be clear to patients. Attendees felt that the word "testing" was more meaningful from a patient perspective since it involved an "actionable activity."

Clinicians are not careful or consistent in their communications, as the various terms in use are largely interchangeable to them.

It is important to come up with definitions of each of these words and explain "why" they are being used interchangeably. Another point raised was: how do we deal with definitions for papers and websites? It is easy to explain differences during an in-person patient interaction but not possible in other forms of communication. Whatever terminology we decide on should be broad enough to encompass newer tests such as those for PD-L1.

Pathology reports provided to clinicians should include information that can clearly be shared with patients. The report should be broad–starting from histology and then segue into biomarker analysis.

In addition, attendees discussed whether targeted therapy, immunotherapy, and angiogenesis inhibitors should all be called "targeted therapy," or whether they should be described as three separate treatment categories. **The consensus was to treat them as three different treatment**

options, with industry/medical representatives particularly clear on this topic. The following includes the reasoning:

- Mode of action of immunotherapy—for ex., checkpoint inhibitors—is very different from that of targeted therapy drugs
    - Targeted therapy usually implies hitting the "driver" in lung cancer. Immunotherapy does not function in this way
- VEGF inhibitors have different approach as well, and should be called angiogenesis inhibitors to capture that function
- Precedent: Immunotherapy is separate from targeted therapy in the melanoma space
- Noted: We should delineate therapies that function in different ways, and we should educate patients about the differences so they know what to ask their doctors

CONCLUSIONS

Scientific understanding and treatment options around lung cancer have increased tremendously in a relatively short period of time. Those advances are largely driven by research at academic medical centers, and then need to be implemented in the community setting, where 85% of patients are treated.

In addition, most cases of lung cancer are diagnosed at a late stage, and the one-year survival rate is still less than 50%, necessitating quick selection of the most effective therapeutic choices. Patients and caregivers across cancer types report being overwhelmed during the first year after a diagnosis. Therefore, ensuring as clear as possible an understanding of therapeutic options and the information required to access those options is vital. As the science has evolved from the research institutions to clinical use, the language used for treatment options and related tests has to support empowered understanding by the end user—the patient.

To that end, consistent use of the term “biomarker testing” to encompass both targetable molecular mutations and PD-L1 protein expression is recommended for all stakeholders, allowing for additional elaboration on specific tests. A follow-up paper will specifically explore and delineate how those specific tests under the umbrella of biomarker testing are described.

APPENDIX

Appendix 1

Summary of Terms

Search Terms in Use by Sector

Searched Terms	Pharma/Biotech	Testing	Gov't/Private	Cancer Orgs	Lung Cancer Orgs
Genetic Testing	77	65	1082	295	395
Molecular Testing	173	270	742	124	331
Mutation Testing	21	111	485	143	274
Biomarker Testing	109	172	390	29	156
Genetic Diagnostic	26	66	770	111	109
Molecular Diagnostics	113	231	798	94	98
Mutation Profiling	22	78	254	2	88
Molecular Pathways	74	91	787	35	88

Additional Terms Observed

Pharma/BioTech	Testing	Gov't/Private	Lung Cancer Orgs
Biomarker panel			
Companion diagnostic	Companion diagnostics		
	Comprehensive genomic profiling		
		Genomic profiling	Genomic testing
		Individualized medicine	
Molecular companion diagnostic tests			
Molecular profiling	Molecular profiling		
Personalized medicine		Precision medicine	Precision medicine
		Tumor gene panel testing	
		Tumor marker tests	

Appendix 2

Testing Terminology Meeting Attendees
Denver, CO
Monday, September 7, 2015

Organization	Name	Title
Advocacy		
Addario Lung Cancer Foundation	Scott Santarella	President & CEO
Cancer Support Community	Allison Harvey	Senior Director, Education & Outreach
Free to Breathe	Sara Ifert	Marketing and Communications Director
Lung Cancer Foundation of America	Jim Baranski	Executive Director
Lung Cancer Foundation of America	Kim Norris	Co-Founder/President
Lung Cancer Foundation of America	David Sturges	Co-Founder/Treasurer
LUNGevity Foundation	Andrea Ferris	President
LUNGevity Foundation	Susan Mantel	Senior Vice President, Research & Education
LUNGevity Foundation	Upal Basu Roy	Director, Science Communications & Programs
Industry		
AstraZeneca	Lise Hall	Portfolio Marketing, Lung Cancer
AstraZeneca	Mike Petrucelli	Senior Manager, Alliance and Advocacy, Specialty Care
Boehringer Ingelheim	Lara Crissey	Associate Director, Advocacy
Boehringer Ingelheim	William Tunno	Director, Global Patient Advocacy & Professional Relations
Genentech	Nicole Fitzpatrick	Medical Science Director
Genentech	Steve Hack	Associate Group Medical Director
Merck	Jeff Emch	Biomarker and CDx Lead
Merck	Courtney Ronaldo	Associate Director, Global Communications

Merck	Jarrett Roth	Associate Director, US Oncology Marketing
Novartis	Elyse Caplan	Director, Patient Advocacy Public Affairs and Communications
Novartis	Alexey Salamakha	Manager, Patient Advocacy
Pfizer	Bob Donovan	Director, Strategic Alliances