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ORIGINAL ARTICLE

The International Association for the Study of Lung Cancer Global Survey on Molecular Testing in Lung Cancer

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ABSTRACT

Introduction: Access to targeted therapies for lung cancer depends on the accurate identification of patients' biomarkers through molecular testing. The International Association for the Study of Lung Cancer (IASLC) conducted an international survey to evaluate perceptions on current practice and barriers to implementation of molecular testing.

Methods: We distributed the survey to IASLC members and other health care professionals around the world. The survey included a seven-question introduction for all respondents, who then answered according to one of three tracks: (1) requesting tests and treating patients, (2) performing and interpreting assays, or (3) tissue acquisition. Barriers to implementing molecular testing were provided in free-response fields. The chi-square test was used for regional comparisons.

Results: A total of 2537 respondents from 102 countries participated. Most respondents who test and treat patients believe that less than 50% of patients with lung cancer in their country receive molecular testing, but reported higher rates within their own practice. Although many results varied by region, the five most frequent barriers cited in all regions were cost, quality and standards, access, awareness, and turnaround time. Many respondents expressed dissatisfaction with the current state of molecular testing for lung cancer, including 41% of those performing and interpreting assays. Issues identified included trouble understanding results (37%) and the quality of the samples (23% reported >10% rejection rate). Despite concerns regarding the quality of testing, 47% in the performing and interpreting track stated there is no policy or strategy to improve quality in their country. In addition, 33% of respondents who request tests and treat patients were unaware of the most recent College of American Pathologists, IASLC, and Association for Molecular Pathology guidelines for molecular testing.

Conclusions: Adoption of molecular testing for lung cancer is relatively low across the world. Barriers include cost, access, quality, turnaround time, and lack of awareness.

Keywords: Molecular testing; Targeted therapy; EGFR; ALK

Introduction

Worldwide, more than 2 million people are diagnosed with lung cancer annually, of which most have NSCLC.[1] As the leading cause of cancer death globally, lung cancer has 5-year survival rates less than 20% and consists predominantly of advanced-stage adenocarcinoma and squamous cell carcinoma.[1,2] Development of novel targeted therapies for patients with advanced-stage NSCLC with specific genetic alterations ("driver mutations") has dramatically improved response rate and survival compared with previously available treatments.[3–5]

There are highly effective targeted therapies approved in many parts of the world for patients with *EGFR* activating mutations, *ALK* fusions, and *ROS1* fusions.[3–13] In addition, targeted therapies are available through clinical trials or in certain parts of the world as the standard of care for patients with $BRAF^{V600E}$, *HER2*, $KRAS^{G12C}$, *MET* exon 14 skipping mutations, *NTRK*, or *RET* fusions.[14–16] The risk of death for patients with NSCLC is substantially reduced when a gene alteration is identified and the available targeted therapy is administered.[3,5,6,11,17]

Patient selection for molecularly targeted therapies depends on accurate and timely identification of actionable genomic alterations. The most frequently identified actionable alterations are *EGFR* mutations (exon 21 *L858R* mutation and exon 19 deletions) and *ALK* rearrangements, with prevalence varying by region.[18] A mutation in *KRAS* is the most frequent alteration overall, with promising target therapies in early clinical trials for patients with the $KRAS^{G12C}$ mutation.[16] These alterations can be detected in tumor samples used for lung cancer diagnosis (cytology, biopsies, or surgical resections). Detection by blood cell-free DNA (circulating tumor DNA) or immunohistochemical tests are also possible for some alterations. Clinicians integral to this process include those who order the test and treat the patients (medical oncologists), those who acquire the tissue (surgeons, pulmonologists, interventional radiologists), and those who perform and interpret the results (pathologists).

Evidence-based standards for the selection of patients with NSCLC for molecular testing were established

by the College of American Pathologists (CAP), International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) in 2013.[19] These guidelines recommended testing of *EGFR* and *ALK* in all patients with NSCLC with advanced-stage adenocarcinoma, regardless of sex, race, smoking history, or other demographic factors. Consensus statements followed from the European Society for Medical Oncology, the Spanish Societies of Medical Oncology and Pathology, and others.[20,21] The CAP, IASLC, and AMP guidelines were revised in 2018, and although the recommendations for *EGFR* and *ALK* were reaffirmed, additional recommendations included *ROS1* testing in patients with NSCLC with an adenocarcinoma component and *HER2, MET, BRAF, KRAS*, and *RET* testing in laboratories performing next-generation sequencing.[22]

Despite the reported benefit of targeted therapy and consensus recommendations, there are still many eligible patients who are not treated with available targeted agents.[23–25] Therefore, it is critical to characterize patterns of local practices and identify barriers to testing throughout the world, to define and implement specific strategies to increase the use of targeted therapies. With this objective in mind, the IASLC conducted an international survey to evaluate perceptions on current practice and barriers to implementation of molecular testing in an effort to inform future initiatives to address these issues.

Materials and Methods

We distributed a survey on the prevalence and practices of molecular testing in lung cancer to IASLC members and nonmembers engaged in the care of patients with lung cancer, including physicians, nurses, advanced practice providers, pharmacists, and other allied health professionals around the world through an email to those who, at some point, provided an email address to IASLC or through other methods, as outlined below. The initial distribution of the survey started on May 24, 2018. The survey was conducted on a web-based platform with options for personalized or anonymous links. Individual links were sent to 34,621 contacts from the IASLC email database. An anonymous link to the online survey was made available worldwide through multiple channels, including email, website posting, scientific journal advertisements (including Chest, Clinical Lung Cancer, Lung Cancer, Human Pathology, Journal of Molecular Diagnostics, and Lancet Oncology), Salesforce Marketing Cloud, and an advertised quick response code. Potential or partial respondents received follow-up reminder emails. The survey remained open until December 31, 2018.

The survey included a seven-question introduction for all respondents and then allowed respondents to choose one of three tracks. The tracks included 34 questions for those requesting tests and treating patients (e.g., medical oncologists), 47 questions for those who peform and interpret assays (pathologists), and 26 questions for those who acquire tissue samples (surgeons, pulmonologists, radiologists) (Supplementary Material). Respondents also provided feedback on the barriers to implementing or offering molecular testing in free-response fields. The survey was compiled and administered using Qualtrics software. Surveys were available in seven languages including English, French, Japanese, Chinese, Arabic, Portuguese, and Spanish. A professional service translated all responses into English before analysis.

Respondents' countries were grouped into five geographic regions on the basis of IASLC criteria: Asia, Europe, Latin America, the United States and Canada, and the rest of the world (which includes parts of the Middle East, Africa, and the Pacific Islands). The economic status of each country was categorized as developing or developed on the basis of World Bank Atlas data on gross national income per capita (World Development Indicators, The World Bank). Developing countries were defined as having median incomes below 12,275 (in currency of U.S. dollars) according to the World Bank definition of gross national income per capita (formerly gross national product per capita). However, IASLC has grouped a few countries that technically fell into high income with other similarly situated countries, particularly in Latin America. Details of the regional classifications, economic classifications, and responses per country are presented in the Supplementary Material.

Statistical Analysis

Quantitative results are presented as frequency (percent) with the respondent as the unit of analysis. Chi-square test was used for regional comparisons. All quantitative analyses were conducted in SAS version 9.4. The p values less than 0.05 were considered statistically significant.

NVivo 12 Plus was used to analyze the free-response data regarding barriers to molecular testing. A word frequency query was performed on the pooled data set for the top 50 most frequent words used using stemmed words grouping. The analysis was repeated within each regional and economic stratum.

Results

We analyzed 2537 responses from 102 countries (Supplementary Fig. 1). After grouping countries into global regions, we found that 52% of responses were

Table 1. Frequency of Molecular Testing by Region for Each Survey Track

Question	Total	Asia	Europe	Latin America	The United States and Canada	Rest of World	*p* Value
Requesting and treating track	**N = 1683**	**N = 1023**	**N = 257**	**N = 170**	**N = 148**	**N = 85**	
In your opinion what percent of patients with lung cancer are molecularly tested in your country?	n = 1446	n = 876	n = 229	n = 152	n = 118	n = 71	
<50%	885 (61)	560 (64)	98 (43)	112 (74)	60 (51)	55 (77)	< 0.0001
≥50%	561 (39)	316 (36)	131 (57)	40 (26)	58 (49)	16 (23)	
In your opinion what percent of patients with lung cancer are molecularly tested in your clinic?	n = 1444	n = 874	n = 230	n = 153	n = 116	n = 71	
<50%	520 (36)	381 (44)	49 (21)	38 (25)	11 (10)	41 (56)	< 0.0001
≥50%	924 (64)	493 (56)	181 (79)	115 (75)	105 (91)	30 (42)	
Do you request molecular testing on liquid biopsies from patients with lung cancer?	n = 1516	n = 923	n = 237	n = 159	n = 123	n = 74	
No	193 (13)	75 (8)	23 (10)	42 (26)	19 (15)	34 (46)	< 0.0001
Yes	1323 (87)	848 (92)	214 (90)	117 (74)	104 (85)	40 (54)	
Performing and interpreting assays track	**N = 316**	**N = 96**	**N = 114**	**N = 33**	**N = 55**	**N = 18**	
Does your laboratory offer molecular testing on liquid biopsies?	n = 200	n = 61	n = 86	n = 20	n = 23	n = 10	
No	62 (31)	18 (30)	17 (20)	8 (40)	12 (52)	7 (70)	0.0013
Yes	138 (69)	43 (70)	69 (80)	12 (60)	11 (48)	3 (30)	
What percentage of molecular tests are performed on liquid biopsies?	n = 128	n = 42	n = 61	n = 12	n = 10	n = 3	
≤10%	81 (63)	25 (60)	42 (69)	7 (58)	5 (50)	2 (67)	0.7257
>10%	47 (37)	17 (40)	19 (31)	5 (42)	5 (50)	1 (33)	
Tissue acquisition track	**N = 334**	**N = 123**	**N = 74**	**N = 52**	**N = 50**	**N = 35**	
In your opinion, which percentage of patients with lung cancer are molecularly tested for lung cancer in your country?	n = 242	n = 86	n = 54	n = 41	n = 39	n = 22	
<50%	162 (67)	46 (53)	41 (76)	36 (88)	25 (64)	14 (64)	0.0017
≥50%	80 (33)	40 (47)	13 (24)	5 (12)	14 (36)	8 (36)	
In your opinion, which percentage of patients with lung cancer are molecularly tested for lung cancer in your institution?	n = 243	n = 88	n = 54	n = 41	n = 39	n = 21	
<50%	100 (41)	27 (31)	23 (43)	23 (56)	13 (33)	14 (67)	0.0060
≥50%	143 (59)	61 (69)	31 (57)	18 (44)	26 (67)	7 (33)	

from Asia, 19% from Europe, 11% from Latin America, 11% from the United States and Canada, and 7% from the rest of the world. Developed countries accounted for 44% of respondents and developing countries for 56%.

Respondents varied by medical specialty, with 45% medical oncologists, 12% pulmonologists, 12% thoracic surgeons, 9% pathologists, and 22% nonclinical scientists or others. The respondents chose the most appropriate survey track, with 66% choosing requesting and treating, 12% performing and interpreting assays, and 13% tissue specimen acquisition track, whereas 8% were not involved with molecular testing. The respondents' types of institutions, allowing for multiple selections, included the following: 43% academic, 47% government, 21% private, and 5% other. Overall, the IASLC membership status of 43% of respondents was unknown, whereas 19% were active members, 8% were lapsed members, and 30% were nonmembers.

Frequency of Molecular Testing

We evaluated the respondents' perceptions of the frequency of molecular testing for patients with lung cancer. Most respondents (61%) who request tests and treat the patients believed that less than half of the patients in their country currently receive molecular testing (Table 1 and Fig. 1*A*). These perceptions varied

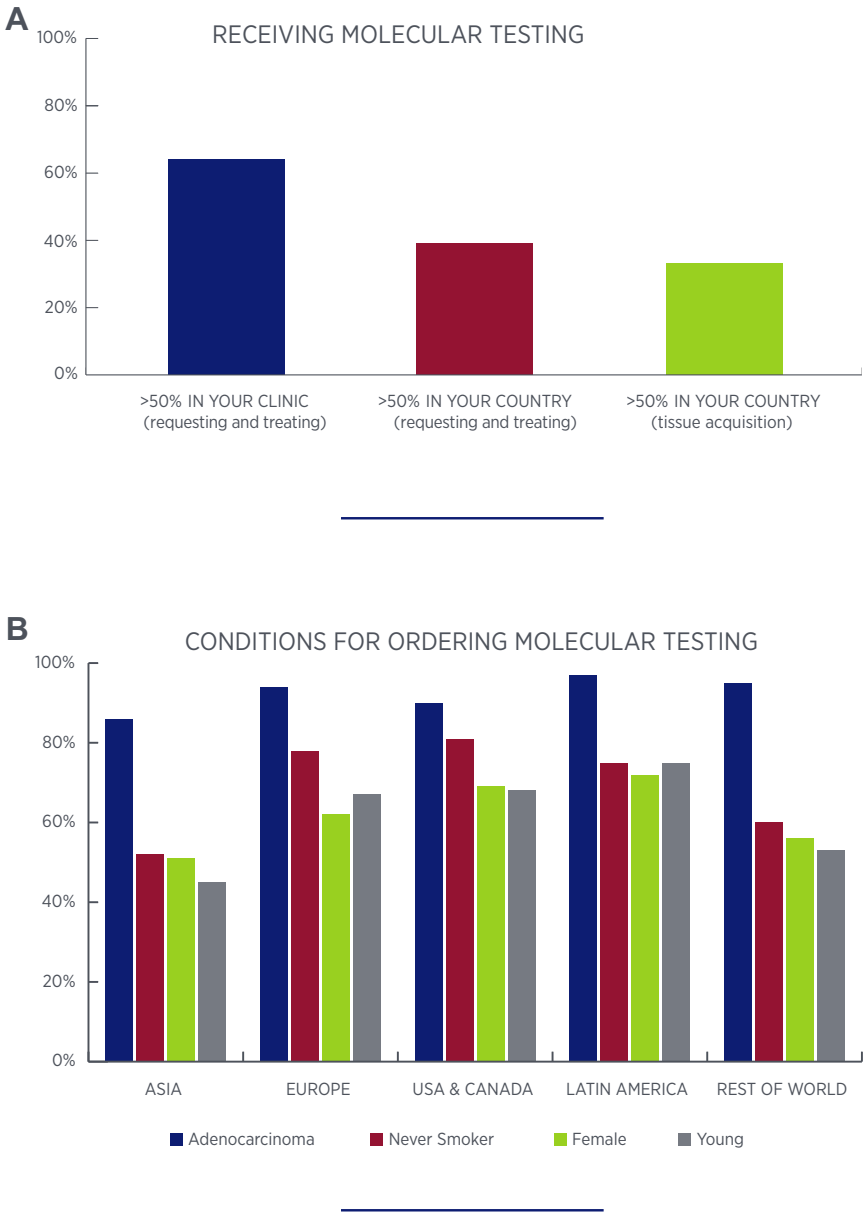

Figure 1. *(A)* The percentage of respondents in each track who reported that greater than 50% of patients with lung cancer undergo molecular testing in their country. *(B)* The conditions in which clinicians that request tests and treat patients reported ordering molecular testing.

significantly by region, with most responses indicating lower rates of molecular testing in Latin America and the rest of the world than other regions ($p < 0.0001$, Table 1). However, when respondents were asked about their own clinic, 64% reported that more than half of patients in their clinic receive molecular testing. This also varied significantly by region (Table 1, $p < 0.0001$). Similarly, in respondents from the tissue acquisition track, 67% perceived that less than half of the patients in their country receive molecular testing, with comparable regional variation ($p = 0.0017$, Table 1). However, 59% reported that more than half of patients in their institution receive molecular testing.

We also asked which specific molecular tests were typically ordered when requesting physicians ordered molecular tests. We found that, overall, 99% of respondents in the requesting and treating track ordered *EGFR*, 95% *ALK*, 79% *ROS1*, and less than 50% ordered other tests (Table 2). However, although *EGFR, ALK,* and *ROS1* were the top three tests ordered across all regions, all were less frequently ordered in the rest of the world (EGFR $p = 0.0002$, ALK $p = 0.0264$, ROS1 $p < 0.0001$). More than half (53%) of the requesting and treating track respondents order multiplex assays, with the frequency of such testing being less in Latin America and the rest of the world ($p < 0.0001$, Table 2).

Table 2. Types of Molecular Tests Offered by Region for Both the Requesting and Treating and the Performing and Interpreting Assays Tracks

Question	Total	Asia	Europe	Latin America	The United States/ Canada	Rest of World	*p* Value
Requesting and treating track	**N = 1683**	**N = 1023**	**N = 257**	**N = 170**	**N = 148**	**N = 85**	
Which molecular tests do you usually order for your patients with lung cancer? Please select all that apply.	n = 1508	n = 922	n = 234	n = 158	n = 121	n = 73	
EGFR mutation	1494 (99)	919 (99.7)	231 (99)	158 (100)	116 (96)	70 (96)	0.0002
ALK rearrangement	1434 (95)	879 (95)	226 (97)	152 (96)	113 (93)	64 (88)	0.0264
ROS1 rearrangement	1192 (79)	762 (83)	192 (82)	98 (62)	98 (81)	42 (58)	< 0.0001
BRAF mutation	731 (48)	434 (47)	127 (54)	58 (37)	88 (73)	24 (33)	< 0.0001
KRAS mutation	700 (46)	451 (49)	116 (50)	39 (25)	74 (61)	20 (27)	< 0.0001
MET amplification	580 (38)	435 (47)	63 (27)	17 (11)	59 (49)	6 (8)	< 0.0001
HER2 mutation	542 (36)	369 (40)	78 (33)	26 (16)	60 (50)	9 (12)	< 0.0001
RET rearrangement	500 (33)	360 (39)	65 (28)	9 (6)	62 (51)	4 (5)	< 0.0001
MET exon 14 skipping	434 (29)	299 (32)	66 (28)	11 (7)	54 (45)	4 (5)	< 0.0001
Other	168 (11)	44 (5)	47 (20)	30 (19)	39 (32)	8 (11)	< 0.0001
Do you request PD-L1 expression status on patients with lung cancer?	n = 1516	n = 925	n = 237	n = 158	n = 122	n = 74	
Yes	1274 (84)	736 (80)	226 (95)	142 (90)	121 (99)	49 (66)	< 0.0001
No	242 (16)	189 (20)	11 (5)	16 (10)	1 (1)	25 (34)	
Is lung cancer molecular testing done with single or multiplex assays?	n = 1506	n = 919	n = 235	n = 158	n = 121	n = 73	
Multiplex	801 (53)	505 (55)	129 (55)	57 (36)	86 (71)	24 (33)	< 0.0001
Single	473 (31)	303 (33)	66 (28)	65 (41)	18 (15)	21 (29)	
Unknown	232 (15)	111 (12)	40 (17)	36 (23)	17 (14)	28 (38)	
Performing and interpreting assays track	**N = 316**	**N = 96**	**N = 114**	**N = 33**	**N = 55**	**N = 18**	
Which molecular tests does your laboratory perform for patients with lung cancer? Please check all that apply:	n = 270	n = 80	n = 105	n = 28	n = 39	n = 18	
EGFR mutation	254 (94)	77 (96)	97 (92)	25 (89)	38 (97)	17 (94)	0.5034
ALK rearrangement	223 (83)	69 (86)	88 (84)	22 (79)	31 (79)	13 (72)	0.5961
KRAS mutation	185 (69)	49 (61)	79 (75)	17 (61)	31 (79)	9 (50)	0.0407
BRAF mutation	184 (68)	45 (56)	78 (74)	16 (57)	34 (87)	11 (61)	0.0037
ROS1 rearrangement	172 (64)	48 (60)	76 (72)	15 (54)	28 (72)	5 (28)	0.0027
HER2 mutation	151 (56)	37 (46)	67 (64)	11 (39)	26 (67)	10 (56)	0.0307
MET amplification	104 (39)	26 (33)	44 (42)	10 (36)	20 (51)	4 (22)	0.1631
RET rearrangement	100 (37)	23 (29)	44 (42)	10 (36)	20 (51)	3 (17)	0.0398
MET exon 14 skipping	91 (34)	19 (24)	45 (43)	8 (29)	16 (41)	3 (17)	0.0256
Other	53 (20)	11 (14)	25 (24)	7 (25)	9 (23)	1 (6)	0.2005
Does your laboratory perform PD-L1 IHC assays?	n = 189	n = 57	n = 81	n = 20	n = 22	n = 9	
Yes	129 (68)	35 (61)	60 (74)	15 (75)	15 (68)	4 (44)	0.2602
No	60 (32)	22 (39)	21 (26)	5 (25)	7 (32)	5 (56)	
Does your laboratory perform single or multiplex assays for lung cancer molecular testing?	n = 267	n = 79	n = 104	n = 27	n = 39	n = 18	
Multiplex	153 (57)	37 (47)	67 (64)	11 (41)	26 (67)	12 (67)	0.0204
Single	114 (43)	42 (53)	37 (36)	16 (59)	13 (33)	6 (33)	

IHC, immunohistochemistry; PD-L1 programmed death-ligand 1.

When respondents who perform or interpret assays were asked about the tests offered from their own laboratory, results indicated that, overall, 94% perform *EGFR*, 83% *ALK*, 69% *KRAS*, 68% *BRAF*, 64% *ROS1*, 56% *HER2*, and less than 50% ordered other tests (Table 2). *EGFR*, *ALK*, and *KRAS* are the top three tests performed across all regions, with no significant regional differences (Table 2). Similar to those who request tests and treat patients, more than half of respondents who perform and interpret the molecular tests used multiplex assays (57%), with the frequency of utilizing these assays being less in Asia and Latin America ($p = 0.0204$ Table 2). These percentages suggest that some multiplex assays may not

include some potentially important tests (e.g., *MET, RET*, etc.).

Respondents also reported on the acquisition and testing of liquid biopsies. The 87% of respondents from the requesting and treating track reported that they sometimes request molecular testing on liquid biopsies from patients with lung cancer, although the frequency of liquid biopsy utilization was not reported. The proportions of respondents who sometimes utilize liquid biopsy varied by region and were the lowest in Latin America and the rest of the world ($p < 0.0001$, Table 1). According to respondents who perform and interpret the assays, 69% of laboratories offer tests on liquid biopsies. This also varied significantly by region, with the lowest frequencies in the United States and Canada and the rest of the world ($p = 0.0013$, Table 1). Of those laboratories that offered liquid biopsies, only 37% reported that greater than 10% of molecular tests are performed on liquid biopsies.

Though not a molecular marker per se, programmed death-ligand 1 (PD-L1) testing is a standard part of initial tumor evaluation and was included in the survey. We found that 84% of respondents in the requesting and treating track order PD-L1 and 68% of respondents who perform or interpret assays reported that PD-L1 is offered in their own laboratory.

Barriers to Testing

Results from the free-response fields included information by each respondent on the top three barriers to molecular testing they believe their country encounters (Supplementary Fig. 2). The top five barriers identified in each region are illustrated in Figure 2*A*. The most

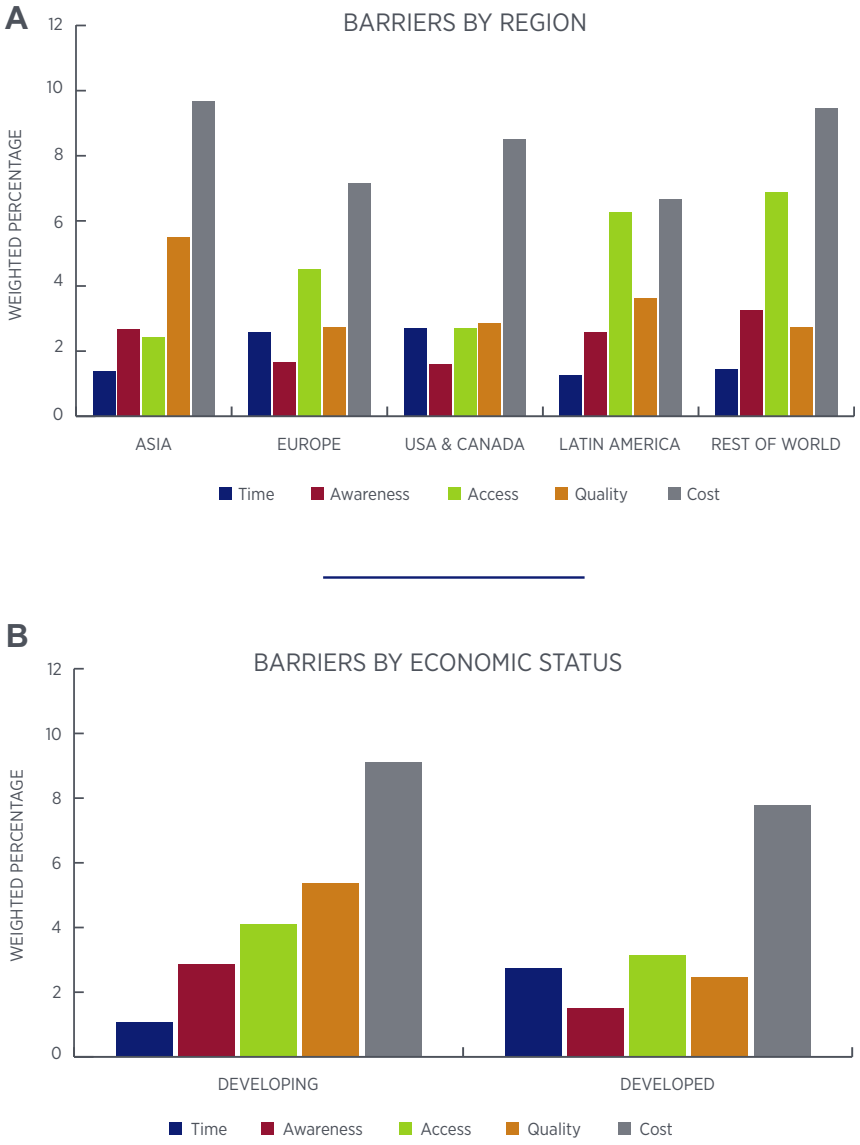

Figure 2. Most frequently reported barriers to molecular testing by *(A)* region of the world and *(B)* the economic status of the respondents' countries.

Table 3. Main Reasons for Failure for the Laboratory to Obtain a Result by Region

Reason	Total	Asia	Europe	Latin America	The United States and Canada	Rest of World	*p* Value
Combined Tracks	**N = 1660**	**N = 961**	**N = 308**	**N = 174**	**N = 138**	**N = 79**	
Insufficient tumor cells provided	1380 (83)	777 (81)	285 (93)	142 (82)	117 (85)	59 (75)	<0.0001
Inadequate tissue quality	911 (55)	499 (52)	170 (55)	116 (67)	79 (57)	47 (59)	0.0068
Sensitivity of assay or assay use failure	307 (18)	207 (22)	50 (16)	21 (12)	22 (16)	7 (9)	0.0018
Inadequate technical expertise in the laboratory	167 (10)	114 (12)	26 (8)	14 (8)	8 (6)	5 (6)	0.0584
Requesting and treating track	**N = 1479**	**N = 905**	**N = 232**	**N = 155**	**N = 117**	**N = 70**	
Insufficient tumor cells provided	1221 (83)	730 (81)	213 (92)	125 (81)	100 (85)	53 (76)	0.0007
Inadequate tissue quality	791 (53)	467 (52)	120 (52)	101 (65)	64 (55)	39 (56)	0.0359
Sensitivity of assay or assay use failure	266 (18)	193 (21)	31 (13)	16 (10)	19 (16)	7 (10)	0.0006
Inadequate technical expertise in the laboratory	142 (10)	106 (12)	17 (7)	10 (6)	5 (4)	4 (6)	0.0120
Performing and interpreting assays track	**N = 181**	**N = 56**	**N = 76**	**N = 19**	**N = 21**	**N = 9**	
Insufficient tumor cells provided	159 (88)	47 (84)	72 (95)	17 (89)	17 (81)	6 (67)	0.0374
Inadequate tissue quality	120 (66)	32 (57)	50 (66)	15 (79)	15 (71)	8 (89)	0.2167
Sensitivity of assay or assay use failure	41 (23)	14 (25)	19 (25)	5 (26)	3 (14)	0 (0)	0.4290
Inadequate technical expertise in the laboratory	25 (14)	8 (14)	9 (12)	4 (21)	3 (14)	1 (11)	0.8651

frequent barrier to molecular testing in every region was cost. Quality and standards were the second most frequent barrier reported in Asia and the United States and Canada, whereas access was the second-highest barrier cited in Europe, Latin America, and the rest of the world. After cost, access and turnaround time were the most common barriers in developed countries, whereas quality and access were the second and third most common barriers in developing countries (Fig. 2*B*).

Barrier 1: Cost. The most frequently identified barrier to molecular testing in every region was cost. Respondents were asked to select who pays for molecular testing for their patients, with the option of selecting more than one answer. The most common response among those in the requesting and treating track was that the patient pays directly (63%), followed by public or governmental support (40%), pharmaceutical companies' sponsorship (29%), and private health insurance (16%). The highest response among those in the performing and interpreting assays track was public or government support (61%) followed by the patient paying directly (44%), pharmaceutical companies' sponsorship (29%), and private health insurance (27%).

Barrier 2: Quality. The main reasons reported for molecular testing failures include an insufficient amount of provided tumor cells (83%), inadequate tissue quality (55%), lack of sensitivity of assay or assay use failure (18%), and inadequate technical expertise in the laboratory (10%) (respondents selected all that apply). Table 3 summarizes the most common causes of failure to provide results by region.

Most (82%) respondents in the ordering and treating track felt that the laboratories they use probably or definitely performed appropriate validation of molecular tests for lung cancer, and 74% believe the laboratories are probably or definitely involved in external quality control programs for molecular testing. A total of 95% of those performing and interpreting the assays reported that they perform validation tests in their laboratories. The most frequent reasons for not performing the validation tests included lack of financial support (71%), inadequate technical expertise (57%), and lack of time (14%).

Barrier 3: Access. We found that 30% of respondents who request tests and treat patients have access to molecular testing laboratories within their own institutions, 43% completely outsource molecular testing, and 28% test partially in-house and partially outsource. Of those who outsource molecular tests, 89% remains within the same country, 5% use foreign laboratories, and 6% were not sure. Among those performing and analyzing the tests, most respondents mentioned that molecular testing was not centralized in their country (58%).

Barrier 4: Awareness. Although one-third of the respondents who request tests and treat patients were unaware of the most recent guidelines, we found that 75% hold multidisciplinary tumor boards to discuss lung

cancer cases. Primary participants in tumor boards include medical oncologists (91%), thoracic surgeons (90%), pathologists (85%), pulmonologists (71%), interventional radiologists (68%), and nursing and allied health professionals (32%). However, only 55% reported that the multidisciplinary tumor boards meet at least on a monthly basis.

Barrier 5: Timing. The time it takes from ordering to receiving molecular testing results, or turnaround time, is a barrier to molecular testing across the world. A total of 29% of the requesting and treating respondents reported that it typically takes 10 or more days to receive results from molecular testing, with the highest percentage in North America ($p < 0.0001$). Those in the performing and interpreting assays track reported an average turnaround time for providing the results to the physician or patient of 0 to 5 days (29%), 6 to 10 days (53%), 11 to 15 days (16%), and longer than 15 days (2%), with no significant difference between regions ($p = 0.3154$).

Evidence-Based Guidelines

We evaluated awareness of the most recent guidelines for molecular testing in lung cancer, published in 2018 by CAP, IASLC, and AMP. Overall, 67% of requesting and treating respondents were aware of the most recent guidelines; the frequency of awareness by region was 65% in Asia, 74% in Europe, 70% in Latin America, 74% in the United States and Canada, and 54% in rest of the world ($p = 0.0041$) (Table 4). When the respondents were asked about the patient subsets for which they typically order molecular testing (select all that apply), the most frequent responses were adenocarcinoma (89%), never-smoker (61%), women (57%), and younger age (54%). These percentages also varied by region ($p < 0.0001$) (Table 4).

Satisfaction With Molecular Testing

A substantial number of respondents were not satisfied with the current state of molecular testing for lung cancer. Specifically, 41% of those who perform and interpret assays reported dissatisfaction with the conditions of molecular testing in their country. The United States and Canada had the lowest rate of dissatisfaction ($p = 0.0106$). When asked whether they thought patients and physicians were satisfied with the state of molecular testing, 17% of respondents who perform and interpret assays felt the patients and physicians were not satisfied with the state of molecular testing, and 35% were unsure. The results suggested that patients and physicians are least satisfied in Latin America compared with other regions ($p = 0.0066$) (Table 5).

Respondents were also asked to rank the conditions around molecular testing in their country. A total of 39% of those who request tests and treat patients ranked the conditions of molecular testing in their country as average or below, with the worst rankings in Latin America and the rest of the world ($p < 0.0001$). In the tissue

Table 4. Knowledge of and Current Practice on Evidence-Based Guidelines for the Requesting and Treating Track

Question	Total	Asia	Europe	Latin America	The United States and Canada	Rest of World	*p* Value
Requesting and treating track	**N = 1683**	**N = 1023**	**N = 257**	**N = 170**	**N = 148**	**N = 85**	
Are you aware of the CAP, IASLC, and AMP Molecular Testing Guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors?	n = 1501	n = 916	n = 233	n = 158	n = 122	n = 72	
Yes	1007 (67)	595 (65)	172 (74)	111 (70)	90 (74)	39 (54)	0.0041
No	494 (33)	321 (35)	61 (26)	47 (30)	32 (26)	33 (46)	
Please select all conditions in which you request molecular testing in patients with lung cancer:	n = 1508	n = 923	n = 232	n = 158	n = 122	n = 73	
Adenocarcinoma histology	1344 (89)	793 (86)	218 (94)	154 (97)	110 (90)	69 (95)	< 0.0001
Predominant histology other than adenocarcinoma but an adenocarcinoma component present	1085 (72)	650 (70)	178 (77)	112 (71)	101 (83)	44 (60)	0.0033
Never-smoker	924 (61)	481 (52)	181 (78)	119 (75)	99 (81)	44 (60)	< 0.0001
Female	854 (57)	472 (51)	144 (62)	113 (72)	84 (69)	41 (56)	< 0.0001
Young age	812 (54)	417 (45)	156 (67)	108 (68)	92 (75)	39 (53)	< 0.0001
Other	269 (18)	141 (15)	54 (23)	23 (15)	40 (33)	11 (15)	< 0.0001

AMP, Association for Molecular Pathology; CAP, College of American Pathologists; IASLC, International Association for the Study of Lung Cancer.

Table 5. Satisfaction With Molecular Testing by Region for Each Survey Track

Question	Total	Asia	Europe	Latin America	The United States and Canada	Rest of World	*p* Value
Requesting and treating track	**N = 1683**	**N = 1023**	**N = 257**	**N = 170**	**N = 148**	**N = 85**	
How would you rank the conditions of lung cancer molecular testing in your country (quantity and quality based on ideal standards)?	n = 1450	n = 880	n = 230	n = 151	n = 117	n = 72	
Average, poor, or insufficient	567 (39)	356 (40)	72 (31)	76 (50)	29 (25)	34 (47)	< 0.0001
Good or excellent	883 (61)	524 (60)	158 (69)	75 (50)	88 (75)	38 (53)	
Performing and interpreting assays track	**N = 316**	**N = 96**	**N = 114**	**N = 33**	**N = 55**	**N = 18**	
Are you satisfied with the conditions of molecular testing in your country?	n = 186	n = 59	n = 80	n = 20	n = 19	n = 8	
Yes	109 (59)	27 (46)	53 (66)	10 (50)	16 (84)	3 (38)	0.0106
No	77 (41)	32 (54)	27 (34)	10 (50)	3 (16)	5 (63)	
In your opinion, are the patients and physicians satisfied with the conditions of molecular testing in your country?	n = 187	n = 59	n = 80	n = 20	n = 20	n = 8	
Yes	89 (48)	26 (44)	43 (54)	4 (20)	11 (55)	5 (63)	0.0066
No	32 (17)	12 (20)	7 (9)	8 (40)	2 (10)	3 (38)	
Unsure	66 (35)	21 (36)	30 (37)	8 (40)	7 (35)	0 (0)	
Tissue acquisition track	**N = 334**	**N = 123**	**N = 74**	**N = 52**	**N = 50**	**N = 35**	
How would you rank the conditions of lung cancer molecular testing in your country (quantity and quality based on ideal standards)?	n = 247	n = 88	n = 55	n = 42	n = 39	n = 23	
Average, poor, or insufficient	103 (42)	31 (35)	21 (38)	27 (64)	7 (18)	17 (74)	< 0.0001
Good or excellent	144 (58)	57 (65)	34 (62)	15 (36)	32 (82)	6 (26)	

acquisition track, 42% of respondents ranked the conditions of molecular testing in their country as average or below, with the worst rankings in Latin America and the rest of the world ($p < 0.0001$) (Table 5).

Possible reasons for dissatisfaction as reported by respondents included difficulty in understanding the molecular testing process and the corresponding results. Specifically, we found 37% of respondents in the requesting and treating track have trouble understanding test results, most of whom cited a need for more technical and scientific knowledge (Table 6). Respondents from Asia reported more difficulty understanding the results than those from other regions ($p < 0.0001$) (Table 6).

Another explanation for the dissatisfaction with the current state of molecular testing reported by respondents was the low quality of the samples. In the requesting and treating track, a total of 66% reported that molecular tests failed to generate a conclusive result in less than or equal to 10% of patients, 27% reported that it occurs in greater than 10% to 30% of patients and 7% reported that tests fail to generate a conclusive result in greater than 30% of patients. These results varied signficantly by region ($p = 0.0023$, Table 6). A total of 23% of respondents from the performing and interpreting assays track reported that greater than 10% of cases were rejected owing to inadequate samples. Furthermore, 47% stated that there was no policy or strategy to improve the quality of the tissue samples in their country, with no difference between regions ($p = 0.1602$, Table 6).

Regional Variation

All survey results were compared across regions of the world (Tables 1–6, Figs. 1 and 2). In summary, reported proportions of tested patients with lung cancer were lower in Latin America and the rest of the world than the other regions ($p < 0.0001$). The proportion of tests that include *EGFR* and *ALK* was high in every region, but Latin America and the rest of the world reported the lowest rates for other tests, including *ROS1* ($p < 0.0001$), *BRAF* ($p < 0.0001$), and *KRAS* ($p < 0.0001$) (Table 2). Multiplex assays are used least frequently in Latin America and the rest of the world ($p < 0.0001$) (Table 2).

Overall, Asia had the highest respondents reporting the need for more scientific and technical knowledge in interpreting test results ($p < 0.0001$) (Table 6). Asia and the rest of the world had the lowest awareness of molecular testing guidelines ($p = 0.004$). Cost and quality

Table 6. Reasons for Dissatisfaction With Molecular Testing by Region for Both the Requesting and Treating and the Performing and Interpreting Tracks

Question	Total	Asia	Europe	Latin America	The United States and Canada	Rest of World	*p* Value
Requesting and treating track	N = 1683	N = 1023	N = 257	N = 170	N = 148	N = 85	
Do you usually have trouble understanding the report displaying the molecular testing results?	n = 1504	n = 922	n = 234	n = 157	n = 119	n = 72	
No	949 (63)	443 (48)	216 (92)	136 (87)	93 (78)	61 (85)	< 0.0001
Yes, I need more scientific and technical knowledge	312 (21)	285 (31)	7 (3)	10 (6)	6 (5)	4 (6)	
Yes, they have too much information	154 (10)	126 (14)	5 (2)	4 (3)	15 (13)	4 (6)	
Yes, they have too little information	89 (6)	68 (7)	6 (3)	7 (4)	5 (4)	3 (4)	
How often do the molecular tests of your patients fail to generate a conclusive result?	n = 1501	n = 919	n = 234	n = 156	n = 120	n = 72	
≤10%	993 (66)	639 (70)	152 (65)	90 (58)	74 (62)	38 (53)	0.0023
>10%	508 (34)	280 (30)	82 (35)	66 (42)	46 (38)	34 (47)	
Performing and interpreting assays track	**N = 316**	**N = 96**	**N = 114**	**N = 33**	**N = 55**	**N = 18**	
What is the fraction of cases that are rejected owing to inadequate samples?	n = 186	n = 58	n = 78	n = 19	n = 21	n = 10	
≤10%	143 (77)	43 (74)	63 (81)	14 (74)	17 (81)	6 (60)	0.5590
>10%	43 (23)	15 (26)	15 (19)	5 (26)	4 (19)	4 (40)	
In your region or country, is there any policy or strategy to improve the quality of the tissue samples for molecular testing?	n = 187	n = 59	n = 80	n = 20	n = 20	n = 8	
Yes	99 (53)	38 (64)	38 (48)	8 (40)	12 (60)	3 (38)	0.1602
No	88 (47)	21 (36)	42 (53)	12 (60)	8 (40)	5 (63)	

were cited as the largest barriers to molecular testing in Asia. Within Asia, we found that respondents from Japan cited less need for technical knowledge than the People's Republic of China or the rest of Asia (16% versus 64% versus 30%, $p < 0.0001$). However, respondents from Japan had less awareness of CAP, IASLC, and AMP guidelines than the People's Republic of China or the rest of Asia (52% versus 65% versus 79%, $p < 0.0001$).

The United States and Canada and Europe reported higher rates of testing. Despite barriers identified, they also reported the highest levels of satisfaction (Table 5). United States and Canada and Europe also reported more utilization of multiplex assays than Asia and Latin America ($p = 0.0204$) (Table 2). Along with Latin America, the United States and Canada and Europe more frequently considered age, sex, and smoking status as conditions for ordering molecular testing (Fig. 1*B*). Cost and quality were the largest barriers in the United States and Canada, whereas in Europe, it was cost and access (Fig. 2*A*).

Discussion

Molecular testing of lung cancer is important to ensure that patients receive optimal treatment; however, the current state of molecular testing is not well understood. To address this gap, the IASLC survey on molecular testing evaluated perspectives on the current state of molecular testing across the world. Respondents from a variety of countries, economic regions, and medical specialties participated.

Providers worldwide reported suboptimal molecular testing. Most clinicians surveyed believe that less than half of patients with lung cancer currently receive molecular testing in their country, although they reported testing more frequently in their own clinic. A possible explanation for this discrepancy is that many responders who were contacted through the IASLC are highly specialized clinicians familiar with molecular testing, yet aware of the disparities regarding the implementation of the tests in their own countries.

We found that more than one-third of clinicians are dissatisfied with the current state of molecular testing in lung cancer. Possible reasons for this include time delays, difficulty understanding testing results, and lack of sample reliability. Consistent with other reports, respondents of our survey reported difficulty in understanding results of molecular tests.[26,27] The complexity of molecular testing and the rapid pace at which it

changes may account for some of the problems in understanding.[26–28] Reporting of results also varies depending on the testing facility.[27] We have not included specific questions regarding the attendance to dedicated meetings, training sessions or workshops on molecular tests, or access to up-to-date scientific literature; however, our results could help evaluate the need for training sessions organized by pathologists toward oncologists in various parts of the world. Patients also experience barriers to understanding molecular testing results, which are often reported to them directly from the testing facilities without involvement from healthcare providers.[27] These patient and physician barriers may lead to discordance between the interpretation of results the patient understands from the testing facility versus what they understand from the physician.[27] Concerns about quality and reliability may also contribute to dissatisfaction, although many respondents reported that there are no strategies to address the quality of molecular testing in their country.

We found that one-third of respondents were not aware of the most recent guidelines for molecular testing in lung cancer. Responses on the reasons for testing, specific tests ordered, and less than 50% testing rates all suggest that the current CAP, IASLC, and AMP guidelines are not always followed. Associations between age and other potential risk factors may encourage the risk-based selection of patients for molecular testing in lung cancer on the basis of demographic information.[29] However, CAP, IASLC, and AMP guidelines recommend molecular testing of *EGFR, ALK*, and *ROS1* for all patients with advanced-stage lung cancer with an adenocarcinoma component.[22] In some countries, the indication has been extended to nonsquamous NSCLC.[17] Many respondents reported that the reasons they perform molecular testing involve demographic risk-based criteria including age, sex, and smoking status, suggesting that current guidelines are not fully understood or implemented in practice. This gap could be addressed with better education on current guidelines and widespread standardization of testing practices. To our knowledge, relevant local or regional guidelines are concordant with CAP, IASLC, and AMP guidelines, which have been endorsed by the American Society for Clinical Oncology. However, if guidelines are updated at an accelerated pace in the future, special attention should be paid to ensuring regional guidelines remain concordant. These results suggest that CAP, IASLC, and AMP should work more closely with partners in Asia in the future to ensure concordance and reach of guidelines in this region.

Specific protocols to initiate reflex testing for guideline-recommended molecular markers would help providers consider molecular testing earlier and optimize tissue. Pathologists can remove the barrier of limited tissue by utilizing two slides for tissue diagnosis (P40 for squamous cell and TTF1 adenocarcinoma), leaving remaining tissue for molecular testing and PD-L1 assessment. Most often, core biopsies have become standard rather than cytology specimens, and in multidisciplinary setting, pulmonologists and radiologists are typically aware of this.[22,30,31] Systematic processing of samples and results should be developed and implemented more broadly.[25]

When molecular testing was performed, it was encouraging to find high availability of tests for *EGFR* mutation and *ALK* rearrangement. However, many providers are not utilizing multiplex assays or not including all suggested biomarkers within multiplex tests. Current guidelines recommend testing for *ROS1* rearrangement, with the possible testing of *HER2, MET, BRAF, KRAS, NTRAK*, and *RET* in laboratories utilizing next-generation sequencing panels.[22] Increased utilization of these next-generation sequencing panels can aid physicians in selecting therapies, especially with the rapid development of additional targeted agents.[14] We did not evaluate the physicians or patients access to targeted therapies in this study, but unavailability of specific therapies may be a cause of lower testing rates in some regions of the world.

We found that many providers do not have access to molecular testing within their own institutions. Because most testing occurs at external laboratories, initiatives should focus on assisting laboratories in the development and utilization of multiplex assays, and, in turn, educating treating physicians on the enhanced laboratory capabilities. This could help ensure that less common targetable biomarkers are identified, allowing patients to receive optimal treatment.

Both awareness of and concordance with evidence-based guidelines are important issues that need to be addressed further by the lung cancer community. Furthermore, given the rapidly evolving science around targeted therapies in lung cancer, more frequent guidelines may be warranted. For instance, with the recent Food and Drug Administration indications for therapies targeting both BRAF and NTRK, the 2018 guidelines are already in need of revision.[22,32] A recent expert statement highlighted the increasingly important role of liquid biopsy.[33] The increased utility and availability of liquid biopsy and next-generation sequencing panels are primed to enhance the need for up-to-date guidelines and recommendations.

The time it takes to receive results from molecular testing was also identified as an obstacle. Reports of longer turnaround times to receive results may lead to delays in treatment decisions. PD-L1 immunohistochemistry results are typically available before the full molecular testing panel, and physicians may be tempted to initiate treatment with immunotherapy immediately

to avoid further delays. This could be deleterious for some patients who would likely benefit more from therapies targeting their specific oncogene driver than from immunotherapies. The benefit of waiting on oncogene driver results to provide patients with an optimal treatment strategy should be emphasized in future outreach. Increasing utilization of liquid biopsy may improve this issue by allowing more rapid identification of oncogene drivers and subsequent initiation of targeted therapies in some patients.

In addition, our results illustrate the difference in perspectives on timeliness between pathologists and medical oncologists. Not all molecular reports are sent rapidly to the oncologist, who is not always clearly mentioned by the clinician who acquired tissue samples.[34–36] Additional work to improve timeliness could focus on the identification of bottlenecks and the use of verifiable communication to increase the rigor of the process. Ultimately, reducing the total time from lung cancer diagnosis to the treating physician's receipt of molecular testing results will increase opportunities for patients to receive optimal care and may improve patient and provider satisfaction with molecular testing.

Cost is the most important barrier we identified across all regions, and we found substantial variation in the payer type between regions of the world. With molecular testing as a standard of care for most patients with lung cancer, reducing barriers related to cost should be a critical area of focus moving forward. A large number of respondents stated that patients pay directly for molecular tests. In most countries in the European Union, next-generation sequencing is not reimbursed by health insurance given that targeted therapies are not yet available for the most information attained. For situations in which next-generation sequencing is cost-prohibitive, a less expensive multiplex panel that includes all genes that are validated for clinical decision-making is a potential solution. A standard recommended panel could be developed and subsequently updated in concordance with the latest evidence. With strong recommendations from the scientific community and regulatory bodies, an endorsement from third-party payers might be attainable. As the evidence grows, the need for more molecular testing is expected.[27] Improvement in understanding and communication between providers, third-party payers, and patients is paramount to ensure that patients receive testing without cost being a deterrent.

Some barriers varied across regions of the world whereas many remained consistent. The findings of this survey can inform the development of solutions that can be applied broadly and those that can be tailored to specific regions. The IASLC and other groups should develop educational initiatives aimed to improve technical knowledge and awareness of guidelines with increased education. Guidelines could be revised more frequently to remain updated on the latest evidence-based practices. Expanding guidelines to establish minimal standards for molecular testing in lung cancer and finding additional avenues to promote best practices could improve the frequency and quality of testing. IASLC initiatives such as awareness campaigns and educational efforts (multimodal methods of delivery, in-person meetings, online interactive content, podcasts, etc.) are promoting molecular testing for all patients with lung cancer with an adenocarcinoma component. In addition, the Lung Ambition Alliance is an important effort by the IASLC, and one of its pillars is to bring about increased molecular testing for all patients with lung cancer.

Limitations

To our knowledge, this is the largest and most comprehensive evaluation of providers' perspectives on molecular testing in lung cancer; however, it is not without limitations. First, responses were received on a voluntary basis and multiple responses from the same institutions may be similar. Regional oversampling and undersampling suggest our estimates may not be fully representative of the entire world. We have worked to address this limitation by evaluating results by region, to understand how the regional patterns might influence the overall findings. Substantial representation from both developed and developing countries may also improve our generalizability. Furthermore, all results presented are on the basis of self-reported perceptions, which may not accurately represent the true state of molecular testing. Although this limits our ability to obtain valid estimates of prevalence, we believe it is still useful for identifying and understanding the general landscape of and barriers to molecular testing in lung cancer. We also acknowledge that there is likely selection bias in this sample on the basis of nonresponse to the survey and nonresponses to some specific questions. We chose to target the broadest audience possible with multimodal anonymous response options, sacrificing the ability to estimate a response rate. Although this is a limitation, we hypothesize that providers who learned about and agreed to take a survey on molecular testing in lung cancer are more informed about molecular testing in lung cancer than those that did not respond. This may suggest that issues with the state of molecular testing and barriers to optimal testing are underreported in our study. When evaluating rates of molecular testing, we asked about issues regarding patients with lung cancer in general, not specifically for patients with advanced-stage adenocarcinoma. The distribution of stage and histologic structure may also influence molecular testing rates, limiting our ability to quantify the

specific proportion of guideline-recommended patients who were not tested. In addition, one important aspect that has not been addressed in our current analysis is whether the suboptimal frequency of molecular testing in patients with advanced NSCLC led to inferior outcomes for the different molecular subcategories compared with countries having a high frequency of molecular testing.

Conclusions

We have identified suboptimal awareness and application of guideline-based molecular testing across all regions of the world. Most barriers identified were consistent across global regions, although the relative magnitude varied by region. Many of the barriers identified can be addressed with improved awareness and standardization of processes. The landscape of molecular testing is complex and rapidly evolving, highlighting the need for regular updates to expert statements and guidelines. Continuous education around molecular testing in lung cancer should be intensified on national and international levels to ensure that patients receive optimal therapy.

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Supplementary Data

Note: To access the Supplementary Material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2020.05.002.

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