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SPECIAL ARTICLE

LungCARD - Report on worldwide research and clinical practices related to lung cancer

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Summary

Purpose: *The management of advanced lung cancer has evolved tremendously over the past two decades. Increasing understanding of the molecular changes that drive tumor progression has transformed the treatment of this disease. Nevertheless, various countries differ in the degree of implementation of genetic tests and the availability of innovative drugs. The LungCARD consortium created a questionnaire to collect information about the local research and clinical practices related to lung cancer diagnosis and therapy.*

Methods: *A survey composed of 37 questions related to specific lung cancer pharmacogenomics and therapy, was distributed among 18 countries.*

Results: *All together 36 responses were gathered, answered mainly by clinicians. The majority attends 50-200 cancer cases per month, 20-50% of all cancer cases are lung cancer patients, and more than 80% are with non-small-cell lung cancer (NSCLC). Targeted therapy is applied to 50% on average of all NSCLC patients. Forty five percent of participating medical oncologists are treating their patients with immunotherapy. More than 90% of the respondents are guided by results of genetic tests in introducing targeted treatment. As expected, the majority orders EGFR gene testing (85%), followed by ALK (58%) and KRAS testing (32%). Almost all (96%) agreed that more biomarkers should be included in routine genetic testing (ROS1, anti-PDL1, KRAS, MET, HER2, BRAF...), and that blood test is useful in pharmacogenomic testing.*

Conclusion: *There is a great variation between countries with respect to all discussed topics. However, the majority recognized a necessity of introducing next generation sequencing (NGS)-based diagnostics and potential of testing from blood. The biggest problem in the treatment of NSCLC is still an access to innovative drugs.*

Key words: *biomarkers, NSCLC, questionnaire, targeted therapies*

Introduction

Although lung cancer (LC) is still one of the most common malignant diseases worldwide and a leading cause of cancer-related deaths [1], the management of this disease has evolved tremendously over the past two decades. Increasing understanding of the molecular changes that drive tumor progression has transformed the treatment of LC, especially in the advanced stages of disease when most patients are initially diagnosed [2]. Surgical resection of early-stage LC leads to favorable survival rates (around 80%), but it is usually not a viable option for advanced stages where 5-year survival rates drop to 2-5% for stage IV [2].

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Absence of alarming symptoms in the early stages of LC complicates the diagnostic process, treatment and outcome, and highlights the need for an efficient screening system [3]. However, various countries differ in the degree of implementation of screening, diagnostic tests and availability of innovative drugs. Smoking cessation campaigns have had only limited success worldwide. Also, only around 11% of life-long smokers develop LC, whereas it occurs in around 15-25% of individuals who had no significant history of tobacco use [4]. Most recent LC screening guidelines propose periodical low-dose computed chest tomography of high-risk individuals, with a history of heavy smoking, current smokers or those who have quit less than 15 years ago and are between 55 and 80 years old [5]. But the side effects (repeated screening increases radiation exposure) of this procedure as well as the cost of its implementation are too high, especially in developing countries, so an intense global debate over its implementation is still ongoing [6]. Other proposed measures range from societally more intensive anti-smoking campaigns to scientific improvements of risk models for prediction of LC occurrence [7]. Assessing new population-specific genetic risk factors for LC is proposed as an attractive, low-cost alternative that might lower national mortality rates and reduce the yearly number of patients in need of periodical screenings with more expensive methods [8-10]. The WHO/IARC/UN consortium recommended a similar approach in 2017, in order to strengthen the collaboration of research groups working on profiling LC risk factors and tumorigenesis mechanisms, and efficiently exploit the acquired data into potential screening programs [3].

Immense efforts have been employed by the scientific, health and pharmaceutical community to develop drugs for advanced LC that would target specific molecular signatures in a specific disease moment in a specific patient, which is the gold standard of precision medicine. It has been shown that the presence of targetable driver mutations or other alterations leads to prolonged survival of LC patients, especially in the advanced setting [2,11]. The most frequent single mutations in LC are found in the following genes: EGFR, ALK, KRAS, TP53, ERBB2, BRAF, PIK3CA, SMAD4, AKT1 and NRAS. Targeting EGFR mutations with tyrosine kinase inhibitors (EGFR TKI_s) has transformed the treatment of advanced NSCLC and is an excellent example of fast and efficient targeted therapy implementation into clinical practice. Starting with the first generation of inhibitors (gefitinib, erlotinib) that were approved in 2009, next-generation TKI_s have emerged to overcome the appearance of acquired resistance (neratinib, afatinib, dacomitinib, osimertinib, rociletinib, EAI045) [12]. A range of anaplastic lymphoma kinase (ALK) fusion kinase targeting drugs (crizotinib, ceratinib, lorlatinib, brigatinib, alectinib, ensartinib) have shown a significant benefit in properly selected molecular subsets of NSCLC patients [13]. Immune checkpoint inhibitors (pembrolizumab, nivolumab, atezolizumab) have also had a large impact on the overall survival of NSCLC patients. The first predictive biomarker for immunotherapy was the expression of programmed cell death ligand 1 (PD-L1), but currently determination of tumor mutational burden (TMB) has become a priority [14,15]. Although TMB and PD-L1 expression do not correlate well, they are both regarded as similarly precise predictive parameters, and it has been proposed to use them concurrently for a more reliable prediction of immunotherapy response in LC [16]. The detection of actionable molecular changes in a non-invasive manner has also become imperative, so various liquid biopsy-based approaches are being evaluated [17,18].

The LungCARD consortium created a questionnaire to investigate local research and clinical practices related to LC diagnosis and therapy on a global level, with the aim to implement the obtained data in creating a reliable companion diagnostic NGS-based test from blood to guide the treatment in NSCLC patients.

Methods

LungCard consortium created an online questionnaire to collect data mainly from medical oncologists working in different parts of the world.

The study was conducted during 2017 and 2018 and consisted of an invitation pack distributed to all members of LungCard consortium by email. The invitation pack included a brief project description and the questionnaire. All participants were offered the opportunity to complete either a word form of questionnaire or to do it via online access (Google Forms).

The instrument used for this study consisted of an online questionnaire, composed of 37 questions encompassing the areas of LC diagnosis, treatment, and pharmacogenomics. The questionnaire is provided in the Appendix.

Results

Altogether, 36 responses were gathered, filled out mainly by clinicians from 18 countries (Figure 1). In some cases, the questionnaire was responded by clinicians and geneticists. Employed at hospitals were 66.7%, while 25% were working at Universities.

The majority of them attended 50-200 cancer cases per month. Of all cancer cases 20-50% were LC patients, and more than 80% were with NSCLC histology. Regarding imaging methods, most of the doctors were using low dose CT, x-ray and PET. From other methods, bronchoscopy and sputum cytology were most used. Depending on the stage of disease, surgery, radiotherapy, chemotherapy (in most cases) and targeted therapy were applied.

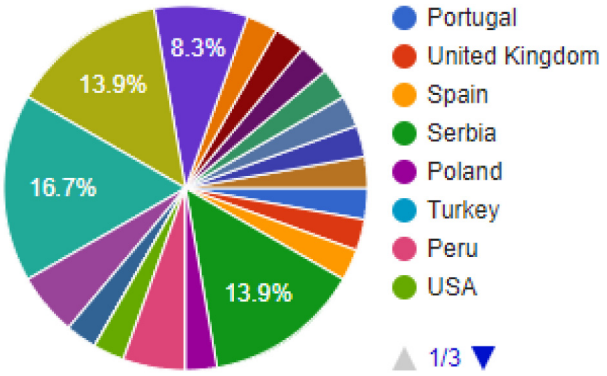

Figure 1. Countries participating in the survey. The full list: Portugal, Serbia, Morocco, United Kingdom, Azerbaijan, Uzbekistan, Peru, Brazil, Kuwait, France, Spain, Austria, Estonia, Belgium, Montenegro, Nigeria, USA, Poland.

Regarding targeted therapies, over 80% of clinicians were prescribing 1st and 2nd generation TKI_s, erlotinib and afatinib, 48% crizotinib and 40% were giving nivolumab. In few cases, some other immune therapies such as pembrolizumab or 3rd generation TKI_s were also present. Interestingly, 2nd generation ALK inhibitors were given in 24% of the cases (Figure 2).

Targeted therapies were applied to 50% on average of all NSCLC patients. More than 90% of the respondents were guided by the results of genetic tests in introducing targeted treatment. As expected, the majority of EGFR gene testing orders (85%) followed ALK (58%) and KRAS testing (32%). The tests were performed mainly from formalin-fixed paraffin-embedded tissue (FFPET) samples (96%) and blood samples (46%). Of the clinicians, 50-75% were waiting 1-2 weeks for the results of genetic testing and 3-10% of genetic tests were producing inconclusive results in 55% of the cases.

The responses about costs of genetic testing were very miscellaneous. The range varied from 50 to more than 300 euro per test and this was caused by different methodologies, number of genes analyzed, and largely depending whether analyses were performed on site or were outsourced.

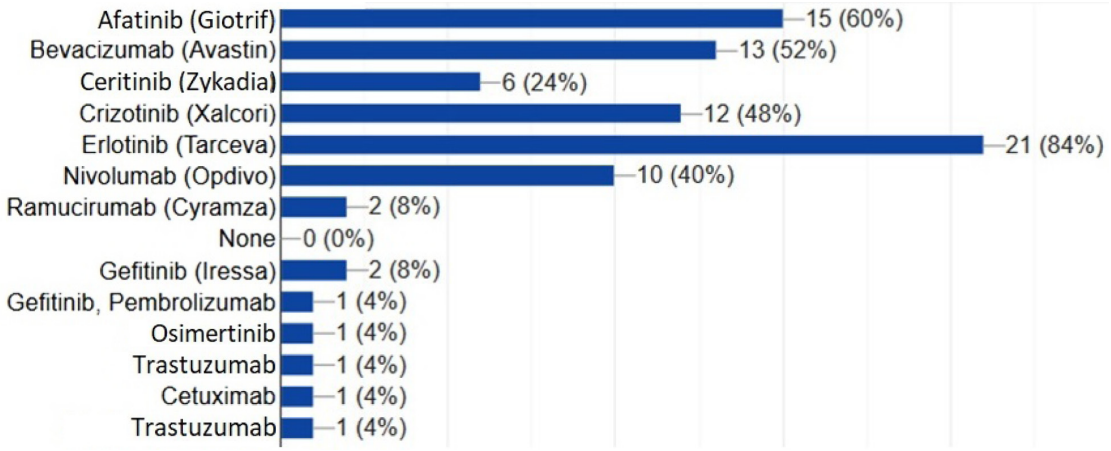

Figure 2. Targeted drugs and immunotherapies prescribed by respondents.

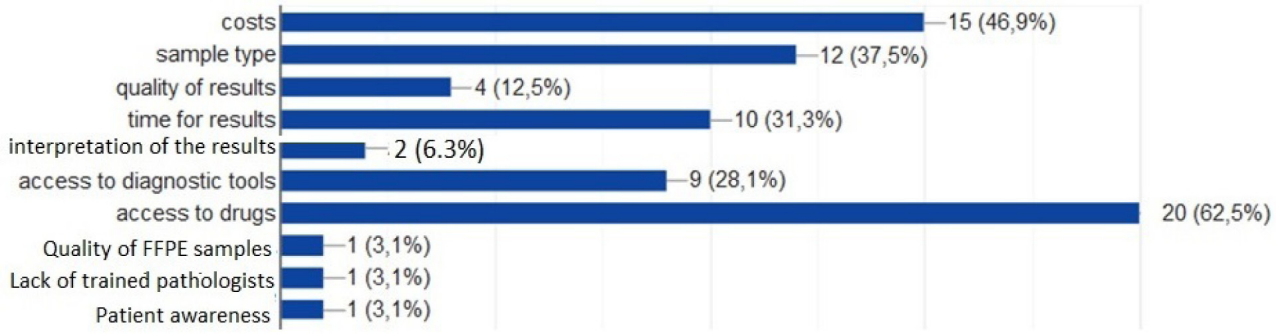

Figure 3. The most common problems in diagnosis and treatment of non-small cell lung cancer.

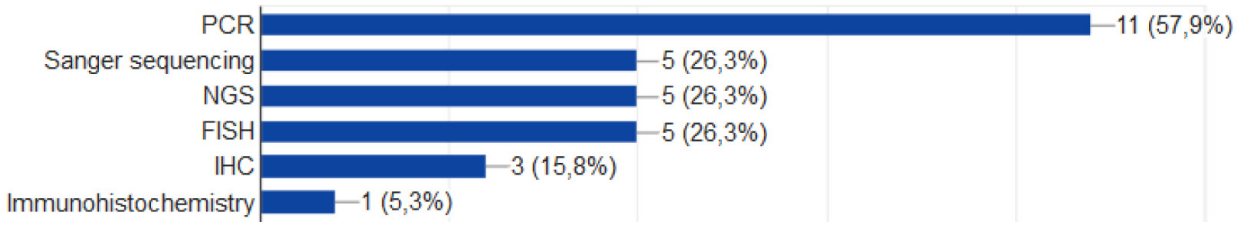

Figure 4. Methods used for genetic testing in patients with NSCLC.

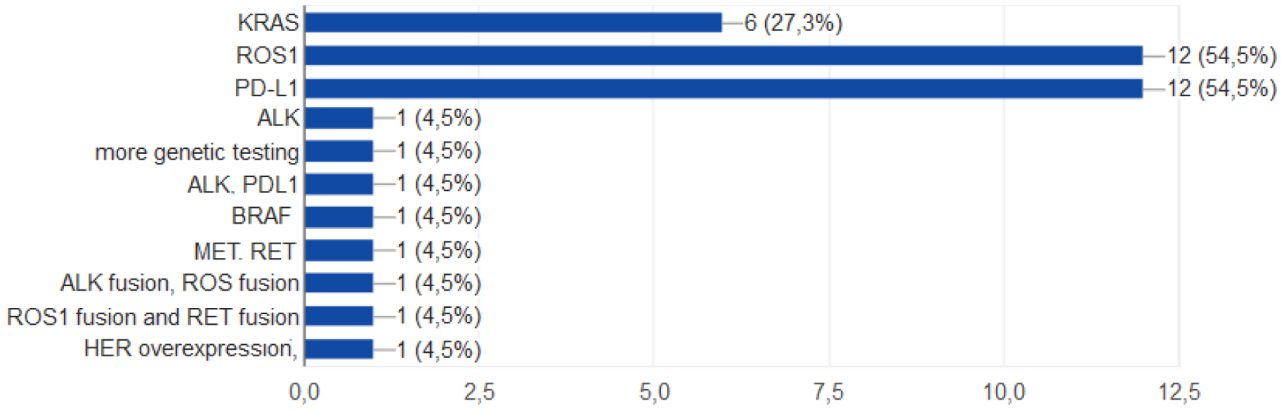

Figure 5. Biomarkers besides EGFR that, based on survey, should be included in routine diagnostics.

One of the main remarks was that countries differed considerably concerning payment of a genetic test. Even 38% of doctors replied that the patient was paying for the test. In 29 and 23% of the cases, the expenses were covered by insurance or hospital fund, respectively.

As expected, the most frequent response to the question "What do you consider in your experience the most common problems in diagnosis and treatment of NSCLC" was access to innovative drugs (82%). Predictably, the modern treatments were more accessible for the participating clinicians from USA, UK and EU, comparing with their colleagues from Africa, non-EU countries, Asia, South America or Eurasia. Of the examinees 37% were having problems with quality of tissue sample and 12.5% were not satisfied with the quality of the results (Figure 3).

Laboratories are using various genetic tests: 57.9% are employing PCR-based technology, 26.3% Sanger sequencing, 26.3% NGS methodology (Figure 4). Of the included respondents 65% were performing full pharmacogenomic analysis in-house, 25% subcontracted some parts, and 15% subcontracted the full process.

The majority (96%) agreed that more biomarkers should be included in routine genetic testing. Of the examinees 54.5% thought that, besides EGFR and ALK, ROS1 and anti-PDL testing have to be mandatory. KRAS, MET, HER2, and BRAF mutation analysis should also be a part of routine testing (Figure 5).

It is interesting that 100% of the respondents agreed that blood test is useful in pharmacogenomics testing and there were no technical difficulties to send blood samples to a central laboratory for testing, if needed.

Predictably, there was a great variation between countries regarding accreditation of the laboratories, existence of national accreditation bodies, having standard operational procedure (SOP), regulative about personnel and clinical data protection.

Discussion

EGFR TKI therapy is the standard of care for LC patients with detectable activating EGFR mutations. Various phase III studies have demonstrated the superiority of gefitinib, erlotinib (first generation of TKI_s) or afatinib (second generation) over chemotherapy in PFS and response rates [19-21], so that detection of EGFR mutations has become the standard of care worldwide since 2009. This is in concordance with our survey showing that 85% of respondents are ordering EGFR testing.

Besides EGFR, it was shown that even 70% of patients with NSCLC are having an oncogenic driv-

er mutation. For most of these alterations, matched targeted treatments are available, which expand treatment options. Activating genetic mutations or fusions in EGFR, ALK, ROS1, and BRAF are now targets for kinase-inhibitor therapy in NSCLC [22]. However, acquired therapeutic resistance to these agents is inevitable. Over the past 10 years, the molecular mechanisms of EGFR TKI resistance are mostly elucidated which led to strategies to overcome this unwanted condition. Approximately 60% of patients with acquired resistance to the EGFR TKI_s (erlotinib, gefitinib and afatinib) develop a new mutation, T790M, altering drug binding to EGFR. The current standard therapy is osimertinib, a mutant-selective, 3rd generation EGFR TKI which was designed to overcome the T790M resistance mutation [12]. A survey showed that 80% of the clinicians are prescribing the 1st and 2nd generation TKI_s, erlotinib and afatinib, 48% crizotinib and 40% of them are giving nivolumab. Only a few are applying pembrolizumab or 3rd generation of TKI_s. The 2nd generation ALK inhibitor was given in 24% cases (Figure 2).

In response to increasing molecular alterations in NSCLC, the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) recently updated their recommendations for molecular testing for the selection of patients with LC for treatment with targeted TKI_s [23]. Besides obligatory EGFR and ALK testing, new for 2018 are recommendations for ROS1 and BRAF testing with additional confirmation testing in all patients with advanced lung adenocarcinoma, and RET, ERBB2 (HER2), KRAS, and MET testing as part of larger panels. It is also stated that multiplexed genetic sequencing panels are preferred where available over multiple single gene tests.

From data shown on Figure 4, it is obvious that more than half laboratories are still using PCR-based technology for single gene testing. Already employing NGS methodology are 26.3%, which is encouraging. Nonetheless, the majority of examinees agreed that more biomarkers should be included in routine genetic testing (Figure 5), which will ultimately lead to a shift from single gene analysis to NGS based panel testing.

It is interesting that all clinicians reached a full agreement on the usefulness of pharmacogenomic testing from blood. This is not surprising knowing all possibilities of liquid biopsy. Lack of available tissue for performing molecular profiling, the location or size of the tumour, the risk of complications (pneumothorax), are major limitations for performing biopsies in NSCLC [24]. In EGFR-mutant NSCLC patients with acquired resistance to EGFR TKI_s, re-biopsies are feasible in only half of the patients [25]. Even then, 12-30% of samples are not sufficient for genotyping [26]. This is in accordance with the survey data showing that one third of respondents were having problems with the quality of tissue sample (Figure 3). Furthermore, it is well known that LC has high level of intratumor heterogeneity which increases over the different lines of therapy due to the selection of multiple resistant clones In this case, only the liquid biopsy is able to provide a comprehensive molecular portrait of the tumor that cannot be derived from a small biopsy [27,28]. Additionally, NGS-based blood test will facilitate the identification of resistance mechanisms (e.g. mutation V600E in BRAF oncogene) after each line of treatment.

The most discouraging data gathered by this survey are shown on Figure 3. Even 82% of the clinicians are having limited access to innovative drugs. That represents the biggest problem in modern treatment of patients with NSCLC. In the era of rapidly expanding immune therapies, some countries do not have access to 1st or 2nd generation of TKI_s.

Of all tumours, LC has the highest economic cost, accounting for 15% of the overall cancer costs followed by breast cancer (12%), colorectal cancer (10%) and prostate cancer (7%) [29]. The increasing cost of anticancer drugs is mainly a result of introduction of innovative therapies (monoclonal antibodies, small molecule targeted therapies and more recently immunotherapies). It is obvious that anticancer drugs are less accessible in middle-income countries than in high-income countries [30]. In the future, all the efforts should be made to provide global access to innovative therapies.

Conclusion

There is a great variation between countries regarding all the discussed topics. As expected, the most striking difference is in the availability of innovative drugs. All participants understand the inevitability of implementation of NGS-based tests in routine clinical practice. Concerning intratumor heterogeneity and limited feasibility of LC re-biopsies, NGS blood test is only having a potential to provide accurate molecular portrait of the tumour.

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Project Acronym: LungCARD
Project title: Blood test for clinical therapy guidance of non-small cell lung cancer patient

Conflict of interests

The authors declare no conflict of interests.

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Appendix

Report on research and clinical practices related to lung cancer pharmacogenomics and therapy in [country name, city].

(Deliverable D2.1)

[Interviewer's name]

Project's title

Blood test for clinical therapy guidance of non-small cell lung cancer patients - LungCARD

Project's abstract

Lung cancer is the most common cancer worldwide. NSCLC alone make up about 75% of all lung cancers and most hospitals currently test all NSCLC patients for EGFR mutations (pharmacogenomics) for treatment decision (personalized medicine) – i.e., patients with mutation(s) in EGFR gene should receive a EGFR-Tyrosine Kinase Inhibitor (TKI) drug (e.g. afitinib) treatment; while those that do not present mutations in such gene, should be treated with chemotherapy. Currently, the laboratories use PCR and Sanger sequencing technologies to perform the EGFR analysis from tumour biopsies – Fixed Paraffin Embedded (FFPE) samples. Still, some patients (e.g., 30% in UK) may never get histological confirmation because they are too sick to make a biopsy. Furthermore, the results obtained with current methods still present low quality, mainly due to poor quality/low yield of DNA extracted from FFPE samples. The FP7 LungCARD project (www.lungcard.eu) has developed and demonstrated a LungCARD system - an automatic system composed by microfluidic chip and chip analyser - that allows to capture circulating tumour cells (CTCs) from blood samples, amplify by multiplex PCR and detect EGFR mutations, including also a software for data analysis and report. Although this new blood test has proven to be faster, cost effective and human error-free, the detection of somatic mutations in EGFR gene at frequencies lower than 20% is still a weak point.

Therefore, the main project's goal is to benefit from this technology, through the development, improvement, integration and validation of the LungCARD system with NGS workflow and development of a software for automatic reporting clinical results.

However, LungCARD project aims to go further, by putting together a global and unique network of multidisciplinary scientists for exchange of knowledge and research training focused on non-small cell lung cancer.

Interwiewer's information

Organisation name: .....
Type of organisation (e.g university, hospital, diagnostic and/or research laboratory): .....
Organisation address: .....
Interviewee name: .....
Position (in the organization): .....
Interview date/period: .....

Questionnaire

This questionnaire aims to collect information about the local research and clinical practices related to lung cancer pharmacogenomics and therapy in order to design and built a LungCARD system in accordance with legal, technical and research/clinical requirements. There are some questions that might not be applicable to the interviewee since some of them are targeting the clinicians and other the diagnostic/research laboratories who perform the diagnosis/pharmacogenomics of cancer, specially in non-small cell lung cancer (NSCLC). For such questions please write "Not applicable".

A. Do you attend/receive cancer cases?

B. What number of patients/samples per month?

C. What number/percentage is lung cancer?

D. What percentage of the lung cancer case is non-small cell lung cancer (NSCLC)?

E. What method(s) do you use in diagnosis of non-small cell lung cancer?
   a. imaging test (low-dose computed tomography, LDCT, CT, X-ray, PET-CT scans)
   b. sputum cytology
   c. tissue sample (biopsy)
   d. other (please specify)

F. What therapy do you use?
   a. surgery
   b. chemotherapy
   c. radiation therapy
   d. targeted therapy
   e. other (specify)

G. If you use targeted drug therapy, which of the following drugs do you prescribe?
   a. AfatinIb (Giotrif)
   b. Bevacizumab (Avastin)
   c. CeritinIb (Zykadia)
   d. Crizotinib (Xalkori)
   e. Erlotinib (Tarceva)
   f. Nivolumab (Opdivo)
   g. Ramucirumab (Cyramza)
   h. Other (please specify)

H. How often do you use target drug therapy?
   (1) 0% of NSCLC cases
   (2) <50% of NSCLC cases
   (3) 50-75% of NSCLC cases
   (4) >75% of NSCLC cases

I. Do you request/perform a genetic test to guide the therapy (pharmacogenomics of NSCLC)? Which genetic variants are you analyzing (e.g specify the variants in EGFR gene, KRAS gene, etc)?

J. Which type of sample is collected for genetic test (e.g. blood, FFPE-tissue)?

K. Are you requesting an informed consent to the patient before collecting the sample?

L. How long it takes from sample collection to report? Is this time compatible with clinicians/patients need?

M. How much will cost the genetic test?

N. What number/percentage of cases produce inconclusive/low quality genetic results?

O. Who is paying the genetic test (e.g. patient, insurance, hospital, etc)

P. What do you consider in your experience the most common problems in diagnosis and treatment of non-small cell lung cancer (e.g. costs, sample type, quality of results, time for results, difficulty in the interpretation of results, access to drugs, etc)?

Q. Do you think that more biomarkers should be analyzed to improve the therapy in NSCLC? Which one?

R. Do you think that a blood test for NSCLC pharmacogenomics testing will be useful?

S. Will be practical to send fresh blood to the laboratory for analysis? What could be the maximum blood volume to be collected?

T. What do you think that could be done to improve the treatment of NSCLC patients?

U. In case you are a diagnostic laboratory, are you certified or accredited (e.g. ISO 9001, ISO 15189, etc), in particular for the genetic test (pharmacogenomics) of NSCLC patients?

V. Is it mandatory by legislation to have a license and accreditation to perform genetic diagnostic?

W. Who are your clients (e.g. hospitals, etc) and from which countries (e.g. only national, other countries such as....)?

X. Are you using IVD reagents only and/or in-house developed tests?

Y. Which method (s) is (are) used in the laboratory for the genetic test (pharmacogenomics) of NSCLC patients?

Z. Do you find limitations to the current method used?

AA. Are you performing the complete analysis (from sample to report) in-house or do you subcontract some parts or the analysis? Which parts and why?

BB. What type of samples do you receive for the genetic test (pharmacogenomics) of NSCLC patients?

CC. Do you have Standard Operational Procedures (SOP) to be used by the health professionals to collect and sending the samples to the laboratory for analysis?

DD. Do you follow technical guidelines (or legislation applied) to analyze the samples (including storage, ersonal and clinical data protection)?

Additional comments: .....
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