Inequalities in lung cancer: a world of *EGFR*

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ABSTRACT Epidermal growth factor receptor gene (*EGFR*) mutation status has emerged as a crucial issue in lung cancer management. Availability and cost of tests and tyrosine kinase inhibitors (TKIs) may vary as a function of country development.

We conducted a prospective specialist opinion survey to map *EGFR* test and EGFR-TKI availability and detect associations with the Human Development Index (HDI). A questionnaire was sent to specialists in thoracic oncology in all United Nations Member States.

We obtained responses from 74 countries, comprising 78% of the worldwide population. Nonresponding countries had significantly lower HDI rank than responding countries. *EGFR* mutation analysis was routinely available in 57 countries (70% of the worldwide population). The cost of the test was <US$500 in 49 countries (42.5% of the worldwide population). Test availability and cost were both significantly linked to HDI. Erlotinib, gefitinib, afatinib and icotinib were routinely available in 75%, 66%, 31% and 23% of the worldwide population, respectively, also associated with HDI.

EGFR mutation testing and EGFR-TKIs are widely accessible in routine practice worldwide. However, there are large discrepancies in access to this innovative treatment path and in its cost for patients as a function of country development.

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Introduction

With 1.8 million new cases diagnosed in 2012, lung cancer is the third most frequent cancer worldwide and the leading cause of cancer-related death (1.59 million deaths in 2012). Furthermore, 58% of lung cancer cases are reported in lesser-developed regions [1].

In the past decade, the occurrence of somatic mutations has emerged as a key oncogenic outcome in lung cancer. The presence of activating mutations in the epidermal growth factor receptor gene (*EGFR*) in tumours is the best predictive factor for response to EGFR tyrosine kinase inhibitors (TKIs) [2]. Thus, *EGFR* status has become a major prognosis factor. Indeed, the IPASS randomised phase 3 study found a significantly higher rate of disease-free survival for patients with a sensitising *EGFR* mutation and treated with gefitinib compared with those treated with standard carboplatin and paclitaxel chemotherapy (hazard ratio 0.48, 95% CI 0.34–0.67) [3]. In contrast, patients with no *EGFR*-activating mutation have shorter survival with EGFR-TKIs than with standard chemotherapy (hazard ratio 3.85, 95% CI 2.09–7.09). Similar results have been demonstrated with erlotinib [4], icotinib [5] and afatinib [6].

EGFR mutations are more frequent in women, Asian populations and never-smoker lung cancer patients [7]. However, the determination of *EGFR* status using a validated screening test remains the unique end-point before prescribing a first-line EGFR-TKI-based therapy [8]. Therefore, a number of countries have developed *EGFR* testing facilities. The French initiative was particularly original and led to a better understanding of *EGFR* mutations [9, 10]. Similar initiatives have emerged in other countries, such as the USA, the UK and Canada. However, there is currently no clear overview of the worldwide availability of *EGFR* mutation testing in routine practice. It is probably to be expected that many low-income countries have not developed such facilities.

Thus, with the present study, we aimed at determining the availability and cost of *EGFR* mutation testing and EGFR-TKIs in all countries.

Methods

We performed a prospective, noninterventional survey-based study to collect nation-specific information from specialists. Our main objective was to create a worldwide map of the availability of *EGFR* mutation testing. Our secondary objectives were to assess the cost of *EGFR* mutation testing, and the availability and cost of EGFR-TKIs, and to correlate these variables with country development indicators.

Selection of specialists

Specialists were selected: 1) *via* partner institutions (the European Respiratory Society (ERS), the Asian Pacific Society of Respirology (APSR), the Asociación Latinoamericana de Tórax (ALAT), and the Thoracic Society of Australia and New Zealand) who sent participation invitations directly to their members; 2) by manual search of E-mail addresses on the internet (websites of the primary hospitals and national institutions, French Embassy correspondents, the website of the Union for International Cancer Control); and 3) using the online directory of the International Association for the Study of Lung Cancer for certain countries.

Questionnaire

We used the Google Drive Form tool (Google, Mountain View, CA, USA) to create an online 20-item questionnaire comprising mostly single-answer drop-down menu or multiple-choice questions (see online supplementary file S1). The questionnaire was available in French and English. The specialists first had to provide their consent to participate by ticking a box. After completing several institutional and framework questions, they then responded, for the country or subnational division (province, state, region, etc.) where they practiced, to questions on the availability of *EGFR* mutation testing in daily practice in their country, the rate of *EGFR* mutation in their country (self-estimated), the cost of this test and the delay for obtaining results. Thereafter, they were questioned on the availability (in routine practice) and cost (per month; standard dosage) of the following EGFR-TKIs: erlotinib (Roche, Basel, Switzerland), gefitinib (Astra Zeneca, London, UK), afatinib (Boehringer-Ingelheim, Ingelheim am Rhein, Germany) and icotinib (Beta Pharma, Princeton, NJ, USA). All costs were expressed in US$. A hyperlink to a currency converter tool (www.xe.com) was provided in the questionnaire. All costs were expressed as those remaining for the patients themselves and/or their private (nonpublic/nonmandatory) health insurance. Costs charged to government-supplied health insurance were not expressed.

Responses to the questionnaire were collected between April 2014 and November 2014.

Interpretation of specialist responses

We defined *a priori* rules to interpret differing responses obtained from multiple specialists responding for the same country or subnational division. When responses were received from two specialists, those

provided by a clinician were retained over those of the other specialist; if two clinicians responded, the most "pejorative" response was retained. If more than two specialists answered, we kept the modal response to each question.

Country data

We used the Human Development Index (HDI) (http://hdr.undp.org) to assess development in each country. According to the United Nations Development Programme (UNDP), this composite indicator is "a summary measure of average achievement in key dimensions of human development: a long and healthy life, being knowledgeable and have a decent standard of living". We categorised countries according to their 2013 HDI rank as presented on the UNDP website (http://hdr.undp.org): very high human development (HDI 1.0–0.800), high human development (HDI 0.799–0.700), medium human development (HDI 0.699–0.550) and low human development (HDI $\leqslant$0.549).

We used the Member States of the United Nations (www.un.org/en/members/) and included the possibility of subnational divisions. Data on country populations were obtained from 2013 dataset of the UNData online database (http://data.un.org).

For mapping, we used a blank world map. Countries were considered globally, *i.e.* with their noncontiguous territories (e.g. data for Greenland were integrated with those of Denmark).

EGFR *mutation frequency*

We aimed to report the *EGFR* mutation frequency in each country. Thus, we obtained this data following two approaches: 1) experts were asked to report the known (or published) frequency of mutation in their country in a dedicated field of the questionnaire and 2) we conducted an advanced search on PubMed with the following terms: ((egfr mutation) AND lung cancer) AND [Name of the country].

Ethics

The study was categorised as a noninterventional prospective study by the Sud-Est IV ethics committee (L14-44), and was declared to the Commission nationale de l'informatique et des libertés (CNIL, the French data protection authority) as required by French law (14-21).

Statistics

Categorical variables were expressed as percentages and compared using the Chi-squared test or the Fischer exact test as required. Nonnormally distributed variables were expressed as median (interquartile range (IQR)) and compared using the Mann–Whitney U-test (two independent samples). All tests were two-sided. A p-value of <0.05 was considered significant. Statistical analyses were performed using SPSS statistics version 19.0 (IBM, Armonk, NY, USA).

Results

Responding countries

We received at least one response from 74 of the 194 (38%) UN Member States. The responding countries accounted for 5 151 308 272 people, *i.e.* 78% of the total worldwide population. HDI ranks were available for 187 countries.

Countries that did not respond had significantly lower HDI ranks than those that did (median (IQR) 0.676 (0.239) *versus* 0.769 (0.228), respectively, $p<10^{-4}$). Nonresponding countries were mainly located in Oceania (12 nonresponding countries for 14 countries in the region; 86%), Latin America and the Caribbean (23/33; 70%), Africa (37/54; 69%), and Asia (32/48; 67%). Online supplementary table S1 provides a list of responding and nonresponding countries.

Main characteristics of the responding specialists

Clinicians, biologists or pharmacists made up 88% of the responding specialists. Places of work were cancer centres, hospitals or health centres for 79% of them (online supplementary table S2).

EGFR *mutation frequency*

Online supplementary table S3 reports the percentage of *EGFR* mutation analysis available by country. Data were available for 49 countries (35 experts' answers and 21 from literature search).

EGFR *mutation test*

The organisation of routine *EGFR* mutation testing was provided by public institutions in 36 countries (37.5% of the worldwide population) and by private companies in 12 countries (28% of the worldwide population) (data missing for 18 countries). The worldwide availability of *EGFR* mutation testing is

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mapped in figure 1. *EGFR* testing was available across the entire national territory for 40% of the responding countries (41/74), but 70% of the responding countries had the test available in at least some subnational divisions (table 1). Countries where the test was not available or available only in another country were exclusively located in Africa (n=14; 82%) and Asia (n=3; 18%). There was a significant difference for *EGFR* test availability according to HDI ranking: 67% of the responding low or medium HDI countries did not have access to the test compared with 6% in high and very high HDI countries ($p<10^{-4}$). Conversely, the median (IQR) HDI was 0.830 (0.144) in countries where *EGFR* mutation testing was available (either in the whole country or in some subnational divisions) compared with 0.501 (0.092) in countries where it was not available ($p<10^{-4}$) (figure 2a).

EGFR mutation testing was free of charge for the patient in 18 countries (6.5% of the worldwide population) or cost the patient <US$500 in 31 countries (36.1%). The test was thus free or cost <US$500 for 42.6% of the worldwide population) (table 1). Although marginally significant, *EGFR* mutation testing was more frequently free in countries with high to very high HDI compared with those with low to medium HDI: 36.7% *versus* 0% (p=0.024). Similarly, the median (IQR) HDI was higher in countries where the test was free compared with those where it was not: 0.862 (0.103) *versus* 0.765 (0.209) (p=0.036) (figure 2b).

The results of *EGFR* mutation testing were available in less than 30 working days in most of the responding countries (n=59; 71% of the worldwide population) (online supplementary table S3). We found a marginally significant difference in delay for mutation results regarding the HDI category: all countries with medium and low HDI obtained results in more than 7 working days compared with 68% of very high and high HDI countries (p=0.052).

EGFR-TKI availability and cost

Erlotinib was the most widely available EGFR-TKI in the responding countries (n=64; 75% of the worldwide population), but free of charge for the patient in only 10% of the worldwide population (n=28 countries). Gefitinib was available in 54 countries (67% of the worldwide population), afatinib in 28 countries (31% of the worldwide population) and icotinib in only four countries (23% of the worldwide population). The availability and costs of EGFR-TKIs are mapped in figures 3 and 4 and online supplementary figures S1 and S2, and the relevant data are summarised in online supplementary table S4.

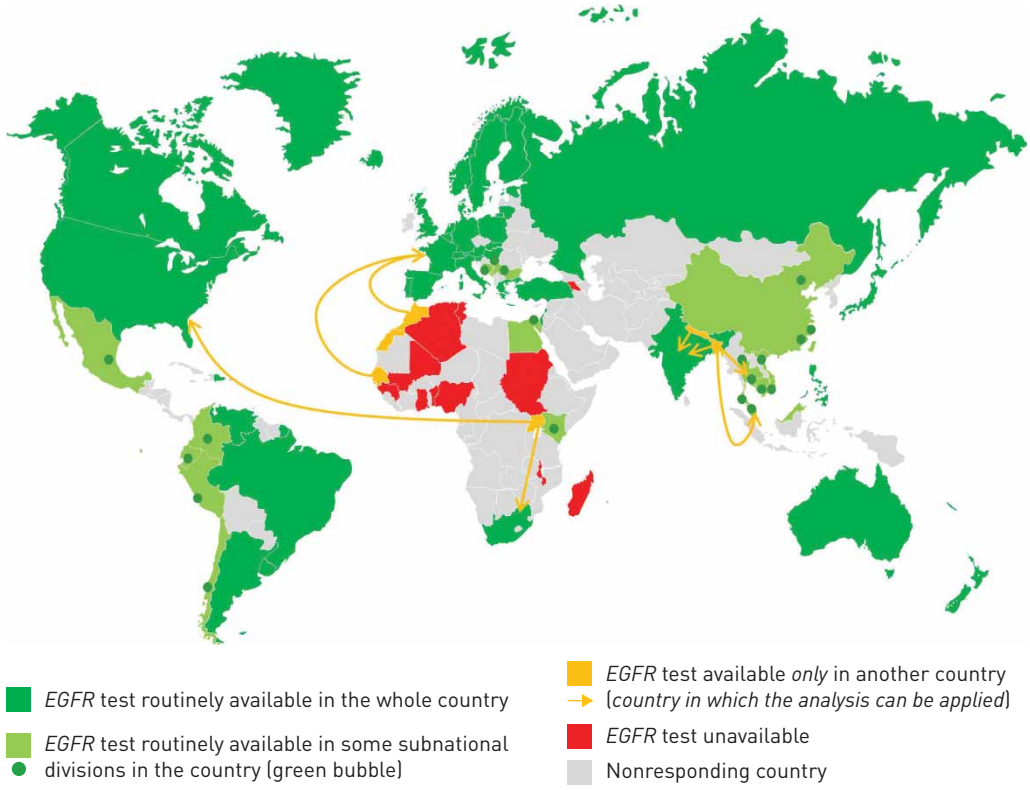

FIGURE 1 Worldwide map of the availability of epidermal growth factor receptor gene (*EGFR*) mutation testing. Study conducted between April 2014 and November 2014.

TABLE 1 Epidermal growth factor receptor gene (*EGFR*) mutation test availability and cost in routine practice[#]

	Countries	Percentage of all countries worldwide	Percentage of responding countries	Population	Percentage of worldwide population
Availability					
Available in the entire country	41	21.1	55.4	2 659 009 211	40.3
Available only in some subnational divisions of the country	16	8.2	21.6	1 939 114 316	29.4
Not available locally but available in another country	5	2.6	6.8	249 076 633	3.8
Not available	12	6.2	16.2	304 108 112	4.6
Subtotal	74	38.1	100.0	5 151 308 272	78.1
Missing	120	61.9		1 440 063 291	21.9
Total	194	100.0		6 591 371 563	100.0
Cost US$					
Free	18	9.3	30.0	428 904 771	6.5
<100	6	3.1	10.0	247 280 672	3.8
100–499	25	12.9	41.7	2 127 197 588	32.3
500–1000	7	3.6	11.7	459 828 372	7.0
>1000	2	1.0	3.3	21 405 361	0.3
Unknown but not free	2	1.0	3.3	14 456 044	0.2
Subtotal	60	30.9	100.0	3 299 072 808	50.1
Missing	134	69.1		3 292 298 755	49.9
Total	194	100.0		6 591 371 563	100.0

Data are presented as n or %. [#]: study conducted between April 2014 and November 2014.

The availability and cost of both erlotinib and gefitinib were positively and negatively, respectively, associated with HDI. Data for afatinib were similar (not shown). The availability and cost of icotinib were not associated with HDI (not shown). Therefore, erlotinib was available in 98% of very high and high HDI countries, but only in 57% of low and medium HDI countries ($p<10^{-4}$). We observed similar results for gefitinib, which was available in 85% of very high and high HDI countries and 43% of low and medium HDI countries ($p<10^{-4}$). Finally, erlotinib and gefitinib were free in 53% and 49%, respectively, of very high and high HDI countries, but they were not free in any medium and low HDI countries ($p<10^{-4}$ for all) (figure 5 and online supplementary table S6 for area/country of specific interest).

Discussion

The results of the present study covered 78% of the worldwide population. We showed that *EGFR* mutational analysis was available for 70% of the worldwide population and for 42.6% thereof at a mean cost of <US$500. Erlotinib was the most widely available EGFR-TKI, accessible for 75% of the worldwide

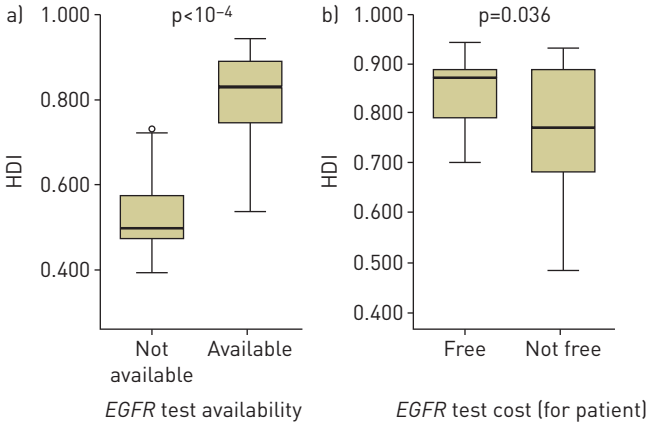

FIGURE 2 Epidermal growth factor receptor gene (*EGFR*) test a) availability in the country (whole or some subnational divisions only) and b) cost. Data are presented as boxplots showing median (interquartile range) of the 2013 Human Development Index (HDI). An outlier is indicated by a circle. Study conducted between April 2014 and November 2014.

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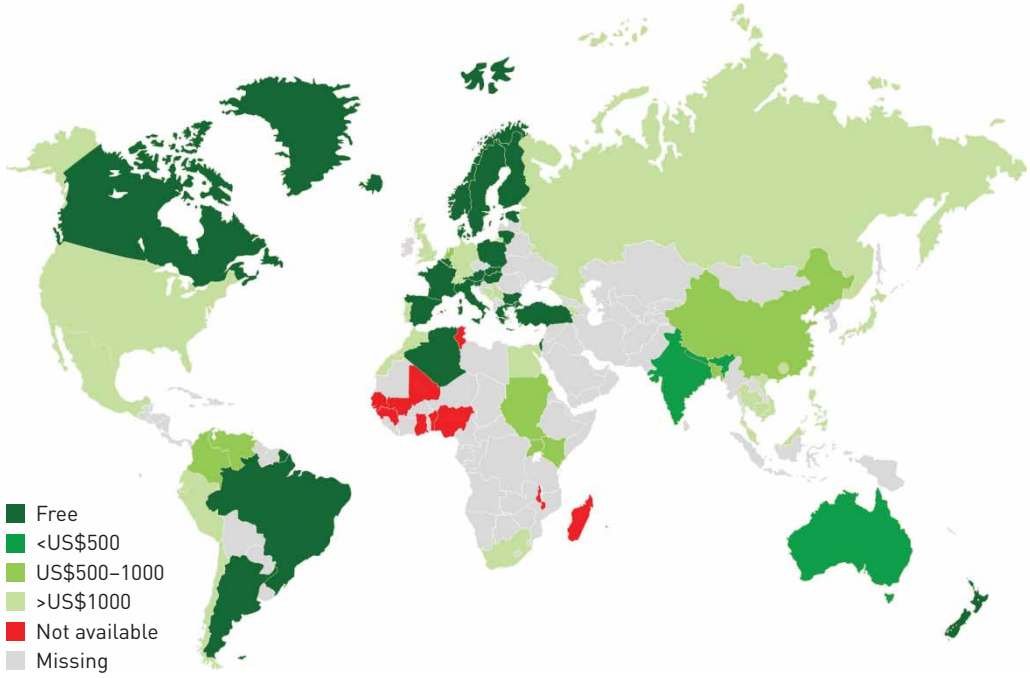

FIGURE 3 Erlotinib availability and cost. Study conducted between April 2014 and November 2014.

population and for 30% thereof at a mean cost of <US$500. We found a clear association between a low/medium HDI rank and the unavailability of *EGFR* testing or EGFR-TKIs. Similarly, we illustrated an association between low/medium HDI rank and higher costs for tests or treatments.

To the best of our knowledge, our study is the first of its kind. Yatabe *et al.* [11] published a retrospective study involving 40 sites in 11 Asian-Pacific countries. Their objective was to determine the proportion of patients who benefited from *EGFR* analysis in routine practice in 2011. They reviewed 22 000 medical files and reported that 31.8% of the patients had been tested for *EGFR* mutations. Although they found disparities between countries (64.8% of patients tested in Japan *versus* 18.3% in China), they performed no comparisons. Other retrospective studies have focused on *EGFR* mutation risk factors, patient eligibility for the analysis, mutation

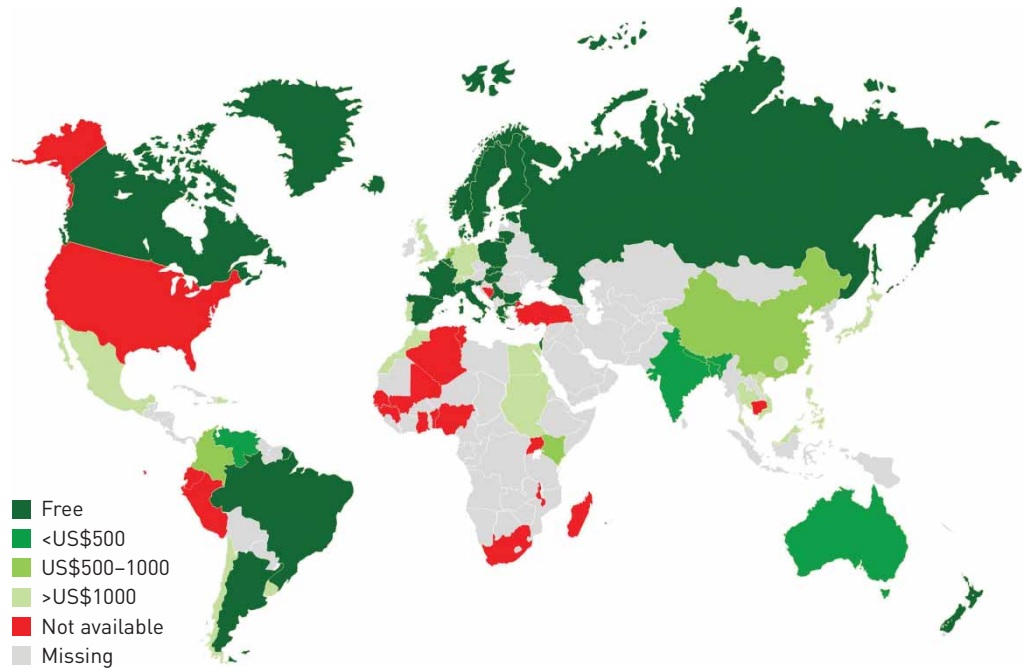

FIGURE 4 Gefitinib availability and cost. Study conducted between April 2014 and November 2014.

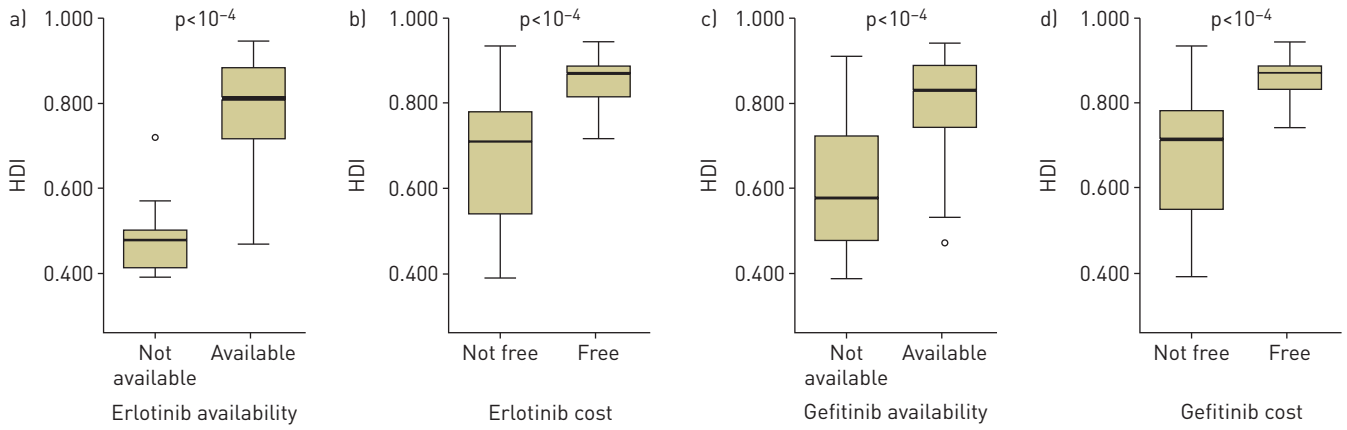

FIGURE 5 Erlotinib a) availability and b) cost. Gefitinib c) availability and d) cost. Data are presented as boxplots showing median and interquartile range of the 2013 Human Development Index (HDI). An outlier is indicated by a circle. Study conducted between April 2014 and November 2014.

analysis techniques and the application of national therapeutic recommendations when they exist [12–14], but these efforts were uniquely national in scope, with no international comparisons.

Our present study illustrated differences in patient access to diagnostic tests and their associated treatments as a function of country development level. These differences may have several explanations, including not only the specificity of the equipment and knowledge needed for mutation testing, but also delays in the transfer of competencies to lesser developed countries. Furthermore, the costs of the techniques and the deployment of networks require substantial investments at the national level. Another limiting factor is cost remaining for the patient. Indeed, our study illustrated that only very highly developed countries provide these analyses and treatments with no direct out-of-pocket expenses for the patient. This problem surely limits the development of and access to innovative practices and treatments, even though early diagnosis and surgery remains the best way to cure lung cancer [15]. Finally, despite the fact that lung cancer causes more deaths than any other cancer worldwide and that 80% of these deaths occur in low-resource countries, the malignancy is not a public health priority in numerous underdeveloped countries, where infectious diseases remain the leading cause of mortality [16, 17].

As is the case for all specialist opinion surveys, our study does have limitations. First, we received responses from only 74 of the 194 UN Member States, which creates a selection bias in our study. We did, however, demonstrate that most of the nonresponding countries had a low HDI. Furthermore, many had a political context poorly suited to responding to this type of survey (see online supplementary material) and many had small populations. Given the low HDI rank of the nonresponding countries, we feel that it is unlikely that they have this analysis routinely available and consequently it is unlikely that our results are underestimated. Second, our survey is based on responses provided by specialists, which introduces an interpretation bias in our study. Indeed, it is possible that some of the responding specialists were unfamiliar with the situation at the national scale, noting that for some countries we had difficulties just finding someone willing to respond to our survey. We were pleasantly surprised, however, to observe that in countries where there were multiple responding specialists, these latter usually provided comparable responses concerning the most important issues, *e.g.* the availability of *EGFR* testing and EGFR-TKIs. Moreover, costs should be interpreted with caution since experts may have misinterpreted the order to retain remaining cost for the patient and not the global cost (*i.e.* for patient and public health insurance/system). However, our results are linked to the HDI, which may be interpreted as an indirect evidence of data quality. Third, there is likely variability in the availability (and the cost) of *EGFR* testing and EGFR-TKIs in nations functioning on a federal model, within which subnational divisions have autonomy in health provision. This is all the more so a problem in that it often concerns nations with large populations (USA, India, Brazil, China, *etc.*). Results may also be biased by the type of health insurance system in each country (ranging from fully government to fully private) which is not assessed by the HDI. Moreover, some other factors, not recorded in this study, may influence EGFR-TKI availability and/or cost, such as reimbursement status or local formulary approval. For EGFR testing, the method of testing (panel *versus* single gene) may also impact our results. Fourth, our study is a cross-over survey (conducted between April 2014 and November 2014). Thus, some data may have been outdated when published. One strong example is the recent approval of gefitinib for the USA [18].

Despite these limits, our study does provide a glimpse of the current, worldwide availability of *EGFR* mutation testing and associated treatments. We hope that our results can be a launching point for the creation of a worldwide network to implement and follow-up upon such mapping in the future.

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Our study also has strengths. To the best of our knowledge, it is the first to assess the availability of *EGFR* mutation testing and resulting treatments at a worldwide level. Furthermore, we used a very simple questionnaire that could be sent by E-mail and completed rapidly. It comprised single-response questions, from which homogenous and comparable data were collected. With this questionnaire, we were able to collect responses from 100 specialists capable of describing the situation for 78% of the worldwide population. Our study also benefited from the support of several international academic associations (ERS, APSR, ALAT, and the Thoracic Society of Australia and New Zealand), which strengthened its reach and stature. To the best of our knowledge, the present study is also the first to consider its end-points in comparison with a reliable index of national development.

Thus, 10 years after the arrival of molecular analysis and targeted therapies in thoracic oncology, our study is the first to underline the lack of access to these undeniably efficacious technologies and treatments [3] in low HDI countries.

The data retrieved from our survey enabled an unprecedented cartography of worldwide access to *EGFR* molecular analysis techniques and EGFR-TKIs. Therefore, in 2014, essentially in poor countries, a significant number of patients may have been candidates for these highly effective treatments, but incapable of receiving them. Participating in clinical trials, developing generics, deploying molecular genetics networks, creating public–private partnerships, and strengthening the roles of international institutions and academic associations are all possibilities that must be explored to improve access to these effective but costly innovative technologies.

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