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Review

Plasma *EGFR* mutation testing in non-small cell lung cancer: A value proposition

Michael Oellerich[a,*], Robert H. Christenson[b], Julia Beck[c], Philip D. Walson[a]

[a] Department of Clinical Pharmacology, University Medical Center Goettingen, Goettingen, Germany
[b] Department of Pathology, University of Maryland, Baltimore, MD, USA
[c] Chronix Biomedical, Goettingen, Germany

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ABSTRACT

Genomics-driven precision medicine using targeted therapies requires advanced molecular diagnostic tests. Decisions about the use and reimbursement for such tests are increasingly being made on the basis of more outcome-based and value-based approaches. The value proposition concept is a tool to assess the benefits of laboratory testing to each stakeholder of the care pathway with respect to outcomes. This concept was applied to the use of noninvasive plasma epidermal growth factor receptor (EGFR) mutation testing in patients with advanced or metastatic non-small cell lung cancer (NSCLC) to guide treatment with EGFR tyrosine kinase inhibitors (TKIs). Using the value proposition framework, we evaluated published key evidence regarding clinical validity, economic implications, and limitations of this approach. It has been shown that plasma *EGFR* mutation testing is essential for guiding clinical decisions regarding prediction of eligibility of individual patients for TKI treatment, real-time monitoring, or adjustment of treatment regimens and tracking resistance. The appropriate use of plasma *EGFR* mutation testing has been shown to deliver both clinical and economic benefits to stakeholders across the entire care pathway; especially in clinical situations where biopsy material is inadequate or unavailable and where it leads to fewer tissue biopsies.

1. Introduction

Healthcare systems are more pressed than ever to be cost effective. For this reason there is growing acceptance of value based assessments, judging outcomes relative to costs, i.e. the Benefit/Cost ratio, to optimize efficiency and determine the value of treatment [1]. For laboratory medicine, development of value-based strategies will be essential for providing more accurate, cost-effective tests for precision diagnostics [2]. A value proposition for individual test utility must be assessed in the context of a patient-centered care pathway. Precision diagnostics allow physicians to predict more accurately which treatment strategies for a particular disease will be effective for individual patients, in contrast to a one-size-fits-all approach. Precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle for each person" [3]. As a result of this approach, there is increasing integration of new molecular and genetic analysis into clinical diagnosis and treatment. One of the fastest growing areas is in oncology. Healthcare systems must be prepared to accept and adopt the use of next-generation sequencing and digital PCR for diagnosis and therapeutic guidance. Emerging clinical applications in molecular diagnostics include use of circulating tumor DNA as a "liquid biopsy" to assess tumor genomes.

A useful value proposition approach for laboratory medicine has been described [4] where the value of an individual test is expressed in terms of outcomes resulting from its use in guiding clinical decision making, the process of care delivered, and resources required to deliver that care. The work for this document was performed on behalf of the IFCC/WASPaLM Committee for the Value Proposition in Laboratory Medicine.

We applied the value proposition concept to the use of plasma based testing for *EGFR* mutations in patients with advanced non-small cell

Abbreviations: BEAMing, beads emulsion amplification magnetics; ddPCR, droplet digital polymerase chain reaction; EGFR, epidermal growth factor receptor; FFPE, fresh formalin-fixed paraffin-embedded; IASLC, International Association for the Study of Lung Cancer; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TMB, tumor mutational burden

* Corresponding author.
E-mail address: michael.oellerich@med.uni-goettingen.de (M. Oellerich).

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Table 1
Key steps in a value proposition for laboratory tests.
Adapted from Ref. [4].

1. Define the unmet clinical need
2. Identify the test
3. Patient population
4. Test intervention utility
5. Define outcome
6. Location where test performed
7. Quality of evidence available
8. Part of care pathway in which the test will be used
9. Stakeholders involved in delivering and receiving care identified in the care pathway
10. Define benefits to each stakeholder in relation to the outcome identified above
11. Define any potential risks associated that might be associated with introduction of the test, and propose mitigation strategy
12. Resource/activity contributed by each of the service lines involved in the care pathway with and without the test intervention
13. Determine the reimbursement received for delivering the care pathway with and without (before and after the test intervention)
14. Briefly set out a proposed implementation plan including the metrics for monitoring appropriate adoption
15. Summary of the Value Proposition in two sentences

lung cancer (NSCLC).

2. Methods

The value proposition concept for laboratory medicine involves applying a framework of 15 steps [4]. Key steps include identifying the unmet clinical need, the patient population that will benefit, the quality of evidence available, and the benefits to each stakeholder involved in delivering or receiving the care (Table 1).

We have applied these steps to selected, published literature describing the use of testing for *EGFR* mutations in patients with advanced NSCLC as an example of companion diagnostic markers that are rapidly gaining relevance in cancer precision medicine.

Published data from studies with evidence determined to be relevant for the 15 steps were used to construct the value proposition for plasma based testing for *EGFR* mutations as a guide to personalized treatment of NSCLC patients. When multiple mutation test options were available, their uses were compared with respect to cost, practicality, and validity. Where gaps in available data necessary to complete the value proposition were identified, suggestions were made for bridging these gaps.

3. Results and discussion

3.1. Unmet clinical needs

Lung cancer is a leading cause of cancer-related death [5], with 1.6 million cases worldwide of which 85% of patients have NSCLC [6]. Over 60% of NSCLC patients present with advanced or metastatic disease at the time of diagnosis so that a curative surgical resection is often not an option. The discovery of *EGFR* gene alterations as drivers of NSCLC has led to the development of targeted therapy using TKIs (inhibitors of the EGFR tyrosine kinase domain). Targeted therapy has become the standard of care and has led to improved clinical outcomes in patients whose tumors harbor such *EGFR* activating mutations. There is an unmet need to rapidly, accurately and cost-effectively predict the eligibility for the molecular targeted therapy with TKIs over time in all patients with NSCLC. This is especially important when an invasive biopsy is impractical or tumor tissue is either unavailable or insufficient for testing [5].

The tumor genome plays an important role in the response to TKIs. Specific tumor *EGFR* encoding activating mutations within the kinase domain (*EGFR* mutations in exons 18, 19, 21) result in enhanced tumor sensitivity to the kinase inhibitors [7]. Most mutations in exon 20 are associated with resistance to TKIs (e.g. *EGFR* T790 M). The EGFR-TKI sensitizing mutation prevalence at initial diagnosis varies; it is only 13% in European, but 47% in Asian patients with lung adenocarcinoma [8]. Furthermore, because the tumor genome often changes over time and in response to therapy, repetitive, real-time molecular monitoring of NSCLC tumor dynamics, in particular for drug resistance mutations, is needed to personalize and increase the cost effectiveness of therapy of patients with advanced NSCLC [9].

Additionally, when *EGFR* independent resistance mechanisms [10] occur alternative sequencing methods of circulating tumor DNA (ctDNA) are required, especially when non-targeted approaches, such an immunotherapy, are used (see Section 3.11 below).

3.2. Identify the test

Different technologies have been developed to detect *EGFR* mutations in plasma ctDNA [7]; including sensitizing and T790 M resistance mutations. Currently utilized tests include: therascreen® (Qiagen), cobas® EGFR Mutation Test v2 (Roche), digital PCR with BEAMing technology (beads, emulsions, amplification, magnetics; Inostics), droplet digital PCR™ (BioRad) as well as next-generation sequencing (NGS) with e.g. MiSeq (Illumina) [10,11]. An adequate diagnostic specificity is of particular importance for detecting sensitizing mutations to prevent treatment failure. There are both fully quantitative plasma *EGFR* mutation tests (e.g. ddPCR™, BioRad, (BEAM)ing dPCR, Sysmex Inostics) and only semi-quantitative tests (e.g. therascreen®, Qiagen; cobas® EGFR Mutation Test v2, Roche) [7]. While some preliminary data on the diagnostic performance of these platforms have been published [7,10,12] as yet there is no established 'gold standard' available against which to evaluate these evolving tests. High sensitivity (78–100%), specificity (93–100%) and concordance (95–97%) using a tissue test as a non-reference standard has been observed (Table 2) with the cobas® EGFR Mutation Test, the therascreen® EGFR ARMS assay, ddPCR™, and the (BEAM)ing dPCR for *EGFR* sensitizing mutation L858R [12]. For the detection of plasma T790 M resistance mutation a cross comparison study of 4 platforms, cobas®, therascreen®, ddPCR™, and BEAMing (Table 3), showed a sensitivity of 41%, 29%, 71%, and 71% respectively, and a specificity of 100%, 100%, 83%, and 67 respectively [12]. Digital platforms appeared to detect a higher percentage of T790 M mutations (concordance 70–74%) compared with non-digital platforms (57–48%) [12]. In a further study, the cobas® plasma test detected the T790 M mutation in 61% of tissue-positive patients [13] demonstrating why patients with a negative plasma result should undergo tissue testing, if possible. In addition, the respective sensitivity, specificity, and concordance of the cobas® EGFR Mutation Plasma Test as compared with a plasma MiSeq NGS (Illumina) analysis was 93%, 92%, and 92% for the detection of T790 M [13].

In Table 4, discordant results between tissue and plasma testing from a study of 72 patients are shown [12]. Negative results in plasma from patients with positive tissue results were associated with low T790 M allelic fraction ($\leq$ 0.2%). Negative results in tumor tissue from patients with positive plasma results may be due to tumor heterogeneity. On the basis of clinical responses, it was suggested that in patients where plasma was positive but tumor tissue was negative for T790 M, the plasma result was more predictive for outcome [12]. A

Table 2
Performance of platforms for plasma testing of L858R *EGFR* mutation.
Data from Ref. [12].

Platform	Sensitivity %	Specificity %	Concordance %
cobas® EGFR, qPCR	90	100	97
therascreen® qPCR	78	100	95
ddPCR™	90	100	97
BEAMing dPCR	100	93	95

Tissue test result as non-reference standard.

Table 3
Performance of platforms for plasma testing of *EGFR* T790M resistance mutation.
Data from Ref. [12].

Platform	Sensitivity %	Specificity %	Concordance %
cobas® EGFR, qPCR	41 (73)	100 (67)	57
therascreen® qPCR	29	100	48
ddPCR™	71	88	74
BEAMing dPCR	71 (81)	67 (58)	70

Detectable tumor fraction required: ≤ 1%.
Tissue test result as non-reference standard.

Table 4
Discordant results for tissue and plasma testing in 20 patients for detection of *EGFR* T790M.
Data from Ref. [12].

Tissue		Plasma
cobas® EGFR Mutation Test	BEAMing* dPCR	cobas® EGFR Mutation Test
Positive *N* = 11	Positive *N* = 4 Negative *N* = 7	Negative N = 11
Negative *N* = 9	Positive *N* = 9	Positive N = 7 Negative N = 2
% mutant DNA in positive samples (BEAMing): mean: 0.24; range: 0.021–1.11		

statement paper from the International Association for the Study of Lung Cancer (IASLC) [14] concluded that validated qPCR-based methods are acceptable for targeting *EFGFR* mutations. However, NGS can achieve higher values of sensitivity compared to PCR-based methods. NGS multiplex panel methods detect not only the common T790 M resistance mechanism but are also capable of detecting a spectrum of alterations and may, therefore, be preferred. A positive *EGFR, ALK, ROS1,* or *BRAF* result obtained by NGS in plasma should be considered adequate to initiate first line therapy in NSCLC. A negative result requires a confirmation from tumor biopsy [14,15]. However, NGS multiplex panels are more costly and not widely available and have a much longer turnaround time than qPCR-based methods [14]. A minimum requirement for any utilized testing is detection of ≤1% tumor fraction [16].

3.3. Patient population

The population being considered for the diagnostic intervention described below consists of all patients who have advanced NSCLC [5]. *EGFR* molecular assessment is performed at diagnosis to detect TKI sensitizing mutations and serial (real-time) monitoring is done in patients with disease progression [5,10,12,14].

3.4. Test intervention utility

EGFR testing is useful to identify NSCLC patients that carry the specific *EGFR* activating mutations because they are eligible for TKI treatment with erlotinib, gefitinib, afatinib, or osimertinib. In addition TKI resistance mutations (e.g. T790 M) can be detected. Serial quantification of plasma genotype is useful for early detection of response and disease progression, real-time monitoring or adjustment of treatment regimens, predicting recurrences, and tracking resistance, all of which are required for more effective, 'personalized' use of TKIs [6,17].

3.5. Define outcome

The primary outcomes are longer progression-free (PFS) and overall survival (OS). In addition, there are a number of potential quality of life, operational, and economic outcomes associated with plasma based testing. These include cost savings due to more rational use of TKIs, fewer tissue biopsies, the potential for decreasing turn-around-times, as well as reductions in surgical/biopsy complications and associated costs [7].

3.6. Location where test is performed

The test will be performed in specialized molecular diagnostics laboratories [8] which fulfill the following requirements:

- Laboratory medicine/molecular pathology specialists familiar with specific technology, e.g. NGS, ddPCR, or real-time PCR
- Adequate internal/external quality control
- Appropriate specific laboratory software
- Bioinformatics support

3.7. Quality of evidence available

There are FDA recommendations, a meta-analysis on the use of blood as a substitute for tumor tissue, and various clinical investigations regarding molecular *EGFR* mutation testing available [5–8,17,18].

Cancer pharmacogenomics allows prediction of the efficacy of TKI therapy. The tumor genome plays an important role in the susceptibility to TKIs used in advanced NSCLC and therefore disease response. Tumor *EGFR* encoding activating mutations within the kinase domain result in enhanced tumor sensitivity to these drugs [17].

Originally, *EGFR* activating mutations were tested in tumor tissue. However, because 10 to 50% of patients with NSCLC do not have adequate tumor tissue available for testing *EGFR* mutations and hence guiding therapy, blood has been investigated as an alternative to tumor tissue [5]. In a systematic review, 25 studies including > 2000 patients were evaluated. Most of these studies used targeted sequencing. It was concluded that blood is a good substitute when tumor tissue is insufficient for testing *EGFR* mutations to guide EGFR tyrosine kinase inhibitors treatment. In cases with negative plasma test results (e.g. cobas® EGFR Mutation Test v2) an additional tumor tissue (FFPE) *EGFR* test is recommended if possible.

In addition to *EGFR*, there are a number of other genomic alterations in late stage NSCLC [19]. These include rearrangements of *ALK*, *ROS1*, *NTRK*, rearrangement or mutations of *RET*, mutations of *BRAF*, mutations or amplification of *HER2*, or *MET*. All of these genomic alterations can be easily detected by tissue biopsy. *EGFR* and *BRAF* mutations detection using blood are considered equivalent to tissue biopsy and *HER2* and *MET* as an intermediate reliability option [19]. During treatment, acquired resistance is often the cause of treatment failure after an initially successful therapy. By monitoring of plasma ctDNA, it is possible to identify specific mutations selected by treatment. Of particular interest is a resistance-conferring mutation in *EGFR* (i.e. T790 M), following treatment with first- and second-generation TKIs (e.g. gefitinib, afatinib). This mutation inhibits binding of gefitinib to the EGFR-TKI domain [11], which causes a resistance to this drug. About 50–60% of cases of resistance are mediated by the T790 M mutation [10]. Patients with this mutation must be switched to an alternative therapy with osimertinib. Osimertinib is a mutant-selective TKI with retained potency against NSCLC cells harboring the *EGFR* T790 M resistance mutation with an objective response rate (ORR) of 61% and a median PFS of 9.6 months in T790 M-positive cases [20,21]. It has now also been approved as first line treatment for patients with *EGFR* driver mutations. In one multicenter clinical trial, median PFS for patients receiving first line osimertinib was 18.9 months compared with 10.2 months for patients receiving standard of care EGFR-TKI treatment with first line gefitinib or erlotinib [21]. It remains to be clarified whether baseline T790 M status is a deciding factor in identifying patients that may have greater benefit from osimertinib treatment upfront [21]. There are, however, also additional mutations (e.g. *EGFR* C797S and G724S), which cause resistance to osimertinib [20,21]. *EGFR*

independent resistance mechanisms also occur including alternative kinase activation and over-expression of *HER2* or *MET*. A wide diversity of resistance mechanisms has been described in patients with advanced NSCLC [10]. For example, in a study of ctDNA monitoring in 15 osimertinib-treated subjects positive for T790 M, three molecular subtypes emerged [9]. Six cases acquired the C797S mutation, four cases maintained the T790 M mutation without C797S mutation, and four cases even lost the T790 M mutation despite *EGFR* activating mutations. As this example shows, serial ctDNA monitoring can be useful for guiding changes in EGFR TKI treatment. It has been demonstrated that increasing plasma levels of mutant *EGFR* could be detected up to 16 weeks before radiographic evidence of tumor progression [17]. Plasma T790 M could be identified at progression, generally at somewhat lower levels than the *EGFR* sensitizing mutation.

3.8. Part of the care pathway in which the test will be used

The test will be used in oncology care where current guidelines recommend *EGFR* frontline (i.e. at initial diagnosis) mutation testing in all patients with advanced or metastatic NSCLC to identify patients eligible for therapy with EGFR TKI inhibitors [7,22,23]. Furthermore, the test is used in TKI treated patients with systemic progression. *EGFR* T790 M testing is a standard-of-care predictive biomarker for therapeutic stratification. It has also been shown that in case of a false negative result for T790 M mutation in tumor tissue, the liquid biopsy test result was helpful in making the correct clinical decision [24]. In patients with the *EGFR* T790 M mutation whose disease progresses despite treatment with erlotinib, gefitinib, or afatinib, the standard therapy is osimertinib.

3.9. Stakeholders involved in delivering and receiving care identified in the care pathway

The stakeholders involved include:

- patients whose care is impacted by the results and who need reassurance they are receiving the most effective treatment;
- oncologists who make decisions based on the findings and need evidence that they are providing the best care possible;
- laboratory medicine specialists/molecular pathologists who analyze and interpret the test results;
- hospital management and insurance companies/public payers who are involved in providing value-based healthcare.

3.10. Define benefits to each stakeholder in relation to the outcome identified above

Patients benefit from having their treatment tailored to the genetic make-up of their tumor. If an *EGFR* driver mutation is detected they are eligible for TKI therapy, with a relatively low adverse event profile and proven chances of prolonged OS. The detection of resistance mutations during TKI treatment allows for timely change of treatment; up to 12–24 weeks before radiological confirmation of progression. Consequently, there is a potential for longer PFS. Plasma *EGFR* testing can be particularly useful for patients with disease progression and resistance to their current TKI therapy. Avoiding repeated biopsy is a further significant benefit as patients with advanced or metastatic NSCLC have an increased risk of complications such as pneumothorax.

Oncologists benefit from being able to identify patients with NSCLC targetable with TKIs, providing a treatment option vs. conventional chemotherapy. Blood based *EGFR* testing allows for real-time molecular monitoring of TKI treatment, predicting recurrence, tracking resistance, personalizing therapy and more effective use of TKIs.

Laboratory medicine specialists/molecular pathologists can benefit from the expansion of their specialized laboratory services in molecular diagnostics and by providing specialized consultation regarding the use and interpretation of ctDNA *EGFR* tests.

Hospital managements and insurance companies/public payers benefit from cost savings from avoiding ineffective use of expensive new anticancer drugs and fewer biopsies.

3.11. Define any potential risks that might be associated with introduction of the test, and propose mitigation strategies

False negative results can occur, in particular in small tumors (i.e. < 1 cm), due to insufficient mutant DNA fraction < 0.01% (≤ 1 cp ctDNA) [25]. In such cases, an additional tumor tissue (FFPE) *EGFR* test is necessary. The detectable tumor fraction (≤ 1% required) using the employed test must be considered in the interpretation [16].

EGFR-independent resistance mechanisms such as alternative kinase activation or over-expression of *HER2* or *MET*, can be responsible for disease progression despite a negative T790 M result [10,19]. In such T790 M negative cases, standard treatments include platinum- and taxane-based chemotherapies. A possibility for monitoring therapeutic responses when such EGFR-independent mechanisms are present is the use of a more global molecular approach based on chromosomal instability assessment in tumor-derived cell-free DNA expressed as a copy number instability (CNI) score [26]. Studies, for example, are ongoing to assess the role of immune checkpoint inhibitors in the treatment of T790 M negative patients with *EGFR* TKI resistant tumors [10]. Previous investigations have shown that the CNI score was useful for outcome prediction during immunotherapy with checkpoint inhibitors in patients with several cancer types including NSCLC [26].

Immunotherapies (e.g. PD-1 or PD-L1 inhibitors) have become an alternative to conventional chemotherapy. For selection of patients for immunotherapy biomarkers such as PD-L1 expression, tumor mutational burden, and microsatellite instability [27–29] are available. Studies on the effectiveness of such therapy in NSCLC with correlation to tumor mutational burden (TMB) in plasma suggest a higher rate of response if the TMB is found to exceed a certain (yet not well defined) threshold [30]. In a study with fist-line nivolumab plus ipilimumab in advanced NSCLC the objective response rate was 30% [31]. TMB ≥ 10 mut/Mb determined in tumor biopsy specimens was associated with improved response in both tumor PD-L1 expression ≥1% and < 1% subgroups [31]. To date, however, there is no published study showing that the TMB in plasma can be effectively used as an eligibility criterion for identifying which NSCLC patients are more likely to benefit from potentially life prolonging immunotherapy. A large study of patients with metastatic NSCLC [32] compared the outcomes of treatment with either the PD-L1 inhibitor atezolizumab or docetaxel and measured TMB in plasma cfDNA. Treatment was successful in 75% of patients and the concordance with tumor tissue was 69%. From the deposited data of the validation group (OAK-trial analyzable: $n = 290$ docetaxel and $n = 293$ atezolizumab), it could be shown that the OS was substantially better in the PD-L1 inhibitor treated group compared to patients given the taxane based regimen (Hazard ratio 0.6378; CI^{95}: 0.527 to 0.772; $p < .001$). Nevertheless, in the PD-L1 inhibitor treated group no difference in OS between the high and low plasma TMB group was detected (Hazard ratio 1.071; CI^{95}: 0.777 to 1.475; $p = .67$). Another, smaller study [30] of NSCLC and melanoma patients which compared responses and TMB, showed that 6 of 9 patients with complete or partial response (assessed by RECIST) had high TMB (2/3); showing that if the TMB was used for therapy selection 1/3 of patients with objective benefit would have been excluded from effective immunotherapy.

PD-L1 expression measured by immunohistochemistry [31] and (as shown above) overall TMB are imperfect predictors of response in NSCLC [33]. At present a pharmacodynamic monitoring approach testing the individual tumor cfDNA changes in plasma (CNI score) when receiving immunotherapy seems to be a better approach [26]. Using the CNI score individual patients can be identified who do versus do not benefit from treatment with immune checkpoint inhibitors; including

some who might otherwise be excluded from immunotherapy based on their TMB results. Payers would benefit from such identification since it would allow for early discontinuation of expensive therapies when no therapeutic effect is detected. Patients would also benefit by avoiding the burden of adverse effects from receiving an ineffective therapy.

For reliable test results using NGS, ddPCR or real-time PCR, competent and experienced laboratory medicine specialists are required. Appropriate validation of the employed methods and adequate internal and external quality control are also necessary. A recent external quality control trial for *EGFR* T790 M mutation testing in blood samples showed that this procedure can be successfully integrated into routine molecular diagnostics [34]. In addition, a recent publication demonstrated that standard clinical chemistry assay validation protocols can be applied to quantitative ddPCR *EGFR* assays. This will allow accurate quantitative monitoring of patients using cell-free DNA in oncology applications [35]. In addition, appropriate specific laboratory software and bioinformatics support are required (especially if NGS methods are used). Further automation would be useful, in particular for ctDNA extraction.

3.12. Resource/activity contributed by each of the service lines involved in the care pathway with and without test intervention

Initial choice of TKI therapy and monitoring for resistance and selection of alternative treatments is not possible without tissue and/or plasma EGFR mutation testing.

3.13. Determine the reimbursement received for delivering the care pathway with and without (before and after) test intervention

EGFR mutation testing has a relevant economic impact on costs of care (Table 5). TKI treatment is expensive; the costs per day are, for example, 96 € for erlotinib (150 mg/day), or 150 € for gefitinib (150 mg/day) [36]. According to a survey from the National Institute for Health and Care Excellence in England (based on data from 7 companies), the average costs for a plasma *EGFR* mutation test is 196 € (172 £) [7]. The costs per tumor tissue *EGFR* test are 165 € (145 £) without tissue biopsy, 1835 € (1610 £) for a biopsy of paratracheal and peribronchial intraparenchymal lung lesions, and 492 € (432 £) for CT-guided biopsy. Reduction of biopsies due to noninvasive *EGFR* mutation testing using plasma cell-free DNA can save costs.

Use of immune checkpoint inhibitors in the treatment of NSCLC is also associated with high costs (nivulomab 1804 € for 100 mg/10 ml; pembrolizumab 4433 € for 100 mg). In patients receiving such treatments, early detection of response is essential. Use of new therapy monitoring tests like the CNI score can be used to detect lack of response before this is obvious using imaging tests [26]. This therefore may have major potential for costs savings.

Compared to the treatment costs, plasma *EGFR* testing costs are low.

Table 5
Costs for TKI treatment and *EGFR* mutation testing.
Data from Ref. 7, 36.

TKI treatment costs per day
• 96 € for erlotinib
• 115 € for gefitinib
Standard *EGFR* mutation tissue testing
Costs:
• 165 € without tissue biopsy
• 1835 € with biopsy (EBUS-TBNA)*
• 492 € with CT-guided biopsy
Plasma *EGFR* mutation testing
Costs:
• 196 €
Reimbursement
• 426 € without tissue biopsy (EBM, Germany)

* Endobronchial ultrasound-guided transbronchial needle aspiration.

Reimbursement structures vary in different countries. In Germany, the reimbursement from the statutory health insurance system is 426 € for determination of plasma *EGFR* activating mutations (exons 18–21) alone or in combination with the T790 M *EGFR* mutation [16].

Previously tumor tissue was primarily used for detecting *EGFR* mutations [37]. There are limitations associated with this approach, such as availability of biopsy specimens, especially when re-biopsy is necessary to evaluate resistance. In addition, there are biopsy risks (e.g. pneumothorax) and the presence of intra-tumor heterogeneity within the same patient may result in misdiagnosis. Current and future practice in molecular pathology/laboratory medicine involves an increased use of noninvasive genotyping for detecting *EGFR* mutations in plasma ctDNA [5,19,38]. Tumor tissue testing however is necessary in the absence of positive plasma ctDNA results. In cases with disease progression and negative *EGFR* T790 M mutation results, alternative noninvasive methods for detecting resistance are required, such as the CNI score [26].

3.14. Briefly set out a proposed implementation plan including the metrics for monitoring appropriate adoption

Implementation requires the availability of an appropriate PCR system, e.g. cobas, ddPCR, or an NGS instrument. The cost for a mid-size Illumina system (e.g. NextSeq 550) is approximately 350,000 €; the cost for a ddPCR device is approx. 80,000 €. In either case, qualified laboratory medicine specialists and technicians are required. It is possible that the availability of appropriate reference centers could both decrease costs and increase the quality of such testing.

Metrics for monitoring appropriate adoption include the number of tests performed, the quality of the results produced, the number of patients correctly assigned to treatment options, as well as improvements in clinical outcomes (e.g. PFS, OS, ORR), as well as overall costs of care. A recent study has shown that the use of tissue biopsy alone was not cost-effective [39]. Adding liquid biopsy to the diagnostic pathway would identify a greater number of cases and thereby help to improve treatment. Plasma-based testing for *EGFR* mutations is now entering clinical use after initial approvals by regulatory authorities [38]. It has accelerated clinical decision-making and translational research.

3.15. Summary of the value proposition

EGFR mutation testing based on plasma ctDNA in combination with tumor tissue (when required and feasible) is necessary to decide whether TKIs can be used in a patient diagnosed with NSCLC. For serial monitoring plasma *EGFR* testing is useful to track the dynamic genomic evolution of a patient's tumor, and for detection of acquired resistance mutations. Cost savings due to a more effective use of expensive treatments, reduction of biopsies, and improved outcomes are further important considerations.

4. Conclusion

The value proposition concept framework was applied to the use of plasma tumor DNA testing, such as *EGFR* mutation detection in adult patients with locally advanced or metastatic NSCLC. The framework was useful to demonstrate the overall value and innovative aspects of this new, noninvasive testing strategy based on ctDNA in plasma rather than universally used histopathological assessment of tumor tissue. The value proposition indicates that plasma *EGFR* mutation tests are changing clinical practice as an addition to tissue *EGFR* testing. Positive results can be used to inform decisions about prescribing TKIs. Detection of *EGFR* resistance (e.g. T790 M mutation) in plasma has been useful for identifying patients eligible for alternative treatments. Identification of *EGFR*-independent resistance mechanisms is important to identify patients most likely to respond to immunotherapy and biomarkers for monitoring response to these new treatment options. The

efficient allocation of existing resources is essential for healthcare systems [40] and the value proposition concept will be helpful to support this. There is potential for positive economic impact of plasma *EGFR* mutation testing as a result of cost savings generated by more effective treatment selection and fewer tissue biopsies. We concur with a recent statement by a panel of experts from the International Association for the Study of Lung Cancer (IASLC) that implementation of the discussed liquid biopsy approaches is justified in specific therapeutic settings relevant to NSCLC [14]. On a broader scale, monitoring responses using tumor cell-free DNA dynamics during therapy has the potential to further improve the management of NSCLC patients.

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