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Original Article

Full cost of diagnostic pathology for lung carcinoma in Italy: results from four Pathology Units

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Summary

Objective. To calculate the full cost of diagnostic pathology tests for Non-Small Cell Lung Cancer (NSCLC) across four Italian Pathology Units.

Methods. Pathology Units were located in private (2) and public (2) hospitals distributed across the Italian territory (North: 2; Centre: 1; South: 1). Pathologists provided via questionnaire data on tests on NSCLC samples along with the identification and quantification of the necessary healthcare resources (diagnostic technologies, laboratory instruments and personnel). Resources were valued according to hospital-specific unit, yearly and hourly costs (disposables; technologies; professional clusters).

Results. The full cost per NSCLC tissue sample included histopathological immunophenotypic and required molecular analysis. Overall, it reached € 659.77 and it was mainly composed of direct costs (77.69%). The processing of a NSCLC tissue sample was labour intensive, as a relevant share of the full cost (44.98%) was actually due to personnel costs, with laboratory technicians, biologists and pathologist driving this finding (17.09%,12.43% and 10.81%, respectively).

Conclusions. The results of this research can facilitate the negotiation of new dedicated tariffs for NSCLC sample processing with the national or local third party-payers.

Key words: Non-Small Cell Lung Cancer, diagnostic molecular pathology, molecular tests, cost, Italy

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Introduction

In Italy, in 2020, there had been about 41,000 cases of lung cancer (LC) which remains the second most frequent cause of malignancy in men and the third in women. Compared to recent years that take into account the population cancer registries from 2008 to 2016, the incidence trend decreased by 1.7% in men and increased by 3.4% in women. In terms of mortality, LC represents the first cause of death in men and the second in women among all cancers [1,2].

The histopathological classification includes four main histotypes: squamous cell carcinoma; adenocarcinoma; large cell carcinoma; small cell carcinoma [2,3].

The diagnosis can be performed on the basis of a careful evaluation of conventional morphological criteria on hematoxylin-eosin or specific stains (e.g., May-Grunwald-Giemsa or Papanicolaou) for cytological samples. Immunohistochemical (IHC) investigations are fundamental for the precise definition of the poorly differentiated or not otherwise specified Non-Small Cell Lung Cancer (NSCLC) types [3].

The IHC investigations can be applied both to biopsy samples fixed in formalin and to cytological preparations. The preparation of cell-blocks starting from cytological material on effusion or aspiration is of great practical value, especially in consideration of the possibility of analyzing through IHC some of the predictive biomarkers of response to medical therapy, such as the Programmed Death-Ligand 1 (PD-L1) [4].

Lately, the use of molecular investigations like next generation sequencing (NGS) has grown in specialized centers with highly experienced pathologists. The molecular characterization of lung tumors is a fundamental element of the patient's diagnosis and treatment process, in light of the possibility of recommending molecular targeted treatments in populations selected for the presence or expression of a certain marker. In this regard, in all patients with NSCLC in stage IIIB-IIIC (not candidates for loco-regional treatments), and IV, it is recommended to integrate the morphological diagnosis with the molecular characterization of the following genes: EGFR (Epidermal Growth Factor Receptor); BRAF (B-Raf proto-oncogene) mutations; ALK (Anaplastic Lymphoma Kinase); ROS-1 (Proto-oncogene tyrosine-protein kinase ROS); RET gene rearrangements; NTRK (Neurotrophic Tyrosine Receptor Kinase) translocations [2,5].

In addition, there are molecular alterations for which there are currently no drugs approved and reimbursed in Italy, but available only in the context of clinical trials and compassionate use programs or early access programs, such as: MET exon 14, KRAS exon 2 (G12C), PI3KCA, PTEN and activating HER-2 gene mutations or FGFR1 and PDGFR amplifications [4-6].

The current recommendations developed by the collaboration of SIAPeC (Società Italiana di Anatomia Patologica e Citologia diagnostica) and AIOM (Associazione Italiana di Oncologia Medica) suggest the concomitant evaluation of gene mutations, of ALK, ROS1, NTRK 1-3 rearrangements, and the PD-L1 expression profile in tumor cells for the choice of the best therapeutic strategy mostly in advanced stage NSCLC patients [7].

This paper reports on an empirical cost description [8] of the diagnostic pathology tests performed on NSCLC samples across four Italian Pathology Units at the forefront of NSCLC diagnosis.

Materials and methods

Data collection

A questionnaire was developed and sent out by e-mail to a convenience sample [9] of six pathologists between October-November 2020 to receive their feedbacks and validation.

Pathologists practiced in four Pathology Units located in private (2) and public (2) hospitals distributed across the Italian territory (North: 2; Centre: 1; South: 1). Four out of six pathologists practiced in the same Pathology Unit (FB, MA), or in the Pathology Department of the same hospital (PC, MGP); the other two pathologists (MB, PG) worked in different Pathology Units.

Table I. Methods - Patients, diagnostic/predictive tests and staining.

Items	Overall (N)	NSCLC (N)
Patients	**39,357**	**421**
Tissue samples	**58,530**	**724**
Surgery specimen		*149*
Biopsy		*247*
Citology		*178*
Liquid biopsy		*150*
Blocks	**102,008**	**2537**
Surgery specimen		*2162*
Biopsy		*247*
Citology		*128*
Slides	**222,440**	**5120**
H&E		***3351***
Surgery specimen		*2601*
Biopsy		*459*
Citology		*291*
Diagnostic IHC[a]		***720***
Surgery specimens		*253*
Biopsy		*395*
Citology		*72*
Predictive IHC [b]		***1049***
Surgery specimen		*345*
Biopsy		*595*
Citology		*109*
Staining		**2**
Special staining		*2*
Molecular Tests		**582**
FISH		*155*
NGS		*103*
RealTime PCR		*323*

[a] The following diagnostic IHC tests were performed (mean volumes between brackets): TTF-1 (192); p40/p63 (192); CK5/6 (83); CK7 (117); Napsin A (86); Synaptophysin (33); INSM1 (17).
[b] The following predictive IHC tests were performed (mean volumes between brackets): ALK (273); BRAF (46); EGFR (183); ROS1 (165); HER2 (23); NTRK (17); MET (17); RET (18); PD-L1 (307).

All the Pathology Units are endorsed as healthcare service providers by the Italian National Health Service (INHS).
Upon questionnaire approval, experts were requested to provide the following quantitative data: overall number of patients referred to their Pathology Unit; overall volume of tissue samples, blocks, and slides along with the fraction of these specimens related to NSCLC diagnosis (Tab. I).
Data on tests for NSCLC along with the identification and quantification of the necessary healthcare resources (diagnostic technologies, laboratory instruments and personnel) were also detailed in the questionnaire.
When needed, follow-up teleconferences and on-site visits were scheduled with the experts to fix inconsistencies.
All data deliberately refer to 2019, the year before the COVID 19 pandemic outbreak. This methodological choice seems justified in the light of the possible standard activity reduction in all the non-COVID 19-dedicated hospital wards in 2020 that, if considered as a yardstick, might have provided an unreliable representation of the average number of patients and tests processed by each Pathology Unit included in this study.
As the present research did not require patients' enrollment, no Ethics Committee approval of the questionnaire was required by the current Italian legislation [10].

Cost

A cost description [8] (i.e., the valuation of the resources needed to perform a given healthcare service) of two cost objects [11] (i.e., two items of interest for which the cost is calculated, that is NSCLC tissue sample and NSCLC patient in this research) was carried out.
The cost description followed the Pathology Unit viewpoint [8]. Therefore, only costs borne by the Pathology Units that participated in this research were considered.
The cost of a NSCLC patient was obtained by multiplying the cost of a NSCLC tissue sample by the NSCLC tissue samples/NSCLC patient ratio (1.720).
The cost description adopted a full cost approach [11].
The full cost approach implies three types of costs: direct and indirect costs of the Pathology Unit, and overheads [11].
Direct costs value all the resources that can be specifically referred to a single cost object (e.g., the number of minutes needed by a biologist to perform a KRAS test on a NSCLC tissue sample multiplied by her/his gross hourly wage).
Indirect costs include the value of resources that are common to many cost objects (e.g., a microscope is used by pathologists for diverse analyses in addition to the confirmation of a suspected NSCLC diagnosis). Therefore, determining the share of their amount to be assigned to a given cost object is physically unfeasible and/or too expensive.
Moreover, oftentimes indirect costs include resources that are expected to contribute to the activity of the Pathology Unit well after the year of purchasing. Therefore, their purchase cost is allocated over their useful life according to different accounting procedures (e.g., straight line approach, in which the overall cost of the microscope is divided into equal shares of cost per year of its useful life, which is estimated to be 10 years in this research) that go under the name of depreciation [8].

Table II. Methods - Unit, yearly and hourly costs (€ 2019).

Items	Costs
Unit cost[a]	
Biocassette	€ 0.25
Sample	€ 0.04
H&E	€ 0.25
IHC	€ 8.00
IHC predictive marker	€ 50.00
Special staining[b]	€ 4.00
FISH	€ 150.00
RealTime PCR[b]	€ 120.00
NGS	€ 300.00
Yearly cost (mean number of equipments per technology)[c]	
Biocassette printers (3.67)	€ 5967.50
Sampler and citology hoods (4.67)	€ 7748.25
Chemical hoods (4.33)	€ 6123.25
Cytocentrifuges (3.67)	€ 3876.00
Tissue processors (3.33)	€ 11,319.25
Tissue embedding systems (3.67)	€ 4136.00
Microtome systems[d] (11.00)	€ 6430.75
H&E stainers (3.00)	€ 12,079.50
IHC stainers (4.67)	€ 32,725.00
Special stainers (1.33)	€ 5000.00
Microscopes[e] (22.00)	€ 2500.00
Hourly cost[f]	
Pathologist	€ 59.85
Lab technician	€ 27.28
Graduated technician	€ 35.07
Biologist	€ 44.89
Practical nurse	€ 16.83
Administrative clerk	€ 20.95

[a] For each test or slide.
[b] Includes reagent and instrument.
[c] Annual leasing instalment if not otherwise specified.
[d] Includes microtome, cold plate and tissue water bath.
[e] Yearly depreciation share (useful life: 10 years; straight line approach); maintenance included.
[f] Full wage rate: includes net wage, retirement contributions and occupational accident insurance contributions.

A share of the indirect costs was imputed (i.e., assigned) to the NSCLC tissue sample via specific allocation bases (e.g., the annual depreciation of the microscope divided by the overall usages made by the pathologists during that year multiplied by the number of slides stained for a specific NSCLC sample).
Overheads represent fair shares of direct and indirect costs totaled by technostructure (e.g., administration; accounting) and support staff (e.g., cleaning; building maintenance) of the hospital [12].
As technostructure and support staff contribute to the activity of hospital wards and services, their costs were imputed pro-quota to Pathology Units. The shares of overheads imputed to Pathology Units were estimated by multiplying the sum of direct and indirect costs of a NSCLC tissue sample and NSCLC patient by 125%.
Resources were valued according to hospital-specific unit costs (technologies; disposables) and personnel costs (gross hourly cost for different professional clusters) (Tab. II).
The full cost of a NSCLC tissue sample was broken down into the four main steps its production is composed of: Step 1 - Pre-analysis; Step 2 - Analysis - Staining; Step 3 - Analysis - Molecular; Step 4 - Finalization and medical reporting. Whenever necessary each step was detailed in substeps (Tabs. SI-SV).
The full cost of a NSCLC diagnostic characterisation was obtained by averaging over the cost of all the tests necessary to confirm a NSCLC diagnosis.
As anticipated, costs, expressed in Euros (€), date back to 2019.

Results

The full cost per NSCLC sample and per patient was € 659.77 and € 1134.61, respectively, and was mainly composed of direct costs (77.69%) (Tab. III).
Step 3 (Analysis – Molecular) was the most expensive step of the NSCLC tissue sample (€ 239.13), whereas Step 1 (Pre-Analysis) was the cheapest one (€ 71.88). No share of indirect costs was imputed to Step 3 (Analysis - Molecular).
The processing of a NSCLC tissue sample was labour intensive, as a relevant share of the full cost (44.98%) was actually due to personnel costs, with laboratory technicians, biologists and pathologist driving this finding (17.09%,12.43% and 10.81%, respectively).
As far as indirect costs are concerned, IHC stainers were the most remarkable cost item (0.91% of the full cost).
The same percentages hold for the full cost per NSCLC patient, as it was calculated by multiplying the cost per NSCLC tissue sample by a 1.720 constant.
The very same trend has been observed by analyzing in detail each one of the four main steps the production of a NSCLC tissue sample was divided into.
The full cost was steadily led by direct costs, with percentages ranging between 71.18% (Step 1 - Pre-analysis) and 80.00% (Step 3 - Analysis - Molecular), with personnel cost still playing a relevant role, varying from 15.07% (Step 2 - Analysis - Staining) to 78.93% (Step 4 - Finalization and medical reporting).
The indirect costs/full cost ratio ranged between 0.00% (Step 3 - Analysis - Molecular) and 8.82% (Step 1 - Pre-analysis).

Discussion

While the INHS introduced the so-called F file to make expensive hospital drugs available on the Italian territory without stringent financial constraints [13], a similar mechanism aimed at facilitating the widespread adoption of advanced healthcare technologies for the diagnosis of NSCLS histotypes via an easy to apply, fair reimbursement scheme does not exist in Italy, yet. In fact, there is always a lag between the pace at which healthcare science and technologies progress and the INHS decision to reimburse the healthcare services that can benefit from them.
A tariff-based system for reimbursing outpatient healthcare services provided by both public and INHS-endorsed private hospitals, was adopted by the INHS in the early 1990s and was last updated in 2013 [14].
For the sake of precision, a more recent outpatient healthcare services' handbook does exist (named Essential Levels of Assistance 2017). However, at the time of writing, the related tariffs proposed by the Ministry of Health in 2022 have not been approved by the State-Regions Conference, yet.
Interestingly, Italian regions are free to adopt their own tariff-based system (that can well include healthcare services that are not reported in the INHS outpatient healthcare services' handbook, with the provision that regional autonomy comes with the local effort to fund them without any support from the central government) or stick with the national one.
At both national and local levels, a tariff-based reimbursement system pursues two different but related goals. First, setting, without any mandatory negotiation with the providers, the price at which the third-party payer, acting as monopsonist (i.e., the agent that purchases the highest share of the inpatient and outpatient healthcare services produced by public and INHS-endorsed private healthcare organizations) is willing to pay for a given healthcare service. Second, allowing the third-party payer to curb the volume of overprescribed healthcare procedures (usually the most profitable ones for the healthcare organizations) by reducing their tariffs, whereas increasing the re-

Table III. Results-cost description per NSCLC sample and patient (€ 2019).

	Step 1 - Pre-analysis	Step 2 - Analysis - Staining	Step 3 - Analysis - Molecular	Step 4 - Finalization and medical reporting	Total cost per sample	Total cost per patient
Direct costs (%)						
Practical nurse	€ 0.28 (0.39%)	-	-	-	€ 0.28 (0.04%)	€ 0.48 (0.04%)
Administrative clerk	€ 1.05 (1.46%)	-	-	-	€ 1.05 (0.20%)	€ 1.80 (0.20%)
Laborarory technician	€ 42.29 (58.83%)	€ 22.40 (12.04%)	-	€ 48.08 (29.56%)	€ 112.77 (17.09%)	€ 193.93 (17.09%)
Graduated technician	-	€ 5.63 (3.03%)	€ 23.48 (16.06%)	-	€ 29.11 (4.41%)	€ 50.06 (4.41%)
Biologist	-	-	€ 66.61 (20.56%)	€ 15.41 (9.47%)	€ 82.02 (12.43%)	€ 141.05 (12.43%)
Pathologist	€ 6.41 (8.91%)	-	-	€ 64.90 (39.90%)	€ 71.30 (10.81%)	€ 122.62 (10.81%)
Biocassettes	€ 0.88 (1.23%)	-	-	-	€ 0.88 (0.13%)	€ 1.52 (0.13%)
Slides	€ 0.26 (0.37%)	€ 0.75 (0.40%)	-	-	€ 1.01 (0.15%)	€ 1.74 (0.15%)
H&E reagent	-	€ 0.41 (0.22%)	-	-	€ 0.41 (0.06%)	€ 0.71 (0.06%)
IHC staining reagent	-	€ 7.96 (4.28%)	-	-	€ 7.96 (1.21%)	€ 13.68 (1.21%)
Predictive IHC staining reagent	-	€ 72.44 (38.93%)	-	-	€ 72.44 (10.98%)	€ 124.58 (10.98%)
FISH stainers	-	€ 32.11 (17.26%)	-	-	€ 32.11 (4.87%)	€ 55.23 (4.87%)
Special staining reagent + equipment	-	€ 0.01 (0.01%)	-	-	€ 0.01 (0.002%)	€ 0.02 (0.002%)
Reagent + equipment	-	-	€ 96.22 (40.24%)	-	€ 96.22 (14.58%)	€ 165.46 (14.58%)
Other reagents (formaline; alcool)	-	-	€ 5.00 (2.09%)	-	€ 5.00 (0.76%)	€ 8.60 (0.76%)
Total direct cost (A)	**€ 51.17 (71.18%)**	**€ 141.72 (76.16%)**	**€ 191.31 (80.00%)**	**€ 128.39 (78.93%)**	**€ 512.58 (77.69%)**	**€ 881.48 (77.69%)**
Indirect costs (%)						
Biocassette printers	€ 1.43 (1.99%)	-	-	-	€ 1.43 (0.22%)	€ 2.46 (0.22%)
Sampler and citology hoods	€ 0.66 (0.92%)	-	-	-	€ 0.66 (0.10%)	€ 1.14 (0.10%)
Cytocentrifuges	€ 0.26 (0.37%)	-	-	-	€ 0.26 (0.04%)	€ 0.46 (0.04%)
Tissue processors	€ 1.17 (1.62%)	-	-	-	€ 1.17 (0.18%)	€ 2.01 (0.18%)
Tissue embedding systems	€ 0.57 (0.79%)	-	-	-	€ 0.57 (0.09%)	€ 0.98 (0.09%)
Microtome systems	€ 2.25 (3.13%)	-	-	-	€ 2.25 (0.34%)	€ 3.87 (0.34%)
H&E stainers	-	€ 1.16 (0.62%)	-	-	€ 1.16 (0.18%)	€ 1.99 (0.18%)
IHC stainers	-	€ 5.99 (3.22%)	-	-	€ 5.99 (0.91%)	€ 10.30 (0.91%)
Microscope	-	-	-	€ 1.75 (1.07%)	€ 1.75 (0.27%)	€ 3.01 (0.27%)
Total indirect cost (B)	**€ 6.34 (8.82%)**	**€ 7.15 (3.84%)**	**€ 0.00 (0.00%)**	**€ 1.75 (1.07%)**	**€ 15.24 (2.31%)**	**€ 26.21(2.31%)**
Overall (A) + (B)	**€ 57.51 (80.00%)**	**€ 148.87 (80.00%)**	**€ 191.31 (80.00%)**	**€ 130.13 (80.00%)**	**€ 527.81 (80.00%)**	**€ 907.69 (80.00%)**
Overheads[a]	**€ 14.38 (20.00%)**	**€ 37.22 (20.00%)**	**€ 47.83 (20.00%)**	**€ 32.54 (20.00%)**	**€ 131.95 (20.00%)**	**€ 226.92 (20.00%)**
Overall + overheads	**€ 71.88 (100.00%)**	**€ 186.08 (100.00%)**	**€ 239.13 (100.00%)**	**€ 162.67 (100.00%)**	**€ 659.77 (100.00%)**	**€ 1134.61 (100.00%)**

[a] Overheads = [(A+B)*125%]-(A + B).

imbursements for less costly alternatives that are expected to have the same diagnostic accuracy or effectiveness on patient's health.

Consequently, the difference between costs and tariffs becomes crystal-clear: while costs express the economic value of the resources needed to perform a given healthcare procedure when displaced from the best available alternative (cost-opportunity principle),

tariffs are an administrative tool aimed at managing the healthcare system procurement activity [15].
Therefore, theoretically speaking, a well-conceived tariff-based reimbursement system should impose on the third-party payer frequent assessments of the full cost actually borne by healthcare organizations to provide patients with a given healthcare service. This would help to align the tariffs to the value of the resources actually consumed by the healthcare organizations.
In addition, a systematic horizon scanning could help the third-party payer to calculate new tariffs for advanced healthcare procedures for a given disease to be adopted by healthcare organizations consistent with the international guidelines.
Is this the case for the NSCLC sample processing? Unfortunately, the answer is not encouraging.
Skimming through the 2013 INHS outpatient healthcare services' handbook, only *in situ* FISH hybridization (four different tariffs, coded 91.37.2-91.37.5, ranging from € 150.29 to € 342.87) and molecular probe hybridization (one tariff only, coded 91.37.1; € 81.60) are reported [14].
It is clear that the generalized lack of specific INHS tariffs aimed at reimbursing NSCLC diagnostic tests disincentives their widespread adoption and creates sustainability issues for the hospitals patients with a suspected NSCLC are referred to. As a consequence, a limited availability of these molecular tests reduces the likelihood of a homogeneous diagnosis across the Italian territory. In turn, this disparity may hamper the equal access to the most appropriate therapy for NSCLC patients.
The main finding of our study is the detailed breakdown of the real full cost borne by a convenience sample [9] of four Pathology Units at the forefront of the diagnosis and molecular characterisation of NSCLC in Italy.
However, the most striking result of the empirical research detailed in the previous paragraphs is the extreme relevance of the personnel contribution.
The relationship between NSCLC tissue sample processing and labour intensity in the Italian setting was previously highlighted [16,17].
A 5-year budget impact analysis proved the Ventana ALK (D5F3) CDx assay to reduce the oncologists' work load in detecting ALK positive NSCLC patients eligible to crizotinib [16].
In a similar research performed on a sample of 1461 NSCLC patients followed up at 5 Italian oncology units, the scenario that assumed the widest adoption of next-generation sequencing resulted in an overall average personnel time of 1975 hours per center totaled by technicians, biologists and pathologists involved in molecular analysis [17]. However, from the data reported in the article the conversion of personnel time in costs was not feasible.
Actually, it takes years of formal education and on-the-job training [12] to become a proficient and autonomous pathologist dealing with NSCLC sample processing, and, likewise other sectors of medical sciences (e.g., diagnostic imaging), technology cannot completely replace human ability, in terms of reliability of the final outcome of the healthcare procedure, which, in this case, has a substantive bearing on the subsequent appropriate target therapy [7].
The main limitation of this study relates to the small number of pathological anatomy centers investigated and their top-level qualification and expertise in the diagnostic pathology of NSCLC. Therefore, the external validity of our results (especially in terms of direct costs/full cost ratio) should be proved by future, larger empirical studies carried out on a larger sample of Italian Pathology Units.

Conclusions

Priority setting in healthcare should be made on the grounds of real-world evidence.
We are confident that, despite its limitation, the approach adopted in this research can facilitate the negotiation of new dedicated tariffs for NSCLC sample processing with the national or local third party-payers. Hopefully, this study will pave the way to future, empirical cost descriptions aimed at addressing the same topic for other human cancers.

Conflicts of interest

SC and FDP are employees of Roche Diagnostics S.p.A. Monza, Italy. The other authors declare no conflict of interest with this research.

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Ethical consideration

Not applicable.

Authors' contribution

Study design: GF, MB, FB, PC, PG, AM, SC, FDP, MGP. Data acquisition; MB, FB, PC, PG, AM, SC, FDP, MGP; Data analysis: CL, GF, MB, FB, PC, PG, AM, SC, FDP, MGP. Data interpretation: CL, GF, MB, FB, PC, PG, AM, SC, FDP, MGP; Manuscript preparation: CL,GF. Manuscript review: CL, GF, MB, FB, PC, PG, AM, SC, FDP, MG.

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Table SI. Results-cost description per NSCLC sample and patient (€ 2019).

Item	Professional		Disposable		Technology		Total cost per	
	Time (hour) (A)	Cost (hour) (B)	Volume (C)	Cost (unit) (D)	Volume (E)	Cost (year) (F)	Sample[a]	Patient[b]
Step 1 - Pre-analysis								
Substep 1a - Sample reception								
Practical nurse	*0.02*	*€ 16.83*	-	-	-	-	*€ 0.28*	*€ 0.48*
Administrative clerk	*0.05*	*€ 20.95*	-	-	-	-	*€ 1.05*	*€ 1.81*
Laboratory technician	*0.05*	*€ 27.28*	-	-	-	-	*€ 1.36*	*€ 2.34*
Total Substep 1a - Professional							**€ 2.69**	**€ 4.63**
Overall Substep 1a							**€ 2.69**	**€ 4.63**
Substep 1b - Tissue sampling/Cytology								
Laboratory technician	*0.46[c]*	*€ 27.28*	-	-	-	-	*€ 12.13[d]*	*€ 20.86*
Pathologist	*0.36[c]*	*€ 59.85*	-	-	-	-	*€ 6.41[d]*	*€ 11.02*
Biocassette printers	-	-	-	-	*58,350[e]*	*€ 23,870.00*	*€ 1.43[f]*	*€ 2.46*
Sampler and citology hoods	-	-	-	-	*58,350[e]*	*€ 38,741.25*	*€ 0.66[f]*	*€ 1.14*
Cytocentrifuges	-	-	-	-	*58,350[e]*	*€ 15,504.00*	*€ 0.28[f]*	*€ 0.48*
Biocassettes	-	-	*3.50*	*€ 0.25*	-	-	*€ 0.88*	*€ 1.51*
Total Substep 1b - Professional							**€ 18.54**	**€ 31.88**
Total Substep 1b - Disposable							**€ 0.88**	**€ 1.51**
Total Substep 1b - Technology							**€ 2.36**	**€ 4.06**
Overall Substep 1b							**€ 21.78**	**€ 37.46**
Substep 1c - Tissue processing								
Laboratory technician	*0.05*	*€ 27.28*	-	-	-	-	*€ 4.78[e]*	*€ 8.22*
Tissue processors	-	-	-	-	*102,008.00[h]*	*€ 33,957.75*	*€ 1.17[f]*	*€ 2.01*
Total Substep 1c - Professional							**€ 4.78**	**€ 8.22**
Total Substep 1c - Technology							**€ 1.17**	**€ 2.01**
Overall Substep 1c							**€ 5.95**	**€ 10.23**

[a] Cost per sample=[(A*B)+(C*D)+(F/E)] unless otherwise stated.
[b] Cost per patient=[Cost per sample*(724/421)], where 724=number of NSCLC tissue samples and 421=number of NSCLS patients.
[c] Weighted average calculated on three NSCLC tissue samples.
[d] Cost per sample={(A*B)*[(149*149/724)+(247*247/724)+(178*178/724]}, where 149= number of NSCLC surgical specimens, 247= number of NSCLC biopsies and 178= number of NSCLC cytologies.
[e] Overall number of tissue samples per year.
[f] Cost per sample=[(F/E)*3.50], where 3.50=average number of biocassettes per NSCLC tissue sample.
[g] Cost per sample=(A*B*3.50), where 3.50=average number of biocassettes per NSCLC tissue sample.
[h] Overall number of tissue blocks per year.

Table SII. Results-cost description per NSCLC sample and patient (€ 2019).

Item	Professional		Disposable		Technology		Total cost per	
	Time (hour) (A)	Cost (hour) (B)	Volume (C)	Cost (unit) (D)	Volume (E)	Cost (year) (F)	Sample[a]	Patient[b]
Step 1 - Pre-analysis								
Substep 1d - Tissue embedding								
Laboratory technician	*0.12*	*€ 27.28*	-	-	-	-	*€ 11.15*[c]	*€ 19.17*
Tissue embedding systems	-	-	-	-	*102,008*[d]	*€ 16,5440.00*	*€ 0.57*[e]	*€ 0.98*
Total Substep 1d - Professional							**€ 11.15**	**€ 19.17**
Total Substep 1d - Technology							**€ 0.57**	**€ 0.98**
Overall Substep 1d							**€ 11.72**	**€ 20.16**
Substep 1e - Tissue slicing								
Laboratory technician	*0.07*	*€ 27.28*	-	-	-	-	*€ 12.86*[f]	*€ 22.12*
Microtome systems	-	-	-	-	*222,440*[g]	*€ 70,738.25*	*€ 2.25*[h]	*€ 3.87*
Slides	-	-	*7.07*	*€ 0.04*	-	-	*€ 0.26*	*€ 0.45*
Total Substep 1e - Professional							**€ 12.86**	**€ 22.12**
Total Substep 1e - Disposable							**€ 0.26**	**€ 0.45**
Total Substep 1e - Technology							**€ 2.25**	**€ 3.87**
Overall Substep 1e							**€ 15.37**	**€ 26.43**
Total Step 1 - Professional							**€ 50.02**	**€ 86.02**
Total Step 1 - Disposable							**€ 1.15**	**€ 1.98**
Total Step 1 - Technology							**€ 6.34**	**€ 10.90**
Overall Step 1							**€ 57.51**	**€ 98.90**

[a] Cost per sample=[(A*B)+(C*D)+(F/E)] unless otherwise stated.
[b] Cost per patient=[Cost per sample*(724/421)], where 724=number of NSCLC tissue samples and 421=number of NSCLC patients.
[c] Cost per sample=(A*B*3.50), where 3.50=average number of biocassettes per NSCLC tissue sample.
[d] Overall number of tissue blocks per year.
[e] Cost per sample=[(F/E)*3.50], where 3.50=average number of biocassettes per NSCLC tissue sample.
[f] Cost per sample=(A*B *7.07), where 7.07=average number of slides per NSCLC tissue sample.
[g] Overall number of tissue slides per year.
[h] Cost per sample=[(F/E)*7.07], where 7.07=average number of slides per NSCLC tissue sample.

Table SIII. Results-cost description per NSCLC sample and patient (€ 2019).

Item	Professional		Disposable		Technology		Total cost per	
	Time (hour) (A)	Cost (hour) (B)	Volume (C)	Cost (unit) (D)	Volume (E)	Cost (year) (F)	Sample[a]	Patient[b]
Step 2 - Analysis - Staining								
Substep 2a - H&E staining								
Laboratory technician	*0.05*	*€ 27.28*	-	-	-	-	*€ 0.66*[c]	*€ 1.14*
H&E stainers	-	-	-	-	*144,586*[d]	*€ 36,238.50*	*€ 1.16*[e]	*€ 1.99*
Slides	-	-	*4.63*	*€ 0.04*	-	-	*€ 0.19*	*€ 0.33*
H&E reagent	-	-	*4.63*	*€ 0.21*	-	-	*€ 0.97*	*€ 1.67*
Total Substep 2a - Professional							**€ 0.66**	**€ 1.14**
Total Substep 2a - Disposable							**€ 1.16**	**€ 1.99**
Total Substep 2a - Technology							**€ 1.16**	**€ 1.99**
Overall Substep 2a							**€ 2.97**	**€ 5.11**
Substep 2b - IHC, FISH and Special stainings								
Graduated technician (FISH staining only)	*0.75*	*€ 35.07*	-	-	-	-	*€ 5.63*[f]	*€ 9.68*
Laboratory technician (FISH staining only)	*0.40*	*€ 27.28*	-	-	-	-	*€ 2.34*[f]	*€ 4.02*
Laboratory technician (IHC and Special stainings)	*0.05*	*€ 27.28*	-	-	-	-	*€ 3.34*[f]	*€ 5.74*
IHC stainers	-	-	-	-	*66,732*[g]	*€ 163,625*	*€ 5.99*[h]	*€ 10.30*
IHC staining reagent	-	-	*1*	*€ 8.00*	-	-	*€ 7.96*[i]	*€ 13.69*
Predictive IHC staining reagent	-	-	*1*	*€ 50.00*	-	-	*€ 72.44*[j]	*€ 124.58*
FISH stainers	-	-	*1*	*€ 150.00*	-	-	*€ 32.11*[k]	*€ 55.22*
Special staining reagent + equipment	-	-	*1*	*€ 4.00*	-	-	*€ 0.01*[l]	*€ 0.02*
Total Substep 2b - Professional							**€ 11.30**	**€ 19.43**
Total Substep 2b - Disposable							**€ 112.52**	**€ 193.50**
Total Substep 2b - Technology							**€ 5.99**	**€ 10.30**
Overall Substep 2b							**€ 129.82**	**€ 223.25**
Substep 2c - Slides preparation								
Laboratory technician	*0.08*	*€ 27.28*	-	-	-	-	*€ 16.07*[h]	*€ 27.64*
Total Substep 2c - Professional							**€ 16.07**	**€ 27.64**
Overall Substep 2c							**€ 16.07**	**€ 27.64**
Total Step 2 - Professional							**€ 28.03**	**€ 48.20**
Total Step 2 - Disposable							**€ 113.68**	**€ 195.50**
Total Step 2 - Technology							**€ 7.15**	**€ 12.30**
Overall Step 2							**€ 148.87**	**€ 256.01**

[a] Cost per sample=[(A*B)+(C*D)+(F/E)] unless otherwise stated.
[b] Cost per patient=[Cost per sample*(724/421)], where 724=number of NSCLC tissue samples and 421=number of NSCLC patients.
[c] Cost per sample=[(A*B)*(3351/724)], where 3351= number of NSCLC tissue slides undergoing H&E staining and 724=number of NSCLC tissue samples.
[d] Assuming that [(65%*222,440 slides)=144,586 slides undergo H&E staining.
[e] Cost per sample=[(F/E)*4.63], where 4.63=average number of slides per NSCLC H&E staining.
[f] Cost per sample=[(A*B)*(155/724)], where 155= number of FISH performed on NSCLC tissue slides and 724=number of NSCLS tissue samples.
[g] Assuming that (35%*222,440 slides)=66,732 slides undergo IHC, FISH and/or Special stainings.
[h] Cost per sample={(F/E)*[(720+1049)/724]}, where 720=number of NSCLC IHC slides, 1049=number of NSCLC predictive IHC slides and 724=number of NSCLC tissue samples.
[i] Cost per sample=[(C*D)*(1049/724)], where 1049=number of NSCLC predictive IHC slides and 724=number of NSCLC tissue samples.
[j] Cost per sample=[(C*D)*(720/724)], where 720=number of NSCLC IHC slides and 724=number of NSCLC tissue samples.
[k] Cost per sample=[(C*D)*(155/724)], where 155= number of FISH performed on NSCLC tissue slides and 724=number of NSCLS tissue samples.
[l] Cost per sample=[(C*D)*(2/724)], where 2= number of Special stainings performed on NSCLC tissue slides and 724=number of NSCLS tissue samples.
[m] Cost per sample=[(A*B)*(5120/724)], where 5120=number of NSCLC tissue slides and 724=number of NSCLC tissue samples.

Table SIV. Results-cost description per NSCLC sample and patient (€ 2019).

Item	Professional		Disposable		Technology		Total cost per	
	Time (hour) (A)	Cost (hour) (B)	Volume (C)	Cost (unit) (D)	Volume (E)	Cost (year) (F)	Sample[a]	Patient[b]
Step 3 - Analysis - Molecular								
Substep 3a - Real Time PCR								
Graduated technician	*1.25*	*€ 37.05*	-	-	-	-	*€ 20.66*[c]	*€ 35.53*
Biologist	*1.25*	*€ 44.89*	-	-	-	-	*€ 23.93*[c]	*€ 41.15*
Reagent + equipment	-	-	*1*	*€ 120.00*	-	-	*€ 53.54*[c]	*€ 92.07*
Total Substep 3a - Professional							**€ 44.59**	**€ 76.68**
Total Substep 3a - Disposable							**€ 53.54**	**€ 92.07**
Overall Substep 3a							**€ 98.13**	**€ 168.76**
Substep 3b - NGS								
Graduated technician	*4.00*	*€ 37.05*	-	-	-	-	*€ 20.75*[d]	*€ 35.68*
Biologist	*4.00*	*€ 44.89*	-	-	-	-	*€ 24.75*[d]	*€ 42.56*
Reagent + equipment	-	-	*1*	*€ 300.00*	-	-	*€ 42.68*[e]	*€ 73.40*
Other reagents (formaline; alcool)	-	-	*1*	*€ 5.00*[f]	-	-	*€ 5.00*	*€ 8.60*
Total Substep 3b - Professional							**€ 45.50**	**€ 78.25**
Total Substep 3b - Disposable							**€ 47.68**	**€ 82.00**
Overall Substep 3b							**€ 93.18**	**€ 160.24**
Total Step 3 - Professional							**€ 90.09**	**€ 154.93**
Total Step 3 - Disposable							**€ 101.22**	**€ 174.07**
Overall Step 3							**€ 191.31**	**€ 329.00**

[a] Cost per sample=[(A*B)+(C*D)+(F/E)] unless otherwise stated.
[b] Cost per patient=[Cost per sample*(724/421)], where 724=number of NSCLC tissue samples and 421=number of NSCLC patients.
[c] Cost per sample=[(A*B)*(323/724)], where 323= number of NSCLC tissue sample undergoing Real Time PCR and 724=number of NSCLC tissue samples.
[d] Cost per sample=[(A*B)*(103/724)], where 103= number of NSCLC tissue sample undergoing NSG and 724=number of NSCLC tissue samples.
[e] Cost per sample=[(C*D)*(103/724)], where 103= number of NSCLC tissue sample undergoing NSG and 724=number of NSCLC tissue samples.
[f] Cost per year.

Table SV. Results-cost description per NSCLC sample and patient (€ 2019).

Item	Professional		Disposable		Technology		Total cost per	
	Time (hour) (A)	Cost (hour) (B)	Volume (C)	Cost (unit) (D)	Volume (E)	Cost (year) (F)	Sample[a]	Patient[b]
Step 4 - Finalization and medical reporting								
Substep 4a - Finalization								
Pathologist (Slides read)	*0.15*	*€ 59.85*	-	-	-	-	*€ 63.49*[c]	*€ 109.18*
Pathologist (FISH read)	*0.75*	*€ 59.85*	-	-	-	-	*€ 9.61*[d]	*€ 16.53*
Biologist (FISH read)	*0.75*	*€ 44.89*	-	-	-	-	*€ 7.21*[d]	*€ 12.40*
Microscope	-	-	-	-	*222,440*[e]	*€ 55,000*	*€ 1.75*[f]	*€ 3.01*
Total Substep 4a - Professional							**€ 80.31**	**€ 138.11**
Total Substep 4a - Technology							**€ 1.75**	**€ 3.01**
Overall Substep 4a							**€ 82.06**	**€ 141.12**
Substep 4b - Medical reporting								
Laboratory technician	*0.17*	*€ 27.28*	-	-	-	-	*€ 48.08*[g]	*€ 82.68*
Total Substep 4b - Professional							**€ 48.08**	**€ 82.68**
Overall Substep 4b							**€ 48.08**	**€ 82.68**
Total Step 4 - Professional							**€ 128.39**	**€ 220.79**
Total Step 4 - Technology							**€ 1.75**	**€ 3.01**
Overall Step 4							**€ 130.13**	**€ 223.79**
Grand total Steps 1-4 - Professional							**€ 296.53**	**€ 509.95**
Grand total Steps 1-4 - Disposable							**€ 216.04**	**€ 371.53**
Grand total Steps 1-4 - Technology							**€ 15.24**	**€ 26.21**
Grand total Steps 1-4 - NSCLC testing							**€ 527.81**	**€ 907.69**
Overheads[h]							**€ 131.95**	**€ 226.92**
Grand total Steps 1-4 - NSCLC testing + Overheads							**€ 659.77**	**€ 1134.61**

[a] Cost per sample=[(A*B)+(C*D)+(F/E)] unless otherwise stated.
[b] Cost per patient=[Cost per sample*(724/421)], where 724=number of NSCLC tissue samples and 421=number of NSCLC patients.
[c] Cost per sample=[(A*B)*(5120/724)], where 5120=number of NSCLC tissue slides and 724=number of NSCLC tissue samples.
[d] Cost per sample=[(A*B)*(155/724)], where 155= number of FISH performed on NSCLC tissue slides and 724=number of NSCLC tissue samples.
[e] Overall number of tissue slides per year.
[f] Cost per sample={F/[222,440*(5120/724)]}, where 222,440 overall number of tissue slides, 5120= number of NSCLC tissue slides and 724=number of NSCLC tissue samples.
[g] Cost per sample=[(A*B)*(2537+5120)/724)], where 2537=overall number of NSCLC tissue blocks, 5120=overall number of NSCLC tissue slides and 724=number of NSCLC tissue samples.
[h] Overheads =(Grand total Step 1-4 – NSCLC testing * 125%).