







# Predictive molecular pathology in the time of coronavirus disease (COVID-19) in Europe

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## ABSTRACT

**Aims** Lung cancer predictive biomarker testing is essential to select advanced-stage patients for targeted treatments and should be carried out without delays even during health emergencies, such as the coronavirus (COVID-19) outbreak.

**Methods** Fifteen molecular laboratories from seven different European countries compared 4 weeks of national lockdown to a corresponding period in 2019, in terms of tissue and/or plasma-based molecular test workload, analytical platforms adopted, number of cases undergoing programmed death-ligand1 (PD-L1) expression assessment and DNA-based molecular tests turnaround time.

**Results** In most laboratories (80.0%), tissue-based molecular test workload was reduced. In 40.0% of laboratories (6/15), the decrease was >25%, and in one, reduction was as high as 80.0%. In this instance, a concomitant increase in liquid biopsy was reported (60.0%). Remarkably, in 33.3% of the laboratories, real-time PCR (RT-PCR)-based methodologies increased, whereas highly multiplexing assays approaches decreased. Most laboratories (88.9%) did not report significant variations in PD-L1 volume testing.

**Conclusions** The workload of molecular testing for patients with advanced-stage lung cancer during the lockdown showed little variations. Local strategies to overcome health emergency-related issues included the preference for RT-PCR tissue-based testing methodologies and, occasionally, for liquid biopsy.

patients with non-small cell lung cancer (NSCLC) were recommended to continue unaltered.<sup>6</sup> To this end, molecular predictive pathology activities should have been carried out without delays. This is crucial considering that patients with advanced-stage disease have short life expectancies, on the order of 4–5 months in the absence of treatment.

However, clinical recommendations do not always take into consideration real-world issues. As an example, oncologists, recruited at the outbreak peak to attend COVID-19 wards and hospitals, might have requested less molecular tests than usual.<sup>7–8</sup> Moreover, endobronchial ultrasound procedures might have been limited considering the not negligible risk of healthcare providers infection.<sup>9–11</sup> In addition, molecular laboratory activities might have been influenced by the need to respect social distancing measures leading to a reduction of laboratory staff and less productivity.<sup>12</sup> A study from the University of Naples Federico II reported that the number of patients with lung cancer undergoing biomarker testing before (March–April 2019) and during (March–April 2020) the Italian lockdown was similar.<sup>13</sup> However, single laboratory experience is not sufficient to reliably generate robust conclusions at the European level. Thus, a well-established collaborating group of European pathologists from Belgium, France, Germany, Italy, Portugal, Spain and Sweden joined the forces to generate a large database in order to assess whether and what impact COVID-19 has had on lung cancer predictive molecular testing carried out in Europe during the spring 2020 lockdown.

## INTRODUCTION

The coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 has rapidly spread across the whole of Europe, in the early months of 2020.<sup>1–5</sup> The aggressive containment measures, deemed necessary by most European governments, prioritised unquestionable, urgent and not postponable patient care procedures. The European Society of Medical Oncology guideline recommended that lung cancer procedures should not have been de-intensified, delayed or cancelled.<sup>6</sup> In particular, tyrosine kinase inhibitor and immune-checkpoint inhibitor therapies for

## MATERIALS AND METHODS

### Study design

Fifteen European molecular predictive pathology laboratories, specialised in NSCLC biomarker testing, were contacted by the University of Naples Federico II (figure 1). The aim was to extend the previous analysis carried out in Naples with data derived from different laboratories in different European countries; each laboratory reported data derived from the activity carried out during 4 weeks (March–April) of national lockdown compared



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in the Time of Coronavirus Disease (COVID-19) in Europe

**Figure 1** Geographical distribution on the involved institutions: Italy (University of Naples Federico II, Naples; European Institute of Oncology IRCCS, Milan; University of Bologna, Bologna; University Hospital of Udine, Udine; University of Padua, Padua; University of Pisa, Pisa; University of Turin, Orbassano), France (INSERM, Nice; CHU Henri Mondor, Creteil); Germany (University of Cologne, Cologne; Hospital of the Private University Witten/Herdecke, Cologne); Belgium (University Hospitals Leuven, Leuven); Portugal (IPATIMUP and Medical Faculty of Porto, Porto); Spain (Pangaea Oncology, Barcelona); Sweden (Lund University, Lund).

with the same period of the year 2019. In particular, every single institution reported for different genomic biomarkers the number of tissue samples (histological and cytological) analysed, the number of liquid biopsies performed and the median turnaround time (TAT, from sample receipt to clinical report). The platforms adopted for molecular testing were also reported distinguishing between highly multiplexing assays, including next-generation sequencing (NGS) and mass spectrometry genotyping (Sequenom, Diatech Pharmacogenetics, Jesi, Italy) and real time polymerase chain reaction (RT-PCR)-based approaches, such as Idylla (Biocartis, Mechelen, Belgium) and Easy PGX (Diatech Pharmacogenetics). In addition, data on the difference in the number of programmed death-ligand1 (PD-L1) immunohistochemical assessments between the lockdown and the corresponding period of 2019 were also obtained from the laboratories.

All information regarding human material was managed using anonymous numerical codes, and all samples were handled in compliance with the Declaration of Helsinki (<http://www.wma.net/en/30publications/10policies/b3/>).

## RESULTS

### Predictive molecular analysis of tissue samples

On the overall, the data obtained from the 15 participating laboratories were 1118 (ranging from 15 to 329) and 963 (ranging from 5 to 362) lung cancer samples tested in 2019 and 2020, respectively. Most laboratories (12/15; 80.0%) showed a variable reduction in the number of tissue samples analysed. The drop was <25% in six laboratories, between 25% and 40% in the other five instances and of 80% one institution.

Twelve laboratories further detailed the type of tissue samples, distinguishing histological from cytological specimens. In 10 of 12 institutions, only slight variations in the relative number of histological and cytological samples (<15%) were observed in the two periods, except for two laboratories reporting a drastic

**Table 1** Sample characteristics of the analysed tissue lung cancer samples in 2019 and 2020

Laboratory	Histological	Cytological	Total cases
<b>2019</b>			
1	11	9	20
2	19	23	42
3	287	42	329
4	33	16	49
5	36	8	44
6	10	5	15
7	26	1	27
8	36	13	49
9	NR	NR	132
10	NR	NR	167
11	61	6	67
12	NR	NR	39
13	25	0	25
14	77	1	78
15	30	5	35
<b>2020</b>			
1	10	8	18
2	11	27	38
3	307	55	362
4	33	17	50
5	22	6	28
6	10	10	20
7	21	1	22
8	31	0	31
9	NR	NR	97
10	NR	NR	140
11	41	11	52
12	NR	NR	24
13	5	0	5
14	45	2	47
15	22	7	29

NR, not reported.

reduction of either histological samples (laboratory #2) or cytological ones (laboratory #8) (table 1).

### Predictive molecular analysis on liquid biopsy

Only four institutions (laboratory #1, #6, #13 and #14) reported data regarding liquid biopsy. On the overall, 56 and 49 liquid biopsies were analysed in 2019 and 2020, respectively. In particular, laboratories #1 and #14 reported a drastic reduction (laboratory #1 from 14 to 2 and laboratory #14 from 25 to 16), whereas laboratory #6 and #13 showed an increasing number of liquid biopsy-based analysis (laboratory #6 from 4 to 8 and laboratory #13 from 10 to 23).

### The platforms adopted for molecular testing and TAT

As far as platforms adopted for DNA-based molecular tests are concerned, data were provided by 12 laboratories. In 2019, the vast majority of samples had been analysed by NGS (74.0%, 619/836), followed by conventional RT-PCR (10.9%, 91/836), Sequenom (9.1%, 76/836) and automated real-time PCR (RT-PCR) approaches (6.0%, 50/836). In 2020, most of the sample analysis have been analysed by NGS (73.9%, 555/751), followed by classical RT-PCR (10.9%, 82/751), automated RT-PCR approaches (9.3%, 70/751) and Sequenom (5.9%, 44/751).

**Table 2** Platforms adopted for DNA-based tests in 2019 and 2020

Laboratory	NGS	Idylla	RT-PCR	Sequenom	Easy PGX	Total cases
<b>2019</b>						
1	31	3	0	0	0	34
2	42	0	0	0	0	42
3	306	0	23	0	0	329
4	43	0	6	0	0	49
5	0	0	0	44	0	44
6	0	0	4	15	0	19
7	0	0	0	17	10	27
8	12	37	0	0	0	49
11	67	0	0	0	0	67
13	35	0	0	0	0	35
14	48	0	58	0	0	106
15	35	0	0	0	0	35
<b>2020</b>						
1	2	18	0	0	0	20
2	38	0	0	0	0	38
3	328	0	34	0	0	362
4	48	0	2	0	0	50
5	0	0	5	23	0	28
6	0	0	8	20	0	28
7	0	0	0	1	21	22
8	0	31	0	0	0	31
11	52	0	0	0	0	52
13	28	0	0	0	0	28
14	30	0	33	0	0	63
15	29	0	0	0	0	29

NGS, next-generation sequencing; RT-PCR, real-time PCR.

The results are summarised in [table 2](#). Considering as a group the highly multiplex assays (NGS and Sequenom) versus the RT-PCR-based assays (Idylla, conventional RT-PCR and Easy PGX), not negligible variations were observed in four laboratories (4/12; 33.3%). In fact, the RT-PCR increased (laboratory #1 from 8.8% to 90.0%, laboratory #5 from 0.0% to 17.9%, laboratory #7 from 37.1% to 95.5% and laboratory #8 from 75.5% to 100.0%).

As far as TAT is concerned, in the median, TAT was very similar (7.6 days, ranging from 3.5 to 11.9 days, in 2019 and 7.4 days, ranging from 3.8 to 11.5 days, in 2020; data obtained from nine laboratories).

### Programmed death-ligand 1

Nine laboratories submitted PD-L1 testing data. In 2019, on the overall, among 414 total NSCLC cases, PD-L1 testing was requested in 85.3% (384/450). In 2020, on the overall, among 365 total NSCLC cases, PD-L1 testing was requested in 89.6% (327/365). Most laboratories (8/9; 88.9%) showed slight variations either with an increase or reduction in the number of tissue samples analysed ([table 3](#)). Only one laboratory (#5) reported an unquestionable decrease in the volume of PD-L1 testing (37.1%).

### DISCUSSION

As a general rule, most activities in many areas of medicine have undergone a remarkable reduction; in particular, this is true for those procedures that are not crucial for immediate clinical decision making.<sup>14</sup> Although predictive molecular testing is key in selecting patients with advanced-stage NSCLC for target treatments,<sup>15</sup> it is conceivable that also in this field, fewer samples

**Table 3** PD-L1 requests and results obtained in 2019 and 2020

Laboratory	≥50	≥1 and <50	<1	Inadequate	NR	Total cases
<b>2019</b>						
1	4	4	9	0	17	34
2	13	12	9	6	2	42
4	12	14	14	4	5	49
5	12	15	8	0	9	44
6	7	4	3	1	4	19
7	4	2	9	0	12	27
9	33	60	20	6	13	132
11	20	23	20	0	4	67
15	8	7	21	0	0	36
<b>2020</b>						
1	2	3	12	0	3	20
2	8	12	10	3	5	38
4	20	9	13	4	4	50
5	5	13	4	0	6	28
6	4	7	8	1	8	28
7	1	8	4	0	9	22
9	32	46	11	8	0	97
11	16	13	20	0	3	52
15	6	9	13	2	0	30

NR, not requested; PD-L1, programmed death-ligand 1.

have been processed, reflecting the slowdown of routine activities. However, this perception has not been corroborated by a systematic analysis to assess at which degree the COVID-19 impacted on predictive molecular pathology practice. Our data, collected from 15 laboratories in seven European countries (Belgium, France, Germany, Italy, Portugal, Spain and Sweden), highlighted a reduction in tissue-based molecular testing workload in most laboratories (80.0%). In 40.0% of laboratories (6/15), the reduction was not negligible (>25%).

As different laboratories in the same countries did not report overlapping evidence, it is conceivable that differences may reflect more local than national issues. In particular, laboratory #13 data underlined a dramatic reduction (80.0%) in tissue-based molecular testing and a remarkable increase of plasma-based liquid biopsy that increased from 28.6% in 2019 to 82.1% in 2020. Further investigation is warranted to assess whether, in other institutions during the COVID-19 outbreak, liquid biopsy represented a surrogate of tissue-based analysis. Only one of the other three laboratories, including in this study that performed the liquid biopsy, confirmed a liquid biopsy increase.

As far as analytical methodological procedures are concerned, it is remarkable that in the 33.3% of the laboratories favoured less cumbersome RT-PCR-based methodologies, including fully automated platforms that require limited hands-on-times.<sup>16</sup> The reason behind this switch in testing strategies may reflect the need to reduce the number of staff personnel during the emergency and the fact that more simple genotyping workflows better adapt the need to maintain social distancing measures. These latter are more difficult to be strictly respected when NGS is adopted as more than one operator may be involved in different analytical phases. As highly multiplex workflow assays require a larger number of reagents than RT-PCR, delivery chain issues may also have played a role in laboratory testing activities.<sup>17</sup> The possibility that more simple and faster analytical procedures have been less influenced by the laboratory organisation changes concurs with the observation that TAT did not feature major variations. In addition, most laboratories did not report

significant variations in PD-L1 volume. As a matter of the fact, PD-L1 immunostaining that requires general expertise in using automated immunostaining platforms that are also exploited for different diagnostic antibodies can be carried out by a larger number of laboratory personnel.<sup>18</sup> Moreover, PD-L1 immunohistochemistry can be effectively evaluated by digital pathology means,<sup>19</sup> avoiding the traditional assessment on a microscope that could expose the pathologists to unnecessary risk during the pandemic.<sup>20</sup>

During the COVID-19 pandemic, all non-urgent medical procedures, including screening procedures, were postponed.<sup>5 21–25</sup> Conversely, on the overall, the degree of predictive biomarker testing decrease was only slight.<sup>13</sup> However, to ensure laboratory staff security, molecular laboratory activities were, in some instances, reshaped and reorganised.<sup>12 13</sup> In this setting, fully automated technologies, needing slight hands-on work, may be useful to limit the amount of time spent to process lung cancer samples.<sup>13</sup> Thus, it is hoped to endorse a technological improvement in terms of automation in molecular pathology laboratories.<sup>13</sup> However, it should be borne in mind that automation is not a surrogate for skilled laboratory staff members. A critical attitude is required to interpret and validate the results provided by automated workflows. Highly trained molecular pathologists are crucial to visually inspect the RT-PCR curves of undetermined interpretation and to select cases requiring a second confirmatory technique.<sup>26 27</sup>

In conclusion, our collaborative, multi-institutional, European study underlines that molecular testing for patients with advanced-stage NSCLC was in general effective even during the lockdown. This study may represent an opportunity that should be seized to develop a common strategy effective to face healthcare emergencies ensuring a consistent testing strategy and reliable algorithms of tissue and liquid biopsy diagnostic procedures.

### Take home messages

- ▶ Even during the COVID-19 healthcare emergency, the European Society of Medical Oncology guideline recommended that lung cancer procedures, including predictive biomarker testing, should not have been de-intensified, delayed or cancelled.
- ▶ However, molecular laboratory activities might have been significantly influenced by the need to respect social distancing measures leading to a reduction of laboratory staff and less productivity.
- ▶ Our data, collected from 15 laboratories in seven European countries (Belgium, France, Germany, Italy, Portugal, Spain and Sweden), highlighted a slight reduction in tissue-based molecular testing workload.
- ▶ Despite it is hopefully to endorse a technological improvement in terms of automation in molecular pathology laboratories, it should be borne in mind that automation is not a surrogate for skilled laboratory staff members.

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