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### ► **To cite this version:**

Séverine Coquerelle, Meryl Darlington, Morgane Michel, Manon Durand, Isabelle Borget, et al.. Impact of Next Generation Sequencing on Clinical Practice in Oncology in France: Better Genetic Profiles for Patients Improve Access to Experimental Treatments. *Value in Health: the journal of the International Society for Pharmacoeconomics and Outcomes Research*, 2020, 23 (7), pp. 898-906. <10.1016/j.jval.2020.03.005>. <halshs-02983051>

**HAL Id: halshs-02983051**

**<https://shs.hal.science/halshs-02983051v1>**

Submitted on 22 Aug 2022

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## **Impact of Next Generation Sequencing (NGS) on clinical practice in oncology in France: better patients' genetic profile improves access to experimental treatments**

**Running title:** NGS use in oncology and access to matched treatments.

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**Fundings**

The work was supported by a grant from the French National Cancer Institute (INCa) [grant number: 2013-1-NGS-02].

**Précis:** NGS use in oncology: better information on patients' genetic profile improves access to matched treatments and increase survival.

**NGSEco Group**

We would like to thank Pr. Philippe Guardiola and Dr. Ludovic Martin from the Centre Hospitalier Universitaire (Angers) ; Pr. Alain Morel from the Centre de Lutte Contre le

Cancer Paul Papin (Angers) ; Dr. Maud Toulmonde from Institut Bergonié (Bordeaux) ; Pr. Alexis Cortot, Dr. Eric Dansin and Dr. Fabienne Escande from Centre Hospitalier Régional Universitaire (Lille) ; Dr. Maud Kamal from Institut Curie (Paris) ; Pr. Jean Mosser and Dr. Alexandra Lespagnol from Centre Hospitalier Universitaire (Rennes) ; Pr. Michèle Beau-Faller from Hôpitaux Universitaires (Strasbourg) who have contributed to this project. We also want to thank Dr. Etienne Rouleau from Institut Gustave Roussy (Villejuif) for his contribution, his support in study design and project management.

### **Acknowledgments**

We want to thank Johan Gutton (URC Eco) for his support in data entry and project management, Arnaud Nze Ossima (URC Eco) and Kevin Zarca (URC Eco) for their support in statistical methods and analysis.

### **Article content**

Manuscript Type: Original research.

Abstract word counts: 244 words.

Text word counts (Microsoft<sup>®</sup> Word 2010): 3,388 words (Background: 256, Methods: 864, Results: 1,102, Discussion: 1,018; Conclusion: 148); References: 1,120; tables/figures titles, content, table notes and footnotes excluded).

Number of pages and lines: 20 pages.

Number of figures: 2 figures.

Number of table: 4 tables.

Supplement material: 5 pages, 2 figures, 3 tables.

References count: 39

**Impact of Next Generation Sequencing (NGS) on clinical practice in oncology in France:  
better patients' genetic profile improves access to experimental treatments**

**ABSTRACT (244 words)**

Objectives

We evaluated how NGS modified care pathways in an observational impact study in France.

Methods

All patients with lung cancer, colorectal cancer or melanoma who had NGS analyses of somatic genomic alterations in one of seven biomolecular platforms certified by the French National Cancer Institute (INCa) between 2013-6 were eligible. We compared patients' pathways before and after NGS results. Endpoints were turnaround time in obtaining results, number of patients with at least one genomic alteration identified, number of actionable alterations, impact of genomic multidisciplinary tumor board on care pathways, number of changes in the treatment plan, and survival up to one year after NGS analyses.

Results

1,213 patients with a request for NGS analysis were included. NGS was performed for 1,155 patients, identified at least one genomic alteration for 867 (75%) and an actionable alteration for 614 (53%). Turnaround time between analyses and results was on average 8 days [Min: 0- Max: 95] for all cancer types. Before NGS analysis, 33/614 patients (5%) were prescribed a targeted therapy compared to 54/614 patients (8%) after NGS analysis. Proposition of inclusion in clinical trials with experimental treatments increased from 5% ( $n=31/614$ ) before to 28% ( $n=178/614$ ) after NGS analysis. Patients who benefited from a genotype matched treatment after NGS analysis

tended to have a better survival at one year than patients with non-matched treatment: 258 days ( $\pm 107$ ) compared to 234 days ( $\pm 106$ ), (*p value*=0.41).

### Conclusions

NGS analyses resulted in a change of patients' care pathways for 20% of patients (*n*=232/1,155).

### **Highlights:**

- I. Precision medicine enables a better stratification of patients and a better allocation of treatments.
- II. Proposal of experimental treatments increased more than prescription of targeted therapies after NGS analysis.
- III. NGS analyses resulted in a change of patients' care pathways for 20% of patients.

### **Keywords:**

NGS, oncology, clinical practice, somatic alterations.

## **BACKGROUND**

Using patients' genomic profiles to target treatments has been shown to reduce toxicities, adverse effects, tumor progression and to improve survival through better therapeutic efficacy [1-3]. Next Generation Sequencing (NGS) provides prognostic information on sensitivity or resistance to drugs [4-5]. Some studies have evaluated the decision impact of molecular profiling on treatment and survival [6-8]. Several studies evaluated the cost-effectiveness of screening patient genomic alteration profiles in lung and metastatic colorectal cancer [9-15].

Next Generation Sequencing (NGS) allows rapid simultaneous sequencing of DNA or RNA samples with a higher sensitivity than previous techniques such as Sanger. NGS analysis can offer valuable predictive information on oncogene drivers such as EGFR, KRAS or TP53 and guide

prescription of chemotherapy, targeted treatment or immunotherapy [16]. In France, the national cancer plan (2004 to 2009) guaranteed equal access to cancer treatments and genomic alteration profile and stated as a national priority that all cancer patients should benefit from a NGS analysis free of charge [17-19]. French cancer patients are fully covered for all cancer-related expenditures under the national Social Health insurance scheme [20].

In 2014, the French National Cancer Institute (INCa) launched a national project to assess the cost and impact of NGS use at a national level [21]. Cost results have been published previously [22]. In 2016, 35,000 NGS analyses were performed for cancer patients by the 28 French biomolecular platforms for molecular genetics [23]. Our objective was to evaluate the impact of NGS on care pathways and survival for non-metastatic and metastatic lung cancer, colorectal cancer and melanoma.

## **METHODS**

### ***Study design***

We undertook a multicenter observational retrospective decision impact analysis in seven of the 28 French platforms. The platforms in our sample used NGS in routine, were voluntary and certified by INCa: Angers (Centre Hospitalier Universitaire and Centre Paul Papin), Bordeaux (Institut Bergonié), Lille (Centre Hospitalier Régional Universitaire), Paris (Institut Curie), Rennes (Centre Hospitalier Universitaire), Strasbourg (Centre Hospitalier Universitaire) and Villejuif (Institut Gustave Roussy) as well as referring centers (hospitals, clinics and private practices) who sent their samples to the seven platforms. Our sample included data from platforms located in Comprehensive cancer centers (French Centre de Lutte Contre le Cancer - CLCC) and University Hospitals. Each platform received referrals from 6 to 30 different hospitals specialized in oncology

or not. Platforms were either located in Paris and its suburbs (two platforms) or in different regions of France (one platform in the North, one platform in the East and three platforms in the West: two in the Northwest and one in the Southwest).

### ***Study population***

All NGS analyses performed between October 2013 and September 2016 for adult patients treated for lung cancer, colorectal cancer or melanoma, both metastatic and non-metastatic, were included. The three tumor types were selected because on-label targeted therapies were available. We excluded analyses on constitutional genomic alterations, somatic genomic alterations for other cancers and NGS analyses carried out exclusively for research purposes.

### ***Patients' and platforms' characteristics***

Patients' pathways and referrals were obtained from NGS request forms, hospital records, and interviews with biomolecular biologists and clinicians. Demographic information (sex, age class), diagnosis (cancer type), treatment (drugs and treatment line), metastatic status and progression were retrieved from hospital records. We collected data on type and location of referring centers to determine the geographical origin of the patients.

### ***Molecular profiling***

We extracted anonymized data on NGS results from the platforms' information systems. Analyses could be made on existing or new samples. Minimal panel content defined by INCa was: AKT1, ALK, BRAF, CTNNB1, DDR2, EGFR, ERBB2, ERBB4, FBXW7, FGFR1, FGFR2, FGFR3, KRAS, MAP2K1, MET, NOTCH1, NRAS, PIK3CA, PTEN, SMAD4, STK11, and TP53. When available, previous genomic analyses and the treatment considered before NGS analysis were recorded. An alteration was considered actionable if it could be targeted through either an experimental treatment (clinical trial) or by an on-label targeted therapy [24-27]. When available,

we collected reasons for “non actionability” defined as an alteration with no corresponding matched treatment option, either targeted therapy or experimental treatment.

### ***Study endpoints***

The following endpoints were reported: 1) NGS analysis turnaround time, 2) Molecular profiling: number of patients with at least one genomic alteration, number of patients with an actionable genomic alteration, 3) Impact on patient care: impact of genomic multidisciplinary tumor board<sup>1</sup> decisions on care pathways, number of patients for whom results had an impact on their treatment plan (proposition of on-label targeted therapy or experimental treatments/clinical trial inclusion) and patients’ survival measured by deaths up to one year after NGS analyses.

### ***Statistical analyses***

The unit of analysis was the patient. We performed descriptive analyses on patients’ and referring centers’ characteristics. We conducted sub-group analyses by molecular profiling results (nature and frequency of alterations) and cancer (metastatic status, decision by the tumor board, treatment line). We also calculated turnaround time as the number of days between the different stages: sample collection, NGS request, NGS analysis and delivery of the results. We considered the impact of the actionability of an alteration on the care pathway and of the decision of genomic multidisciplinary tumor board. We calculated the number of patients with an identified actionable alteration to determine the number of patients who could benefit from a genotype matched treatment and of a review of their results by a tumor board.

We considered the prescription of matched versus non-matched treatment (based on patient genotype-matched profile) and performed univariate analysis. We compared patients’ matched

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<sup>1</sup> A multidisciplinary tumor board is a group of doctors and healthcare specialists (e.g. oncologist, radiologist, biologist, pathologist, nurse, bioinformatician...) who meet regularly to discuss the best possible therapeutic options according to the patient’s profile.

/non-matched treatments (targeted therapy and clinical trial) before and after the NGS results using a chi squared test. Additionally, we performed a multiple imputation to tackle the existing missing data issue. The methodology used deals with the current purpose of multiple imputation, using the assumption of missing-at-random [28].

Overall survival was measured from the date of the molecular analysis to the date of death or final follow up. We performed multivariable survival analysis to determine the influence of the following variables: matched/non-matched treatment given before and after NGS analysis, line of treatment at NGS analysis on survival for the total population and for different subgroups using Cox proportional hazards regression modeling with an adjustment on the origin of the patient (internal or external to the platform), biomolecular platform, location of the platform, pathology, age class, sex, line of treatment, metastatic status, results and presence or not of an actionable alteration. Adjusted hazard ratios (HRs) with 95% CIs were calculated using a logrank test for survival analysis. All statistical tests were two-sided, and a p value of less than 0.05 was deemed statistically significant. Analyses were performed with SAS 9.3 software (SAS Corp, Carey, NC).

## **RESULTS**

Full records with follow-up information were available for 3,883 patients from 121 participating hospitals, comprehensive cancer centers or private clinics/office based specialists, 1,213 of whom met our inclusion criteria (Figure 1).

### **Figure 1. Flow chart NGS analyses**

[Genomic alteration: at least one alteration identified. NGS not performed: an NGS analysis was requested but not performed.]

#### ***Patients' and platforms' characteristics***

Lung cancer represented 56.3% of our population and 65.1% patients were over 60 years old. Of the 1,213 patients, 69.9% ( $n=848$ ) were treated in a public hospital, approximately half of which had an on-site biomolecular platform. More than half of the NGS analyses were prescribed at the metastatic stage and a similar proportion after a multidisciplinary tumor board review. Information on the line of treatment at the time of the NGS analysis was available for 714 patients, 22.8% of whom had no ongoing treatment. Detailed patients' characteristics are presented in Table 1.

### **Table 1. Description of the population by cancer type**

#### ***Patients before NGS analysis***

For 58 patients the NGS analysis requested was finally not performed or information on the results was not available. Among the 1,155 patients with molecular profiling, 575 (49.7%) had undergone a previous genomic analysis with another technique which identified a genomic alteration in 318 patients, while the NGS analysis found genomic alterations in 443.

For 456 patients, the information about the projected or expected post-NGS treatment was available with nearly half being inclusions in clinical trials (Table S-1).

#### ***NGS analysis turnaround time***

NGS analysis was either conducted on existing samples ( $n=752$ ) or on new samples ( $n=224$ ), data were missing for 179 patients. Turnaround time between analyses and results was on average 8 days [Min: 0- Max: 95] but varied by cancer type as shown in Table 2. Turnaround time depended on the location of the patient (same hospital as the platform or not), due to the additional time required for sending the samples of external patients. For the 39 patients (3.4%) who had an analysis on a liquid biopsy, results were delivered within 6 days [0-27].

**Table 2. Turnaround time in days for patients with a NGS analysis and available data  
(n=976)**

***Molecular profiling***

Among the 1,155 patients with molecular profiling, 867 patients (75.0%) had at least one genomic alteration identified, 150 (13.0%) had no genomic alteration and the genomic alteration status was not available for 138 patients (11.9%). Among patients with at least one genomic alteration, 614 (53.1%) had an actionable genomic alteration (three wild type KRAS were considered as actionable by biologist/clinician and included in the actionable genomic alteration sub-sample) and 259 (22.4%) did not (mainly TP53 and mutated KRAS). For 134/257 patients (52.1%) with melanoma no information on alteration status was available. The most frequent genomic alterations were EGFR, TP53 and KRAS for lung cancer, KRAS, TP53 and PIK3CA for colorectal cancer, BRAF and NRAS for melanoma. Full results are presented in a heatmap (Table S-2).

Non actionability in 256 patients (Table 3) resulted from the lack of either a targeted therapy or a trial for 13%, or the presence of resistant (3.9%) or rare alterations (1.2%).

**Table 3. Classification of alterations and reasons for non actionability**

***Impact on patient care***

*Access to targeted therapies and clinical trials*

Decisions of the multidisciplinary tumor board were available for 689 patients. More experimental treatments available through clinical trials and targeted therapies were proposed following the multidisciplinary tumor board's assessment of NGS results as shown in Table S-3.

Detailed results of the prescription of on-label targeted therapies and the proposition of clinical trials before and after NGS analyses are presented by type of cancer in Table 4 for the 614 patients with an actionable genomic alteration.

**Table 4. Genotype matched and non-matched treatments before and after NGS analyses finding actionable alterations (n=614)**

NGS analyses were followed by the proposition of targeted therapies or inclusion in clinical trials for 232 patients (20.1%) of the total population (n=1,155). For nearly all patient groups NGS analyses resulted in a change in care pathway. The findings with multiple imputation were similar (data not shown).

Out of the 614 patients with an actionable alteration identified by NGS analysis and with ongoing treatment at the time of the NGS test, 96 patients (15.6%) were initially treated by chemotherapy (or chemotherapy associated with another treatment) and 33 (5.4%) by targeted therapy. For the former, trial inclusion was proposed to 31 patients and targeted therapy to 8. For the latter, trial inclusion was proposed to 22 patients and a trial was considered for an additional 9 patients but they were either ineligible (n=5) or eligible at progression (n=2)<sup>2</sup>. Finally, targeted therapy was proposed to 11 patients. Clinical trials proposed following NGS were predominantly phase 1 and 2 trials targeting specific alterations, particularly in the case of lung and colorectal cancers (Supplemental Figure 1). Trials included AcSé Crizotinib 34/178, MOST 32/178 and AcSé Vemurafenib<sup>33</sup> 11/178; these three trials gave access to eight experimental treatments and one association of experimental treatments.

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<sup>2</sup> Data was missing for 2 patients.

<sup>3</sup> Respectively registered on ClinicalTrials.gov as NCT02034981, NCT02029001 and NCT02304809.

A total of 114/614 patients (18.5%) having at least one potentially actionable genomic alteration were classified as not actionable in centers where trials were not available: 83 patients with lung cancer, 28 patients with colorectal cancer and 3 with melanoma.

### ***Patients' survival***

Vital status at one year was available for 1,058 patients. Mean survival by cancer type was 259 days for colorectal cancer [Min: 0<sup>4</sup> – Max: 365], 255 days for melanoma [Min: 4 – Max: 365] and 230 for lung cancer [Min: 0<sup>5</sup> – Max: 365].

We estimated the one-year survival by cancer type and treatment line at the time of NGS analysis. Overall survival was strongly dependent on response, progression and treatment line (supplemental file, Supplemental Figure 2). For lung cancer, patients without ongoing treatment at the time of NGS analysis had significantly better survival compared to those on first line of treatment ( $p$  value=0.0002, HR=3.12, CI: 1.33-7.31), second line of treatment (HR=4.40, CI: 1.81-10.70), third line of treatment and beyond (HR=5.77, CI: 2.42-13.73). For colorectal cancer, patients without ongoing treatment at the time of NGS analysis had significantly better survival compared to those on first line of treatment ( $p$  value=0.0002, HR=2.19, CI: 0.20-24.11), second line of treatment (HR=12.10, CI: 1.59-92.12), third line of treatment and beyond (HR=15.05, CI: 2.03-111.37). For melanoma, ( $p$  value=0.1671, HR=1.67, CI: 0.19-14.97) for first line and for third line (HR= 6.42, CI: 0.72-57.47)<sup>6</sup>.

We compared one-year survival for patients on treatment following the NGS analyses: genotype matched versus non-matched ( $n=614$ ). Patients who benefited from a genotype matched treatment after NGS analysis had non-significant better survival than patients with non-matched treatment:

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<sup>4</sup> Some patients died before delivery of results.

<sup>5</sup> Some patients died before delivery of results.

<sup>6</sup> Information was insufficient for second line patients.

258 days ( $\pm 107$ ) compared to 234 days ( $\pm 106$ ). We present in Figure 2 the survival curve for lung cancer ( $p$  value=0.41, HR=1.31, CI: 0.68-2.52) and the proportionality hypothesis was respected.

**Figure 2. Cox model - Survival one year after NGS results by genotype matched (1)/non-matched treatment (0), lung cancer ( $n=367$ ).**

Finally, 14 patients (1.7%), 10 with lung cancer and 4 with colorectal cancer, including 7 with an actionable alteration, died before the NGS results were available.

## **DISCUSSION**

In our study of 1,155 patients with NGS analyses by seven certified biomolecular platforms in France between 2013 and 2016, a genetic alteration was found in 867 (75.0%) patients and was actionable in 614 (53.2%). Results are consistent with the literature [25-27, 29]. Overall, 20.1% of the 1,155 patients or 26.7% of patients with an alteration and 37.7% with an actionable alteration experienced a change in care pathway with an increase in targeted therapies and proposition of clinical trials. The timeline between request and analysis was longer when NGS was performed on a new sample. The speed with which the clinician receives results may impact the decision taken, depending on the pathology and the urgency to initiate treatment. The relationship between test turnaround time and treatment decision needs to be further explored [26,29]. Platforms that have been performing NGS in routine for some time and with a relatively high volume of tests were more likely to have developed an efficient workflow engendering a shorter time to delivery of the results to clinicians.

Review of patients' files by a multidisciplinary tumor board increased the number of genotype matched therapy proposals [15,30,31]. Comparing one year before and one year after NGS analysis, we observed a greater increase of experimental treatments proposal than of targeted therapies prescription after NGS analysis. This result can be explained by the fact that 437/867

patients (50.4%) had already received one or several lines of treatment prior to NGS analysis (including targeted therapies), clinicians were thus looking for new therapeutic options. Access to targeted therapies and experimental treatments post NGS depended on the French on-label drugs, the availability of clinical trials in the hospital, patient health status and eligibility [32-34]. As expected, overall survival was strongly associated with the line of treatment at NGS analysis, which can be considered as a proxy of severity of the cancer and of the proposition of a matched treatment once NGS results were obtained [16]. We were not able to compare survival between patient with and without NGS analysis due to imbalance between groups. In addition, the presence of actionable alterations did not systematically lead to a treatment switch when prescription of targeted therapy was considered at disease progression as per the drug label.

Since this is a retrospective study, we were not able to collect exhaustive patient-level data for some platforms where clinical and biological databases were not interoperable. We mainly used data from patients treated in public hospitals with a biomolecular platform and recognize that patients referred from other hospitals or private practice may have different outcomes. This highlights the need to improve information linkage in order to obtain consistent information on care pathways outside clinical trials. Regarding trial inclusion, we were able to observe if a trial was proposed to the patient after NGS analysis but not if the patient was actually included.

Other authors reported studies with sample sizes ranging from 97 to 17,664 patients with a percentage of patients with actionable alterations ranging from 40 to 94% and of patient receiving matched treatment from 4 to 44%, which is in line with our results (52.6% and 20.1%, respectively) [3,7]. A comparison is difficult as therapeutic options, especially for experimental treatments, strongly depend on the clinical trials active in a given institution and rapid changes in drug labels as well as the introduction of new drugs. The patient health status, genomic profile and clinical trials available in the prescribing center will influence therapeutic choices. For example, our study

identified 114/614 patients (18.5%) with potentially actionable alterations who could not access the clinical trials available at other centers.

Genomic analysis is supposed to guide treatment prescription, increase overall survival or progression-free survival (PFS) and thus improve clinical decision making. Results of trials involving French centers using genomic analysis in different indications are contrasted with no real increase of progression-free survival in the SHIVA trial (NCT01771458) [33] and more promising results in the MOSCATO trial (NCT01566019) [2]. In the MOSCATO trial, 33% (63/193) of the patients were treated with a targeted therapy matched to a genomic alteration had a PFS2 (current treatment)/PFS1 (previous treatment) ratio >1.3, 11% (22/194) had objective responses and 11.9 months of median overall survival.

A national American survey carried out in 2017 determined that among 1,281 oncologists “34.0% used them [NGS tests] often to guide treatment decisions for patients with advanced refractory disease, 29.1% to determine eligibility for clinical trials, and 17.5% to decide on off-label use” [35]. Another American observational study evaluated that in 2018, 8.3% (50,811/609,640) of patients were eligible for a matched treatment and 4.9% (29,899/609,640) benefited from a genome-targeted treatment. Median overall response rate was estimated up to 54% and median duration of response was 29.5 months [36].

Available data on cost-effectiveness are mainly American and range from \$36,500/QALY to \$115,020/QALY for colorectal cancer, \$120,022/QALY for metastatic melanoma. Total treatment cost decreases from \$10.2 million to \$7.5 million if patients receive investigational targeted therapies [39]. The cost of NGS analysis in France for somatic alterations in solid tumors was estimated in 2018 by Marino et al using a micro-costing method [22] at 607€ (±207) per NGS analysis. This diagnosis cost may be compensated by benefits of matched treatment, as a more relevant treatment plan can be defined based on patient genomic profile. Evaluating effectiveness

of genomic analysis requires the right comparator and quantification of outcomes directly attributable to NGS analysis.

Scarcity of French cost-effectiveness studies on NGS may result from a lack of guidelines on NGS use per pathology, according to patient profile, cancer staging and patient pathways (diagnosis, progression, resistance to treatment). Comparing treatment sequences that integrate NGS analysis with sequences that do not, and evaluating how NGS effectively guides clinical decision making, still need to be evaluated. RuBIH2, a French research program (NCT03750994) in malignant hemopathies is ongoing. This study evaluates the impact of NGS on clinical decision using real-world data from 27 French biomolecular platforms as well as economic cost. In the framework of RuBIH2, experts of pathologies are developing recommendation on NGS use for a number of hematological malignancies. Results should be available in the coming months.

## **CONCLUSION**

The strength of our study was that we obtained a large sample from routine screening at seven molecular platforms and their referring centers, in six different regions for three cancer types. Moreover we were able to identify differences in access to experimental treatments through clinical platforms and centers as the same alteration could be considered as actionable or not depending on the trials available in the centers.

A standardization of outcome measures, at the national or international level, in relation to molecular profiles still needs to be explored.

Other cancers could benefit from a study on the impact of NGS on care pathways. A better understanding of organization of care, practices, differences and difficulties encountered by both biologists and clinicians could ultimately improve the use of NGS. Sharing knowledge and data through all patient pathway actors is key to improve development and implementation of efficient stratified medicine [5,34,38,39].

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## **DISCLOSURE**

The disclosure forms are enclosed for each author.

## **ADDITIONAL INFORMATION**

### **Ethics approval and consent to participate**

This study used anonymous and routinely collected data from different hospitals and platforms. For two platforms, only aggregated data were available and included. The study was conducted prior to the General Data Protection Regulation of May 25<sup>th</sup>, 2018. Hospitals and platforms

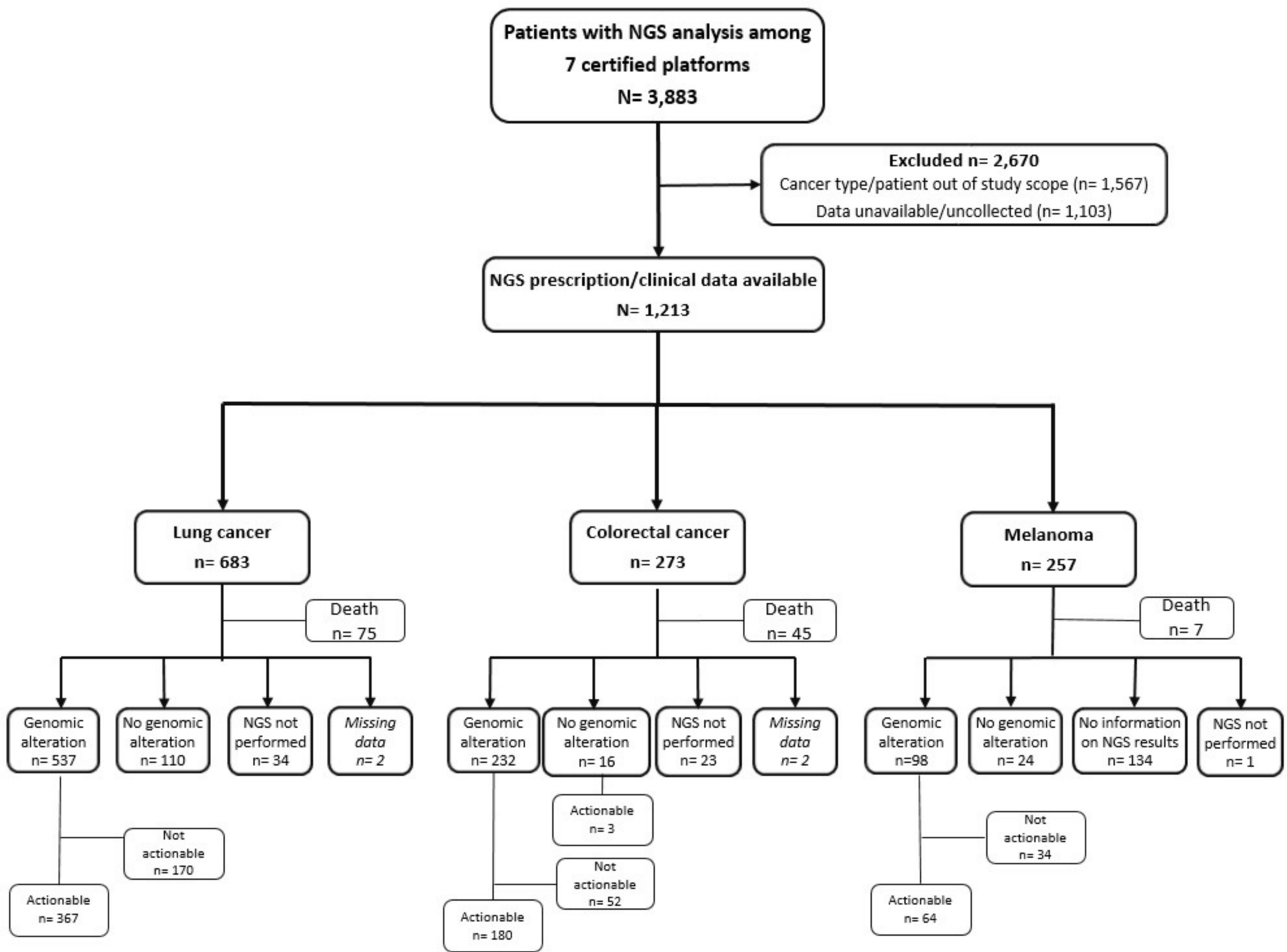
involved collected their patients' consent on the use of their data according to the regulation in effect at the time.

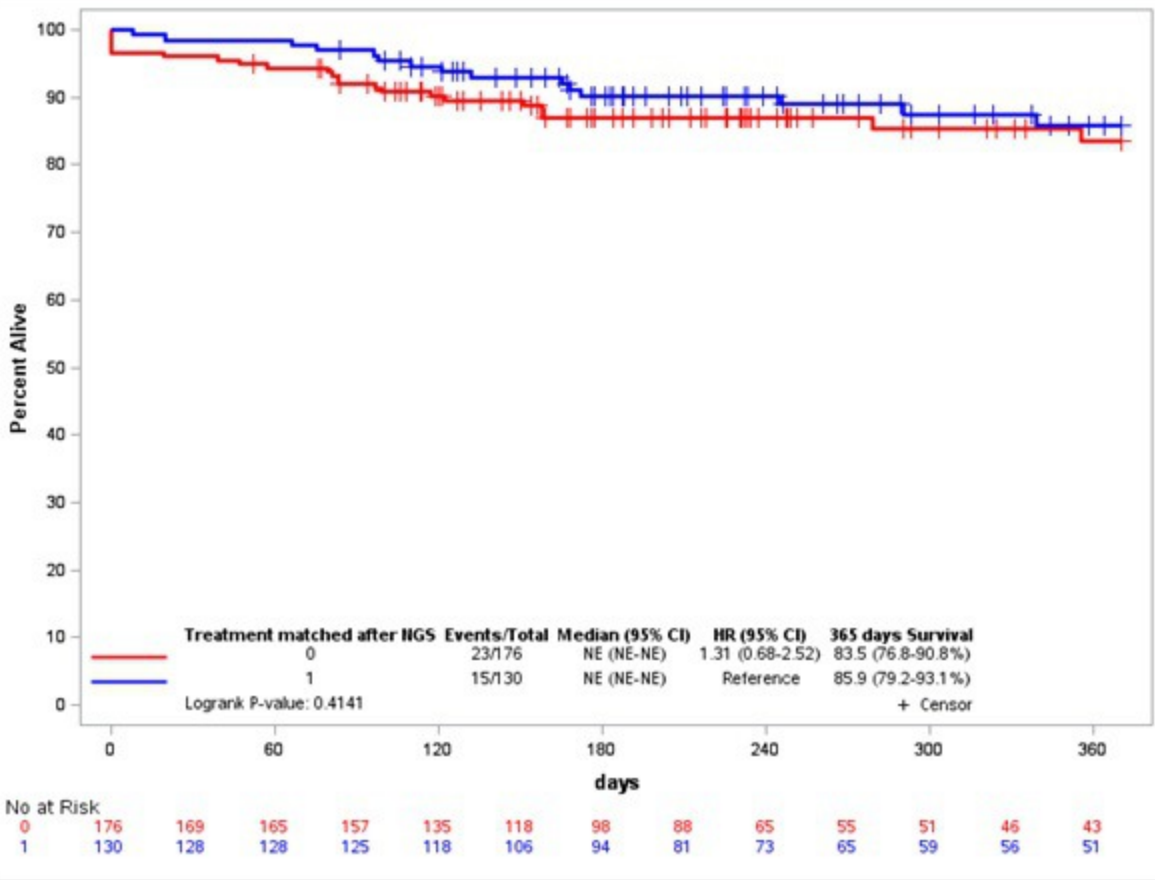
**Consent for publication**

NA.

**Data availability**

The data that support the findings of this study are available from Assistance Publique Hôpitaux de Paris but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Assistance Publique Hôpitaux de Paris.





**Impact of Next Generation Sequencing (NGS) on clinical practice in oncology: better information on patients' genetic profile improves access to experimental treatments**

**Tables (clean)**

**Table 1. Description of the population by cancer type**

|   | <b>Lung cancer</b> | <b>Colorectal cancer</b> | <b>Melanoma</b>   | <b>Total</b>       |
|---|--------------------|--------------------------|-------------------|--------------------|
| <b>Number (%)</b>                         | <b>683 (56.3)</b>  | <b>273 (22.5)</b>        | <b>257 (21.2)</b> | <b>1 213 (100)</b> |
| <b>Sex</b>                                |                    |                          |                   |                    |
| Male                                      | 337 (27.8)         | 122 (10)                 | 38 (3.1)          | 497 (41.0)         |
| Female                                    | 241 (19.9)         | 93 (7.7)                 | 35 (2.9)          | 369 (30.4)         |
| <i>Missing data</i>                       | <i>105 (8.6)</i>   | <i>58 (4.8)</i>          | <i>184 (15.2)</i> | <i>347 (28.6)</i>  |
| <b>Age class</b>                          |                    |                          |                   |                    |
| 18-50                                     | 69 (5.7)           | 40 (3.3)                 | 48 (3.9)          | 157(12.9)          |
| 50-60                                     | 173 (14.3)         | 53 (4.4)                 | 35 (2.9)          | 261 (21.5)         |
| 60-70                                     | 237 (19.5)         | 98 (8.1)                 | 62 (5.1)          | 397 (32.7)         |
| 70-80                                     | 152 (12.5)         | 60 (4.9)                 | 59 (4.8)          | 271 (22.3)         |
| 80-100                                    | 49 (4.0)           | 21 (1.7)                 | 52 (4.3)          | 122 (10.1)         |
| <i>Missing data</i>                       | <i>3 (0.2)</i>     | <i>1 (0.0)</i>           | <i>1 (0.0)</i>    | <i>5 (0.4)</i>     |
| <b>Referring center type</b>              |                    |                          |                   |                    |
| Public hospital with platform             | 264 (21.7)         | 45 (3.7)                 | 72 (5.9)          | 381 (31.4)         |
| Public hospital w/o platform              | 284 (23.4)         | 79 (6.5)                 | 104 (8.6)         | 467 (38.5)         |
| Comprehensive cancer center + platform    | 46 (3.8)           | 68 (5.6)                 | 46 (3.8)          | 160 (13.2)         |
| Private clinic/office based specialist    | 79 (6.5)           | 76 (6.3)                 | 35 (2.9)          | 190 (15.7)         |
| <i>Missing data</i>                       | <i>10 (0.8)</i>    | <i>5 (0.4)</i>           | <i>0</i>          | <i>15 (1.2)</i>    |
| <b>Referring center location</b>          |                    |                          |                   |                    |
| Same department                           | 474 (39.1)         | 222 (18.3)               | 146 (12)          | 842 (69.4)         |
| Same region, other department             | 193 (15.9)         | 38 (3.1)                 | 111 (9.1)         | 342 (28.2)         |
| Other region                              | 7 (0.6)            | 7 (0.6)                  | 0                 | 14 (1.2)           |
| Other country                             | 0                  | 1 (0.0)                  | 0                 | 1 (0.0)            |
| <i>Missing data</i>                       | <i>9 (0.7)</i>     | <i>5 (0.4)</i>           | <i>0</i>          | <i>14 (1.2)</i>    |
| <b>Smoking status</b>                     |                    |                          |                   |                    |
| Smoker                                    | 215 (31.5)         | 10 (3.7)                 | 11 (4.3)          | 236 (19.5)         |
| Non smoker                                | 49 (7.2)           | 3 (1.1)                  | 12 (4.7)          | 64 (5.3)           |
| <i>Missing data</i>                       | <i>419 (61.3)</i>  | <i>260 (95.2)</i>        | <i>234 (91.1)</i> | <i>913 (75.3)</i>  |
| <b>Metastatic status</b>                  |                    |                          |                   |                    |
| Metastatic                                | 387 (56.7)         | 179 (65.6)               | 75 (29.2)         | 641 (52.8)         |
| Non metastatic                            | 130 (19.0)         | 26 (9.5)                 | 33 (12.8)         | 189 (15.6)         |
| <i>Missing data</i>                       | <i>166 (24.3)</i>  | <i>68 (24.9)</i>         | <i>149 (58.0)</i> | <i>383 (31.6)</i>  |
| <b>Patient file review by tumor board</b> |                    |                          |                   |                    |
| Yes                                       | 384 (56.2)         | 205 (75.1)               | 72 (28.0)         | 661 (54.5)         |
| No  | 36 (5.3)           | 18 (6.6)                 | 185 (72.0)        | 239 (19.7)         |
| <i>Missing data</i>                       | <i>263 (38.5)</i>  | <i>50 (18.3)</i>         | <i>0</i>          | <i>313 (25.8)</i>  |
| <b>Line of Treatment</b>                  |                    |                          |                   |                    |
| First                                     | 129 (18.9)         | 39 (14.3)                | 18 (7.0)          | 186 (15.3)         |

|                      |            |           |            |            |
|----------------------|------------|-----------|------------|------------|
| Second               | 65 (9.5)   | 49 (17.9) | 0          | 114 (9.4)  |
| Third and beyond     | 61 (8.9)   | 72 (26.4) | 4 (1.6)    | 137 (11.3) |
| No ongoing treatment | 124 (18.2) | 44 (16.1) | 109 (42.4) | 277 (22.8) |
| Missing data         | 304 (44.5) | 69 (25.3) | 126 (49.0) | 499 (41.1) |

[Smoker: includes ex or current smokers. No ongoing treatment: NGS was performed at diagnosis or patient previously had surgery, radiotherapy or was under medical supervision at the time of NGS analyses.]

**Table 2. Turnaround time in days for patients for whom NGS was performed and data available**

**(n=976)**

|   | <b>Lung cancer<br/>n=439</b> | <b>Colorectal<br/>cancer<br/>n=83</b> | <b>Melanoma<br/>n=230</b> |
|---|------------------------------|---------------------------------------|---------------------------|
| <b>For NGS analyses carried out on an existing sample (n=752)</b> |                              |                                       |                           |
| Mean [Min-Max]  |                              |                                       |                           |
| Days between sampling and request                                 | 63 [1-1,791]                 | 331 [1-3,291]                         | 184 [1-5,474]             |
| Days between request and analysis                                 | 11 [0-312]                   | 13 [0-201]                            | 12 [0-62]                 |
| Days between request and results delivery                         | 25 [0-525]                   | 34 [0-266]                            | 14 [0-68]                 |
|   | <b>Lung cancer<br/>n=125</b> | <b>Colorectal<br/>cancer<br/>n=84</b> | <b>Melanoma<br/>n=15</b>  |
| <b>For NGS analyses carried out on a new sample (n=224)</b>       |                              |                                       |                           |
| Mean [Min-Max]  |                              |                                       |                           |
| Days between request and sampling                                 | 30 [0-380]                   | 15 [0-366]                            | 18 [0-172]                |
| Days between sampling and analysis                                | 66 [0-397]                   | 73 [0-224]                            | 13 [0-28]                 |
| Days between request and results delivery                         | 91 [7-462]                   | 89 [0-399]                            | 22 [2-67]                 |
| <b>For all NGS analyses (n=976)</b>                               |                              |                                       |                           |
| Mean [Min-Max]  |                              |                                       |                           |
| Days between analysis and results delivery                        | 10 [0-95]                    | 9 [0-48]                              | 2 [0-24]                  |

[Missing data were excluded from the turnaround time analysis. 0 indicates that some of steps were performed the same day. As the distribution is not normal, we presented the results in mean [Min-Max]. \*Five lung cancer patients were excluded from the analysis. They had a turnaround time between analysis and results delivery above 100 days, three patients had mutational results obtained in the meantime by pyrosequencing and two were referred to palliative care.]

**Table 3. Classification of alterations and reasons for non actionability**

| <b>Alteration status and actionability<br/>Number (%)</b> | <b>Lung<br/>cancer<br/>649 (56.1)</b> | <b>Colorectal<br/>cancer<br/>250 (21.6)</b> | <b>Melanoma<br/>256 (22.1)</b> | <b>Total<br/>1,155 (100)</b> |
|---|---------------------------------------|---|--------------------------------|------------------------------|
| <b>Missing data/No information on<br/>NGS results</b>     | <b>2 (0.3)</b>                        | <b>2 (0.8)</b>                              | <b>134 (52.3)</b>              | <b>138 (11.9)</b>            |
| <b>No alteration identified</b>                           | <b>110 (16.9)</b>                     | <b>16 (6.4)</b>                             | <b>24 (9.4)</b>                | <b>150 (13.0)</b>            |
| - Wild type KRAS <sup>1</sup>                             |                                       | 3 (1.2)                                     |                                | 3 (0.3)                      |
| <b>Alteration identified</b>                              | <b>537 (82.7)</b>                     | <b>232 (92.8)</b>                           | <b>98 (38.3)</b>               | <b>867 (75.1)</b>            |

<sup>1</sup> Three wild type KRAS were considered as actionable by biologist/clinician and included in the actionable genomic alteration sub-sample.

|  |            |            |           |            |
|--|------------|------------|-----------|------------|
| - Actionable alteration                  | 367 (56.5) | 180 (72.0) | 64 (25.0) | 611 (52.9) |
| - No actionable alteration               | 170 (26.1) | 52 (20.8)  | 34 (13.3) | 256 (22.1) |
| <i>No eligible alteration/trial</i>      | 97 (14.9)  | 29 (11.6)  | 25 (9.7)  | 151 (13.0) |
| <i>Rare alteration</i>                   | 12 (1.8)   |            | 2 (0.8)   | 14 (1.2)   |
| <i>Resistant alteration</i>              | 34 (5.2)   | 10 (4.0)   | 1 (0.4)   | 45 (3.9)   |
| <i>Lack of information on alteration</i> | 5 (0.7)    |            |           | 5 (0.4)    |
| <i>Non-progressive disease</i>           | 3 (0.4)    | 1 (0.4)    | 2 (0.7)   | 6 (0.5)    |
| <i>Death of the patient</i>              | 4 (0.6)    | 5 (2.0)    |           | 9 (0.8)    |
| <i>Patient status too impaired</i>       | 5 (0.7)    | 1 (0.4)    | 2 (0.7)   | 8 (0.7)    |
| <i>Lost to follow up</i>                 | 1 (0.1)    | 1 (0.4)    |           | 2 (0.1)    |
| <i>Ineligible patient</i>                | 6 (0.9)    | 5 (2.0)    | 2 (0.7)   | 13 (1.1)   |
| <i>Missing data</i>                      | 3 (0.4)    |            |           | 3 (0.4)    |

[Resistant alteration with possibility of treatment such as T790 were classified as actionable. Three wild type KRAS were considered as actionable by biologist/clinician and included in the actionable genomic alteration sub-sample.]

**Table 4. Genotype matched and non-matched treatments before and after NGS analyses finding actionable alterations (n=614)**

| Number (%)   | Lung cancer<br>367 (59.7) |                   | Colorectal cancer<br>183 (29.8) |                   | Melanoma<br>64 (10.4) |                  | Total<br>614 (100) |                   |
|--|---------------------------|-------------------|---------------------------------|-------------------|-----------------------|------------------|--------------------|-------------------|
|  | Before                    | After             | Before                          | After             | Before                | After            | Before             | After             |
| <b>Genotype-matched</b>                                    | <b>37 (10.1)</b>          | <b>133 (36.2)</b> | <b>21 (11.4)</b>                | <b>60 (32.8)</b>  | <b>6 (9.4)</b>        | <b>39 (60.9)</b> | <b>64 (10.4)</b>   | <b>232 (37.8)</b> |
| <i>Targeted therapies prescribed</i>                       | 18 (5.0)                  | 33 (8.9)          | 10 (5.5)                        | 9 (4.9)           | 5 (7.8)               | 12 (18.7)        | 33 (5.4)           | 54 (8.7)          |
| <i>Targeted therapies only</i>                             | 18 (5.0)                  | 31 (8.4)          | 10 (5.5)                        | 5 (2.7)           | 5 (7.8)               | 12 (18.7)        | 33 (5.4)           | 48 (7.8)          |
| <i>Targeted therapy +chemotherapy</i>                      | 0                         | 2 (0.5)           | 0                               | 4 (2.2)           | 0                     | 0                | 0                  | 6 (0.9)           |
| <i>Clinical trials proposed</i>                            | 19 (5.1)                  | 100 (27.2)        | 11 (6.0)                        | 51 (27.87)        | 1 (1.5)               | 27 (42.2)        | 31 (5.0)           | 178 (28.9)        |
| <i>p value (matched treatment before versus after NGS)</i> |                           |                   |                                 |                   |                       |                  | <b>0.0001</b>      |                   |
| <b>Non genotype-matched</b>                                | <b>191 (52.0)</b>         | <b>199 (54.2)</b> | <b>119 (65.0)</b>               | <b>109 (59.6)</b> | <b>58 (90.6)</b>      | <b>23 (35.9)</b> | <b>368 (59.9)</b>  | <b>331 (53.9)</b> |
| Chemotherapy   | 50 (13.6)                 | 31 (8.4)          | 21 (11.5)                       | 10 (5.4)          | 0                     | 0                | 71 (11.6)          | 41 (6.7)          |
| Radiotherapy   | 7 (1.9)                   | 11 (2.9)          | 2 (1.0)                         | 2 (1.0)           | 1 (1.5)               | 0                | 10 (1.6)           | 13 (2.1)          |
| Chemotherapy+(radiotherapy or surgery)                     | 19 (5.2)                  | 4 (1.1)           | 6 (3.3)                         | 0                 | 0                     | 0                | 25 (4.1)           | 4 (0.6)           |
| Surgery  | 21 (5.7)                  | 4 (1.1)           | 20 (10.9)                       | 0                 | 34 (53.1)             | 9 (14.0)         | 75 (12.2)          | 13 (2.1)          |
| Clinical surveillance                                      | 3 (0.8)                   | 9 (2.4)           | 6 (3.3)                         | 2 (1.0)           | 2 (3.1)               | 6 (9.4)          | 11 (1.8)           | 17 (2.7)          |
| Palliative care  | 1 (0.2)                   | 5 (1.3)           | 0                               | 0                 | 0                     | 2 (3.1)          | 1 (0.1)            | 7 (1.1)           |
| Complementary test/examination                             | 0                         | 0                 | 0                               | 1 (0.5)           | 0                     | 1 (1.5)          | 0                  | 2 (0.3)           |
| Other treatment  | 0                         | 0                 | 0                               | 5 (2.7)           | 0                     | 0                | 0                  | 5 (0.8)           |
| No treatment/No modification of treatment                  | 52 (14.2)                 | 5 (1.1)           | 11 (6.0)                        | 6 (3.3)           | 21 (32.8)             | 5 (7.8)          | 84 (13.7)          | 16 (2.6)          |
| Unknown treatment  | 38 (10.3)                 | 130 (35.4)        | 53 (28.9)                       | 83 (45.3)         | 0                     |                  | 91 (14.8)          | 214 (34.8)        |
| <i>Missing data</i>  | 139 (37.8)                | 35 (9.5)          | 43 (23.5)                       | 14 (7.6)          | 0                     | 2 (3.1)          | 182 (29.6)         | 51 (8.3)          |

[Results of targeted therapy prescription and clinical trials proposition after NGS analyses based on the results of genomic profile. Unknown treatment: no genotype matched treatment.]