Known and unknown gene fusion detection capabilities of solid tumor laboratories conducting next generation sequencing in 6 countries

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INTRODUCTION

- Developments in next generation sequencing (NGS) are revolutionizing biomarker detection in oncology. Recent therapeutic developments targeting oncogenic gene fusions rather than the traditional single-nucleotide polymorphisms (SNPs) mean that comprehensive genomic assessment is required to avail the latest targeted therapies. Gene fusions are commonly found in patients with solid tumors such as non–small cell lung cancer (NSCLC), sarcoma, and bladder cancer.[1] Targeting gene fusion biomarkers such as *NTRK, RET,* and *FGFR* has proven to be an effective therapeutic approach in various cancers.[2,3] For example, in the setting of non-squamous NSCLC, it is now standard practice to target *ALK* and *ROS1* fusions.[2] Additionally, *NTRK1/2/3, RET,* and *FGFR* gene fusions are now considered therapeutic targets in multiple indications.[2,3,4]
- Therefore, accurately detecting *NTRK* gene fusions is crucial to determining the appropriate therapeutic approach for individual patients. However, some gene fusions, such as *NTRK*, are "promiscuous" and have multiple fusion partners, making accurate detection more difficult.[4,5]
- To complicate matters more, NGS testing approaches are not uniform within the current solid tumor lab landscape, and biomarkers are not necessarily validated nor run in routine use on lab platforms, and labs are potentially missing crucial biomarkers. And when biomarkers are missed, patients are missed. Oncologists, therefore, have the added challenge of identifying the lab that has the appropriate NGS test to correctly identify patients and avoid lost patients.
- While NGS is becoming more prevalent in certain markets, in others NGS adoption for routine clinical purposes remains low, with labs preferring to use single gene methodologies that are perceived to be more cost-effective.
- The objective of this study was to determine the current NGS capability of solid tumor labs to detect unknown fusions.

METHODS

- This study used real-world clinical data from solid tumor labs from the United States, United Kingdom, France, Spain, Italy, and Germany that conduct NGS. The Diaceutics proprietary global data lake of more than 2500 commercial, reference, and academic labs was analyzed across these markets in Q4 2018 to understand NGS testing capabilities currently available within the routine clinical lab setting.

RESULTS

- Of the 131 labs in the US performing NGS, only 50 were able to detect fusions. Of those 50 labs, 42 were restricted to using panels designed to detect specific known fusions. Only 8 labs in the US were able to detect known and unknown fusions. This pattern was reflected in labs surveyed in 5 European markets. While a high number of labs within the US and 5 EU markets use NGS panels, Figure 1 demonstrates that only approximately a third of labs use panels that can detect gene fusions.

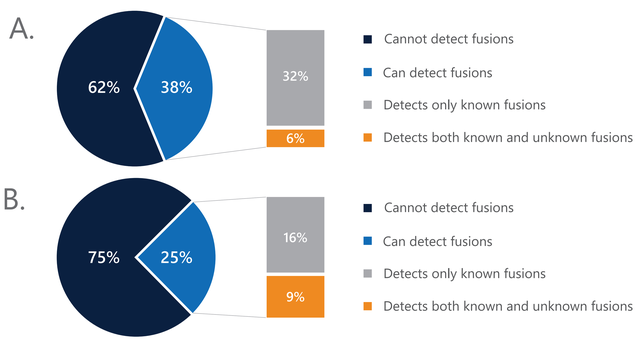

Figure 1. NGS panel capabilities in A). the US and B). European markets

RESULTS

- Further analysis reveals that these panels are commonly targeted/hotspot panels designed to detect only known fusions with a minority of labs using NGS panels that can detect unknown fusions, usually RNA based (Figure 2). Analysis of NGS testing rates in NSCLC samples show that across the US and the 5 EU countries, a steady increase in the use of NGS is observed for the testing of routine clinical samples (Figure 3). This excludes testing done within a clinical trial remit. We see testing at >50% in markets where testing is:
  - Centralized to key reference labs, such as Foundation Medicine in the US;
  - Driven by national networks, such as the INCa network in France and the genomic hubs in England

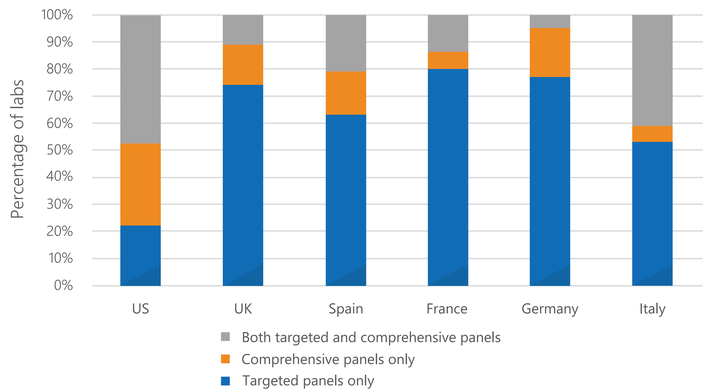

Figure 2. Types of panels commonly used for routine NGS testing

RESULTS

- Unlike the US, labs in European markets prefer to use targeted "hotspot" NGS panels for routine clinical purposes. These panels are rarely designed to detect known or unknown fusions within genes. Only a minority of labs used comprehensive (>100 gene panels, exome panels) for routine clinical purposes as this is associated with higher costs and more complex downstream bioinformatics. In the UK, we would perceive that this will evolve to reflect the situation in France due to the ongoing implementation of Genomics England by NHS England to support the consolidation of genomic services.[6]

CONCLUSION

- Due to a lack of sufficient funding, labs in the EU have not kept up with the technical advances in NGS testing. While pan oncology targeted treatments and companion diagnostics usher in a new age of precision medicine in cancer and extend survival times, many labs are still unable to accurately identify gene fusion biomarkers, especially unknown fusions. Many lab are equipped with the proper platforms but are not using the appropriate kits/panels and bioinformatics to detect unknown fusions, which is likely due to cost of kits, complex bioinformatics pipelines, and the lack of clinical need. Although advancements have promoted the use of genetic testing and high-profile genetic plans, the lab testing ecosystem has not kept up, and deficiencies in platform capabilities to detect unknown fusions continue, leading to the ongoing loss of patients. Additionally, RNA sequencing is not being utilized enough in Europe. We believe this will have increased in 2019 from the time this data analysis was performed. These deficiencies result in both confusion among physicians regarding testing adequacy and missed opportunities for improved outcomes among patients.

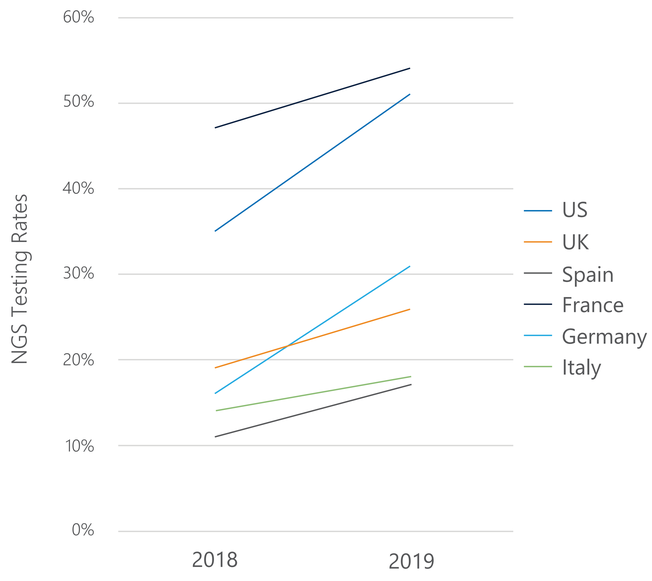

Figure 3. NGS uptake in routine clinical NSCLC samples

ACKNOWLEDGEMENTS

The study was sponsored by Diaceutics Ltd.

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