The French initiative paves the way: routine molecular profiling of advanced non-small-cell lung cancer fights inequalities in access to molecular targeted therapy and improves patient outcome

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This month's issue of the *Lancet* showcases the results of the French Cooperative Thoracic Intergroup (IFCT) 1-year nationwide program of routine molecular profiling of patients with advanced non-small-cell lung cancer (NSCLC). In its sheer size and logistic complexity, the endeavor is unprecedented, and its results highlight an impact of targeted therapy on outcome that extends well beyond what can be attributed to baseline prognostic characteristics. Moreover, it represents a striking example of health-policy implementation mobilizing pre-existing but previously scattered resources.

Advances in multiplex genotyping and high-throughput genomic profiling by next-generation sequencing (NGS) allow physicians to routinely gather therapy-relevant molecular information in a timely fashion. As a result of wide genetic mapping of several cancer types, lung adenocarcinoma as a subtype nowadays encompasses a cluster of discreet subtypes characterized by a single driver alteration, potentially actionable through a matching drug. Since 2004, several targeted therapies for molecularly-defined subsets of NSCLC have successfully found their place in the therapeutic armamentarium. Identification of mutations within the *EGFR* gene resulting in ligand-independent activation (1,2) rapidly led to widespread development and use of EGFR tyrosine kinase inhibitors (TKI), doubling median survival time to more than two years when compared to a similar population not exposed to targeted therapy (3). Following closely with a more efficient development path, the successful targeting of ALK in patients with lung adenocarcinoma bearing rearrangements

in the *ALK* gene yielded similar survival benefits in terms of survival, not explained by baseline prognostic factors, but solely attributable to exposition to the specific targeted therapy (4). In recent reports, median overall survival (OS) of advanced ALK positive NSCLC using optimized sequencing of treatment options has been shown to extend beyond four years (5). Beyond these two oncogenic drivers, for which TKIs are now established as the present standard of care from first-line onwards, other smaller oncogene-addicted NSCLC subsets have been reported with similar sensitivity to targeted approaches (6-8).

Recognizing that lung cancer remains by far the leading cause of death in countries with very high or high human development index (HDI), the translation of these development into nationwide everyday practice is expected to yield tremendous benefits (9). Yet from a public-health point of view, there are further conditions for true personalized medicine in the face of an ever-growing list of molecularly targeted drugs: broad availability of testing, high quality of testing, timeliness of test results compatible with patient care, as well as satisfactory cost-effectiveness. Importantly these parameters may harbor some very distinct definitions across countries. In this regard, the French initiative is remarkable: acting on the Cancer Plan 2009–2013 calling for equal access to innovative and existing therapy, the French National Cancer Institute and the Ministry of Health have set up a nation-wide network of regional hubs for molecular testing that perform tests free of charge for patients and institutions. Between April 2012 and April 2013, 17,664 NSCLC patients were routinely screened for *EGFR* mutations, *ALK* rearrangements, as well

as *HER2*, *KRAS*, *BRAF*, and *PIK3CA* mutations. Considering an estimated annual incidence of close to 39,000 new NSCLC cases with an estimated 85% of which either initially present with advanced stage or with subsequent metastatic relapse, and considering that only 5% of the samples analyzed were of squamous histology, the number of samples tested demonstrates a very high nation-wide testing rate, with very little selection bias. The study thus provides a very comprehensive cohort that carries general applicability.

This high coverage dataset suffers from obvious limitations regarding missing clinical annotations, in particular demographic information, tumor staging details as well as outcome indicators. Capture of such parameters would have brought invaluable knowledge to the field, Nonetheless, the study clearly succeeds in demonstrating the feasibility of the implementation of large-scale nationwide decentralized testing, fulfilling one crucial public health requirement, namely broad unrestricted access to testing.

Quality and reproducibility of molecular analyses represent basic conditions for success, impacting the expected magnitude of benefit of the testing strategy. The authors do not dwell on quality considerations, which are beyond the scope of the article. Nonetheless, the program involved central coordination of the regional centers by the National Cancer Institute, which included the setup of external quality evaluations, the implementation of new molecular assessments, fostering standardization and ensuring high-quality molecular testing in all 28 sites. Turnaround time, a well-known bottleneck in patient management, directly affects physicians' compliance and their willingness to use a particular test provider and might encourage them to initiate therapy before molecular test results are available. In this particular initiative, overall turnaround time form sample collection to report of the analysis was 19 days for *EGFR*, 28 days for *ALK*, 26 days for *HER2*, and 23 days for *BRAF*. Most clinicians will consider this long and borderline acceptable for optimal patient care, and this was indeed the case for 23% of patients in the study, whose therapy was started before the molecular information became available, disregarding this information for initial treatment decision-making. Maximal reduction of turnaround time is obviously limited by diverse in-laboratory factors. Some sample require multiple attempts at library preparation, as sample quality and quantity are often an issue in the lung cancer setting, where most tests must be performed on small biopsies or endobronchial ultrasound guided cytological samples. Formalin-fixed and paraffin-embedded samples do often yield poor-quality DNA and contamination with non-tumor cells hampers the detection of tumor-specific mutations. While the French program used sequential Sanger sequencing, or a more sensitive validated allele-specific technique with confirmation by Sanger-sequencing (similarly to the Lung

Cancer Mutation Consortium), many laboratories have now implemented NGS methods (10). These usually allow for more rapid sequencing of a large panel of genes in parallel, with time requirements nonetheless ranging from more than ten days for earlier platforms to less than 24 hours for the newest platforms in use (11). As sequencing time falls, the overall turnaround time will then be dominated by human factors such as variant interpretation and report sign-out, as the time required to interpret a large panel of gene sequences and a fortiori whole-gene sequence data is undoubtedly slower than hotspot genotyping because of the wider range of variations detected. In summary, the long turnaround time reported by the French initiative will rapidly shorten as the technology evolves.

From a public health perspective, cost effectiveness remains a key issue when implementing large-scale molecular profile guided therapy. While the cost effectiveness of first-line crizotinib therapy has been called into question, this seems to be mainly a consequence of drug pricing, and not of the magnitude of benefit (12). The cost effectiveness of EGFR mutation testing has already been demonstrated by several studies (13). In Frances health-care system, that relies mainly on public centralized State funding by the Sécurité Sociale, the extrapolation of these savings to the nationwide population may lead to a significant relief of the financial burden.

With regards to patient outcome, the study highlights major differences in progression free survival (PFS) both in first and second line, and OS. OS was 4.7 months longer when a genetic alteration was detected, including alterations not actionable currently, suggesting both a prognostic advantage in some molecular subsets, mixed with the impact of targeted therapy. This is especially striking when considering the median PFS of first-line treatment of patients with *EGFR*-mutated NSCLC of 15.4 *vs.* 8.3 months in the overall population, and the median PFS of second-line treatment of patients with *ALK*-rearranged NSCLC of 9.3 *vs.* 3.1 months in the overall population. These differences dramatically exceed what is to be expected from baseline prognostic differences and pinpoint the immediate effect of EGFR and ALK TKIs, respectively. Interestingly, the inclusion rate into clinical trials was not improved by the initiative. This finding may be related to the specific panel of alterations being tested, that were either of uncertain predictive value for targeted therapies, disappointingly altered to date by available compounds (KRAS, PIK3CA, HER2) or for whom established and registered drugs were already available (EGFR and ALK). Another likely explanation may be insufficient coordination between molecular pathologists and clinical trials investigators; and possibly a lack of collaborative efforts across centers in building shared and distributed clinical trials or in

systematically referring patients for research protocols. National registers listing recruiting clinical trials might support maximizing patient enrollment into clinical trials—these were probably not part of this French program.

The recent initiatives aiming at addressing the complex molecular landscape of lung tumors through the design of widely distributed umbrella trials (Battle trials, SAPHYR, Lung-MAP, SPECTAlung,…) is probably the way to move forward, reinforcing an academic and transversal research of quality across regions and countries.

The French program should further encourage worldwide initiatives to provide NSCLC patients with access to personalized therapy; and we anticipate they will demonstrate that molecular stratification of NSCLC for therapeutic purposes is a cost-effective strategy that can be successfully implemented in a centralized health-care system.

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Footnote

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