Editor's note:
In the era of personalized medicine, a critical appraisal new developments and controversies are essential in order to derived tailored approaches. In addition to its educative aspect, we expect these discussions to help younger researchers to refine their own research strategies.

Controversies on Lung Cancer: Pros and Cons

Rebuttal from Dr. Hofman and Dr. Ilié

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We would like to thank Dr. Mino-Kenudson for her accurate review of this topic. We strongly support the conclusion that liquid biopsy has screening as well as complementary roles in clinical management of advanced NSCLC patients and may replace tissue biopsy to some extent in the future. In total agreement with Dr. Mino-Kenudson, based on the current development of liquid biopsy, it appears unlikely that liquid biopsy will entirely replace tissue biopsy in the near future. In this context, Dr. Mino-Kenudson clarifies the current significant limits of liquid biopsy for instance for diagnosis and subtyping of lung cancer as well as for histological transformation reported in 5–7% of *EGFR* TKI resistant cases for which histology is mandatory. However, we are more optimistic about the clinical guidance of liquid biopsy for cancer treatment in the near future. By validating, developing and refining techniques for sequencing ctDNA, researchers may rapidly overcome several hurdles for liquid biopsies that could help clinicians to make better choices of treatment and to adjust decisions as conditions changes (1).

We want to emphasize that the results of liquid biopsies will not necessarily replace tissue biopsies but will be a pivotal additional tool. There is always going to be a role for tissue-based biopsy, as it yields information about morphology (including the microenvironment), tumor type, and possible site of origin. More likely, liquid biopsy will be used when tumor tissue is of insufficient quality or quantity to allow a broader array of testing. Probably, the most important role for analysis of liquid biopsies will occur for real-time serial monitoring of progression under treatment (per ASCO Post 2016, Dr. Philip C. Mack) (2).

At the last Molecular Analyses for Personalized medicine (MAP) conference, a panel of worldwide experts agreed that ctDNA has convincing analytical validity to detect hotspot mutations using digital PCR, based on several studies that compared the detection of mutations in biopsies versus in plasma (3). However, the threshold that defines a clonally dominant alteration is not yet consensual, and more effort is needed to implement NGS for ctDNA-based assays (4). Moreover, while progress is rapid, suitable methods need to be applied, and more evidence is required to support the validity of liquid biopsies for detection of clinically relevant mutations in tumor suppressor genes or copy number alterations (3).

The next step is to increase the sensitivity of sequencing assays in the detection of mutations at an extremely low ctDNA level, which is necessary for some tumors and will also enable its use in earlier-stage cancers as a complement

to radiological-based screening approaches.

A deeper understanding of the spatial and temporal dynamics of the evolution of lung cancer may lead to new therapeutic approaches. Efforts toward understanding these issues are being made in studies such as TRACERx, for which researchers are harnessing assiduous approaches to spatial and temporal tumor sampling linked to autopsy programs and developing their understanding of circulating biomarkers (5). Moreover, the value of circulating tumor cells in combination with unenhanced low dose chest computed tomography in the screening of lung cancer is currently being investigated in large national multicenter efforts (AIR project; http://www.projet-air.org/; NCT02500693).

With the paradigm shift brought by liquid biopsies in cancer treatment, pathologists must be aware of the changes in practice in oncology and in particular those in the field of precision medicine. In the future, additional qualifications combining clinical pathology, molecular pathology and molecular biology should be developed. This will give rise to the practice of "molecular biopathology". The adoption of the liquid biopsy approach within a pathology department will require dramatic changes to the organization (e.g., dedicated pre-analytical area, solutions for plasma conservation and secure storage before and after cfDNA extraction, accreditation for ctDNA sequencing assays).

In summary, the current indications of liquid biopsy in lung cancer are still limited. There is no doubt that tissue biopsy remains currently the gold standard for diagnosis and treatment in advanced non-small cell lung cancer. However, the combination of tissue and liquid biopsy will help us to get additional information that will help to treat lung cancer patients better and in a more informational way.

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Footnote

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