Response to Letter to the Editor Titled "Seize the Opportunity With Small Tissue Samples: The Tailor Teaches!"

To the Editor:

Trisolini et al.[1] raise an important issue in their letter "Seize the Opportunity With Small Tissue Samples: The Tailor Teaches!" Notably, they point out that small sample sizes and limited sequence panels can provide significant clinical information for patient care decision-making in the community setting and that larger panels are not necessary. Support for this comes largely from a manuscript by Stoy et al.[2] who report a 91% success rate for cytology-based genomic sequencing. Nevertheless, the authors fail to note several limitations of this study which prevents it from being widely applicable.

As Stoy et al.[2] described in his methodology section, to achieve this near-perfect next-generation sequencing (NGS) yield, a pathologist needs to be at bedside providing real-time assessment of tumor cellularity on the smears and guiding the bronchoscopist to continue taking biopsy samples until a sufficient sample is achieved. Most academic institutions do not have this kind of manpower support, let alone the average community hospital. Furthermore, the workflow for the study at the University of Chicago was to only send highly cellular smears for NGS (>20% tumor density); those that did not pass bedside screening criteria were not sent for NGS, thus their study population was enriched with only successful specimens, which the authors readily acknowledged. In addition, although smears have been found in select studies to be a better source of undamaged tumor cells compared with formalin-fixed, paraffin-embedded cell blocks, it is not yet standard of care and many NGS companies will not accept cytology specimens for molecular profiling.[3]

There are many other reasons to justify the use of large-panel NGS sequencing. We are living in a time of unprecedented advances in cancer care. During the span of February 2020 to September 2021, there were 18 new drug treatments approved by the Food and Drug Administration for lung cancer.[4] Limiting our search to only actionable mutations which have a commercially available drug means that patients will be deprived of the opportunity to find out whether they qualify for the "next" big therapy. At the University of Southern California Norris Cancer Center, we switched from limited panel NGS testing to a 592-gene panel because we knew that the former could not test for NTRK fusions, foreseeing that an unknown NTRK status might deny some patients newer therapies in the coming year. In addition, otherwise nontargetable comutations now affect therapeutic decisions. As one example, the POSEIDON trial recently revealed that resistance to checkpoint inhibition conferred by STK11, KEAP1, or NFE2 might be overcome by adding a CTLA-4 agent to the programmed death-ligand 1 agent.[5]

In summary, although we acknowledge that comprehensive NGS panels may not be feasible for every patient and all practice situations, we hope that our manuscript "Biopsy Method and Needle Size on Success of Next-Generation Sequencing in Non–Small Cell Lung Cancer: A Brief Report" will provide assistance and guidance for practices that do use large-panel NGS testing to plan their biopsy pathways.

CRediT Authorship Contribution Statement

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