In Response to Dr. Steven Sorscher

To the Editor:

We thank Dr. Sorscher for his interest and compliments on our report on germline *CHEK2* mutation (*gCHEK2m*).[1] First, we agree that routine germline testing of patients with NSCLC is neither practical nor recommended as most patients with NSCLC have a smoking history. Even among never-smokers with NSCLC, *gCHEK2m* is extremely rare. Nevertheless, the routine use of plasma genotyping in assessing resistance to targeted therapies, to perform initial genomic profiling to identify actionable alterations, or to monitor response to treatment is in fact in the majority of the cases performing de facto germline testing because (at least a subset of, but not all) most plasma genotyping assays sequence most of the common hereditary genetic mutations (*APC*, *ATM*, *BRCA1*, *BRCA2*, *CHECK2*, etc.) even if they are not purposed for germline testing. An allele frequency near 50%, particularly in a cancer susceptibility gene, should prompt consideration of germline testing, as this was, in fact, how the *gCHECK2m* in our report was discovered. Thus, clinicians who order plasma genotyping of NSCLC should review the report carefully in detail including any indication of secondary germline mutation findings.

Second, we completely agree that patients with suspected *gCHEK2m* must be referred for genetic counseling, and their siblings and descendants should be checked for the same *gCHEK2m* so that these family members can be enrolled into appropriate cancer screening per guidelines. Furthermore, as we gather more information on *gCHEK2m*, more cancer surveillance may need to be performed as our knowledge of *gCHEK2m* expands and more NSCLC patients with *gCHEK2m* are identified.

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Cite this article as: Zhang SS, Schrock A, Nagasaka M, Ou SHI. In response to Dr. Steven Sorscher. *JTO Clin Res Rep*. 2022;4;100453.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2022.100453

Third, we agree that we need to investigate how *gCHEK2m* may modulate response to targeted therapy, especially to current approved and investigational KRAS inhibitors, but given the very low incidence of *gCHEK2m* in NSCLC (<1%), preclinical investigations will likely provide the clue way ahead of clinical investigations but we remain optimistic the pace of clinical development of combination of inhibitors may get us to the finish line earlier that we anticipate.

Fourth, we thank Dr. Sorscher for summarizing the goal of our brief report: to spur further research on whether *gCHEK2m* increases predisposition to NSCLC.

CRediT Authorship Contribution Statement

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Reference

1. Zhang SS, Lee JK, Tukachinsky H, Schrock AB, Nagasaka M, Ou SI. A high percentage of NSCLC with germline CHEK2 mutation harbors actionable driver alterations: survey of a cancer genomic database and review of literature. *JTO Clin Res Rep*. 2022;3:100387.