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Letter to the Editor

Somatic Mutations in Breast Cancer: The Tip of the Iceberg

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▸ See the article "Somatic Mutations of *TP53* and Prognostic Factors for Primary Operable Breast Cancer: Correspondence" in volume 25 on page 522.

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The authors declare that they have no competing interests.

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We appreciate Dr. Pathum Sookaromdee and Dr. Vrioj Wiwanitkit for their comments on our recent article [1]. Their commentary [2] proposed compensating for the potential confounding effects of genetic alterations other than *TP53*. Potential prognostic factors mentioned include *HER2* copy number in cell-free DNA, genetic polymorphism of the *ESR1* gene, and expression level of a long non-coding RNA. We reviewed the articles in the references, and we would like to clarify the position of our study.

Cancer is a complex disease involving genetic and epigenetic mechanisms [3]. A multi-omic approach is necessary to comprehend the complex biology of breast cancer. The original work by The Cancer Genome Atlas integrated data on DNA methylation, whole-exome sequencing, RNA sequencing, and proteomics for the tumors [4]. However, multi-omic analysis is resource-intensive and is not practical. In clinical practice, scoring systems using selected gene-expression markers are commonly used. The most commonly used genomic assays for breast cancer are solely based on mRNA expression levels [5,6].

Targeted next-generation sequencing (NGS) is widely used because it is readily available in the clinical setting [7]. It can be performed using tumor samples preserved in paraffin-embedded tissue blocks. Only a small amount of stored sample is required for testing, which directly identifies multiple targetable genetic alterations and allows patients to participate in the clinical trials [8]. Our study is meaningful because it shows that targeted NGS can identify a prognostic marker for the patients with breast cancer in a curative setting.

Targeted NGS is not a perfect method because it can only identify genetic alterations in the genes included in the panel. There is no standard gene panel for targeted NGS, and it varies by institutions. Targeted NGS can only detect genetic alterations in selected areas of the tumor tissue. Intra-tumoral heterogeneity may limit the reproducibility of targeted NGS results for a single tumor [9]. However, this rapidly evolving sequencing technology is expected to overcome the limitations of bulk sequencing [10].

Nevertheless, we are particularly interested in detecting *HER2* amplification through targeted NGS. Immunohistochemistry and *in situ* hybridization are used together as the standard method to identify *HER2* amplification [11]. The sensitivity of targeted NGS in our study was

only 47.4% (n = 28/59) for identifying HER2-positive breast cancers classified by the standard method; 32.4% (n = 12/37) for the luminal B/HER2-positive subtype; and 72.7% (n = 16/22) for HER2-enriched subtypes. Intra-tumoral heterogeneity and stromal cell contamination may partially explain the low sensitivity of targeted NGS for identifying *HER2* amplifications [10,12].

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