Letter to the Editor

Looking Beyond the Numbers in NCCN Evidence Blocks

Re: Mitchell AP, Tabatabai SM, Dey P, et al. Association between clinical value and financial cost of cancer treatments: a cross-sectional analysis. *J Natl Compr Canc Netw* 2020;18(10):1349–1353.

In the October 2020 issue of *JNCCN*, Mitchell et al¹ assessed the association between the cost of cancer treatments and 4 NCCN Evidence Blocks (EB) measures of clinical value: efficacy, safety, quality of evidence, and consistency of evidence. Using generalized estimating equations for 1,386 treatments, the authors found that the clinical value of cancer treatments does not seem to be a primary determinant of treatment cost. We appreciate the authors for addressing value of cancer treatments to curb increasing healthcare spending and improve patient outcomes. However, from the health economist and pharmacist perspective, we found 2 concerns regarding their statistical analysis.

According to the NCCN EB, the affordability measurement is not a hard cost to each patient, but rather represents an estimate of overall total cost of a therapy, including the costs of drugs, administration, supportive care, toxicity monitoring, and hospitalization. However, Mitchell et al only included upfront costs associated with each treatment (ie, drug costs, administration fee, growth factor support, and antiemetic therapy), omitting long-term costs associated with

monitoring and management adverse events. This can be problematic because such long-term costs can be a substantial portion of overall total cost of care.^{2–4}

Additionally, it appears that each NCCN EB measure was entered as a continuous variable in the multivariable models. In doing so, the authors made an implicit assumption that a marginal impact of a unit change is constant (ie, a marginal impact of changing the quality-of-evidence score from 1 to 2 on treatment cost is the same as changing it from 3 to 4). Based on the descriptive statistics presented in Table 1, such an assumption does not appear to be true because there is no clear increasing or decreasing linear trend between each NCCN EB measure and treatment cost. Furthermore, NCCN EB measures are qualitative measures assigned by experts based on current evidence and their clinical experience, with the score of 1 being the “least favorable” and 5 being the “most favorable.”⁵ A drug with an affordability score of 2 is not exactly twice more affordable than a drug with a score of 1.

Failure to capture long-term costs and assuming each unit change in NCCN EB measures has a constant marginal impact on treatment cost may have introduced bias in the estimated impact of NCCN EB measures on treatment cost. This may perhaps explain the inconsistent association between treatment cost and NCCN EB measures.

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Authors' Reply

To Letter to the Editor by Cho and Jun

Dr. Cho and Ms. Jun critique 2 analytic choices in our manuscript and suggest that these may have introduced bias into our results.

The first is our measurement of cost. The authors appear to have interpreted our methods as attempting to replicate the NCCN Evidence Blocks (EB) Affordability measure. That measure includes ancillary costs such as management of adverse effects and monitoring. But this was not our intent. We measured costs associated with drug purchasing and administration, which result directly from the treatment selected and which are similar among patients receiving the same treatment. Ancillary costs are unpredictable, highly variable, and

driven by patient-specific factors such as performance status and comorbidity. We believe that measuring the costs that directly and predictably result from treatment is the most appropriate analytic choice. It is unlikely that inclusion of ancillary costs would have substantially altered our findings. For that to occur, cancer treatments' EB scores would need to be strongly correlated with their ancillary costs. This seems highly unlikely, and the authors provide no evidence to suggest that such an association would be expected.

The authors also critique our treatment of the EB scores as continuous variables in our primary analysis. The authors

point out that these scores are ordinal rather than continuous. This is why we repeated our analysis using the Kruskal-Wallis nonparametric rank-order test. This analysis is presented in supplementary eTable 7, where we report that our overall results were largely robust in this alternate modeling approach. We found no statistically significant associations among the time-limited treatments, and among time-unlimited treatments, higher Efficacy scores were associated with higher treatment costs, while higher Safety scores (score of 4 vs score of 3 or 2) were associated with lower treatment costs (scores of 3 and 2). To the extent that Kruskal-Wallis model results differed from the

continuous variable models (eg, the Quality score), a consistent association between EB scores and costs appeared *less* likely, not more likely. In other words, this supplementary analysis supported our overall conclusion that treatment costs are not consistently associated with treat-

ment benefit (as encapsulated in the EB scores).

We therefore find it unlikely that these methodologic choices biased our analyses, or that they may have resulted in us “missing” meaningful associations between EB scores and treatment costs as the authors suggest.

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