Screening for Lynch Syndrome in the General Population—Response

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We thank Sadeghi and co-authors for their comments regarding our article (1). They are correct in their assertion that models such as $PREMM_{1,2,6}$ (2) will benefit from broad testing in the general population. In the larger context, however, we would like to note that the results of our study are not specific to the $PREMM_{1,2,6}$ model, which is only one of several available tools to estimate mutation probability. Our study was an investigation using the Archimedes model to determine the cost-effectiveness and health outcomes associated with genetic testing in individuals who were at risk of but had not (yet) developed Lynch syndrome–associated cancers. The $PREMM_{1,2,6}$ model played a role as a screening tool to determine, in effect, inclusion/exclusion thresholds for enrollment in each arm of a virtual trial in which individuals were subsequently given genetic tests. However, other appropriate tools, including clinical judgment, may be implemented by a physician to estimate an individual's likelihood of carrying a mismatch repair (*MMR*) mutation and to inform choices about genetic testing. Because of its ease of use, $PREMM_{1,2,6}$ is convenient, but the results of our study are not contingent upon it. If in the physician's judgment, or if based upon any well-validated risk calculation tool such as $PREMM_{1,2,6}$ or MMRPro, a patient has more than 5% pretest probability of carrying a mutation, reasonable consideration of genetic testing is suggested. Furthermore, while our findings suggest a 5% threshold, there are other thresholds, as shown in Tables 2 and 3, at which genetic testing remains appropriate. This allows for a reasonable range of accuracies in whichever screening approach the clinician takes with his or her patient.

The purpose of $PREMM_{1,2,6}$ in the model, therefore, was to serve as a surrogate for and to affix a quantifiable value to the level of suspicion a clinician develops around a patient's risk for carrying a mutation. Its favorable sensitivity and an area of 0.88 under the receiver operator characteristic curve make $PREMM_{1,2,6}$ a good screening test. While Sadeghi and colleagues utilize a general population prevalence of 1 in 440 for their calculations, the prevalence of mutation among those with $PREMM_{1,2,6}$ scores of more than 5% is certainly much higher. Consequently, by the estimates of our analysis, approximately 1,500 genetic tests are performed in a population of 100,000, resulting in a favorable number needed to screen of approximately 7.5 to identify each additional mutation carrier.

The primary concerns of Sadeghi and colleagues however, hinge on the economic implications of their assumptions that (i) using $PREMM_{1,2,6}$ necessitates the inclusion of additional costs that were not accounted for in the model and (ii) false-positive results generated by $PREMM_{1,2,6}$ require an accounting for disutility that diminishes cost-effectiveness. $PREMM_{1,2,6}$ can be self-administered online by individuals at no actual or opportunity cost to the physician, or it can be done in approximately 2 minutes in the clinic visit. In our sensitivity analysis of Figure 2, we have made the range of costs associated with genetic testing broad enough that the clinical cost of using $PREMM_{1,2,6}$, if any, has no detriment on cost-effectiveness outcomes. Furthermore, as described in Table 1, Gritz and colleagues (3) showed that disutility among those individuals whose genetic tests are positive for *MMR* mutation is transient, returning to baseline within 6 to 12 months. Implicit, therefore, is the conclusion that disutility is negligible for those whose genetic test results are negative (i.e., false-positive PREMM results). The evidence from Gritz et al. is consistent with similar findings of disutility in other genetic conditions, supporting the principle that those with false-positive screening results (i.e., normal genetic tests) suffer negligible decrement in quality of life.

Disclosure of Potential Conflicts of Interest

Tuan Dinh and Benjamin Rosner are full time employees of Archimedes, Inc. Other authors disclose potential conflicts of interest: C. Richard Boland (Myriad Genetic Laboratories, Inc.), Stephen B. Gruber (Archimedes, Myriad Genetic Laboratories, Inc.), and Randall Burt (Archimedes, Myriad Genetic Laboratories, Inc., Caris Inc.).

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