In Reply

Rehm et al. raised concerns regarding our analysis of discordant *BRCA1* and *BRCA2* variant classifications between a single testing laboratory (Myriad Genetic Laboratories) and ClinVar, a database of user-submitted variant classifications. Due to recent efforts to resolve discrepancies within ClinVar, the authors suggest that the reported discordance would be lower if current ClinVar entries were used. However, 14.5% of evaluated variants did not have any ClinVar entries that were concordant with the testing laboratory at the time of analysis and would not be affected by reduced discordance within ClinVar. The authors also assert that our analysis should have been restricted to "criteria provided, single submitter" entries. However, discordance remained high (14.56%–19.3%) in a subgroup analysis of ClinVar entries from clinical testing laboratories that meet these criteria. Furthermore, the default setting in ClinVar displays all entries for a variant and using filters to exclude some entries is not intuitive. Because the goal of this publication was to inform providers of what they may find when consulting ClinVar after clinical genetic testing, we believe our analysis was appropriate.

Rehm et al. also suggest that variants of uncertain significance (VUS) and benign variants should not be considered discordant because recommended medical management is identical [1, 2]. However, this is often not the case in clinical practice, with increased surgical intervention and anxiety reported among women with a *BRCA1* or *BRCA2* VUS [3–5]. Moreover, guidelines specifically distinguish these classifications and the required evidence for classification [2]. Therefore, we believe the clinical implications of discordant variant classifications must include VUS and benign variants.

The authors take issue with the perceived assertion that the variant classifications from Myriad are correct. Although we are highly confident in the accuracy of the laboratory variant classification process (identical to Myriad's U.S. Food and Drug Administration-approved process) [6, 7], we reported *differences* in variant classifications.

Rehm et al. disagree with our conclusion that the clinical benefit of consulting ClinVar is unclear and argue that sharing knowledge improves clinical practice. Although we recognize the value of sharing information, we believe it should be done in a clinically responsible manner that respects patient privacy. If a clinician is to manage a patient in a fashion that may appear inconsistent with an issued clinical laboratory test report, documentation and discussion of the evidence that underlies that decision (as afforded by peer-reviewed publication) is vital to ensure appropriate care and reduce liability. Although Rehm et al. recommend ClinVar as a viable "second opinion" resource, many entries are outdated and/or include little to no explanation of the reported classification. This makes it challenging—even impossible—for clinicians to appropriately utilize this "second opinion." Whereas Rehm et al. state that the five case examples included in our manuscript demonstrate the benefit of sharing knowledge, it is noteworthy that ClinVar entries for these variants have not changed since publication. Therefore, we maintain our initial conclusion that the clinical benefits of consulting ClinVar after clinical hereditary cancer testing are unclear.

Our publication highlights classification discrepancies that clinicians may encounter when consulting ClinVar after clinical genetic testing. Notably, many discordant ClinVar entries reflect actual reports that have been issued to patients. Given the widespread use of genetic test results in medical management decisions, we maintain that it is ultimately the responsibility of the testing laboratory to review all available evidence and ensure that the most accurate information is reported to patients and providers. This enables providers to base clinical decisions on robust, accurate, and complete information.

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Disclosures

Krystal Brown: Myriad Genetic Laboratories, Inc. (E); **Erin Mundt**: Myriad Genetic Laboratories, Inc. (E); **Susan Manley**: Myriad Genetic Laboratories, Inc. (E, OI). The other author indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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http://dx.doi.org/10.1634/theoncologist.2017-0320