We demonstrate that 2.5% (50/2000) of patients tested carried a variant. Limited research has assessed the frequency of conflict among patients. Various commercial laboratories are used in cancer genetics practice, leading to conflicting categorizations of genetic variants. A prospective cohort study of 2,000 patients undergoing MyRisk testing was recruited from 3 cancer genetics clinics from 2014 to 2016. A review of ClinVar archives was performed to identify clinically significant conflicts between ClinVar and the test report, defined as either a variant of uncertain significance (VUS) on the test report with a pathogenic/likely pathogenic (P/LP) classification by major laboratory in ClinVar, or a P/LP variant on the test report with a VUS classification by a major laboratory in ClinVar. For patients carrying a VUS with a conflict, study case report forms and results disclosure clinic notes were analyzed to determine if there was evidence that providers were aware of the conflict. Patients in this cohort with clinically significant conflicts were then compared to patients with the same variants outside the cohort, tested by the same providers utilizing different laboratories.

We demonstrate that 2.5% (50/2000) of patients tested carried a variant with a clinically significant conflict in ClinVar when the test report was issued, including 19 patients with a P/LP variant reported in APC or MUTHY, and 31 patients with a VUS reported in CDKN2A, CHEK2, MLH1, MSH2, MUTHY, RAD51C, or TP53 (Figure 2). For patients with a VUS on their report who had a clinically significant conflict, only 10/28 (36%) of patients appeared to be counseled by a provider who was aware of the conflict (Figure 3). A detailed case analysis led to the finding that discrepant counseling strategies were utilized for different patients with the same variant, within the same institution and even by the same counselor.

**Background**

Various commercial laboratories are used in cancer genetics practice, leading to conflicting categorizations of genetic variants. 96% of cancer genetic counselors report encountering a variant interpretation discrepancy, and 99% have concerns about counseling patients with these variants. Significant discrepancies between the test report and ClinVar have been reported in 11% of patients with germline findings. Limited research has assessed the frequency of conflict among solely clinical laboratories and its impact on patient care. We describe the frequency of this occurrence, analyze genetics providers’ awareness of conflicting interpretations, and compare management recommendations provided to patients with discrepant classifications of the same variant.

**Methods**

A prospective cohort study of 2,000 patients undergoing MyRisk testing was recruited from 3 cancer genetics clinics from 2014 to 2016. A review of ClinVar archives was performed to identify clinically significant conflicts between ClinVar and the test report, defined as either a variant of uncertain significance (VUS) on the test report with a pathogenic/likely pathogenic (P/LP) classification by major laboratory in ClinVar, or a P/LP variant on the test report with a VUS classification by a major laboratory in ClinVar. For patients carrying a VUS with a conflict, study case report forms and results disclosure clinic notes were analyzed to determine if there was evidence that providers were aware of the conflict. Patients in this cohort with clinically significant conflicts were then compared to patients with the same variants outside the cohort, tested by the same providers utilizing different laboratories.

**Results**

We demonstrate that 2.5% (50/2000) of patients tested carried a variant with a clinically significant conflict in ClinVar when the test report was issued, including 19 patients with a P/LP variant reported in APC or MUTHY, and 31 patients with a VUS reported in CDKN2A, CHEK2, MLH1, MSH2, MUTHY, RAD51C, or TP53 (Figure 2). For patients with a VUS on their report who had a clinically significant conflict, only 10/28 (36%) of patients appeared to be counseled by a provider who was aware of the conflict (Figure 3). A detailed case analysis led to the finding that discrepant counseling strategies were utilized for different patients with the same variant, within the same institution and even by the same counselor.

**Conclusions**

A proportion of patients undergoing genetic testing have results that are interpreted differently by another major laboratory. Laboratory classification of variants is complex and variable. Genetics providers are not routinely incorporating ClinVar into their VUS counseling, and rely on their laboratory of choice. Initiatives to harmonize variant classifications may be useful in resolving discrepant interpretations and supporting clinicians in providing accurate risk assessment.

**References**