The paperwork matters! Phenotypic information significantly impacts variant interpretation in hereditary cancer testing

**BACKGROUND**
- The validity and utility of genetic testing require evidence-based, objective, and systematic variant interpretation.
- Well-described published clinical case reports and patients’ phenotypic clinical information provided by the ordering clinician serve as the primary sources for case report data used in variant interpretation.
- As an extension of our laboratory’s evidence-based variant classification framework, Sherloc, we developed point-based criteria for the objective inclusion of clinical information. As part of this process, we established a set of pre-defined clinical criteria for approximately 130 oncology genes.
- In this study, we sought to determine the impact of incorporating critically-evaluated clinical phenotypic information into our variant classification system for over 100,000 patients undergoing testing for hereditary cancer.

**METHODS**
- A series of de-identified patients who underwent hereditary cancer testing over a 2-year period (September 2015 – November 2017) are included in this study.
- Only cases for which at least one of 32 pre-selected cancer genes were analyzed (APC, BMPRYA, CASR, CDG3, CDH1, DICER1, EPCAM, FH, FLCN, MAX, MEN1, MLH1, MSH2, MSH6, NF1, NF2, PMS2, PTCH1, PTEN, RB1, RET, SDHB, SDHC, SDHD, SMAD4, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL).
- These genes were selected because:
  - They are commonly requisitioned for hereditary cancer indications.
  - Internal clinical case report criteria have been developed, tested, and implemented in variant classification.
  - Among this cohort of patients, Pathogenic and Likely Pathogenic (P/LP) variants for which clinical case report evidence was applied were selected.
  - We assessed how frequently exclusion of this clinical evidence would have resulted in a classification of Variant of Uncertain Significance (VUS) instead of P/LP, possibly affecting clinical management of patients.

**RESULTS**

**Impact of objective inclusion of clinical information on variant classification**

<table>
<thead>
<tr>
<th>Evidence category</th>
<th>Description of the evidence types</th>
<th>Pathogenic points</th>
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<tbody>
<tr>
<td>Case reports</td>
<td>4 unrelated case reports</td>
<td>3</td>
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<tr>
<td></td>
<td>3 unrelated case reports</td>
<td>2</td>
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<td>2 unrelated case reports</td>
<td>1</td>
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- The clinical case report evidence category has been further expanded into three sub-evidence types, allowing for the additive nature of evidence towards classifying a variant as Pathogenic (5 pathogenic points).
- For genes that have established consensus clinical diagnostic criteria, like STK11, NF1, RB1, MEN1, etc., our interpretation criteria are nearly identical to the consensus clinical diagnostic criteria.
- For genes that lack a formal consensus, such as SDHB, we have taken a rigorous, conservative approach in establishing internal criteria that considers age of onset of disease, phenotypic specificity, penetrance, prevalence, and the existence of phenoopies.

**CASE EXAMPLE**

Clinician-provided patient information is particularly valuable as many classified variants are only observed in the clinical testing laboratory setting.

Here we illustrate a FH variant classified as LP due to the inclusion of clinician-provided, detailed phenotypic information.

**Table 2. Pathogenic evidence for LP variant in FH**

**CONCLUSIONS**
- Patient phenotypic data can play a critical role in the variant interpretation process.
- We demonstrate that a substantial proportion of our P/LP cases would have otherwise remained VUSs, suggesting our current pool of VUSs hold the potential for reclassification considering additional case report evidence.
- Ordering providers may profoundly influence variant classification by sharing complete, accurate personal and family history data.

Disclosures: All authors are stockholders and employees of Invitae.