Variant classification and reporting

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Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

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Guidelines for diagnostic next-generation sequencing

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ACMG classes: 5 to 1 (or 1 to 5)

5 - Pathogenic
4 - Likely pathogenic (90% / 95% for cancer)
3 - Uncertain significance – a VUS
2 - Likely benign (90% / 95% for cancer)
1 - Benign

The classification system is made for Mendelian disorders.
**Penetrance** is not part of the classification system, but should be stated in the report.
Should a VUS be reported to the clinican?

**YES**, because
- The referring physician should have all information about a test
- It is the responsibility of the clinician and not the laboratory to treat the patient
- A VUS may later turn out to be pathogenic
- The laboratory may later be sued for not reporting a "pathogenic VUS"
- The VUS is considered a "good candidate" that should be investigated further ("VUS+")

**NO**, because
- The referring physician may think that a VUS is pathogenic
  (quote: "uncertain significance" just means that the pathogenic mechanism is unknown)
- The referring physician will be overwhelmed by variants (variant overload)
- A wrong diagnosis may be given
- The right diagnosis is no longer looked for
Should ESHG/EUGT pioneer a classification system? A starting point for further thoughts could be:

- **Molecular grading**: 0-5, call a VUS class 0 and only a VUS+ class 3:
  - 0 = VUS, i.e. insufficient knowledge for grading  NORMAL
  - 1-2 = benign and likely benign  NORMAL
  - 3 = variant of potential interest (VUS+)?
  - 4-5 = likely pathogenic and pathogenic  FINDING

- **Clinical grading**: 0-5, penetrance- and phenotype-based:
  - 0 = “wrong gene” or “highly unlikely cause”  NORMAL/IF
  - 1 = ”right gene”  ?
  - 2 = risk factor  FINDING
  - 3-5 = low (0-25) - moderate (25-50) – high (50-100)  FINDING
# Combined system

<table>
<thead>
<tr>
<th>Mol grade</th>
<th>Clin grade</th>
<th>Sum</th>
<th>Comb class</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (= VUS)</td>
<td>0</td>
<td>0-3</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1 (&quot;right gene&quot;)</td>
<td>4-5</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2 (risk factor)</td>
<td>6-7</td>
<td>2</td>
</tr>
<tr>
<td>3 (= VUS+)</td>
<td>3 low (&lt; ~25%)</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>4 moderate</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>5 high (&gt; ~50%)</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
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Examples:

1: Suspect variant in gene that suits phenotype  
3+1/3+2/4+1 = 4/5

2: FactorV-Leiden / dup1q21.1  
5+2 = 7

3: del 1q21.1 or a mutation in KCNH2 (LQTS2)  
5+3 = 8

4: likely LoF in EHMT1  
4+5 = 9

**Inheritance pattern:** if likely recessive and "right gene", consider Bayes
DELIVERABLES

* ESHG- and ERN-endorsed recommendations
* Publish in medical journal
* Refer to existing documents
* Focus on issues not extensively addressed previously, e.g. better correlation of clinical characteristics and VUS interpretation, bioinformatic prediction

BOTTOM LINE
Closer collaboration between clinicians, lab specialists and bioinformaticians