# Variant classification and reporting

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ACMG STANDARDS AND GUIDELINES | Genetics inMedicine

# 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

Sue Richards, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5], Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12], Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15]; on behalf of the ACMG Laboratory Quality Assurance Committee

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POLICY

# Guidelines for diagnostic next-generation sequencing

Gert Matthijs*[,1,8], Erika Souche[1,8], Mariëlle Alders[2], Anniek Corveleyn[1], Sebastian Eck[3], Ilse Feenstra[4], Valérie Race[1], Erik Sistermans[5], Marc Sturm[6], Marjan Weiss[5], Helger Yntema[4], Egbert Bakker[7], Hans Scheffer[4] and Peter Bauer[6]

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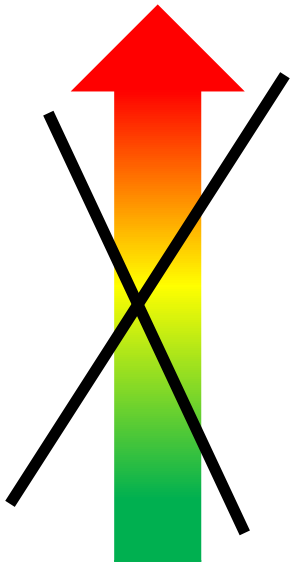
# ACMG classes: 5 to 1 (or 1 to 5)



5 - Pathogenic

4 - Likely pathogenic (90% / 95% for cancer)

3 - Uncertain significance – a VUS

2 - Likely benign (90% / 95% for cancer)

1 - Benign

The classifiaction 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 pioner 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

| Mol grade | Clin grade | Sum | Comb class | |
|---|---|---|---|---|
| 0 (= VUS) | 0 | 0-3 | 0 | Normal |
| 1 | 1 (“right gene”) | 4-5 | 1 | Unclassified variant of potential interest (all VUS+) |
| 2 | 2 (risk factor) | 6-7 | 2 | Susceptibility variant |
| 3 (= VUS+) | 3 low (< ~25%) | 8 | 3 | Disease-contributing genetic variant |
| 4 | 4 moderate | 9 | 4 | Disease-causing genetic variant; likely / moderate grade |
| 5 | 5 high (> ~50%) | 10 | 5 | Disease-causing genetic variant; definite / high grade |

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

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## 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

# Gene Curation Coalition

ClinGen
Clinical Genome Resource


TGMI

Genetics Home Reference

50 YEARS OMIM
Human Genetics Knowledge for the World

orphanet