Variant classification and reporting

Gunnar Houge MD, PhD
ESHG President

ESHG
EUROPEAN SOCIETY OF HUMAN GENETICS

EuroGentest

ACMG/AMP classes

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.

Genetics inMedicine | ORIGINAL RESEARCH ARTICLE

Modeling the ACMG/AMP variant classification guidelines as a Bayesian classification framework

Sean V. Tavtigian, PhD[1], Marc S. Greenblatt, MD, PhD[2], Steven M. Harrison, PhD[3], Robert L. Nussbaum, MD[4], Snehit A. Prabhu, PhD[5], Kenneth M. Boucher, PhD[6] and Leslie G. Biesecker, MD[7];
on behalf of the ClinGen Sequence Variant Interpretation Working Group (ClinGen SVI)

Should a VUS be reported to the clinician?

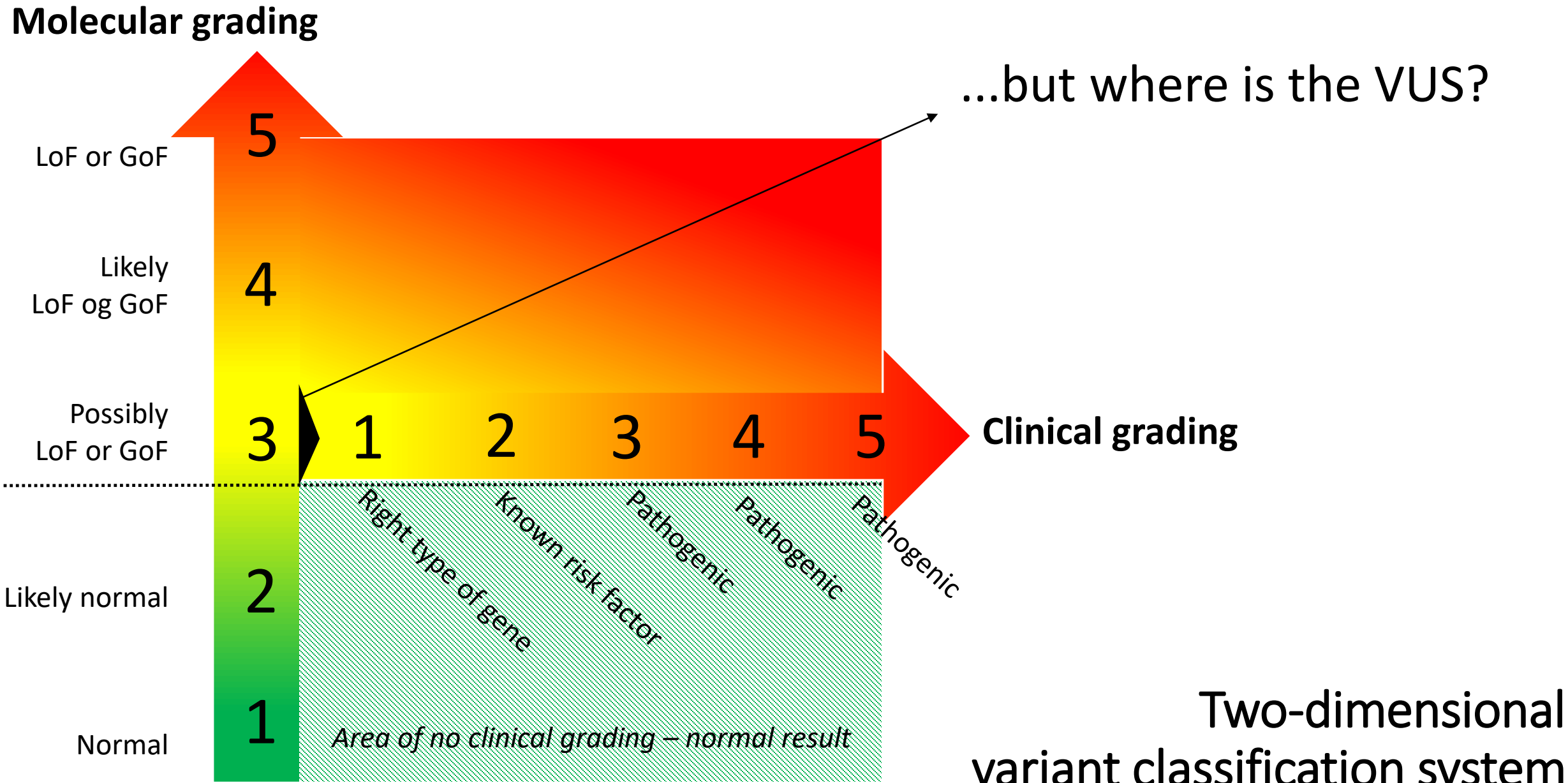
- **YES**, because
  - The referring physician should have all information about a test
  - It is the responsibility of the clinician and not the laboratory to treat the patient
  - A VUS may later turn out to be pathogenic
  - The laboratory may later be sued for not reporting a «pathogenic VUS»
  - The VUS is considered a ”good candidate” that should be investigated further (a 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 do not know what to do with this information
  - A wrong diagnosis may be given...
  - ...and the right diagnosis is no longer looked for!

ESHG prototype system

- **A**: Molecular grading 1-5 - based on the ACMG/AMP system
- **B**: Clinical grading 1-5 – considering e.g. penetrance and gene type
- **Grading is impossible** = **a VUS** (= 0). Can be a VUS in A or B or both.
- **A+B**: Combined grading (2 numbers: e.g. 3+4)
- Standarized variant explanations (9 alternatives)
- May utilise DECIPHER's clinical fit estimator
- Promotes teamwork

ESHG variant classification task force:

Hans Scheffer (Eurogentest)
Johan den Dunnen (LOVD/HGVS)
Nicole de Leeuw (molecular cytogenetics)
Helen Firth (DECIPHER)
Gunnar Houge (ESHG)


Molecular grading
5
LoF or GoF
4
Likely
LoF og GoF
3
Possibly
LoF or GoF
2
Likely normal
1
Normal
1
2
3
4
5
Clinical grading
Right type of gene
Known risk factor
Pathogenic
Pathogenic
Pathogenic
Area of no clinical grading – normal result
...but where is the VUS?
Two-dimensional
variant classification system
for variants that can be classified

… it is a zero because a true VUS cannot be graded

Molecular VUS

A variant with little/no molecular information = 0

Clinical VUS

Gene with poor fit to phenotype or of unknown function = 0

A Molecular grading

		Score	Odds	Description
ACMG	Protective variant («den Dunnen variant»)	**-1?**		Variant known to be protective, i.e. hinder a given phenotype
3	Variant of unknown biological significance *- a molecular VUS*	**0**	0.10-0.50?	Variant of unknown **biological** significance - usually due to lack of knowledge
1	Benign variant	**1**	0.00-0.01	High frequency variant with no reason to suspect a recessive or hypomorphic role, or certainly neutral after functional family studies
2	Likely benign variant	**2**	0.01-0.10	Lower frequency variant with no reason to suspect a recessive or hypomorphic role, or likely neutral after functional/family studies
"3+"	Variant of potential interest, possibly pathogenic	**3**	0.50?-0.90	Rare variant that could affect gene function based on biological knowledge aided by bioinformatic tools, i.e. a variant of potential biological significance
4	Hypomorphic (R) or likely pathogenic variant (D)	**4**	0.90-0.99	**Recessive**: Variant that reduces gene function, but that only causes a biochemical abnormality - or disease - if *in trans* to a LoF allele. **Dominant**: likely LoF, or variant of functionally important consequence
5	Pathogenic variant	**5**	0.99-1.00	Variant that is certain to disrupt gene function or to be disease causing

B Clinical grading

	Score	Description
Variant of unknown clinical significance - *a clinical VUS*	**0**	Variant of unknown **clinical** significance, i.e. variant in a gene that is unlikely to be directly linked to the patient's phenotype
Variant of potential interest	**1**	"The right type of gene" **because the gene fits the phenotype**: Dominant variant that could be pathogenic, or a single hypomorphic variant that could be linked to a recessive cause
Known risk factor variant	**2**	Low penetrance dominant variant, like the *F2* R506Q (APCR-Leiden) variant, or single certainly pathogenic variant in recessive gene
Mild penetrance pathogenic variant (< 20%)	**3**	Mild penetrance variants, e.g. a single *ATM* pathogenic variant
Moderate penetrance pathogenic variant (20-40%)	**4**	Moderate penetrance variants, e.g. a single *KCNH2* pathogenic variant
High penetrance pathogenic variant (> 40%)	**5**	High penetrance variants, e.g. a *BRCA1* pathogenic variant

A+B class	Combined grading (NB: both numbers should be listed)		Examples of reporting recommendations (policy dependent)
		Combined	
0	Mol 1 / Mol 2 / 0+0 / 0+1 / 0+2	**«0-2»**	Usually not reported - *clinical grading not necessary if molecular class 1-2*
F	Mol or Clin VUS group: 0+3 / 3+0	**«3»**	Not reported if the gene in question is unlikely to explain the phenotype
E	**3+:** 3+1 / 3+2 / 4+0 / 4+1 / 5+0	**«4-5»**	Reporting optional: Variant of potential interest (VUS+), or single recessive allele in a gene that might explain the phenotype
D	**4+:** 4+2 / 4+3 / 5+1 / 5+2	**«6-7»**	Reporting usually recommended if dominant or verified recessive: **Susceptibility variant**
C	4+4 / 5+3	**«8»**	Reporting recommended: Disease-associated variant (of low penetrance)
B	4+5 / 5+4	**«9»**	Reporting recommended: Disease-associated variant (of moderate penetrance)
A	5+5	**«10»**	Reporting recommended: Disease-associated variant (of high penetrance)

Standard variant explanations (not interpretations): This system is not for making diagnoses - it is made to better help the physician

Class

0	Normal findings
0	Normal findings – no pathogenic or likely pathogenic variants detected
F/E	Normal findings – no pathogenic variants that could be related to the phenotype detected
E/D	Normal findings - pathogenic variants that could explain the phenotype were not detected
E/D	Genetic variant of potential interest detected
E/D	Heterozygosity for a recessive genetic variant of potential interest detected
D	A genetic variant that increases susceptibility for this phenotype was detected
C/B/A	Disease-associated pathogenic variant detected (+/- penetrance if known)
X	Genetic variant unrelated to the phenotype detected

DECIPHER’s clinical fit estimator can be used as an aid in borderline cases:

C

DECIPHER's clinical fit estimator	Lowers likelihood			Increases likelihood		
	Substantially	Mildly	Mildly	Moderatedly	Substantially	Strongly
Genetic heterogeneity of the phenotype						
Age of onset of symptoms						
Gene could explain phenotypic features						
Severity and progression of clinical features and signs						
Relevant family history						

A Bayesian-based odds ration calculation for ACMG scoring has been published and implemented in DECIPHER

New system advantages

- Separates variant classification into a molecular and clinical arm
- Both systems score a true VUS as 0
- Penetrance is taken into account
- Hypomorphic alleles can be classified
- It does not matter if the phenotype has a recessive or dominant cause
- Allows standarized «semiautomatic» variant explanations

New system challenges

- Clinical geneticists must know more about basic biology
- Clinical information is essential – including family history
- Genetic laboratories must have evaluation teams for challenging variants