Exec report for 2019

- Moving ESHG to Austria
- Strengthening our reserves
- Positive development in the number of members (> 3000)
- Closely following PlanS that may affect EJHG income
- Closer relationship with ASHG
- ESHG courses going well
- ESHG educational fund is soon a reality (in collaboration with Illumina)
- New ESHG courses in planning: Prenatal genetics and Bioinformatics
- Policy issues: https://www.eshg.org/index.php?id=909

Two-dimentional variant classification

ESHG variant classification task force:

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

ESHG
EUROPEAN SOCIETY OF HUMAN GENETICS

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

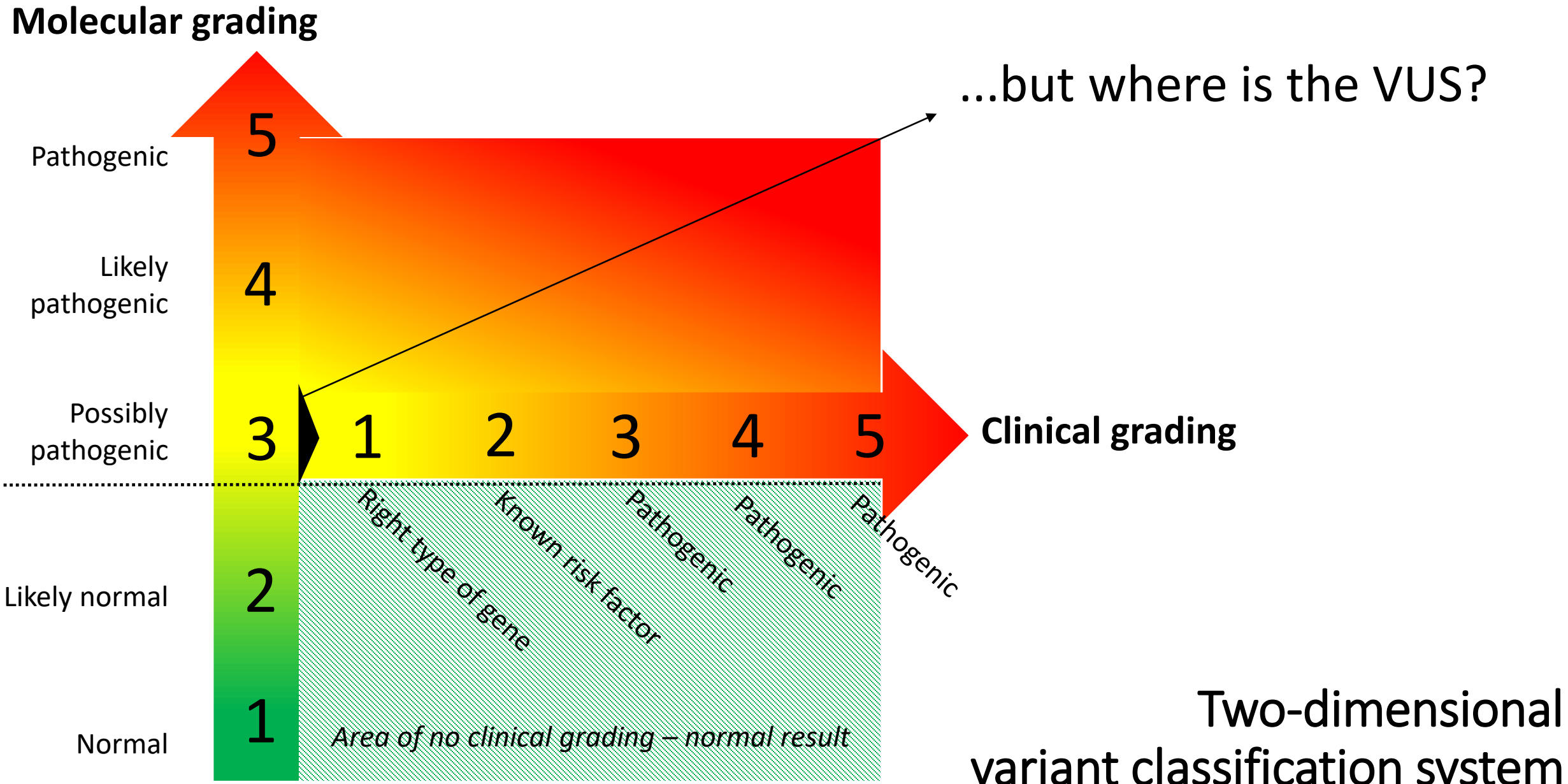
The classification system is made for Mendelian disorders.
Penetrance is not part of the classification system, but should be stated in the report.

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


Molecular grading
5
Pathogenic
4
Likely pathogenic
3
Possibly pathogenic
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

ACMG		Score	Odds	Description
	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 benign 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 benign 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 pathogenc variant
5	Pathogenic variant	**5**	0.99-1.00	Variant that is ~certain to disrupt gene function or 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	Combined grading	Combined	Examples of reporting recommendations (policy issue)
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

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