**The ABC system in brief** version 2.0 - June 2024

The ABC system tries to answer the question: Is the variant or finding of clinical relevance?
To do that, the system has 3 steps, each trying to answer a different question:
 **Step A**: Has the variant or finding a functional effect? Grades are from 0-5.
 **Step B**: Has the variant or finding clinical relevance? Grades are from 0-5.
 **Step C**: Should the variant or finding be reported or not?

The A+B grade (from 0-10) leads to a joint grade from F to A, and that guides variant reporting by selection of a standard comment in step C, adapted to the clinical question.

Unlike ACMG/AMP classification, ABC does not ask about pathogenicity, and therefore all kinds of genetic findings can be classified, including benign variants associated with human traits, or findings like extensive homozygosity on a SNP-array test or an EpiSign profile.

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| **Step A: Functional grading of a variant or finding5 – FE – F**unctional **E**ffect: Known LoF or GoF variant**4 – LFE – L**ikely **F**unctional **E**ffect – or known **H**ypomorphic **A**llele**3 – HFE –** VUSwith a **H**ypothetical **F**unctional **E**ffect – or a **de novo** VUS**0 – VUS –** VUS without a hypothetical functional effect**2 – LNF – L**ikely **N**ormal **F**unction |
| **1 – NF – N**ormal **F**unction\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |

**Step B: Clinical grading of a single variant or finding\*

0 – NO MATCH variant,** i.e.the gene is unlikely to be linked to the phenotype – or no clinical information

**1 – VOI** - **v**ariant **o**f potential **i**nterest in a gene that fits or could fit the phenotype

**2 – RISK FACTOR** – variant known to increase phenotype likelihood (recessive or oligofactorial)

**3 – Dominant pathogenic** variant of unknown or low (e.g. <25% lifetime) penetrance

**4 – Dominant pathogenic** variant of moderate (e.g. 25-50% lifetime) penetrance

**5 – Dominant pathogenic** variant or high (e.g. >50% lifetime) penetrance

\*Exception: Homozygosity for a recessive pathogenic variant should be graded from 3 to 5
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**Classification from 0/F to A: Combined A+B grade gives the variant class**

**Class**

**0** Step A = 0-2 (no step B) **NORMAL** - Not reported – and clinical grading not usually done

**F** Step A + step B = 3 **NORMAL** - Not reported
**E** Step A + step B = 4-5 **NORMAL/VOI/RISK FACTOR**, reporting optional
**D** Step A + step B = 6-7 **NORMAL/VOI/RISK FACTOR**, report if clinical match

**C** Step A + step B = 8 **PATH**ogenic, unknown or low penetrance (e.g. lifetime <25%)

**B** Step A + step B = 9 **PATH**ogenic, moderate penetrance (e.g. lifetime 25-50%)

**A** Step A + step B = 10 **PATH**ogenic, high penetrance (e.g. lifetime >50%)

**X** Step A + step B = 7-10 Incidental or secondary finding

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**Step C: Standard variant comments**

**A grade 0-2 (no step B grading needs to be done, but variants should contribute to variant databases)**

 NORMAL findings

**A+B grade 3 (class F)**

 NORMAL findings – no pathogenic or likely pathogenic variants were detected

**A+B grade 4-5 (class E) and 6-7 (class D)**

 NORMAL findings – no pathogenic variants that could be related to the phenotype were detected

 NORMAL findings – no pathogenic variants that could explain the phenotype were detected

 VOI – A genetic variant of potential interest was detected

 VOI – Heterozygosity for a recessive variant of potential interest was detected

 VOI – Hemizygosity for a variant of potential interest was detected

 VOI – Homozygosity for a variant of potential interest was detected

 RISK FACTOR – A variant that increases susceptibility for this phenotype was detected

 RISK FACTOR – Heterozygosity for a recessive variant of interest was detected

PATH – Likely compound heterozygosity for recessive pathogenic variants was detected

PATH – Heterozygosity for a dominant likely pathogenic variant was detected
**A+B grade 8 (class C – pathogenic), 9 (class B – moderate penetrance) and 10 (class A – high penetrance)**

 PATH – Homozygosity for a recessive pathogenic variant was detected

 PATH – Heterozygosity for a dominant pathogenic variant was detected

 PATH – Heterozygosity for a dominant pathogenic variant of moderate penetrance was detected

 PATH – Heterozygosity for a dominant pathogenic variant of high penetrance was detected
**Incidental/unexpected findings and A+B grade 7-10 (class X)**

 IF – A genetic variant unrelated to the clinical question was detected

 IF – No obvious match between genotype and phenotype. Further clinical investigations necessary

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**Tentative/preliminary suggestion for integration of ACMG criteria in the ABC system:**

**Step A**

5-FE PVS1 PS1 PS3 1 criterium enough to grade

4-LFE PP1-Strong PM4 PM5 2 criteria or more: upgrade to FE

3-HFE PS2 PS4 PM1 PM2 PM6 PP1 PP2 PP3 PP5 3 criteria or more: upgrade to LFE

0-fVUS not enough data to classify
2-LNF BS1 BS2 BS3 BP1 BP2 BP3 BP4 BP5 BP6 BP7

1-NF BA1

 Note: One “pathogenic” ACMG criterium is enough to grade.
 Known hypomorphic alleles are by default grade 4 - LFE.

**Step B**

0-cVUS BS4, no clinical match or clinical Information
1-VOI gene fits phenotype

2-RISK FACTOR PM3 PP4 1 criterium is enough
3-PATH known pathogenic (AR or AD)
4-PATH known pathogenic (AD, moderate penetrance)
5-PATH known pathogenic (AD, high penetrance)