

**(Reference from *Genetics in Medicine* instructions to authors)**

**Terminology**

Please use the following terms:

- variant instead of mutation
- pathogenic variant to denote a disease-causing variant
- Single nucleotide polymorphism (SNP) is generally discouraged except for use in polygenic risk score (PRS) or GWAS (genome-wide association study) manuscripts: SNV (Single nucleotide variant) is also acceptable in such manuscript types. Note GWAS studies are generally low priority for GIM.
- heterozygote (rather than carrier) when referring to a person's genotype/genetic test result. Explanation: The usage is intended to deal with the issue that "heterozygote" describes the presence of a variant, regardless of classification, but "carrier" typically implies that the variant is disease-causing.
- carrier screening when referring to testing populations; screening when searching asymptomatic populations for P/LP variants; surveillance (rather than screening) when referring to use of imaging, labs, or other clinical evaluation in individuals at risk for disease manifestations
- genome sequencing instead of whole genome sequencing
- exome sequencing instead of whole exome sequencing
- prenatal screening by cell-free DNA
  - In [accordance with the ACMG](#), please use the term "prenatal cell-free DNA screening" or prenatal screening by cell free DNA to describe this screening test.
  - The term "cell-free DNA" can be abbreviated as cfDNA; no other abbreviated forms of this term are permitted.
  - When using the term "cell-free DNA" to describe its application in settings other than prenatal (such as in oncology), after being defined in the manuscript as cell-free DNA, the abbreviation cfDNA should be used.
- Incidental findings when results are not being intentionally sought though they may be anticipated (known to be potentially associated with the test) or unanticipated (not typically associated)

- Secondary findings when results are actively sought but not the primary reason for testing
- chromosomal microarray analysis or CMA instead of array-based comparative genomic hybridization or aCGH. Explanation: current array platforms either do not utilize aCGH, or use it in combination with SNPs to detect both copy number and absence of heterozygosity. For all manuscripts, unless the focus of the manuscript is specifically aCGH we ask authors to use the term "chromosomal microarray analysis" or "CMA".
- When referring to persons included in research studies, 'participant' is preferred. A research 'participant' (preferred to 'subject'; see below) is a person who undergoes an intervention as part of a scientific investigation. A 'patient' is a person under medical care and 'patient' is not expected to be widely used in GIM articles; rather 'participant' or 'person' are generally preferred. 'Subject' (as in study/research subject) is impersonal, perhaps derogatory, suggesting a subservient role and should not be used.
- somatic vs acquired and germline vs constitutional

Retain consistency in use of these terms as much as possible, but there is flexibility to use what the authors think fits best in the context.

#### General Principles:

- “constitutional” refers to the context of cytogenetic testing, or to refer to chromosome testing results, but we do not expect that to be used for molecular testing. In other words, we prefer the authors use “germline” rather than “constitutional” to describe a germline variant (already the default in molecular)
- We prefer the use of “somatic” for non-cancer somatic variants.
- We allow the use of "acquired" or "somatic" for cancer-related somatic variants.

Please note: these terms are usually enforced during review, but we may also make those changes at copy editing if necessary.

For more information please refer to: [Jarvik GP, Evans JP. Mastering genomic terminology.](#)

#### **Guidance on language and reporting on diversity, disability, race, ethnicity, sex and gender**

When writing your manuscript please bear in mind the following:

- Is there a description in the methods section of race/ethnicity, sex/gender variables that were collected?
- Is the source of racial/ethnic, sex/gender classification reported? (e.g., database, electronic health record, survey)
- Is there a description of how participant race/ethnicity, sex/gender was assigned? (e.g., participant self-report, participant selection of pre-determined categories, investigator or clinician assignment)
- Participant self-report or selection is more rigorous than investigator- or clinician-assigned
- Is a scientifically-justified reason for collection of race/ethnicity, sex/gender data provided? Is a scientifically-justified reason for classification by sex vs. gender provided?
- Is race and/or ethnicity being used as a proxy for genetic ancestry?
- If so, this is inappropriate.
- Is sex being used as a proxy for gender or vice versa?
- In most cases this would be considered inappropriate
- Are White populations or European ancestry groups being used as reference categories in analysis?
- If so, is there a scientific justification for this comparison?
- In studies of genetic contributions to health disparities, are social determinants of health, environmental exposures and other likely-relevant variables included?
- If not, is the possible role of these non-genetic factors discussed as a limitation?
- Is the study providing findings from underrepresented populations?
- If not, is a rationale provided, and discussion of the limitations of the generalizability of the study?
- Are terms used that make assumptions about the gender of persons based on anatomy, physiology, or biology? For example, is "pregnant women" being used rather than "pregnant persons"? "Women" rather than "persons with uteruses"?
- Are study findings inclusive of LGBTQIA+ persons?

- If not, is a rationale provided, and discussion of the limitations of the generalizability of the study?

Inclusive language acknowledges diversity, conveys respect to all people, is sensitive to differences, and promotes equal opportunities. Content should make no assumptions about the beliefs or commitments of any reader; contain nothing which might imply that one individual is superior to another on the grounds of age, gender, race, ethnicity, culture, sexual orientation, disability or health condition; and use inclusive language throughout. Authors should ensure that writing is free from bias, stereotypes, slang, reference to dominant culture and/or cultural assumptions. We advise to seek gender neutrality by using plural nouns (“clinicians, patients/clients”) as default/wherever possible to avoid using “he, she,” or “he/she.” We recommend avoiding the use of descriptors that refer to personal attributes such as age, gender, race, ethnicity, culture, sexual orientation, disability or health condition unless they are relevant and valid. These guidelines are meant as a point of reference to help identify appropriate language but are by no means exhaustive or definitive.

### **Race, Ethnicity, and Genetic Ancestry**

For race, ethnicity, and genetic ancestry terms please refer to "[Updated Guidance on the Reporting of Race and Ethnicity in Medical and Science Journals published in JAMA](#)" and follow the copy editing guidelines in the [AMA Style guide](#).

### **Amino acid three letter codes**

Our preference is that you follow [International Union of Biochemistry and Molecular Biology](#) guidelines on the three letter codes that should be used to describe amino acids.

### **Description of genetic disorders**

Genetic disorders should be accompanied by their corresponding OMIM numbers if available. For details on OMIM numbers, please refer [here](#). Otherwise, please include other suitable disease identifiers e.g., [MONDO disease term](#).

### **Gene nomenclature requirements**

Approved gene symbols and nomenclature can be obtained from the [HUGO Gene Nomenclature Committee \(HGNC\)](#). Authors must include the approved gene symbol and corresponding HGNC identifier in the manuscript text, for example *P3H1* (HGNC:19316). The gene symbol must not be confused with the gene name e.g., "*P3H1*" is the gene symbol and "*prolyl 3-hydroxylase 1*" is the gene name. The ID provides a stable reference for the gene since gene symbols and gene names can change over time. Human gene symbols

and loci are given in italicized capital letters and Arabic numbers. Protein products are not italicized. Use ISCN nomenclature for cytogenetic notation (<https://iscn.karger.com/>).

Mouse gene/variant nomenclature should use the [International Committee on Standardized Genetic Nomenclature for Mice](#).

### **Human chromosome nomenclature**

*GIM* follows the [International System for Human Cytogenomic Nomenclature \(ISCN\)](#) for cytogenomic variations. Many users will have institutional access through this link: <https://iscn.karger.com/>.

### **Nomenclature of DNA sequence variants and variant data sharing**

Documenting variation in our genomes is an important undertaking for human research and clinical care. Accuracy in the notation of DNA sequence variants is essential for the success of this endeavor. Accurately naming and deposition of variants in appropriate databases ensures that the clinical literature is discoverable and usable by other researchers.

Because of the importance of the issue and the consensus on the rules *Genetics in Medicine (GIM)* require compliance with the Human Genome Organization (HUGO) [Human Genome Variation Society \(HGVS\)](#) variant nomenclature committee recommendations for describing sequence variants before manuscripts can be accepted and published. *GIM* also strongly encourages all authors to submit DNA sequence variants reported in manuscripts to a public database (e.g., [ClinVar](#) or shared [LOVD](#)) prior to publication.

### **MANDATORY: Compliance with HGVS nomenclature**

All instances of variants, in the manuscript and tables, **must** be verified using variant description validation software, [VariantValidator](#).

VariantValidator provides two ways to validate variant descriptions depending on the number of variants you have to validate:

- [Submission of up to 10 variants](#)  
Input each variant as prompted on the webpage then find the "Print PDF" button under the "Recommended Variant Descriptions" table. Save a copy of each PDF and upload each PDF with your submission.
- [Submission of 10 or more variants](#)  
Use the batch tool. Instructions and help for this tool can be found [here](#). Please upload the results with your submission as an Excel table that includes all the variants.

## Errors and Warnings

If you receive errors or warnings, these are provided as guidance to authors and editors to help you report your variants according to the recommendations. Please refer to <https://variantvalidator.org/help/instructions/> for a list of potential warnings from VariantValidator.

Please contact the software systems admin to resolve the errors or warnings prior to submitting the variant file to the journal.

## Contact Information

VariantValidator: <https://variantvalidator.org/help/contact/>. Or join the discussion on [https://app.gitter.im/#/room/#variantValidatorDiscuss\\_community:gitter.im](https://app.gitter.im/#/room/#variantValidatorDiscuss_community:gitter.im) where you can report issues, discuss variants or even request features.

This tool is freely available on the web and relies on funding from the host universities, grant income and community contribution. Please support these tools by citing them in your manuscript if they have been helpful or by making a contribution to their chosen charities and providing a supportive comment. These contributions really help when it comes to securing funding and helps keep the software free.

## Citing VariantValidator

Freeman, PJ, Hart, RK, Gretton, LJ, Brookes, AJ, Dagleish, R. VariantValidator: Accurate validation, mapping and formatting of sequence variation descriptions. *Human Mutation*. 2018;39:61-68. <https://doi.org/10.1002/humu.23348>.

DNA sequence variant nomenclature should follow [current recommendations](#) of the [HGVS](#) Variant Nomenclature Committee. *Acceptance and/or publication of your manuscript may be delayed if authors do not follow these guidelines*. Please visit [HGVS](#) for the latest nomenclature updates, for examples of acceptable nomenclature, guidance concerning reference sequences, or if you have further questions. The following section provides instructions for the presentation of variants in *GIM*.

## Presentation of variants in GIM

When reporting variation, it is important that the identifying variant be described; all other variant descriptions are considered annotative. Authors **must** include a relevant variant table in the supplement text of each manuscript, selecting the most appropriate from the below criteria:

- For variants identified by NGS sequencing techniques, the genomic description must be provided. This includes RNA Seq methodologies where sequences are aligned to a reference genome rather than a reference transcript.
- Gene descriptions, e.g., RefSeqGene or LRG are no longer recommended by the HGVS gene nomenclature committee. Instead, authors should refer to HGVS guidance on the use of MANE Select and MANE Plus Clinical transcripts
- This prevents spurious reporting in the context of a reference sequence which was not used to identify variation, but was inferred from mapping via a transcript reference sequence
- For variants identified by RNA/cDNA sequencing, an RNA level (r.) description must be provided
- In such cases the g. and c. description should not be provided unless they have been confirmed at the DNA level e.g., the genomic variant is confirmed by DNA sequencing methodologies

For examples we direct the authors to: <https://varnomen.hgvs.org/>

### **Other important considerations**

Reference sequences defined in the [HGVS nomenclature guidelines](#) must be used for reporting sequence variants. Authors should always include the Accession Number of the relevant reference sequence(s), with version number where applicable (e.g.: RefSeq NM\_003002.3, or GenBank NC\_000011.10), in the Materials and Methods section and as a footnote in any tables listing variants. Please note: RefSeq and Ensembl transcript reference sequences that have been denoted as the default reporting references through the Matched Annotation from the NCBI and EBI (MANE) project *may be used once approved by the HGVS variant nomenclature working group*.

If alternative nomenclature schemes are commonly found in the literature, they may also be used in addition to approved nomenclature, but they must be clearly defined.

Standard HGVS nomenclature using g. annotation and identifying the genome build must be used for non-coding variation, including those variants identified in GWAS studies (e.g., NC\_000017.11:g.50201450C>T). Variants may also be described using dbSNP genomic location identifiers, *in addition to approved nomenclature*, if the specific nucleotide change is also included.

## Classification of Variants

We expect articles submitted to an official journal of the ACMG will adhere to standards and guidelines promulgated in the [ACMG/AMP classification of sequence variants](#) (Richards et al, *Genet Med.* 2015 May;17(5):405-424) and the [ACMG consensus statement on reporting copy-number variants](#) (Riggs et al, *Genet Med.* 2020 Feb;22(2):245-257). For research reporting classification of newly described variants or reclassification of variants, we require authors to describe the variants using the [ACMG/AMP classification system](#). In addition to the classification, the Variant scoring results should be listed in a table (this can be supplementary, and should cross reference the variant table (see and link to **"Presentation of variants in GIM"**)).

For manuscripts reporting previously classified variants whose classification was assigned using a different standard, we will accept that classification with proper documentation and explanation in the methods section. However, including the [ACMG/AMP classification](#) of that sequence variant alongside the previous classification is strongly encouraged. We are aware that other classification standards exist and in special cases with prior discussion with the editorial office, newly described variants may be classified using other standards, but generally with [ACMG/AMP classification](#) also listed. Please contact the editorial office at [geneticsinmedicine@acmg.net](mailto:geneticsinmedicine@acmg.net) for questions or further details.