GDC MAF Format v.1.0.0

Introduction

Mutation Annotation Format (MAF) is a tab-delimited text file with aggregated mutation information from VCF Files (../VCF_Format/) and are generated on a project-level. MAF files are produced through the Somatic Aggregation Workflow (https://docs.gdc.cancer.gov/Data_Dictionary/viewer/#?view=table-definition-view&id=somatic_aggregation_workflow&_top=1) The GDC produces MAF files at two permission levels: **protected** and **somatic** (or open-access). One MAF files is produced per variant calling pipeline per GDC project. MAFs are produced by aggregating the GDC annotated VCF files generated from one pipeline for one project.

Annotated VCF files often have variants reported on multiple transcripts whereas the MAF files generated from the VCFs (*protected.maf) only report the most critically affected one. Somatic MAFs (*somatic.maf), which are also known as Masked Somatic Mutation (https://docs.gdc.cancer.gov/Data_Dictionary/viewer/#?view=table-definition-view&id=masked_somatic_mutation) files, are further processed to remove lower quality and potential germline variants. For tumor samples that contain variants from multiple combinations of tumor-normal aliquot pairs, only one pair is selected in the Somatic MAF based on their sample type. Somatic MAFs are publicly available and can be freely distributed within the boundaries of the GDC Data Access Policies (https://gdc.cancer.gov/access-data/data-access-policies).

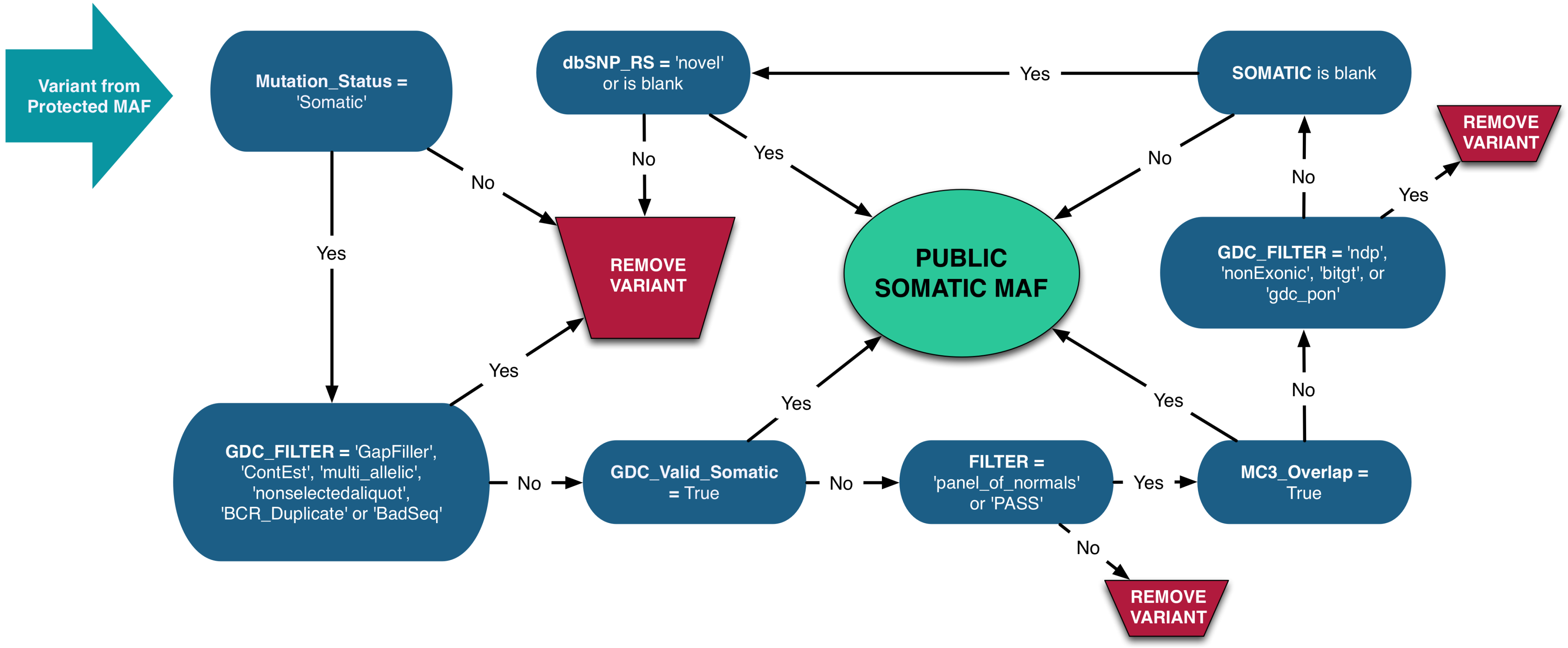
The GDC MAF file format is based on the TCGA Mutation Annotation Format (https://wiki.nci.nih.gov/display/TCGA/Mutation+Annotation+Format+(MAF)+Specification) specifications, with additional columns included.

Note: The criteria for allowing mutations into open-access are purposefully implemented to overcompensate and filter out germline variants. If omission of true-positive somatic mutations is a concern, the GDC recommends using protected MAFs.

Somatic MAF File Generation

The process for modifying a protected MAF into a somatic MAF is as follows:

- Aliquot Selection: only one tumor-normal pair are selected for each tumor sample based on the plate number, sample type, analyte type and other features extracted from tumor TCGA aliquot barcode.
- Low quality variant filtering and germline masking:
  1. Variants with **Mutation_Status != 'Somatic'** or **GDC_FILTER = 'Gapfiller', 'ContEst', 'multiallelic', 'nonselectedaliquot', 'BCR_Duplicate' or 'BadSeq'** are **removed**.
  2. Remaining variants with **GDC_Valid_Somatic = True** are **included** in the Somatic MAF.
  3. Remaining variants with **FILTER != 'panel_of_normals' or PASS** are **removed**. Note that the `FILTER != panel_of_normals` value is only relevant for the variants generated from the MuTect2 pipeline.
  4. Remaining variants with **MC3_Overlap = True** are **included** in the Somatic MAF.
  5. Remaining variants with **GDC_FILTER = 'ndp', 'NonExonic', 'bitgt', 'gdc_pon'** are **removed**.
  6. Remaining variants with **SOMATIC != null** are **included** in the Somatic MAF.
  7. Remaining variants with **dbSNP_RS = 'novel' or null** are **included** in the Somatic MAF.
  8. Remaining variants are **removed**.
- Removal of the following columns:
  - vcf_region
  - vcf_info
  - vcf_format
  - vcf_tumor_gt
  - vcf_normal_gt
  - GDC_Valid_Somatic
- Set values to be blank in the following columns that may contain information about germline genotypes:
  - Match_Norm_Seq_Allele1
  - Match_Norm_Seq_Allele2
  - Match_Norm_Validation_Allele1
  - Match_Norm_Validation_Allele2
  - n_ref_count
  - n_alt_count


Variant from Protected MAF
Mutation_Status = 'Somatic'
No
Yes
REMOVE VARIANT
dbSNP_RS = 'novel' or is blank
No
Yes
SOMATIC is blank
Yes
No
PUBLIC SOMATIC MAF
REMOVE VARIANT
Yes
No
GDC_FILTER = 'ndp', 'nonExonic', 'bitgt', or 'gdc_pon'
No
GDC_FILTER = 'GapFiller', 'ContEst', 'multi_allelic', 'nonselectedaliquot', 'BCR_Duplicate' or 'BadSeq'
Yes
No
GDC_Valid_Somatic = True
Yes
No
FILTER = 'panel_of_normals' or 'PASS'
Yes
No
REMOVE VARIANT
MC3_Overlap = True
Yes

Protected MAF File Structure

The table below describes the columns in a protected MAF and their definitions. Note that the somatic (open-access) MAF structure is the same except for having the last six columns removed.

Column	Description
1 - Hugo_Symbol	HUGO (http://www.genenames.org/) symbol for the gene (HUGO symbols are always in all caps). "Unknown" is used for regions that do not correspond to a gene
2 - Entrez_Gene_Id	Entrez gene (https://www.ncbi.nlm.nih.gov/gene) ID (an integer). "0" is used for regions that do not correspond to a gene region or Ensembl ID

Column	Description
3 - Center	One or more genome sequencing center reporting the variant
4 - NCBI_Build	The reference genome used for the alignment (GRCh38)
5 - Chromosome	The affected chromosome (chr1)
6 - Start_Position	Lowest numeric position of the reported variant on the genomic reference sequence. Mutation start coordinate
7 - End_Position	Highest numeric genomic position of the reported variant on the genomic reference sequence. Mutation end coordinate
8 - Strand	Genomic strand of the reported allele. Currently, all variants will report the positive strand: '+'
9 - Variant_Classification	Translational effect of variant allele
10 - Variant_Type	Type of mutation. TNP (tri-nucleotide polymorphism) is analogous to DNP (di-nucleotide polymorphism) but for three consecutive nucleotides. ONP (oligo-nucleotide polymorphism) is analogous to TNP but for consecutive runs of four or more (SNP, DNP, TNP, ONP, INS, DEL, or Consolidated)
11 - Reference_Allele	The plus strand reference allele at this position. Includes the deleted sequence for a deletion or "-" for an insertion
12 - Tumor_Seq_Allele1	Primary data genotype for tumor sequencing (discovery) allele 1. A "-" symbol for a deletion represents a variant. A "-" symbol for an insertion represents wild-type allele. Novel inserted sequence for insertion does not include flanking reference bases
13 - Tumor_Seq_Allele2	Tumor sequencing (discovery) allele 2
14 - dbSNP_RS	The rs-IDs from the dbSNP (https://www.ncbi.nlm.nih.gov/projects/SNP/) database, "novel" if not found in any database used, or null if there is no dbSNP record, but it is found in other databases
15 - dbSNP_Val_Status	The dbSNP validation status is reported as a semicolon-separated list of statuses. The union of all rs-IDs is taken when there are multiple
16 - Tumor_Sample_Barcode	Aliquot barcode for the tumor sample
17 - Matched_Norm_Sample_Barcode	Aliquot barcode for the matched normal sample
18 - Match_Norm_Seq_Allele1	Primary data genotype. Matched normal sequencing allele 1. A "-" symbol for a deletion represents a variant. A "-" symbol for an insertion represents wild-type allele. Novel inserted sequence for insertion does not include flanking reference bases (cleared in somatic MAF)

Column	Description
19 - Match_Norm_Seq_Allele2	Matched normal sequencing allele 2
20 - Tumor_Validation_Allele1	Secondary data from orthogonal technology. Tumor genotyping (validation) for allele 1. A "-" symbol for a deletion represents a variant. A "-" symbol for an insertion represents wild-type allele. Novel inserted sequence for insertion does not include flanking reference bases
21 - Tumor_Validation_Allele2	Secondary data from orthogonal technology. Tumor genotyping (validation) for allele 2
22 - Match_Norm_Validation_Allele1	Secondary data from orthogonal technology. Matched normal genotyping (validation) for allele 1. A "-" symbol for a deletion represents a variant. A "-" symbol for an insertion represents wild-type allele. Novel inserted sequence for insertion does not include flanking reference bases (cleared in somatic MAF)
23 - Match_Norm_Validation_Allele2	Secondary data from orthogonal technology. Matched normal genotyping (validation) for allele 2 (cleared in somatic MAF)
24 - Verification_Status	Second pass results from independent attempt using same methods as primary data source. Generally reserved for 3730 Sanger Sequencing
25 - Validation_Status	Second pass results from orthogonal technology
26 - Mutation_Status	An assessment of the mutation as somatic, germline, LOH, post transcriptional modification, unknown, or none. The values allowed in this field are constrained by the value in the Validation_Status field
27 - Sequencing_Phase	TCGA sequencing phase (if applicable). Phase should change under any circumstance that the targets under consideration change
28 - Sequence_Source	Molecular assay type used to produce the analytes used for sequencing. Allowed values are a subset of the SRA 1.5 library_strategy field values. This subset matches those used at CGHub
29 - Validation_Method	The assay platforms used for the validation call
30 - Score	Not in use
31 - BAM_File	Not in use
32 - Sequencer	Instrument used to produce primary sequence data
33 - Tumor_Sample_UUID	GDC aliquot UUID for tumor sample
34 - Matched_Norm_Sample_UUID	GDC aliquot UUID for matched normal sample
35 - HGVSc	The coding sequence of the variant in HGVS recommended format
36 - HGVSp	The protein sequence of the variant in HGVS recommended format. "p.=" signifies no change in the protein

Column	Description
37 - HGVSp_Short	Same as the HGVSp column, but using 1-letter amino-acid codes
38 - Transcript_ID	Ensembl (http://useast.ensembl.org/index.html) ID of the transcript affected by the variant
39 - Exon_Number	The exon number (out of total number)
40 - t_depth	Read depth across this locus in tumor BAM
41 - t_ref_count	Read depth supporting the reference allele in tumor BAM
42 - t_alt_count	Read depth supporting the variant allele in tumor BAM
43 - n_depth	Read depth across this locus in normal BAM
44 - n_ref_count	Read depth supporting the reference allele in normal BAM (cleared in somatic MAF)
45 - n_alt_count	Read depth supporting the variant allele in normal BAM (cleared in somatic MAF)
46 - all_effects	A semicolon delimited list of all possible variant effects, sorted by priority ([Symbol,Consequence,HGVSp_Short,Transcript_ID,RefSeq,HGVSc,Impact,Canonical,Sift,PolyPhen,Strand])
47 - Allele	The variant allele used to calculate the consequence
48 - Gene	Stable Ensembl ID of affected gene
49 - Feature	Stable Ensembl ID of feature (transcript, regulatory, motif)
50 - Feature_type	Type of feature. Currently one of Transcript, RegulatoryFeature, MotifFeature (or blank)
51 - One_Consequence	The single consequence of the canonical transcript in sequence ontology (http://www.sequenceontology.org/) terms
52 - Consequence	Consequence type of this variant; sequence ontology (http://www.sequenceontology.org/) terms
53 - cDNA_position	Relative position of base pair in the cDNA sequence as a fraction. A "-" symbol is displayed as the numerator if the variant does not appear in cDNA
54 - CDS_position	Relative position of base pair in coding sequence. A "-" symbol is displayed as the numerator if the variant does not appear in coding sequence
55 - Protein_position	Relative position of affected amino acid in protein. A "-" symbol is displayed as the numerator if the variant does not appear in coding sequence
56 - Amino_acids	Only given if the variation affects the protein-coding sequence
57 - Codons	The alternative codons with the variant base in upper case
58 - Existing_variation	Known identifier of existing variation

Column	Description
59 - ALLELE_NUM	Allele number from input; 0 is reference, 1 is first alternate etc.
60 - DISTANCE	Shortest distance from the variant to transcript
61 - TRANSCRIPT_STRAND	The DNA strand (1 or -1) on which the transcript/feature lies
62 - SYMBOL	The gene symbol
63 - SYMBOL_SOURCE	The source of the gene symbol
64 - HGNC_ID	Gene identifier from the HUGO Gene Nomenclature Committee if applicable
65 - BIOTYPE	Biotype of transcript
66 - CANONICAL	A flag (YES) indicating that the VEP-based canonical transcript, the longest translation, was used for this gene. If not, the value is null
67 - CCDS	The CCDS (https://www.ncbi.nlm.nih.gov/projects/CCDS/CcdsBrowse.cgi) identifier for this transcript, where applicable
68 - ENSP	The Ensembl protein identifier of the affected transcript
69 - SWISSPROT	UniProtKB/Swiss-Prot (http://www.uniprot.org/) accession
70 - TREMBL	UniProtKB/TrEMBL identifier of protein product
71 - UNIPARC	UniParc identifier of protein product
72 - RefSeq	RefSeq identifier for this transcript
73 - SIFT	The SIFT (http://sift.jcvi.org/) prediction and/or score, with both given as prediction (score)
74 - PolyPhen	The PolyPhen (http://genetics.bwh.harvard.edu/pph2/) prediction and/or score
75 - EXON	The exon number (out of total number)
76 - INTRON	The intron number (out of total number)
77 - DOMAINS	The source and identifier of any overlapping protein domains
78 - GMAF	Non-reference allele and frequency of existing variant in 1000 Genomes (http://www.internationalgenome.org/)
79 - AFR_MAF	Non-reference allele and frequency of existing variant in 1000 Genomes combined African population
80 - AMR_MAF	Non-reference allele and frequency of existing variant in 1000 Genomes combined American population
81 - ASN_MAF	Non-reference allele and frequency of existing variant in 1000 Genomes combined Asian population
82 - EAS_MAF	Non-reference allele and frequency of existing variant in 1000 Genomes combined East Asian population

Column	Description
83 - EUR_MAF	Non-reference allele and frequency of existing variant in 1000 Genomes combined European population
84 - SAS_MAF	Non-reference allele and frequency of existing variant in 1000 Genomes combined South Asian population
85 - AA_MAF	Non-reference allele and frequency of existing variant in NHLBI-ESP (http://evs.gs.washington.edu/EVS/) African American population
86 - EA_MAF	Non-reference allele and frequency of existing variant in NHLBI-ESP European American population
87 - CLIN_SIG	Clinical significance of variant from dbSNP
88 - SOMATIC	Somatic status of each ID reported under Existing_variation (0, 1, or null)
89 - PUBMED	Pubmed ID(s) of publications that cite existing variant
90 - MOTIF_NAME	The source and identifier of a transcription factor binding profile aligned at this position
91 - MOTIF_POS	The relative position of the variation in the aligned TFBP
92 - HIGH_INF_POS	A flag indicating if the variant falls in a high information position of a transcription factor binding profile (TFBP) (Y, N, or null)
93 - MOTIF_SCORE_CHANGE	The difference in motif score of the reference and variant sequences for the TFBP
94 - IMPACT	The impact modifier for the consequence type
95 - PICK	Indicates if this block of consequence data was picked by VEP's pick feature (http://useast.ensembl.org/info/docs/tools/vep/script/vep_options.html#opt_pick) (1 or null)
96 - VARIANT_CLASS	Sequence Ontology variant class
97 - TSL	Transcript support level (http://useast.ensembl.org/Help/Glossary?id=492), which is based on independent RNA analyses
98 - HGVS_OFFSET	Indicates by how many bases the HGVS notations for this variant have been shifted
99 - PHENO	Indicates if existing variant is associated with a phenotype, disease or trait (0, 1, or null)
100 - MINIMISED	Alleles in this variant have been converted to minimal representation before consequence calculation (1 or null)
101 - ExAC_AF	Global Allele Frequency from ExAC (http://exac.broadinstitute.org/)
102 - ExAC_AF_Adj	Adjusted Global Allele Frequency from ExAC
103 - ExAC_AF_AFR	African/African American Allele Frequency from ExAC
104 - ExAC_AF_AMR	American Allele Frequency from ExAC

Column	Description
105 - ExAC_AF_EAS	East Asian Allele Frequency from ExAC
106 - ExAC_AF_FIN	Finnish Allele Frequency from ExAC
107 - ExAC_AF_NFE	Non-Finnish European Allele Frequency from ExAC
108 - ExAC_AF_OTH	Other Allele Frequency from ExAC
109 - ExAC_AF_SAS	South Asian Allele Frequency from ExAC
110 - GENE_PHENO	Indicates if gene that the variant maps to is associated with a phenotype, disease or trait (0, 1, or null)
111 - FILTER	Copied from input VCF. This includes filters implemented directly by the variant caller and other external software used in the DNA-Seq pipeline. See below for additional details.
112 - CONTEXT	The reference allele per VCF specs, and its five flanking base pairs
113 - src_vcf_id	GDC UUID for the input VCF file
114 - tumor_bam_uuid	GDC UUID for the tumor bam file
115 - normal_bam_uuid	GDC UUID for the normal bam file
116 - case_id	GDC UUID for the case
117 - GDC_FILTER	GDC filters applied universally across all MAFs
118 - COSMIC	Overlapping COSMIC variants
119 - MC3_Overlap	Indicates whether this region overlaps with an MC3 variant for the same sample pair
120 - GDC_Validation_Status	GDC implementation of validation checks. See notes section (#5) below for details
121 - GDC_Valid_Somatic	True or False (not in somatic MAF)
122 - vcf_region	Colon separated string containing the CHROM, POS, ID, REF, and ALT columns from the VCF file (e.g., chrZ:20:rs1234:A:T) (not in somatic MAF)
123 - vcf_info	INFO column from VCF (not in somatic MAF)
124 - vcf_format	FORMAT column from VCF (not in somatic MAF)
125 - vcf_tumor_gt	Tumor sample genotype column from VCF (not in somatic MAF)
126 - vcf_normal_gt	Normal sample genotype column from VCF (not in somatic MAF)

Notes About GDC MAF Implementation

1. Column #4 **NCBI_Build** is GRCh38 by default

2. Column #32 **Sequencer** includes the sequencers used. If different sequencers were used to generate normal and tumor data, the normal sequencer is listed first.
3. Column #61 VEP name "STRAND" is changed to **TRANSCRIPT_STRAND** to avoid confusion with Column#8 "Strand"
4. Column #94 **IMPACT** categories are defined by the VEP software and do not necessarily reflect the relative biological influence of each mutation.
5. Column #122-125 **vcf_info, vcf_format, vcf_tumor_gt, and vcf_normal_gt** are the corresponding columns from the VCF files. Including them facilitates parsing specific variant information.
6. Column #120 **GDC_Validation_Status**: GDC also collects TCGA validation sequences. It compares these with variants derived from Next-Generation Sequencing data from the same sample and populates the comparison result in "GDC_Validation_Status".
    - "Valid", if the alternative allele(s) in the tumor validation sequence is(are) the same as GDC variant call
    - "Invalid", if none of the alternative allele(s) in the tumor validation sequence is the same as GDC variant call
    - "Inconclusive" if two alternative allele exists, and one matches while the other does not
    - "Unknown" if no validation sequence exists
7. Column #121 **GDC_Valid_Somatic** is TRUE if GDC_Validation_Status is "Valid" and the variant is "Somatic" in validation calls. It is FALSE if these criteria are not met

FILTER Value Definitions (column 111)

- **oxog :** Signifies that this variant was determined to be an OxoG artifact. This was calculated with D-ToxoG (http://archive.broadinstitute.org/cancer/cga/dtoxog)
- **bPcr :** Signifies that this variant was determined to be an artifact of bias on the PCR template strand. This was calculated with the DKFZ Bias Filter (https://github.com/eilslabs/DKFZBiasFilter).
- **bSeq :** Signifies that this variant was determined to be an artifact of bias on the forward/reverse strand. This was also calculated with the DKFZ Bias Filter (https://github.com/eilslabs/DKFZBiasFilter).

Impact Categories

VEP

- **HIGH (H)**: The variant is assumed to have high (disruptive) impact in the protein, probably causing protein truncation, loss of function, or triggering nonsense mediated decay
- **MODERATE (M)**: A non-disruptive variant that might change protein effectiveness
- **LOW (L)**: Assumed to be mostly harmless or unlikely to change protein behavior
- **MODIFIER (MO)**: Usually non-coding variants or variants affecting non-coding genes, where predictions are difficult or there is no evidence of impact

PolyPhen

- **probably damaging (PR)**: It is with high confidence supposed to affect protein function or structure
- **possibly damaging (PO)**: It is supposed to affect protein function or structure
- **benign (BE)**: Most likely lacking any phenotypic effect
- **unknown (UN)**: When in some rare cases, the lack of data does not allow PolyPhen to make a prediction

SIFT

- **tolerated**: Not likely to have a phenotypic effect
- **tolerated_low_confidence**: More likely to have a phenotypic effect than 'tolerated'
- **deleterious**: Likely to have a phenotypic effect
- **deleterious_low_confidence**: Less likely to have a phenotypic effect than 'deleterious'

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