varsomeclinical varsomepremium

WHITEPAPER

Implementation of AMP Guidelines

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DOCUMENT VERSION
1.0

About AMP

Our implementation is derived from the ”Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer” was published in 2017 by Marilyn Li et al. in their seminal paper : AMP Guidelines

Interpretation Process

Our guiding principle throughout, following the advice of our clinical advisors, has been to implement a rigorous evidence-based approach to identifying potential cancer variants. We have leveraged a wide range of public-domain and commercial cancer databases, therefore the end result will partially depend in part on the user's subscription level.

All the rules provide clear natural language explanations of why they were triggered and which evidence was used, or, conversely, a full explanation of why the criteria were not met (these 'negative' explanations are displayed if 'show full detail' is ticked, but they are not retained in the Clinical platform for Tier IV variants).

Implementation Rules

Unlike the ACMG guidelines, the AMP Guidelines do not have a strict set of named rules nor a strict method of calculation detailing how to combine various strengths of evidence to reach a verdict. Rather they consider a series of evidence types and set certain criteria that should be met in order to reach an overall tier I, II, III or IV verdict.

Our implementation considers the following types of evidence, each of these is given a 4-letter acronym for convenience which is displayed in VarSome

- Path: Disease-associated pathways
- Drug: Drug-gene interaction, therapies & clinical studies
- Type: Mutation type and coding impact
- Freq: Allele frequency & Mosaicism
- Pred: In-silico and splicing predictions
- Soma: Somatic sample databases
- Crtd: Curated somatic variants
- Pubs: Supporting scientific publications
- Germ: Evidence from germline databases

We then combine the evidence from all these sources to reach an overall recommended classification.

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Implementation of ACMG Guidelines

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Overall Verdict

Once all the rules have been evaluated and a tier assigned to each level of evidence, we estimate an overall recommended tier, in line with the AMP guidelines.

This is operation is performed in two steps:

01. We consider all the evidence for the variant itself to establish a base tier.

02. We then adjust the resulting tier based on the availability of FDA approved drugs.

We assign tiers as follows:

Verdict	Minimum Rules	Explanation
Tier I	Path II, Type I, Freq I, Soma I, Pubs II	Cancer pathway, LOF, somatic variant, many somatic samples, with supporting publications
Tier II	Path II, Type II, Freq II, Soma II	Cancer pathway, deleterious coding impact, low frequency, some somatic samples
Tier III	Path II, Freq II, Soma II	Cancer pathway, low frequency, some somatic samples
Tier IV	No pathway or mostly Tier III & IV evidence	Clear benign evidence or insufficient cancer evidence.

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Detection of low-frequency variants

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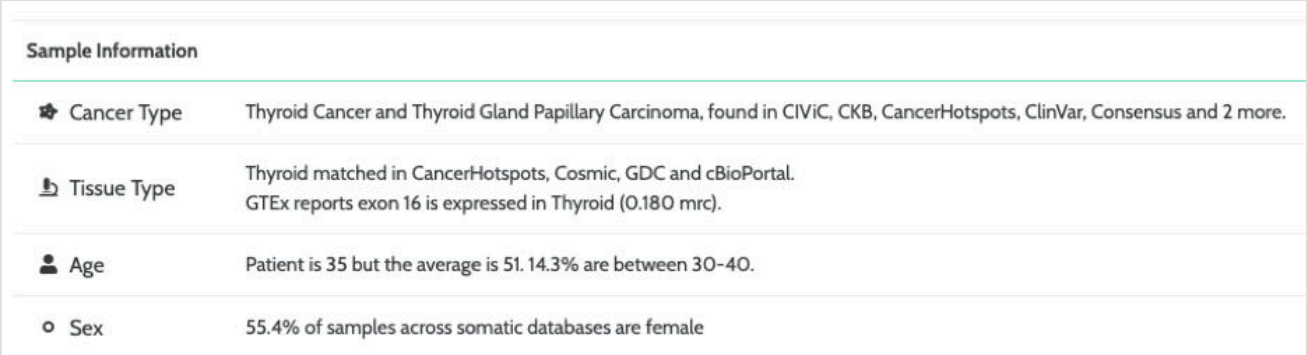
As a result the AMP classification can differ significantly from the ACMG annotation:

- Tier I is only accorded to variants for which there are **FDA-approved treatments.**
- Variants in genes that are not associated with cancer will be assigned Tier IV.
- There is a substantial emphasis on curated evidence - **VarSome Clinical users will benefit from Jackson Labs' "Cancer Knowledgebase".**

Sample Information

The AMP classifier is able to leverage data from the sample itself in order to provide additional findings to the clinician and help prioritize which variants to review. These findings do not modify the actual tier assigned to a variant, but show up as flags in the report table in VarSome Clinical.

- Cancer type: this highlights any variants for which evidence is found linking to the same cancer type as the sample.
- Tissue: similarly this will highlight any evidence associating the variant or gene to the sample tissue.
- Age: we are able to obtain an age histogram for certain cancer-types and display the patient's age relative to that.
- Ethnicity: allele frequencies can differ between populations and we report the variant's frequency in the relevant ethnic group.
- Sex: we highlight if the provided sex matches the majority of reported cases across somatic sample databases.



Sample Information	
Cancer Type	Thyroid Cancer and Thyroid Gland Papillary Carcinoma, found in CIViC, CKB, CancerHotspots, ClinVar, Consensus and 2 more.
Tissue Type	Thyroid matched in CancerHotspots, Cosmic, GDC and cBioPortal. GTEx reports exon 16 is expressed in Thyroid (0.180 mrc).
Age	Patient is 35 but the average is 51. 14.3% are between 30-40.
Sex	55.4% of samples across somatic databases are female

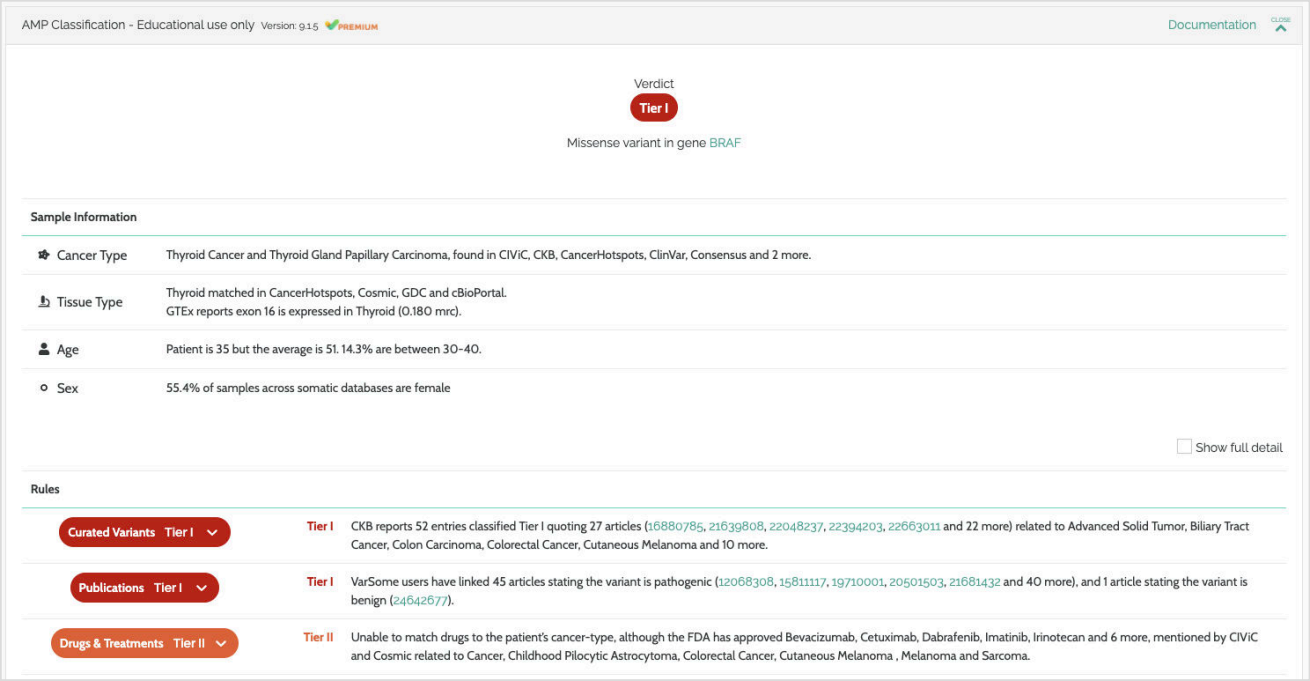
AMP classifier

In addition to the databases used for ACMG, the AMP classifier leverages information from:

01. **TP53 Somatic**, provided by IARC
02. **TP53 Germline**, provided by IARC
03. **Cancer Gene Census**, provided by Sanger
04. **PMKB**, provided by Weill Cornell Medicine
05. **PharmGKB**
06. **Mondo**, provided by Monarch
07. **ICGC somatic**, provided by ICGC
08. **GHR Genes**, provided by NLM
09. **Cosmic Licensed**, provided by Sanger
10. **CKB,** provided by JAX
11. **CIViC,** provided by WUSTL
12. **cBioPortal**, provided by MSK
13. **AACT**, provided by CTTI
14. **CancerHotspots**, provided by MSK
15. **CPIC Genes-Drugs**, provided by CPIC
16. **DGI**, provided by WUSTL
17. **Pharmacogenomic Biomarkers**, provided by FDA
18. **GDC**, provided by NIH

Saphetor updates all these databases on a monthly basis if any new data is available.

The new AMP Module and Classification is available in VarSome Clinical, VarSome Premium, and VarSome API.



Further learning resources

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VarSome Clinical is a CE-IVD-certified and HIPAA-compliant platform allowing fast and accurate variant discovery, annotation, and interpretation of NGS data for whole genomes, exomes, and gene panels. VarSome Clinical helps molecular geneticists and clinicians reach faster and more accurate diagnoses and treatment decisions for genetic conditions.

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