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VarClaMM: A Reference Meta-Model to Understand DNA Variant Classification

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Abstract

Determining the significance of a DNA variant in patients' health status – a complex process known as *variant classification* – is highly critical for precision medicine applications. However, there is still debate on how to combine and weigh diverse available evidence to achieve proper and consistent conclusions. Indeed, currently, there are more than 200 different variant classification guidelines available to the scientific community, aiming to establish a framework for standardizing the classification process. Yet, these guidelines are qualitative and vague by nature, hindering their practical application and potential automation. Consequently, more precise definitions are needed.

In this work, we discuss our efforts to create VarClaMM, a UML meta-model that aims to provide a clear specification of the key concepts involved in variant classification, serving as a common framework for the process. Through this accurate characterization of the domain, we were able to find contradictions or inconsistencies that might have an effect on the classification results. VarClaMM's conceptualization efforts will lay the ground for the operationalization of variant classification, enabling any potential automation to be based on precise definitions.

Keywords:
Conceptual Modeling, Genomics, Variant Classification

1. Introduction

Precision medicine has emerged as a disruptive medical approach that aims to transform historically reactive medicine into a proactive one. To do so, this new perspective prioritizes individualized clinical actions based on the unique characteristics of each patient [1]. The most distinguishing characteristic of an individual is its DNA sequence, which differs slightly between individuals.

Individual DNA sequences are compared to a DNA reference sequence that reflects an "ideal" individual, leading to the identification of differences. These differences among individuals are known as DNA variants[1], and they determine our physical characteristics, predisposition to disorders, or a different response to treatments.

Identifying variants in an individual's DNA sequence has become easier and faster thanks to Next Generation Sequencing (NGS) [2]. This technique uses massive parallelization to obtain the entire DNA sequence of an individual; The connected technological advancement has significantly improved our ability to identify and analyze DNA variants [2]. However, the scientific community must overcome numerous challenges (costs, ethics, security of shared data,

[1] https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/variant

and data integration and interpretation, among others) [3] before achieving the paradigm shift proposed by precision medicine. In the context of data integration and interpretation, one of the most difficult challenges is determining the role of a DNA variant in our health status (that is, whether it will cause a particular disorder or affect treatment response), a process known as *variant classification*.

Variant classification is a complex process that involves weighing various contextual information about variants, such as the variant's frequency among the population, whether it has previously been linked to a disorder, etc. Geneticists and clinical experts are still debating how to achieve a systematic way of correctly weighing the available evidence in order to achieve proper variant classification. To address this issue, several authors have developed *variant classification guidelines*. A variant classification guideline is a set of instructions designed to guide the classification process by assessing whether the contextual information of a variant meets specific criteria. These guidelines have quickly been accepted by geneticists [4] and have been adapted to the peculiarities of several disorder-causing genes [5].

In our previous work [6], we presented a preliminary version of a meta-model, described using the Unified Modeling Language (UML) [7], representing the main constructs in variant classification guidelines. Building on that work, here we report an extended version of this meta-model, which we have called VarClaMM, that: i) provides more precise definitions of the constructs conforming to *variant classification guidelines*, ii) introduces the representation of the *contextual evidence* used for the variant classification process, and iii) extends the representation of the guidelines' *evaluation results* to improve traceability. These enhancements have allowed VarClaMM to focus on all the constructs required for variant classification in general, rather than just on those referring to variant classification guidelines.

The proposed extension provides the following benefits: (a) Definition of a common framework for variant classification, disentangling the intricate details of the process and resolving aspects whose definitions are implicit or ambiguous; (b) Identification of inconsistencies or conflicts within or between the variant classification guidelines; (c) Set the foundations to operationalize variant classification, allowing potential tools to be grounded on precise and concrete definitions rather than relying on personal interpretations.

The remainder of the paper is organized as follows. Section 2 provides the background that has motivated our work. Section 3 gives an overview of the related work. Section 4 describes the proposed conceptual meta-model, VarClaMM, instantiating it in a simple example of use. Section 5 proposes to use the conceptual meta-model mentioned above to define a set of misclassification patterns. Section 6 discusses lessons learned and, finally, Section 7 concludes the paper with a future outlook.

2. Background

In 2015, the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) proposed a joint consensus recommendation for variant classification [8]. The ACMG-AMP were among the earliest variant classification guidelines proposed. Since then, other authors and institutions have proposed revised classification guidelines to provide more specifics or consider the unique characteristics of various types of disorders and variants. In fact, at the time of writing, more than 200 guidelines have been used to interpret the variants available in the ClinVar database [9], which stores the relationshipsbetween millions of variants and human health.

From all the classification guidelines that have been made available since 2015, only some of them support specific types of disorders such as those caused by variants in a single gene (Mendelian disorders, e.g., Hungtinton disorder and Cystic Fibrosis) [10, 11], rare disorders that affect a small percentage of the population [12] (e.g., Bone Brittle disorder and Kawasaki syndrome), disorders caused by variants in the X chromosome [13] (X-linked disorders, e.g., Daltonism and Hemophilia), and disorders with a specific inheritance pattern (recessive or autosomal dominant). Other guidelines are only applicable to specific types of variant, such as those that occur after conception in specific body tissues (somatic variants) [14], variants affecting mitochondrial DNA [15], or variants that affect the number of copies of a specific gene (copy number variants) [16]. Finally, other guidelines have been developed to interpret variants affecting specific genes [17].

Even though all these guidelines have attempted to improve and standardize the variant classification process in different contexts, they are far from being a shared and widely-adopted solution. In fact, different works [18, 19] have highlighted a number of issues that arise when using variant classification guidelines. A frequently expressed concern involves the qualitative nature of guidelines, which do not provide the needed specificity [20, 21]; consequently,

their practical application is left open to expert interpretation [22]. In this context, inconsistent classifications among experts become common, leading to serious consequences in healthcare applications. A real-case scenario involved an initial assessment in prenatal care revealing that an unborn child was at high risk of developing Muscular Dystrophy disorder. The assessment was later revised by a different team of experts, who finally determined that it was incorrect [23]. Families often have to make decisions on pregnancy management within limited timeframes; then, improperly classified variants can unfortunately lead to irreversible consequences. Moreover, the more complex the disorder (e.g., cancer), the more inconsistencies usually emerge in variant classification [24].

To provide more exact definitions and streamline the process by reducing the complexity and time required to complete the classification, several tools have been created that automate the variant classification process (see [25, 26, 27, 28, 29, 30]). Among these, VarSome [25], InterVar [26], and CharGer [28] operate within a broad scope, i.e., with variants associated with any kind of disorder. Instead, CardioVAI [27], and CardioClassifier [29] focus on inherited cardiac conditions. All of them are based on the ACMG/AMP 2015 guidelines, meaning that they assign a label representing the disorder-causing potential of the variants based on a set of applied criteria from the guidelines. Following a different approach, Tavtigian et al. [30] modeled the ACMG/AMP 2015 guidelines as a Bayesian framework, which allowed the authors to provide a probabilistic score of pathogenicity associated with each variant.

These tools can provide automated support for the variant classification – aiming for a more effective and reproducible process than manual application. However, the qualitative nature and insufficient specificity of variant classification guidelines cause different tools to make assumptions and interpret the data in disagreeing ways. Furthermore, some guideline criteria are frequently omitted by these tools because of the complexity of applying them (e.g., requiring heterogeneous information [31]).

In such cases, the inconsistencies that arise naturally in a manual variant classification process are inevitably reiterated, and automating this process does not provide the expected value, since it is not based on precise and concrete definitions. This further motivates our systematization effort.

3. Related Works

In the field of genomics, the use of conceptual models for specifying genomics-related processes has already been explored. More specifically, conceptual modeling techniques have proven to be effective to achieve high levels of concreteness and standardization. A recent work [32], has considered general genomic data types represented in datasets for analysis and connected them to an abstract conceptual representation, to resolve their heterogeneity. Other modeling efforts have focused on the inherent temporal dimension associated with genomic data by mapping their evolution over time [33]; such an approach is particularly sensitive in cases of changes in variant classification due to the update of gene-related data [34]. Conceptual models have also been proposed to target the use of multi-omics data for precision medicine [35] and the identification of relevant high-quality data records [36].

Aside from conceptual models, ontological approaches have also been attempted. Ferrandis et al. [37] promoted the use of foundational ontologies to avoid errors while creating and curating genomic domain models for personalized medicine. The approach of ontological clarification has been employed to support the explanation of complex domains such as human metabolic pathways [38] and the viral genome with the related events of infection, sampling, sequencing, and annotation for SARS-CoV-2 sequences [39, 40]. Similarly, OntoRepliCov [41] showed an initial conceptual framework targeting the translation event during SARS-CoV-2 replication.

Despite the growing interest in conceptual models in the area of genomics and some technological efforts to gather and integrate different human variant data [42, 43, 44], to the best of our knowledge, the proposal presented here is the first explicit and reusable reference meta-model that targets the variant classification process.

4. VarClaMM: A Meta-model for Variant Classification

VarClaMM (Figure 1) has three well-differentiated parts: i) the constructs that conform to the variant classification guidelines (depicted in pink), ii) the results of evaluating a guideline over a DNA variant to obtain its classification (depicted in orange), and iii) the contextual information required to perform the classification (depicted in blue). Here it should be noted that some attributes (depicted in orange) are part of the variant classification guideline's structure (shown in pink) but are used for evaluation. Custom data types defined for specifying unique attribute types are depicted in white.

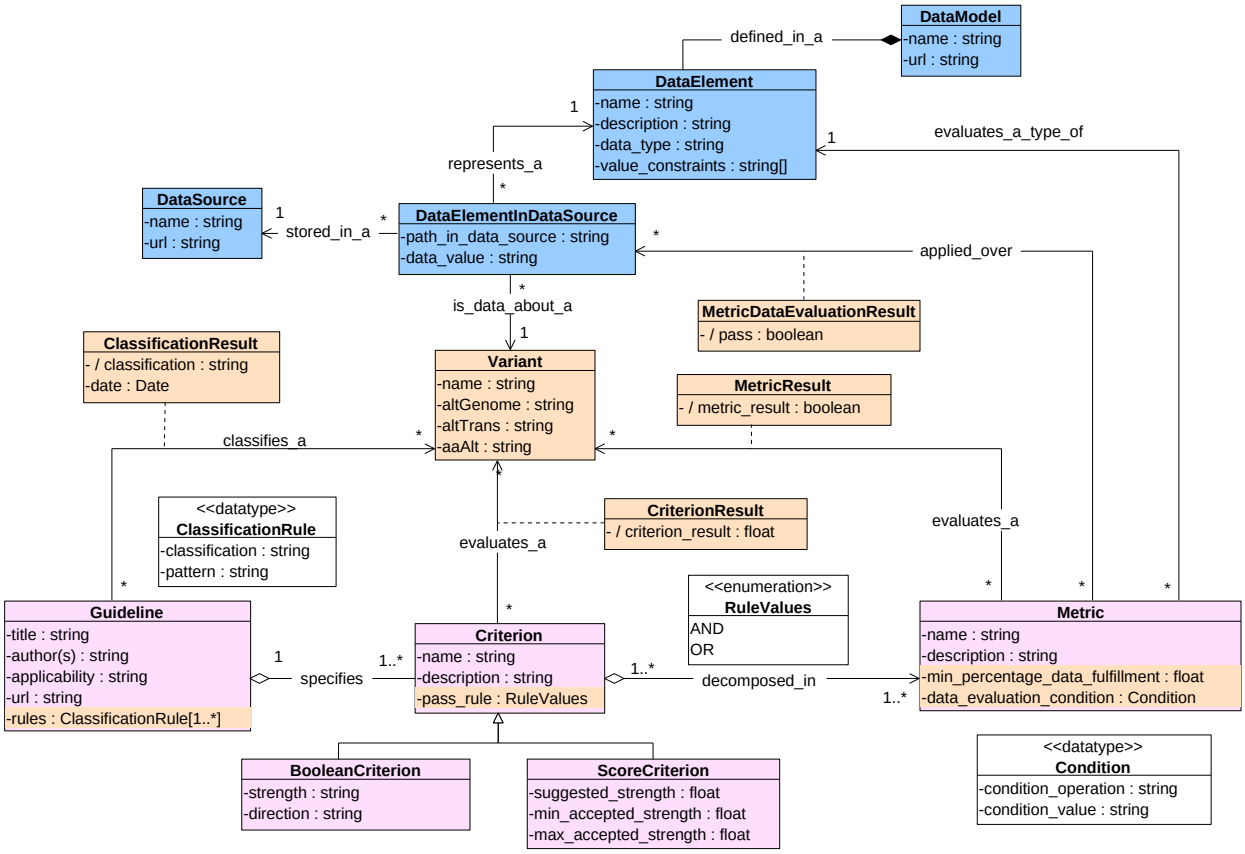

Figure 1. The VarClaMM meta-model for variant classification.

Guidelines constructs

Each classification GUIDELINE is characterized by its *title*, *authors*, and *applicability*. The *applicability* of a guideline refers to the specific context in which the guideline is applicable, as some guidelines are intended to interpret variants related to a particular type of disorder or to focus on specific variant types. Concrete examples include the ACMG-AMP 2015 guidelines [8], which only apply to disorders of Mendelian inheritance, and the ACMG-ClinGen 2020 guidelines [16], which only apply to copy number variants. Guidelines also have a *url* that points to the publication or file in which they are described.

To obtain the classification of a variant, guidelines evaluate if a variant conforms to a set of pre-established specifications included in a CRITERION. For example, the 'PVS1' criterion of the ACMG-AMP 2015 guidelines evaluates if the variant is null and if it is in a gene where null variants are to cause disease. Guidelines define criteria of one of two types, that is, BOOLEANCRITERION or SCORECRITERION.

A BOOLEANCRITERION evaluates to true or false. Commonly, in guidelines that use this type of criteria some of the criteria contribute more than others to the final classification of the variant. The degree of importance of each criterion in the final variant classification is represented by the *strength* attribute (e.g., 'strong' or 'moderate'). Each criterion

supports the hypothesis of pathogenicity or benignity of a variant, as represented in the *direction* attribute. Following the example of the PVS1 criterion mentioned above, this criterion offers 'very strong' evidence of the 'pathogenicity' of the variant.

On the contrary, the ScoreCriterion evaluation returns a numerical value. This type of criterion is more lenient because, instead of providing a binary result, its evaluation reflects the degree to which the criterion is met. It is characterized by a *suggested_score*, which is the value the guideline recommends assigning to the criterion if it is considered met, and a *score_range*, which represents the acceptable range of values for that criterion. The direction of the criterion here is represented by the sign of the score. Typically, criteria with negative scores contribute to the benignity of the variant, while criteria with positive scores contribute to the pathogenicity of the variant. For example, criterion 5H of the ACMG-ClinGen 2020 guidelines has a *suggested_score* of 0.1, and an accepted *score_range* of [0, 0.30], providing evidence of the pathogenicity of the variant.

Both types of criteria define specific conditions whose fulfillment determines whether the criterion is met. In this model, we call these conditions Metrics. Consider the example of the PVS1 criterion mentioned above. In its definition, this criterion establishes two well-differentiated, independent conditions: i) the variant must be null, and ii) the gene affected must cause disease through null variants. Our model represents these two conditions as metrics associated with the PVS1 criterion. Metrics are characterized by a *name* and a *description* of the condition they evaluate. Additionally, each Metric has the attributes *data_evaluation_condition* and *min_percentage_data_fulfillment* for guiding the Metric evaluation, as explained later in this section. It is worth noting that the same Metric can be used to evaluate multiple criteria (as represented by the cardinalities between the Metric and the Criterion classes).

Results of evaluation

The guideline, criterion, and metric constructs are evaluated over a specific Variant to obtain its classification. For describing a variant, we restrict to its most frequent name (preferred_name) and a list of all possible names. For example, the 'NC_000014.9:g.73136505T>G' variant is also known as 'NC_000014.8:g.73603213T>G' or 'NM_000021.3:c.-214T>G'.[2]

The classification of a Variant based on a particular Guideline is represented in the *classification* attribute of the ClassificationResult class, together with the *date* when the classification was generated. The *classification* is calculated by applying a set of operations or rules defined in the *rules* attribute of the Guideline class to the results of evaluating each Guideline's Criterion over the variant. These results are represented in the *criterion_result* attribute of the CriterionResult class, which takes values '0' or '1' for BooleanCriteria, or a numerical value within the *score_range* for ScoreCriteria.

In guidelines that use BooleanCriteria, the *rules* are logical operations that must be applied to CriterionResults. These *rules* establish the combination of criteria with a given strength and direction that must be met to achieve a certain *classification* for the Variant. For instance, the set of rules of the ACMG-AMP 2015 guidelines classifies a variant as pathogenic if a criterion with 'very strong' strength and a 'pathogenic' direction is found together with at least one 'strong' criterion in the same direction. According to the guidelines, the logical operation in this case is: '1 very strong AND >=1 strong'. In contrast, in guidelines that use ScoreCriteria, the rules establish the classification depending on the results of the sum of all the CriterionResults of the guideline criteria. For example, the ACMG-ClinGen 2020 guidelines state that those variants whose CriterionResults adds up to > 0.99 are considered 'pathogenic'. In both cases, the rules are composed of a *classification* and a *pattern* – either logical expressions or a summation – that evaluates CriterionResults. This internal structure of the rules is represented in the ClassificationRule data type.

Each *criterion_result* is calculated by applying the criterion's *pass_rule* over the results of the metrics the criterion defines, which are represented in the *pass* attribute of the MetricResult class. The *pass_rule* can take the values 'AND' when all metrics must be fulfilled for the criterion to be met, or 'OR' when only one of the metrics is required. For example, both metrics of the PVS1 criterion must be fulfilled for the criterion to be met. In this case, the *pass_rule* attribute will take the value 'AND'.

Contextual information

[2]The same variant can be identified with different names. According to the HGVS Nomenclature, an internationally recognized standard for describing sequence variants, the same variant can be represented by different names based on the DNA, RNA, or protein sequence used for reference.

Each metric result depends on the evaluation of contextual information about the given variant under study. Each piece of information required to interpret a variant must be structured according to a DataModel, which will provide a shared definition of the different pieces of information (e.g., the variant's allele frequency, its consequence at the protein level, etc.) that are evaluated during in the classification process. Furthermore, a DataModel will facilitate both data integration and any automation of the classification process based on this meta-model. Each piece of information is represented in the DataElement class, which is characterized by the *name* and *description* of the element, its *data_type* (e.g., float, string), and any possible *value_constraint* (e.g., an allele frequency always takes values between 0 and 1).

The value of each DataElement for a given variant comes from external DataSources, which are characterized by their *name* and the *url* where the data is available. Each DataSource will have its own data schema due to the particularly problematic heterogeneity of genomic information [45]. Consequently, to identify a concrete DataElement in the original DataSource schema, a mapping process is required. The results of this mapping are represented in the DataElementInDataSource class, whose properties are the *path* where the DataElement is available in the DataSource schema as well as the element's *value*. For example, the allele frequency DataElement has the path '1000g2015aug_all' in the 1000g database, and 'AF' in the ExAC database. In both cases, the *path* represents the name of a CSV file column containing information about the allele frequency DataElement. Note that different DataElementInDataSource can be mapped to the same DataElement, since the same piece of information is commonly found in different DataSources, taking the same or different *data_values*.

Finally, to obtain each MetricResult, we evaluate all the pieces of information (DataElementInDataSource) representing the DataElement evaluated by the Metric. For instance, if a Metric focuses on evaluating the variant's allele frequency, we must consider the allele frequency provided by all the available genomic DataSources. The way to evaluate the data is specified in the *data_evaluation_condition* attribute of the Metric class. This attribute follows a Condition data structure, which is composed of the *operation* to perform and a *value*. For example, if we want to evaluate in the metric that the allele frequency of the variant must be greater than 0.01, the operator is '>' and the value is '0.01'. The result of applying the *data_evaluation_condition* to each DataElementInDataSource is represented in the *pass* attribute of the MetricDataEvaluationResult class. These results are used to obtain the final MetricResult, by evaluating the percentage of cases in which *data_evaluation_condition* is fulfilled, that is, the percentage of MetricDataEvaluationResult that are true. If this percentage is greater than the one specified in the *min_percentage_data_fulfillment* attribute of the Metric class, the MetricResult will be set to true. If not, the MetricResult will be false.

4.1. Example: BS1 criterion

VarClaMM can be instantiated by focusing on a specific example: the BS1 criterion from the ACMG-AMP 2015 guidelines for variant classification. Figure 2 shows in pink the ACMG-AMP guidelines structure focused on BS1 criterion constructs, in orange their evaluation, and in blue the contextual information used to evaluate the BS1 criterion. These guidelines list the criterion as one of the four that provide strong evidence of the variant's benignity. More specifically, the purpose of the BS1 criterion is to evaluate whether the *allele frequency of a given variant is greater than expected for a given disorder*.

The instantiation of the BS1 criterion revealed a significant problem related to its imprecise definition. What is the exact meaning of *higher than expected frequency*? How do we choose the correct cutoff value to assess the variant's frequency? Answering these questions is outside the scope of this research. Nonetheless, the concept of Metric represented in the meta-model allows us to clearly and precisely define the decisions made by the clinical expert. Indeed, in this example, the metric associated with the criterion (metric M1) states that the frequency of the variant must exceed 1%, which, as opposed to the criterion, is a concrete indication that can be accurately evaluated.

The M1 metric assesses the concept (i.e., DataElement) of allele frequency, which is the frequency of a variant in a given population. This frequency is a float that takes values between 0 and 1, representing the percentage of the population affected by that variant. Information about the allele frequency DataElement is stored in multiple DataSources such as the 1000 Genomes Project (1000G) [46], the Exome Aggregation Consortium (ExAC) [47], the Genome Aggregation Database (gnomAD) [12], and the ALlele Frequency Aggregator (ALFA) dataset [48]. Only ExAC and 1000G data sources have been represented in the model for brevity. Both resources follow a tabular-like structure, where the allele frequency data is stored in the 'AF' and '1000g2015aug_all' fields, respectively.

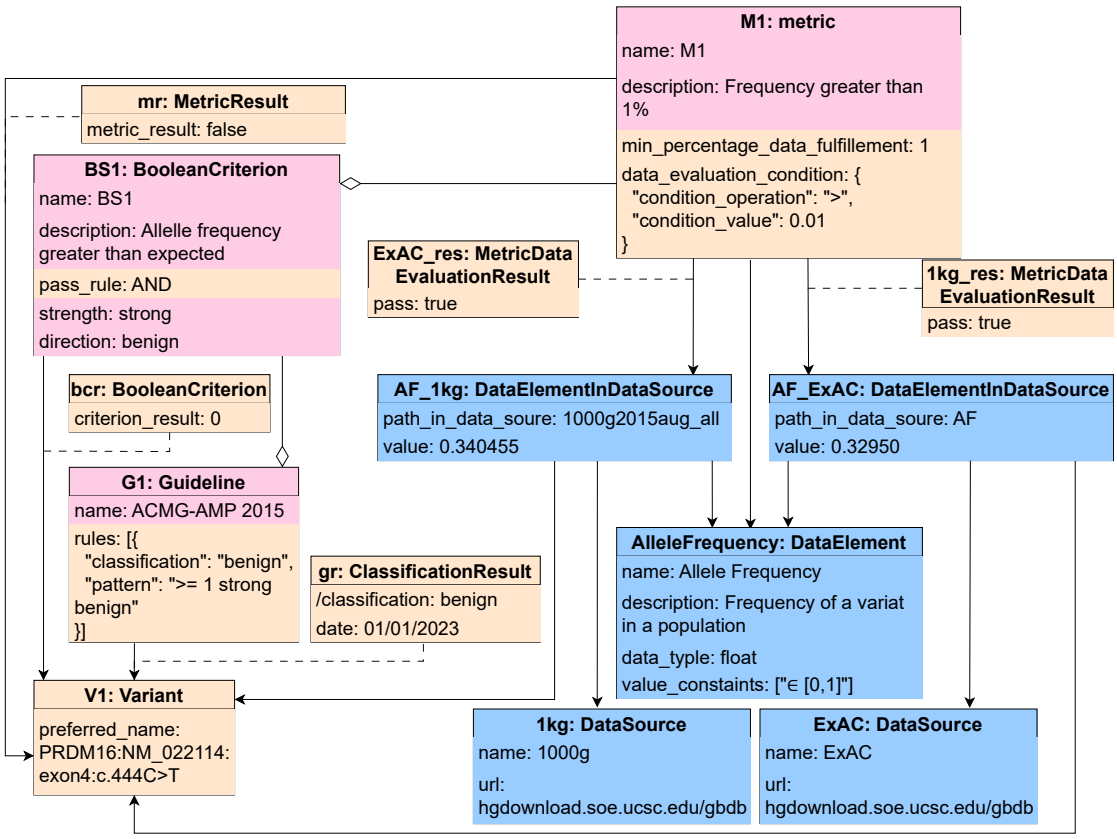

Figure 2. Instantiation of the BS1 criterion of the ACMG-AMP guidelines using the meta-model.

To evaluate the constructs of the BS1 criterion, we focus on the PRDM16:NM_022114:exon4:c.444C T variant. Based on 1000G and ExAC data sources, the variant allele frequency is 0.34 and 0.33, respectively. According to the min_percentage_data_fulfillment of the metric, every piece of data must comply with the established data_evaluation_condition. In the particular case of the variant under study, the M1 metric is met. As this is the only metric considered in the definition of the BS1 criterion, it is also evaluated as true.

Weighting the results of the criteria established by the selected guidelines yields the final variant classification. To simplify the example, we have considered that the ACMG-AMP only establishes one rule (i.e., whether or not the BS1 criterion is met) to determine the variant's classification. The PRDM16:NM_022114:exon4:c.444C T is classified as benign since the BS1 criterion is met.

VarClaMM has allowed us to unpack and make the constructs underlying the ACMG-AMP BS1 criterion explicit, while these were previously hidden in the convoluted nature of its description. This unpacking process was supported by the aggregation relationships defined between the Guideline and Criterion classes, and between the Criterion and Metric classes. These part-hood relationships are made explicit using the formulas defined in the *pass_rule* and *rules* attributes. A Criterion's classification result is based on the evaluation of its metrics. In turn, a Guideline's classification result is based on the evaluation of its criteria. Moreover, the evidence used to perform each metric evaluation is made explicit, enhancing the traceability and explainability of the process. This example shows how our meta-model enables the decomposition of the classification process into more precise constructs, which will serve as a solid foundation for the process's future operationalization.

5. Variant Misclassification Patterns

VarClaMM characterizes the constructs and underlying structure of the variant classification process. This characterization has led us to identify five patterns that hinder the variant (mis)classification process. These patterns highlight the main inconsistencies in the classification processes when used by different experts and elucidate the disparities in the variant classification results. We have identified five different patterns: 1) the use of different DataSources, leading to different MetricResults; 2) the use of one Metric, but with different levels of compliance requirements in DataSources; 3) the use of the same Criterion, but measured according to different Metrics; 4) the use of the same Guideline, but applying diverse Criteria; and 5) the use of one Criterion with different purposes within diverse Guidelines. All such patterns are allowed in VarClaMM and are represented by several real-world examples; however, they are at the base of unclear/incoherent classifications of variants. Details and examples are provided in the following sections.

5.1. Same metric – different data sources

One of the experts' most frequently expressed concerns is the lack of a central database proving all the required evidence for the variant classification process [49]. Instead, the information is spread across more than 1,800 data sources [50]. In this chaotic situation, experts are expected to rely on publicly available data to perform their assessments [18]. As a result, different experts may evaluate the same metric differently depending on the data they access.

Let us consider the following example. Determining whether a variant has already been reported as pathogenic in reputable data sources is frequently regarded as proof of the variant's pathogenicity under investigation [8]. A study reports that more than 83% of clinical experts make continuous use of this kind of resource in their classification process [49]. The evidence provided by these data sources is often found to be incomplete and discordant with one another [45]. Consequently, when the metric "*the variant has been reported as pathogenic in a reputable data source*" is evaluated, different metric results may be obtained depending on the consulted data source.

Figure 3 depicts a practical example of such a situation. In the first scenario, the variant rs1234A>T has met the metric evaluating whether the variant has already been reported (metric M1) because the ClinVar data source [9] reports the variant as pathogenic. However, in the second scenario, the variant fails the metric M1 because the consulted data source –Leiden Open Variation Database (LOVD) [51] – reports the variant as VUS (Variant of Uncertain Significance). VarClaMM allows us to identify that the misclassification of the M1 metric is due to using different data sources.

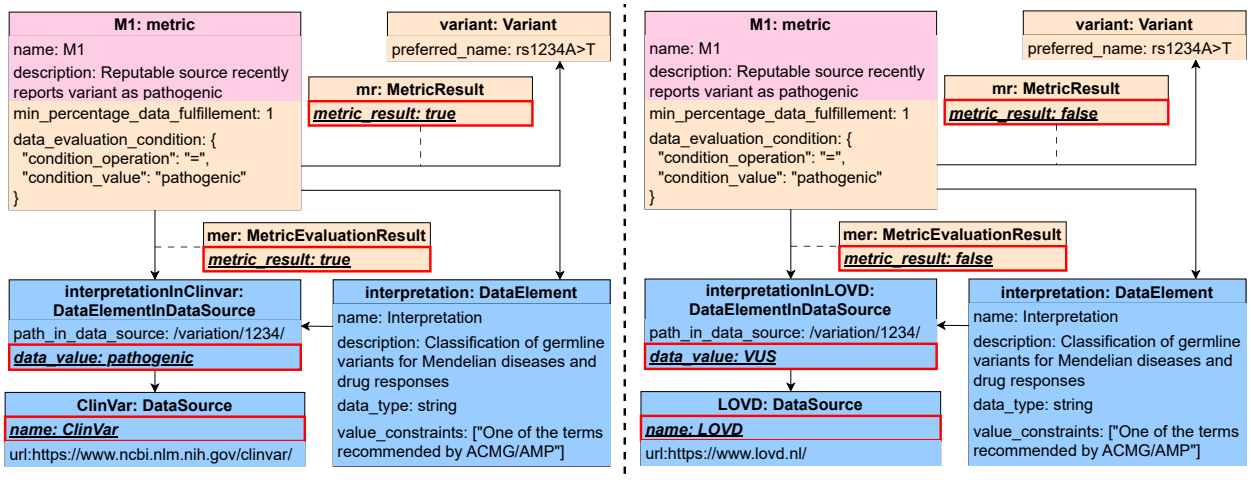

Figure 3. Example model of pattern "Same metric – different data sources". The relationships between the Variant and the DataElementInDataSource classes are not depicted for simplicity.

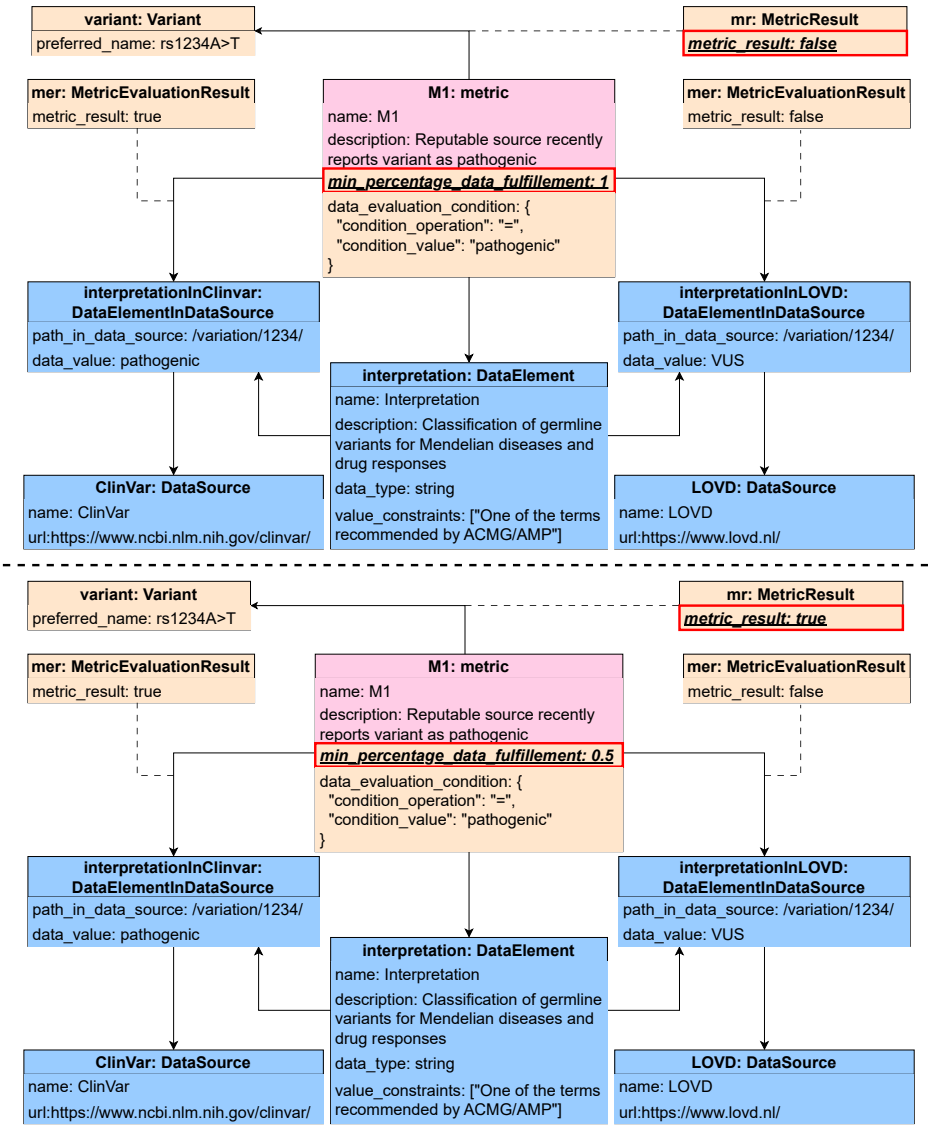

Figure 4. Example model of pattern "Same metric – different compliance requirements"

5.2. *Same metric – different compliance requirements*

Since the technological breakthroughs in Next Generation Sequencing, a vast amount of data about DNA variants is being made available every day [52]. This data is critical for understanding how variants affect our health status. However, dealing with this volume of information can be difficult. Indeed, some experts argue that one of the most relevant challenges in variant classification is how to best evaluate all the available information [24].

In this context, different classifications of the same piece of evidence became one of the most frequent sources of discrepancies among experts [18, 24]. Building on the example in Section 5.1, Figure 4 represents a scenario where both experts access the ClinVar and LOVD data sources to apply the metric "*the variant has been reported as pathogenic in a reputable data source*" over the rs1234A>T variant. These data sources provide contradictory information about the rs1234A>T variant, one considering it pathogenic and the other VUS. The expert whose decision process is represented at the top of Figure 4 considers that both data sources should provide consistent information about the variant's pathogenicity (as evidenced by the min_percentage_data_fulfillment attribute set to one). Consequently, the metric M1 is considered not to be met. However, the expert represented at the bottom only requires that

50% of data sources provide a consistent pathogenicity assessment. For this second expert, the metric M1 is met.

This example highlights how different experts can interpret the same data points differently. Similar examples with a metric that evaluates if "*the variant has been reported together with another pathogenic variant*" have also been reported in the literature [18]. The precise representation of the variant classification process provided by VarClaMM has allowed us to achieve clear insight into how the evidence used in the classification is evaluated. This allows us to precisely pinpoint the source of conflicting assessments at the lowest possible level.

5.3. Same criterion – different metrics

Classification guidelines have contributed to standardizing the variant classification process. However, due to the lack of specificity in these guidelines, different experts can apply the same criterion differently [22]. According to VarClaMM, different metrics have been employed to evaluate the same guideline's criterion.

This is especially common when determining a variant's allele frequency [18]. The variant classification guidelines frequently recommend using the frequency of the variant allele as a benignity criterion if it is *greater than expected for that specific disorder* (see criterion BS1 in Section 4.1). Such a definition makes the frequency's cutoff entirely dependent on the knowledge and experience of the expert performing the classification [53].

As a result, given the criterion for evaluating allele frequency, an expert could define a metric that states, for instance, that "*the variant should have an allele frequency greater than 0.5%*". In contrast, an alternative expert with a stricter approach could define a different metric stating that "*the variant should have an allele frequency greater than 1%*". This difference in metrics may result in different assessments of whether or not the same criterion is met.

Figure 5 depicts an actual instance model of this situation. In this example, the variant rs1234A>T has an allele frequency of 0.0082 (see the DataElementInDataSource instance). When the criterion BS1 is applied to this variant, it produces different results depending on the different definitions of the (only) metric on which this criterion depends. Again, VarClaMM can pinpoint the origin of criterion assessment differences.

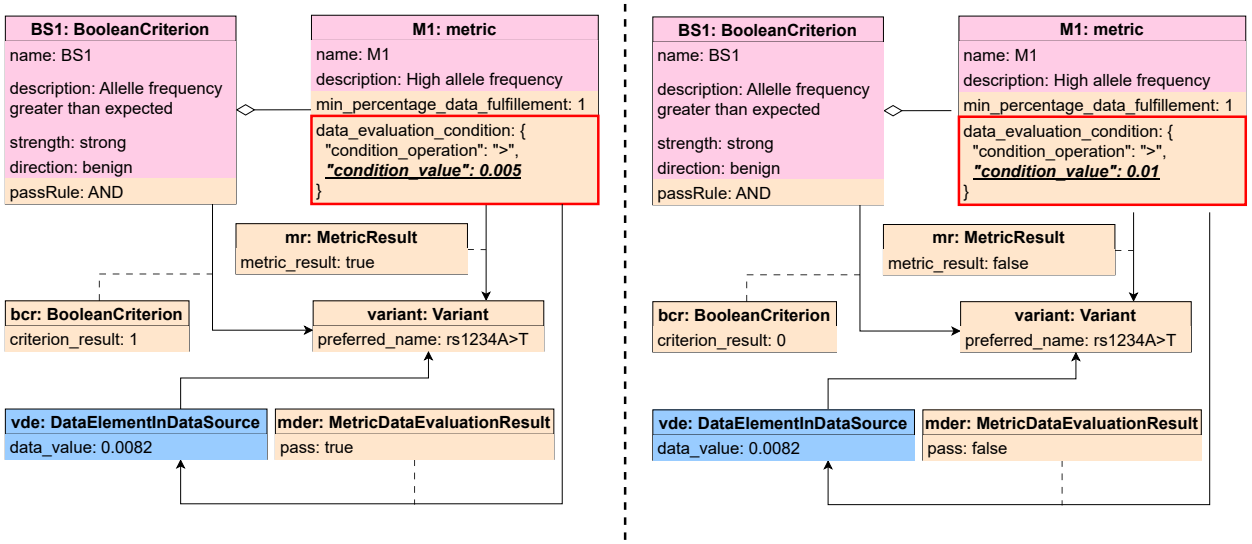

Figure 5. Example model of pattern "Same criterion – different metrics"

5.4. Same guideline – different criteria

Most common misclassifications occur when merging results from different sources following different guidelines. One would expect this not to happen *within* a specific guideline, as guidelines intend to create a well-defined framework for selecting the most appropriate classification for a variant. Surprisingly, differences in classification results are common even when using the same classification guideline [54, 55]. This is related to the fact that laboratories that perform the classification activity may be unable (for diverse reasons, e.g., economic, time-related, or

motivational) to apply all of the criteria specified in the guidelines. This is frequently the case in functional studies. Many variant classification guidelines recommend the use of well-designed functional studies to assess the potential impact of a variant in a gene or gene product [8, 56]. However, pursuing this type of research is extremely difficult due to the required significant monetary and time investments. As a result, only 36% of clinical experts apply this criterion during the variant classification process [49].

Since functional studies provide strong evidence of the variant pathogenicity, the choice of the expert to use this type of evidence will significantly impact the classification of the variant. This is especially important for variants whose significance is unclear, and a functional study can determine whether the variant should be discarded as benign or investigated further due to its potential to cause disorder [57, 58].

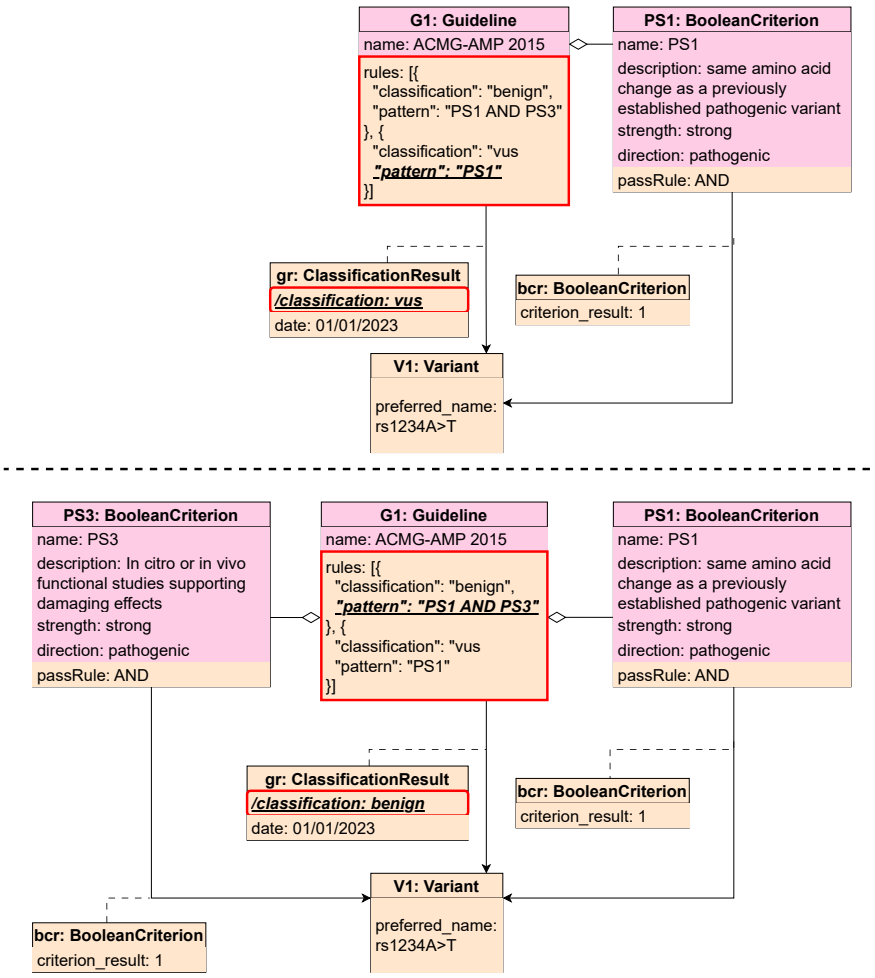

Figure 6. Example model of pattern “Same guideline – different criteria”

The potential of the criteria used on the classification of a variant is demonstrated practically in Figure 6. The expert in the top scenario only considered criterion PS1, thus concluding that the variant has an Uncertain Significance (VUS) based on this information. However, the expert in the bottom scenario considered both PS1 and PS3; according to the classification rule that assigns the “pathogenic” value when both PS1 and PS3 hold, or the “VUS” value when only PS1 holds, this expert concluded that the variant should be classified as pathogenic. Additional evidence provided by functional studies (criterion PS3) was fundamental in this case. VarClaMM represents each expert’s classification process and pinpoints the source of inconsistencies in the classification of variant rs1234A>T.

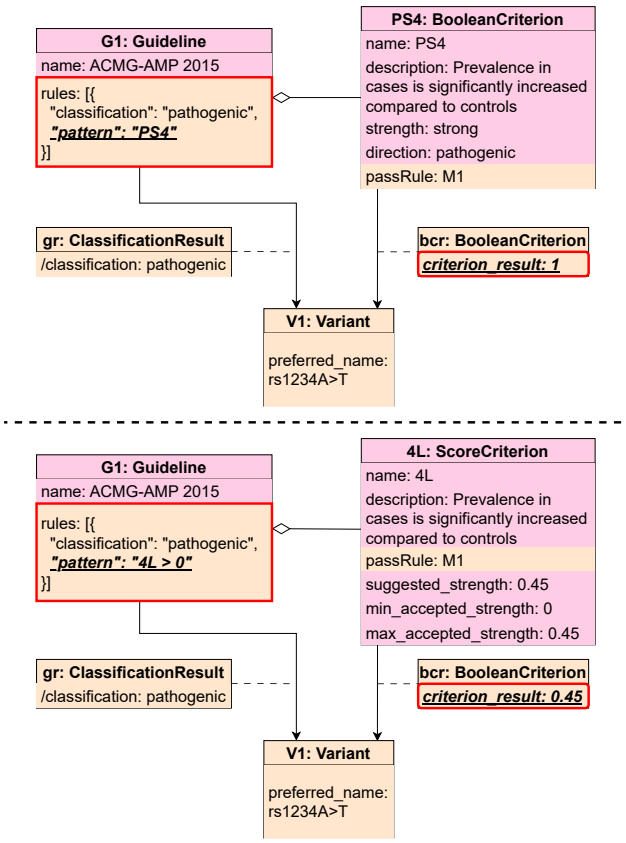

Figure 7. Example model of pattern "Same guideline – different guidelines"

5.5. Same criterion – different guidelines

Different variant classification guidelines establish different criteria and metrics depending on their applicability. Nevertheless, there are well-established criteria that usually appear in multiple guidelines.

In classification guidelines, each criterion is defined as boolean-based or score-based. As discussed in Section 4, each type of criterion follows a different evaluation strategy. Consequently, even when guidelines include the same criterion, their assessment may differ depending on the approach adopted by the guideline.

A typical case when this difference emerges involves the criterion that evaluates whether a variant is more frequent in cases than in controls. The criterion is evaluated by the ACMG-AMP 2015 guidelines as a Boolean criterion [8], and in the ACMG-ClinGen as a score criterion [16]. Figure 7 illustrates the example. In the ACMG-AMP Guideline, the criterion PS4 analyzes whether the frequency of the variant rs1234A>T is increased in affected individuals – using the metric M1. The M1 result is evaluated as true and, consequently, the PS4 criterion results are also evaluated as true. In the ACMG-ClinGen Guideline, the equivalent criterion 4L evaluates the same metric for the same variant. In this case, the result of the criterion is a particular score (0.45), whose value is obtained based on the range of scores and the suggested score stated in the definition of the criterion.

VarClaMM clearly illustrates the differences between both guidelines and – in general – allows experts to identify variant classification differences that arise from the use of different approaches for variant classification.

6. Discussion

Variant classification is a critical step in achieving better diagnoses and treatments based on each individual's genomic information. However, the imprecise and vague nature of the variant classification process poses difficulties

in its application in a real clinical setting. We have used a conceptual modeling approach to define VarClaMM, a meta-model that allows us to identify the structure and constructs behind the variant classification process.

With the proposed meta-model, we have defined and explained the common framework for representing the classification process (Section 4); we then identified patterns of misclassification of variants (Section 5); finally, the previous results enabled us to disentangle the intricate details of the variant classification process, as we analyzed in the examples of the previous section. Below, we summarize the lessons learned during this process.

Bridging the gap between decisions and evidence: In the critical context of clinical care, decisions taken must be supported by reliable and complete evidence. However, it is frequently challenging to clarify the relationship between the decisions made and the supporting evidence due to the data dispersion problem that affects genomics [45]. Section 5.1 illustrates how using different pieces of information can directly affect clinical assessments. Thanks to the representation of the data elements and data sources in VarClaMM, we achieve complete traceability of the classification process.

Unpacking variant classification results: Differences in variant classification can have important consequences on a patient's health. The reason behind these differences is typically not the use of different guidelines/criteria but a conflicting evaluation of the same metric. Thanks to the description of a criterion as an aggregation of metrics, we can now identify a different evaluation of a variant and the specific metric that caused such a difference. Section 5.2 illustrates this case. This allows for a precise unpacking of the variant classification results.

Disambiguating criterion definitions: Since classification guidelines are often not clear enough to allow for their unambiguous application, various experts will use different measurements to determine whether a criterion is met. As seen in Section 5.3, the metric definition has allowed us to identify the collection of constructs an expert uses to assess a certain criterion. This enables us to provide a standard framework for comparing various classifications of the same criterion.

Clarifying classification process application: A precise set of criteria are specified in the classification guidelines to direct the classification outcome. As Section 5.4 shows, not all experts employ all criteria, making it difficult to derive *a posteriori* the used procedure. VarClaMM enables a precise characterization of the particular criteria applied for variant classification as well as the components assessed in each criterion, enabling full traceability of the outcomes.

Making connections between guidelines explicit: Currently available classification guidelines differ substantially in their applicability, in the criteria considered most important to assess the role of a variant in the disorder process, or even in their approach for evaluating such criteria (boolean or score). Precisely identifying the differences and commonalities among the guidelines is key to comparing the classification approach followed by different experts and the possible implications for the classification results. Section 5.5 reflects how VarClaMM has allowed us to make explicit connections among different classification guidelines.

Operationalization of guidelines: The variant classification process was originally defined abstractly, thus hampering straightforward operationalization. VarClaMM poses the basis for building workflows that systematically: 1) explain the complex classification domain (along the lines of [59]) and the related process in place (a sort of process explainability [60]); 2) highlight current differences, inconsistencies, and misclassifications; 3) propose refinements to current criteria and metrics; and 4) derive a complete operationalization of the classification process. A conceptual model can serve as the foundation for operationalizing variant classification by making it more accessible, guiding decision-making, facilitating interdisciplinary collaboration, and encouraging continuous improvement. As an overall result, inconsistencies in their application will be reduced.

Empirical assessment: VarClaMM has been applied in a clinical setting in collaboration with two experts from the Chilean Hereditary Cancer Group, a multidisciplinary network in Chile of health professionals dedicated to investigating the genetics of hereditary cancer. During this practical experience, VarClaMM was employed to instantiate the variant classification framework used by these specialists. The experts emphasized important advantages of using the model, particularly its capacity to enhance the explicability of classification outcomes. They further noted that a tool based on this model would systematize the definition of their classification processes, increase result traceability, and deliver high standards of transparency and clarity. While this initial application provided valuable insights and validated the framework's practical utility within a hereditary cancer research group, we acknowledge the need for a comprehensive, more formal empirical validation across diverse diseases and specialties. To address this need for broader validation, we have initiated collaborations with multiple expert groups. These include the original experts from the Chilean Hereditary Cancer Group, as well as specialists in cardiology and retinopathies, in order to conduct

a robust and multifaceted validation. This ongoing work aims to strengthen the validation of the model's applicability and utility across diverse clinical domains, building upon its initial success within the hereditary cancer context.

Current limitations of VarClaMM: First, external elements that may impact classification results have not been represented. These elements include, for example, the fact that some variants are pathogenic only when combined with other variants or that other variants may overcome a variant's pathogenic effect. Second, this work did not examine variant classification in the context of complex disorders. In these disorders, many variants are required to cause the manifested disorder. Extra factors such as penetrance and population specificities must also be considered, but have been disregarded here. Third, the actors participating in the interpreting process are not modeled. Knowing who performed the classification, what annotation tool was used, or what information they relied on to evaluate each criterion helps increase the interoperability and reproducibility of the classification results.

7. Conclusions

In this paper, we proposed VarClaMM, a novel meta-model to represent the variant classification process. Variant classification is a common process in the working routine of clinicians and geneticists; managing it accurately is of critical importance to ensure patients' well-being. Unfortunately, current practice still presents many shortcomings, including the presence of several guidelines with criteria and metrics definitions often dependent on the expert's opinion, the use of different sources of information, and the potential classification of the same piece of evidence differently is hampering the reliability of the classification results.

We propose a meta-model to pave the path towards achieving comprehensive standardization and systematization of this process by elucidating the morphology of classification guidelines and their constituent elements. Furthermore, we introduce a series of patterns highlighting instances where these guidelines may inadvertently lead to misclassification of variants. These patterns shed light on typical challenges faced in variant classification, each accompanied by a practical use case demonstrating its relevance. In conclusion, we reflect on the lessons learned from our modeling endeavor and their implications on the aforementioned challenging use cases.

In the future, we plan to address VarClaMM's limitations, which are identified above. First, we intend to represent the variant's genomics context to show how the existence of other variants may influence the variant's classification. Second, our model will incorporate a classification of variant groups that operate together to produce a disorder. This will facilitate the classification of complex disorders. Third, we will continue to enhance the empirical validation of the method, as outlined in the discussion section. In addition, we plan to use VarClaMM as the foundation of a tool that supports variant classification operationalization. Finally, we plan to expand the patterns catalog further, proposing operational rules to avoid such incorrect situations from occurring.

Authorship contribution statement. *Mireia Costa*: Conceptualization, Source investigation, Examples, Writing - original draft; *Alberto García S.*: Conceptualization, Model design, Examples, Writing - review & editing; *Ana León*: Conceptualization, Writing - review & editing; *Anna Bernasconi*: Source investigation, Examples, Writing - review & editing; *Oscar Pastor*: Conceptualization, Writing - review & editing.

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