Application of qualifying variants for genomic analysis

Dylan Lawless*[1], Ali Saadat[2], Mariam Ait Oumelloul[2], Simon Boutry[2], Veronika Stadler[1], Sabine Österle[3], Jan Armida[3], David Haerry[4], D. Sean Froese[5], Luregn J. Schlapbach[1], and Jacques Fellay[2]

[1]Department of Intensive Care and Neonatology, University Children's Hospital Zürich, University of Zürich, Switzerland.
[2]Global Health Institute, School of Life Sciences, École Polytechnique Fédérale de Lausanne, Switzerland.
[3]SPHN Data Coordination Center, SIB Swiss Institute of Bioinformatics, Basel, Switzerland.
[4]Positive Council, Zürich, Switzerland.
[5]Division of Metabolism and Children's Research Center, University Children's Hospital Zürich, University of Zurich, Zurich, Switzerland.

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*Addresses for correspondence: Dylan.Lawless@kispi.uzh.ch

Abstract

Motivation:

Qualifying variants (QVs) are genomic alterations selected by defined criteria within analysis pipelines. Although crucial for both research and clinical diagnostics, QVs are often seen as simple filters rather than dynamic elements that influence the entire workflow. While best practices follow variant classification standards and standardised workflows, a unified framework to integrate and optimise QVs for advanced applications is missing.

Results:

Our aim is to embed the concept of a "QV" into the genomic analysis vernacular, moving beyond a single filtering step. By decoupling QV criteria from other pipeline variables and code, our approach facilitates easier discussion and application. Our framework, with its new terminology and reference model, offers a flexible approach for integrating QVs into analysis pipelines, thereby enhancing reproducibility, interpretability, and interdisciplinary communication. A validation case study implementing ACMG criteria in a disease cohort shows that our approach matches conventional methods while offering improved clarity and scalability.

Availability:

The source code and data are accessible at https://github.com/DylanLawless/qv2025lawless. The QV file used in this work is available from https://doi.org/10.5281/zenodo.15105594 (`qv_acmg_svnindel_criteria_20250225.yaml`). The QV framework is available under the MIT licence, and the dataset will be maintained for at least two years following publication.

Acronyms

ACMG American College of Medical Genetics and Genomics 5

CNV Copy Number Variant 6

GWAS Genome Wide Association Study 4

IRI Internationalised Resource Identifier 6

MAF Minor Allele Frequency 8

PPIE Public and Patient Involvement and Engagement 5

PRS Polygenic Risk Score 4

QC Quality Control 4

QV Qualifying variant 4

RDF Resource Description Framework 6

SF Secondary Findings 5

SHA-256 Secure Hash Algorithm 256 6

SNV/INDEL Single Nucleotide Variant / Insertion Deletion 6

SNOMED CT Systematized Nomenclature of Medicine-Clinical Terms 6

UUID Universally Unique Identifier 6

VEP Variant Effect Predictor 8

WGS Whole Genome Sequencing 4

1 Introduction

Qualifying variant (QV)s are genomic alterations selected by specific criteria within genome processing pipelines, serving as dynamic elements essential for both research and clinical diagnostics. QVs are not merely static filters applied at a single step in an analysis pipeline; rather, they are dynamic, multifaceted elements that permeate the entire workflow, from initial data quality control to final result interpretation. This nuanced perspective underscores that QVs play an integral role in shaping the fidelity and reproducibility of genomic analyses, enabling the iterative refinement of data and facilitating the integration of diverse analytical strategies throughout the pipeline.

Often, QV selection adheres to established variant classification and reporting standards (1–5) and standardised workflows (6–8). However a unified framework for QVs is lacking, despite the recognised benefits of similar initiatives, such as Polygenic Risk Score (PRS) reporting standards (9; 10). For instance, tools like vcfexpress (11) enable flexible, rapid filtering and formatting of VCF files using user-defined expressions. The application of independently defined QV criteria would complement such tools. This role is particularly important for reproducibility across distributed computing environments (12) and would also integrate with workflow managers such as Snakemake (13) or Nextflow (14), streamlining genomic processing tasks.

The criteria for QV selection vary by application. For example, Genome Wide Association Study (GWAS) may focus on common variants, while clinical analyses usually target rare or known pathogenic variants. Previous studies have demonstrated the utility of QVs (15; 16), yet no common approach exists. Here, we detail four typical applications of QV sets:

1. **QV passing Quality Control (QC) only**: Generates large datasets (e.g. $>$ 500,000 variants per subject) for GWAS or initial Whole Genome Sequencing (WGS) pre-processing.

2. **Flexible QV**: Balances between QC and false positives, yielding intermediate datasets (e.g. fewer than 100,000 variants per subject) for uses such as rare variant association testing.

3. **QV for rare disease**: Applies stringent filtering to produce smaller datasets (e.g. $<$ 1,000 variants per subject), targeting known genes or single causal variants.

4. **Known disease panel QV set**: Focuses on well-established gene panels

with pathogenic variants (e.g. the American College of Medical Genetics and Genomics (ACMG) Secondary Findings (SF) set) for clinical reporting (17).

These examples illustrate a few common applications without providing an exhaustive classification of all possible QV uses. The careful selection and categorisation of QVs are thus critical for accurate reporting and reproducibility, sometimes even more so than the choice of the analysis pipeline itself (18).

As WGS becomes standard for large cohorts (19; 20), the integration of diverse QV protocols is critical for data cleaning and analysis. During sequencing analysis several layers can be responsible for triggering QV protocols, including pre-existing metadata, technical QC results, and post-calling annotations, highlighting the need for a clear, unified approach.

We propose treating the QV as a standalone entity, independent from other pipeline variables. We suggest structured human- and machine-readable criteria, aligned with FAIR principles (21) to facilitate integration across databases (22; 23). We advocate for the use of standard vocabularies, unique identifiers, and flexible file formats to support this integration.

2 Methods

2.1 Implementation

Implementation configurations and roles within analysis pipelines include, for example: theoretical pipelining of QV sets, establishing public or standardised QV sets for specific analytical scenarios, and recognition that QVs are integral throughout the analysis pipeline rather than confined to a single end-stage. We introduce a simple framework for the effective use of QV protocols, comprising four components as illustrated in **Figure 1 (A)**:

- **1. Variables**: The criteria variables sourced as part of the pipeline (see **Box 2**).
- **2a. Technical description**: An optional narrative detailing each step within the overall QV set (see **Box 2**).
- **2b. Public and Patient Involvement and Engagement (PPIE) description**: An optional narrative providing a patient-focused interpretation of the protocol, incorporating preferences and priorities.

- **3. QV set ID**: A unique identifier that links analysis records.
- **4. Source code**: The implementation of the variables file within the pipeline code, for example through custom scripts or workflow managers.

We propose the QV set ID as a unique identifier linking variant sets used in analyses. This facilitates integration into databases, by representing data in formats such as Resource Description Framework (RDF) schemas (23), and allows for features including Secure Hash Algorithm 256 (SHA-256) hash functions, Universally Unique Identifier (UUID)s, semantic combinations, Internationalised Resource Identifier (IRI) incorporation, registry-based allocation, and standard mapping such as Systematized Nomenclature of Medicine-Clinical Terms (SNOMED CT). The results can be used alongside other genomic-specific concepts spanning from sample processing to the sequencing run (22).

This framework efficiently manages QV-specific variables (e.g. allele frequency thresholds) separately from general pipeline settings, ensuring clarity and specificity. Its versatile format supports applications across genomic analyses and by linking the QV set ID to both results and raw data sources in a database for downstream interpretation and reporting.

2.2 Example application of qualifying variants in WGS analysis

Multiple QV protocols can be combined to generate progressively filtered datasets tailored to specific analytical needs. Often, different QV sets are applied sequentially, with the final outcomes merged to address distinct objectives. For instance, a comprehensive analysis pipeline might integrate:

- `QV SNV/INDEL` Single Nucleotide Variant / Insertion Deletion (SNV/INDEL),
- `QV CNV` Copy Number Variant (CNV),
- `QV structural variation`,
- `QV rare disease known`, and
- `QV statistical association QC`.

The final analysis yields (1) a joint cohort disease association (e.g. variant P-values) and (2) individual single-case results (e.g. clinical genetics diagnosis for a patient) (24; 25). As an example, in **Figure 1 (A)** we focus on a SNV/INDEL pipeline employing two QV sets: `QV SNV INDEL 1` for flexible cohort-level filtering, and `QV SNV INDEL 2` for stricter filtering in subsequent single-case analysis. The pipeline is illustrated in **Box 1**, and can be summarised as follows:

"A cohort of patient WGS data was analysed to identify genetic determinants for phenotype X. Initially, a flexible QV set was applied using the `pipeline DNA SNV INDEL v1`, which implements the `QV SNV INDEL 1` criteria to produce the prepared dataset (`dataset DNA SNV INDEL v1`). This dataset was then analysed alongside other modules (e.g. `PCA SNV INDEL v1` and `statistical genomics v1`) to derive a cohort-level association signal (Result 1). Next, the same prepared dataset was re-filtered with the stricter `QV SNV INDEL 2` criteria to identify known causal variants for each patient, yielding the final dataset (`dataset DNA SNV INDEL v2`) and resulting in individual case reports (Result 2)."

Box 1: Example diagrammatic representation

```
pipeline DNA SNV INDEL v1
└─ Flexible QV criteria
   ├─ QV SNV INDEL 1 → dataset DNA SNV INDEL v1
   │  ├─ PCA SNV INDEL v1
   │  └─ statistical genomics v1 → Result 1
   ├─ dataset DNA SNV INDEL v1
   │  └─ Rare disease QV criteria
   │     └─ QV SNV INDEL 2 → dataset DNA SNV INDEL v2
   │        └─ single case report SNV INDEL v1 → Result 2
   └─ Joint analysis output
```

Joint analysis output from:
Result 1 = Cohort-level association signal (e.g. variant P-value).
Result 2 = Single variant report per patient.

2.3 Usage in a Validation Study

In a validation study, we demonstrate the use of our QV criteria framework compared to the conventional manual approach. This analysis was performed on an in-house rare disease cohort of 940 individuals, which had been pre-processed for QC. We

used genome-wide set of variants which was filtering to target rare varaints (Minor Allele Frequency (MAF) < 0.01) restricted to known disease genes based on the Genomics England panel "Primary immunodeficiency or monogenic inflammatory bowel disease," retrieved using our PanelAppRex R repository (https://github.com/DylanLawless/PanelAppRex) (26). This provided us with a prepared dataset of 6026 candidate variants annotated with 376 information sources. The dataset was prepared in R using GuRu, our variant interpretation tool that consolidates all annotation sources and scores variants as candidate causal, and was imported from gVCF format as output by Variant Effect Predictor (VEP).

We selected the first eight ACMG criteria for assigning pathogenicity scores to variants (1); six of these were relevant for this cohort. First, the analysis was performed manually by hard-coding each criterion in the pipeline script, reflecting a typical workflow. Second, the same criteria were imported from the QV YAML file for the new framework approach, using the file "qv acmg svnindel criteria 20250225.yaml" (see **Box 2** or https://doi.org/10.5281/zenodo.15105594). The outputs from both methods were captured and compared.

Additional details of the YAML criteria in this QV set included definitions for `ACMG_PS1` (identifying previously established pathogenic amino acid changes), `ACMG_PS3` (supporting functional studies with matching inheritance patterns), and `ACMG_PS5` (covering compound heterozygosity with high-impact variants). The criteria for `ACMG_PM2` and `ACMG_PM3` assess variant frequency and in trans occurrences, respectively, while `PS2` and `PS4` were not applicable to this cohort.

Box 2: qv_files/acmg_criteria.yaml

```
qv_set_id: acmg_sf_v3.2

acmg_pvs1:
  description_technical: >
    Null variants (IMPACT = HIGH) in genes where
    loss-of-function causes disease.
    Includes homozygous variants, dominant inheritance,
    and compound heterozygous cases.
    Compound heterozygosity is considered when both
    variants are HIGH impact. WARNING: Not phase checked.
  logic: "or"
  conditions:
    - condition:
        field: IMPACT
        value: "HIGH"
        operator: "=="
...
shasum -a 256 acmg_criteria.yaml | fold -w 32
d91fde41a5fff48631adecba38773d61
9ae8cd5cff9b9b42ef7f5efbd6bbfcdf
acmg_criteria.yaml
```

3 Results

3.1 Validation Case Study

We validated our QV protocol using ACMG-based criteria for a rare disease cohort of 940 individuals. We then conducted the variant classification using two approaches: a conventional manual method with hard-coded criteria, and our new YAML-based implementation As shown in **Figure 1 (B)**, the outputs from both methods were identical, demonstrating a 100% match. This confirmed that our framework of a standalone, shareable, QV criteria file can be imported and applied programmatically with equivalent accuracy, providing a reproducible resource that is adaptable across different pipelines and programming environments.

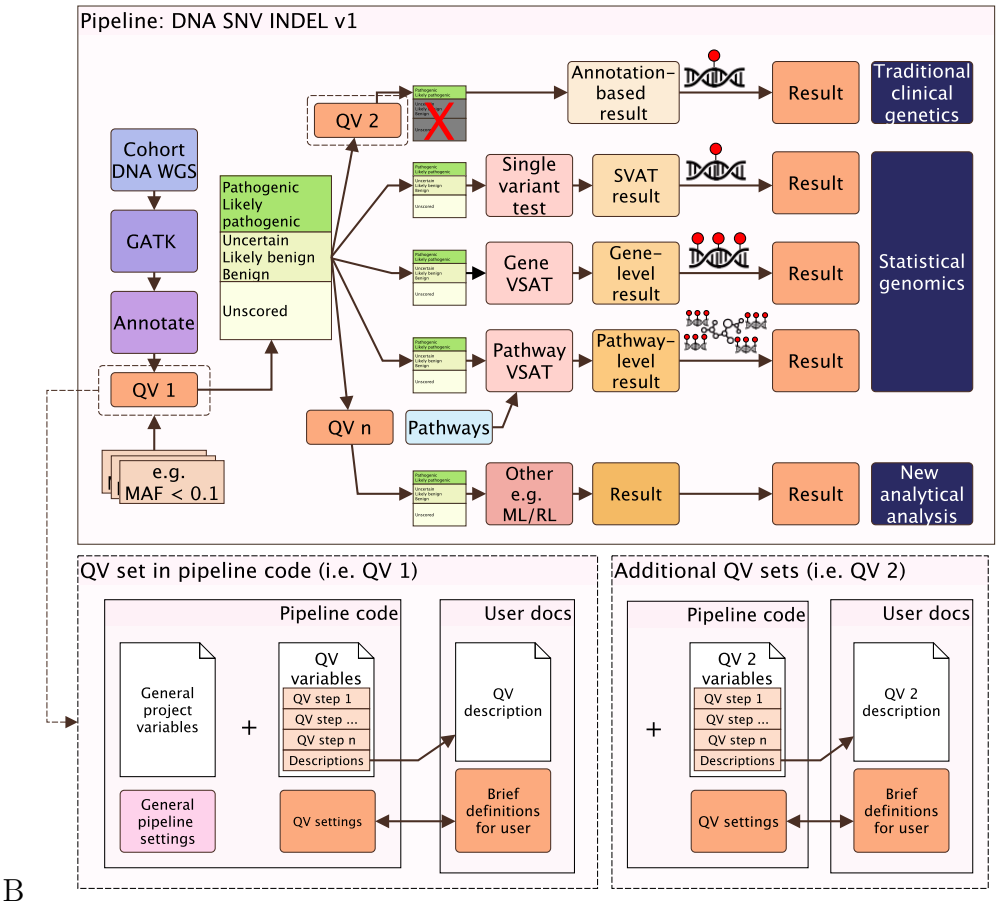
3.2 Implications

In the validation study, we applied ACMG criteria for variant interpretation. In clinical genetics, for instance, the resulting output can be used to retrieve candidate pathogenic variants using ACMG scoring methods (1; 5). Application of additional QV sets, such as the widely used ACMG SF set for clinical reporting (17), can be used to confirm any secondary findings.

In a clinical setting it is necessary to bridge the gap between technical detail and lay understanding. By explicitly documenting variant qualifying criteria and making QV data accessible, our framework builds trust and supports meaningful PPIE (27). The QV file adapts by integrating the main criteria variables with optionally dedicated fields for both technical description and PPIE description. This approach captures the analysis intent defined by the QV set creator and embeds patient preferences from the start.

For example, patient preferences recorded in the PPIE description can be automatically incorporated into a genetic report without additional interpretation, ensuring clarity and consistency throughout the analysis. This transparency guarantees that both experts and laypersons receive information in a format suited to their needs, thereby improving diagnostic traceability and accelerating the translation of genetic research into clinical practice.

A



B

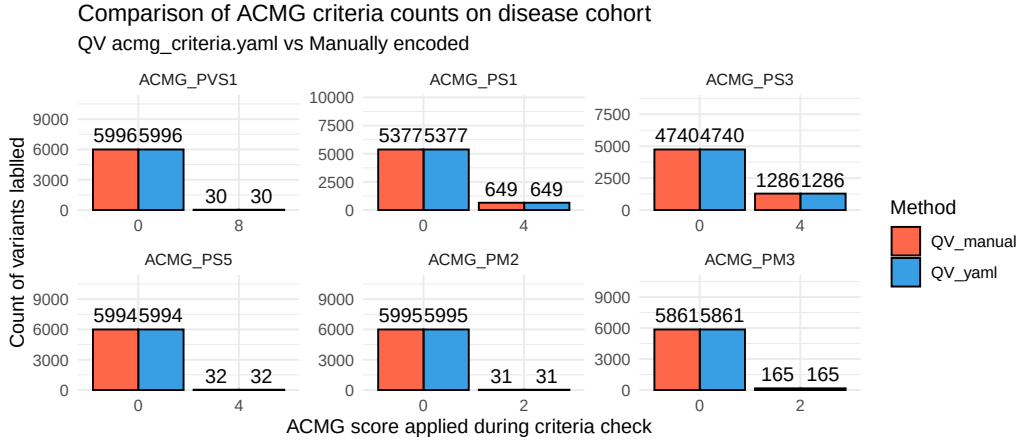


Figure 1: Summary of the QV application for a WGS pipeline. In panel (A), QV1 and QV2 are presented as sequentially piped protocol steps. In this example, QV2 differs from QV1 by retaining only likely/pathogenic variants (indicated by a red X). The QV file loaded by the analysis pipeline comprise a description field (optional) and a variables field (mandatory). The QV criteria may be spread throughout the pipeline. (B) Validation case study using an ACMG criteria subset, demonstrating a 100% match between manually encoded and standalone YAML-based QV (`qv_files/acmg_criteria.yaml`) for assigning pathogenicity scores.

4 Summary

This paper introduces a framework for integrating qualifying variants into genomic analysis pipelines, enhancing reproducibility, interpretability and the seamless translation of research findings into clinical practice.

5 Funding

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7 Contributions

DL designed the work and contributed to the manuscript. AS, SB, VS, DH, SÖ, JA contributed to the manuscript. JF, SF, LJS supervised the work, manuscript, and applied for funding.

8 Competing interests

The authors declare no competing interests.

9 Ethics statement

Summary statistics were used from studies which have been previously reported and approved by the respective ethics committees of all participating centers (Cantonal

Ethics Committee Bern, approval number KEK-029/11) and the study was conducted in accordance with the Declaration of Helsinki.

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