

**Application of qualifying variants for genomic analysis**

Journal:	<i>Bioinformatics</i>
Manuscript ID	Draft
Manuscript type:	Applications Note
Date Submitted by the Author:	n/a
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Portal Keywords:	Annotation, Genome analysis, Classification
Keywords:	qualifying, variants, genomic

# Application of qualifying variants for genomic analysis

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May 11, 2025

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## 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.

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**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; 24). 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 (24), 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.

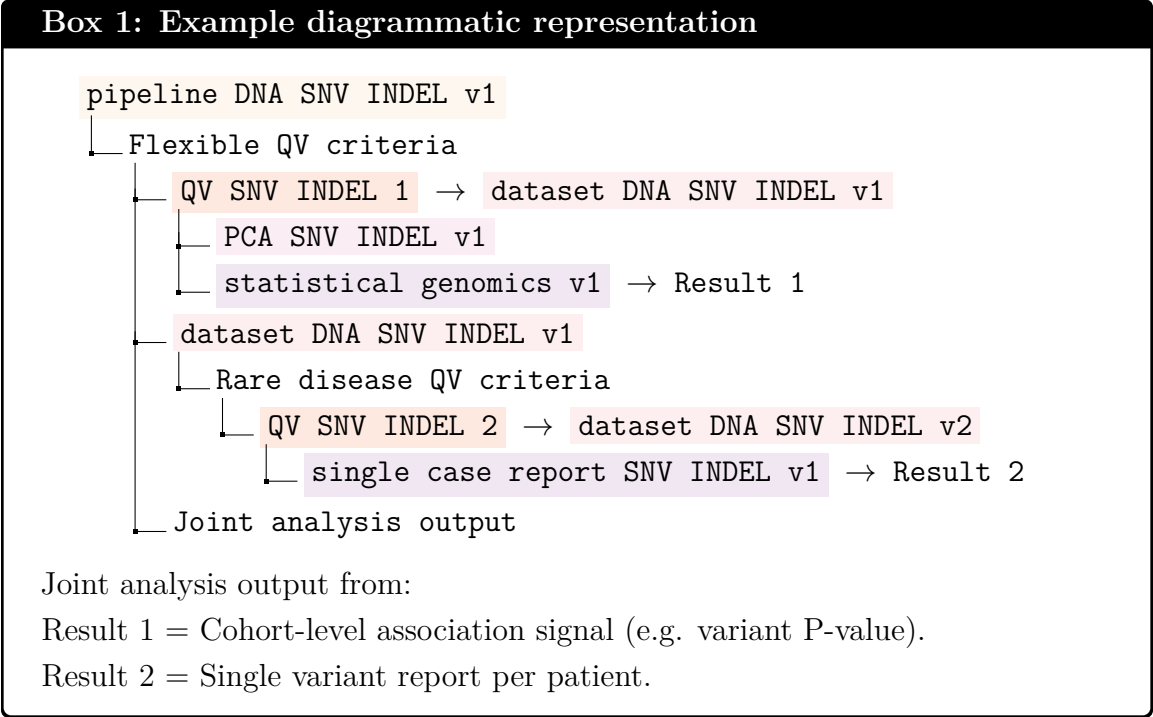
## 2.2 Example application of qualifying variants in WGS analysis

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) (25; 26). 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).”



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 variants (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>) (27). 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
9ae8cd5cff9b9b42ef7f5efbd6bbfcd
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

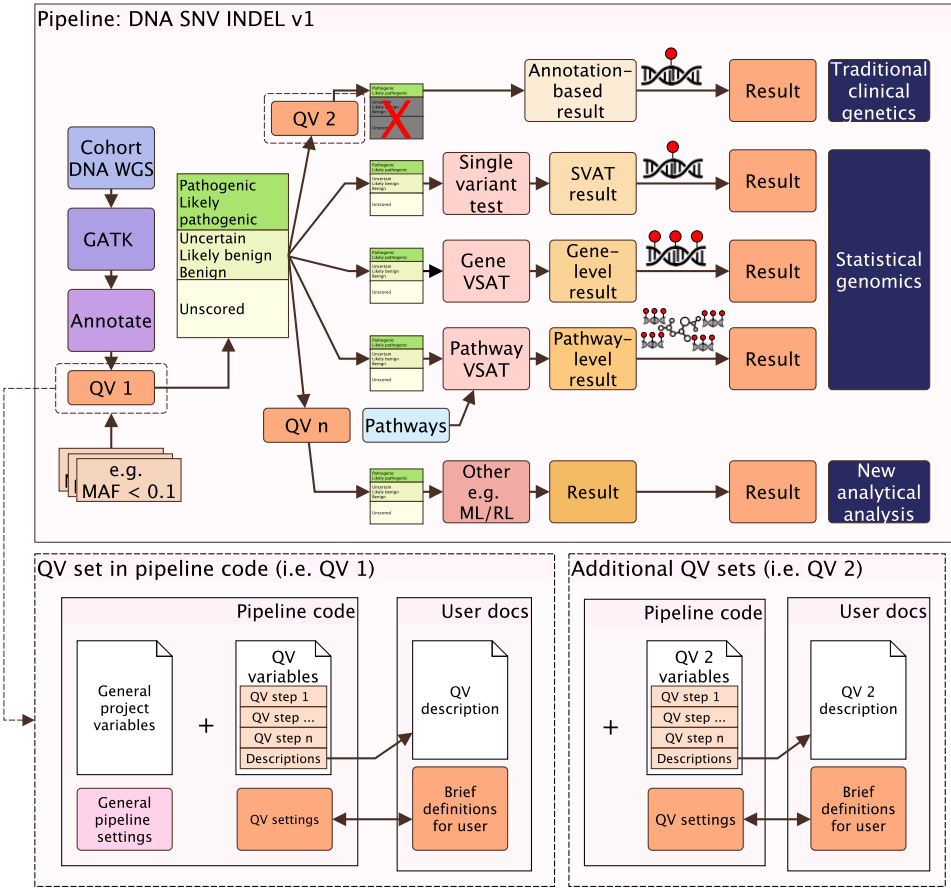
In the validation study, we applied ACMG criteria for variant interpretation. In clinical genetics, for instance, the resulting output can be used to retrieve candidate pathogenic variants using ACMG scoring methods (1; 5). Application of additional QV sets, such as the widely used ACMG SF set for clinical 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 (23). 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.

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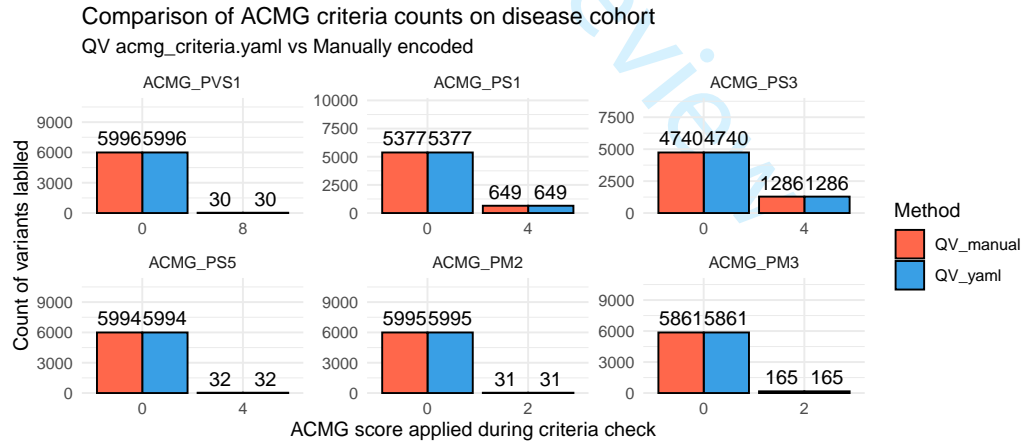


Figure 1: Summary of the QV application for a WGS pipeline. In panel (A), QV1 and QV2 are presented as sequentially piped protocol steps. In this example, QV2 differs from QV1 by retaining only likely/pathogenic variants (indicated by a red X). The QV file loaded by the analysis pipeline comprise a description 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

This project was supported through the grant NDS-2021-911 (SwissPedHealth) from the Swiss Personalized Health Network and the Strategic Focal Area ‘Personalized Health and Related Technologies’ of the ETH Domain (Swiss Federal Institutes of Technology).

## 6 Acknowledgements

Acknowledgements We would like to thank all the patients and families who have been providing advice on SwissPedHealth and its projects, as well as the clinical and research teams at the participating institutions.

## 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.

References

[1] Sue Richards, Nazneen Aziz, Sherri Bale, David Bick, Soma Das, Julie Gastier-Foster, Wayne W Grody, Madhuri Hegde, Elaine Lyon, Elaine Spector, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the american college of medical genetics and genomics and the association for molecular pathology. *Genetics in medicine*, 17(5):405–423, 2015.

[2] Marilyn M Li, Michael Datto, Eric J Duncavage, Shashikant Kulkarni, Neal I Lindeman, Somak Roy, Apostolia M Tsimberidou, Cindy L Vnencak-Jones, Daynna J Wolff, Anas Younes, et al. Standards and guidelines for the interpretation and reporting of sequence variants in cancer: a joint consensus recommendation of the association for molecular pathology, american society of clinical oncology, and college of american pathologists. *The Journal of molecular diagnostics*, 19(1):4–23, 2017.

[3] Quan Li and Kai Wang. Intervar: clinical interpretation of genetic variants by the 2015 acmg-amp guidelines. *The American Journal of Human Genetics*, 100(2):267–280, 2017.

[4] Erin Rooney Riggs, Erica F Andersen, Athena M Cherry, Sibel Kantarci, Hutton Kearney, Ankita Patel, Gordana Raca, Deborah I Ritter, Sarah T South, Erik C Thorland, et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the american college of medical genetics and genomics (acmge and the clinical genome resource (clingen). *Genetics in Medicine*, 22(2):245–257, 2020.

[5] Sean V Tavtigian, Steven M Harrison, Kenneth M Boucher, and Leslie G Biesecker. Fitting a naturally scaled point system to the acmg/amp variant classification guidelines. *Human mutation*, 41(10):1734–1737, 2020.

[6] Brent S Pedersen, Joe M Brown, Harriet Dashnow, Amelia D Wallace, Matt Velinder, Martin Tristani-Firouzi, Joshua D Schiffman, Tatiana Tvrdik, Rong Mao, D Hunter Best, et al. Effective variant filtering and expected candidate

- variant yield in studies of rare human disease. *NPJ Genomic Medicine*, 6(1):1–8, 2021.
- [7] Carl A Anderson, Fredrik H Pettersson, Geraldine M Clarke, Lon R Cardon, Andrew P Morris, and Krina T Zondervan. Data quality control in genetic case-control association studies. *Nature protocols*, 5(9):1564–1573, 2010. URL <https://doi.org/10.1038/nprot.2010.116>.
- [8] Emil Uffelmann, Qin Qin Huang, Nchangwi Syntia Munung, Jantina De Vries, Yukinori Okada, Alicia R Martin, Hilary C Martin, Tuuli Lappalainen, and Danielle Posthuma. Genome-wide association studies. *Nature Reviews Methods Primers*, 1(1):59, 2021. URL <https://doi.org/10.1038/s43586-021-00056-9>.
- [9] Hannah Wand, Samuel A Lambert, Cecelia Tamburro, Michael A Iacocca, Jack W O’Sullivan, Catherine Sillari, Iftikhar J Kullo, Robb Rowley, Jacqueline S Dron, Deanna Brockman, et al. Improving reporting standards for polygenic scores in risk prediction studies. *Nature*, 591(7849):211–219, 2021.
- [10] Samuel A Lambert, Laurent Gil, Simon Jupp, Scott C Ritchie, Yu Xu, Annalisa Buniello, Aoife McMahon, Gad Abraham, Michael Chapman, Helen Parkinson, et al. The polygenic score catalog as an open database for reproducibility and systematic evaluation. *Nature Genetics*, 53(4):420–425, 2021.
- [11] Brent S Pedersen and Aaron R Quinlan. Vcfexpress: flexible, rapid user-expressions to filter and format VCFs. *Bioinformatics*, 41(3): btaf097, March 2025. ISSN 1367-4811. doi: 10.1093/bioinformatics/btaf097. URL <https://academic.oup.com/bioinformatics/article/doi/10.1093/bioinformatics/btaf097/8051444>.
- [12] Henri E. Bal, Jennifer G. Steiner, and Andrew S. Tanenbaum. Programming languages for distributed computing systems. *ACM Computing Surveys*, 21(3): 261–322, September 1989. ISSN 0360-0300, 1557-7341. doi: 10.1145/72551.72552. URL <https://dl.acm.org/doi/10.1145/72551.72552>.
- [13] Felix Mölder, Kim Philipp Jablonski, Brice Letcher, Michael B. Hall, Christopher H. Tomkins-Tinch, Vanessa Sochat, Jan Forster, Soohyun Lee, Sven O. Twardziok, Alexander Kanitz, Andreas Wilm, Manuel Holtgrewe, Sven Rahmann, Sven Nahnsen, and Johannes Köster. Sustainable data analysis with Snakemake. *F1000Research*, 10:33, January 2021. ISSN 2046-1402. doi: 10.12688/f1000research.29032.1. URL <https://f1000research.com/articles/10-33/v1>.

[14] Paolo Di Tommaso, Maria Chatzou, Evan W Floden, Pablo Prieto Barja, Emilio Palumbo, and Cedric Notredame. Nextflow enables reproducible computational workflows. *Nature Biotechnology*, 35(4):316–319, April 2017. ISSN 1087-0156, 1546-1696. doi: 10.1038/nbt.3820. URL <https://www.nature.com/articles/nbt.3820>.

[15] Gundula Povysil, Slavé Petrovski, Joseph Hostyk, Vimla Aggarwal, Andrew S. Allen, and David B. Goldstein. Rare-variant collapsing analyses for complex traits: guidelines and applications. *Nature Reviews Genetics*, 20(12):747–759, 2019. doi: 10.1038/s41576-019-0177-4. URL <https://doi.org/10.1038/s41576-019-0177-4>.

[16] Elizabeth T Cirulli, Brittany N Lasseigne, Slavé Petrovski, Peter C Sapp, Patrick A Dion, Claire S Leblond, Julien Couthouis, Yi-Fan Lu, Quanli Wang, Brian J Krueger, et al. Exome sequencing in amyotrophic lateral sclerosis identifies risk genes and pathways. *Science*, 347(6229):1436–1441, 2015.

[17] David T Miller, Kristy Lee, Noura S Abul-Husn, Laura M Amendola, Kyle Brothers, Wendy K Chung, Michael H Gollob, Adam S Gordon, Steven M Harrison, Ray E Hershberger, et al. Acmg sf v3. 2 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the american college of medical genetics and genomics (acmg). *Genetics in Medicine*, 25(8):100866, 2023.

[18] Nathan D Olson, Justin Wagner, Nathan Dwarshuis, Karen H Miga, Fritz J Sedlazeck, Marc Salit, and Justin M Zook. Variant calling and benchmarking in an era of complete human genome sequences. *Nature Reviews Genetics*, 24(7):464–483, 2023.

[19] James J Lee, Robbee Wedow, Aysu Okbay, Edward Kong, Omeed Maghzian, Meghan Zacher, Tuan Anh Nguyen-Viet, Peter Bowers, Julia Sidorenko, Richard Karlsson Linnér, et al. Gene discovery and polygenic prediction from a 1.1-million-person gwas of educational attainment. *Nature genetics*, 50(8):1112, 2018.

[20] Philip R Jansen, Kyoko Watanabe, Sven Stringer, Nathan Skene, Julien Bryois, Anke R Hammerschlag, Christiaan A de Leeuw, Jeroen S Benjamins, Ana B Muñoz-Manchado, Mats Nagel, et al. Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. *Nature genetics*, 51(3):394–403, 2019.



- [21] Mark D Wilkinson, Michel Dumontier, IJsbrand Jan Aalbersberg, Gabrielle Appleton, Myles Axton, Arie Baak, Niklas Blomberg, Jan-Willem Boiten, Luiz Bonino da Silva Santos, Philip E Bourne, et al. The fair guiding principles for scientific data management and stewardship. *Scientific data*, 3(1):1–9, 2016.
- [22] Eelke van der Horst, Deepak Unni, Femke Kopmels, Jan Armida, Vasundra Touré, Wouter Franke, Katrin Crameri, Elisa Cirillo, and Sabine Österle. Bridging clinical and genomic knowledge: An extension of the sphn rdf schema for seamless integration and fairification of omics data. 2023.
- [23] Zoë Slote Morris, Steven Wooding, and Jonathan Grant. The answer is 17 years, what is the question: understanding time lags in translational research. *Journal of the Royal Society of Medicine*, 104(12):510–520, December 2011. ISSN 0141-0768, 1758-1095. doi: 10.1258/jrsm.2011.110180. URL <https://journals.sagepub.com/doi/10.1258/jrsm.2011.110180>.
- [24] Vasundra Touré, Philip Krauss, Kristin Gnodtke, Jascha Buchhorn, Deepak Unni, Petar Horki, Jean Louis Raisaro, Katie Kalt, Daniel Teixeira, Katrin Crameri, et al. Fairification of health-related data using semantic web technologies in the swiss personalized health network. *Scientific Data*, 10(1):127, 2023.
- [25] Geraldine Van der Auwera and Brian D. O’Connor. *Genomics in the cloud: using Docker, GATK, and WDL in Terra*. O’Reilly, Beijing Boston Farnham Sebastopol Tokyo, first edition edition, 2020. ISBN 978-1-4919-7519-0 978-1-4919-7516-9 978-1-4919-7512-1.
- [26] Xihao Li, Han Chen, Margaret Sunitha Selvaraj, Eric Van Buren, Hufeng Zhou, Yuxuan Wang, Ryan Sun, Zachary R McCaw, Zhi Yu, Min-Zhi Jiang, et al. A statistical framework for multi-trait rare variant analysis in large-scale whole-genome sequencing studies. *Nature Computational Science*, pages 1–19, 2025.
- [27] Dylan Lawless. PanelAppRex aggregates disease gene panels and facilitates sophisticated search. March 2025. doi: 10.1101/2025.03.20.25324319. URL <http://medrxiv.org/lookup/doi/10.1101/2025.03.20.25324319>.