SHARIANT: Sharing Genomic Variant Clinical Interpretations across Laboratories in Australia and New Zealand

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Background

The Australian Genomics initiative, Shariant, is a controlled-access platform to allow inter-laboratory automated sharing of structured evidence for clinically curated variants across Australia and New Zealand.[1]

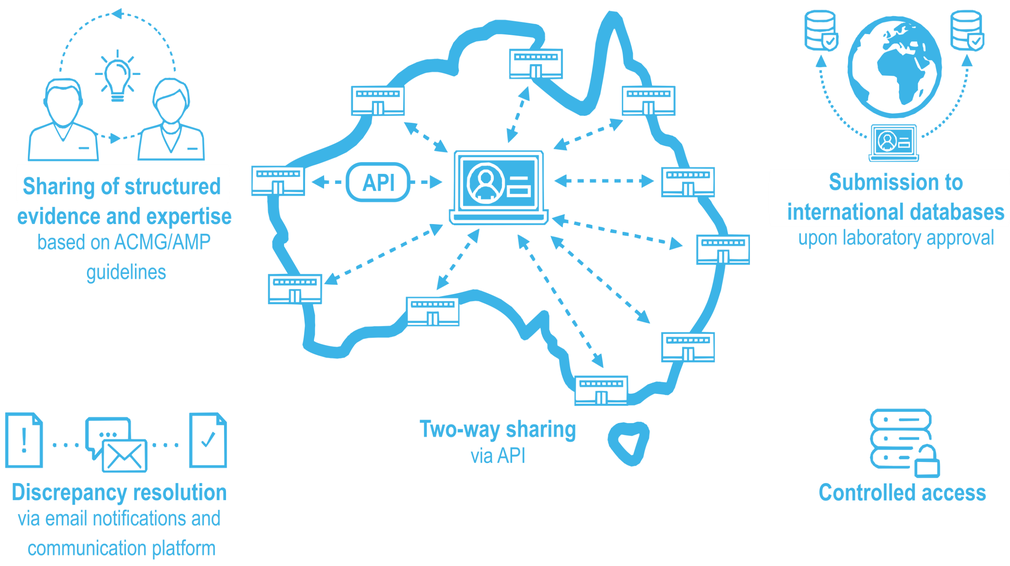

Figure 1. Schematic of the Shariant functionalities. Main features include: two-way sharing via an application programming interface (API) or via upload to the Shariant web portal; sharing of structured evidence against the American College of Medical Genetics and Genomics and Association for Molecular Pathology (ACMG/AMP)[2] guidelines; discrepancy resolution; submission to ClinVar; and controlled access.

International knowledge sharing

Shariant has facilitated submission to ClinVar for >5,800 germline variant interpretations, directly supporting a 1600% increase in Australia's international knowledge sharing from clinical laboratories since platform launch in 2019.

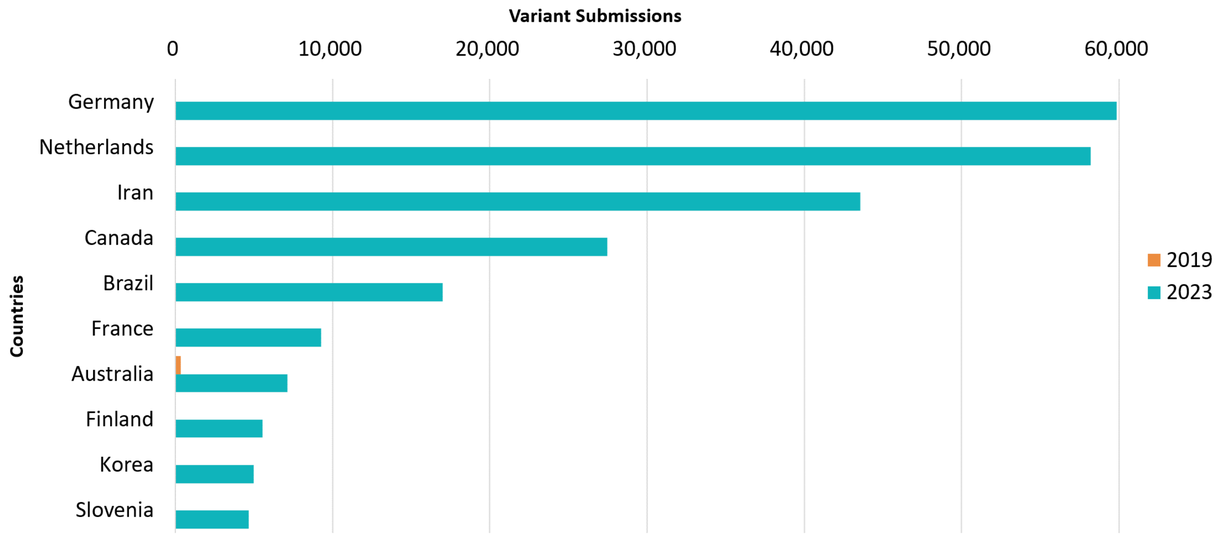

Figure 4. Top 10 countries submitting genetic variant classifications to ClinVar, outside of the United States. The data represent variants identified via clinical testing, as at May 2023. The number of variant submissions in ClinVar in 2019 are shown in orange for Australia only, to illustrate the change in submissions since Shariant launched. Data for the United States not shown (n=2,900,000 submissions).

Submissions

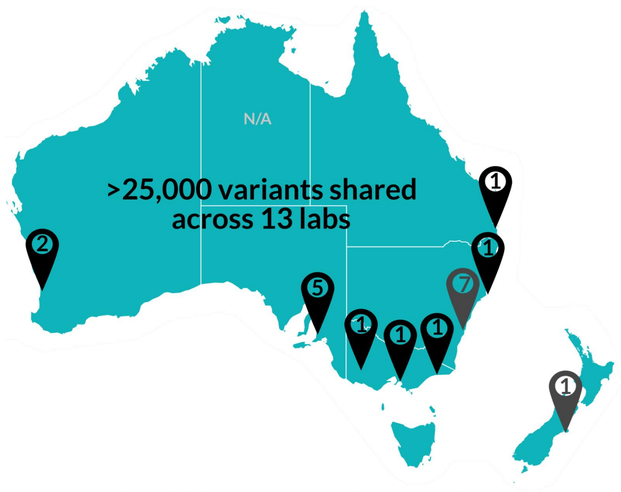

Figure 2. Number of laboratories contributing to Shariant. As at June 2023, >25,000 mostly prospective germline variant interpretations have been shared across 13 clinical genetic testing laboratories.

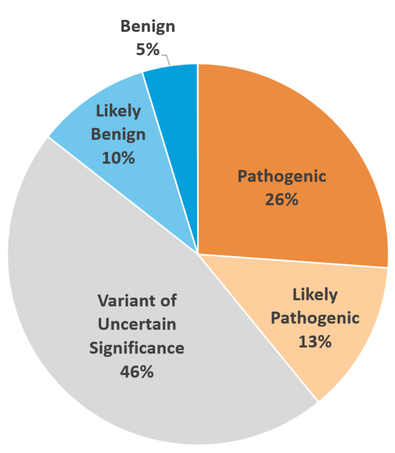

Figure 3. Distribution of germline variants in Shariant by variant classification. Includes unique germline variant classifications (n=20,216).

Discrepancies have been identified for ~12% (n=150) of germline variants submitted by multiple laboratories, with cross-laboratory collaboration so far resolving 43% of medically significant discrepancies (i.e. P/LP vs VUS).

Incorporation of functional assays

Application of RNA and functional assay information (denoted as PS3/BS3) occurs for only ~10% of unique interpretations per laboratory.

Considering variants curated by multiple laboratories:

- 15% had PS3/BS3 applied consistently.
- 50% had PS3/BS3 applied by one lab only.

Easier access to functional assay data, and exploring reasons for different usage of this evidence type, will be crucial for standardisation.

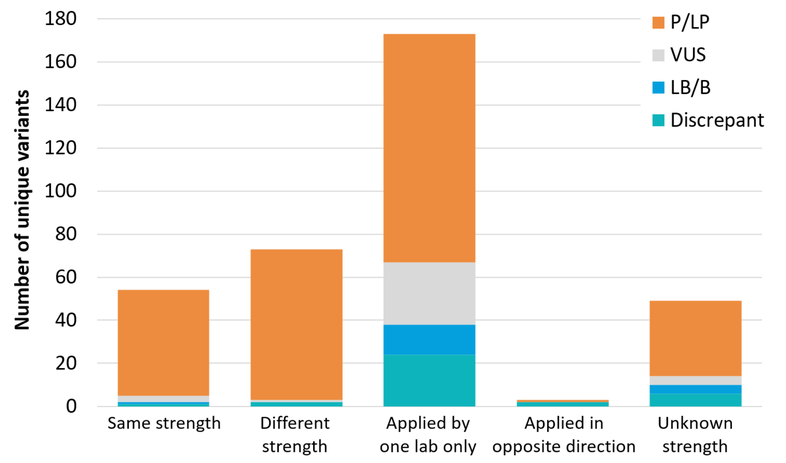

Figure 5. Application of functional assay codes (PS3/BS3) across variants interpreted by multiple laboratories. Number of unique variants where at least one laboratory had applied PS3/BS3 (n=352). Comparison of code strength applied is indicated on the x-axis, and split into variant pathogenicity according to the y-axis. Variants are categorised as unknown if the code was applied by multiple laboratories, with one at an undefined strength (e.g. due to use of a different interpretation guideline).

Somatic Shariant

Shariant has initiated work to capture and share somatic variant interpretations. This is a major platform development, requiring consideration of diagnostic, prognostic and therapeutic implications at the variant and tumour level. The project has involved a landscape analysis of published somatic curation guidelines, and a survey of Australian and New Zealand diagnostic laboratories conducting somatic testing. Results from analysis will inform software design. Development is currently underway to accept somatic variants in Shariant by the end of 2023.

Landscape Analysis → **Diagnostic Laboratory Survey** → **Development & Completion**

Q1 2023 ***Q4 2023***

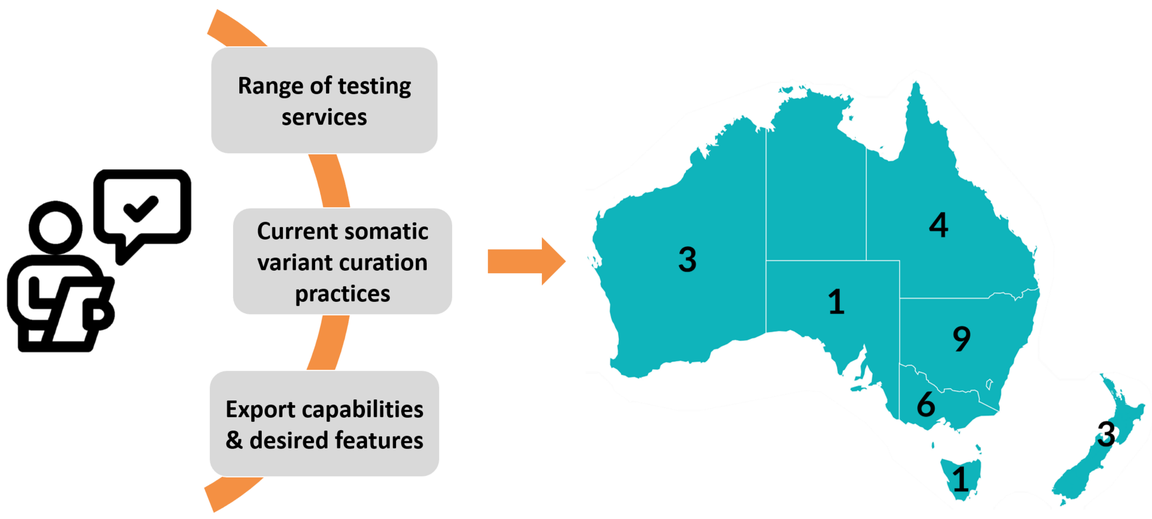

Figure 6. Topics covered in somatic survey and responses by region. All NATA or IANZ accredited diagnostic laboratory groups in Australia and New Zealand with scope for related somatic testing were invited to participate in the survey (n=40). Twenty-seven laboratories provided responses with the number of laboratories per region indicated on the map.

Next steps

Laboratory consultation has identified a need to define approaches to capture copy number variants (CNVs), with inconsistency in nomenclature across cytogenetics and molecular genetics laboratories presenting a major issue. Significant developments are underway to enhance the variant normalisation and liftover process to capture CNVs. Collaboration has been initiated to align with national and international groups addressing similar issues.

As Shariant continues to grow in contributions and functionalities, engaging laboratories remains crucial to provide a platform that benefits its users.

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References

1. Tudini et al 2022. Am J Hum Genet. 3;109(11):1960-1973. PMID: 36332611.
2. Richards et al 2015. Genet Med. 17(5):405-24. PMID: 25741868.

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