Variant Classification and Interpretation Survey

The survey will take approximately 10 minutes to complete.

* Required

Variant Classification and Interpretation Survey

Accurate and consistent classification of germline sequence variant pathogenicity in rare diseases is a major challenge. The ACMG and ACGS guidelines provide a framework for sequence variant clinical interpretation but the implementation of them between laboratories needs consideration. The purpose of this survey is to understand how an alternative automated variant classifier could help reduce intra and inter-laboratory discrepancies and identify solutions to currently available classification software(s).

All responses to this survey are anonymous. Unless you voluntarily include contact information for follow up no personally identifiable information is collected. Any contact information will only be stored for the duration of the project which will conclude in September 2022. All responses are collated in a report to further secure your privacy.

1

Are you completing this as a scientist, clinician, academic or other? *

- ◯ Bioinformatician
- ◯ Clinical Scientist in Bioinformatics
- ◯ Clinical Scientist in Genomics
- ◯ Clinician
- ◯ Genetic Technologist
- ◯ Genetic Counsellor
- ◯ Academic/ Researcher
- ◯ Student
- ◯ Other

2

What guidelines do you implement for sequence variant classification? Please include the version number or source if applicable. e.g., ACMG (Richards et al., 2015) or ACGS (Ellard et al., 2020)

3

Do you use different guidelines for different disease types? *

- ◯ Yes
- ◯ No

4

If you answered yes to question 3, please can you name the disease-specific variant classification guidelines that you use e.g., the CanVIG-UK Consensus Specification for Cancer Susceptibility Genes (CSGs) (Garrett et al, 2022)

5

What software(s) do you currently use to classify sequence variants and how do you rate them on a scale of 1 to 5? (1 being the least useful and 5 being the most).

	1	2	3	4	5	Don't Use
Varsome	◯	◯	◯	◯	◯	◯
Alamut	◯	◯	◯	◯	◯	◯
Golden Helix	◯	◯	◯	◯	◯	◯
Congenica	◯	◯	◯	◯	◯	◯
Exomiser	◯	◯	◯	◯	◯	◯
Variant Effect Predictor	◯	◯	◯	◯	◯	◯
Other (please specify below in question 6)	◯	◯	◯	◯	◯	◯

6

If you answered other for question 5 please name the software that you use to classify sequence variants.

7

How many variants do you normally classify in one batch? *

- ◯ One
- ◯ 2-5
- ◯ 6-10
- ◯ More than 10 (please also answer question 8)

8

If you normally classify more than 10 please state the maximum number of variants you would input per batch.

9

Do you manually enter variant data into the software that you use or batch import? If you batch import what file type(s) do you upload? (tick all that apply) *

- [ ] Manually
- [ ] .csv format
- [ ] .vcf file
- [ ] .bed file
- [ ]

Other

10

How do you describe your variants when entering into variant classification software(s)? *

- [ ] HGVS e.g. NM_153212.3(GJB4):c.35G>A (p.Gly12Asp)
- [ ] Co-ordinate based
- [ ]

Other

What genome build are you using, hg19 or hg38? Please state the patch number under other if known. *

- [ ] GRCh38 (hg38, build38)
- [ ] GRCh37 (hg19, build19)
- [ ] Other

What in-silico predictors do you use to help classify missense variants? *

- [ ] None
- [ ] SIFT
- [ ] Polyphen2
- [ ] REVEL
- [ ] CADD
- [ ] CAPICE
- [ ] MaxEntScan
- [ ] SpliceAI
- [ ] Align GVD
- [ ] Other

What in-silico predictors do you use to help classify frameshift variants? *

- [ ] None
- [ ] SIFT
- [ ] Polyphen2
- [ ] REVEL
- [ ] CADD
- [ ] CAPICE
- [ ] MaxEntScan
- [ ] SpliceAI
- [ ] Align GVD
- [ ] Other

What in-silico predictors do you use to help classify nonsense variants? *

- [ ] None
- [ ] SIFT
- [ ] Polyphen2
- [ ] REVEL
- [ ] CADD
- [ ] CAPICE
- [ ] MaxEntScan
- [ ] SpliceAI
- [ ] Align GVD
- [ ] Other

What in-silico predictors do you use to help classify splice site (+/-2) variants? *

- [ ] None
- [ ] SIFT
- [ ] Polyphen2
- [ ] REVEL
- [ ] CADD
- [ ] CAPICE
- [ ] MaxEntScan
- [ ] SpliceAI
- [ ] Align GVD
- [ ] Other

16

What in-silico predictors do you use to help classify intronic variants? *

- [ ] None
- [ ] SIFT
- [ ] Polyphen2
- [ ] REVEL
- [ ] CADD
- [ ] CAPICE
- [ ] MaxEntScan
- [ ] SpliceAI
- [ ] Align GVD
- [ ] Other

What in-silico predictors do you use to help classify synonymous variants? *

- [ ] None
- [ ] SIFT
- [ ] Polyphen2
- [ ] REVEL
- [ ] CADD
- [ ] CAPICE
- [ ] MaxEntScan
- [ ] SpliceAI
- [ ] Align GVD
- [ ] Other

What in-silico predictors do you use to help classify in-frame indels? *

- [ ] None
- [ ] SIFT
- [ ] Polyphen2
- [ ] REVEL
- [ ] CADD
- [ ] CAPICE
- [ ] MaxEntScan
- [ ] SpliceAI
- [ ] Align GVD
- [ ] Other

19

What gene-level metrics do you use to facilitate classification of sequence variants? *

- [ ] None
- [ ] pLI score (gnomAD)
- [ ] LOEUF (gnomAD)
- [ ] Missense Z-score (gnomAD)
- [ ] Missense o/e (gnomAD)
- [ ] %HI (Decipher)
- [ ] GeVIR (http://gevirank.org/ (http://gevirank.org/))
- [ ] ClinGen Dosage Sensitivity Score
- [ ] Other

20

Would you be interested in using another automated system than the one you currently access? *

- ◯ Yes
- ◯ No (go to question 21)
- ◯ Maybe

21

If the answer to question 20 is no, explain why and what would influence you to change from the system you currently use?

22

If you are willing to have a follow-up, could you please supply an email address so we may contact you.