Building the ClinGen Pathogenicity Calculator Version 2.0 by leveraging ClinGen API Microservices.

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The Clinical Genome Resource (ClinGen) suite of microservices provides a platform to build applications within and outside of ClinGen by leveraging Application Programming Interfaces (APIs). The ClinGen APIs and messaging queues have been employed within ClinGen to support variant curation, which includes data aggregation, curation, and dissemination of published pathogenicity assertions. Version 1.0 of the Pathogenicity Calculator was aimed at non-ClinGen users, supported ACMG/AMP v3.0 2015 guidelines, and was utilized as a classic siloed application. Version 2.0 is upgraded to support an early draft of the

ACMG/AMP/CAP/ClinGen SVC v4.0 2023 guidelines and leverages ClinGen API microservices, including the ClinGen Allele Registry, ClinGen Linked Data Hub, and ClinGen Criteria Specification Registry. In addition to the utility to the end-users, Version 2.0 thus provides a new model for how interfaces and workflows within and outside of ClinGen may leverage the ClinGen Resource.

Calculator 2.0 users first identify a variant of interest, uniquely identified by a stable canonical allele identifier (CA ID) obtained from free, open, on-demand registration within the Allele Registry. Supporting evidence is obtained and aggregated in the form of excerpts linked to a given CA ID in the Linked Data Hub, which facilitates open sharing of linked data from external sources and automated calculation of some evidence codes as Calculator input. ClinGen variant curation expert panel (VCEP) specifications are created, edited, and approved following the ClinGen expert panel process within the Criteria Specification Editor and are publicly-accessible via the Criteria Specification Registry. Criteria specifications are gene and disease specific structured data developed from a combination of empirical analysis and expert recommendations. Calculator 2.0 can use the tailored VCEP-specific gene-condition criteria specifications from the Criteria Specification Registry with a flexible user interface to solicit the required user input and calculate variant pathogenicity scores.

In conclusion, Version 2.0 of the ClinGen Pathogenicity Calculator exemplifies the power of ClinGen API microservices to serve as a platform for rapid development of new applications within and beyond ClinGen. This microservice-oriented model for interface development is particularly relevant for established variant curation and interpretation workflows outside of ClinGen, as they may tap into ClinGen API microservices to accelerate development, leverage ClinGen knowledge within their workflows, and adopt the latest professional guidelines.

Abstract main topic / category:

- Genetic, Genomic, and Epigenomic Resources and Databases

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