ClinVar and ClinGen:
Partners in Curating the Clinical Genome

I. INTRODUCTION

ClinVar and ClinGen, two NIH-based efforts, have formed a critical partnership to improve our knowledge of clinically relevant genomic variation. This partnership includes significant efforts in data sharing, data archiving, and collaborative curation to characterize and disseminate the clinical relevance of genomic variation.

ClinVar

- ClinVar is an archival database that aggregates information about genomic variation and its relationship to human health.
- ClinVar is funded by the Intramural Research Program of the NIH, National Library of Medicine.
- Key ClinVar facts:
    - ClinVar is fully public and freely available.
    - ClinVar is a submission-driven database that holds both primary submissions and expert-curated submissions. The scope of the submission may be as small as a single variant.
    - ClinVar welcomes submissions from clinical testing labs, researchers, locus-specific databases, expert panels, and professional societies.
    - ClinVar adds value to submitted interpretations by standardizing descriptions of variants, conditions, and terms for clinical significance.
        - Variants are mapped to reference sequences and reported in HGVS.
        - Conditions are mapped to concepts in MedGen.
        - Clinical significance terms for Mendelian disorders are reported by ACMG categories.
    - Following variant submission, ClinVar provides a conflict report of any differences in interpretation between their submitted variants and those already in ClinVar.
- More information on ClinVar is available at www.ncbi.nlm.nih.gov/clinvar.

The Clinical Genome Resource (ClinGen)

- ClinGen aims to create an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research.
- ClinGen is funded by the National Human Genome Research Institute (NHGRI), with additional funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Cancer Institute (U41 HG006834, U01 HG007436, U01 HG007437, HHSN261200800001E).
- ClinGen Goals:
    - Share genomic and phenotypic data through centralized databases for clinical and research use
    - Standardize clinical annotation and interpretation of variants
    - Improve understanding of variation in diverse populations

    - Develop machine-learning algorithms to improve the throughput of variant interpretation
    - Implement evidence-based expert consensus for curation of clinical validity
    - Assess the 'medical actionability' of genes and variants to support their use in clinical care systems
    - Disseminate the collective knowledge/resources and ensure EHR interoperability
- More information on ClinGen is available at www.clinicalgenome.org.

II. THE CLINGEN AND CLINVAR PARTNERSHIP

When communicating the extremely close working relationship between ClinGen and ClinVar to researchers, clinicians, and the broader public, it is important to be clear and consistent. The following points should be highlighted:

- ClinGen and ClinVar are close partners and have established a collaborative working relationship. ClinVar has two members on ClinGen's Steering Committee (Melissa Landrum and Steve Sherry) and other NCBI staff participate in various ClinGen Working Groups.
- ClinGen and ClinVar goals are aligned and both projects play a critical role in the growing data sharing movement within the clinical genetics community.
- ClinVar is a critical resource for ClinGen. It serves as the primary site for deposition and retrieval of variant data and annotations from individual labs.
- ClinGen relies on ClinVar as a source for existing data on variants, which are submitted to ClinVar from diverse sources. ClinGen Expert Panels review the data on these variants and submit their standardized interpretations to ClinVar as expert-reviewed records.
- ClinGen is providing input to ClinVar on the structure and layout of the database that is instrumental to its development. However, ClinVar is not subsumed by ClinGen and aims to develop a database and interface that are responsive to all potential users.
- PPT slides summarizing these key points will be developed and shared with ClinGen and ClinVar teams.
- Specific ways in which the two groups are working together:
    - ClinGen provides recommendations to ClinVar related to the underlying data structure and user interface.
    - ClinGen devotes resources to facilitate data submission into ClinVar by soliciting new submissions from many sources as well as working closely with many clinical testing labs and other submitters to map their data to ClinVar fields and structure their submissions in the proper format.
    - The two groups worked closely to develop a star system to define the review level of a submission. This system was launched in ClinVar in July 2015.
    - ClinGen reviews ClinVar Expert Panel applications and sample submissions.
    - ClinGen and NHGRI leadership contributed to the development of ClinVar submission policies and have provided guidance regarding identifiability concerns.
    - ClinVar contributes expertise in numerous areas including development and use of data schemas and ontologies, and appropriate linkages to relevant NCBI resources.

III. PROCESS FOR REQUESTING CLINVAR MODIFICATIONS

ClinGen and ClinVar work very closely to ensure that the underlying data structure and user interface of ClinVar are clear, transparent, and receptive to the needs of the clinical genetics community. ClinGen and ClinVar have a joint weekly call (Friday, noon ET) to discuss these proposed changes.

- Straightforward recommendations that both groups agree upon during a Working Group (WG) call will be immediately added to the NCBI JIRA queue for tracking and processing.
- Recommendations that require deeper consideration by ClinVar will be flagged for additional discussion on a future WG call. This ensures adequate time to carefully consider the impact of proposed modifications. Both groups will return to a future call with a fleshed out proposal and discussion will follow. If consensus is reached the proposal will be added to the JIRA queue.
- Recommendations that have a significant impact on ClinVar may be presented to NCBI's Medical Genetics Working Group of their Board of Scientific Counselors (See Appendix 1 for the roster) for additional input before a decision is made.

APPENDIX 1: NCBI's Medical Genetics Working Group Roster*

Christine Seidman, M.D. - *Chair*
T.W. Smith Professor of Medicine and Genetics
Harvard Medical School
Boston, MA

Leslie Biesecker, M.D.
Senior Investigator and Chief, Genetic Disease Research Branch
National Human Genome Research Institute
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Wendy Chung, M.D., Ph.D.
Herbert Irving Assistant Professor of Pediatrics and Medicine
Director of Clinical Genetics
Columbia University
New York, NY

David S. Konecki, Ph.D.
Senior Scientist/Senior Analyst
GeneDX, Inc.
Gaithersburg, MD

Robert Nussbaum, M.D.
Holly Smith Distinguished Professor in Medicine
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Charmaine D.M. Royal, Ph.D.
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Wendy R. Uhlmann, MS, CGC
Clinical Assistant Professor of Internal Medicine and Human Genetics
Genetic Counselor/Clinic Coordinator, Medical Genetics Clinic
Division of Molecular Medicine & Genetics
University of Michigan Health System
Ann Arbor, MI

Marc S. Williams, MD, FAAP, FACMG
Director, Intermountain Healthcare
Clinical Genetics Institute
Salt Lake City, UT

David Lipman, M.D. - *Executive Secretary*
Director
National Center for Biotechnology Information
National Library of Medicine
National Institutes of Health
Bethesda, MD

* The Medical Genetics Working Group reports to the National Center for Biotechnology Information (NCBI) Board of Scientific Counselors (BSC). The BSC roster is available at http://www.ncbi.nlm.nih.gov/About/glance/science_counselors.html.
* Updated January 2012