GENOMICS IN HEALTH
IMPLEMENTATION FORUM

Welcome to the **Genomics in Health Implementation Forum (GHIF)** Virtual Meeting!

Please note that you will not have access to video or mic when you join.

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

Opening Remarks: Day 1

Kathryn North and Mark Caulfield

Genomics in Health Implementation Forum: GHIF

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GHIF will support the **implementation** and **development** of **GA4GH standards**

In addition, the GHIF will seek to:

- Enable **collective learning** by sharing best practices, challenges, and opportunities with a technical, regulatory, clinical, and educational focus
- Identify areas of **collaboration** and **resource/expertise sharing**
- Advance pilot projects for **global data sharing** using large scale cohorts.

From National Initiatives to GHIF

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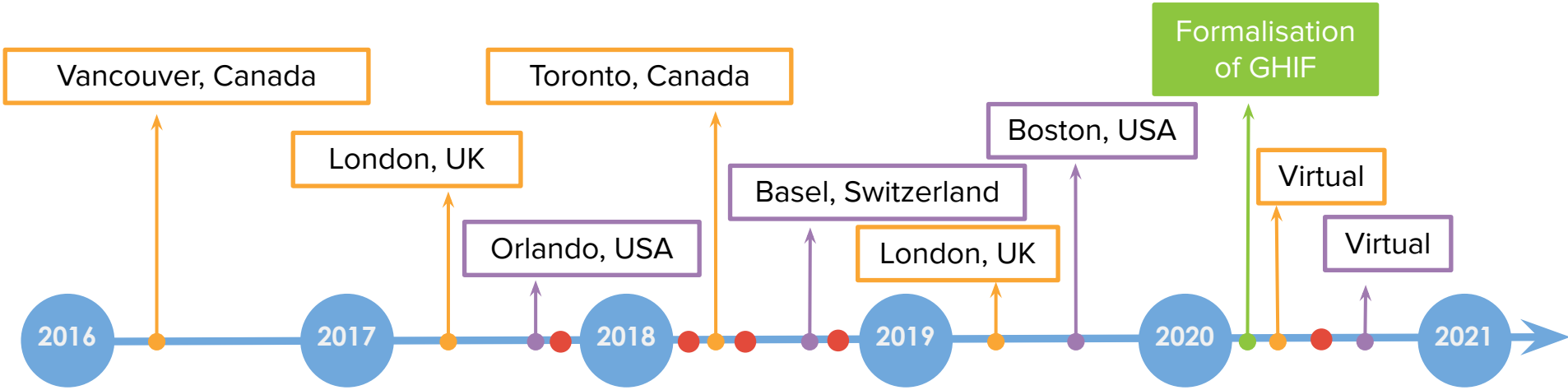

2
foundational members

21
member organisations

From National Initiatives to GHIF - The “Why”

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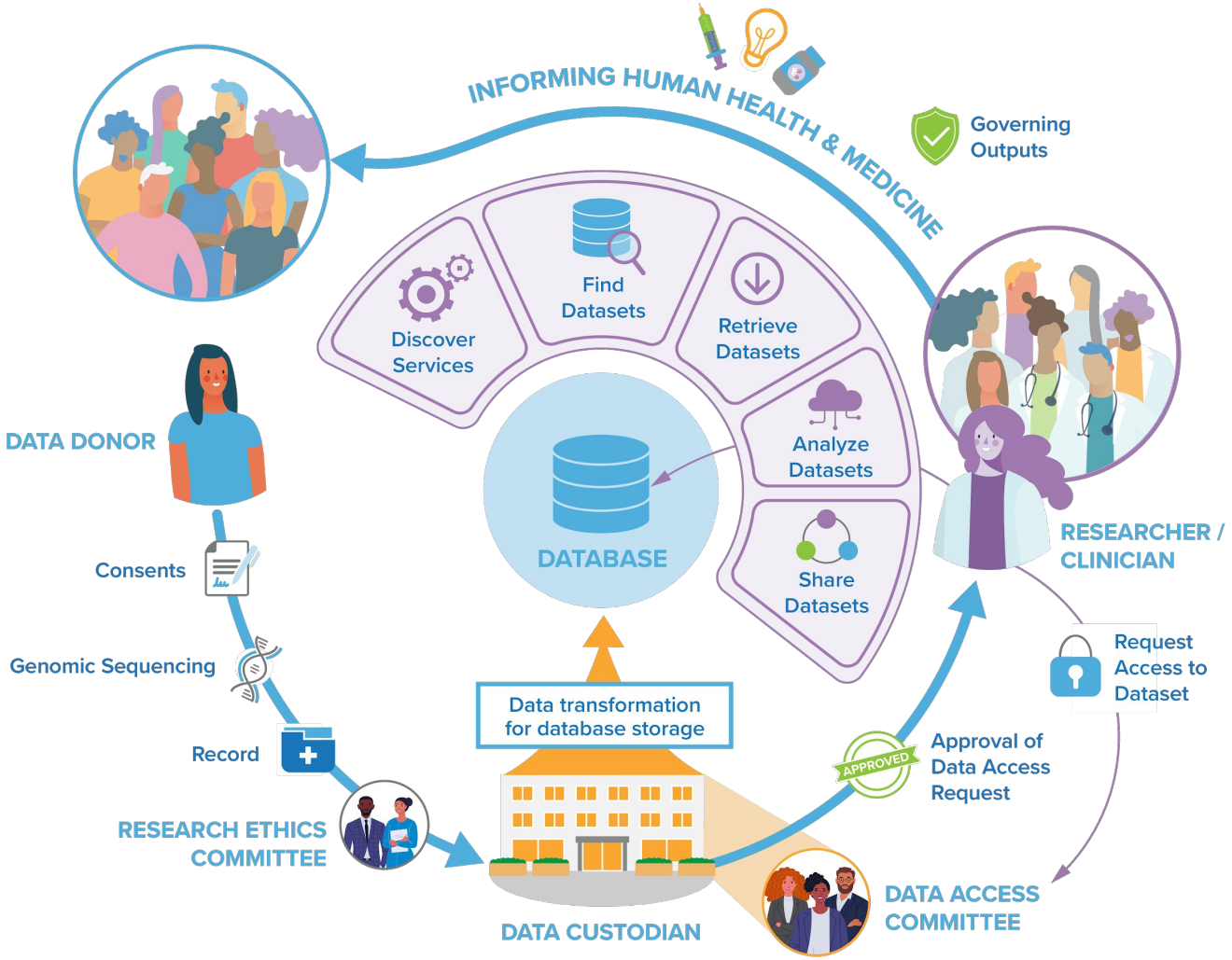
IMPLEMENTATION FORUM

- Ensure that standards **fit needs** across multiple initiatives and healthcare systems
- Increase global membership and involvement in GA4GH, **encouraging diverse input**
- A **scalable** mechanism for incorporating many voices into GA4GH
- A mechanism for bringing standards needs to GA4GH Work Streams for **further development**


INFORMING HUMAN HEALTH & MEDICINE
Governing Outputs
Discover Services
Find Datasets
Retrieve Datasets
Analyze Datasets
Share Datasets
DATABASE
DATA DONOR
Consents
Genomic Sequencing
Record
RESEARCH ETHICS COMMITTEE
Data transformation for database storage
DATA CUSTODIAN
APPROVED
Approval of Data Access Request
Request Access to Dataset
RESEARCHER / CLINICIAN
DATA ACCESS COMMITTEE

The GA4GH Ecosystem

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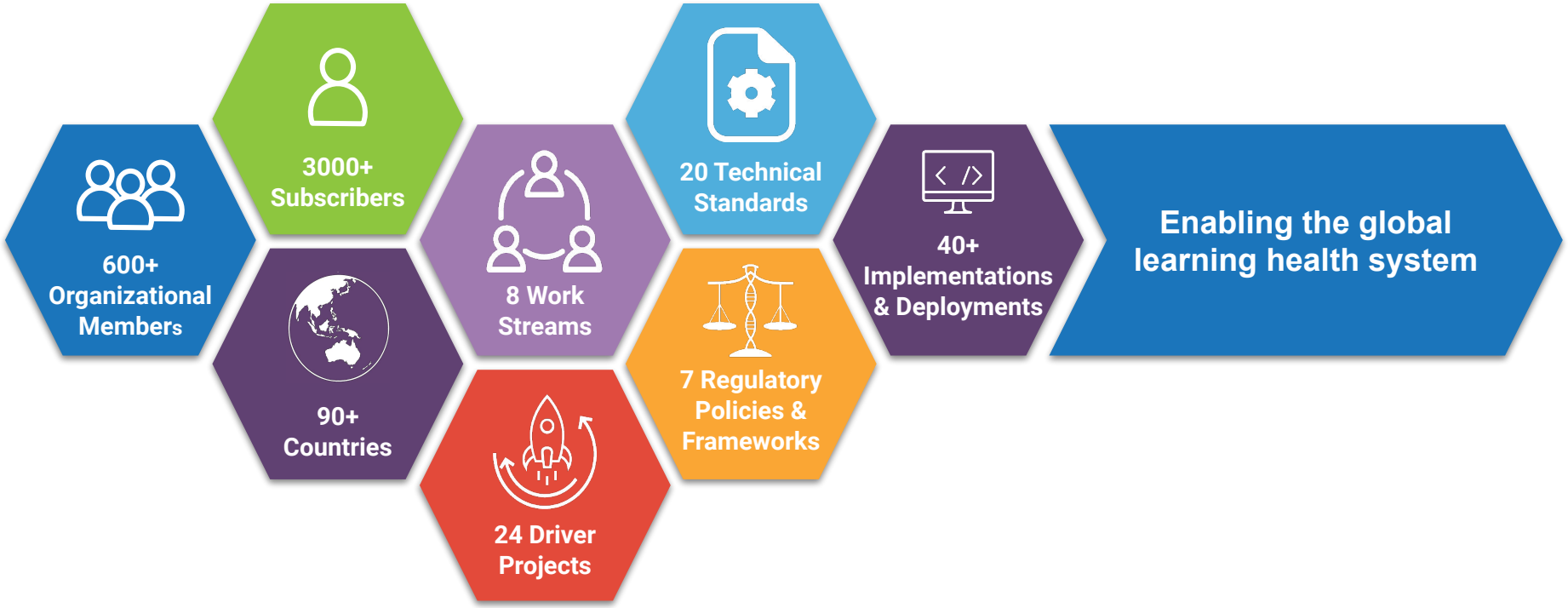
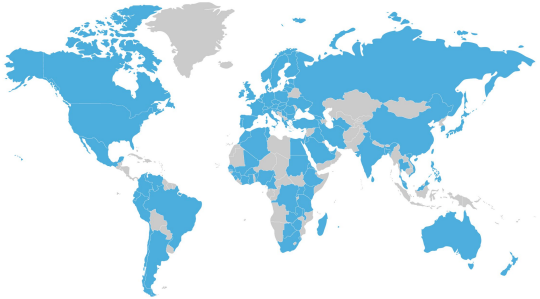


The Global Alliance for Genomics and Health aims to accelerate progress in genomic science and human health by developing standards and policies for responsible genomic and health-related data sharing.



Technical Work Streams

- Discovery
- Large-Scale Genomics
- Data Use & Researcher IDs
- Cloud
- Genomic Knowledge Standards
- Clinical & Phenotypic Data Capture

Foundational Work Streams

- Regulatory & Ethics
- Data Security

Input from Driver Projects as exemplars of community

Output of standards that are taken up by the community

Partner Engagement

RARE DISEASES

Matchmaker Exchange

COMPLEX TRAITS

AUTISM SPEAKS

TOPMed

GEM Japan

Australian Genomics Health Alliance

All of Us Research Program

Genomics England

SPHN

ClinGen

BRCA Exchange

CANCER

ARGO

National Cancer Institute

EU Can Can

VICC Variant Interpretation for Cancer Consortium

elixir

ENA

monarch initiative

epi share

Human Cell Atlas

BASIC BIOLOGY

Real-World Driver Projects

Current GHIF Members

Foundation members:

Australian Genomics Health Alliance

Genomics england

Nordic Alliance for Clinical Genomics

Matchmaker Exchange

Swiss Personalized Health Network

SPHN

AllForOne Canada's Precision Health Partnership

قطر جينوم QATAR GENOME

عضو في مؤسسة قطر Member of Qatar Foundation

ClinGen Clinical Genome Resource

BIPMed Brazilian Initiative on PRECISION MEDICINE

IndiGen Genomics for Public Health in India

H3Africa

CanDIG

International HundredK+ Cohorts Consortium (IHCC)

gms Genomic Medicine Sweden

BIG

elixir

estonian genome center university of tartu

CINECA

Global Genomic Medicine Collaborative

GEM Japan

FINNGEN

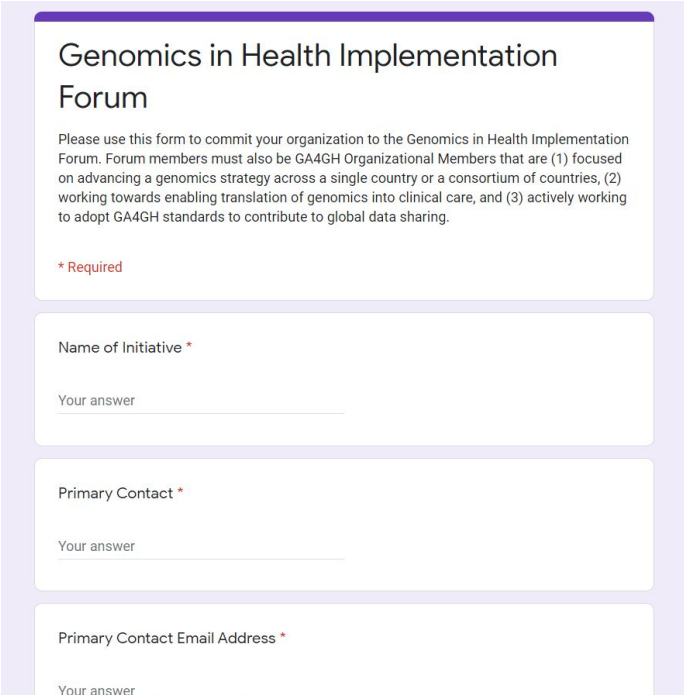
GENOME denmark

Becoming a GHIF Member

GENOMICS IN HEALTH IMPLEMENTATION FORUM

- Short form to ensure that groups meet the criteria for membership
  - Are you a GA4GH organizational member?
  - What is your initiative doing to advance a genomics strategy and implement genomics in healthcare across a single country or a consortium of countries?
  - Which GA4GH technical standards or policy frameworks has your organization adopted in order to contribute to global genomic data sharing? If you have not yet done so already, which GA4GH deliverables are you planning to adopt and when?

- Linked on the GA4GH Website - Community Tab



Genomics in Health Implementation Forum

Please use this form to commit your organization to the Genomics in Health Implementation Forum. Forum members must also be GA4GH Organizational Members that are (1) focused on advancing a genomics strategy across a single country or a consortium of countries, (2) working towards enabling translation of genomics into clinical care, and (3) actively working to adopt GA4GH standards to contribute to global data sharing.

* Required

Name of Initiative *

Your answer

Primary Contact *

Your answer

Primary Contact Email Address *

Your answer

Benefits of GHIF membership

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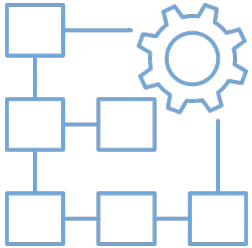
Global learning

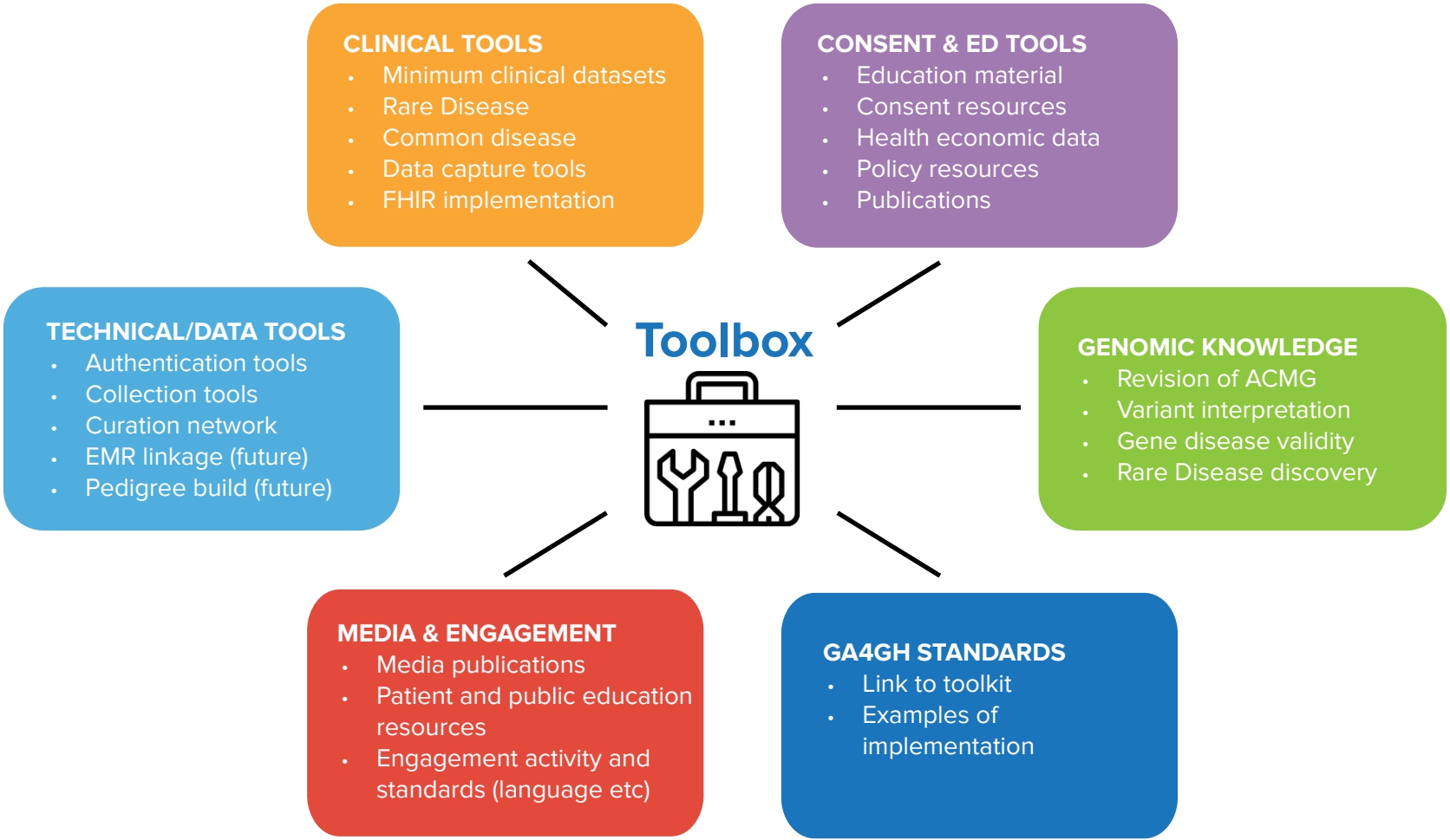
Contribution to GA4GH standards

Access to tools

Potential for collaboration and sharing



Pilot projects


CLINICAL TOOLS
Minimum clinical datasets
Rare Disease
Common disease
Data capture tools
FHIR implementation
CONSENT & ED TOOLS
Education material
Consent resources
Health economic data
Policy resources
Publications
TECHNICAL/DATA TOOLS
Authentication tools
Collection tools
Curation network
EMR linkage (future)
Pedigree build (future)
Toolbox
GENOMIC KNOWLEDGE
Revision of ACMG
Variant interpretation
Gene disease validity
Rare Disease discovery
MEDIA & ENGAGEMENT
Media publications
Patient and public education resources
Engagement activity and standards (language etc)
GA4GH STANDARDS
Link to toolkit
Examples of implementation

Federated Discovery, Access, and Analysis of Global Datasets

Driving improvements in future spec iterations based on real-world lessons

bit.ly/GA4GH-Anna

Meeting Approach

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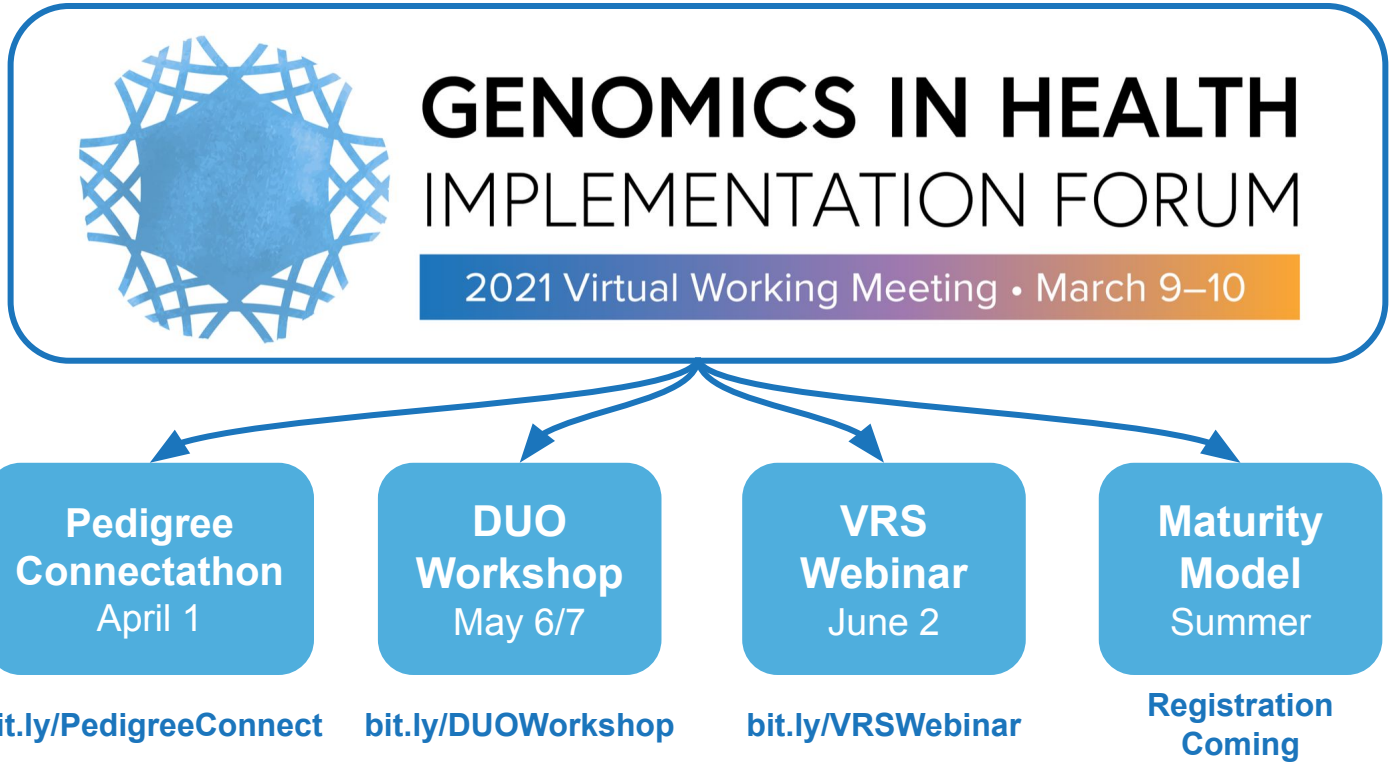


Agenda – Day 1

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

Time (UTC)	Duration	Session Title	Speakers
19:00	10 min	**Opening Remarks**	Kathryn North (AGHA), Mark Caulfield (GEL)
19:10	25 min	**Innovative Approaches to Consent** • Introduction to Data Use Ontology (DUO) • Walkthrough of Policy Submission	Tiffany Boughtwood (AGHA), Jonathan Lawson (Broad Institute)
19:35	20 min	**Application of GA4GH Standards** • GHGA & Medical Genomics in Germany • Medical Genome Initiative (MGI)	• Oliver Stegle (DKFZ/ EMBL) • Shashi Kulkarni (Baylor)
19:55	15 min	**Education and Workforce Training in Genomics** • Restructure of NHGRI Training Programs • African Genomic Medicine Training Initiative (H3A ++)	• Teri Manolio (NHGRI) • Nicola Mulder (H3Africa/H3ABioNet)
20:10	10 min	**Quality Control of WGS Results** • Overview of latest documentation	Oliver Hofmann (AGHA), Mar Gonzalez Porta (Singapore NPM)
20:20	40 min	**Variant Curation** • Shariant: National approaches to knowledge sharing between labs and globally • Clinical Variant Ark : Case-level data in support of variant classification • ClinGen Expert Panels: Development of disease-specific expert consensus to knowledge curation	• Amanda Spurdle (AGHA/BRCA)) • Augusto Rendon (GEL) • Heidi Rehm (MGH/Broad Institute)

Agenda – Day 2

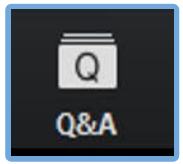
GENOMICS IN HEALTH
IMPLEMENTATION FORUM

Time (UTC)	Duration	Session Title	Speakers
19:00	5 min	**Opening Remarks**	Kathryn North (AGHA), Mark Caulfield (GEL)
19:05	15 min	**Clinical and Phenotypic Data Capture & Exchange - Pedigree & Family Health History** • Introduction to the GA4GH Pedigree Standard and Upcoming Connectathon	Grant Wood (Intermountain), Orion Buske (PhenoTips)
19:20	15 min	**Clinical Interoperability of Variant Evidence**	Alex Wagner (VICC/Nationwide), Larry Babb (Broad Institute)
19:35	25 min	**Getting Clinic Ready** • Accrediting Whole Genomes for Patient Care • Application of CLIA/CAP Standards to Genomic Testing	• Ellen Thomas (GEL) • David Bick (HudsonAlpha)
20:00	15 min	**Building a Framework for the Adoption of GA4GH Standards** • GA4GH::ELIXIR Maturity Model	Melissa Konopko (ELIXIR)
20:15	35 min	**End-to-End Implementations of GA4GH Standards** • Acute Care • GEL Diagnostics Highlights • GA4GH Connections Demo	• Zornitza Stark (AGHA) • Richard Scott (GEL) • Jeremy Adams (GA4GH)
20:50	10 min	**Closing**	Kathryn North (AGHA), Mark Caulfield (GEL)

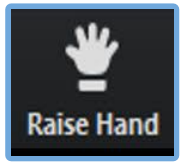
We encourage you to participate!

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

Please use **Q&A** to ask questions during plenary sessions

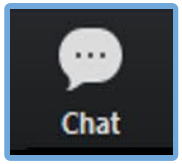


Use the **Raise Hand** button if you would like to make a verbal question or comment



Continue discussions using **Chat**

Please ensure your message is set to "All panelists and attendees"



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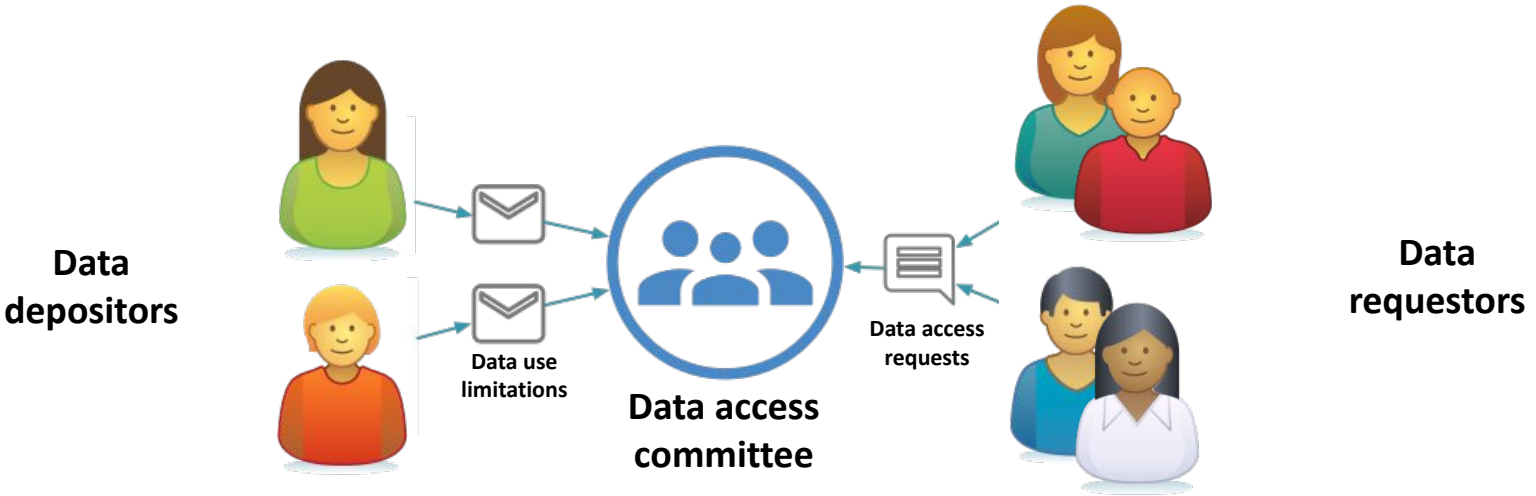
Innovative Approaches to Consent

Data Use Ontology (DUO)

Jonathan Lawson, Broad Institute
Tiffany Boughtwood, Australian Genomics

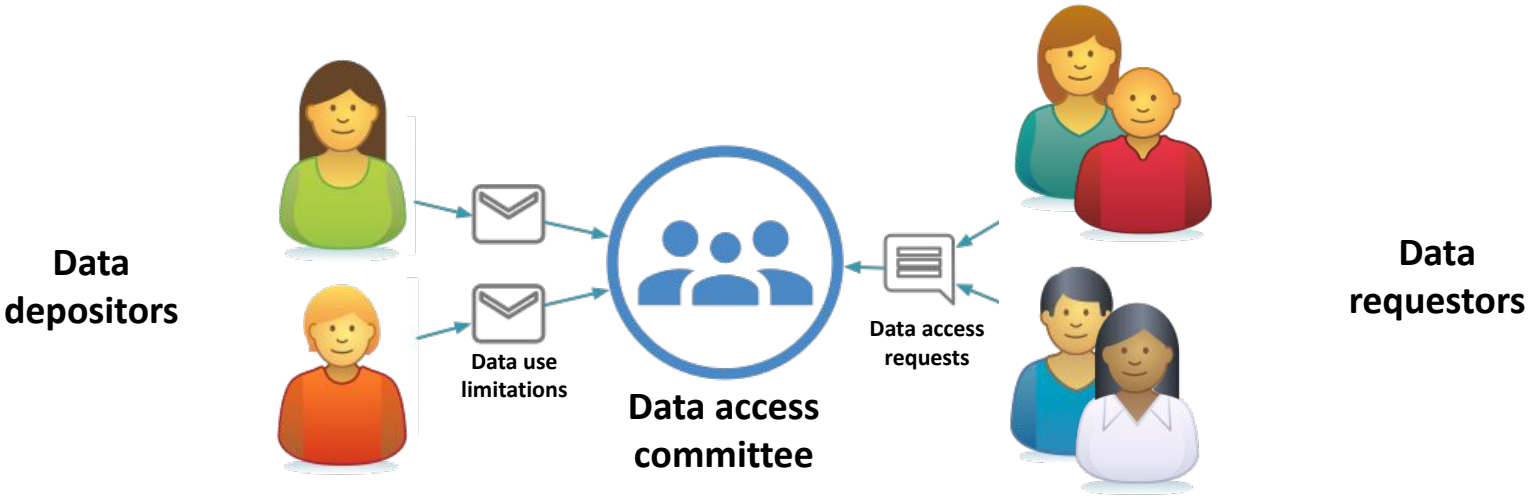
DUO Introduction

Current Data Sharing Model



DUO Introduction

The Challenge



Unique and diverse language in consent forms need to be interpreted by researchers and data access committees

The process to request access to human data is time-consuming. Length of the process hinders maximum data reuse.

Data Use Ontology

Global Alliance for Genomics & Health

DUO is use case driven

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IMPLEMENTATION FORUM

- Small, lightweight resource, evolves with projects and needs
- Clear textual definitions
  - augmented with examples of usage, comments, translations in progress (Japanese, French, Spanish, German)
- Provides automated, machine-readable coding
  - Stable terms and IDs
  - Unambiguous description of datasets restrictions for DACs
  - Leveraging ontological hierarchy

Data Use Ontology

Global Alliance for Genomics & Health

DUO terms overview

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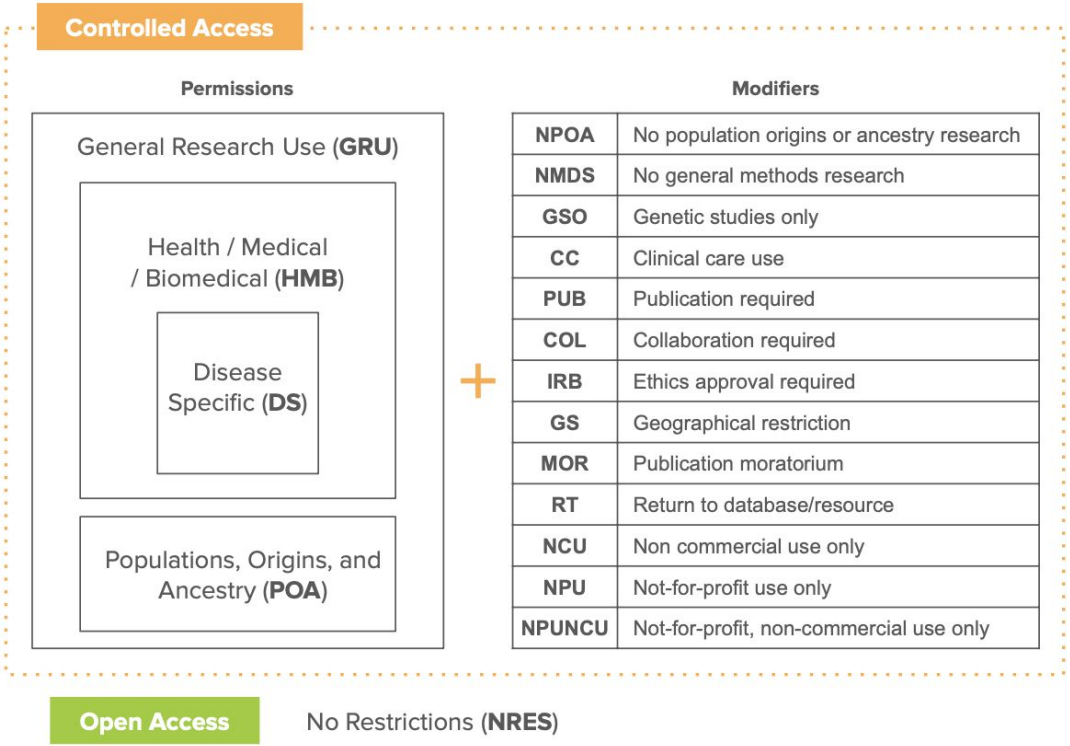
Permissions terms for expressly permitted uses or focused areas of research.

Modifiers terms add requirements, limitations, or prohibitions within the permitted boundary



DUO is a GA4GH standard

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Data
Use
Ontology

- Unanimously approved Jan 2019 as a GA4GH product
- Community contributions
- Scope to promote data sharing
  - Governance policy guides evolution
- DUO IDs are stable, resource is versioned
- Latest release is ***always*** at http://purl.obolibrary.org/obo/duo.owl

Technical backend – simple and reliable

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Open GitHub repository, http://purl.obolibrary.org/obo/duo

Includes consistency tests

Unified issue tracker, http://purl.obolibrary.org/obo/duo/tracker/

Uses GH tag for each release, http://purl.obolibrary.org/obo/duo/releases/

Versioning

- Use of a CNAME + PURL
- Previously released versions remain available (eg http://purl.obolibrary.org/obo/duo/releases/2017-01-31/duo.owl)
- Latest release is *always* at http://purl.obolibrary.org/obo/duo.owl

Data Use Ontology

Global Alliance for Genomics & Health

GENOMICS IN HEALTH
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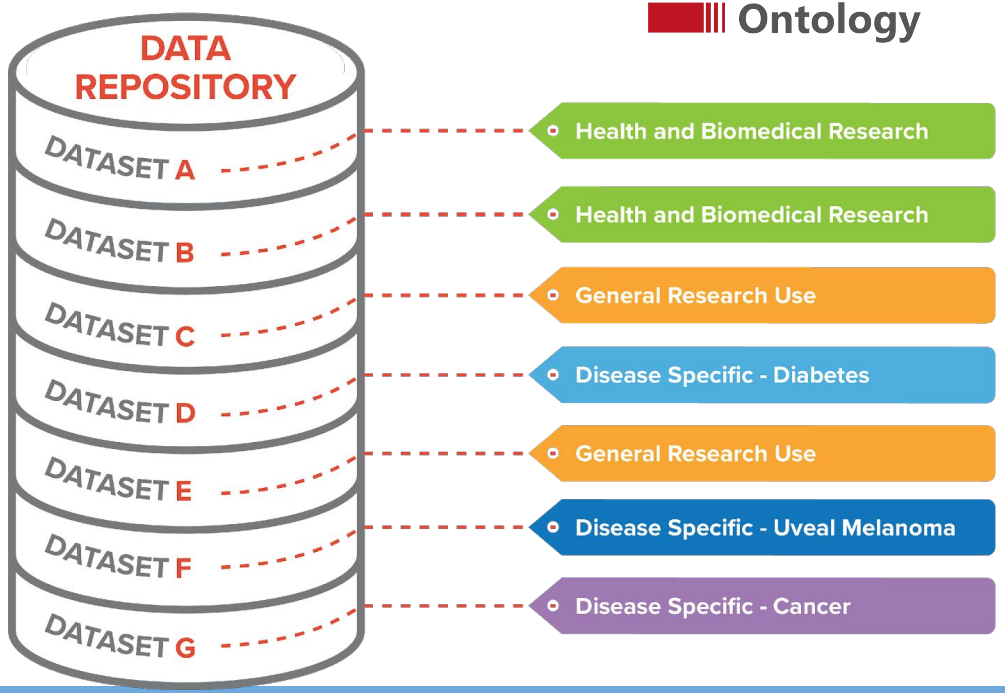
DUO In Action

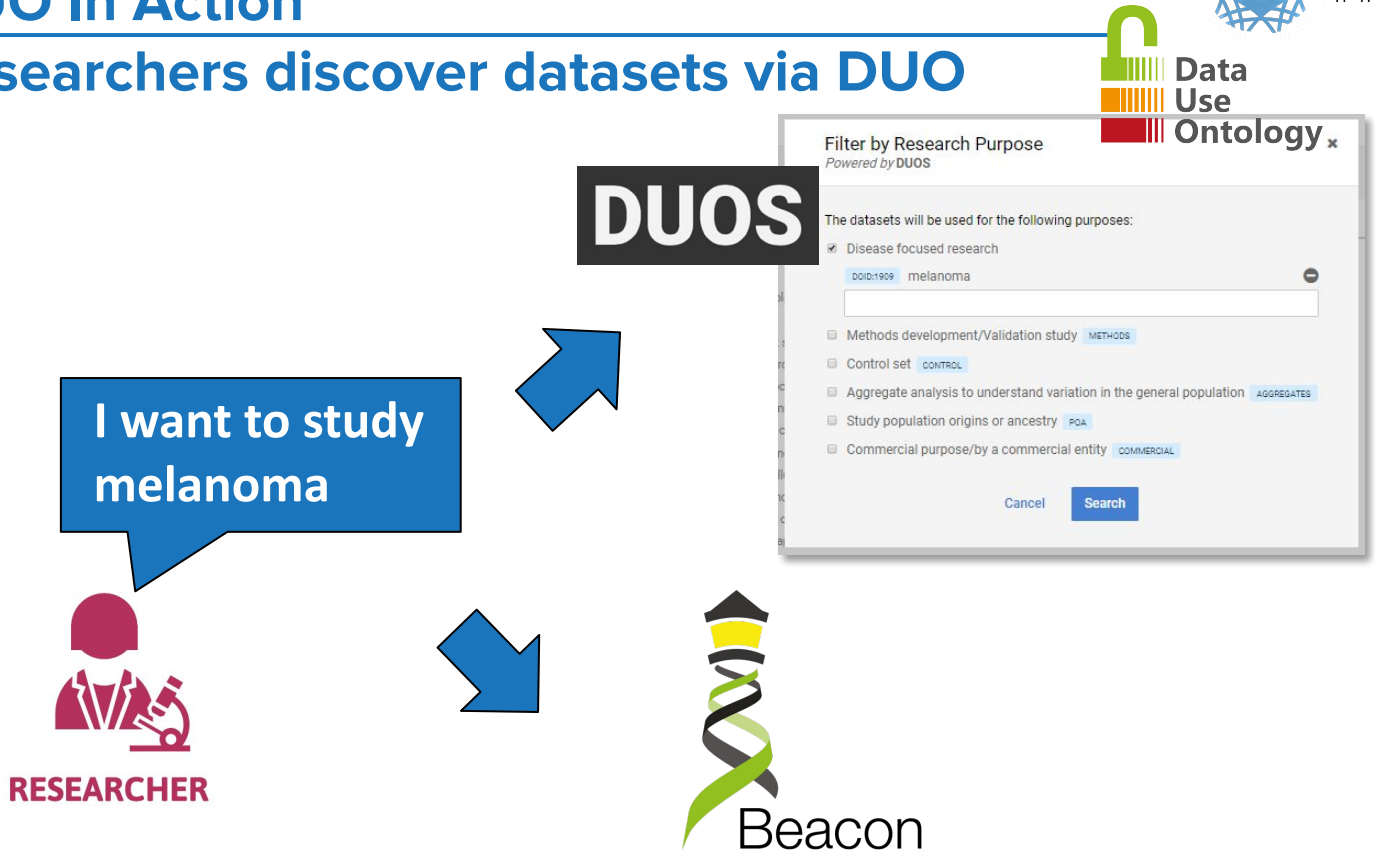
Data repositories tag datasets

Data Use Ontology



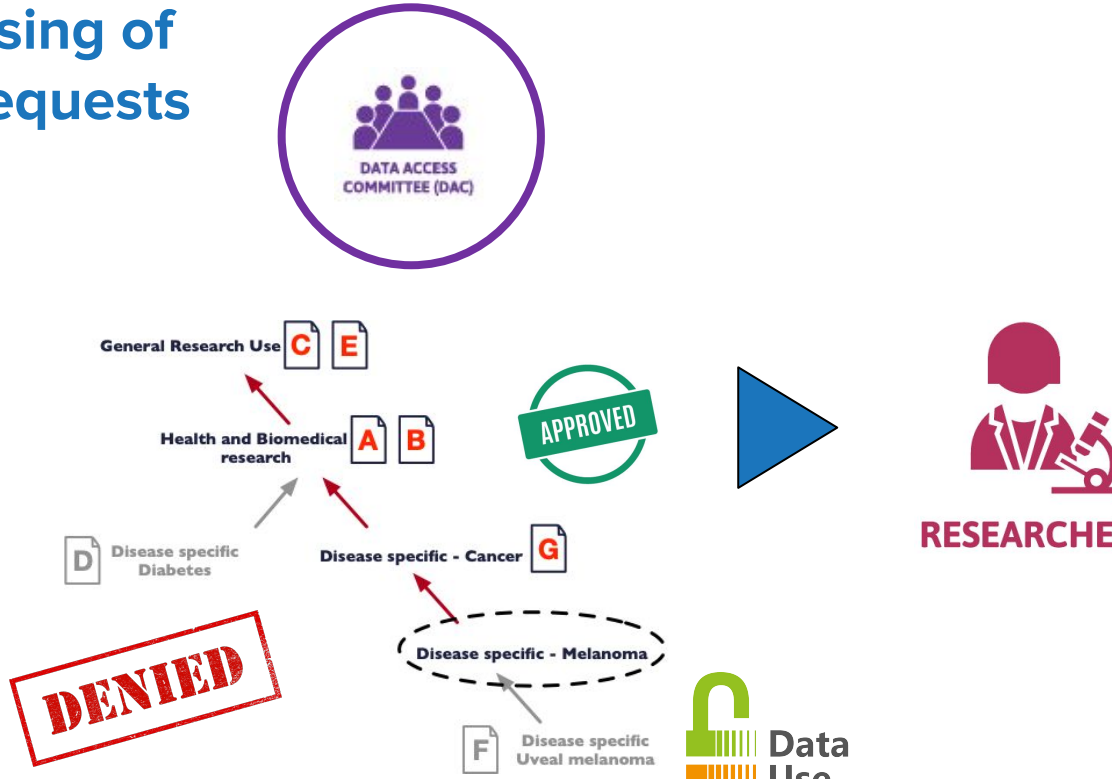
DUO In Action

Researchers discover datasets via DUO



DUO In Action

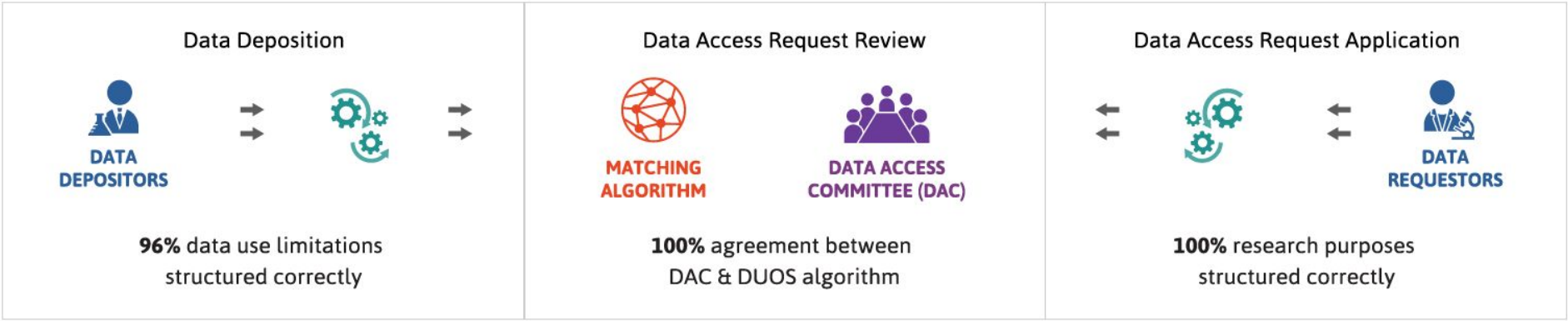
Faster processing of data access requests



Data Use Ontology

DUO Implementations

DUOS

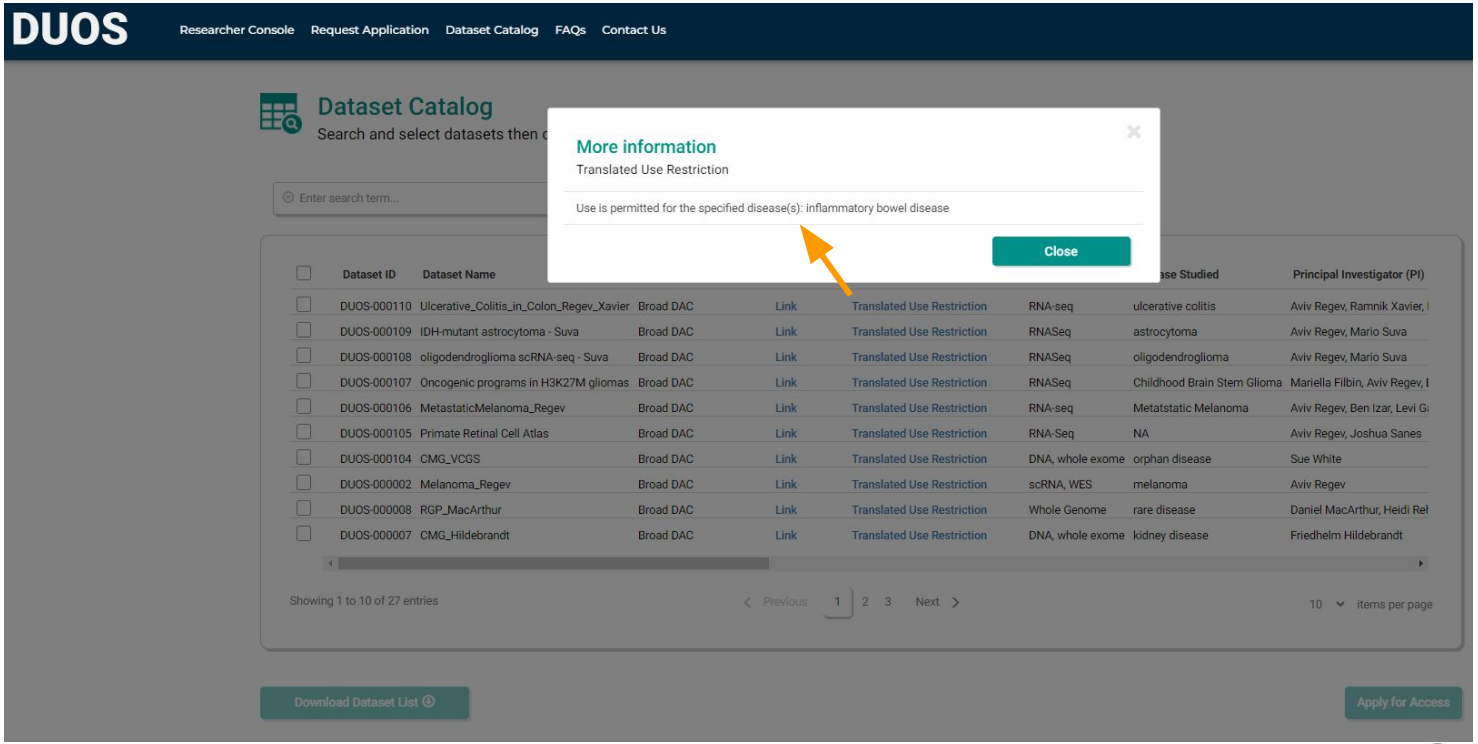


Questions:
DUOS@broadinstitute.org

https://duos.broadinstitute.org/#/home

DUO Implementations

DUOS: Dataset Catalog



DUO Implementations

DUOS: Data Access Request Form

2.7 Data Use Acknowledgements*

Please confirm listed acknowledgements and/or document requirements below

- [ ] I acknowledge that I have selected a dataset limited to use on genetic studies only (GSO). I attest that I will respect this data use condition.

- [ ] I acknowledge that I have selected a dataset which requires results of studies using the data to be made available to the larger scientific community (PUB). I attest that I will respect this data use condition.

- [ ] I acknowledge that the dataset can only be used in research consistent with the Data Use Limitations (DULs) and cannot be combined with other datasets of other phenotypes. Research uses inconsistent with the DUL are considered a violation of the Data Use Certification agreement and any additional terms described in the Addendum.

One or more of the datasets you selected requires local IRB approval for use. Please upload your local IRB approval(s) here as a single document. When IRB approval is required and Expedited or Full Review is required and must be completed annually. Determinations of Not Human Subjects Research (NHSR) by IRBs will not be accepted as IRB approval.

Upload File

One or more of the datasets you selected requires collaboration (COL) with the primary study investigator(s) for use. Please upload documentation of your collaboration here.

Upload File

DUO Implementations

DUOS: DAC Review

APPLICATION SUMMARY

Structured Research Purpose

Primary:

DS The dataset will be used for disease related studies (neurodegenerative disease; cardiovascular system disease; Alzheimer's disease; Parkinson's disease; cancer; melanoma; frontotemporal dementia)

DAR machine-readable format

Data Use Structured Limitations

Use is permitted for the specified disease(s): alcohol dependence

DUL machine-readable format

Data Use Letter

QUESTION 1:

Should data access be granted to this applicant?

YOUR VOTE*

○ YES ◉ NO

RATIONALE

OPTIONAL: Describe your rationale or add comments here

GENOMICS IN HEALTH IMPLEMENTATION FORUM

Data Use Ontology

Global Alliance for Genomics & Health

DUO Implementations

Participant-directed DUO: Machine Readable Consent Guidance

- Guidance on **how to create a consent form that maps directly and unambiguously to the GA4GH DUO**, which renders the consent machine-readable.
- **Three elements**:
  - A short consent clause providing a summary description of the data use term(s);
  - A detailed explanation of the meaning of the data use term(s), to ensure they are understood by the consented individual; and
  - An optional consent form appendix that unambiguously maps the consent language to specific data use term(s) in the GA4GH DUO.

DUO Implementations

Participant-directed DUO: Machine Readable Consent Guidance

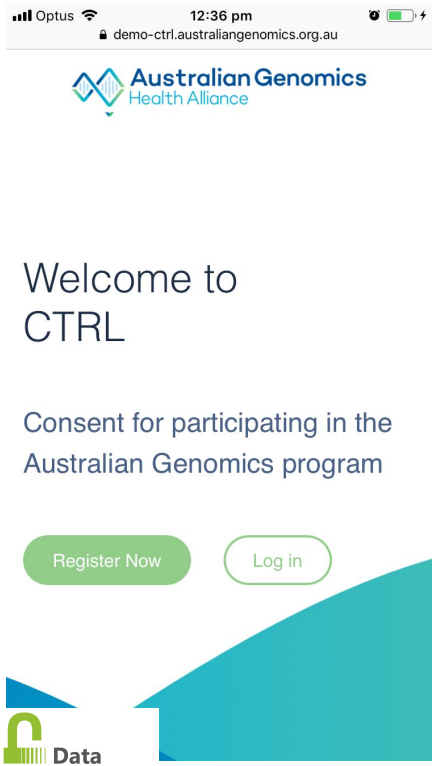
Included DUO codes / consent form elements:

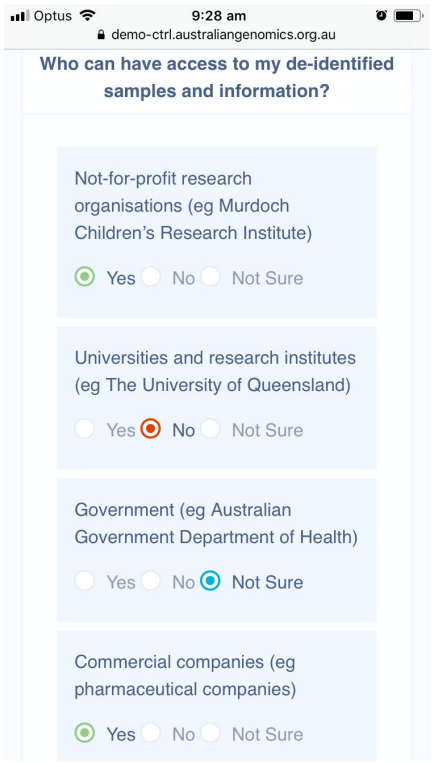
- General Research Use (DUO:0000042)
- Health/Medical/Biomedical Research Use (DUO:0000006)
- Disease Specific Research Use (DUO:0000007)
- Population Origins or Ancestry Research Use (DUO:0000011)
- No Restriction on Use (i.e., Open Data) (DUO:0000004)
- Research Ethics Approval Required (DUO:0000021)
- Not-for-Profit Use Only (DUO:0000018)

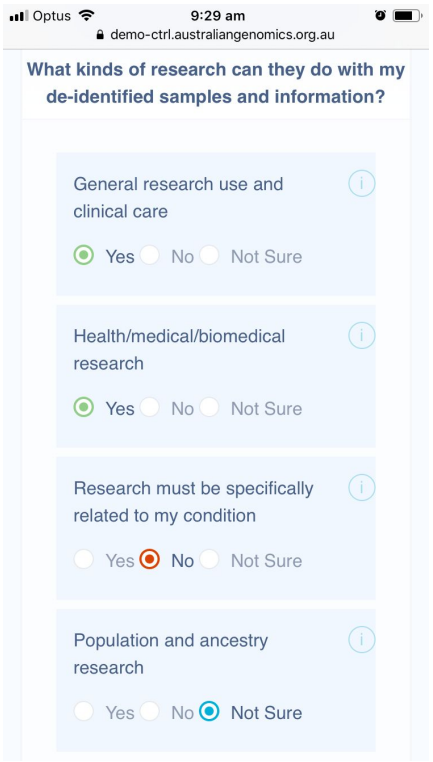
Key considerations, risks and implications of the DUO codes are highlighted in the document document to guide those drafting consent forms

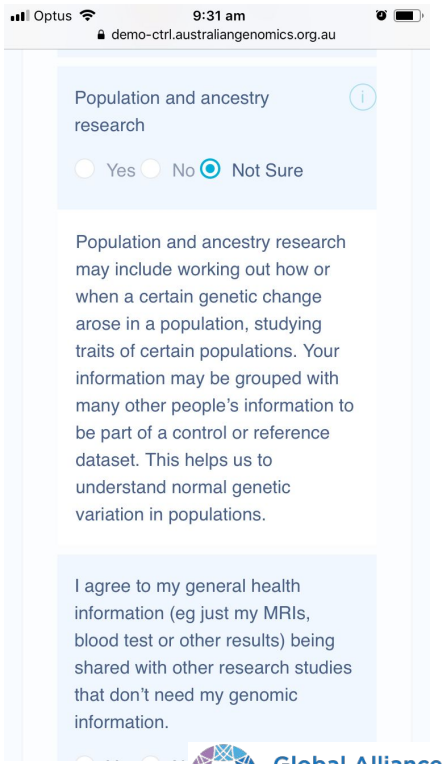
DUO Implementations

Participant-directed DUO: CTRL 'Control'

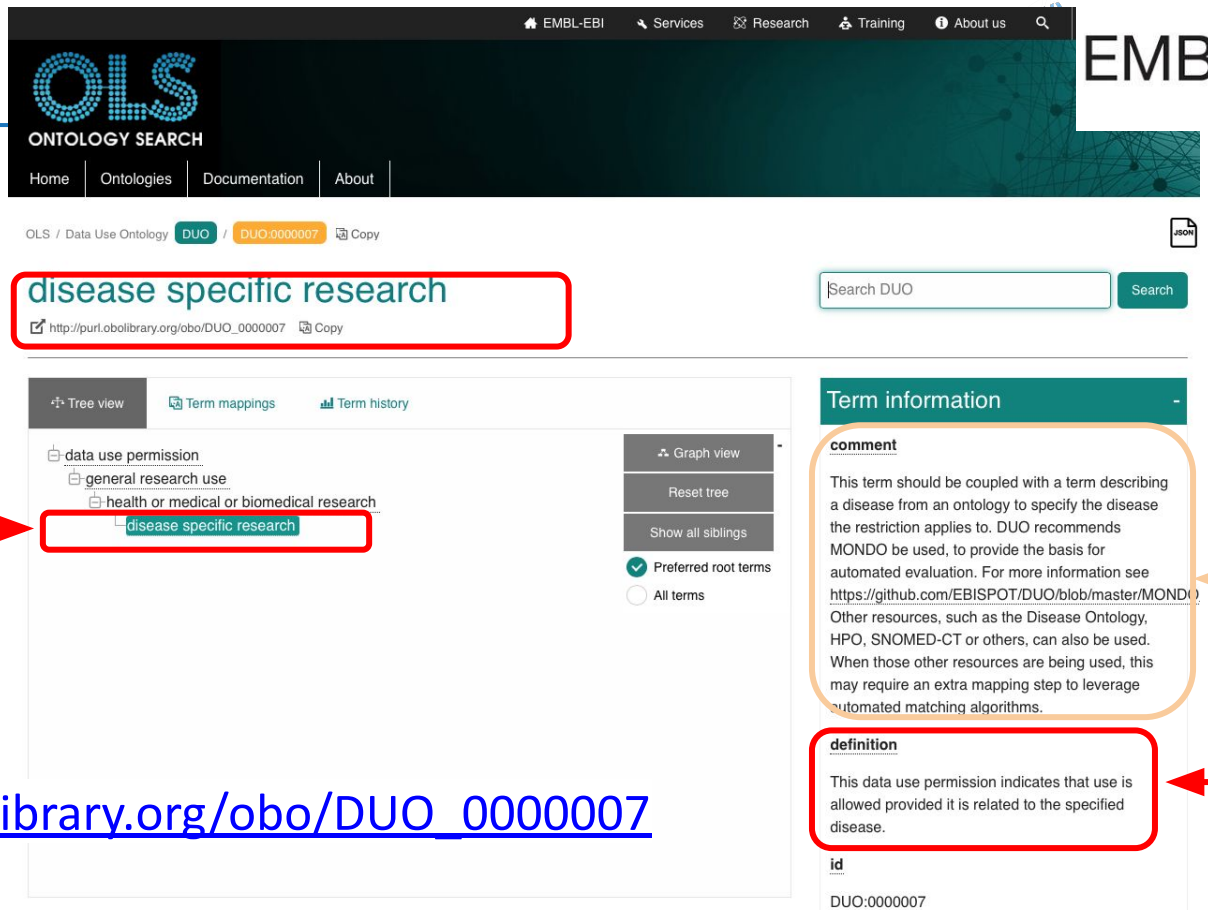








Questions: Dr. Matilda Haas m.haas@australiangenomics.org.au



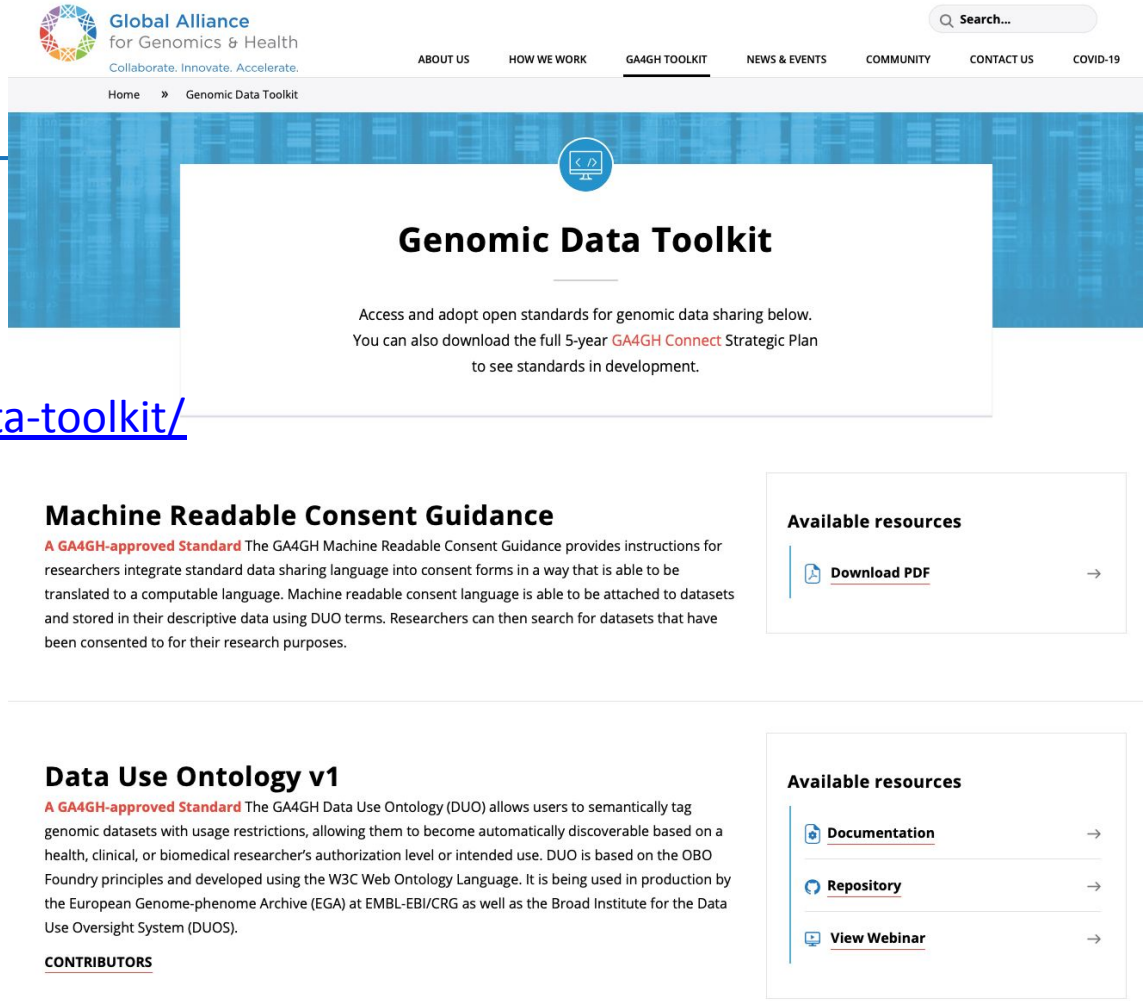
http://purl.obolibrary.org/obo/DUO_0000007

Data Use Ontology

Global Alliance for Genomics & Health

GA4GH
Genomic data toolkit

https://www.ga4gh.org/genomic-data-toolkit/



Data Use Ontology

DUO Implementation – BY YOUR INITIATIVE

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- How do I get started?
- How do I map my consent to DUO?
- What are the technical implications?
- Who can I ask for assistance?

Data Use Ontology

Global Alliance for Genomics & Health

DUO Workshop

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- Workshop purposes:
    - **facilitate uptake of DUO by assisting new adopters**;
    - **expand our international DUO community**
- **May 6 or 7** (depending on best timing for most attendees)
- Submit questions / data sharing language / data use restrictions from the consent forms or data sharing plans **AT REGISTRATION**.

Data Use Ontology

Global Alliance for Genomics & Health

DUO Workshop

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

Optional Consent for Future Research

I also provide consent to:

- Share my sample and information collected through this study, with all personal information removed and replaced with a study code, with other ethically approved research that may or may not be related to this research project.

  ☐ **Yes** ☐ **No** ❱ ***If you want to decide what kinds of future research your information is shared for, and the organisations it is shared with, please select 'yes' and then register to CTRL to make your choices.***

- Being contacted about other related research projects in the future that I may be eligible for. If interested in taking part, I will be asked to sign a separate consent form.

  ☐ **Yes** ☐ **No**

Workshop registration form

Please submit your consent clauses as a list in the box below, using square brackets to separate multiple clauses (eg. [clause],[clause],[clause]...)

If you are unsure of how to extract clauses/policies, please review the slide deck here: http://bit.ly/DUOSubmission. If you require additional assistance, please reach out to lindsay.smith@ga4gh.org.

Your answer

Additional Comments

Your answer

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

Optional Consent for Future Research

I also provide consent to:

- Share my sample and information collected through this study, with all personal information removed and replaced with a study code, with other ethically approved research that may or may not be related to this research project.

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  ☐ **Yes** ☐ **No**

Workshop registration form

Please submit your consent clauses as a list in the box below, using square brackets to separate multiple clauses (eg. [clause],[clause],[clause]...)

If you are unsure of how to extract clauses/policies, please review the slide deck here: http://bit.ly/DUOSubmission. If you require additional assistance, please reach out to lindsay.smith@ga4gh.org.

Your answer

Additional Comments

Your answer

DUO Workshop

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

- Workshop activities:
    - **Address questions**
    - **Work through examples of mapping data use clauses to DUO**
- Note the registration closing date, as we will proceed with / time the workshop based on interest and registrations

Data Use Ontology

Global Alliance for Genomics & Health

Thanks & Contacts

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

- Jonathan Lawson jlawson@broadinstitute.org
- Tiffany Boughtwood t.boughtwood@australiangenomics.org.au
- Melanie Courtot mcourtot@ebi.ac.uk *thanks for the slides!
- Giselle Kerry kerryg@ebi.ac.uk
- Jaime Guidry Auvil jaime.guidryauvil@nih.gov
- Lindsay Smith Lindsay.smith@ga4gh.org

- And all the DUO contributors: https://github.com/EBISPOT/DUO#contribution

Data Use Ontology

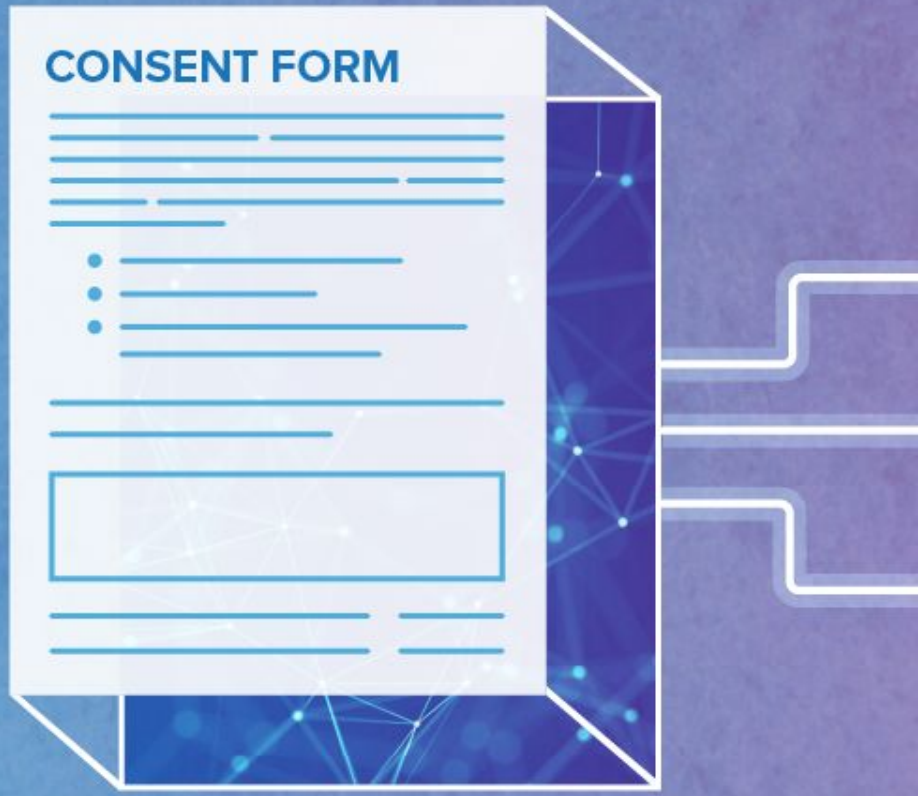
Global Alliance for Genomics & Health

Data Use Ontology

DUO WORKSHOP

May 6 or 7 (depending on best timing for attendees)

- Facilitate uptake of DUO by assisting new adopters
- Expand international DUO community
- Submit questions, data sharing language, data use restrictions, or data sharing plans at registration!



Register:

bit.ly/DUOWorkshop

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

Application of GA4GH Standards

The Medical Genome Initiative

Moving whole-genome sequencing for rare disease diagnosis to the clinic

Shashikant Kulkarni, M.S. (Medicine), PhD, FACMG

Chair, Medical Genome Initiative

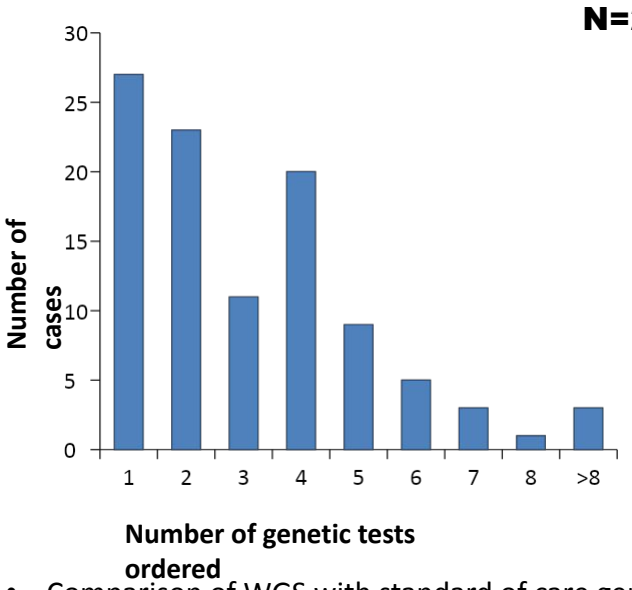
Professor & Vice Chairman for Research

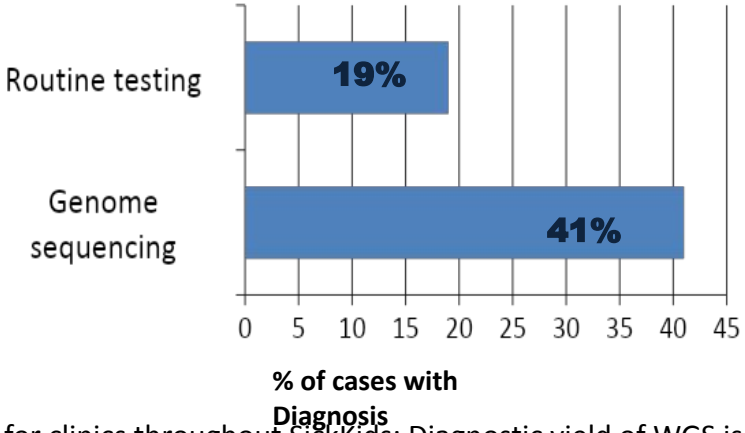
Department of Molecular and Human Genetics

Baylor College of Medicine, Houston, TX

THE MEDICAL GENOME INITIATIVE

Improved diagnostic rates in a single test





- Comparison of WGS with standard of care genetic testing for clinics throughout SickKids: Diagnostic yield of WGS is 41% (73/203) compared with 19% (38/203) using standard testing
- Average of **3** genetic tests per patient; microarray analysis the most utilized
- **Increased yield due to off-target genes but also non-coding (intronic, miRNA) and small copy number changes not detected with other standard methods**

Lionel A. et al Genet Med (2017), Stavropoulos et al. NPJ Gen Med (2016)

THE MEDICAL GENOME INITIATIVE

Diagnostic Utility of WGS as a first-line genetic test

- WGS may be a useful first line genetic test but **Clinical Validation of WGS** is challenging and there are no clear standards in place
- Professional bodies have made progress but specific challenges not addressed

THE MEDICAL GENOME INITIATIVE

Medical Genome Initiative

Launched February 2019

- **Mission:** Expand access to high-quality **clinical whole-genome sequencing** for the diagnosis of **rare genetic germline disease**, through the establishment of common laboratory and clinical **best practices**
- **Goals:** Develop and publish laboratory & clinical best practices for implementing clinical WGS for the benefit of others looking to set up the test
- **Membership:** Consortium made up of institutions which have deployed clinical genome sequencing technology for the diagnosis of those with rare germline disorders

Medical Genome Initiative Consortium Members

BAYLOR GENETICS

BROAD INSTITUTE

illumina

HUDSONALPHA INSTITUTE FOR BIOTECHNOLOGY

MAYO CLINIC

NEW YORK GENOME CENTER | Collaboration Research Discovery

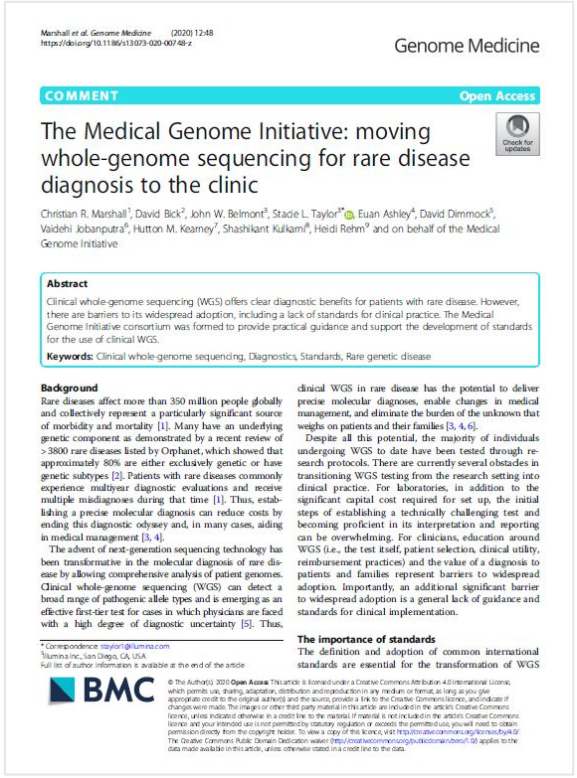
Rady Children's Institute Genomic Medicine

SickKids THE HOSPITAL FOR SICK CHILDREN

Stanford MEDICINE

Roadmap & Working groups

Designing, Validating and Performing Genomic Testing Requires Many Linked Steps



Marshall et al. Genome Medicine (2020) 12:48
https://doi.org/10.1186/s13073-020-00748-z

Genome Medicine

COMMENT Open Access

The Medical Genome Initiative: moving whole-genome sequencing for rare disease diagnosis to the clinic

Christian R. Marshall[1], David Bick[2], John W. Belmont[3], Stacie L. Taylor[4*], Euan Ashley[4], David Dimmock[5], Vaidehi Jobanputra[6], Hutton M. Kearney[7], Shashikant Kulkarni[8], Heidi Rehm[9] and on behalf of the Medical Genome Initiative

Abstract

Clinical whole-genome sequencing (WGS) offers clear diagnostic benefits for patients with rare disease. However, there are barriers to its widespread adoption, including a lack of standards for clinical practice. The Medical Genome Initiative consortium was formed to provide practical guidance and support the development of standards for the use of clinical WGS.

Keywords: Clinical whole-genome sequencing, Diagnostics, Standards, Rare genetic disease

Background

Rare diseases affect more than 350 million people globally and collectively represent a particularly significant source of morbidity and mortality [1]. Many have an underlying genetic component as demonstrated by a recent review of > 3800 rare diseases listed by Orphanet, which showed that approximately 80% are either exclusively genetic or have genetic subtypes [2]. Patients with rare diseases commonly experience multiyear diagnostic evaluations and receive multiple misdiagnoses during that time [1]. Thus, establishing a precise molecular diagnosis can reduce costs by ending this diagnostic odyssey and, in many cases, aiding in medical management [3, 4].

The advent of next-generation sequencing technology has been transformative in the molecular diagnosis of rare disease by allowing comprehensive analysis of patient genomes. Clinical whole-genome sequencing (WGS) can detect a broad range of pathogenic allele types and is emerging as an effective first-tier test for cases in which physicians are faced with a high degree of diagnostic uncertainty [5]. Thus, clinical WGS in rare disease has the potential to deliver precise molecular diagnoses, enable changes in medical management, and eliminate the burden of the unknown that weighs on patients and their families [3, 4, 6].

Despite all this potential, the majority of individuals undergoing WGS to date have been tested through research protocols. There are currently several obstacles in transitioning WGS testing from the research setting into clinical practice. For laboratories, in addition to the significant capital cost required for set up, the initial steps of establishing a technically challenging test and becoming proficient in its interpretation and reporting can be overwhelming. For clinicians, education around WGS (i.e., the test itself, patient selection, clinical utility, reimbursement practices) and the value of a diagnosis to patients and families represent barriers to widespread adoption. Importantly, an additional significant barrier to widespread adoption is a general lack of guidance and standards for clinical implementation.

The importance of standards

The definition and adoption of common international standards are essential for the transformation of WGS

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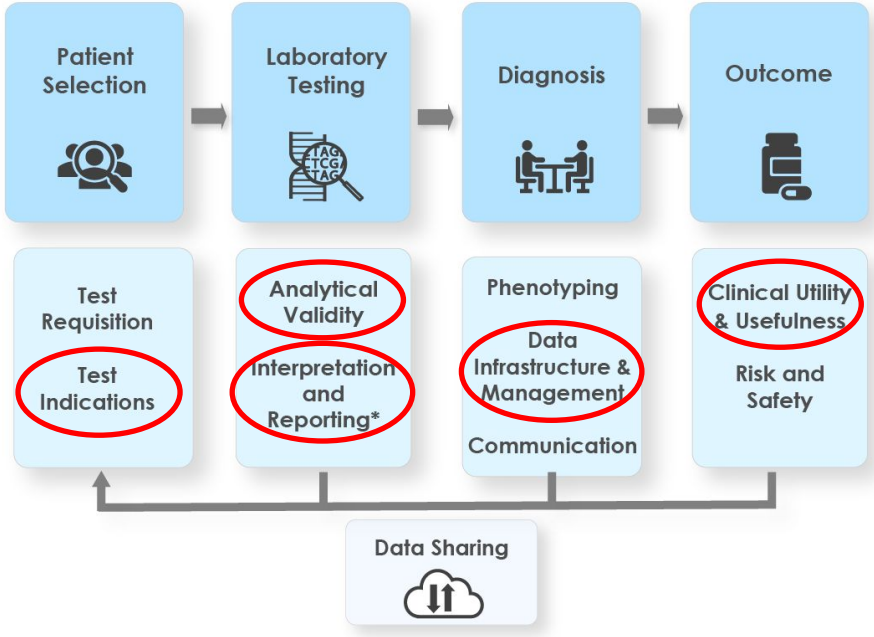
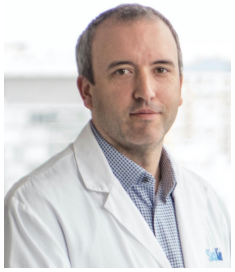


Marshall CM. et al NPJ Gen Med (2020)

THE MEDICAL GENOME INITIATIVE

Analytical Validation Working Group



Christian Marshall
The Hospital for Sick Children

npj | Genomic Medicine

www.nature.com/npjgenmed

REVIEW ARTICLE OPEN

Check for updates

Best practices for the analytical validation of clinical whole-genome sequencing intended for the diagnosis of germline disease

Christian R. Marshall[1✉], Shimul Chowdhury[2], Ryan J. Taft[3], Mathew S. Lebo[4,5], Jillian G. Buchan[6,14], Steven M. Harrison[4,5], Ross Rowsey[7], Eric W. Klee[7,8], Pengfei Liu[9], Elizabeth A. Worthey[10,15], Vaidehi Jobanputra[1,12], David Dimmock[4], Hutton M. Kearney[7], David Bick[10], Shashikant Kulkarni[9,13], Stacie L. Taylor[4], John W. Belmont[3], Dimitri J. Stavropoulos[1], Niall J. Lennon[5] and Medical Genome Initiative*

Whole-genome sequencing (WGS) has shown promise in becoming a first-tier diagnostic test for patients with rare genetic disorders; however, standards addressing the definition and deployment practice of a best-in-class test are lacking. To address these gaps, the Medical Genome Initiative, a consortium of leading healthcare and research organizations in the US and Canada, was formed to expand access to high-quality clinical WGS by publishing best practices. Here, we present consensus recommendations on clinical WGS analytical validation for the diagnosis of individuals with suspected germline disease with a focus on test development, upfront considerations for test design, test validation practices, and metrics to monitor test performance. This work also provides insight into the current state of WGS testing at each member institution, including the utilization of reference and other standards across sites. Importantly, members of this initiative strongly believe that clinical WGS is an appropriate first-tier test for patients with rare genetic disorders, and at minimum is ready to replace chromosomal microarray analysis and whole-exome sequencing. The recommendations presented here should reduce the burden on laboratories introducing WGS into clinical practice, and support safe and effective WGS testing for diagnosis of germline disease.

npj Genomic Medicine (2020)5:47; https://doi.org/10.1038/s41525-020-00154-9

INTRODUCTION

Advances in next-generation sequencing (NGS) over the past decade have transformed genetic testing by increasing diagnostic yield and decreasing the time to reach a diagnosis[1–5]. Targeted NGS multigene panels have come into widespread use and whole-exome sequencing (WES) is a powerful aid in the diagnosis of patients with nonspecific phenotypic features[6–10] and critically ill neonates[11], where the differential diagnosis often includes multiple rare genetic disorders[12]. These approaches, however, have both workflow and test content limitations that may constrain their overall efficacy.

Whole-genome sequencing (WGS) can address many of the technical limitations of other enrichment-based NGS approaches, including improved coverage[13,14] and sensitivity for the detection of structural and complex variants[15]. WGS also enables the identification of noncoding variants, such as pathogenic variations disrupting regulatory regions, noncoding RNAs, and mRNA splicing[16–18]. Emerging uses of WGS include HLA genotyping[19], pharmacogenetic testing[20], and generation of polygenic risk scores[21]. Several studies have demonstrated the advantages of WGS for the identification of clinically relevant variants in a wide range of cohorts[22–26], and have shown the diagnostic superiority of WGS compared with conventional testing in pediatric patients[27–29] and critically ill infants[30,31]. As a more efficient test, WGS is poised to replace targeted NGS or WES and chromosomal microarray (CMA) as a first-line laboratory approach in the evaluation of children and adults with a suspected genetic disorder[28,32,33]. WGS also has the benefit of periodic reanalysis across multiple variant types, which will increase diagnostic efficacy through updated annotation and analysis techniques[34].

Although the stage is set for widespread adoption of clinical WGS, technical challenges remain, and standards that address both the definition and the deployment practices of a best-in-class clinical WGS test have not been fully defined. Professional bodies have made progress in providing guidance for clinical WGS test validation[35,36], and best practices for benchmarking with reference standards and recommended accuracy measures are beginning to emerge[37–39]. It is important to note, however, that these recommendations do not address the specific challenges related to the setup of clinical WGS.

SCOPE AND METHODS

To address these challenges, a working group comprised of experts from the Medical Genome Initiative[40] was created to develop practical recommendations related to the analytical

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- **Rationale**
  - No standards or consensus as to what constitutes a clinical WGS test nor what performance metric thresholds must be met
- **Goal**
  - Define analytic metrics and thresholds for WGS that show no loss in performance compared to microarray and whole-exome sequencing
- **Status**
  - Published
  - Currently inactive
  - Plans to reinstate and expand group to tackle more topics in depth (e.g., repeat expansions)

THE MEDICAL GENOME INITIATIVE

Clinical Utility Working Group

Robin Hayeems
The Hospital for Sick Children

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REVIEW ARTICLE OPEN

Check for updates

Clinical utility of genomic sequencing: a measurement toolkit

Robin Z. Hayeems[1,2], David Dimmock[3], David Bick[3], John W. Belmont[4], Robert C. Green[5], Brendan Lanpher[6], Vaidehi Jobanputra[7,8], Roberto Mendoza[9], Shashi Kulkarni[10,11], Megan E. Grove[12], Stacie L. Taylor[3], Euan Ashley[12] and Medical Genome Initiative*

Whole-genome sequencing (WGS) is positioned to become one of the most robust strategies for achieving timely diagnosis of rare genomic diseases. Despite its favorable diagnostic performance compared to conventional testing strategies, routine use and reimbursement of WGS are hampered by inconsistencies in the definition and measurement of clinical utility. For example, what constitutes clinical utility for WGS varies by stakeholder's perspective (physicians, patients, families, insurance companies, health-care organizations, and society), clinical context (prenatal, pediatric, critical care, adult medicine), and test purpose (diagnosis, screening, treatment selection). A rapidly evolving technology landscape and challenges associated with robust comparative study design in the context of rare disease further impede progress in this area of empiric research. To address this challenge, an expert working group of the Medical Genome Initiative was formed. Following a consensus-based process, we align with a broad definition of clinical utility and propose a conceptually-grounded and empirically-guided measurement toolkit focused on four domains of utility: diagnostic thinking efficacy, therapeutic efficacy, patient outcome efficacy, and societal efficacy. For each domain of utility, we offer specific indicators and measurement strategies. While we focus on diagnostic applications of WGS for rare germline diseases, this toolkit offers a flexible framework for best practices around measuring clinical utility for a range of WGS applications. While we expect this toolkit to evolve over time, it provides a resource for laboratories, clinicians, and researchers looking to characterize the value of WGS beyond the laboratory.

npj Genomic Medicine (2020)5:56; https://doi.org/10.1038/s41525-020-00164-7

INTRODUCTION

Whole-genome sequencing (WGS) is poised to exert a profound influence on clinical care by ushering individualized genomic medicine into routine practice. While technical and interpretive complexities remain, WGS is emerging as one of the most robust strategies for achieving timely diagnoses in undiagnosed rare disease populations[1–4]. However, for a diagnostic test such as WGS to be accepted into practice, commissioned in a health system, or receive coverage and reimbursement through health insurance, evidence of clinical utility and cost-effectiveness is generally required[5–8]. Unlike prospective clinical research where the 'effectiveness' of an intervention can be easily tied to a predefined health outcome, the concept of clinical utility in genetic medicine is rarely uniformly defined nor necessarily directly tied to a specific health outcome. As such, generating and evaluating evidence of clinical utility is complex. The challenge in defining clinical utility today is compounded by the extraordinary heterogeneity of rare diseases, as well as the polygenic nature of more common conditions for which WGS is expected to be relevant. In this paper, we aim to extend earlier conceptualizations of clinical utility as applied to the diagnostic use of WGS and suggest that this framework not only be used as a tool for evidence review[9–11], but as a tool for measurement best practices. Our recommendations are intended for investigators, policy advisory bodies, payors, and health-care systems committed to providing value-based care and improving health and non-health related outcomes through the use of WGS at scale.

Early conceptualizations of clinical utility related to genetic testing emerged from work at the Centers for Disease Control[12]. The "ACCE" framework described analytical validity, clinical validity, clinical utility, and ethical implications as core components to evaluate before recommending genetic testing. Clinical utility was defined as the effect of genetic testing on "the balance of benefits and harms associated with the use of the test in practice, including improvement in measurable clinical outcomes and the usefulness or added value in decision-making compared with not using the test." In the ACCE framework, a series of questions relating to test characteristics, health impacts, economic impacts, education, and implementation considerations are used to guide literature assessment[13].

In the years that followed the development of the ACCE framework, scholars, professional groups, and payors continued to refine the dimensions and definitions of clinical utility. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (EWG), for example, adapted a model proposed by Tatsioni et al.[14], which itself was adapted from Fryback and Thornbury's hierarchical model of efficacy for diagnostic tests[15]. In this model, the outcomes of interest for a test were organized into four groups: diagnostic and prognostic thinking, therapeutic choice, patient impact, and familial and societal impact. To organize and score the evidence reviewed, the

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- **Rationale**
  - Generating and evaluating evidence of clinical WGS is complex (i.e., effectiveness of clinical WGS is not easily tied to a predefined health outcome)
- **Goal**
  - Develop a measurement toolkit to offer resources and practical guidance using objective and validated measures
- **Status**
  - Published
  - Currently inactive

THE MEDICAL GENOME INITIATIVE

Patient Selection/Indication Working Group

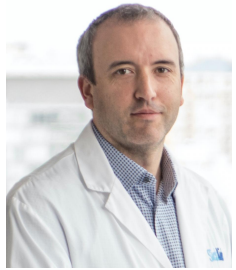
- **Rationale**
  - Selecting patients for whom clinical WGS would offer the **most** benefit can be challenging for healthcare providers
- **Goal**
  - Develop evidence based and consensus-driven best practice recommendations for which patient groups should receive clinical WGS as a first-tier test
- **Method**
  - Clinician survey of current use
  - Systematic evidence review
  - Expert opinion
- **Status**
  - ACTIVE
  - Ongoing working group discussions
  - Estimated publication date: August 2021

Kristen Wigby
Rady Children's

THE MEDICAL GENOME INITIATIVE

Data Infrastructure & Management Working Group

- **Rationale**
  - Guidance and recommendations for what infrastructure is needed to set up clinical WGS are lacking due to the rapid pace at which the field is developing
- **Goal**
  - Describe *current solutions* and develop best practice recommendations for storage and management of the large volume of sequence and health data generated by clinical WGS
  - High level overview,
- **Method**
  - Very high-level overview, target audience are laboratories in the initial stages of setting up clinical WGS
  - Divide into 4 domains
    - Informatics
    - Software development and deployment
    - Information management technology
    - Data security
- **Status**
  - ACTIVE
  - Estimated publication date: August 2021



Christian Marshall
The Hospital for Sick Children
THE MEDICAL GENOME INITIATIVE

Test Interpretation & Reporting Working Group

- **Rationale**
  - Guidance on how best to prioritize detection of variants relevant to the clinical phenotype while minimizing the return of highly uncertain or clinical irrelevant results are lacking
- **Goal**
  - Develop recommendations for selecting and validating appropriate tools to detect and analyze the full range of variant types that can be captured by clinical WGS
- **Method**
  - Requisition/Consent
  - Annotations
  - Analysis
  - Case and Variant Interpretation
  - Reporting
  - Reanalysis
- **Status**
  - ACTIVE
  - Estimated publication date: June 2021

Chrissy Austin-Tse
Broad/Harvard

Vaidehi Jobanputra
New York Genome Center

THE MEDICAL GENOME INITIATIVE

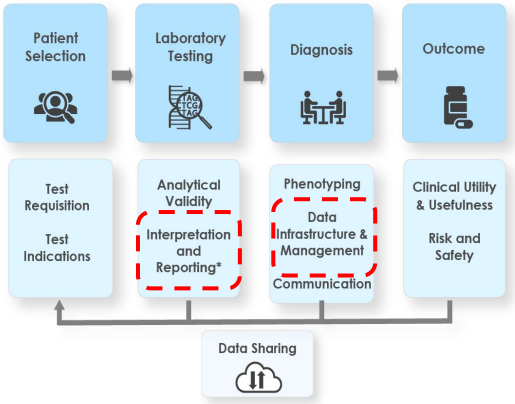
Future Directions

- Complete and publish manuscripts from active working groups
- Reinstate inactive working groups where there is interest and bandwidth
- Revise roadmap to include future topics of interest and work products
  - E.g., Implementation, reimbursement
  - E.g., Webinars, community discussion forums
- Expand membership to capture global representation and perspectives
  - Individual contributor
  - Institutional membership
- Engage with other initiatives and consortia to identify synergistic areas leading to potential collaboration
  - GA4GH
  - GHIF

Opportunities for GA4GH Collaboration

GA4GH standards and tools will be adopted and inform the Medical Genome Initiative

Medical Genome Initiative Working Group	Relevant GA4GH Workstream(s)	Comments
Data Infrastructure and Management	• Data security • Genomic knowledge standards • Large scale genomics • Data use and researcher identities	• File formats • Data privacy and security policy • Variant annotation/representation
Test Interpretation and Reporting	• Regulatory and Ethics • Genomic Knowledge Standards	• Consent Toolkit & Policy • Return of results – Survey of stakeholder perspectives • Variant annotation/representation



THE MEDICAL GENOME INITIATIVE

Acknowledgements

Shashi Kulkarni
Baylor Medicine
Chair

Hutton Kearney
Mayo Clinic

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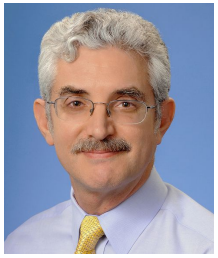
Stanford Medicine

Heidi Rehm
Broad Institute



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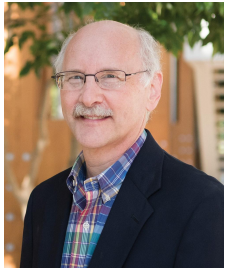
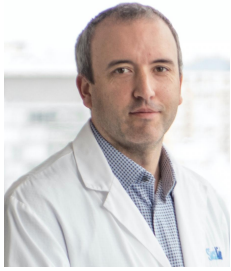


David Bick
HudsonAlpha Institute for Biotechnology

David Dimmock
Rady Children's Institute for Genomics

Vaidehi Jobanputra
New York Genome Center



Christian Marshall
The Hospital for Sick Children

THE MEDICAL GENOME INITIATIVE

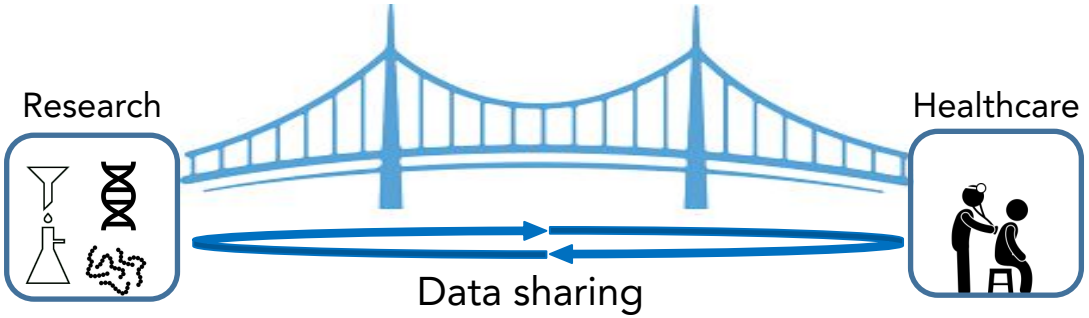
GHGA and its role for Genome Medicine in Germany

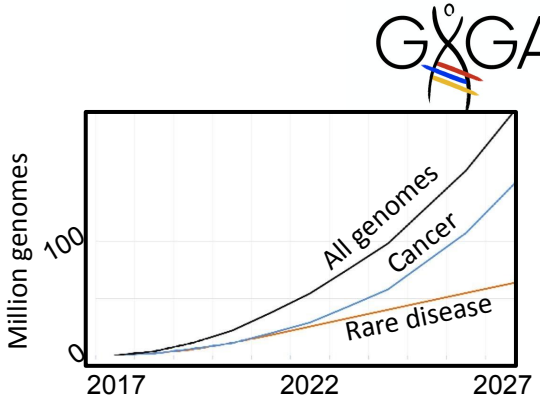
Oliver Stegle

German Cancer Research Center & European Molecular Biology Laboratory

on behalf of the GHGA Directorate

The Vision - Enabling Genomic Medicine



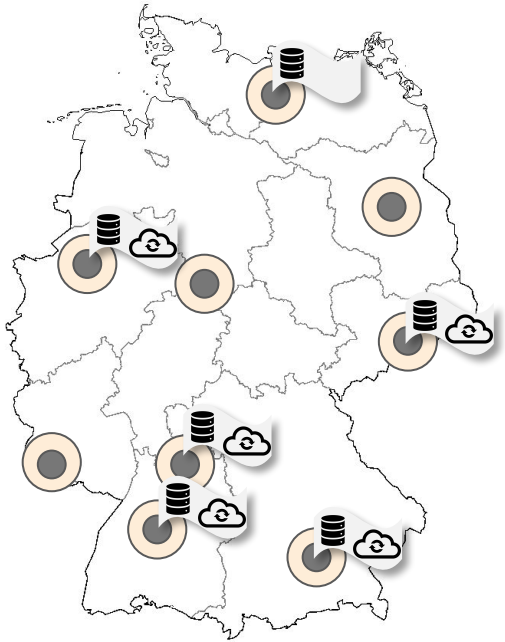


- Secondary use of clinical omics data in research: biological discovery & replication of findings to show validity
- Rapid - exponential - growth of available data is a major challenge and opportunity
- Translation of research insights: delivering value in genomic medicine

- Requires a nationally coordinated infrastructure that integrates genome research and healthcare

Who we are

- One of the nine first-round NFDI consortia
- Network of data hubs co-located with major academic sequencing centers
- German national node within the federated European Genome-Phenome Archive (EGA)
- Connected to national cloud infrastructure (de.NBI cloud) for large-scale analyses



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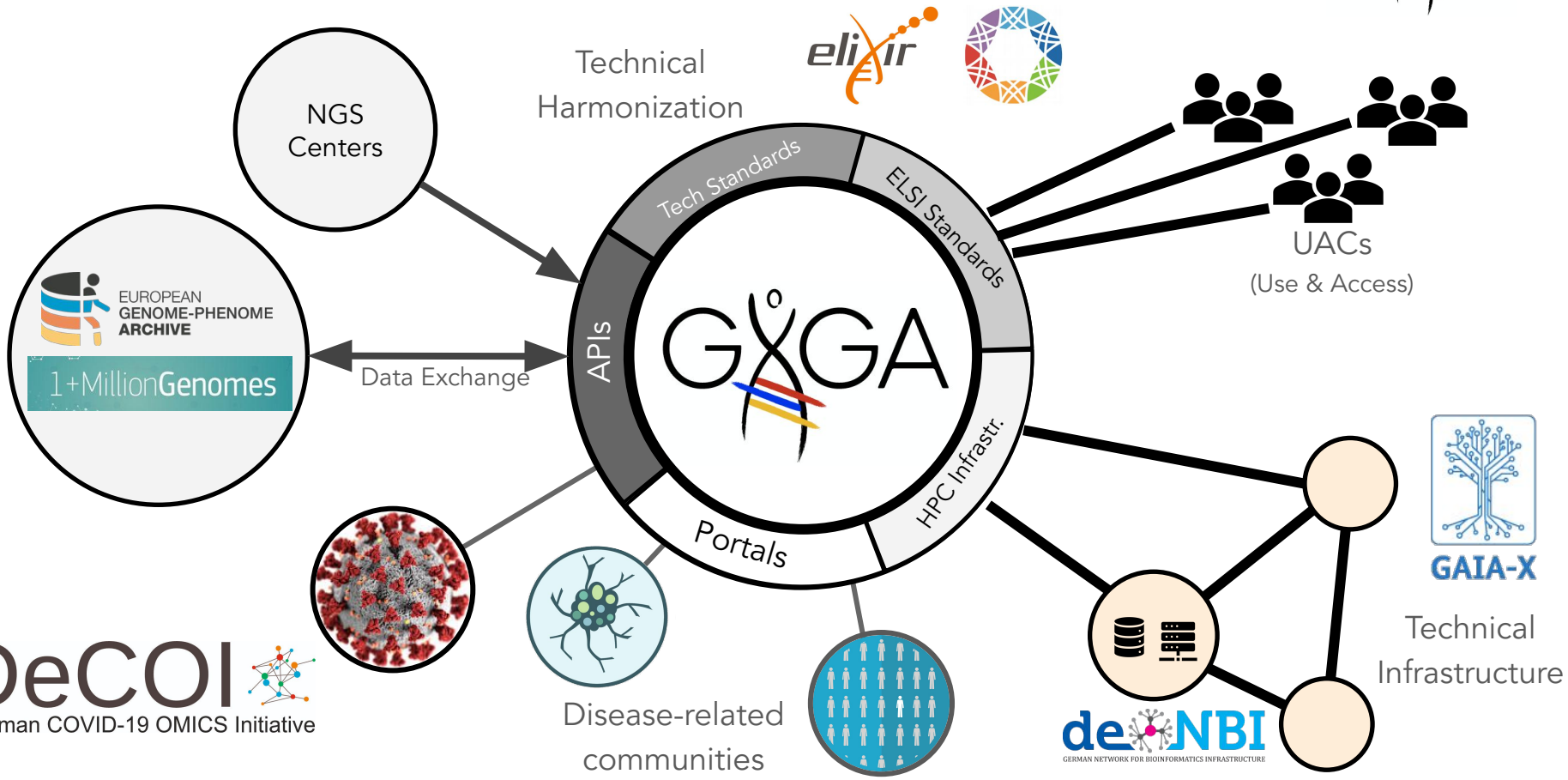
Goals & Core Objectives

Core Mission

Establish a national infrastructure for human omics data (genome, transcriptome, proteome, …).

- Platform for long-term FAIR data archival of human omics data, connected to major omics centers in Germany
- Controlled access management and community-centered data sharing platforms
- Ethico-legal and data use framework for data sharing, protection & analysis
- Distributed analytics platform to democratize data processing and research use
- Establish strong Interfaces with international genome initiatives

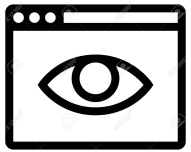
Interfaces and related initiatives

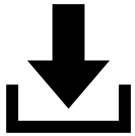


Service portfolio: beyond data archival



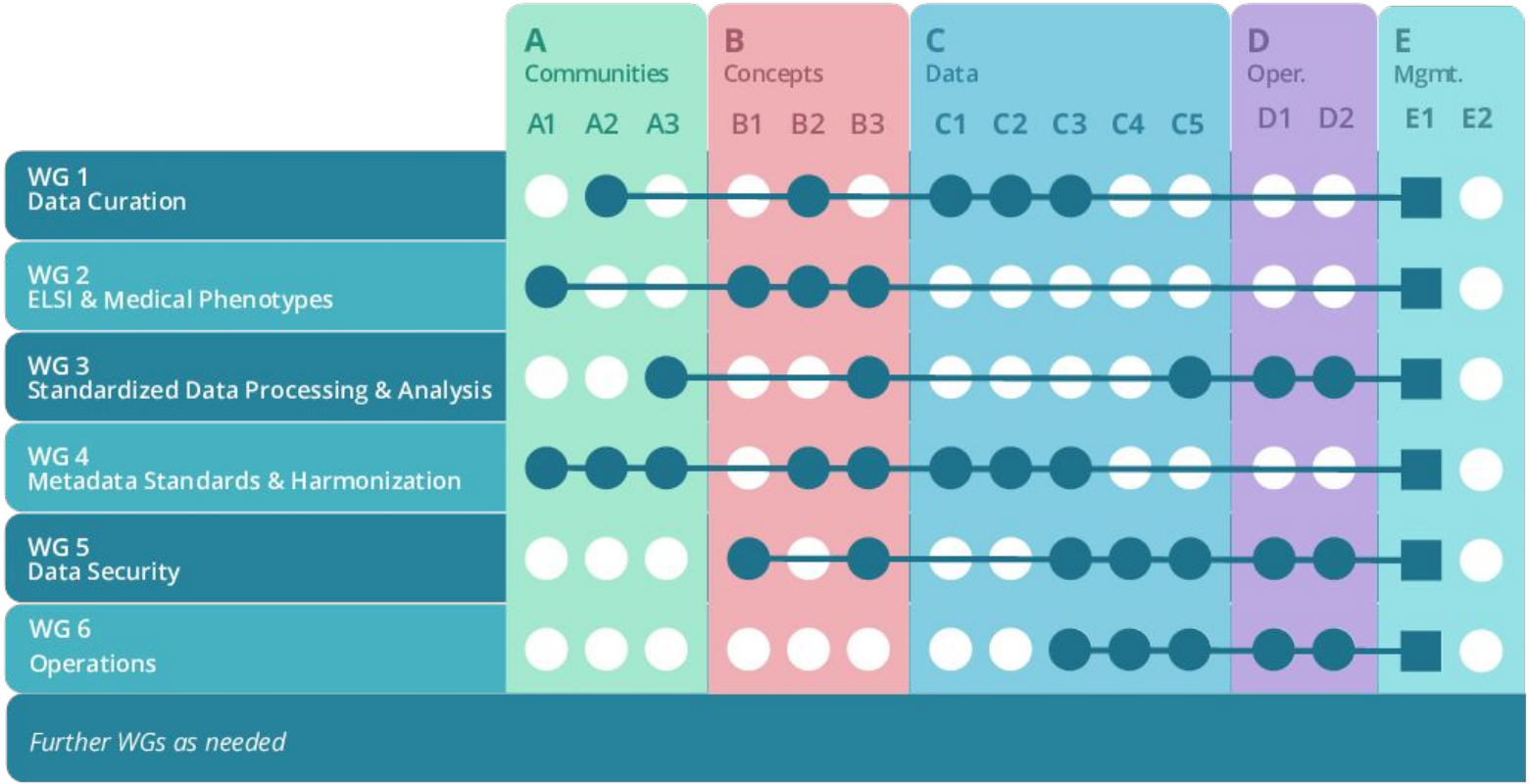

Technical proficiency


Web UIs


Data
Download


Distributed &
cloud computing

Engagement with GA4GH activities



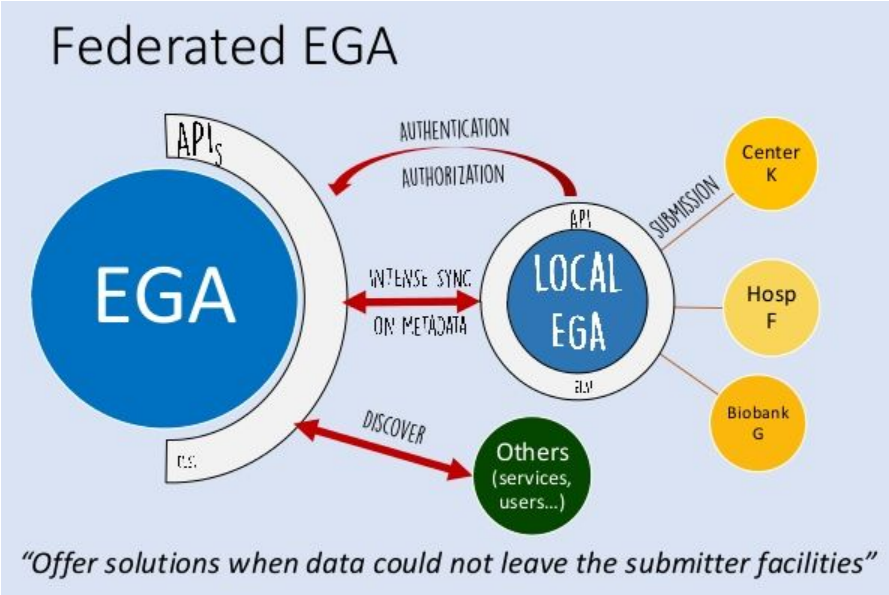
European Genome-Phenome Archive (EGA) - Transition to a Federated Model

Why is international federation needed?

- Growing datasets: bring compute to data.
- Regulatory compliance: country-specific applicable law (based on GDPR*).

Implications

- National infrastructures required.
- International standards & data exchange mechanisms becoming crucial.

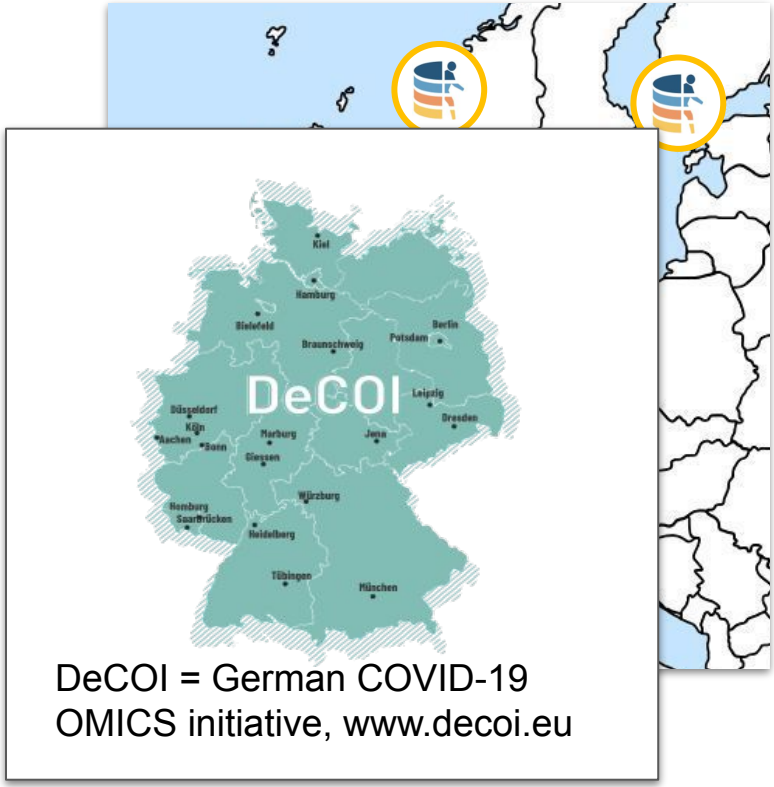


EUROPEAN GENOME-PHENOME ARCHIVE

* *Europe's General Data Protection Regulation (GDPR)*

Saunders *et al. Nat Rev Genet* 2019

Federated infrastructure for European data sharing



DeCOI = German COVID-19 OMICS initiative, www.decoi.eu

1+MillionGenomes

European Commission

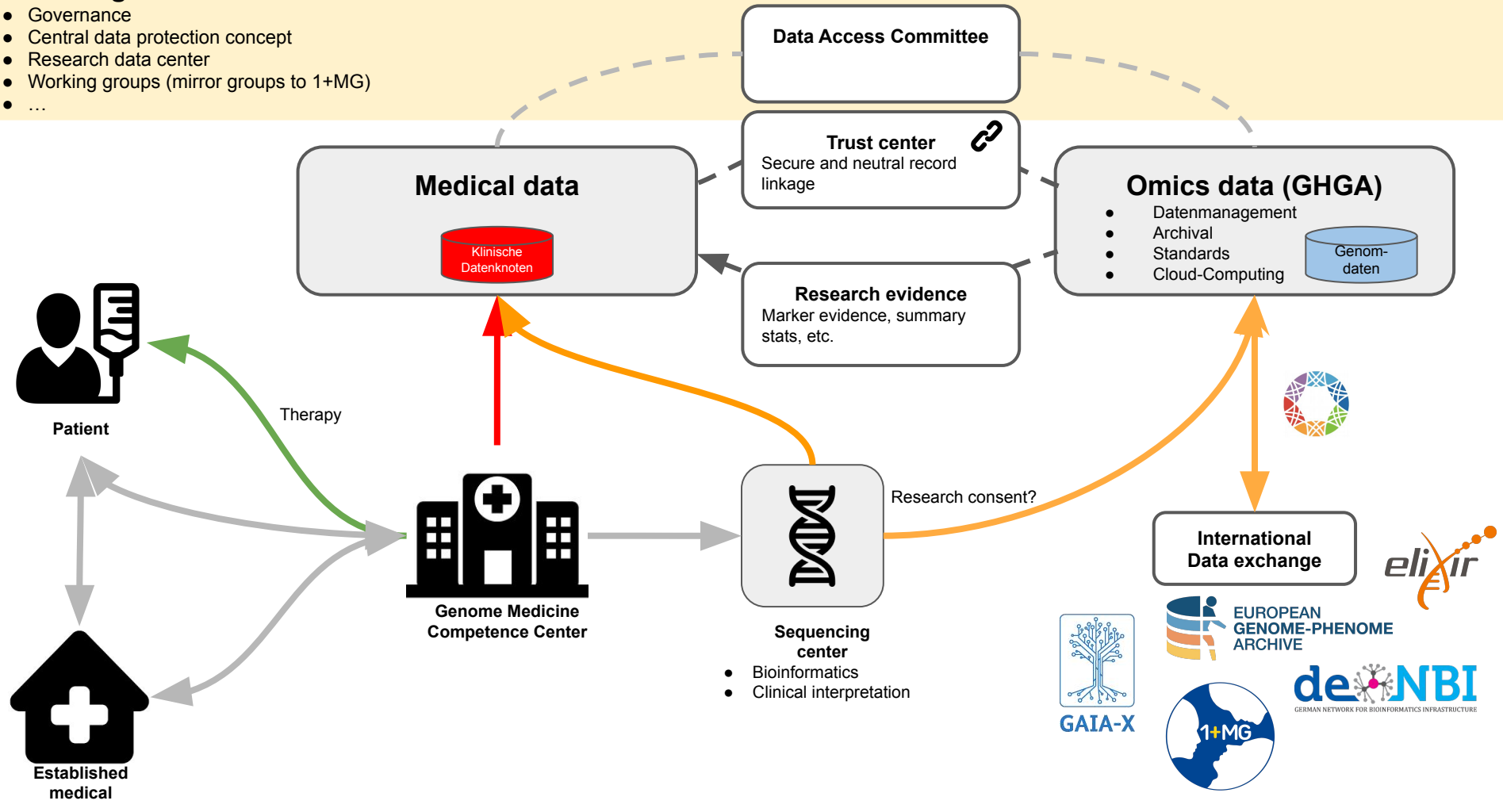
Europ
federa

Central E

Saunders et al. Nat Rev Genet 2019

National genome initiative

- Governance
- Central data protection concept
- Research data center
- Working groups (mirror groups to 1+MG)
- …



Acknowledgements

Board of directors: Oliver Stegle (DKFZ/EMBL), Oliver Kohlbacher (Univ. Tübingen), Jan Korbel (EMBL), Eva Winkler (Univ. Klinikum Heidelberg)

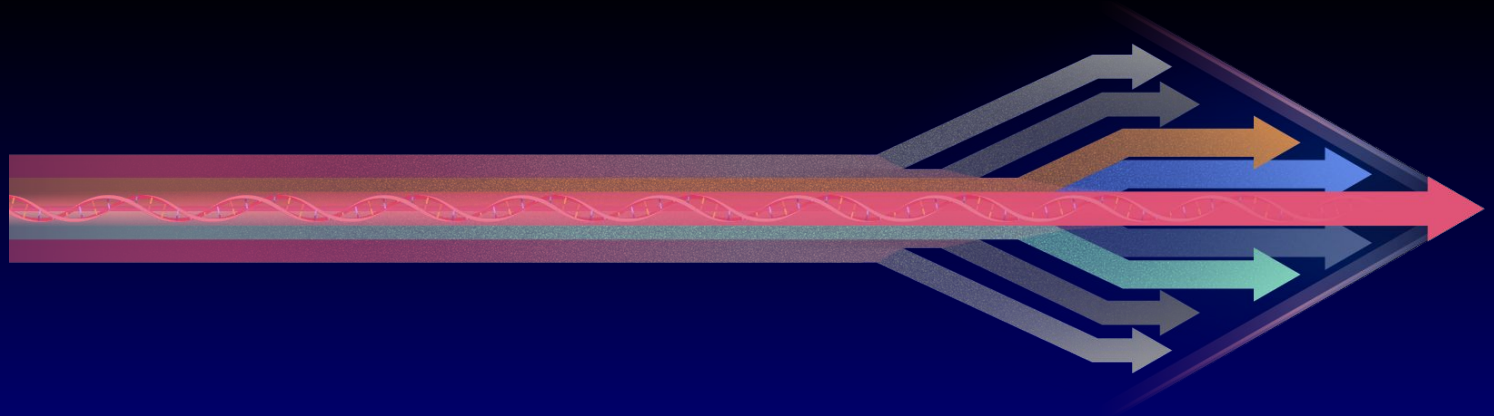
Co-spokespersons: Peer Bork (EMBL), Ivo Buchhalter (DKFZ), Andreas Dahl (TU Dresden), Julien Gagneur (TU Munich), Wolfgang Huber (EMBL), Daniel Hübschmann (DKFZ), Martin Lablans (DKFZ), Ulrich Lang (Univ. Cologne), Peter Lichter (DKFZ), Fruzsina Molnár-Gábor (Akadam. Wiss.), Susanne Motameny (Univ. Cologne), Sven Nahnsen (Univ. Tübingen), Uwe Ohler (MDC), Stephan Ossowski (Univ. Klinikum Tübingen), Annette Peters (HMGU), Olaf Rieß (Univ. Klinikum Tübingen), Philip Rosenstiel (Univ. Klinikum Schleswig-Holstein, Kiel), Thorsten Schlomm (Charité, Berlin), Joachim Schultze (DZNE), Jörn Walter (Univ. Saarland), Thomas Walter (Univ. Tübingen), Juliane Winkelmann (HMGU),

Participants: Thomas Keane (EMBL-EBI), Mario Fritz / Ninja Marnau (CISPA), Alice HcHardy (Helmholtz Center, Infectious Diseases), Stefan Fröhling (NCT Heidelberg), Hanno Glimm (NCT Dresden)

Placeholder for Oliver's Slides

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

Education and Workforce Training in Genomics



The Forefront of Genomics®

Refocusing NHGRI Support of Genomic Medicine Training Programs: NHGRI 2020 Strategic Vision

Teri Manolio, M.D., Ph.D.

Genomics in Health Implementation Forum, 2021 Virtual Working Meeting
March 9, 2021

National Human Genome Research Institute

The Forefront of Genomics®

2020 NHGRI Strategic Vision

Perspective

Strategic vision for improving human health at The Forefront of Genomics

https://doi.org/10.1038/s41586-020-2817-4
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Check for updates

Eric D. Green[1]✉, Chris Gunter[1], Leslie G. Biesecker[1], Valentina Di Francesco[1], Carla L. Easter[1], Elise A. Feingold[1], Adam L. Felsenfeld[1], David J. Kaufman[1], Elaine A. Ostrander[1], William J. Pavan[1], Adam M. Phillippy[1], Anastasia L. Wise[1], Jyoti Gupta Dayal[1], Britny J. Kish[1], Allison Mandich[1], Christopher R. Wellington[1], Kris A. Wetterstrand[1], Sarah A. Bates[1], Darryl Leja[1], Susan Vasquez[1], William A. Gahl[1], Bettie J. Graham[1], Daniel L. Kastner[1], Paul Liu[1], Laura Lyman Rodriguez[1], Benjamin D. Solomon[1], Vence L. Bonham[1], Lawrence C. Brody[1], Carolyn M. Hutter[1] & Teri A. Manolio[1]

Starting with the launch of the Human Genome Project three decades ago, and continuing after its completion in 2003, genomics has progressively come to have a central and catalytic role in basic and translational research. In addition, studies increasingly demonstrate how genomic information can be effectively used in clinical care. In the future, the anticipated advances in technology development, biological insights, and clinical applications (among others) will lead to more widespread integration of genomics into almost all areas of biomedical research, the adoption of genomics into mainstream medical and public-health practices, and an increasing relevance of genomics for everyday life. On behalf of the research community, the National Human Genome Research Institute recently completed a multi-year process of strategic engagement to identify future research priorities and opportunities in human genomics, with an emphasis on health applications. Here we describe the highest-priority elements envisioned for the cutting-edge of human genomics going forward—that is, at 'The Forefront of Genomics'.

Beginning in October 1990, a pioneering group of international researchers began an audacious journey to generate the first map and sequence of the human genome, marking the start of a 13-year odyssey called the Human Genome Project[1–3]. The successful and early completion of the Project in 2003, which included parallel studies of a set of model organism genomes, catalysed enormous progress in genomics research. Leading the signature advances has been a greater than one million-fold reduction in the cost of DNA sequencing[4]. This decrease has allowed the generation of innumerable genome sequences, including hundreds of thousands of human genome sequences (both in research and clinical settings), and the continuous development of assays to identify and characterize functional genomic elements[5,6]. These new tools, together with increasingly sophisticated statistical and computational methods, have enabled researchers to create rich catalogues of human genomic variants[7,8], to gain an ever-deepening understanding of the functional complexities of the human genome[9], and to determine the genomic bases of thousands of human diseases[6,10]. In turn, the past decade has brought the initial realization of genomic medicine[11], as research successes have been converted into powerful tools for use in healthcare, including somatic genome analysis for cancer (enabling development of targeted therapeutic agents)[12], non-invasive prenatal genetic screening[13], and genomics-based tests for a growing set of paediatric conditions and rare disorders[14], among others.

In essence, with growing insights about the structure and function of the human genome and ever-improving laboratory and computational technologies, genomics has become increasingly woven into the fabric of biomedical research, medical practice, and society. The scope, scale, and pace of genomic advances so far were nearly unimaginable when the Human Genome Project began; even today, such advances are yielding scientific and clinical opportunities beyond our initial expectations, with many more anticipated in the next decade.

Embracing its leadership role in genomics, the National Human Genome Research Institute (NHGRI) has developed strategic visions for the field at key inflection points, in particular at the end of the Human Genome Project in 2003[15] and then again at the beginning of the last decade in 2011[16]. These visions outlined the most compelling opportunities for human genomics research, in each case informed by a multi-year engagement process. NHGRI endeavoured to start the new decade with an updated strategic vision for human genomics research. Through a planning process that involved more than 50 events (such as dedicated workshops, conference sessions, and webinars) over the past two years (see http://genome.gov/genomics2020), the institute collected input from a large number of stakeholders, with the resulting input catalogued and synthesized using the framework depicted in Fig. 1.

Unlike the past, this round of strategic planning was greatly influenced by the now widely disseminated nature of genomics across biomedicine. A representative glimpse into this historic phenomenon is illustrated in Fig. 2. During the Human Genome Project, NHGRI was the primary funder of human genomics research at the US National Institutes of Health (NIH), but the past two decades have brought a greater than tenfold increase in the relative fraction of funding coming from other parts of the NIH.

[1]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA. ✉e-mail: egreen@nhgri.nih.gov

The **Forefront** of **Genomics**®

Nature 2020;586:683-92, PMID 33116284

NHGRI Training and Education Task Force Recommendations

- Expand genomic research training opportunities for individuals in **affiliated fields** (e.g. genetic counselors, genetic laboratory fellows, nurses, etc.)
- Develop new grant programs to **develop and disseminate training modules**
- Establish ambitious **goals and milestones** to increase both number/size of awards and the representation of women and underrepresented minorities

Training Implementation Plan Objectives, Apr 2020

1. Expand opportunities for individuals who need **focused research training to become effective genomic researchers**, such as genetic counselors and data scientists.
2. **Attract individuals not traditionally represented in genomics** such as women and underrepresented minorities.
3. **Increase knowledge and use of genomics** among individuals in related non-genomic disciplines such as nurses and physicians.
4. **Assess training programs**, address deficiencies, and disseminate effective approaches.
   - Funding Levels: Increase from 4% to 6% of extramural budget over 5 years; roughly $1.5M/yr x 5 yrs, reassess and consider additional $3-4M increase

Training Nurses in Genomic Research

Support training of nurse researchers in genomics, enabling them to:

- Use informatics and precision medicine approaches to advance health equity and facilitate evidence-based practice in underserved populations
- Conduct interdisciplinary research using informatics and precision medicine approaches to advance health equity and facilitate evidence-based practice in underserved populations
- Conduct biobehavioral research in symptom science, with specialized focus on genomics in symptom research

Training Genetic Counselors in Genomic Research

Provide genomics research experiences for genetic counselors, enabling them to:

- Assist with conduct of research and become more effective members of research team
- Contribute research questions designed to explore implications of living with genomic risk
- Lead research efforts to inform the most effective delivery of genetics/genomics services

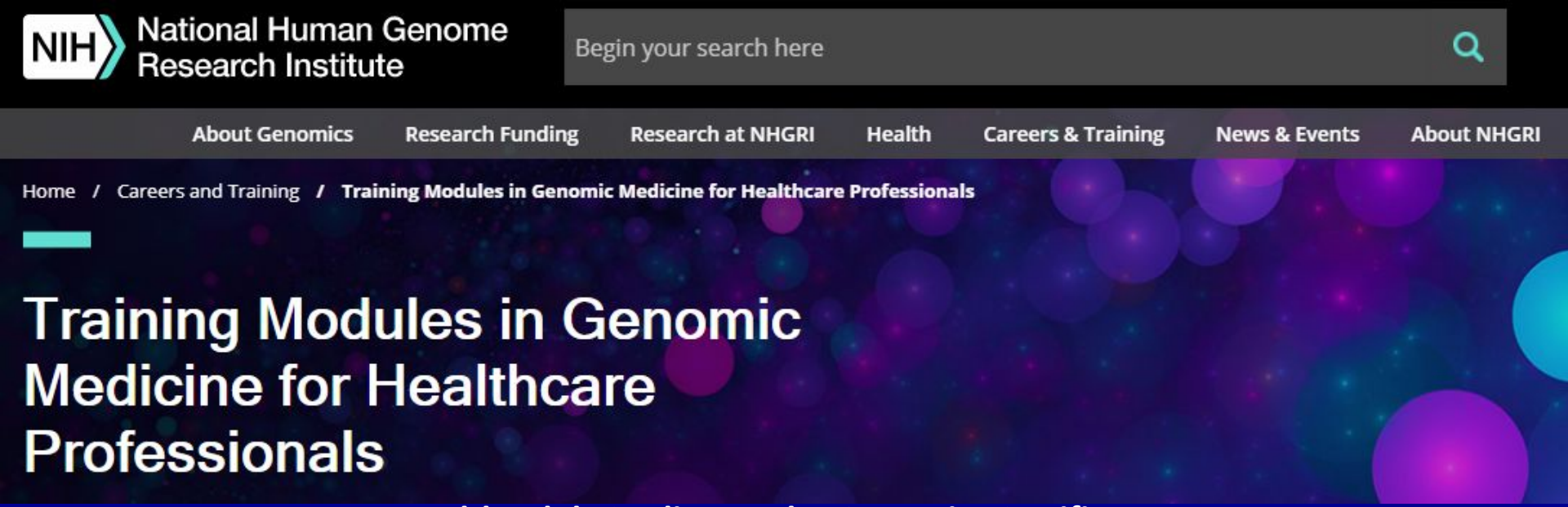
Genomic Medicine Training Modules

Develop and implement modules providing health care professionals training in genomic medicine topics

- Clinical use of genomic data and tests
- Analysis of clinical genomic data
- Pharmacogenomics
- Use of genomic information for preventive medicine,

Health care professionals include physicians, physician assistants, nurse practitioners, nurses, genetic counselors, pharmacists

Modules can be designed to stand alone or to build upon each other to form a certificate in genomic medicine to identify health care professionals with specialized expertise and consultative capabilities



U Texas Houston: UTHealth Adult Cardiovascular Genomics Certificate Program

- Allied health professionals, nurse practitioners, nurses, physicians

Indiana U/Purdue U: *Test2Learn*™ Pharmacogenomics Education for Health Practitioners

- Genetic counselors, nurse practitioners, nurses, pharmacists, physician assistants, physicians

Duke U: Health Professional Rapid Personalized Learning Platform for Genomic Medicine

- Nurses, pharmacists, physician assistants, physicians

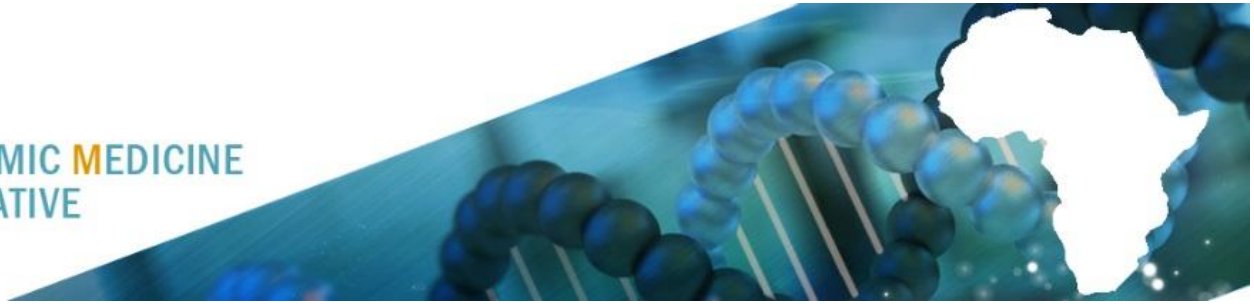
Funding for Research Training

NHGRI Training Mission: Prepare a diverse and talented genomics workforce that is operating at the forefront of genomics in order to accelerate scientific and medical breakthroughs to improve human health.

The National Human Genome Research Institute (NHGRI) provides both institutional and individual funding to help scientists develop their skills as researchers and professionals. Our programs offer opportunities at the undergraduate, postbaccalaureate, graduate, postdoctoral and faculty levels.

Explore this Page

AGMT
AFRICAN GENOMIC MEDICINE TRAINING INITIATIVE



The African Genomic Medicine Training Initiative

Nicky Mulder
On behalf of AGMT team

Slide credits Dr Vicky Nembaware

African genetic diversity & medicine

- Africa suffers a disproportionate burden of disease
- HIV/AIDS, TB & malaria dominate research on the continent
- Increase in prevalence of non-communicable disease
- African genomes have higher diversity, variants for diseases may be specific to African populations
- Different evolutionary exposures -compensatory variants found in African populations
- Genomic medicine knowledge based mostly on other populations
- African genomics is important, but currently a lack of data & skills

African Genomic Medicine Training Initiative -Launch

12 May – 2016: Dakar Senegal

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TRAINING INITIATIVE

Needs Assessment of Targeted Learners

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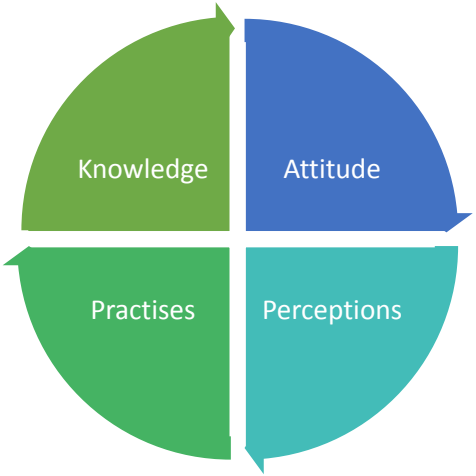
Goals and Specific Objectives for the Training



- Developed different nurse persona
- Developed competencies required for nurses
- Developed curriculum based on competencies

- Patient care - genetic and genomics information (**sensitive to individual and cultural preferences and norms**)
- Offer **basic genetic counselling t**o patients and families
- Conduct genomics research that is **ethical and appropriate** to their context
- Address **stigma and discrimination**

Example modules

Introduction	Ethics, Social and Genetic Counselling	Application of Genomic Medicine
• Patterns of Genetic Transmission in Humans • Genes, Genome Structure and Function • Molecular Diagnostics and Bioinformatics Techniques	• Ethical, Legal & Social Issues in Applied Genomics • Community Engagement in Genomic Research • Basic Genetic Counselling Skills	• Genomics of Monogenic Disorders • Molecular pathology of Cancer and Application in Cancer Diagnosis, Screening and Treatment • Application of Genomics to Non-Communicable disease • The gastrointestinal microbiome • Nutrigenomics • Pharmacogenetics & Pharmacogenomics for nurses in Africa • Clinical Research Skills and Genetic Epidemiology • Infectious Disease
Built on existing content, adapted to African context		

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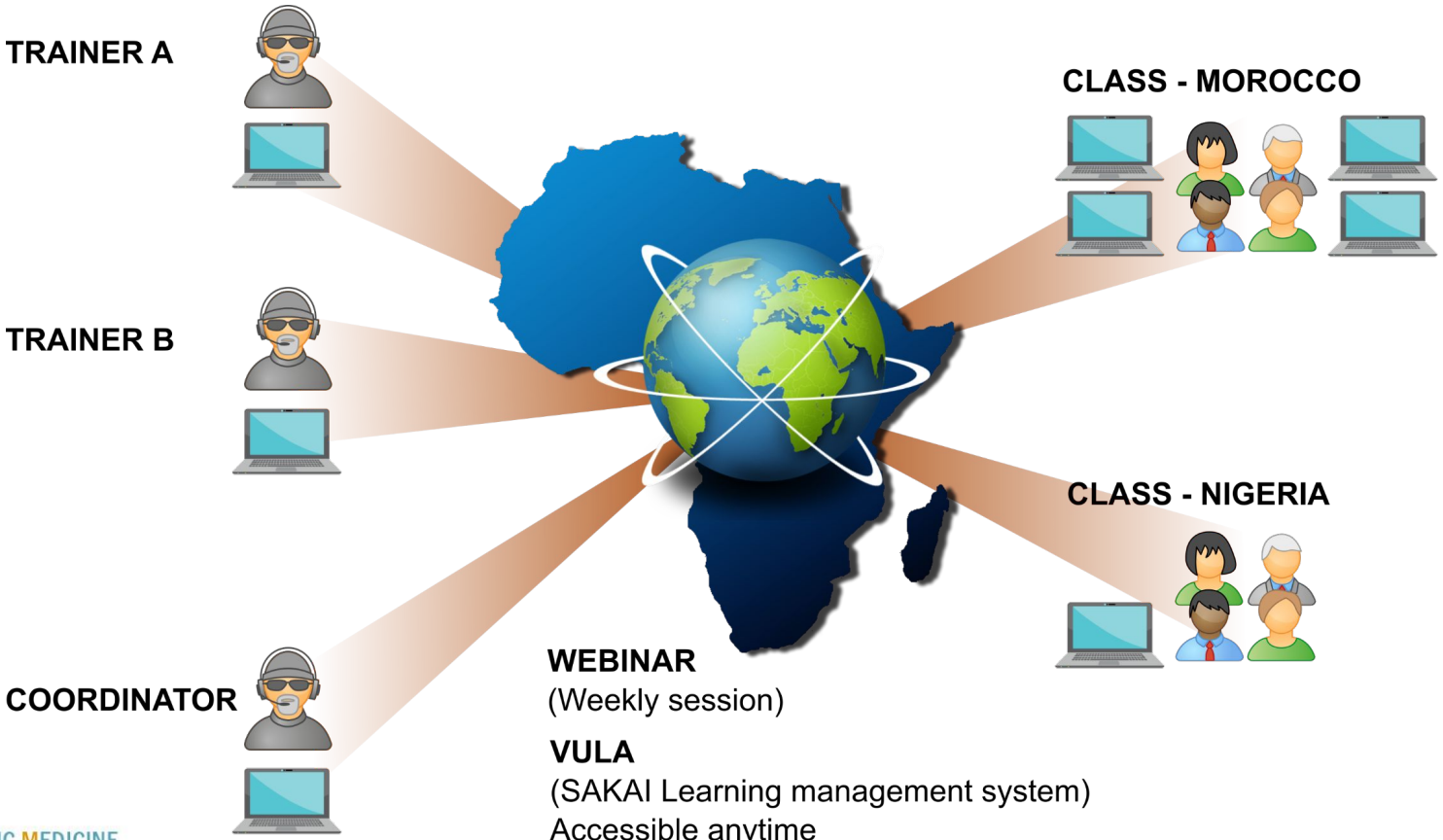
AFRICAN GENOMIC MEDICINE
TRAINING INITIATIVE

Distance, Flipped Class & Problem Based Learning



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TRAINING INITIATIVE

Evaluation and Feedback

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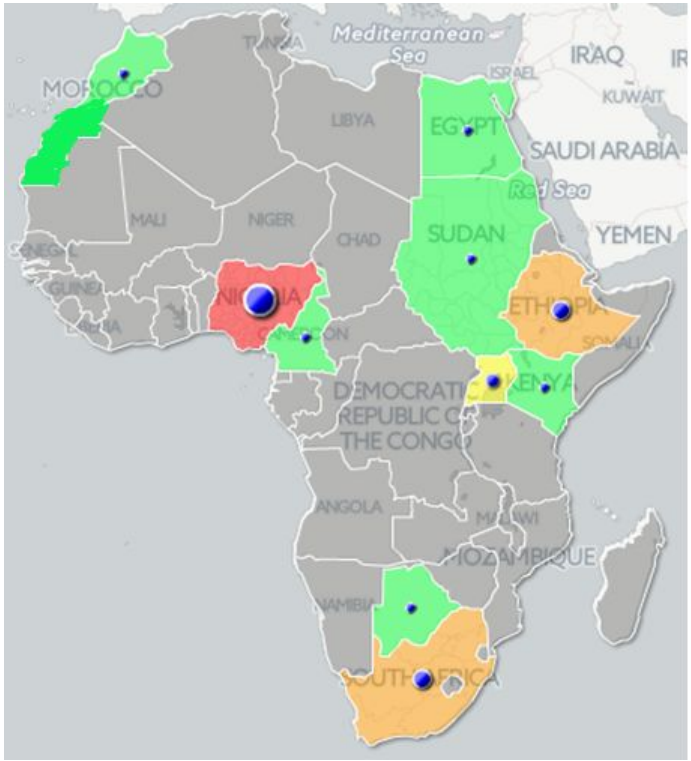
Implementation – run 2 iterations



2017: 19 Classrooms in 11 Countries - Facilitators, 1 Online Class, 225 students registered

2019: 21 Classrooms in 14 Countries – 1300 applications, 367 students registered

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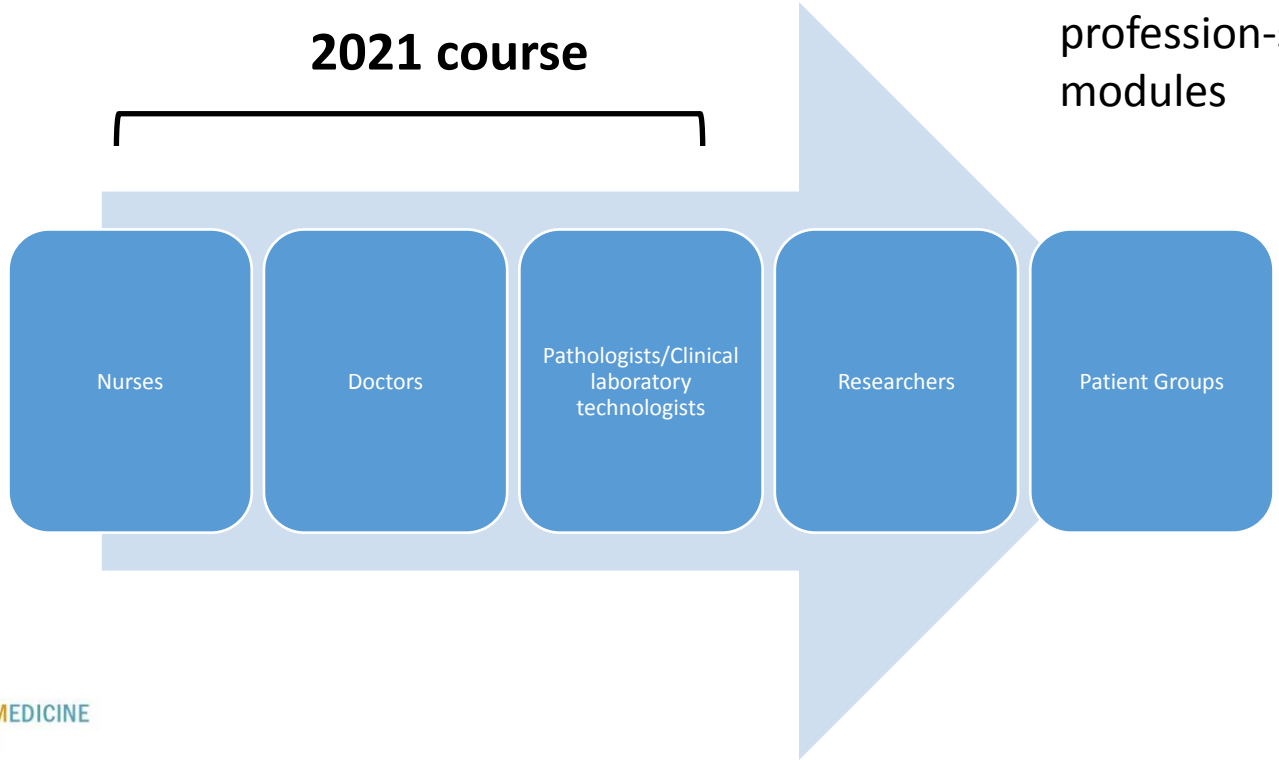
Future Training

- Developing competencies
- Identifying shared versus profession-specific modules



AGMT
AFRICAN GENOMIC MEDICINE TRAINING INITIATIVE

AGMT contributors

- Advisors
- Planning Committee
- Trainers
- Facilitators
- Participants

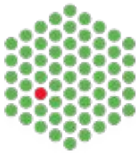
H3ABioNet

Pan African Bioinformatics Network for H3Africa

Global Research Nurses

Southern African Human Genome Programme

EMBL-EBI



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Paballo Chauke
Faisal Fadlemola,
Samar Kassim
Fouzia Radouani
Michael Pepper
Raj Ramesar
Guida Landore
Michele Ramsay
Misaki Wayengera
Sarah Morgan
….

Quality Control of WGS Results

Agency for Science, Technology and Research
SINGAPORE

QUALITY CONTROL OF WGS RESULTS

Oliver Hofmann (AGHA)
Mar Gonzalez-Porta (SG NPM)

2021 March Virtual GHIF Meeting

9 MARCH 2021

Background

MOTIVATION

- Good quality data is a prerequisite for reliable downstream analysis
- Strategies for robust QC:
  - Validation with reference materials (GIAB, SEQC-II) following standardised best practices (GA4GH)
  - Ongoing QC of real samples – multiple guidelines (ACMG, CAP-AMP, MGI…), however the lack of standardised implementations still poses challenges to initiatives

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USER STORIES

- Data generation
  - Choice of metrics and tools requires curation
    e.g. 82 metrics from 13 tools in the SG-NPM QC pipeline
  - Shared metric names ≠ directly comparable results
    e.g. genome coverage, %Q30
- Data sharing
  - QC after downloading vs. accessing only the relevant samples

Hear more:
GHIF Fall 2020 – Day 2
https://youtu.be/qQrdd_3-e5Q?t=2483

CREATING GROWTH, ENHANCING LIVES

Proof of concept: NA12878

SET UP

NA12878 from DRAGEN-1KGP

SG NPM QC
picard
samtools
mosdepth
bcftools
VerifyBamID2
custom tools
multiQC (json)

AGHA QC
indexcov
fastQC
samtools
bcftools
peddy
multiQC (html)

Compare outputs
Yield and quality ◈ Alignment
Variant calling ◈ Contamination & PST

CREATING GROWTH, ENHANCING LIVES

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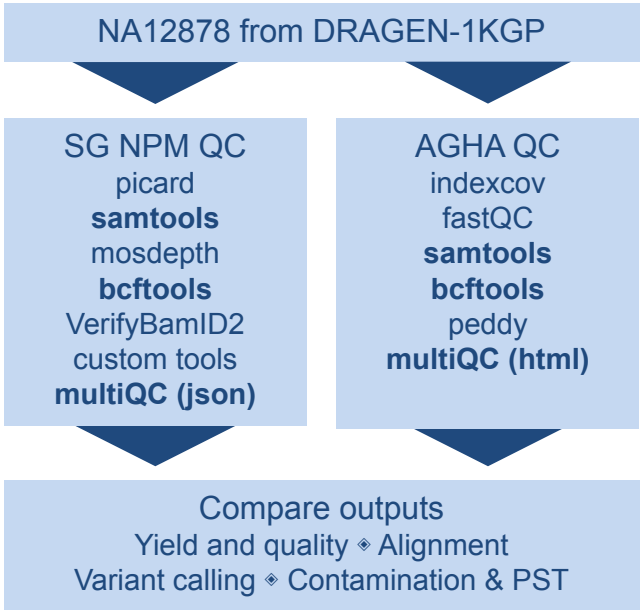

OBSERVATIONS

- Different approaches to QC
  e.g. stand-alone vs. embedded workflows; plot vs. single-value based assessments

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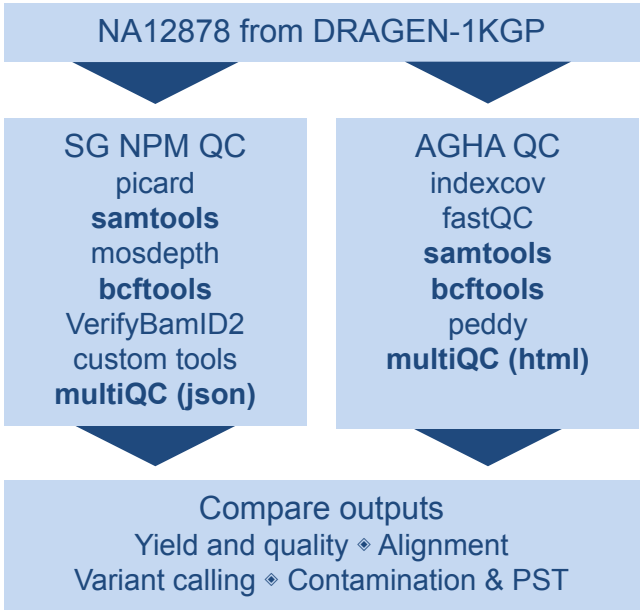

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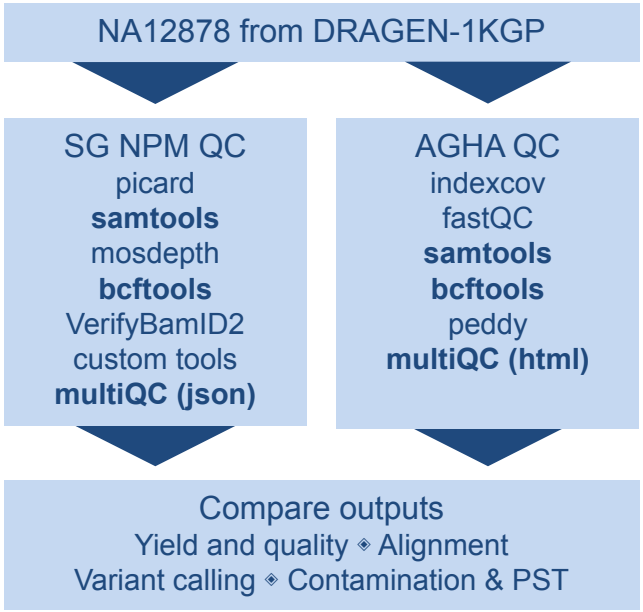

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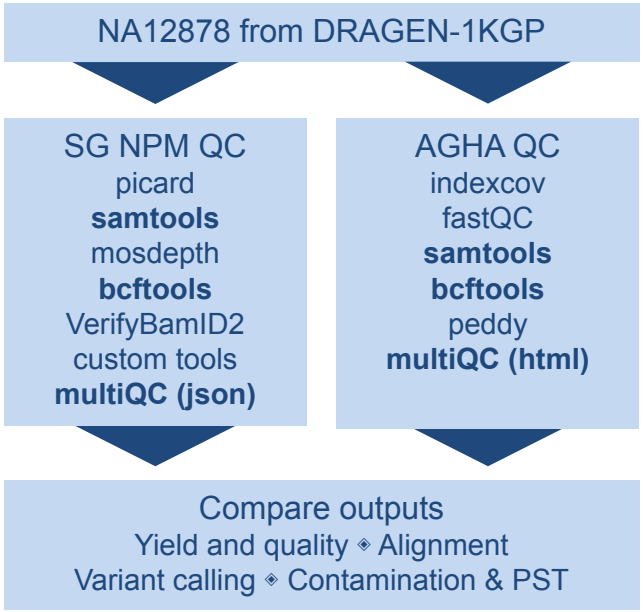

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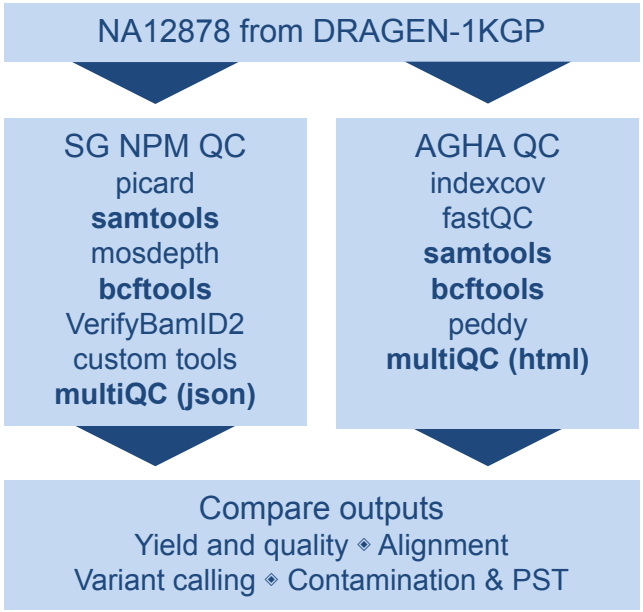

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  e.g. 4X difference in coverage; yield as N reads or Gbp

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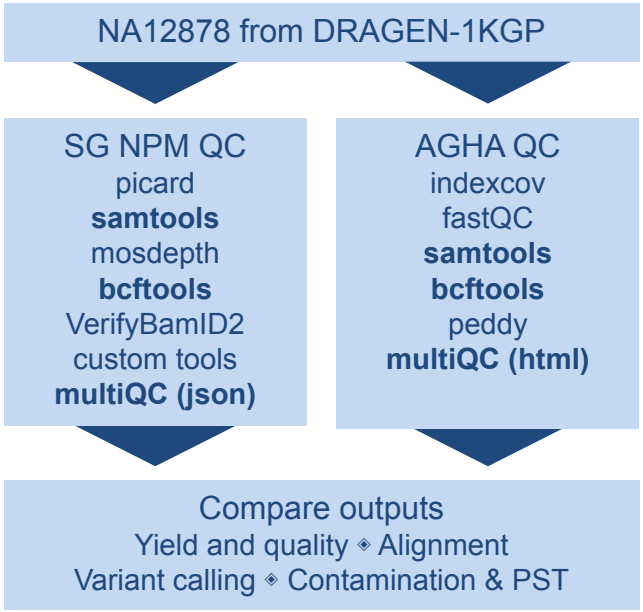

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Agreeing on QC metrics is insufficient – need for standardised definitions

Towards a reference implementation

PROPOSED SCOPE

- Focus on human WGS, germline, short-reads
- Provide:
  - Standardised metric definitions (incl. defining metadata and schema/file formats for sharing)
  - A reference implementation (standalone QC workflow)
  - Benchmarking data (to compare vs. in-house workflows, share QC approaches…)

The main goal is to define a common language – there's no single solution to QC!

Towards a reference implementation

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The main goal is to define a common language – there's no single solution to QC!

NEXT STEPS

- Send your feedback and take part in the proof-of-concept
  http://j.mp/3rqi9lZ
- Explore ties with GA4GH
  e.g. search / discovery of files, refget, file formats

CREATING GROWTH, ENHANCING LIVES

Variant Curation

Shariant: National approaches to knowledge sharing between labs and globally

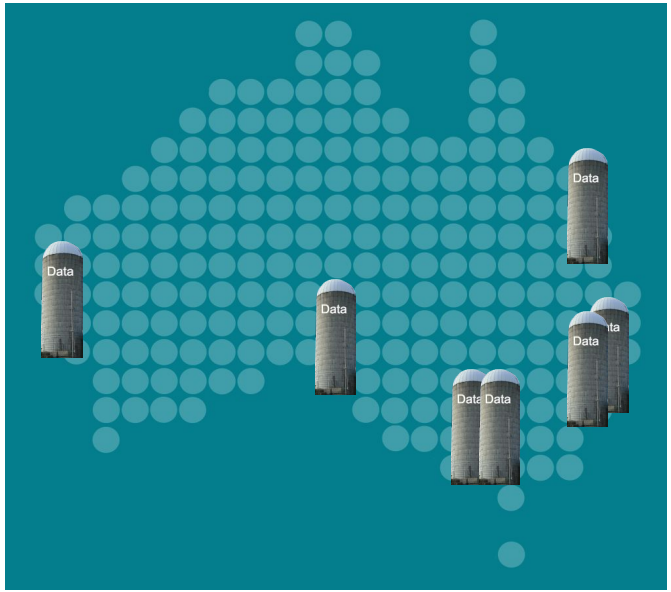
Amanda Spurdle (Lead)
Emma Tudini (Project Co-ordinator)
James Andrews (Lead Developer)
David Lawrence (Developer)
Hamish Scott (Program 1 Reclassification)

Australian Genomics Health Alliance

Australian Context

The problem…

- Australian genetic testing labs worked in silos and did not regularly share knowledge
- Australian clinical accreditation guidelines encourage sharing of variant
- No (formal) between-lab sharing
- Few submissions to ClinVar >> 250 variants at the time of project initiation



Australian Genomics Health Alliance

Consultation is KEY!

Barrier to sharing	Solution
Resources - No time - Limited bioinformatic expertise	- Automated connection to laboratory interpretation tool/database - Shariant developer to assist in connection
Consent - what can be shared and with whom?	- Controlled access platform - Laboratories decide on extent of (clinical) data to be shared
Interpretation tools differ between laboratories, and can change over time	- Sharing agnostic to interpretation tool/s - Flexibility in connection solutions - Work with vendors to improve connection
"Just another (static) database to check" *Paraphrased somewhat…*	- "Real-time" connection from laboratory system to view other variants submitted nationally

Other issues/Incentives to share	Solution
Database stores sufficient evidence to allow review/re-use of existing curations	- Submission of structured evidence against ACMG guidelines
Identification and resolution of discrepancies prior to international sharing	- Discrepancy resolution tooling
Streamlined submission to ClinVar	- Automated formatting to ClinVar specifications, ClinVar API

Australian Genomics Health Alliance

Shariant:
National Clinically Interpreted Variant Sharing Platform

- Needs defined in consultation with Australian diagnostic labs

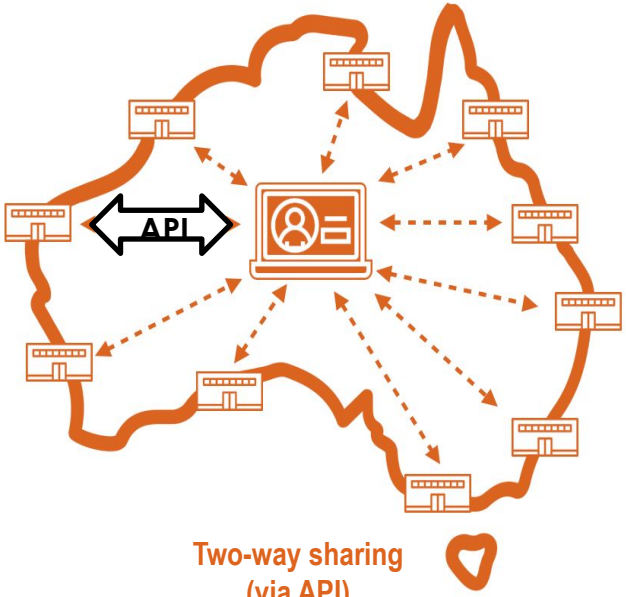
- Documented a set of key criteria to assess potential solutions

- Investigated commercial, open source, national, international options (9)

- Formal trial of three platforms >> Shariant

Platform to automate sharing
- **clinically interpreted (germline) variants**
- **between diagnostic labs**
- **in "real" time**

Sharing of structured evidence and expertise
- Based on ACMG guidelines



Two-way sharing (via API)

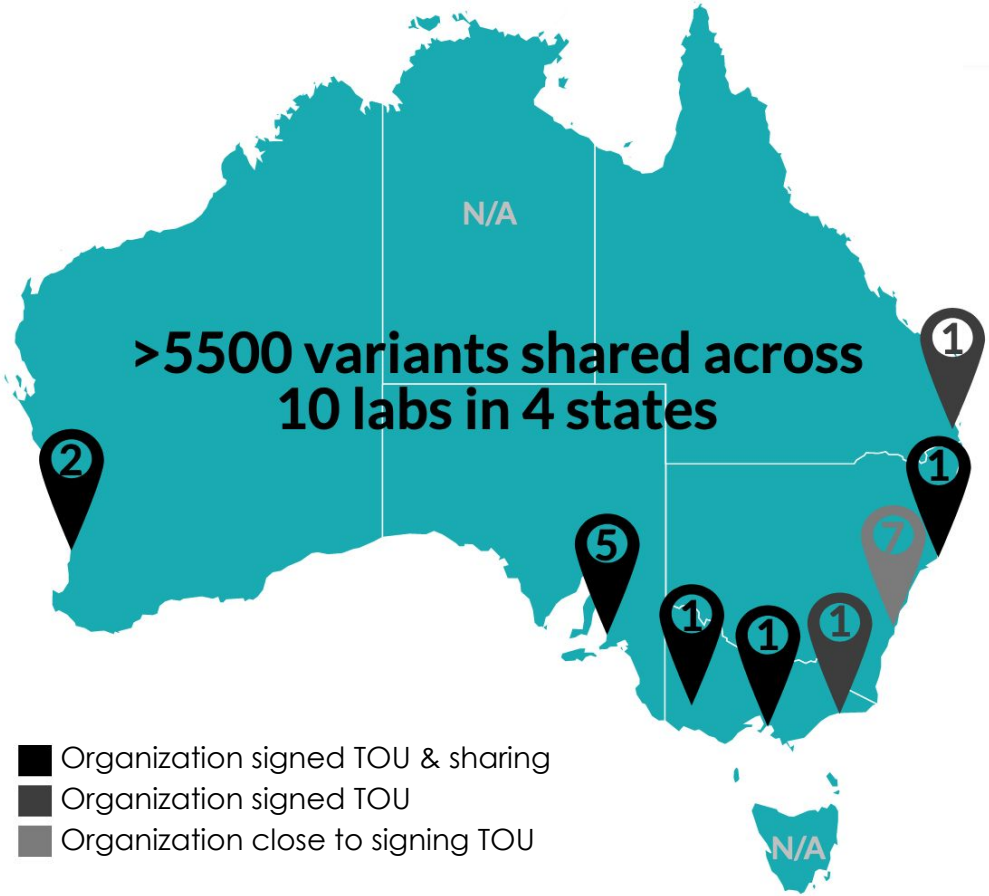
Submission to international databases upon laboratory approval

Discrepancy resolution via email notifications and in-built communication platform

Controlled access

Australian Genomics Health Alliance

Consultation > Engagement



STEP 1: Initial Contact

STEP 2: Send Terms of Use

STEP 3: Mapping of evidence between systems

STEP 4: Technical connection to Shariant

STEP 5: Terms of Use Sign Off

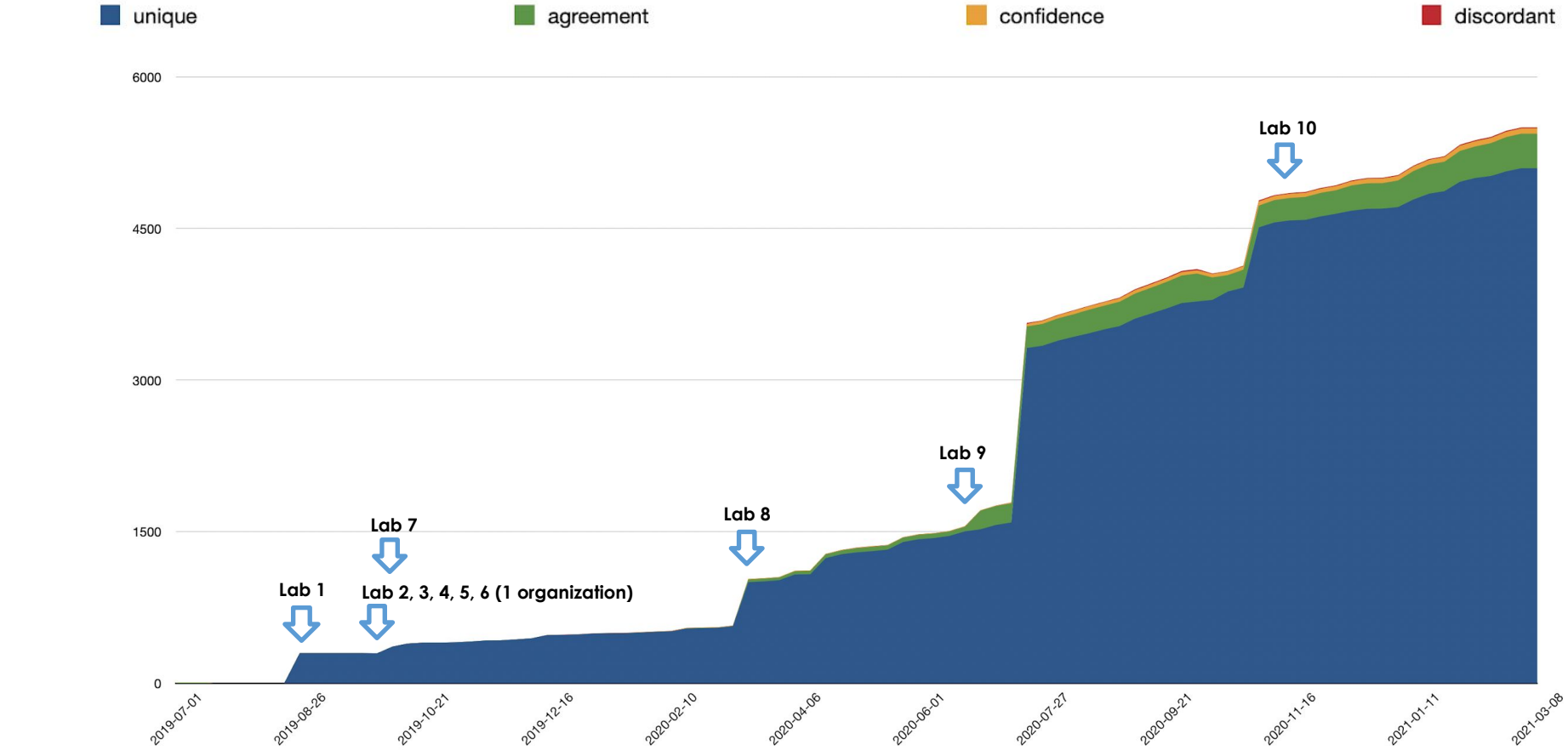
STEP 6: Prospective variant sharing!

Terms Of Use

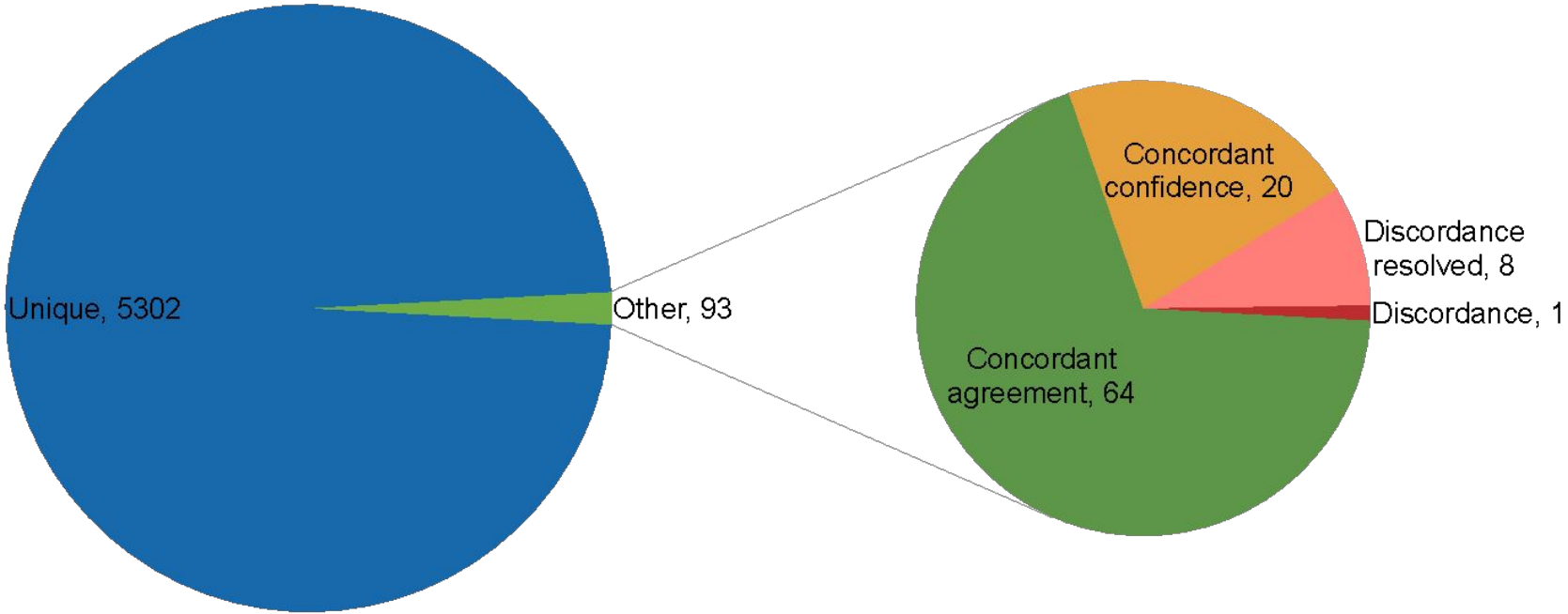
- Limited to Australian clinically accredited laboratories
- Additional documentation around security, and technical connection
- Minor amendments introduced with every new organization
- Automated notification to accept minor amendments
- Significant hurdle (1 week to > 1.5 years)

Australian Genomics Health Alliance

Sharing within Australia over time



Concordance and Discordance



Australian Genomics Health Alliance

Resolution of discordances

Classification Diff

Configure columns Show unmet ACMG criteria	Lab 1 hg19_NM_004360_3_CDH1_c_1913G_A 23/Feb/2021 18:33	Lab 2 hg38_NM_004360_3_CDH1_c_1913G_A 28/Jan/2021 09:14
Variant		
≠ Source ID	Shariant_RMH_GRCh37-Molecular_variants-2020-08-10_05-48-51.json:905	Shariant_VCGS_GRCh38-Molecular_variants-2020-08-10_05-48-06.json:918
Gene symbol	CDH1	CDH1
≠ Genome Build	GRCh37.p13	GRCh38.p2
RefSeq Transcript ID	NM_004360.3	NM_004360.3
c.HGVS	NM_004360.3(CDH1):c.1913G>A	NM_004360.3(CDH1):c.1913G>A
p.HGVS	p.W638*	p.W638*
Zygosity	Heterozygous	Heterozygous
Allele origin	Germline	Germline
Exon	12	12
Gene		
≠ Condition under curation	MONDO:0007648	xx
Patient		
Affected status	Affected	
Test		
Population data		
BA1	Not Met	Not Met
BS1	Not Met	Not Met
BS2	Not Met	Not Met
PM2	Pathogenic Moderate	Pathogenic Moderate
≠ PS4	Pathogenic Supporting*	Pathogenic Strong
gnomAD	0.002%	
Computational and predictive data		
≠ PVS1	Pathogenic Very Strong	Pathogenic Moderate*
BP4	Not Met	Not Met
PP3	Not Met	Not Met
BP7	Not Met	Not Applicable
BP3	Not Met	Not Met
PM4	Not Met	Not Met
BP1	Not Met	Not Met
≠ PM5	Not Met	Pathogenic Very Strong*
PS1	Not Met	Not Applicable

Citations

PMID: 17660459 Masciari et al 2007 Germline E-cadherin mutations in familial lobular breast cancer. Toggle detail	☑	☑
≠ PMID: 30745422 Lo et al 2019 Associations of CDH1 germline variant location and cancer phenotype in families with hereditary diffuse gastric cancer (HDGC). Toggle detail	☑	☐
≠ PMID: 31296550 Xicola et al 2019 Clinical features and cancer risk in families with pathogenic CDH1 variants irrespective of clinical criteria. Toggle detail	☐	☑

- Platform designed and tested to record details of interactions
  - But this aspect is not being used!
- Consultation underway to alter design to meet user needs…..

Flexibility is important

Australian Genomics Health Alliance

Global Sharing

- Laboratories are encouraged to submit to public databases
  - But the decision rests with each laboratory

- So far all laboratories want to submit to ClinVar
  - Prefer Shariant to facilitate submission on their behalf (with recognition to the laboratory)

- ClinVar submission requires standardization of "condition curated against"
  - Majority of Shariant records did not have a standard condition term/ID …

- Shariant functionality extended to convert free text conditions to MONDO terms
  - Incorporates gene-disease relationships from MONDO, Gene Curation Coalition, PanelApp Australia
  - Exact match to MONDO title is auto-assigned condition, with validation
  - Laboratory must review and agree to additional suggested condition-matches
  - Standardized terms can now be returned to the laboratory for re-use

Australian Genomics Health Alliance

Impact – discordance resolution

"We were able to provide a diagnosis to a family as a result of additional information detected via Shariant from another Australian laboratory.*

Sharing information between two Australian laboratories about a specific rare gene variant allowed us to make the diagnosis of a cardiac condition in a family within a matter of weeks.

This result can now be used to guide treatment plans for multiple family members with the aim of preventing long-term complications."

Victorian Clinical Genetics Services

** Segregation data from one laboratory. Review of information by second laboratory..*

Australian Genomics Health Alliance

More recent success story

Real-time classification – Victorian Clinical Genetics Services

- Laboratory WES filtering altered to include lookup to Shariant

- Pathogenic variant identified in “recessive” gene
- Another variant in same gene prioritized by filtering
  - due to presence in Shariant
  - curation evidence available for review
  - variant classified as pathogenic by laboratory

- Rapid diagnosis of recessive condition for critically ill infant

Acknowledgements

The many individuals & labs involved in conception, development and implementation of Shariant!

Australian Genomics Program 2
Amanda Spurdle
Emma Tudini
James Andrews
David Lawrence
Tiffany Boughtwood
Marie-Jo Brion
Natalie Thorne

Australian Genomics Program 1
Hamish Scott
Sarah King-Smith
Matilda Jackson
Matilda Haas
Tessa Mattiske

Australian Genomics Program 4
Stephanie Best

Sites connected
Karin Kassahn
Lesley Rawlings
Kathy Cox
Andrew Dubowsky
Janice Fletcher
Kathryn Friend
Evelyn Douglas
Linda Burrows
Louisa Sanchez
Sinlay Kang
Sebastian Lunke
Zornitza Stark
Naomi Baker
Anthony Marty
James U
Belinda Chong
Dean Phelan
Miriam Fanjul Fernandez
Sarah-Jane Pantaleo
Bryony Thompson
Lauren Akesson
Bruce Bennetts
Gladys Ho
Rahul Krishnaraj
Anja Ravine
Emma Hackett
Katherine Holman
Katrina Fisk
John Beilby
Cheryl Wise
Michael Black
Mark Davis
Richard Allcock
Amanda Hooper

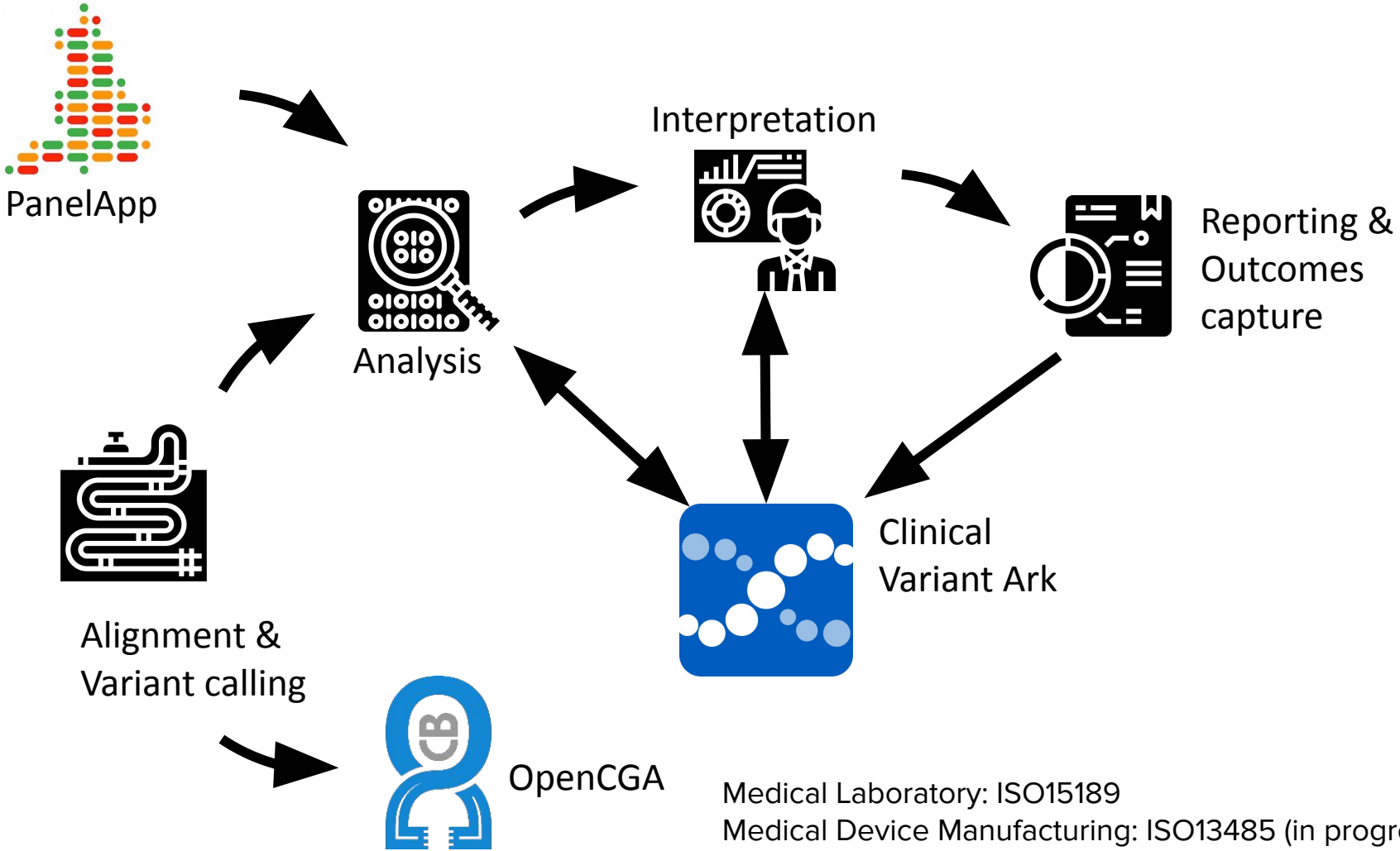
Shariant is built using VariantGrid technology

Australian Genomics Health Alliance

Clinical Variant Ark:
Case-level data in support of variant classification

Augusto Rendon on behalf of a lot of people at Genomics England

augusto.rendon@genomicsengland.co.uk



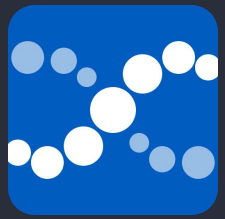
Medical Laboratory: ISO15189
Medical Device Manufacturing: ISO13485 (in progress)

Genomic data and knowledge infrastructure

PanelApp

Crowd-sourced knowledgebase of gene-disease relationships and the evidence behind it.

Clinical Variant Ark



Knowledgebase of clinically relevant variant-phenotype relationships captured throughout the interpretation process

OpenCGA

Population scale database of all variant phenotypes and all phenotypes

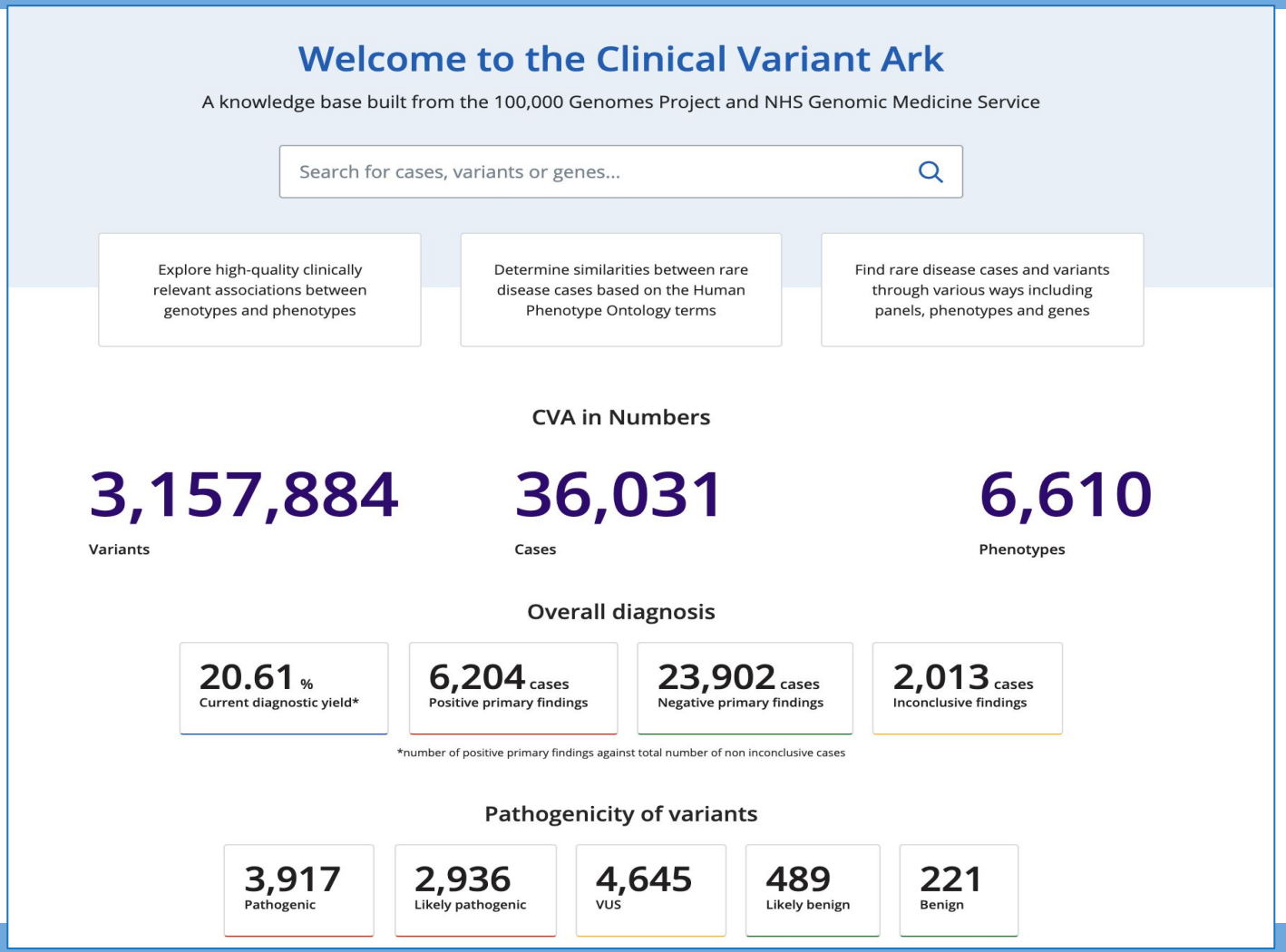
All open source

Key features of CVA

- One knowledge base for all of England (7 lab hubs, for 55 million people)
- Stores the case level information, going beyond the reported variants (think up to 1000 variants per case)
  - Prioritised by humans or by computers
  - Curated
  - Reported
- Operational database, in the sense that updates to cases are manifested in the database in real-time (not an archival or submission system)
- Integrated into the interpretation processes by users in the NHS

Key features of CVA (cont)

- **Case, variant and gene view**
- GUI, python client and REST API
- (to come) Direct submission to ClinVar
- Currently only manages germline findings


Welcome to the Clinical Variant Ark
A knowledge base built from the 100,000 Genomes Project and NHS Genomic Medicine Service
Search for cases, variants or genes...
Explore high-quality clinically relevant associations between genotypes and phenotypes
Determine similarities between rare disease cases based on the Human Phenotype Ontology terms
Find rare disease cases and variants through various ways including panels, phenotypes and genes
CVA in Numbers
3,157,884
Variants
36,031
Cases
6,610
Phenotypes
Overall diagnosis
20.61 %
Current diagnostic yield*
6,204 cases
Positive primary findings
23,902 cases
Negative primary findings
2,013 cases
Inconclusive findings
*number of positive primary findings against total number of non inconclusive cases
Pathogenicity of variants
3,917
Pathogenic
2,936
Likely pathogenic
4,645
VUS
489
Likely benign
221
Benign

CVA Portal

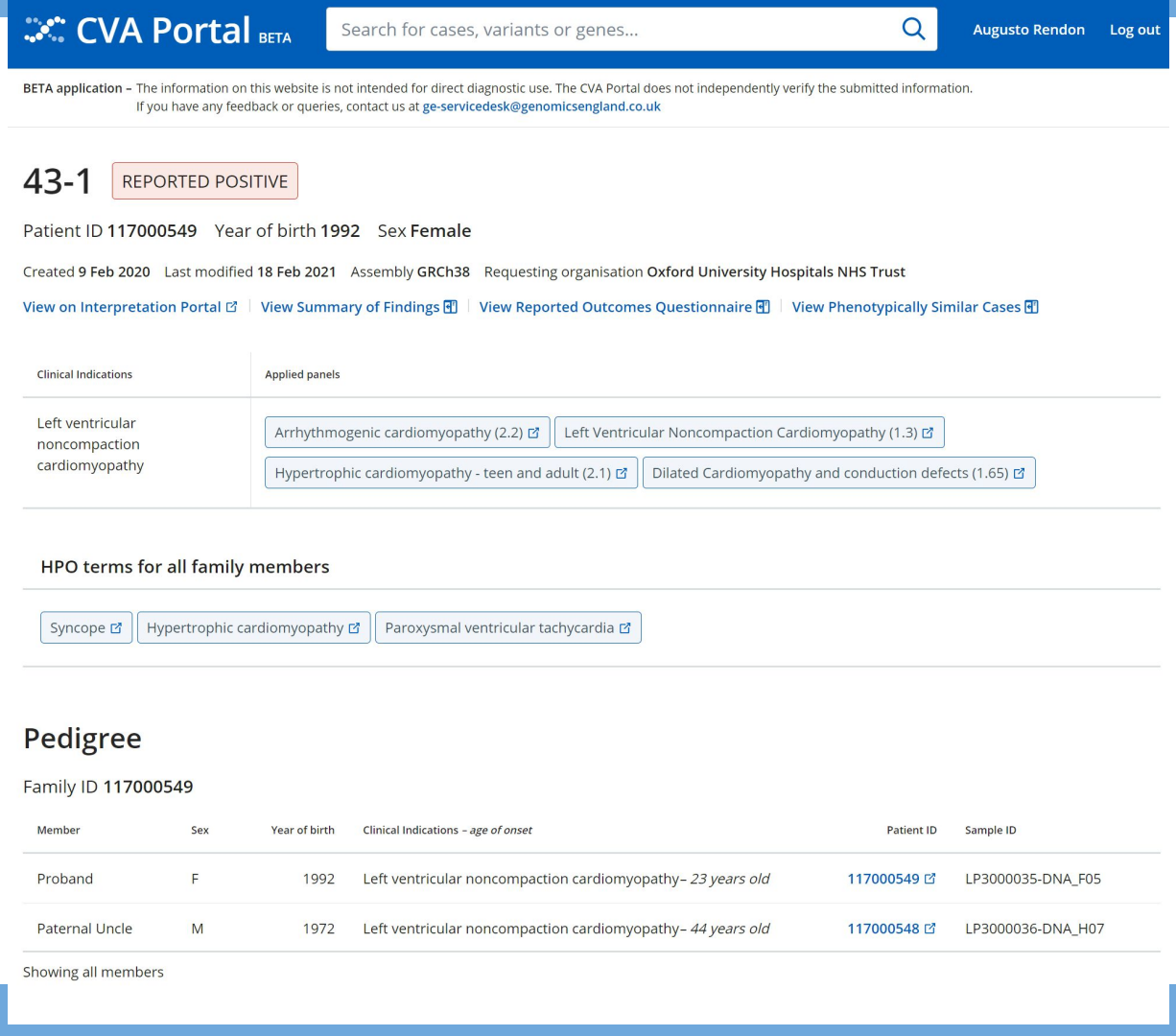
100k
GMS

DxYield

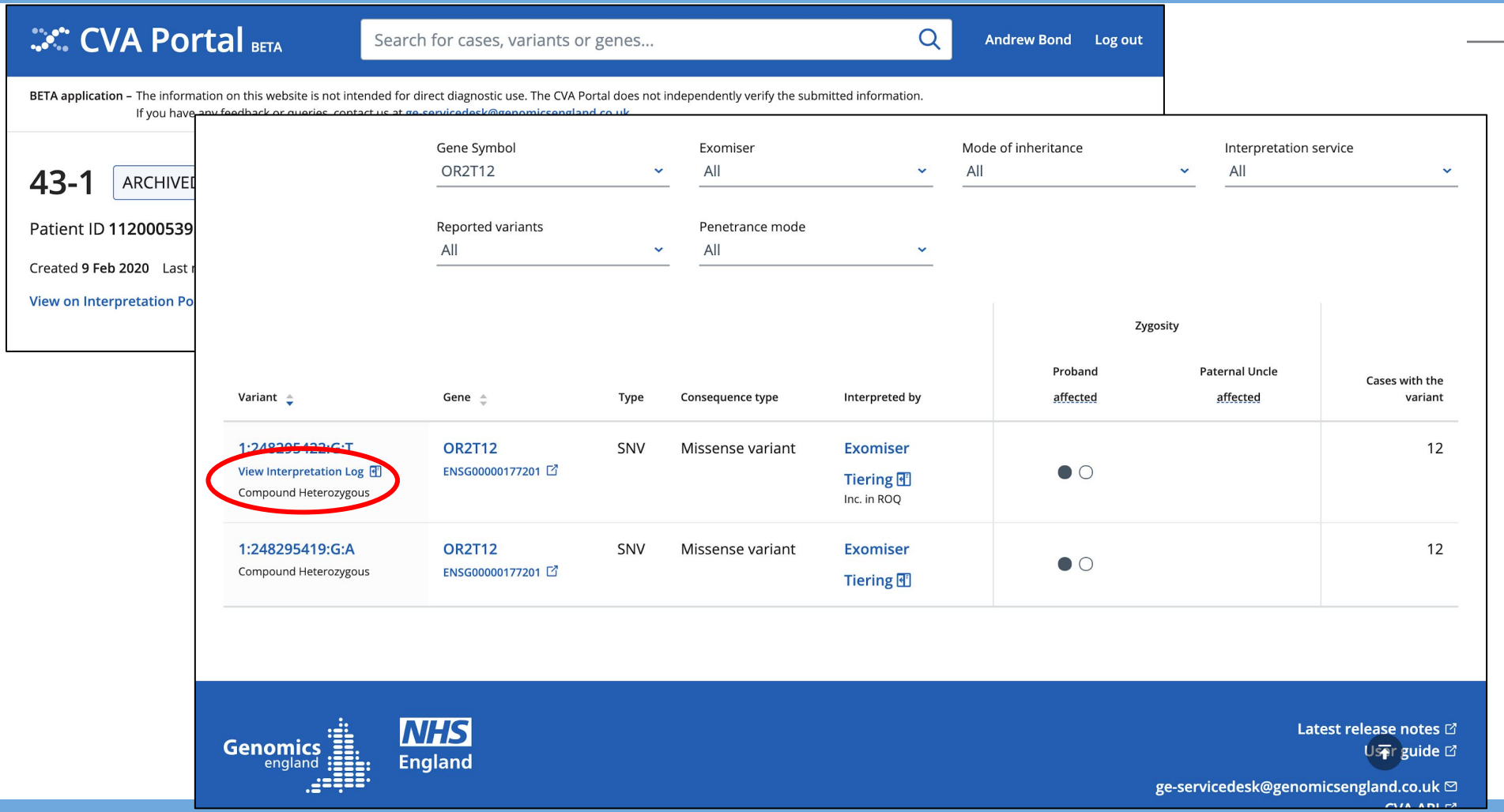
20.61%

Current diagnostic yield*

Clinical Indication	Total Cases	Archived Cases	Positive Diagnosis	Negative Diagnosis	Diagnostic Yield
Intellectual Disability	6716	6030	1470	4043	0.26664248
Ultra Rare Undescribed Monogenic Disorders	1405	1314	177	1069	0.14205457
Cystic Kidney Disease	1325	1292	664	545	0.54921424
Epilepsy Plus Other Features	1386	1170	114	989	0.10335449
Rod Cone Dystrophy	1233	1158	428	666	0.39122486
Congenital Anomaly Of The Kidneys And Urinary Tract (Cakut)	1017	974	46	904	0.04842105



Case View + "Interpretation Log"


CVA Portal BETA
Search for cases, variants or genes...
Andrew Bond
Log out
BETA application – The information on this website is not intended for direct diagnostic use. The CVA Portal does not independently verify the submitted information.
If you have any feedback or queries, contact us at ge.servicedesk@genomicsengland.co.uk
43-1
ARCHIVED
Patient ID 112000539
Created 9 Feb 2020
View on Interpretation Po
Gene Symbol
OR2T12
Exomiser
All
Mode of inheritance
All
Interpretation service
All
Reported variants
All
Penetrance mode
All
Zygosity
Variant
Gene
Type
Consequence type
Interpreted by
Proband affected
Paternal Uncle affected
Cases with the variant
1:248295422:G:T
View Interpretation Log
Compound Heterozygous
OR2T12
ENSG00000177201
SNV
Missense variant
Exomiser
Tiering
Inc. in ROQ
12
1:248295419:G:A
Compound Heterozygous
OR2T12
ENSG00000177201
SNV
Missense variant
Exomiser
Tiering
12
Genomics england
NHS England
Latest release notes
User guide
ge-servicedesk@genomicsengland.co.uk

Clear all filters

All

Gene Symbol

OR2T12

Reported variants

All

Variant	Gene
1:248295422:G:T View Interpretation Log Compound Heterozygous	OR2T12 ENSG00000177201
1:248295419:G:A Compound Heterozygous	OR2T12 ENSG00000177201

1:248295422:G:T

LIKELY-PATHOGENIC

Variant type **SNV**

OR2T12

Variant assembly **GRCh38**

Variant Interpretation Logs

OPA-43-1

LIKELY PATHOGENIC

PM2 PVS1

Comments

[2020-07-24] saw this was LP in CVA so added new evidence

[2020-07-24] chris updated log XXXXXX

[2020-07-10] chris test log

Created by:
christopher.boustred@genomicsengland.co.uk

Created date:
24 Jul 2020

Validation status:
Confirmed

Genomics england

NHS England

Variant view

19:44909101:C>G VUS

ENST00000252486(ENSG00000130203):c.805C>G

Variant type **SNV** Assembly **GRCh38**

Cases with variant **38** De novo variant **0** Max. allele frequency **0.001**

Variant evidence ClinVar | dbSNP

Cases by pathogenicity

0 Pathogenic **0** Likely pathogenic **2** VUS **0** Likely benign **0** Benign

Cases by interpretation services

38 Tiering **1** Exomiser **0** Omicia **3** Congenica

Overlapping genes

APOE

Ensembl ID	Ensembl Transcript ID	Most severe consequence
ENSG00000130203	ENST00000252486	Missense variant

Phenotypic summary of variant

HPO terms present (number of cases)

Global developmental delay (7) | Intellectual disability (7) | Delayed speech and language development (6) | Delayed fine motor development (4)

Delayed gross motor development (4) | Microcephaly (4) | Seizures (4) | Chronic kidney disease (3) | Dyspnea (3) | Dystonia (3) | Hypertension (3)

Proportionate short stature (3) | Urinary urgency (3) | Abnormal facial shape (2) | Arrhythmia (2) | Breast carcinoma (2) | Dysphagia (2)

Enlarged kidney (2) | Falls (2) | Fatigue (2) | Gastroesophageal reflux (2) | Headache (2) | IgM deficiency (2) | Immunodeficiency (2) | Mild (2)

Cases with variant 19:44909101:C:G

There is a possibility of incidental findings being shown. Select Clinical Indications to view cases with this variant.

Clinical Indication by number of cases Clear Clinical Indication filter

Select all Clinical Indications

- [x] Intellectual Disability (8)
- [ ] Ultra Rare Undescribed Monogenic Disorders (3)
- [ ] Congenital Anomaly Of The Kidneys And Urinary Tract (Cakut) (2)
- [ ] Cystic Kidney Disease (2)
- [ ] Epilepsy Plus Other Features (2)
- [ ] Exceptionally Young Adult Onset Cancer (2)
- [ ] Primary Immunodeficiency (2)
- [ ] Arrhythmogenic Right Ventricular Cardiomyopathy (1)
- [ ] Brain Channelopathy (1)
- [ ] Dilated Cardiomyopathy (1)

Filter cases by
Clear case filters

Case status	Requesting organisation	Interpretation service	HPO-based phenotypes
Archived - Inconclusiv...	All	All	All

Case ID	Status	Pathogenicity of 19:44909... in CVA	Clinical Indication	Proband's zygosity	Interpreted by
3446-1 Guy's & St Thomas' Hospital NHSFT	Archived Inconclusive findings		Intellectual disability	● ○	Exomiser Omicia Tiering

Showing all cases

Gene View

Classified variants in LDLR

Variants are those reported in the outcomes questionnaire that are within the chromosomal co-ordinates of the gene with a start and end base of +/- 1000bp.

Transcript used ENST00000558518

Filter variants by

Clear all filters

Consequence type: All

Max allele frequency: All

Max homozygous frequency: All

Variant (GRCh38)	Type	Exon	Consequence type	Max allele frequency	Max homozygous frequency	Pathogenicity in CVA	Cases with the variant
19:11116969:G:T	SNV	12/18	Missense variant	0.0006	0.0000	Pathogenic	22
19:11111538:A:C	SNV	8/18	Missense variant	0.0005	0.0000	VUS	11
19:11120436:C:T	SNV	14/18	Missense variant	0.0005	0.0000	Pathogenic	6
19:11105588:G:T	SNV	4/18	Stop gained	0.0005	0.0000	Pathogenic	4
19:11131339:C:A	SNV	18/18	3 prime utr variant	0.0000	0.0000	VUS	3

PubMed evidence for LDLR

PubMed evidence selected to support annotation of cases.

Effects of familial hypercholesterolemia-associated genes on the phenotype of premature myocardial infarction.

Authors **Lee C, Cui Y, Song J, Li S, Zhang F, Wu M, Li L, Hu D, Chen H**

Published **11 Apr 2019** PubMed ID **30971288**

Whole-Genome Sequencing to Characterize Monogenic and Polygenic Contributions in Patients Hospitalized With Early-Onset Myocardial Infarction.

Authors **Khera AV, Chaffin M, Zekavat SM, Collins RL, Roselli C, Natarajan P, Lichtman JH, D'Onofrio G, Mattera J, Dreyer R, Spertus JA, Taylor KD, Psaty BM, Rich SS, Post W, Gupta N, Gabriel S, Lander E, Ida Chen YD, Talkowski ME, Rotter JI, Krumholz HM, Kathiresan S**

Published **26 Mar 2019** PubMed ID **30586733**

Application of expanded genetic analysis in the diagnosis of familial hypercholesterolemia in patients with very early-onset coronary artery disease.

Authors **Cao YX, Wu NQ, Sun D, Liu HH, Jin JL, Li S, Guo YL, Zhu CG, Gao Y, Dong QT, Liu G, Dong Q, Li JJ**

Published **10 Dec 2018** PubMed ID **30526649**

Genetic and secondary causes of severe HDL deficiency and cardiovascular disease.

Authors **Geller AS, Polisecki EY, Diffenderfer MR, Asztalos BF, Karathanasis SK, Hegele RA, Schaefer EJ**

Published **01 Dec 2018** PubMed ID **30333156**

LDLR

Previous symbols **None** Alias symbols **LDLCQ2**

Gene name **low density lipoprotein receptor** Location **19:11089362-11133816 GRCh38, forward strand** Cases with LDLR reported **57**

Gene evidence HGNC | ClinVar | Decipher | OMIM | PanelApp | Ensembl ID ENSG00000130164 PubMed evidence **48**

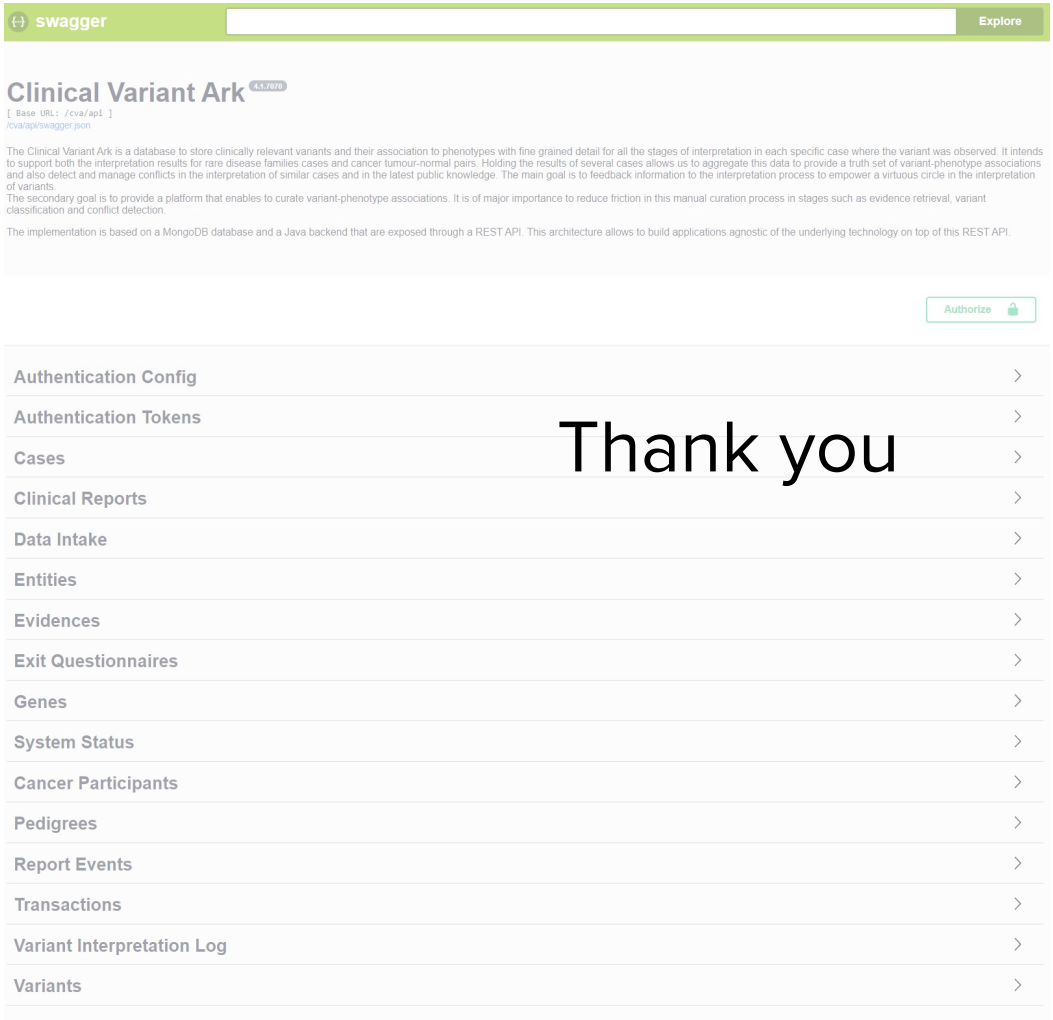
Panels and pathogenicity

Cases in CVA with a classified variant in LDLR split by gene panels. The current panel version and evidence for that gene in the panel is shown.

Note: This may differ from the specific panel version used during Genomics England Tiering.

Panel name	PanelApp evidence	Pathogenic	Likely pathogenic	VUS	Likely benign	Benign
COVID-19 research (1.76)	Low	0	0	0	0	0
Childhood onset dystonia or chorea or related movement disorder (1.83)	Low	0	0	0	0	0
Familial hypercholesterolaemia (1.27)	High	42	20	9	0	0
Familial hypercholesterolaemia - targeted panel (1.8)	High	0	0	0	0	0
Inborn errors of metabolism (2.101)	High	0	0	0	0	0
Severe Paediatric Disorders (1.65)	High	0	0	0	0	0
Undiagnosed metabolic disorders (1.447)	High	0	1	0	0	0

Showing **7** of **7** panels Show less



Thank you

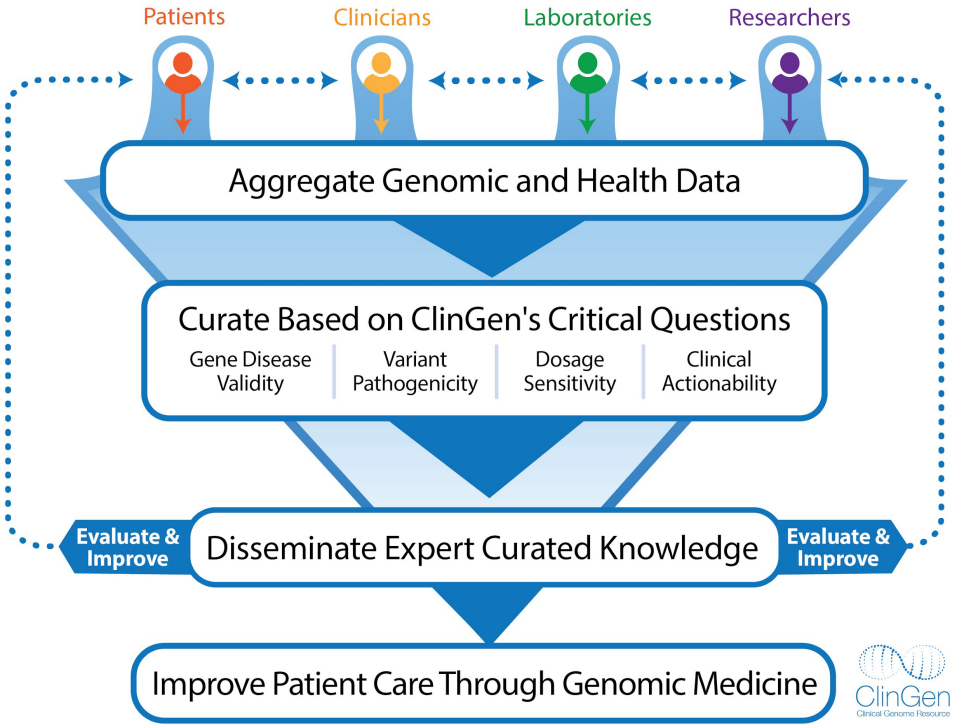
[CVA Documentation]

ClinGen Expert Panels: Development of disease-specific expert consensus to knowledge curation

Heidi L. Rehm, PhD, FACMG
Chief Genomics Officer, Center for Genomic Medicine and Department of Medicine, MGH
Medical Director, Broad Institute Clinical Research Sequencing Platform
Professor of Pathology, MGH, BWH and HMS

@HeidiRehm

The Clinical Genome Resource



www.clinicalgenome.org

Purpose: Create an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research.

- *Started September 2013*
- *Primarily funded by the NIH*
  - *3 Core U41 Grants (NHGRI)*
  - *Disease-focused U24s (NIH)*

1,557 investigators
across 36 countries

Variant curation and classification

- Use of common standards
  - Terminology
  - Rules for variant classification
- Public sharing of variant classifications
  - Creates transparency and crowd-sources the work
- Inter-laboratory conflict resolution
- Engaging experts in systematic consensus driven interpretation of variants (Expert Panels)

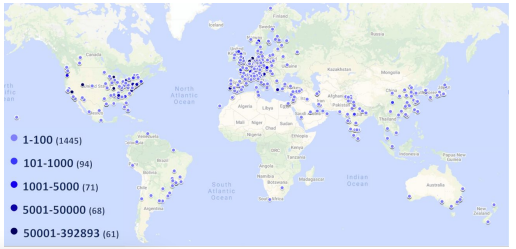
ACMG STANDARDS AND GUIDELINES | Genetics inMedicine

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

Sue Richards, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5], Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12], Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15]; on behalf of the ACMG Laboratory Quality Assurance Committee

ClinGen Sequence Variant Interpretation Working Group

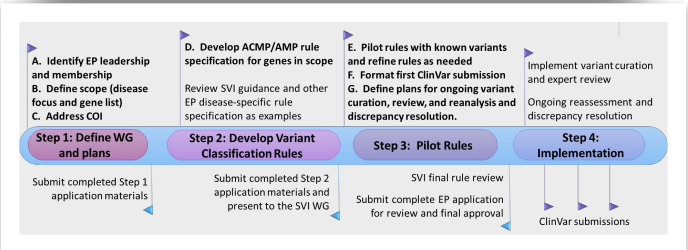
ClinVar
1,354,844 submissions on 863,338 variants
1846 submitters from 78 countries



Scaling resolution of variant classification differences in ClinVar between 41 clinical laboratories through an outlier approach

Steven M. Harrison, Jill S. Dolinksy, Wenjie Chen, Christin D. Collins, Soma Das, Joshua L. Deignan, Kathryn B. Garber, John Garcia, Olga Jarinova, Amy E. Knight Johnson, Juha W. Koskenvuo, Hane Lee, Rong Mao, Rebecca Mar-Heyming, Andrew S. McFaddin, Krista Moyer, Narasimhan Nagan, Stefan Rentas, Avni B. Santani, Eija H. Seppälä, Brian H. Shirts, Timothy Tidwell, Scott Topper, Lisa M. Vincent, Kathy Vinette, Heidi L. Rehm, on behalf of ClinGen Sequence Variant Inter-Laboratory Discrepancy Resolution Working Group ... See fewer authors

All of Us – 4 clincial labs
49,943 variants → 99.9% concordance to date



ClinVar 3 Star Status:
~12,000 variants

reviewed by expert panel
FDA Recognized Database

About ClinGen Expert Panels

ClinGen's Expert Panels are implementing the standards developed by our curation activities to improve genomics knowledge.

Clinical Domain Working Groups	Gene Curation Expert Panels	Variant Curation Expert Panels	Gene Curation Working Group	Dosage Sensitivity Working Group	Clinical Actionability Working Group
Cardiovascular CDWG	Arrhythmogenic Right Ventricular Cardiomyopathy Gene Curation Expert Panel (In Process)				
	Brugada Syndrome Gene Curation Expert Panel				
	Cardiomyopathy Variant Curation Expert Panel				
	Familial Hypercholesterolemia Variant Curation Expert Panel (In Process)				
	Familial Thoracic Aortic Aneurysm and Dissection Gene Curation Expert Panel				
	FBN1 Variant Curation Expert Panel (In Process)				
	Hypertrophic Cardiomyopathy Gene Curation Expert Panel				
	KCNQ1 Variant Curation Expert Panel (In Process)				
	Long QT Syndrome Gene Curation Expert Panel (In Process)				
Hearing Loss CDWG	Hearing Loss Gene Curation Expert Panel				
	Hearing Loss Variant Curation Expert Panel				
Hemostasis/Thrombosis CDWG	Coagulation Factor Deficiency Variant Curation Expert Panel (In Process)				
	Hereditary Hemorrhagic Telangiectasia Variant Curation Expert Panel (In Process)				
	Platelet Disorder Variant Curation Expert Panel (In Process)				
Hereditary Cancer CDWG	Breast/Ovarian Cancer Gene Curation Expert Panel				
	CDH1 Variant Curation Expert Panel				

13 Clinical Doman Working Groups

- Cardiovascular CDWG
- Hearing Loss CDWG
- Hemostasis/Thrombosis CDWG
- Hereditary Cancer CDWG
- Inborn Errors of Metabolism CDWG
- Neurodevelopmental Disorders CDWG
- RASopathy CDWG
- Neuromuscular CDWG
- Ocular CDWG
- Skeletal Disorders CDWG
- Kidney Disease CDWG
- Immunology CDWG
- Somatic Cancer CDWG

32 Gene Curation Expert Panels

37 Variant Curation Expert Panels

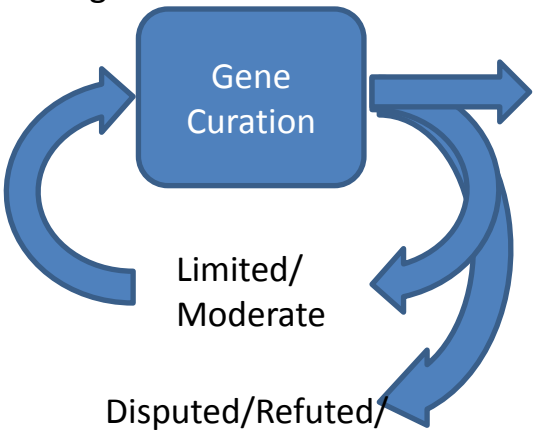
ClinGen Expert Panels Span Many Time Zones!

1557 researchers & clinicians from 36 countries

[Map by Natalie Pino; Time-zone videos from Birgit Funke]

ClinGen Core Curation Activities

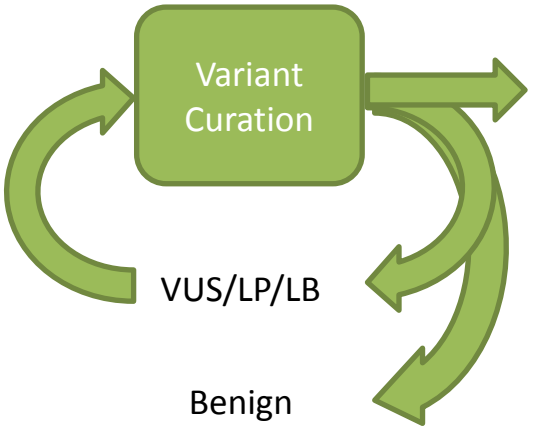
Score aggregate genetic and experimental evidence for a gene's role in disease



Gene-Disease Relationships with Valid Evidence* (Strong & Definitive)

*Note: Gene curation may define more than one disease associated to a given gene based on factors such as inheritance or pathogenicity mechanism.

Score genetic and experimental evidence for a variant's role in disease



<u>Tools & Resources:</u>
ClinGen's Gene Curation Expert Panels & Gene Curation Interface

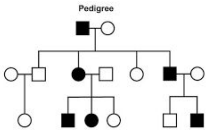
<u>Tools & Resources:</u>
ClinGen's Variant Curation Expert Panels & Variant Curation Interface

ClinGen's semi-quantitative framework to classify the strength of evidence for the role of genes in disease

ARTICLE

Evaluating the Clinical Validity of Gene-Disease Associations: An Evidence-Based Framework Developed by the Clinical Genome Resource

Natasha T. Strande,[1,14] Erin Rooney Riggs,[2,14] Adam H. Buchanan,[3] Ozge Ceyhan-Birsoy,[4,5,6,7] Marina DiStefano,[4] Selina S. Dwight,[8] Jenny Goldstein,[1] Rajarshi Ghosh,[9] Bryce A. Seifert,[1] Tam P. Sneddon,[8] Matt W. Wright,[8] Laura V. Milko,[1] J. Michael Cherry,[8] Monica A. Giovanni,[3] Michael F. Murray,[3] Julianne M. O'Daniel,[1] Erin M. Ramos,[10] Avni B. Santani,[11,12] Alan F. Scott,[13] Sharon E. Plon,[9] Heidi L. Rehm,[4,5,6,7] Christa L. Martin,[2,3,*] and Jonathan S. Berg[1,*]



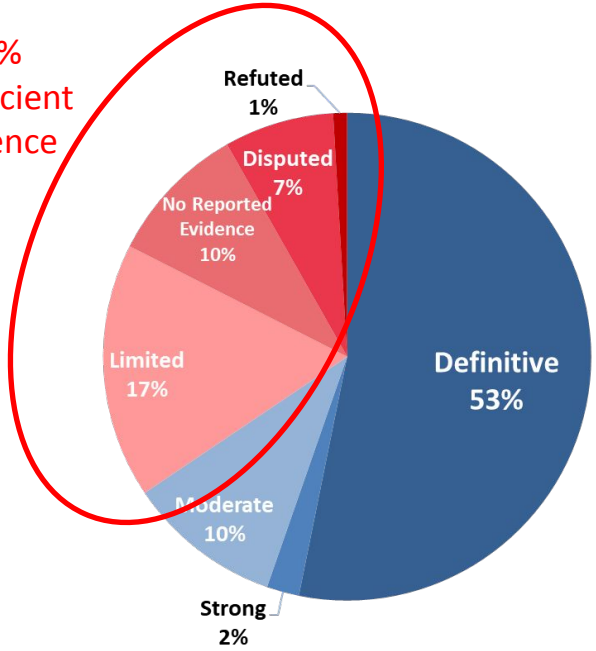
Genetic Evidence: Case-level, family segregation, or case-control data

Experimental Evidence: Expression, model organism, rescue studies, etc.

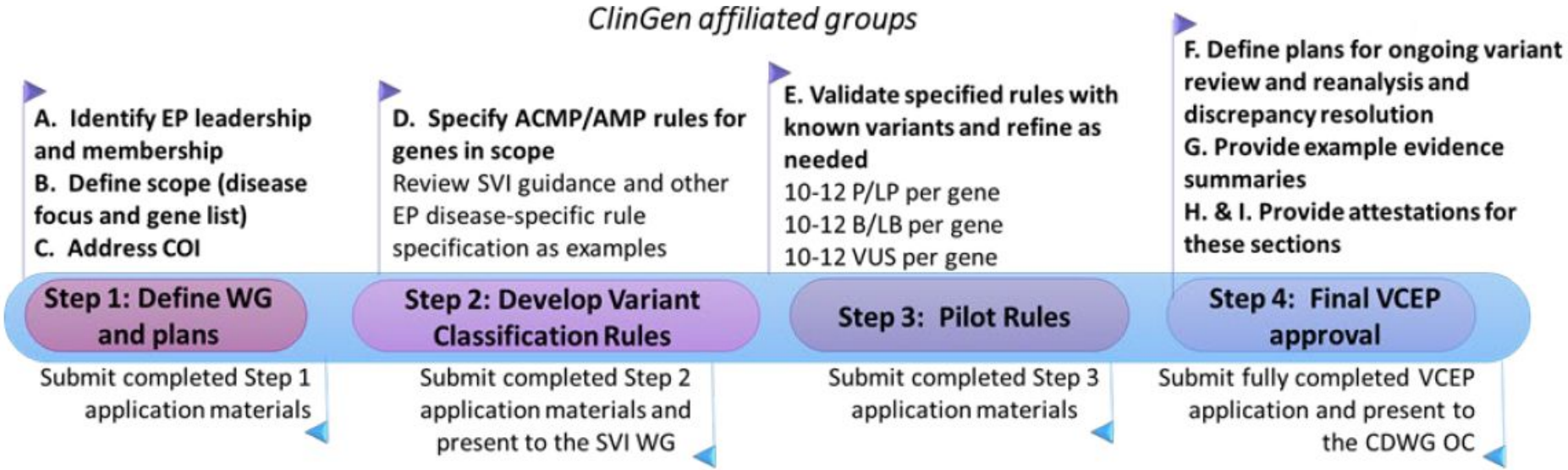
- Definitive
- Strong
- Moderate
- Limited
- No Evidence Reported
- Conflicting Evidence Reported
  - Disputed
  - Refuted

1235 gene-disease pairs

35% insufficient evidence



ClinGen Variant Curation Expert Panel Approval Steps



Criteria requiring gene/disease specification

Gene-specific data, such as:

- PM1: Functional domains / hot spots
- PS3/BS3: Validated functional assays

Disease specific data, such as:

- BA1/BS1/BS2/PM2/BS4: MAF/Prevalence/penetrance
- PP4: Phenotype specificity
- PVS1: Pathogenicity mechanism

RASopathy VCEP:
Final classification of >60% of RASopathy variants were impacted by the specified criteria.
Labs reached **100%** concordance for discrepancies reassessed with RASopathy-specific criteria

	Benign		Pathogenic			
	Strong	**Supporting**	**Supporting**	**Moderate**	**Strong**	**Very strong**
Population data	MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

Sequence Variant Interpretation

The goal of the Sequence Variant Interpretation Working Group (SVI WG) is to support the refinement and evolution of the ACMG/AMP Interpreting Sequence Variant Guidelines to develop quantitative approaches to variant interpretation.

Subgroups | Documents | Tools | Membership

The Sequence Variant Interpretation WG also consults with and supports Expert Panel groups to develop gene- and disease-specific refinements of the ACMG/AMP Interpreting Sequence Variant Guidelines to increase the uniformity and consistency of the Expert Panel recommendations.The SVI WG has representation from the Biocurators WG, CNV Interpretation WG and Variant Curation Interface development team and all ClinGen Expert Panels.

SVI General Recommendations for Using ACMG/AMP Criteria

SVI provides general recommendations for using the ACMG/AMP criteria to improve consistency in usage and transparency in classification rationale.

- Guidance on how to rename criteria codes when strength of evidence is modified
- BA1: Updated Recommendation for the ACMG/AMP Stand Alone Pathogenicity Criterion for Variant Classification
  - BA1 Exception List (July 2018)
  - BA1 Exception List Nomination Form
- PVS1: Recommendations for Interpreting the Loss of Function PVS1 ACMG/AMP Variant Criteria
- PS2/PM6: Recommendation for de novo PS2 and PM6 ACMG/AMP criteria (Version 1.0)
- PS3/BS3: Recommendations for application of the functional evidence PS3/BS3 criterion using the ACMG/AMP sequence variant interpretation framework
- PM3: Recommendation for in trans Criterion PM3 (Version 1.0)
- PP5/BP6: Recommendation for reputable source PP5 and BP6 ACMG/AMP criteria

Chairs

Leslie G. Biesecker, MD

Steven Harrison, PhD

Coordinators

Please contact a coordinator if you have questions.

Danielle Azzariti, MS, CGC

dazzarit@broadinstitute.org

ClinGen

SVI Approved Expert Panel Specified ACMG/AMP Variant Interpretation Guidelines

ClinGen

General SVI Publications

› Recommendations for interpreting the loss of

ClinGen's RASopathy Expert Panel consensus methods for variant interpretation

Bruce D. Gelb, MD[1], Hélène Cavé, PharmD, PhD[2], Mitchell W. Dillon, MS[3], Karen W. Gripp, MD[4], Jennifer A. Lee, PhD[5], Heather Mason-Suares, PhD[6], Katherine A. Rauen, MD, PhD[7], Bradley Williams, MS[8], Martin Zenker, MD[9], Lisa M. Vincent, PhD[8] and for the ClinGen RASopathy Working Group

Adaptation and validation of the ACMG/AMP variant classification framework for *MYH7*-associated inherited cardiomyopathies: recommendations by ClinGen's Inherited Cardiomyopathy Expert Panel

Melissa A. Kelly, MS[1], Colleen Caleshu, MS[2], Ana Morales, MS[3], Jillian Buchan, PhD[1], Zena Wolf, PhD[1], Steven M. Harrison, PhD[1], Stuart Cook, MD[4], Mitchell W. Dillon, MS[1], John Garcia, PhD[5], Eden Haverfield, PhD[5], Jan D.H. Jongbloed, PhD[6], Daniela Macaya, PhD[7], Arjun Manrai, PhD[8], Kate Orland, MS[9], Gabriele Richard, MD[7], Katherine Spoonamore, MS[10], Matthew Thomas, MS[11], Kate Thomson, BSc[12,13], Lisa M. Vincent, PhD[7], Roddy Walsh, PhD[4,14], Hugh Watkins, MD PhD[13], Nicola Whiffin, PhD[4,14], Jodie Ingles, PhD[15], J. Peter van Tintelen, MD PhD[16], Christopher Semsarian, MBBS PhD[15], James S. Ware, PhD MRCP[4,14], Ray Hershberger, MD[3] and Birgit Funke, PhD[1,17,18]; for the ClinGen Cardiovascular Clinical Domain Working Group[19]

Gene-specific criteria for *PTEN* variant curation: Recommendations from the ClinGen PTEN Expert Panel

Jessica L. Mester[1] | Rajarshi Ghosh[2] | Tina Pesaran[3] | Robert Huether[4] | Rachid Karam[3] | Kathleen S. Hruska[1] | Helio A. Costa[5] | Katherine Lachlan[6,7] | Joanne Ngeow[8] | Jill Barnholtz-Sloan[9,10] | Kaitlin Sesock[11] | Felicia Hernandez[3] | Liying Zhang[12] | Laura Milko[13] | Sharon E. Plon[2] | Madhuri Hegde[14,15,*] | Charis Eng[9,10,16,*]

Expert specification of the ACMG/AMP variant interpretation guidelines for genetic hearing loss

Andrea M. Oza[1,2] | Marina T. DiStefano[1,3] | Sarah E. Hemphill[1] | Brandon J. Cushman[1] | Andrew R. Grant[1] | Rebecca K. Siegert[1] | Jun Shen[1,3,4] | Alex Chapin[5] | Nicole J. Boczek[6] | Lisa A. Schimmenti[7] | Jaclyn B. Murry[1] | Linda Hasadsri[6] | Kiyomitsu Nara[8] | Margaret Kenna[2,3] | Kevin T. Booth[9,10] | Hela Azaiez[9] | Andrew Griffith[11] | Karen B. Avraham[12] | Hannie Kremer[13] | Heidi L. Rehm[1,3,14,15] | Sami S. Amr[1,3,4] | Ahmad N. Abou Tayoun[16,17] | on behalf of the ClinGen Hearing Loss Clinical Domain Working Group

Unique aspects of sequence variant interpretation for inborn errors of metabolism (IEM): The ClinGen IEM Working Group and the Phenylalanine Hydroxylase Gene

Diane B. Zastrow[1,2] | Heather Baudet[3] | Wei Shen[4,11] | Amanda Thomas[5] | Yue Si[6] | Meredith A. Weaver[7] | Angela M. Lager[8] | Jixia Liu[9] | Rachel Mangels[2] | Selina S. Dwight[2] | Matt W. Wright[2] | Steven F. Dobrowolski[10] | Karen Eilbeck[11] | Gregory M. Enns[2] | Annette Feigenbaum[12] | Uta Lichter-Konecki[13] | Elaine Lyon[4,11] | Marzia Pasquali[4,11] | Michael Watson[7] | Nenad Blau[14] | Robert D. Steiner[9,15] | William J. Craigen[16] | Rong Mao[4,11] | for the ClinGen Inborn Errors of Metabolism Working Group

https://www.clinicalgenome.org/working-groups/sequence-variant-interpretation

ClinGen VCEPs do not review all variants!

VCEPs priorities include:

1. Resolving discrepancies

2. Classifying the most prevalent pathogenic variants

3. Examining variants that have been observed in multiple cases through which combining data can move them from VUS or LP to Pathogenic or Benign

Expert Panel Submissions Can Resolve Differences in Classification in ClinVar

NM_004004.6(GJB2):c.101T>C (p.Met34Thr)

Interpretation: Pathogenic

Review status: ★★★☆ reviewed by expert panel FDA RECOGNIZED DATABASE

Submissions: 33 (Most recent: Nov 26, 2020)

Last evaluated: Jun 24, 2019

Accession: VCV000017000.25

Variation ID: 17000

Description: single nucleotide variant

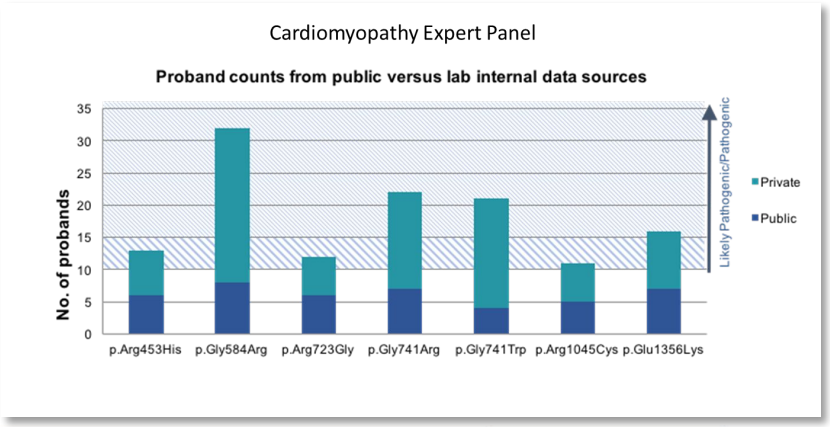
22 Pathogenic
4 Likely Pathogenic
2 VUS
2 Likely Benign
2 Benign

Practice Guideline	★★★★
Expert Panel (EP) Submitter	★★★
Multiple Non-EP Submitters Agree	★★
Single Non-EP Submitter OR Multiple Non-EP Submitters Disagree	★
No Assertion Criteria Submitter(s) Only	0 Stars

Expert panels also combine evidence to reclassify VUSs

NM_000257.4(MYH7):c.2678C>T (p.Ala893Val)

Interpretation:	**Likely pathogenic**
Review status:	★★★☆ reviewed by expert panel FDA RECOGNIZED DATABASE
Submissions:	4 (Most recent: Jun 3, 2020)
Last evaluated:	Dec 15, 2016
Accession:	VCV000177763.5
Variation ID:	177763
Description:	single nucleotide variant

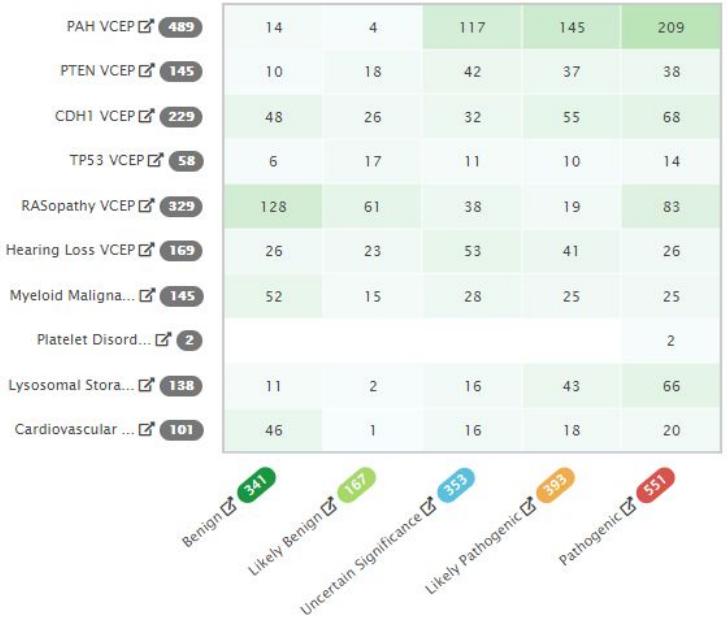


Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Submission accession
Likely pathogenic (Dec 15, 2016)	reviewed by expert panel • ACMG variant classification (MYH7)	curation	Primary dilated cardiomyopathy (Autosomal dominant inheritance) [MedGen | Orphanet]	germline		ClinGen Inherited Cardiomyopathy Expert Panel	SCV000564435.2
Uncertain significance (Jan 21, 2016)	criteria provided, single submitter • LMM Criteria	clinical testing	not specified [MedGen]	germline	• PubMed (2) [See all records that cite these PMIDs]	Laboratory for Molecular Medicine,Partners HealthCare Personalized Medicine	SCV000204046.3
Uncertain significance (Oct 24, 2016)	criteria provided, single submitter • GeneDx Variant Classification (06012015)	clinical testing	not specified [MedGen]	germline		GeneDx	SCV000208493.9

ClinGen VCEP Classified Variants in ClinVar Resolve Conflicts

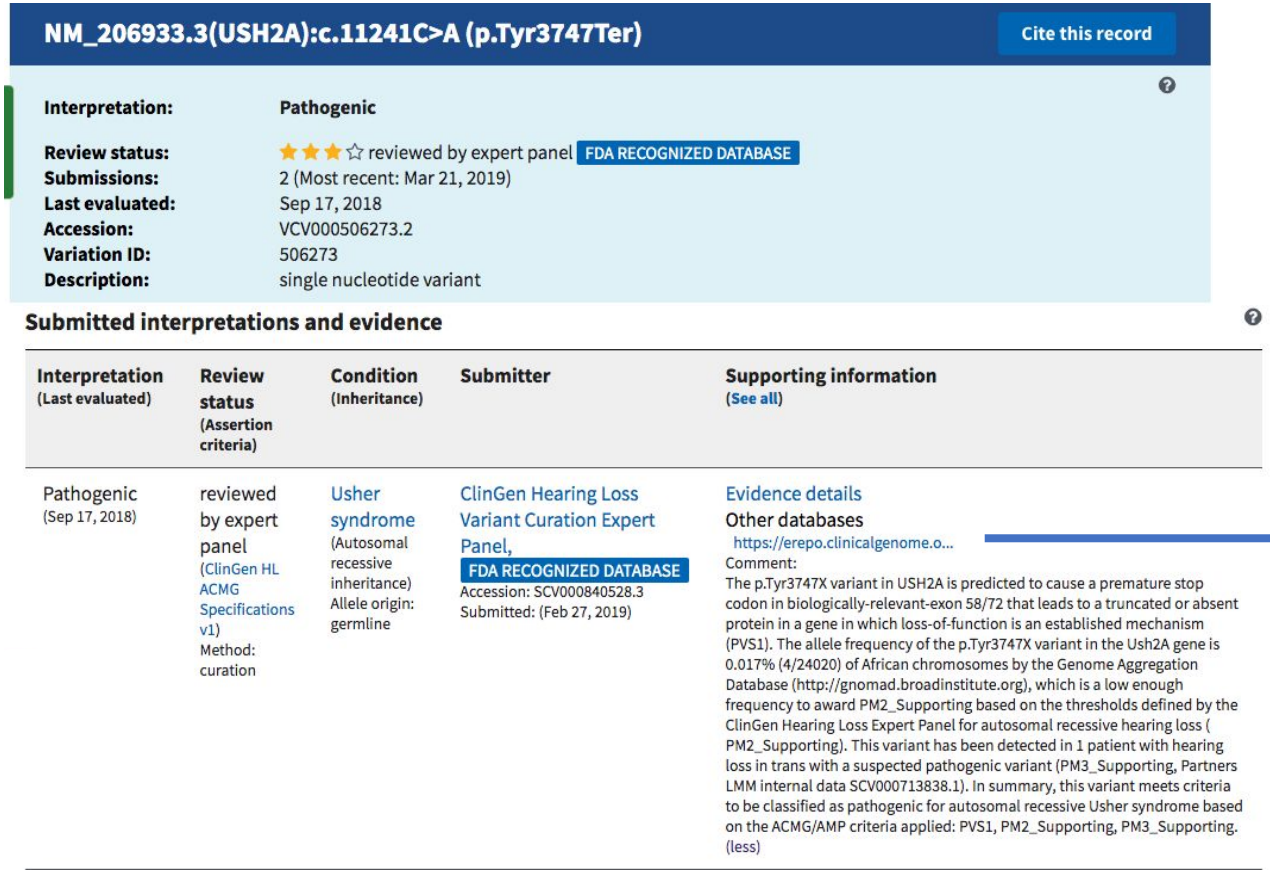
11,674 Expert Classified Variants in ClinVar

	CDH1	Hearing Loss	Cardio-myopathy	Myeloid Malignancy	PAH	PTEN	RASopathy	Total
Total Submission	50	77	102	52	158	111	254	804
P/LP vs VUS/LB/B overwritten	5	19	14	3	10	18	10	79
VUS vs LB/B overwritten	12	14	12	2	2	10	52	104



To track ClinGen FDA-recognized submissions go to:
https://erepo.clinicalgenome.org/evrepo/

VCEP Classifications in ClinVar



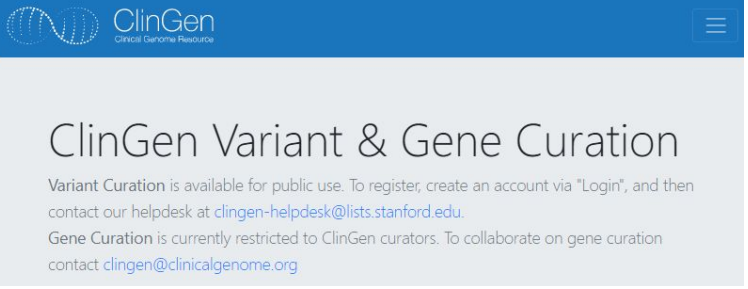
NM_206933.3(USH2A):c.11241C>A (p.Tyr3747Ter) Cite this record

Interpretation:	**Pathogenic**
Review status:	★★★☆ reviewed by expert panel FDA RECOGNIZED DATABASE
Submissions:	2 (Most recent: Mar 21, 2019)
Last evaluated:	Sep 17, 2018
Accession:	VCV000506273.2
Variation ID:	506273
Description:	single nucleotide variant

Submitted interpretations and evidence

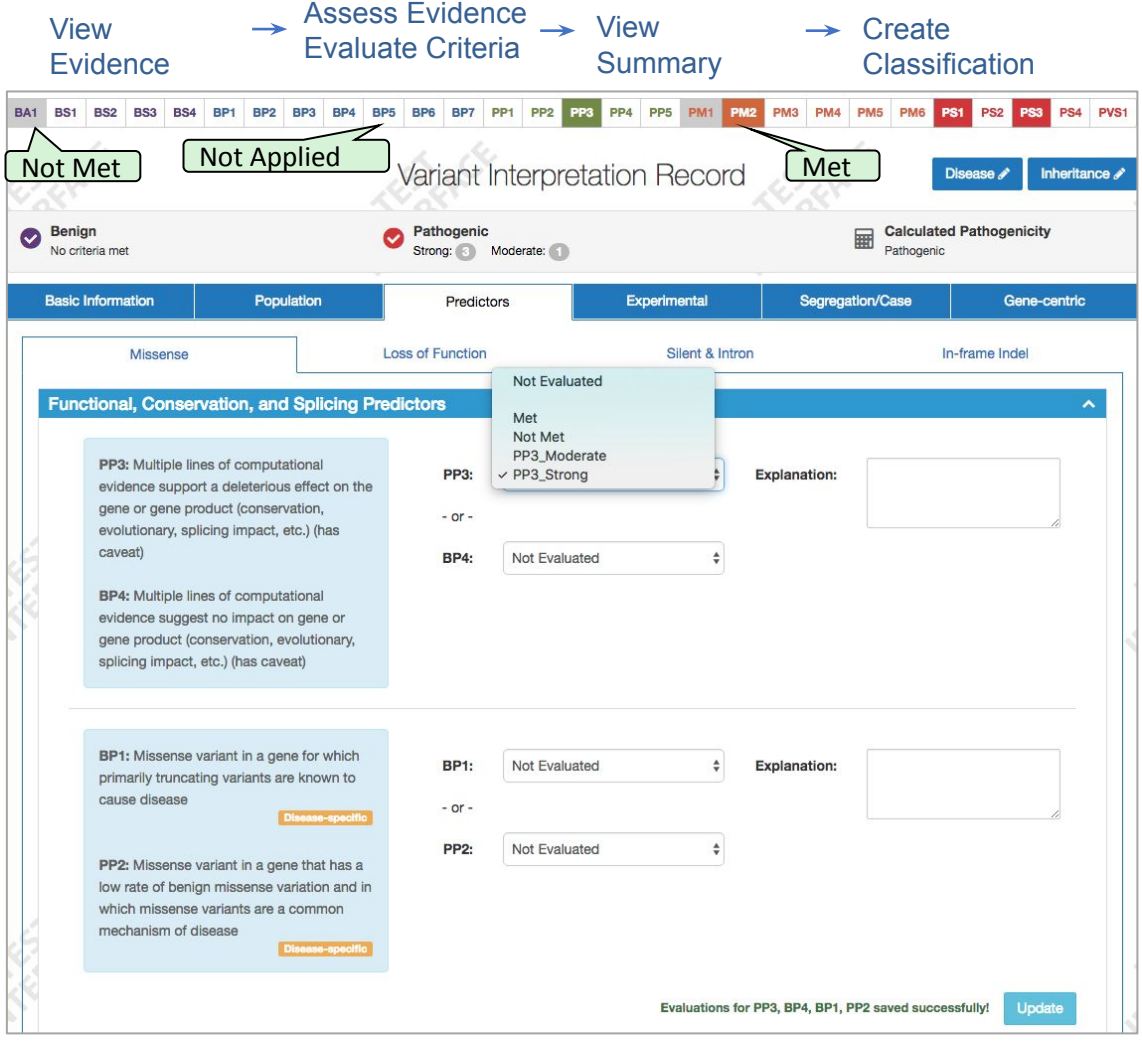
Interpretation (Last evaluated)	Review status (Assertion criteria)	Condition (Inheritance)	Submitter	Supporting information (See all)
Pathogenic (Sep 17, 2018)	reviewed by expert panel (ClinGen HL ACMG Specifications v1) Method: curation	Usher syndrome (Autosomal recessive inheritance) Allele origin: germline	ClinGen Hearing Loss Variant Curation Expert Panel, FDA RECOGNIZED DATABASE Accession: SCV000840528.3 Submitted: (Feb 27, 2019)	Evidence details Other databases https://erepo.clinicalgenome.o... Comment: The p.Tyr3747X variant in USH2A is predicted to cause a premature stop codon in biologically-relevant-exon 58/72 that leads to a truncated or absent protein in a gene in which loss-of-function is an established mechanism (PVS1). The allele frequency of the p.Tyr3747X variant in the Ush2A gene is 0.017% (4/24020) of African chromosomes by the Genome Aggregation Database (http://gnomad.broadinstitute.org), which is a low enough frequency to award PM2_Supporting based on the thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive hearing loss (PM2_Supporting). This variant has been detected in 1 patient with hearing loss in trans with a suspected pathogenic variant (PM3_Supporting, Partners LMM internal data SCV000713838.1). In summary, this variant meets criteria to be classified as pathogenic for autosomal recessive Usher syndrome based on the ACMG/AMP criteria applied: PVS1, PM2_Supporting, PM3_Supporting. (less)

View structured evidence in ClinGen's Evidence Repository



ClinGen Variant Curation Interface (VCI)

Used by VCEPs, laboratories and individuals to facilitate the classification of variants



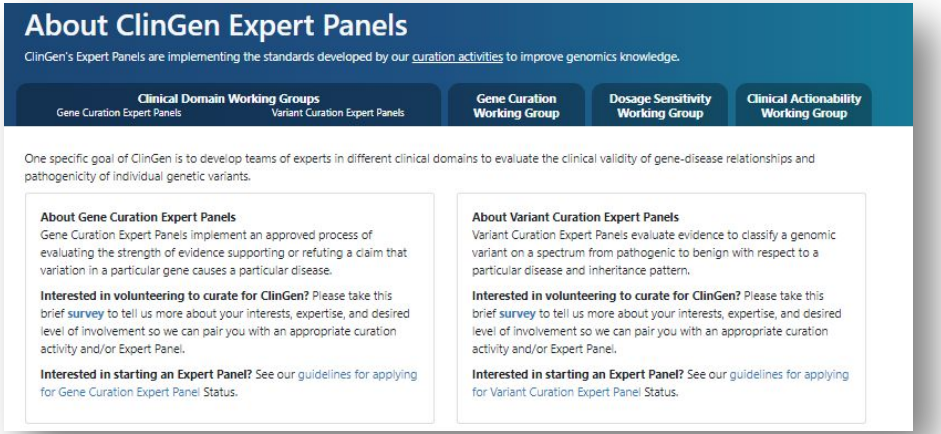
Opportunities to get Involved in ClinGen

https://clinicalgenome.org/start/

www.clinicalgenome.org/volunteer

If you want to volunteer as a biocurator and learn gene and variant curation, fill out our survey:

- If you have specific expertise and would like to join one of our Gene or Variant Curation Expert Panels as an expert:



For a full list of Expert Panels, visit this page:

https://clinicalgenome.org/working-groups/clinical-domain/

Clinical Genome Resource

Steering Committee (*PIs)

Jonathan Berg, UNC*
Adam Buchanan, Geisinger
Carlos Bustamante, Stanford
Andy Freedman, NCI
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Steven Harrison, Broad
Brandi Kattman, NCBI
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Christa Lese Martin, Geisinger*
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Joannella Morales, NHGRI
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Sharon Plon, Baylor*
Heidi Rehm, Broad/MGH*
Erin Ramos, NHGRI
Erin Riggs, Geisinger
Marc Williams, Geisinger*
Matt Wright, Stanford

Consortium Members: >1,557 people from >36 countries
Funding: NIH/NHGRI U41HG006834, U41HG009649, U41HG009650, NIH/NICHD: U24HD093483, U24HD093486, U24HD093487

ClinGen
Clinical Genome Resource

www.clinicalgenome.org
@ClinGenResource

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

Day 1 Closing

Kathryn North and Mark Caulfield