

National Initiatives Meeting

Day 1

Wellcome Collection, London
May 2, 2019

Opening Remarks

Kathryn North
Australian Genomics

Mark Caulfield
Genomics England



Meeting Goals

- How do we share clinical and genomic data between countries? -
 - adoption of GA4GH standards
 - share resources, tools, and expertise
 - identify barriers
 -
- Map current activities of established and nascent NIs
- Identify pilot projects for data sharing using specific cohorts
- Plan ongoing projects
- Identify point(s) of contact for each national initiative



Meeting Overview

DAY 1

- Brief updates on GA4GH driver projects and new National initiatives
- Presentations on current pilot data sharing projects
- **Breakout sessions:** Clinical data, Genomic data sharing
Curation, Regulatory and Ethical barriers
- **Full-group:** Public engagement and ethics workshop
- Cocktail hour and networking dinner

DAY 2

- Feedback from Breakouts: Action plans for pilot data sharing projects
- Panel discussion: Moving genomics from research to clinical care



Genomics England: Current Status and Data Sharing Pilots

A close-up photograph of a young child with blonde hair and blue eyes, smiling.

Australian Genomics

Kathryn North

Director, Murdoch Children's Research Institute

Lead Investigator, Australian Genomics

Vice Chair, Global Alliance for Genomics and Health

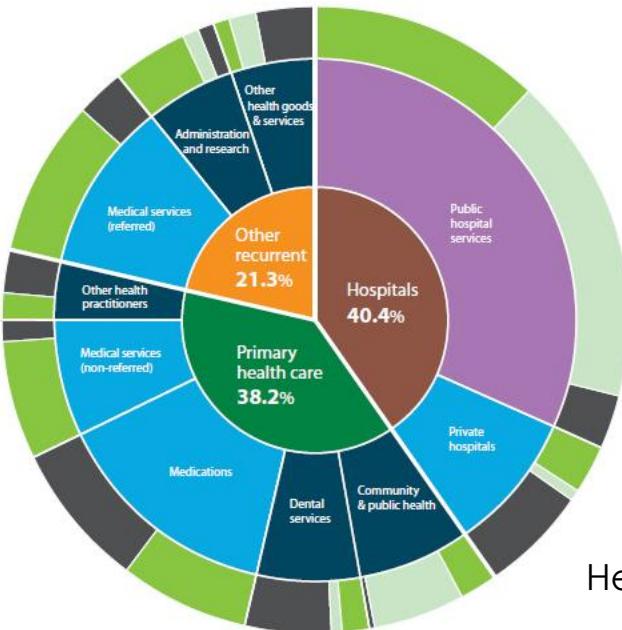
Australian Genomics

TARGETED NHMRC CALL FOR RESEARCH (start date: 2016)

- Demonstrate how **patient benefit** could be maximized through application of genomic data in one or more human diseases.
- Provide evidence to inform analysis on the **cost effectiveness** of implementing genomic data into the Australian health system.
- Demonstrate **practical strategies** for implementation that could be used by Australian health system planners and policymakers.
- Build Australia's research and **research translation capacity** in the area of genomics and healthcare.



The Australian Health Care System



Health service funding and responsibilities

Australia's Health 2014, AIHW

Share of expenditure	Responsibility for services	Funding
Hospitals	Combined private sector and public sector —all levels of government	Australian Government funding share
Primary health care	State and territory governments	State/territory government funding share
Other recurrent	Private providers	Private funding share

A Summary: National Health Genomics Policy Framework

Vision

Helping people live longer and better through appropriate access to genomic knowledge and technology to prevent, diagnose, treat and monitor disease.

To harness the health benefits of genomics in an efficient, effective, ethical and safe way.

Collaborate with the health sector and other sectors.

National Genomic Strategy.

Person-centred approach

Delivering high-quality care for people through a person-centred approach to integrating genomics into health care

Workforce

Building a skilled workforce that is literate in genomics

and strategic investment in cost-effective genomics

utility of genomics in health care

storage, use and management of genomic data

Federal Budget May 2018

AUD\$500M

National Australian Genomics Mission

Australia 2030

Prosperity through

INNOVATION

A plan for Australia to thrive in the global innovation race

GENOMICS MEDICINE IN AUSTRALIA

ACOLA
AUSTRALIAN COLLEGES OF LEARNED ACADEMIES

Australian Genomics

OUR MISSION



Australian Genomics is preparing Australia for the integration of genomic medicine into mainstream healthcare.

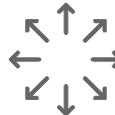
OBJECTIVES



To promote ethical, legal and social responsibility in the application of genomic knowledge.



Develop systems and resources to support genomic implementation: **for the clinician**, for the **researcher**, for the **public**.



Establish robust networks and systems to ensure the **patient is informed, involved and empowered**.

Ensure genomic and medical **data** is **stored safely and shared responsibly** to increase our understanding of health and disease.

Expand Australia's gene discovery, **functional genomics** and drug discovery research capacity.

Engage actively in international genomic initiatives, strengthening Australia's **contribution to**, and **learning from global genomic knowledge**.

Australian Genomics

MORE THAN 80 PARTNERS



Australian Genomics
Health Alliance

INTERNATIONAL PARTNERS

Genomics England
Global Alliance for Genomics and Health
Global Genomic Medicine Collaborative
Baylor College of Medicine
Broad Institute
Osaka University
University of Oxford
UCL Great Ormond Street Institute of Child Health

NATIONAL PARTNERS

Bioplatforms Australia
CSIRO
Mito Foundation
National Computational Infrastructure
Rare Cancers Australia
Rare Voices Australia
Australian Genome Research Facility
BioGrid Australia
FH Australasia Network
Genetic and Rare Disease Network
HeartKids
Kidney Health Australia
Poche Indigenous Health Network
SWAN Australia

PEAK PROFESSIONAL BODIES

Human Genetics Society of Australasia
The Royal College of Pathologists of Australasia
The Royal Australasian College of Physicians
Royal Australian and New Zealand College of
Obstetricians and Gynaecologists

WESTERN AUSTRALIA

Genetic Services of Western Australia
Harry Perkins Institute of Medical Research
PathWest
The University of Western Australia
Perth Children's Hospital

QUEENSLAND

Genetic Health Queensland
QIMR Berghofer Medical Research Institute
Queensland Genomics
Royal Brisbane and Women's Hospital
The University of Queensland
Queensland Children's Hospital
Princess Alexandra Hospital



SOUTH AUSTRALIA

SA Pathology
Centre for Cancer Biology
SAHMRI
The University of Adelaide
University of South Australia
Royal Adelaide Hospital
Women's and Children's Hospital

Royal Perth Hospital
Sir Charles Gairdner Hospital
King Edward Memorial Hospital
Fiona Stanley Hospital
Telethon Kids Institute

The Wesley Hospital
Diamantina Institute
Griffith University
Institute for Molecular Bioscience
Pathology Queensland
Queensland University of Technology

NORTHERN TERRITORY

Royal Darwin Hospital

Prince of Wales Hospital
Sydney Children's Hospitals Network
Royal Hospital for Women
Royal Prince Alfred
Westmead Hospital
Children's Cancer Institute
Children's Medical Research Institute
Hunter Genetics
Victor Chang Cardiac Research Institute

NEW SOUTH WALES

Garvan Institute of Medical Research
Genome.One
Kinghorn Centre for Clinical Genomics
Macquarie University & AIHI
NSW Health Pathology
The University of Sydney
University of New South Wales
Centre for Genetics Education
John Hunter Children's Hospital
Liverpool Hospital
Nepean Hospital

AUSTRALIAN CAPITAL TERRITORY

The Australian National University
Canberra Hospital
National Centre for Indigenous Genomics

VICTORIA

Murdoch Children's Research Institute
Melbourne Genomics Health Alliance
Monash University
Peter MacCallum Cancer Centre
The University of Melbourne
Victorian Clinical Genetics Services
Austin Health
Monash Health
The Royal Melbourne Hospital

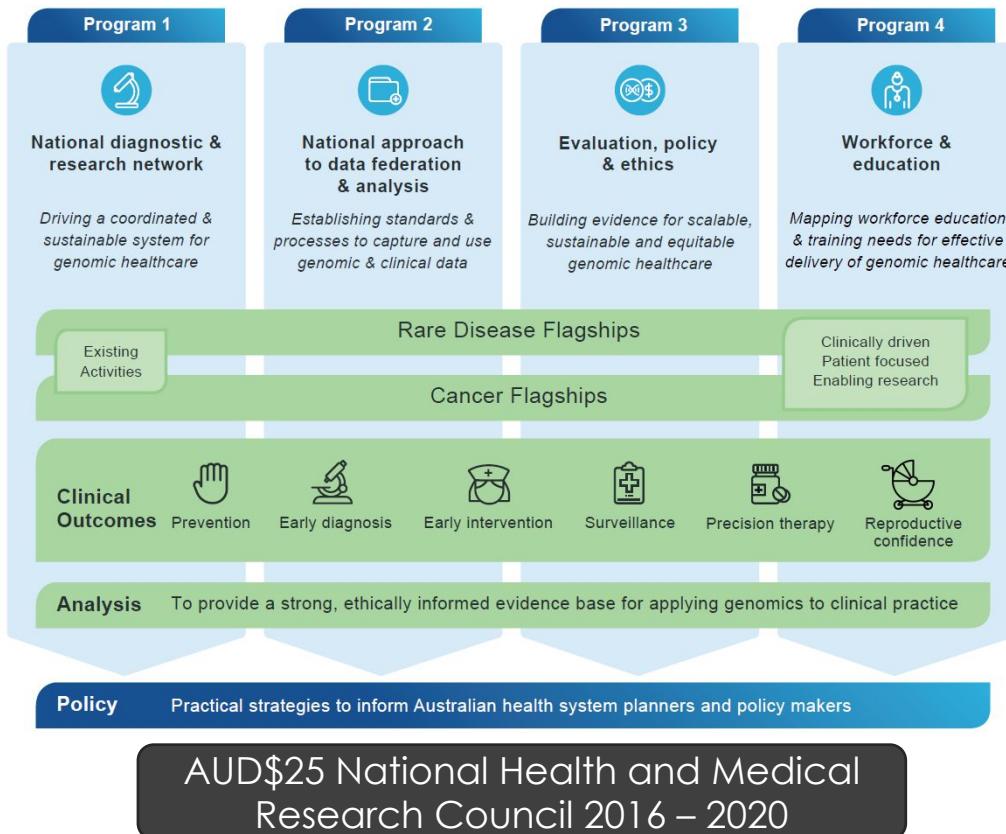
The Royal Children's Hospital
The Alfred
The Royal Women's Hospital
The Florey
Genetic Support Network of Victoria
Melbourne Bioinformatics
Victorian Comprehensive Cancer Centre
Walter and Eliza Hall Institute

TASMANIA

Royal Hobart Hospital

Australian Genomics

PROGRAMS, FLAGSHIPS



New clinical projects:

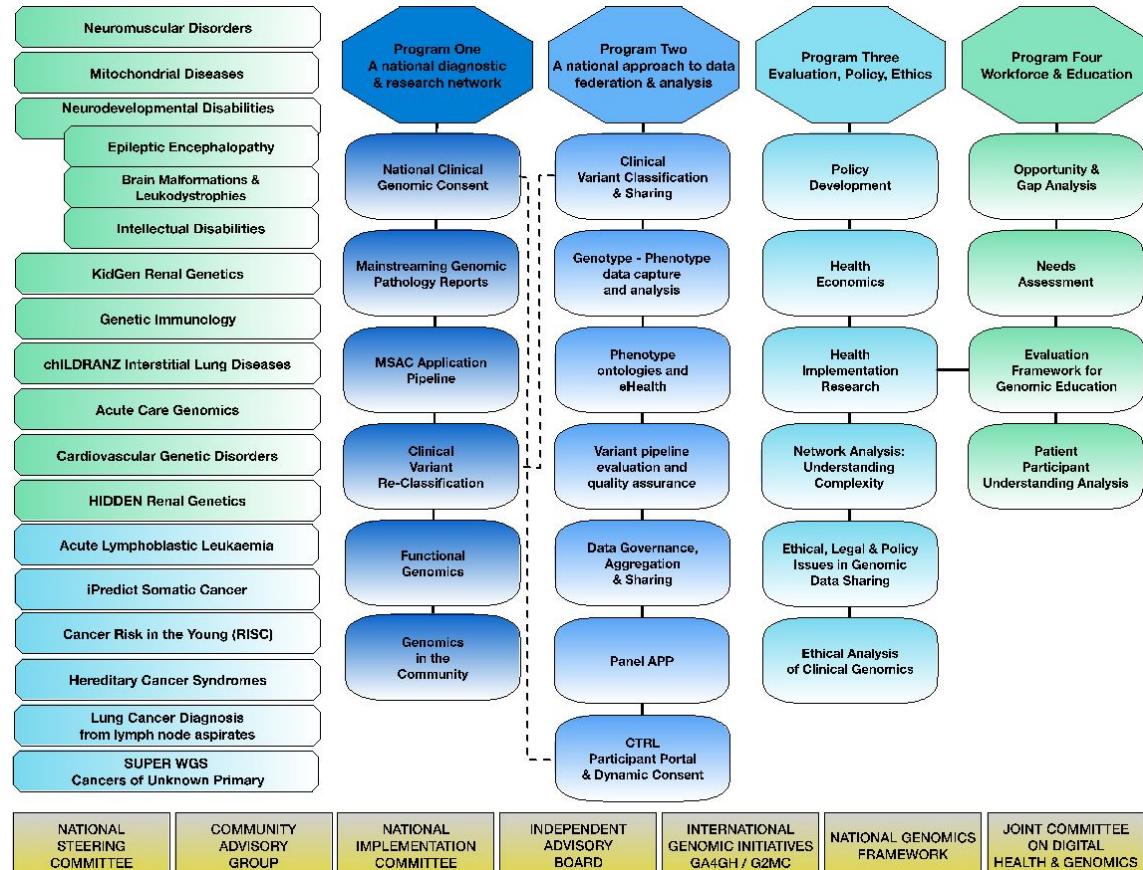
- **Reproductive Carrier Screening (AUD\$20million)**
- **Cardiac Genetic Disorders (AUD\$6 million)**
- **Rare Childhood Brain Disorders (AUD\$3million)**

AUD\$29 Australian Government Medical Research Future Fund 2019~2022

Australian Genomics Model

PROGRAMS, FLAGSHIPS AND PROJECTS

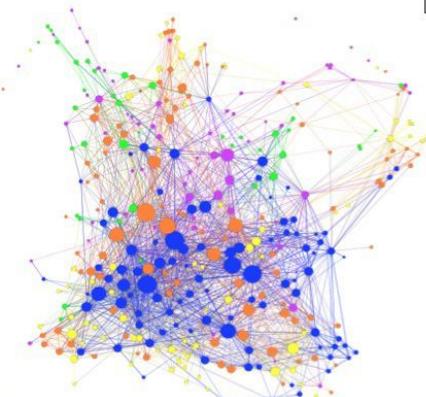
Total planned recruitment based on funding to date ~25,000 individuals (includes new MRFF funded projects)



Building a learning community of clinical genomics

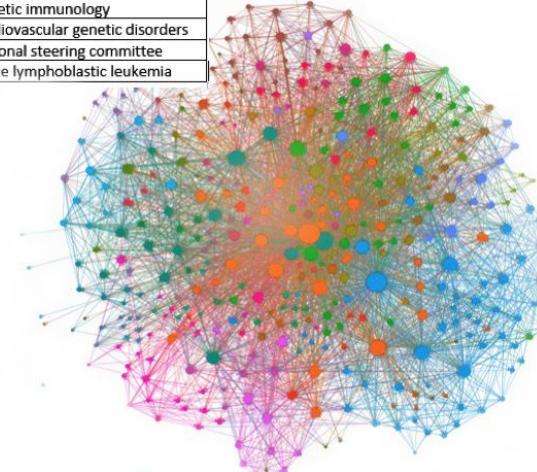
A SOCIAL NETWORK STUDY

●	Medical scientist
●	Genetic specialist
●	Other
●	Medical specialist
●	Researcher



Pre-2016
(before Australian Genomics)

●	Operations
●	KidGen renal genetics
●	Acute care genomic testing
●	Genetic immunology
●	Cardiovascular genetic disorders
●	National steering committee
●	Acute lymphoblastic leukemia



2018: The Australian Genomics
socio-professional network

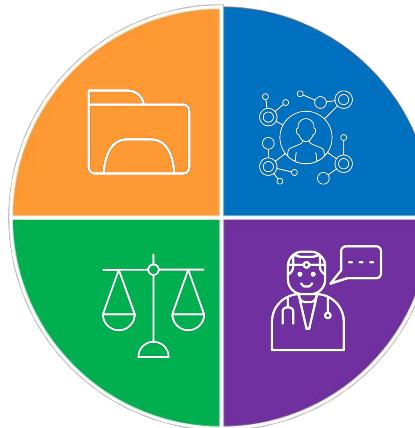
Long JC, Pomare C, Best S, Boughtwood T, North K, Ellis LA, Churruca K, Braithwaite J. **Building a learning community of Australian clinical genomics: a social network study of the Australian Genomic Health Alliance.** BMC Medicine. 2019; 17 (1) : 44.

Australian Genomics

RESOURCES DEVELOPED / STANDARDS IMPLEMENTED

Data

- CRAM
- WES endpoint testing (Cloud)
- Local EGA: Crypt4GH, htsget (Large Scale Genomics)
- Phenotype standards through HPO and SNOMED CT
- Piloting implementation of DUO (ADAM/Consent codes)
- Breach response protocol
- Landscape governing genomic data ownership and sharing (2017)
- FHIR based clinical data models (OntoServer, Shrimp)
- 'Shariant' platform for the sharing of curated variants between Australian diagnostic laboratories, and contributing to international databases (ClinVar)



Evaluation, Policy And Ethics

- Position statements on use of genetic information in insurance (2018)
- Personalised electronic health data capture (2018)
- Understanding public preferences around genomic testing (discrete choice experiments) (2018/2019)
- Catalogue of genomic initiatives with G2MC

Diagnostic Network, Clinical Implementation

- National consent form for genomic testing (2017-2019)
- CTRL 'control' participant platform incorporating dynamic consent (2018/2019)
- **genomicsinfo.org.au** online resources for public and patients –information about genomics, data sharing, testing and support (2018/2019)

Workforce & Education

- Needs analysis of education and training for the genomic workforce (2016).
- 5P health professional education survey for non-genetic health professionals (2018/2019)
- Workforce survey regarding educational needs and implementation readiness for rapid genomic testing in acute paediatrics (2018)
- Program logic for the development of genomic education activities / draft evaluation framework (2018/2019)

Australian Genomics Flagships

TECHNOLOGY

- WGS
- WES
- Capture panels
- RNASeq

CANCERS

- Acute Lymphoblastic Leukaemia
- Somatic cancer
- Cancer risk in the young
- Hereditary Cancer Syndromes
- Lung Cancer
- Cancers of Unknown Primary

REPRODUCTIVE CARRIER SCREENING

- ‘Mackenzie’s Mission’

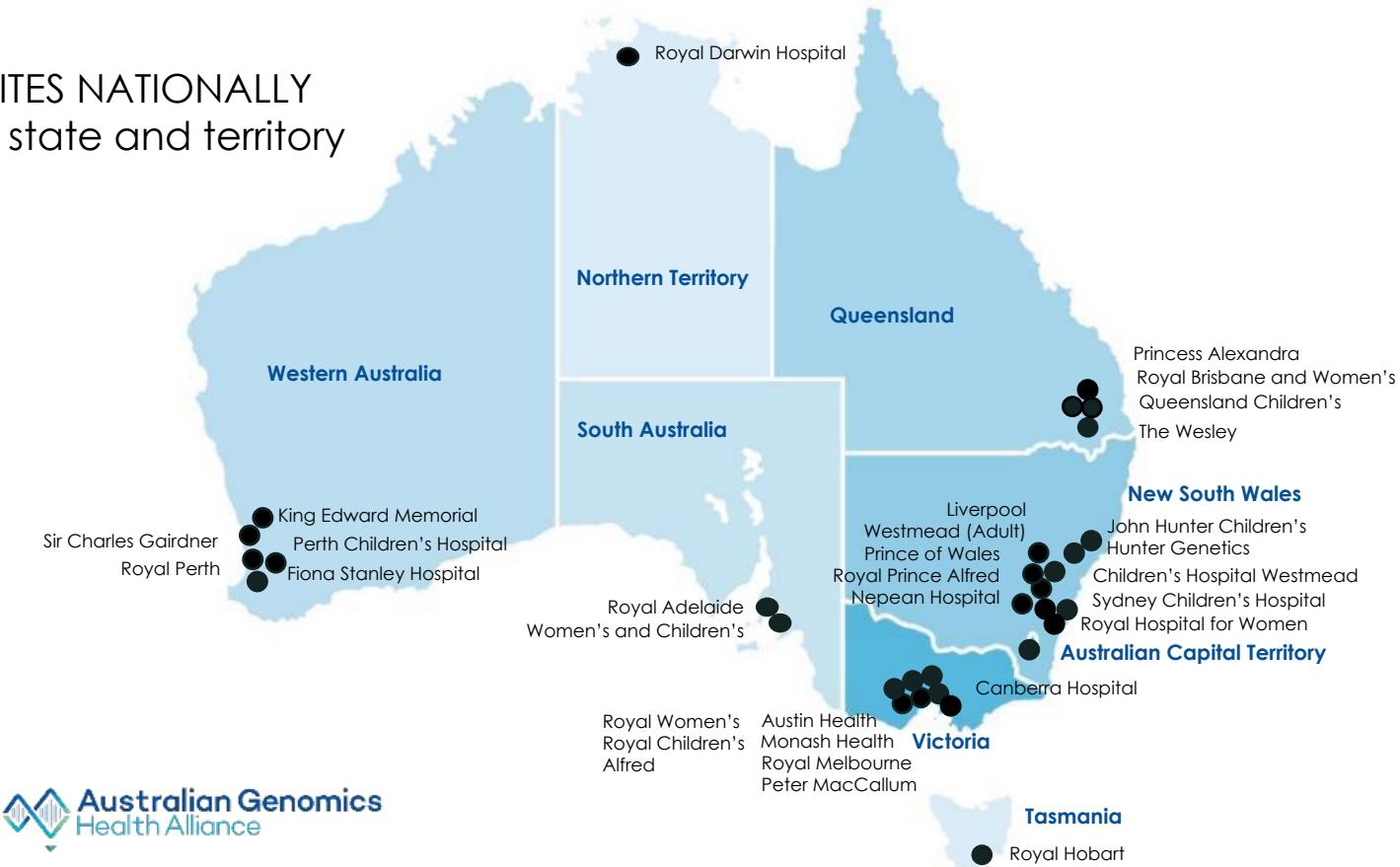
RARE DISEASE

- Mitochondrial Diseases
- Neuromuscular Disorders
- Epilepsy
- Kidney genetics
- Neurodevelopmental Disabilities
- Genetic Immunology
- Interstitial lung diseases
- Acute care genomics
- Cardiovascular disorders

Australian Genomics

CLINICAL RECRUITMENT SITES

32 SITES NATIONALLY
every state and territory



Mainstreaming genomics

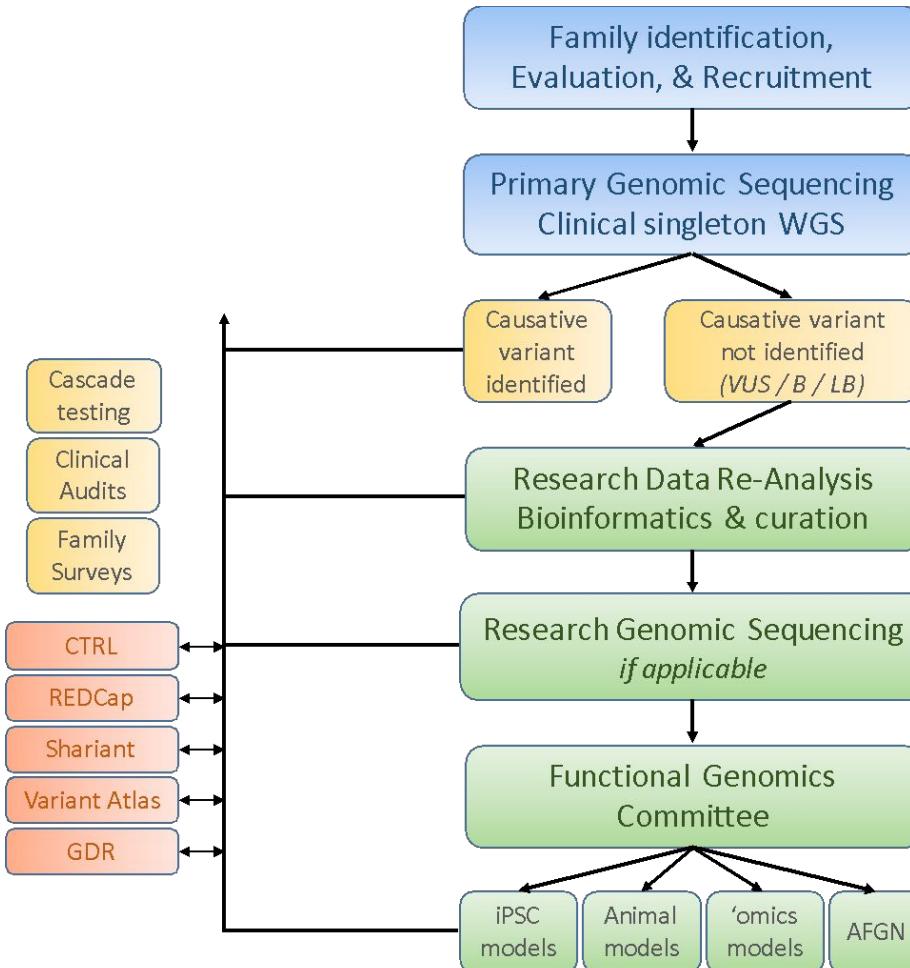
MACKENZIE'S MISSION

- Mackenzie Casella died at 7 months from **spinal muscular atrophy** in 2017
- Her parents, Rachael and Jonathan Casella, lobbied the Australian Government **to make carrier screening available nationally**, for those who wish to access it.
- Mackenzie's Mission established: AUD\$20M over 3 years
- This is the first project of **Australia's Genomic Health Futures Mission (\$550M over 10 years for genomic research)**
- It will offer carrier testing to **10,000 couples for carrier status for around 500 autosomal and X-linked recessive conditions** pre or early in pregnancy.



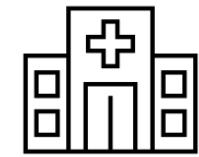
Rachael and Jonathan Casella, with Mackenzie.

The Cardiovascular Genetic Disorders Flagship



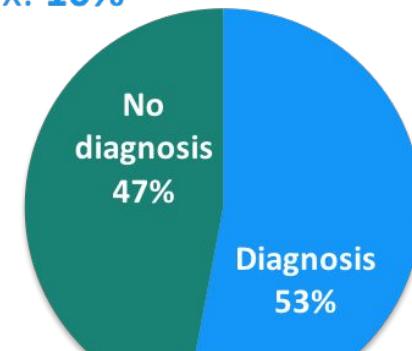
Developing a clinical pipeline
that identifies families (**up to**
600) without diagnostic
resolution to a network of
researchers for **functional**
studies

Acute Care Genomics



100 cases, ave TAT: 3 days, cost: \$1,123,000
Dx yield □: mito seq, small CNVs, real-time MME, RT-PCR

Change in Mx: 10%



Change in Mx: 75%

National Standards

CLINICAL GENOMIC CONSENT

Challenge: No single national approach to obtaining consent from patient to undertake genetic or genomic testing.

Topics that need to be addressed by consent form:

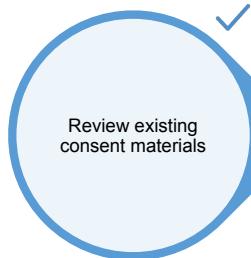
- Intention of the test
- Risks associated with genomic testing
- Implications for families & insurance
- Return of results: actionable and non-actionable findings
- Additional findings
- Use of samples and data for research
- Re-contact for further studies
- Storage of samples and use by the diagnostic laboratory
- Overall language and readability



Latest

- National consent materials are being piloted in three states (6 months) from 2019
- Share results of the pilot with working group under Australia's National Health Genomics Policy Framework.

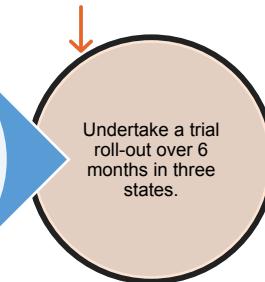
2017



May/June 2018



2019



National Standards

FUNDING OF GENOMIC TESTING

Australian Genomics building a **pipeline of applications to Australia's Medical Services Advisory Committee**, to enable Medicare funding for genomic testing in **disease areas where there** is appropriate clinical and economic evidence.

Outcome: The Medical Services Advisory Committee **recommended to Health Minister, genomic testing in children with syndromic and non-syndromic intellectual disability.**

Funding of three key elements

- **WEA childhood syndromes / moderate ID**
- **Re-analysis of the data**
- **Cascade / segregation testing**

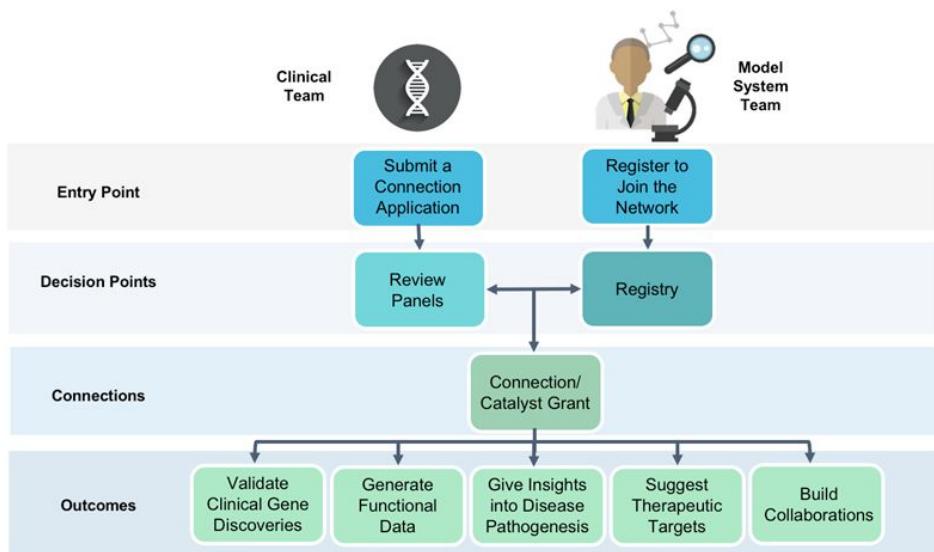
Able to be ordered by clinical geneticist or specialist paediatrician after consultation with a CG

Now awaiting ministerial approval



National Functional Genomics Network

Australian Functional Genomics led researchers and clinicians from across Australia. Aims to **integrate functional genomics into the diagnostic paradigm** for managing rare diseases and cancer in Australian patients.



- The network **connecting clinicians with researchers** to investigate function of newly discovered genes and variants of unknown significance
- Close to 250 members to date and 1600 genes
- **Based upon the successful Canadian RDMM network**
- Support of Catalyst Grants

functionalgenomics.org.au

The community

genomicsinfo.org.au



Shares a range of resources on:

- Genetics
- Genomic testing
- Insurance
- Data sharing
- Guidance on discussing genetic test results with family

Includes links to resources from other national genomics initiatives

genomicsinfo.org.au

is a collaboration between Australian Genomics and Australian patient advocacy groups.



“CTRL” PARTICIPANT PORTAL

DYNAMIC CONSENT

We understand that participants want to **have more control** over their involvement in research.

This is why we have developed a new **online research consent and engagement platform** for our participants called **CTRL** (control)

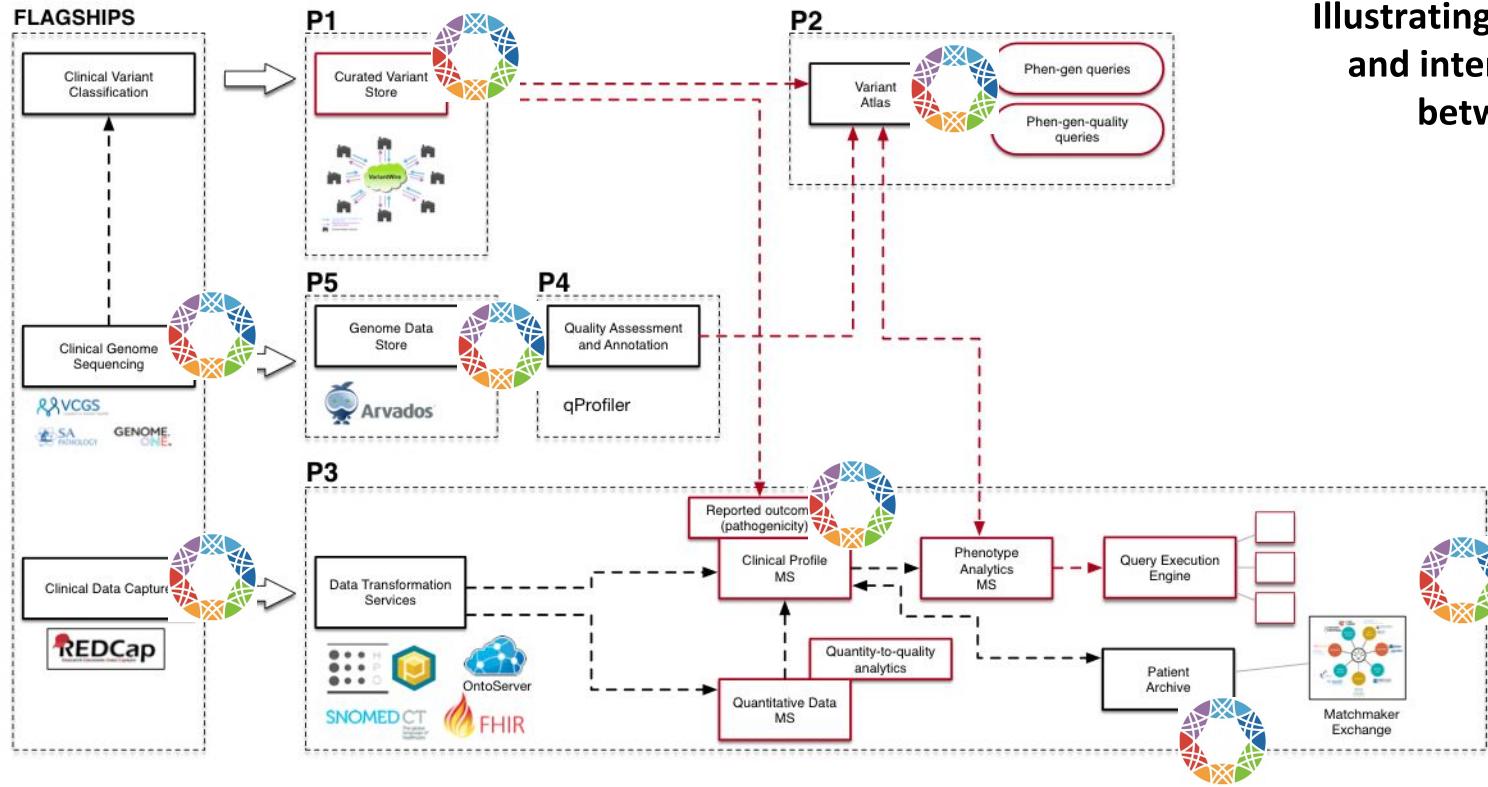
CTRL gives **granular, dynamic consent** options, access to **information, surveys and reports**, and a means to **communicate** with study investigators.

We aim to make the platform widely available to other research programs.



Data Federation and Analysis

PROGRAM LOGIC



Illustrating the activities and interrelationships between our data projects

Data Tools and resources



REDCap

REDCap is the Australian Genomics study database.

Manages the clinical, demographic and survey data of all our participants.

Hosted at Murdoch Children's Research Institute



Standardised, computer-readable clinical descriptions

The clinical information in REDCap is translated into standardized codes (phenotype ontologies: HPO/SNOMED) to allow computerized search, discovery and coding.



Genomic Data Repository (GDR)

The cloud-based GDR stores Australian Genomics' genomic sequencing data (BAM/VCF/FASTQ).

Data ingest QC; links a subset clinical data, to facilitate meaningful analysis and sharing.

Hosted at University of Melbourne

Data Tools and resources



Variant Atlas

Variant Atlas is an interactive **Genotype-Phenotype data platform**. Visualise aggregated Flagship variant data, and filter by key clinical features.
Hosted at Garvan Institute of Medical Research



Shariant

Shariant is an **online platform for laboratories to share curated variant classifications**. Shariant builds on international variant databases like ClinVar to display variant information, the submitting lab, and the evidence underpinning the classification.



Data access Agreements and Policies

Clinicians and researchers can request access to Australian Genomics datasets,

This will be granted according to the level of data sensitivity; the specific consent of the participant; and the researcher's HREC, where applicable.

Australian Genomics ascribe to **GA4GH policies and standards**.

Australian Genomics/Genomics England exchange

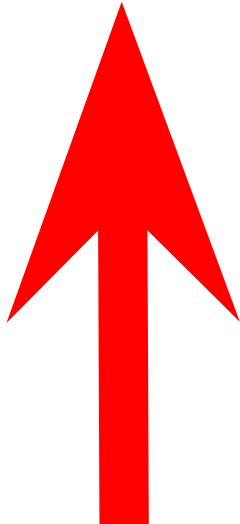
Zornitza Stark, Clara Gaff, Kate Birch, Alejandro Metke



James Holman

Australian Genomics/Genomics England

completion



- **Virtual gene panels:** content, process, platform
- **Clinical and phenotypic data capture:** content, process
- **Education Evaluation Framework**
- Making data available for research in a secure environment: platform
- Health professional education needs survey
- Evaluation
- Consent

exploration

Updates from Select Projects

NIH *All of Us* Research Programme
Swiss Precision Health Network
Genome Medical Japan
H3Africa

ELIXIR & data sharing across Europe
Matchmaker Exchange
Qatar Genome Programme
Genome Canada
BIPMed

NIH All of Us Research Program

United States of America

David Glazer
Verily Life Sciences

All of Us
RESEARCH PROGRAM



Australian
Genomics
Health Alliance

Global Alliance
for Genomics & Health

All of Us
RESEARCH PROGRAM

All of Us: Aims

Core values:

- Participation is open to all.
- Participants reflect the rich **diversity** of the U.S.
- Participants are partners.
- Trust will be earned through transparency.
- **Participants have access** to their information.
- Data will be **accessed broadly for research** purposes.
- Security and privacy will be of highest importance.
- The program will be a catalyst for positive change in research.

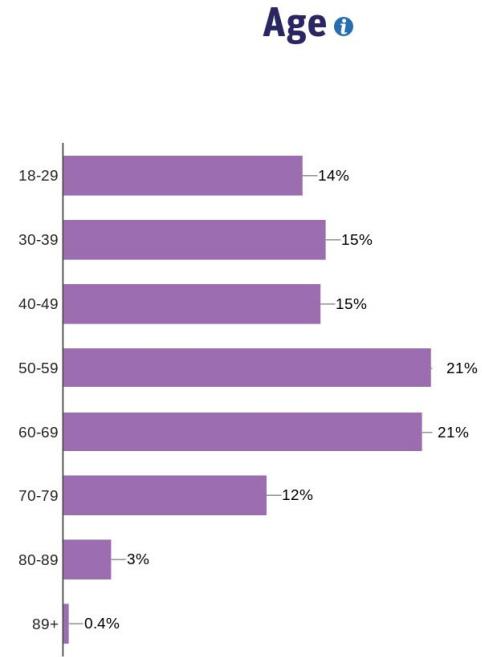
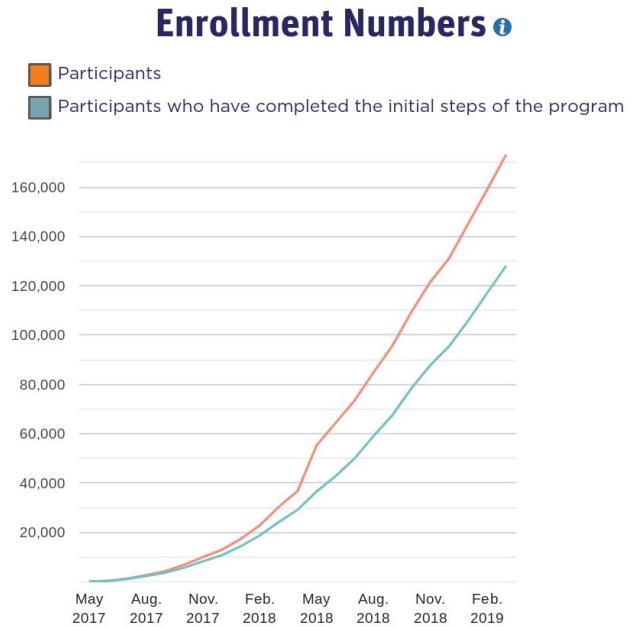
The All of Us Research Program is a historic effort to gather data from one million or more people living in the United States to accelerate research and improve health. By taking into account individual differences in lifestyle, environment, and biology, researchers will uncover paths toward delivering precision medicine.



All of Us: Timeline

- May 2017: beta enrollment opens
- May 2018: public enrollment launch
- May 2019: public data release (aggregated data) ⇐ next week!
- Winter: first researcher data release (row-level data)
- 2020: first genomic data release

All of Us: Status



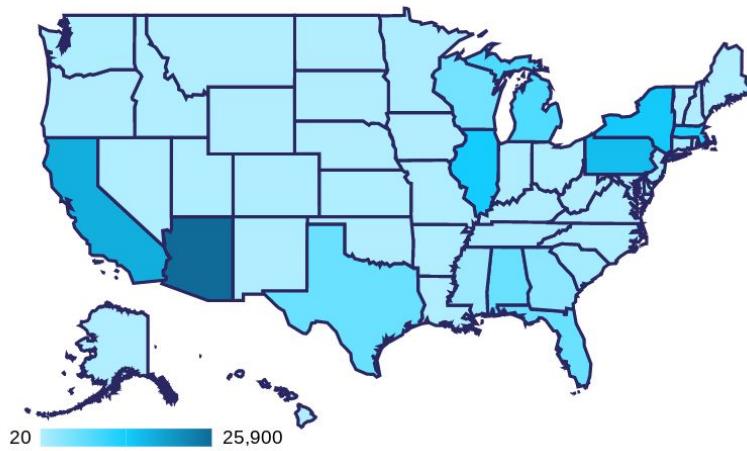
All of Us: Status

100+

Funded Partner Organizations

300+

Sites Collecting Samples and Measurements



80,000+

Electronic Health Records

132,000+

Biosamples



Global Alliance
for Genomics & Health

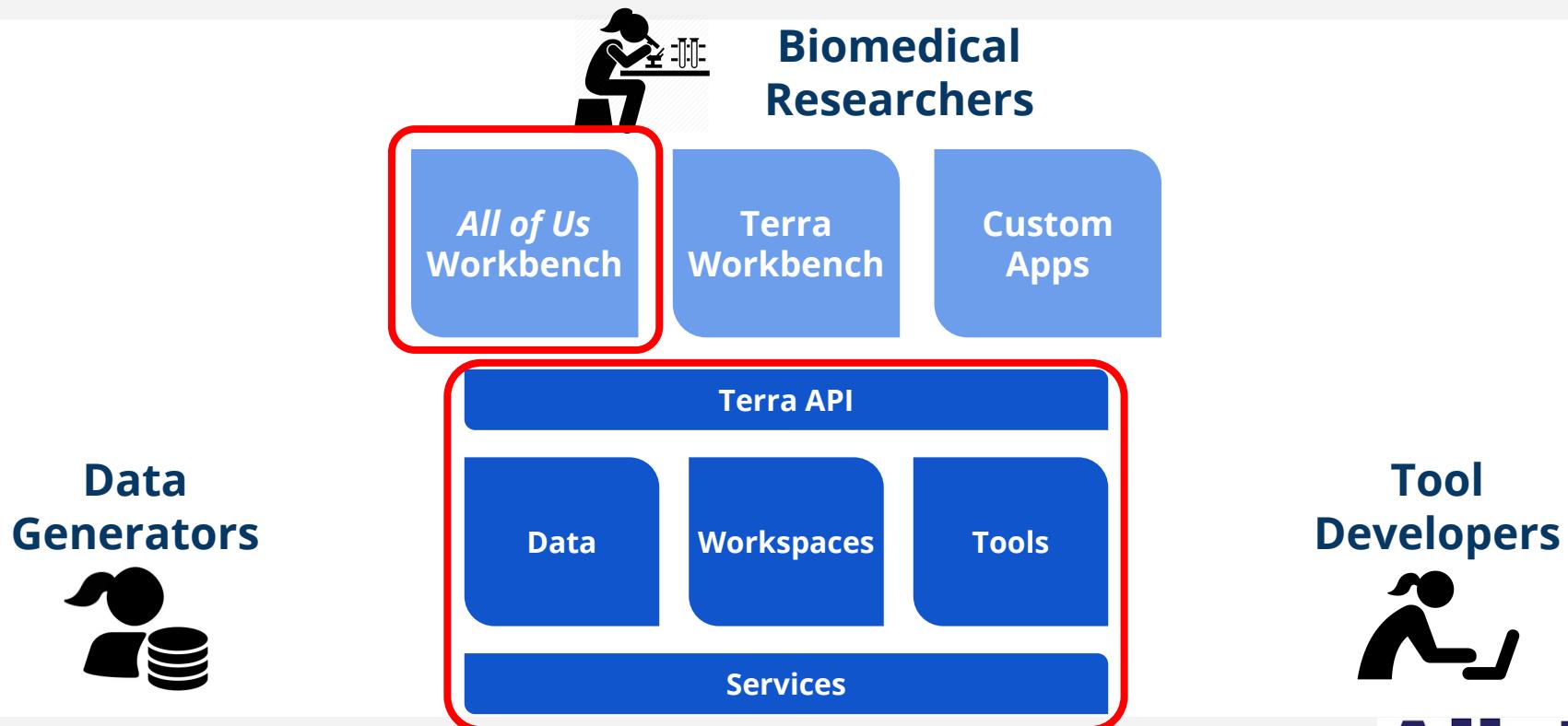
All of Us
RESEARCH PROGRAM

All of Us: Current level of adoption of GA4GH standards

- Low today; more in 2020
- Cloud WES+DRS
 - will be used for genomic data release
- DURI
 - informing access policy discussion today
 - future use depends on how policy lands
- Clin/Pheno
 - exploring integration as we add new data types



All of Us: Open-source technology platform

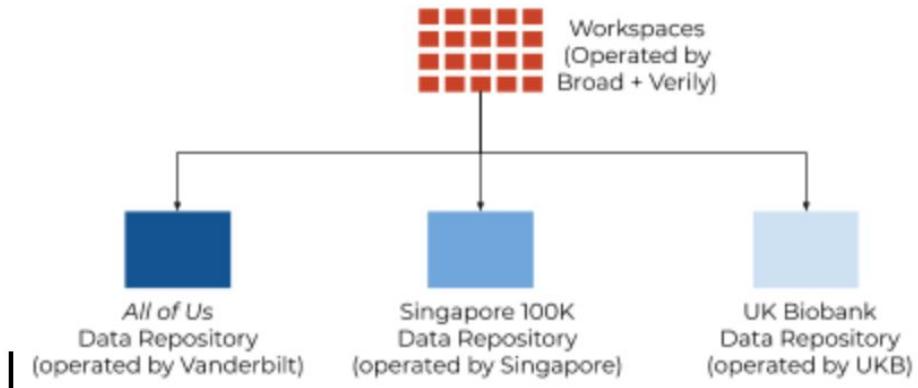


All of Us: Exploring data sharing projects

IHCC proposal: create a federated system that allows each cohort to maintain control of their data, while also allowing these cohorts to be easily cross-analyzed.

Model architecture

1. A system of three data repositories holding the All of Us, UKB, and SG100K cohorts, respectively. Each repository will be operated by its own initiative.
2. A system of workspaces -- secure environments where researchers can analyze data -- that point to the data in each of these repositories.



SPHN

Swiss Personalized Health Network

Switzerland

Torsten Schwede

University of Basel & SIB Swiss Institute for Bioinformatics



SPHN: Aims and Status

nationwide interoperability of biomedical information

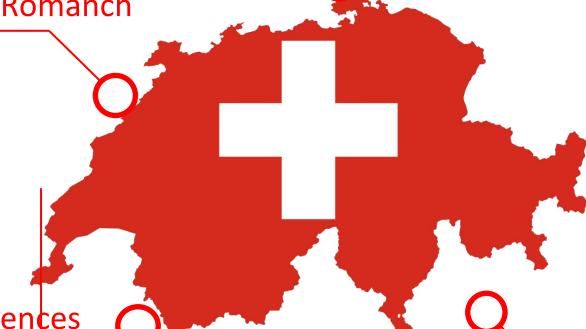
Switzerland

Population: 8.3 Million

Legal system: Confederation with 26 cantons

Healthcare: public, private and subsidized providers

Languages: German, French, Italian, Romanch



SPHN

Government funded initiative: 68 Mio

Co-mandated to:

- SAMS Swiss Academy of Medical Sciences
- SIB Swiss Institute of Bioinformatics

Phase 1: 2017-2020 Patient data

Phase 2: 2021-2024 Consolidation and expansion of the network, healthy citizen data and citizen controlled data

Main collaboration partners

5 University Hospitals

Cantonal Hospitals

ETH Domain and Universities

SPHN funded projects (examples)

Oncology

Variant Interpretation Platform

Pathology

Frailty

Immune repertoire

Immunotherapy

Sepsis

Citizen data

Radiomics

Ophthalmics

Heart failure

Data governance

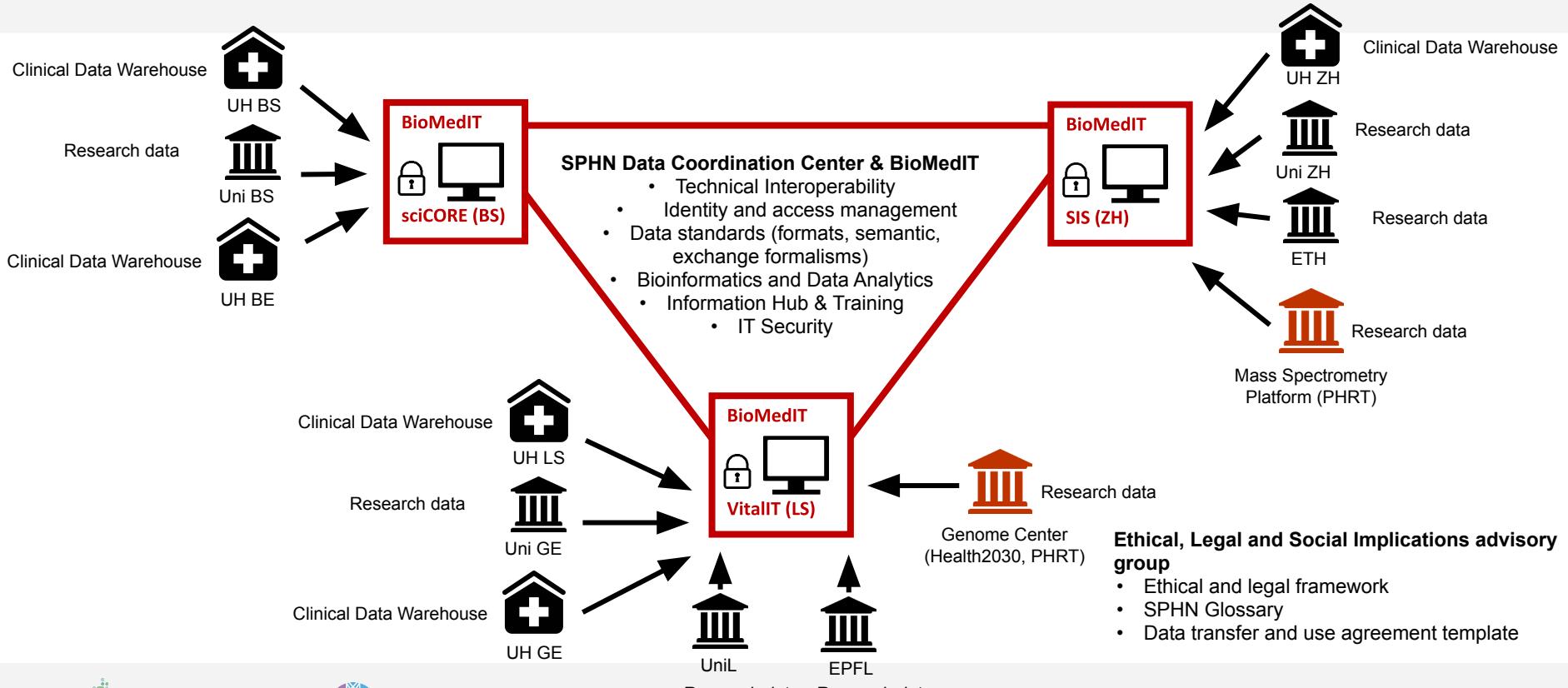
E-/dynamic consent

De-identification

Data standards

Data security/privacy

SPHN: A decentralized approach



SPHN: Current level of adoption of GA4GH standards

- Cloud API standards (Investigating implementations)
 - TES/WES: Multi-site workflow execution
 - Data Repository Service: Improve the findability of data in SPHN
- EGA implementations
 - pilot, test and evaluate the Local EGA
- Beacon
 - to be implemented in SPHN resources and driver projects



SPHN: Tools and resources available to share

Policy documents:

- Ethical Framework for Responsible Data Processing within SPHN
- IT Security Policy
- Data transfer and use agreement template

Tools:

- Potential tools to share: products of the SPHN Development Projects e.g. de-identification algorithms, blockchain system for citizen centered consent management

SPHN: Cohorts for pilot data sharing projects

SPHN driver project “**SACR: The Swiss Ageing Citizen Reference**” (starting 2019) builds on the existing Swiss citizen cohorts SAPALDIA, CoLaus/PsyCoLaus, and SKIPOGH. In the future, it will integrate additional data and biological material of other cohorts including of an additional 1'000 participants from the Swiss Health Study Pilot, which is funded by the Swiss Office of Public Health. The pilot study conducted under the scientific lead of N. Probst-Hensch and the database lead of M. Bochud is the preparation phase for a Swisswide citizen cohort of at least 100'000 participants.

PHRT (<https://www.sfa-phrt.ch/>) call 3 for “**Pioneer Projects: multi '-omics' data collection and interpretation of clinical sample cohorts**” is open now. PHRT invites clinical scientists, who have access to an extensive sample cohort, to create an inter-institutional, interdisciplinary consortium to formulate a well-defined clinical question to request funding to generate matched genomic, transcriptomic and proteomic data by the two PHRT platforms.



GEM Japan: Japanese Initiative for Clinical Human Genetics

Makoto Suematsu, Hidewaki Nakagawa,
Kenjiro Kosaki

New 2019 Driver Project





GEnome Medical alliance Japan

- Variant Aggregation and Allele Frequencies
- Collection and integration of Pathogenic Variants
- Contribution to Standardization and Data Sharing
- Biobank Cross-search System

Nation-wide systems for genomic medicine



IRUD

Initiative on Rare
and Undiagnosed
Diseases



Medical Genomics
Japan Variation
Database

Biobanks in large scale



157,000
healthy
individuals



270,000 patients
with ~50 adult
common
diseases



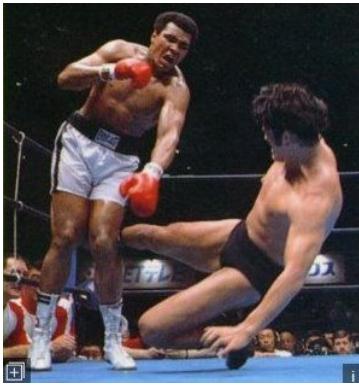
National Center Biobank Network

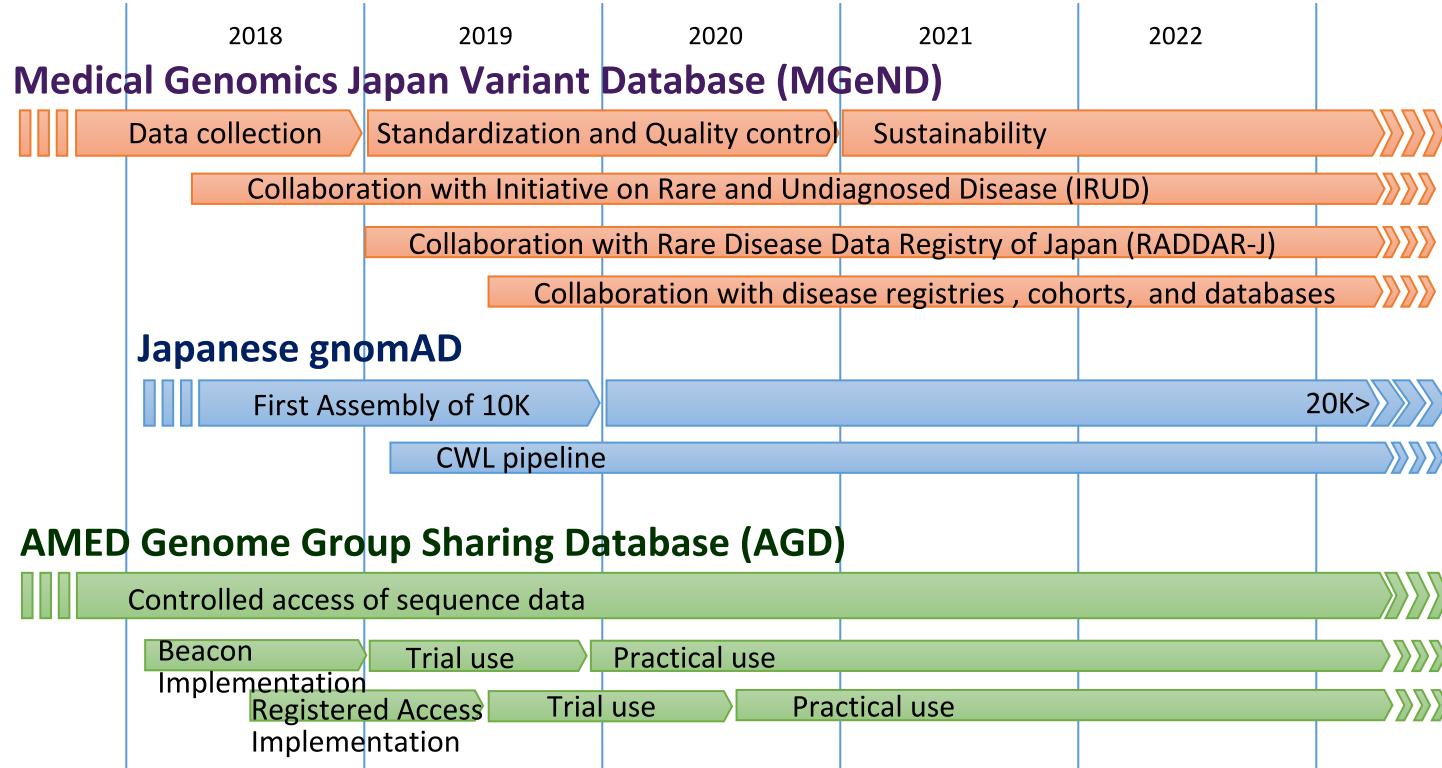
74,000 patients with
major common and
various rare
diseases



Vision / Mission / Goals

- To harmonize our existing projects with the international standards for the genome based health system
- To promote sharing our Japanese genomic and phenotypic information with global community
- To link genome and clinical information among East Asian populations which are thought to be genetically close to Japanese population





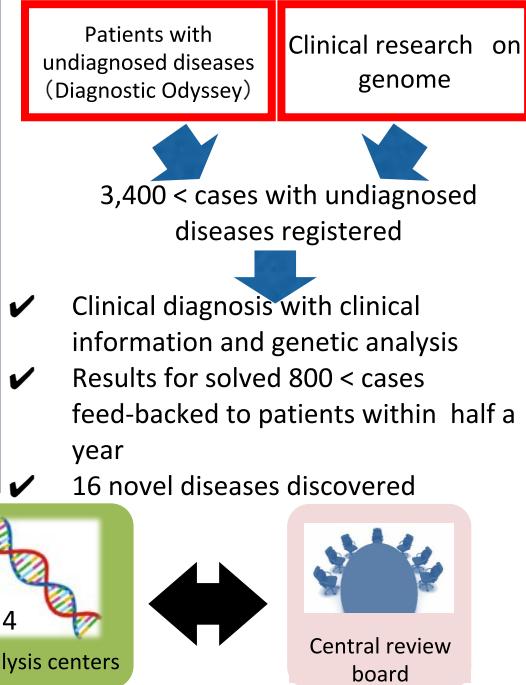
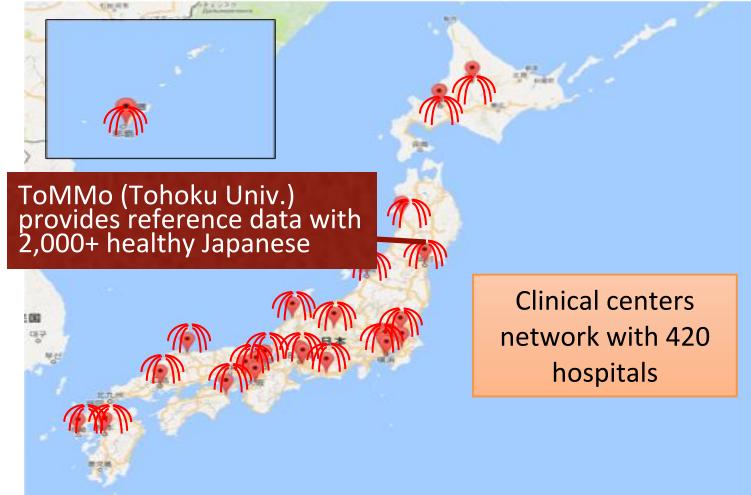


Future collaboration and interaction with GA4GH		Technical Work Stream										
		Large Scale Genomics		Clinical & Phenotypic Data capturing			Genomics Knowledge Standards		Discovery	Data Use & Researcher IDs		Cloud
Category	Database / Project	VCF Aggregator	HLA	Multi-lingual adaptation of phenotypic data capture	PhenoPackets	Family Health History	Variant Representation	Variant Annotation	Beacon API	Researchers ID	Data Use Ontology	CWL
Data Platform	Patient Archive (IRUD Exchange)			★	○		○					
	HPO Japanese Version			★								
	Biobank Cross-search				○	○				○	○	
	AGD								○	○	○	
Integrated DB (Open DB)	MGeND		★				○	○			○	
	Japanese gnomAD	★					○	○			○	

IRUD

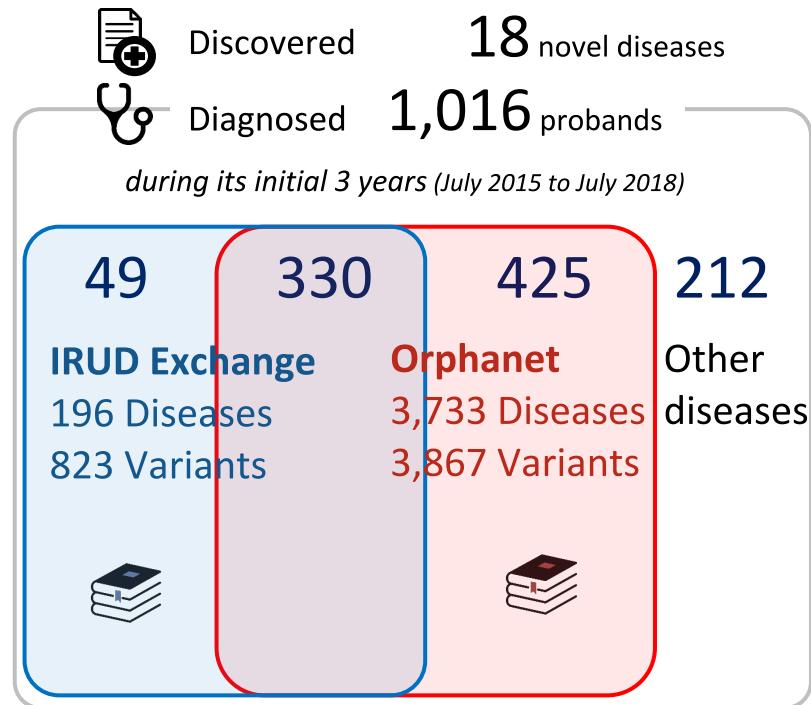
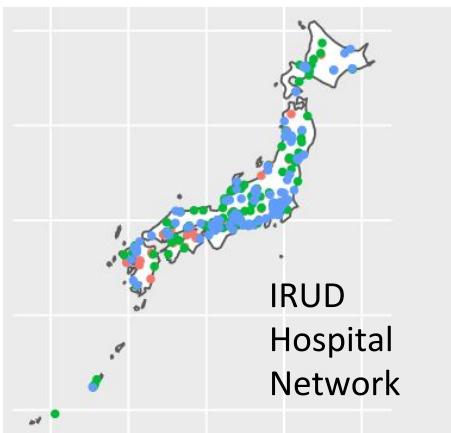
Initiative on Rare and Undiagnosed Diseases

Clinical research program for supporting the diagnosis of patients with undiagnosed diseases in Japan



IRUD research group supports the diagnosis of patients with undiagnosed disease via data sharing with a globally compatible and active data sharing system

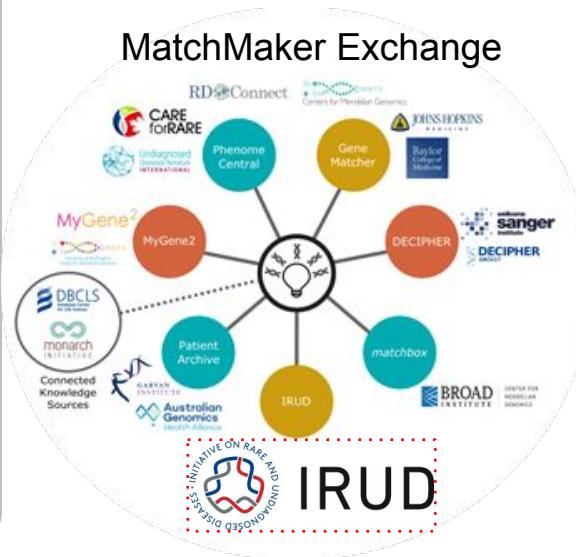
Domestic Data Sharing

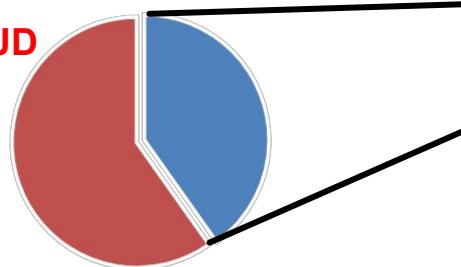


Global Data Sharing



MatchMaker Exchange





■ Registered ■ Unregistered



All Japan Alliance
Universities - Institutes - Hospitals

As of September 2017

	Rare Variants	Common Variants
438	111	82
17,384	14,557	28,429
13,513	25,073	157,082



Clinical
Annotation
Committee



As of April 2019

International Collaboration



MRC (UK)
FY2016



MOH (Lithuania)
FY2016



SEIDI (Spain)
FY2017



A*STAR (Singapore)
FY2015



Agency for
Science, Technology
and Research
SINGAPORE



NIH (USA)
FY2015

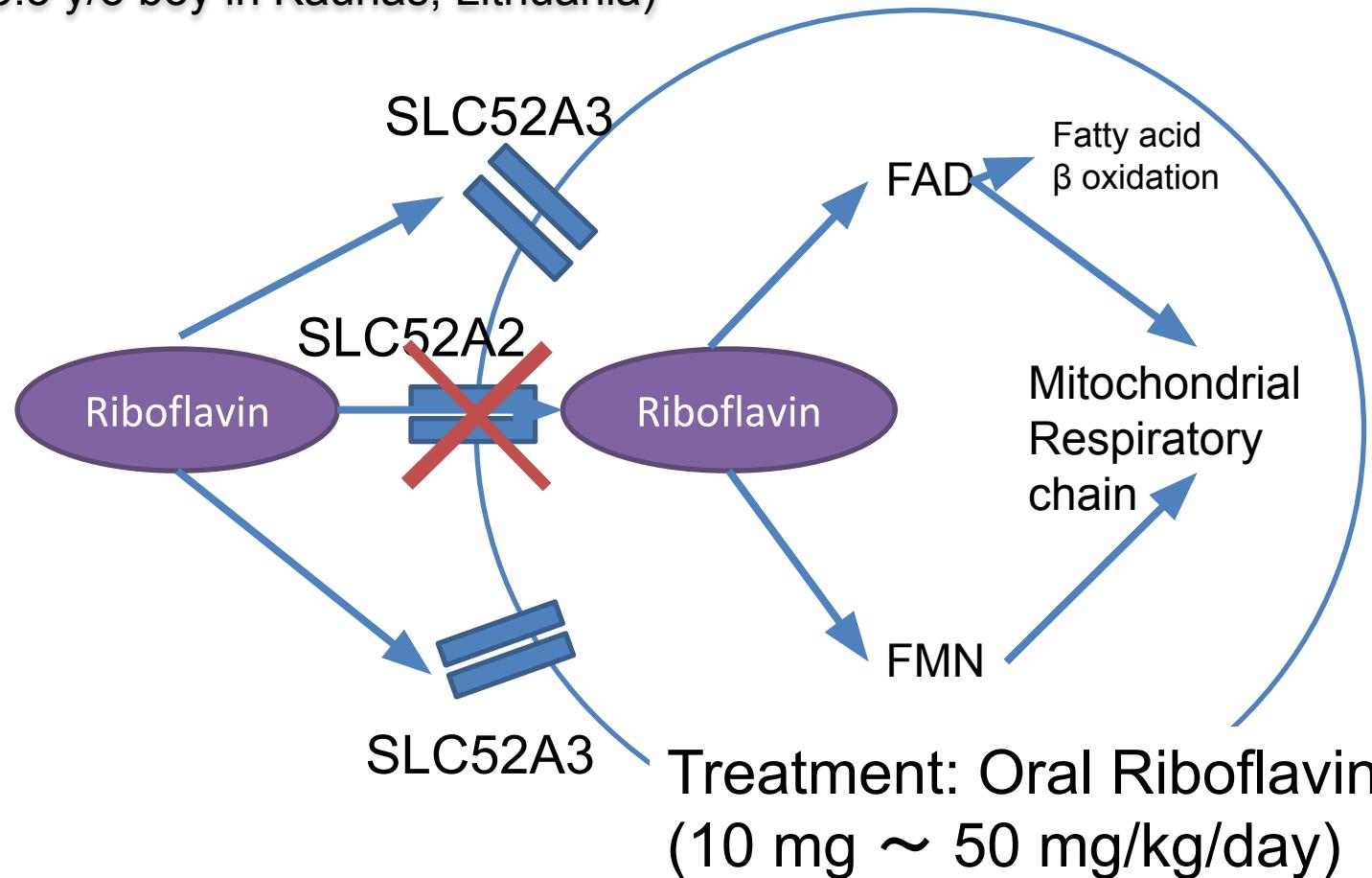
Washington DC
Office

MOC Research Program



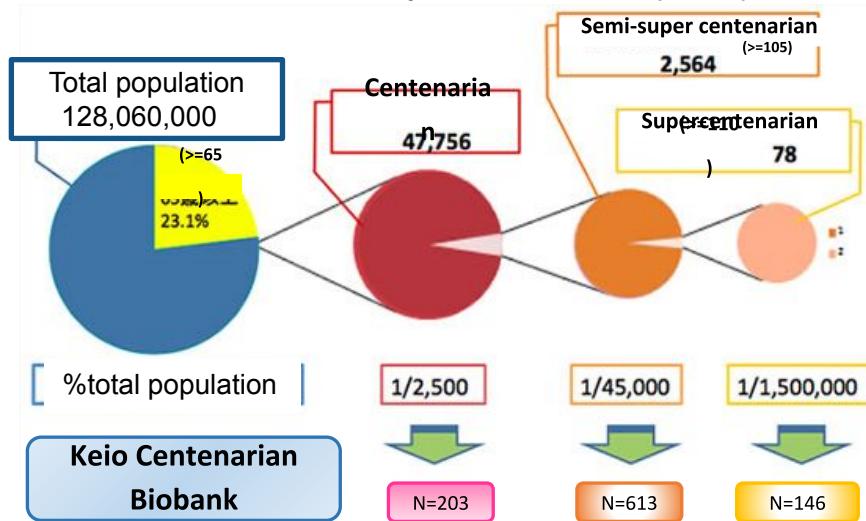
HIROs

Riboflavin transporter deficiency causes severe muscle weakness
(3.5 y/o boy in Kaunas, Lithuania)

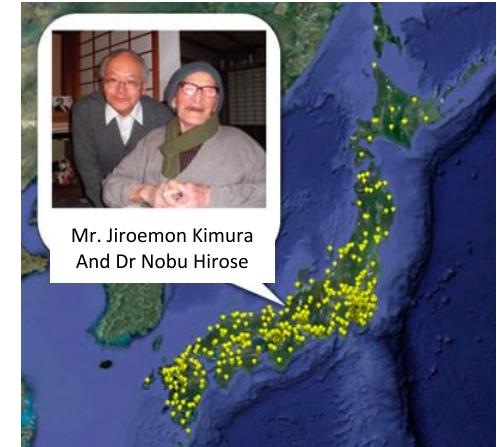


**Super centenarian >110 y/o
Semi-super centenarian 105~110 y/o
YOUNG centenarian 100~105 y/o**

% of Centenarian and Supercentenarian (2010)



Distribution of Supercentenarians



International Collaborative Researches

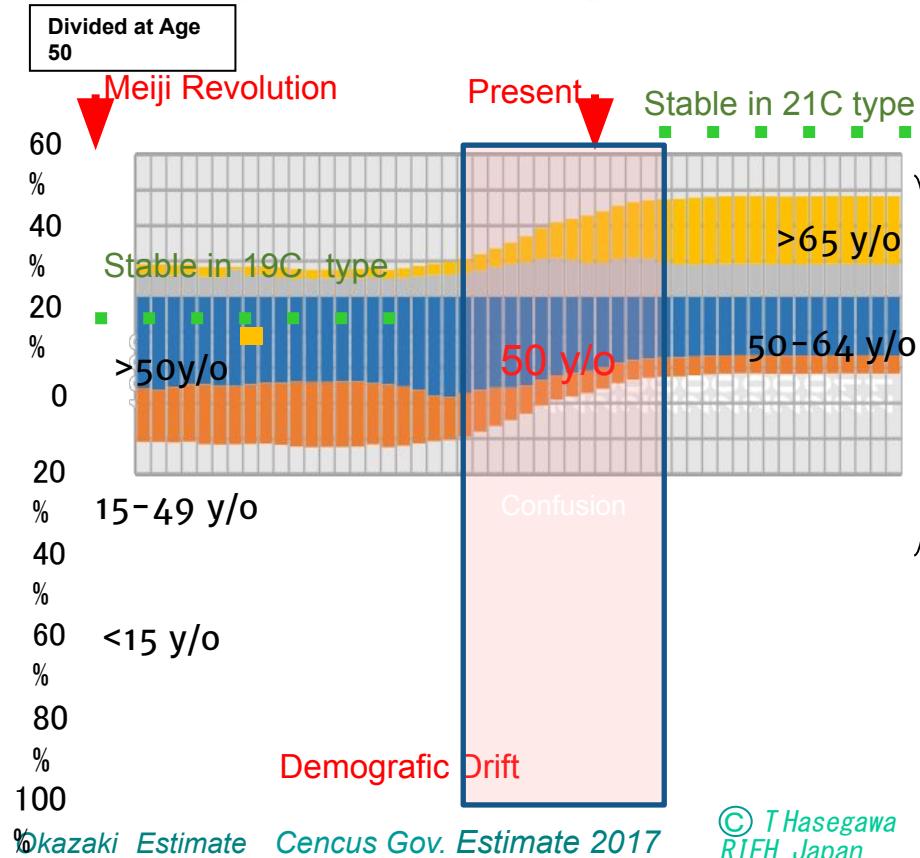
- 5 Country Oldest Old Project (5COOP)



- WGS: 496 centenarians including 126 Supercentenarians.
- Allele frequency of variants for 57 genetic disease genes
- Allele frequency of variations in 40 dementia-associated genes

Data Sharing

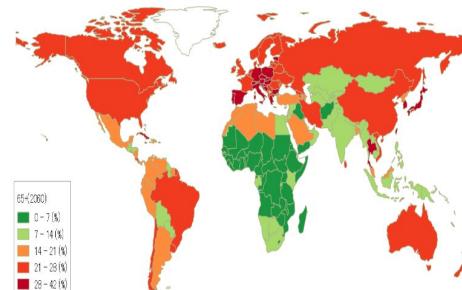
Great Demographic Transition: Japan first, and your countries will share



Population(%) age over 65 years in 2015



in 2060



© T Hasegawa
RIFH, Japan

H3Africa

Pan-Africa

—

Mogomotsi Matshaba

Botswana-Baylor Children's Clinical Centre of Excellence

Background: H3Africa Initiative



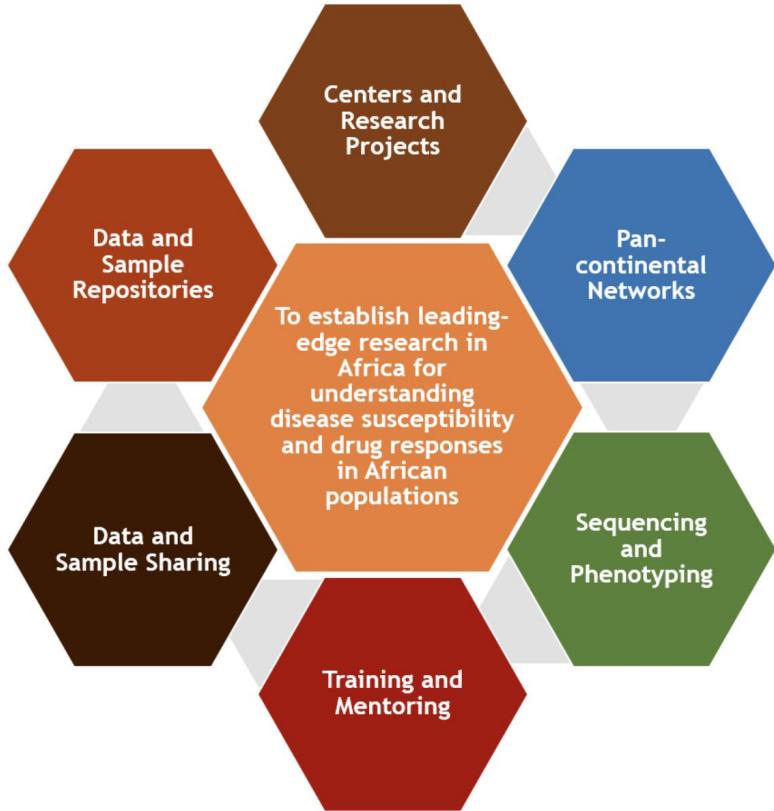
“The peoples of Africa
suffer a disproportionate
burden of avoidable
illness....”



Objectives

1. To develop within Africa the study of genomic/genetic/environmental contributors of human health and disease using cutting-edge genomic research tools
2. To increase capacity for biomedical research in Africa, in terms of building infrastructure, including data and research resources
3. To increase the genomic proficiency of researchers and trainees in Africa

H3AFRICA VISION



H3Africa: Aims and Status

Vision: To facilitate an African-based research approach to the study of genomic and environmental determinants of common diseases with the goal of improving the health of African populations

Status:

- 51 projects across 34 African countries
- Round 1 projects complete: ~70,000 participants recruited, 40,000 samples run on H3Africa chip
- Some data in EGA: AwiGen pilot, chip sequence data (~500)
- Round 2 projects in progress, additional recruitment

Cardiovascular diseases

Infectious diseases

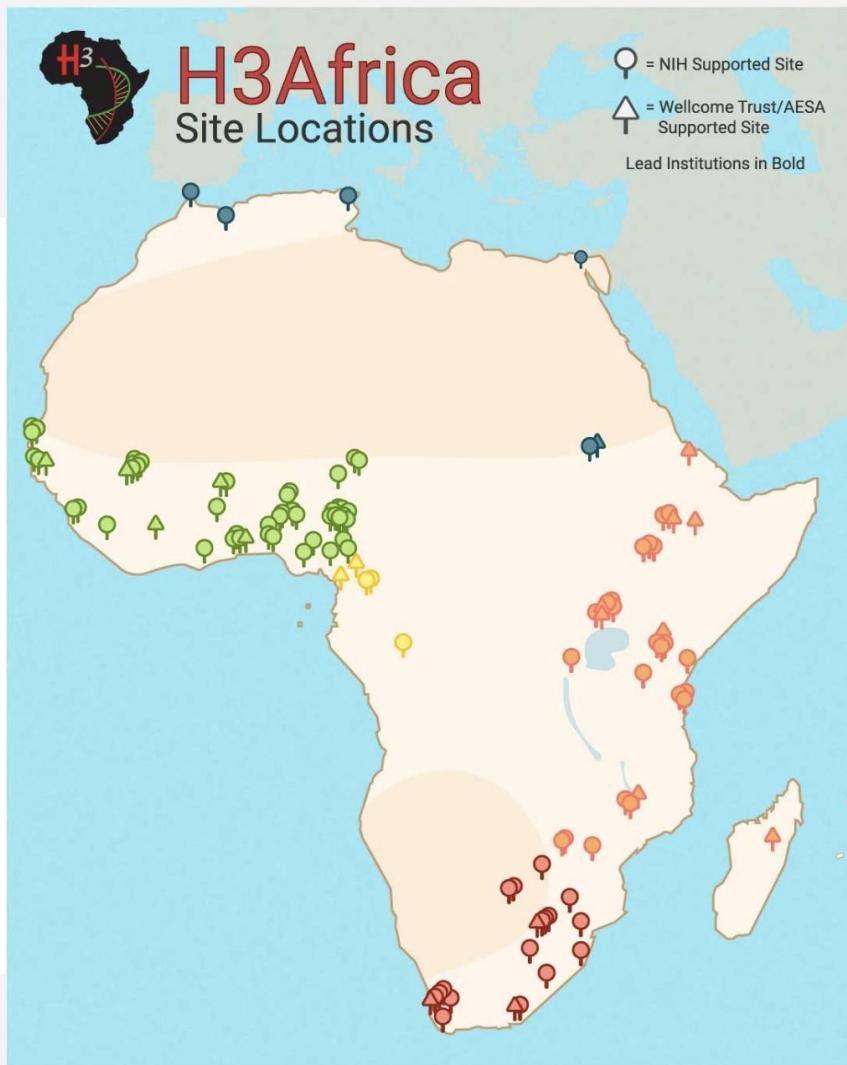
Mental Health

Cancer & rare diseases

Developmental disorders

CURRENT SITES ACROSS ARICA

- ❖ 3 BIOBANKS
- ❖ 3 COMMUNITY ENGAGEMENT PROJECTS
- ❖ 51 PROJECTS ALL TOGETHER
- ❖ USD 170 MILLION ALLOCATED OVER 10 YEARS



H3Africa: Current level of adoption of GA4GH standards

In progress, just become a driver project

So far:

- Using CRAM format for data storage and transfer
- Using Data Use Ontology for mapping consent information

Plan to:

- Provide use cases for some of the standards and tools, e.g. Crypt4GH, Beacon
- Contribute to clinical data -minimum reporting guidelines
- Aligning with GA4GH ethics policies

H3Africa: Tools and resources available to share

Phenotyping:

- Standard CRF for core demographic, anthropometric and phenotype data with REDCap data dictionary and xml template
- Guidelines on developing a CRF
- Adding modules for pediatrics, environmental, mental health, infectious diseases, CVD
- Minimum reporting guidelines for kidney disease and stroke

Clinical:

- IFGenera project on clinically actionable variants
- Guidelines for data governance

Ethics and community engagement:

- H3Africa Guidelines for Community Engagement
- H3Africa Guidelines for Informed Consent
- Framework for African genomics and biobanking

Tools:

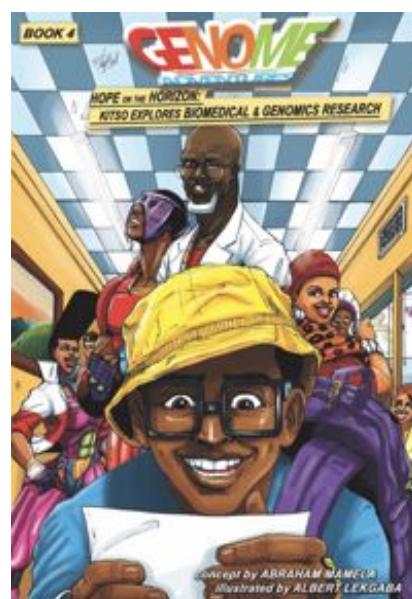
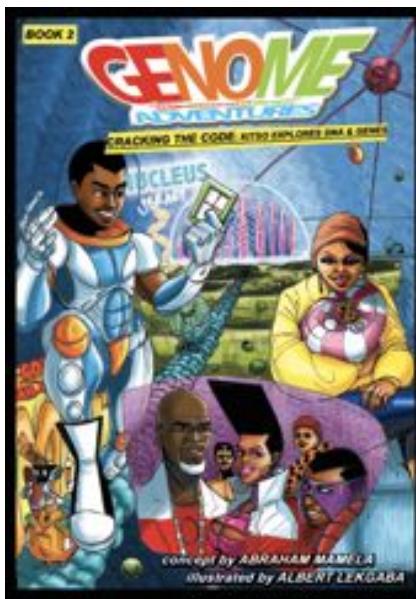
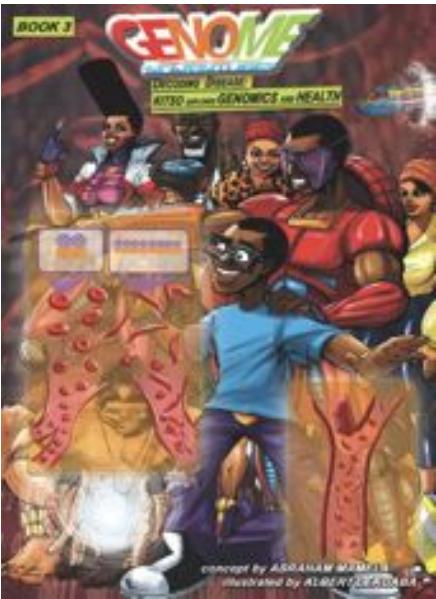
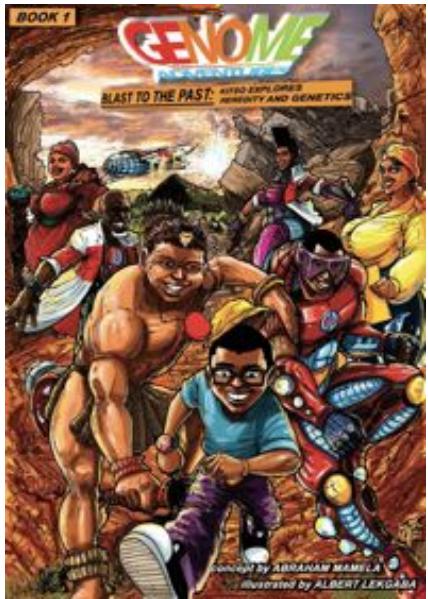
- Participant recruitment database
- Containerized workflows for variant calling, GWAS, imputation
- H3Africa genomic & biospecimen catalogue
- Custom chip design

Training:

- Genomic medicine online training for nurses
- Extending curriculum to doctors, pathologists and clinical researchers



SAMPLE CE PROJECT: GENOME ADVENTURES



H3Africa: Cohorts for pilot data sharing projects

- Data in EGA can be requested
- Can request collaboration with researchers in specific disease areas
- CVD group ~6 projects harmonized data may be willing to collaborate



BREAK

20 minutes



ELIXIR

Managing human data across Europe



ELIXIR-EXCELERATE is funded by the European Commission within the Research Infrastructures programme of Horizon 2020, grant agreement number 676559.

Serena Scollen, Head of Genomics and Translational Data
serena.scollen@elixir-europe.org

www.elixir-europe.org





ELIXIR Members



ELIXIR Observers



Cyprus

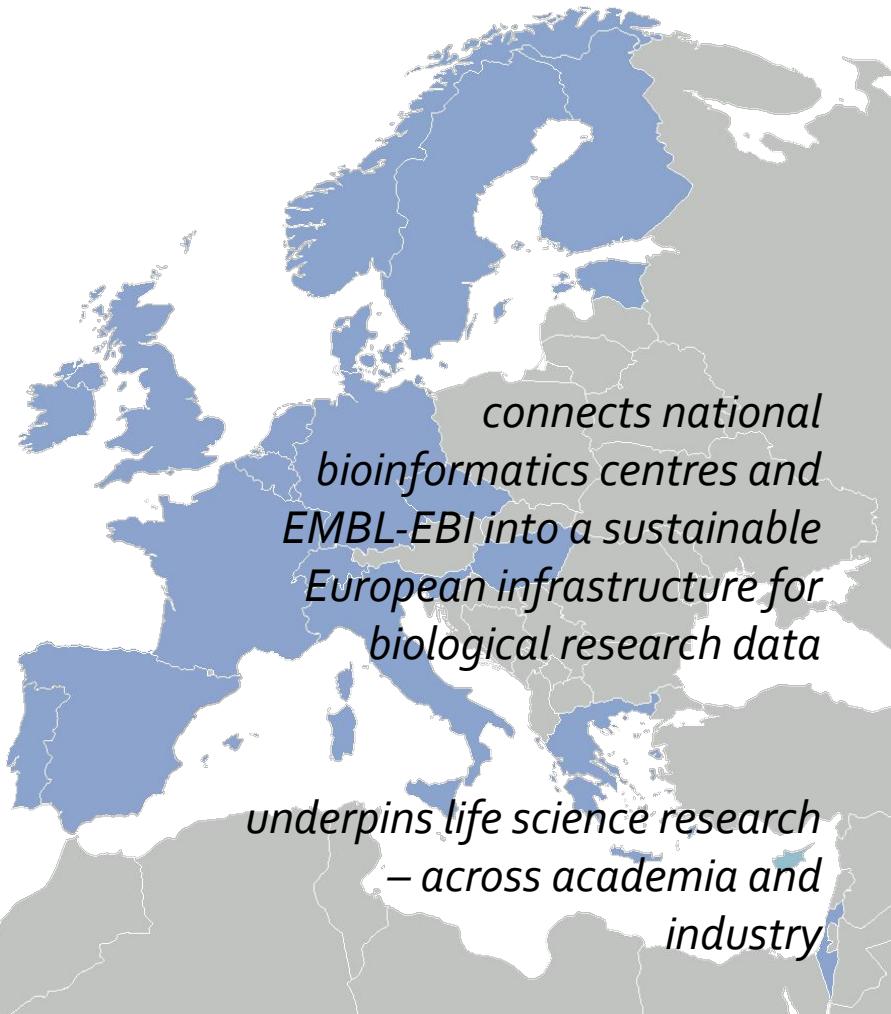
www.elixir-europe.org



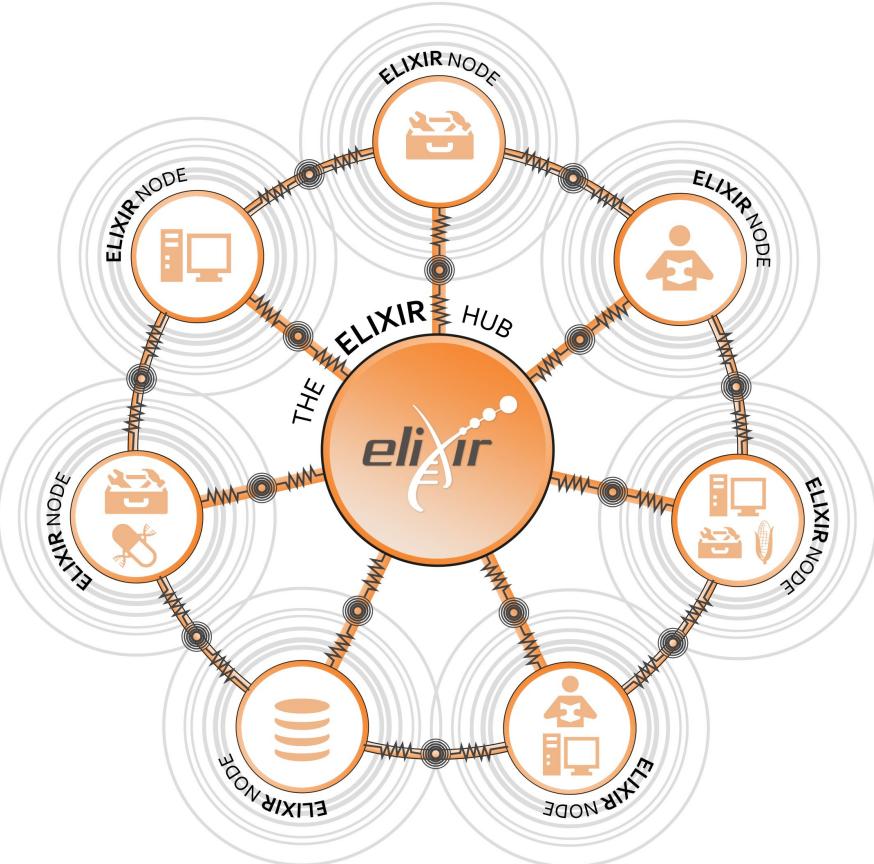
[@ELIXIREurope](https://twitter.com/ELIXIREurope)



[/company/elixir-europe/](https://www.linkedin.com/company/elixir-europe/)



A distributed infrastructure of data-related services



Databases

Deposition, knowledge-bases, data management support



Bioinformatics tools:

Bio.tools, software development



Compute:

Secure data transfer, cloud computing, AAI



Interoperability:

Standards, Identifiers, FAIR, Ontologies



Training:

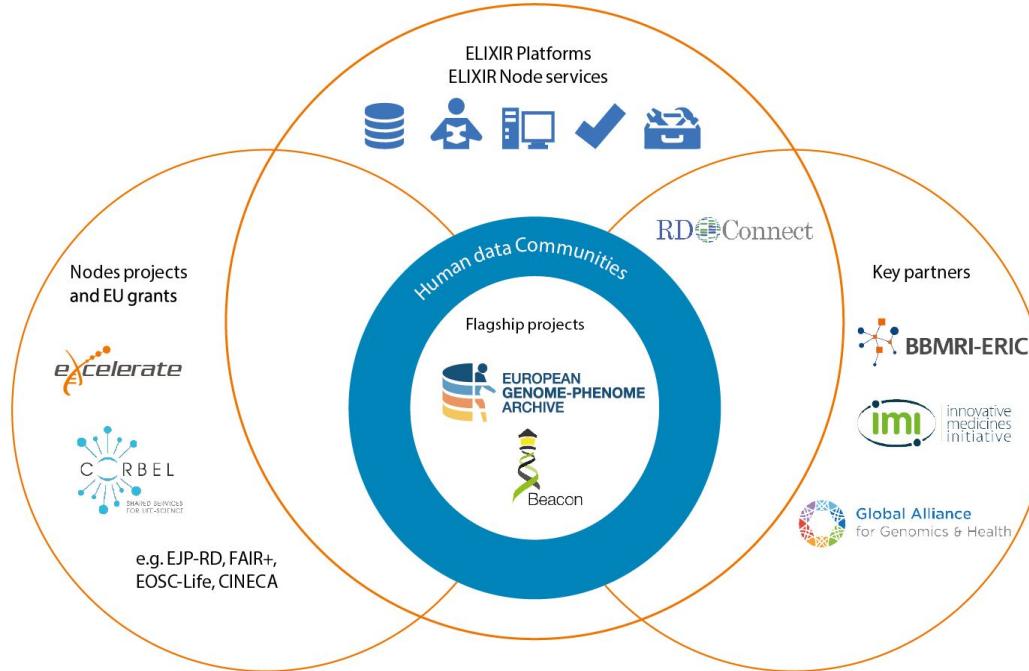
Training registry, face to face courses, eLearning



Industry:

Staff exchange, Innovation and SME Forum, Bioinformatics Suppliers Forum

Human Genomics and Translational Data



- Bring together ELIXIR's experts in a particular domain, data type or technology
- Ensure that the Platforms develop services that are fit for purpose

Human Data Communities

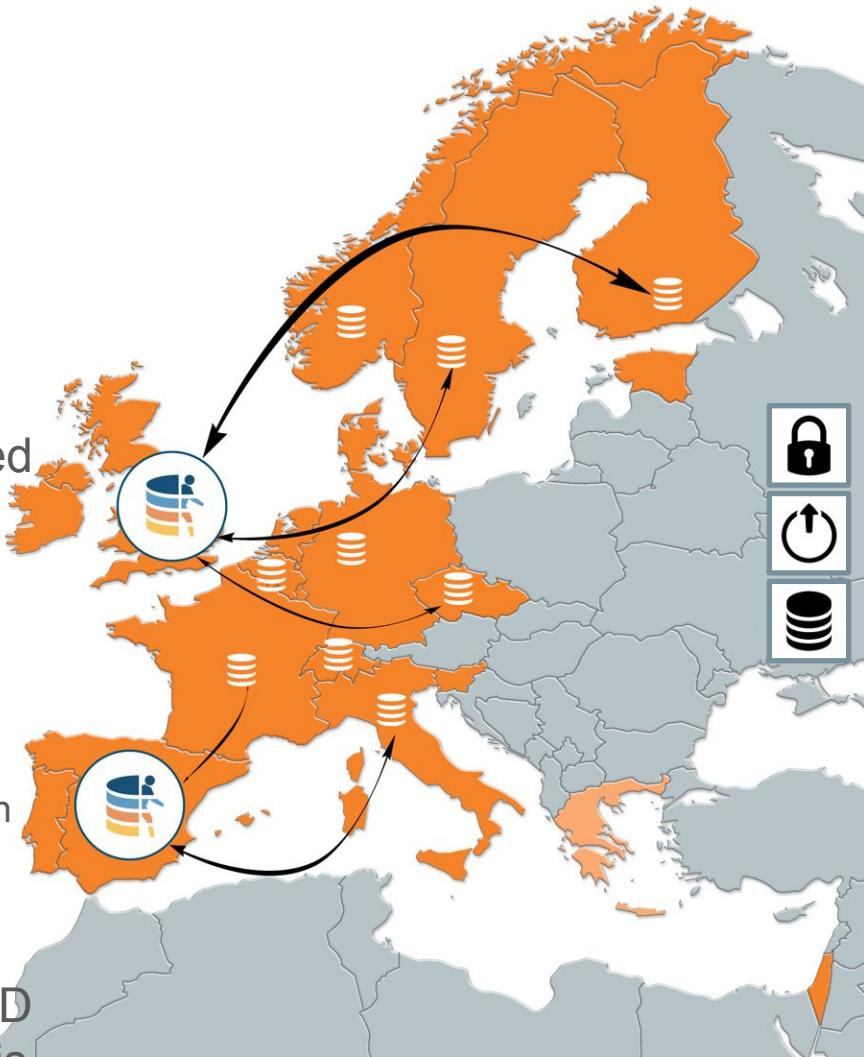
- Federated Human Data
- Rare Diseases
- human Copy Number Variation

To facilitate discoverability, access, sharing and analysis of genomics data, including rare disease, linked to other data types, at scale (4-5M participants)

To demonstrate how use of infrastructure can impact translation of genomics research into medicine

Federation of human genome data

- Many national datasets from human research participants needs to be stored locally
- ELIXIR developing a federation with shared metadata (FAIR) and local data store (secure)
- Linking local EGA to
 - national clouds
 - international access (ELIXIR-AAI - Authentication and Authorisation Infrastructure)



17/23 of ELIXIR Nodes are funded in the FHD community and we are looking to build on this

Examples of relevant European funded projects



- Bridging biomedical sciences research infrastructures
- EOSC-Life to implement in different fields



- CINCEA - Adoption of GA4GH standards in collaboration with Canada
- Linked to technology development of EOSC-Life (WP5, WP7)



- Key Use Cases in Human Data, and Rare Diseases
- Building coordinated infrastructure and Communities of people working together



EJP RD

European Joint Programme on Rare Diseases

- Pillar 2 to build a platform for RD data discovery and access



- Federated network of aligned and interoperable infrastructures



- IMI project to develop tools and guidelines for making life science data FAIR (Findable, Accessible, Interoperable, Reusable)



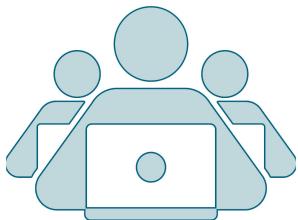
Aligning with international initiative



Global Alliance
for Genomics & Health
Collaborate. Innovate. Accelerate.

STRATEGIC PARTNERSHIP

Simplify the way people search for and request access to potentially identifiable data in international and national genomic data resources

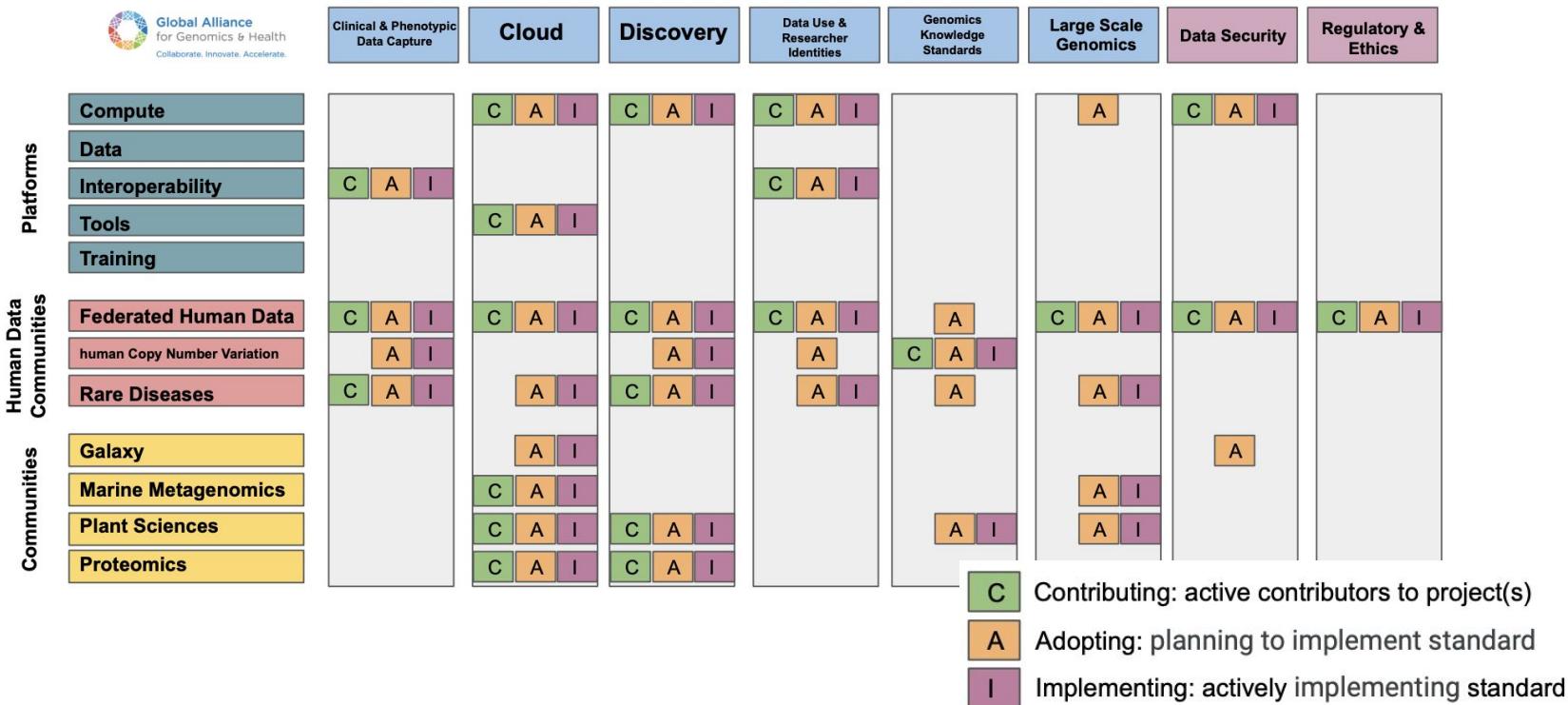


Working towards GA4GH standards, APIs and toolkits to be used throughout ELIXIR Nodes for human data discovery and access – **GA4GH into Europe**



ELIXIR::GA4GH Strategic Partnership

ELIXIR Platform and Community activities (contributing, adopting, implementing) across the GA4GH Work Streams.



ELIXIR::GA4GH Strategic Partnership

ELIXIR contributes to all approved GA4GH standards and all but two of the GA4GH Genomic data toolkit

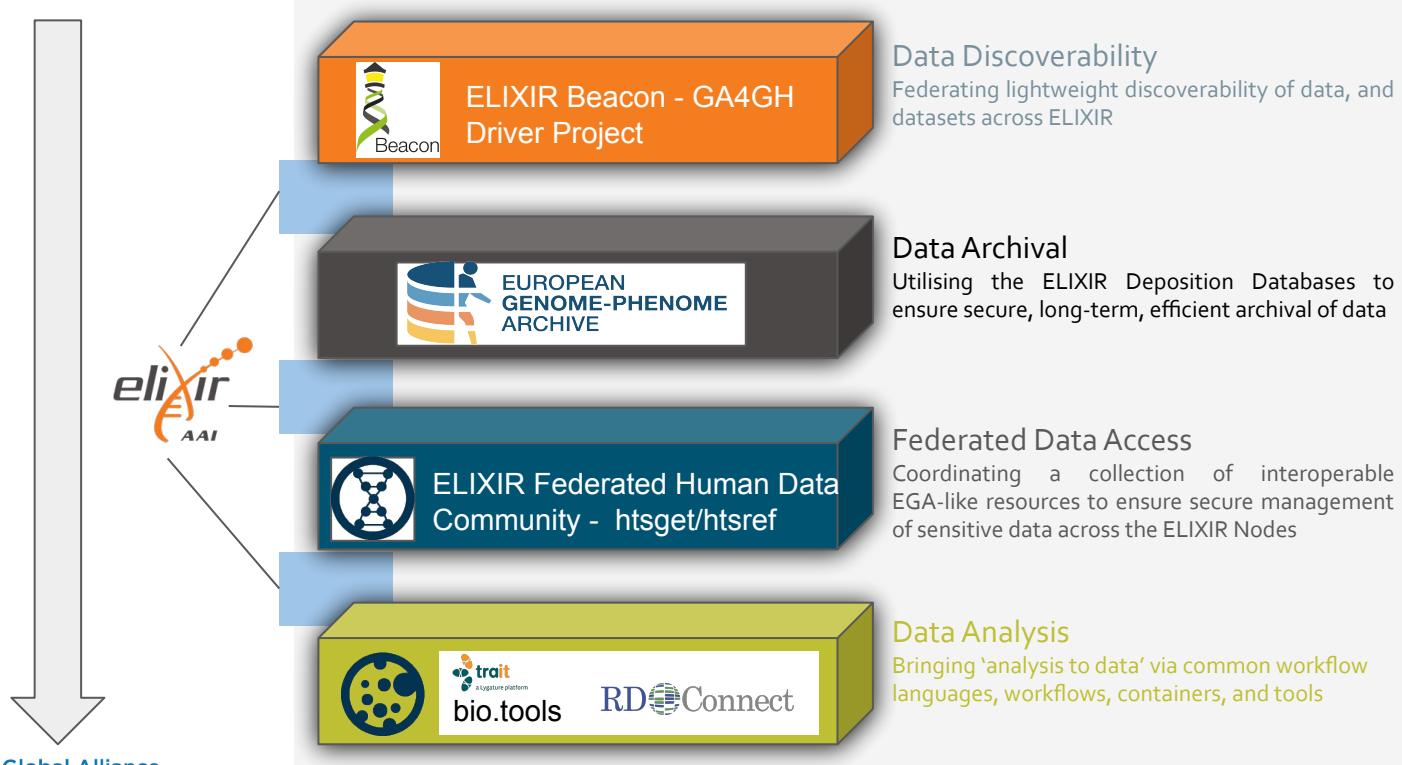
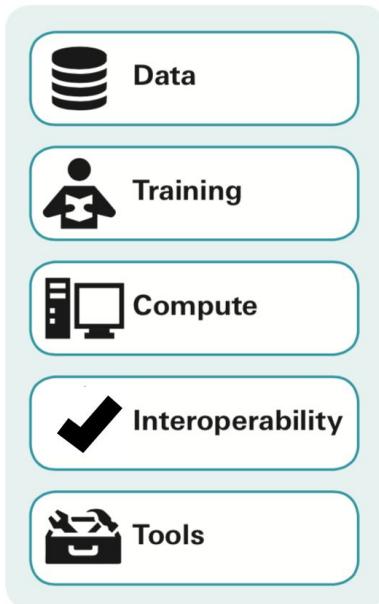
- Data Use Ontology v1*
- Beacon API v1*
- htsgt API v1*
- refget API v1*
- Workflow Execution Service (WES) API v1*
- CRAM File Format v3
- Family History Tools Inventory
- SAM/BAM File Formats v1
- Variant Benchmarking Tools
- VCF v4 / BCF v2 File Formats

*GA4GH approved standards

ELIXIR contributions

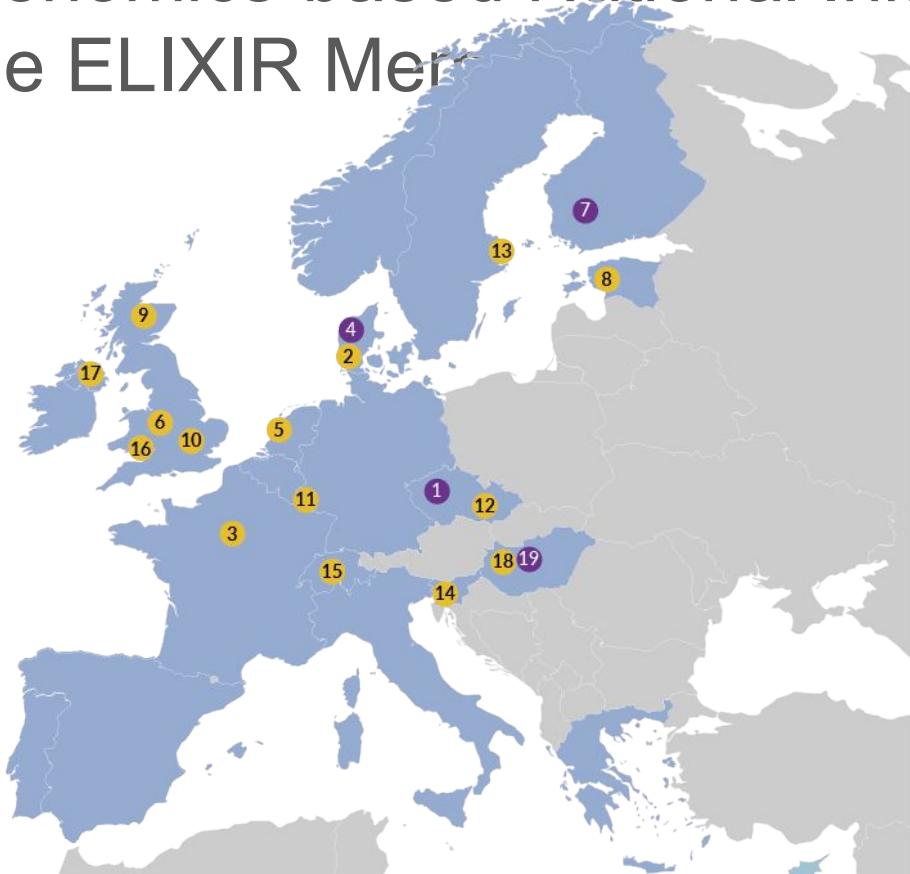


ELIXIR: stacking the GA4GH Genomic Toolkit



Global Alliance
for Genomics & Health
Collaborate. Innovate. Accelerate.

Genomics-based National Initiative projects across the ELIXIR Member States



Yellow circle: Public funding

Purple circle: Public-private funding

Sharing genomic data across borders



DECLARATION OF COOPERATION

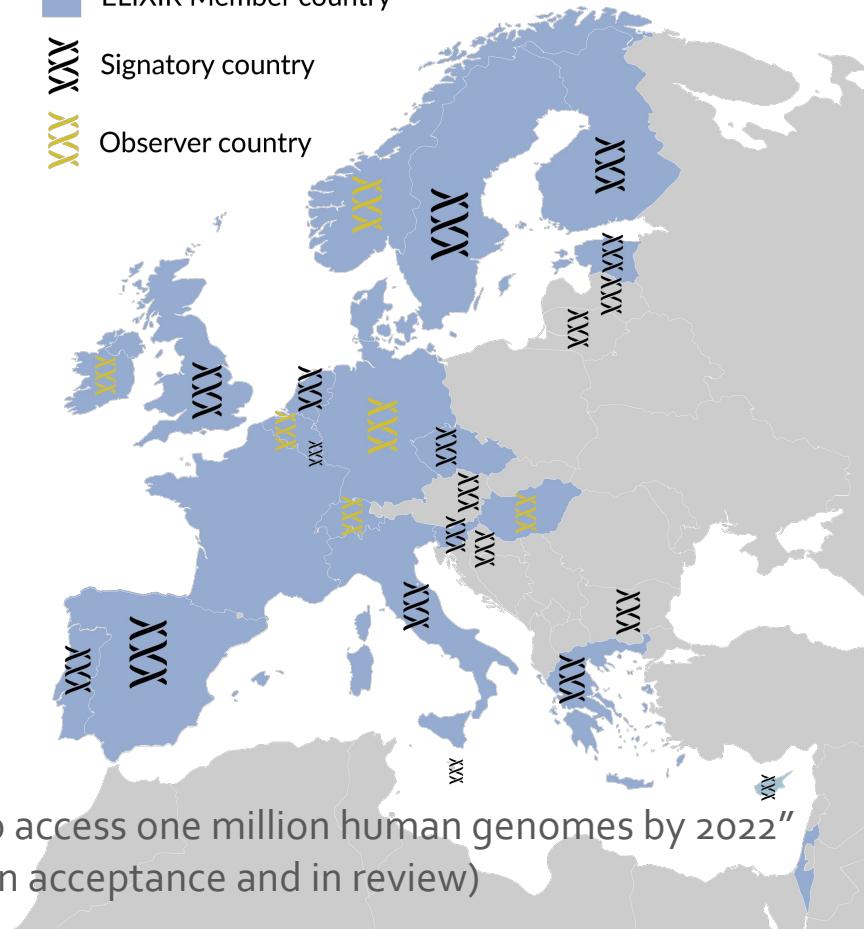
Towards access to at least 1 million sequenced genomes in the European Union by 2022

Currently signed but not ELIXIR members:
Austria, Bulgaria, Croatia, Latvia, Lithuania, Malta

ELIXIR Member country

Signatory country

Observer country

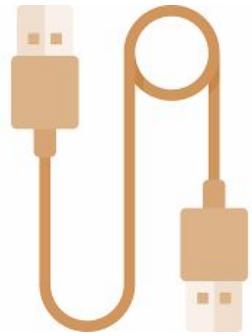


[Saunders G et al.](#), "Leveraging European infrastructures to access one million human genomes by 2022"
Nature Genetics Reviews (pre-submission acceptance and in review)

Conclusions

- ELIXIR is developing transnational interoperable infrastructure to manage sensitive human data
- Our mandate has been renewed (19-23 ELIXIR programme) to continue these efforts
 - Exploring funding opportunities to build on implementation plans
- As National Initiatives explore sharing data - consider use of knowledge and sustainable infrastructure e.g. ELIXIR





Standards



Networks of trust

Genome Canada

Marc LePage
Genome Canada
Canada

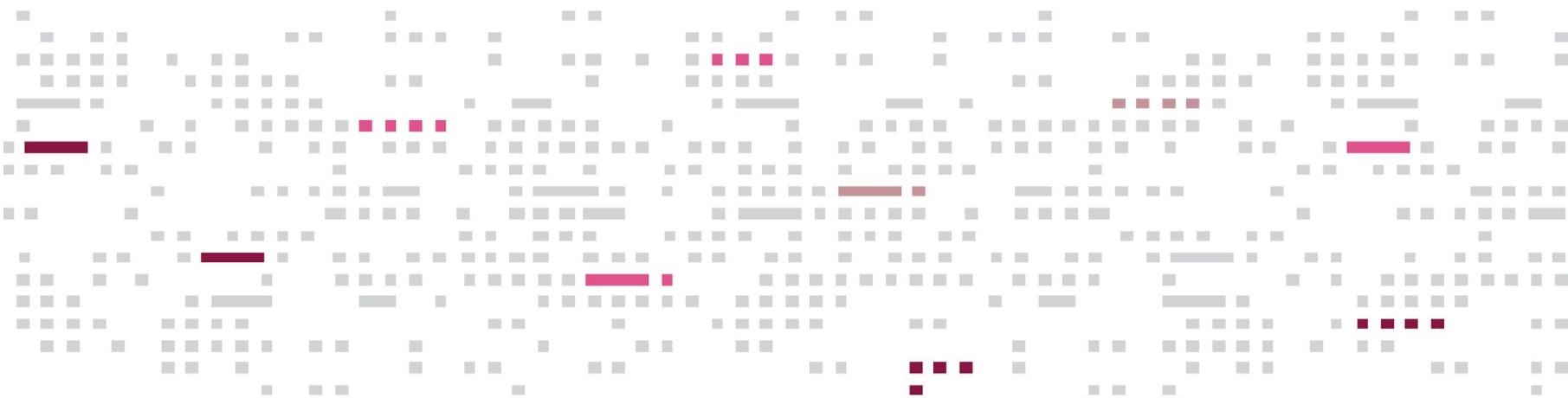
Qatar Genome Programme

Said Ismail
Qatar Foundation
Qatar



Member of Qatar Foundation

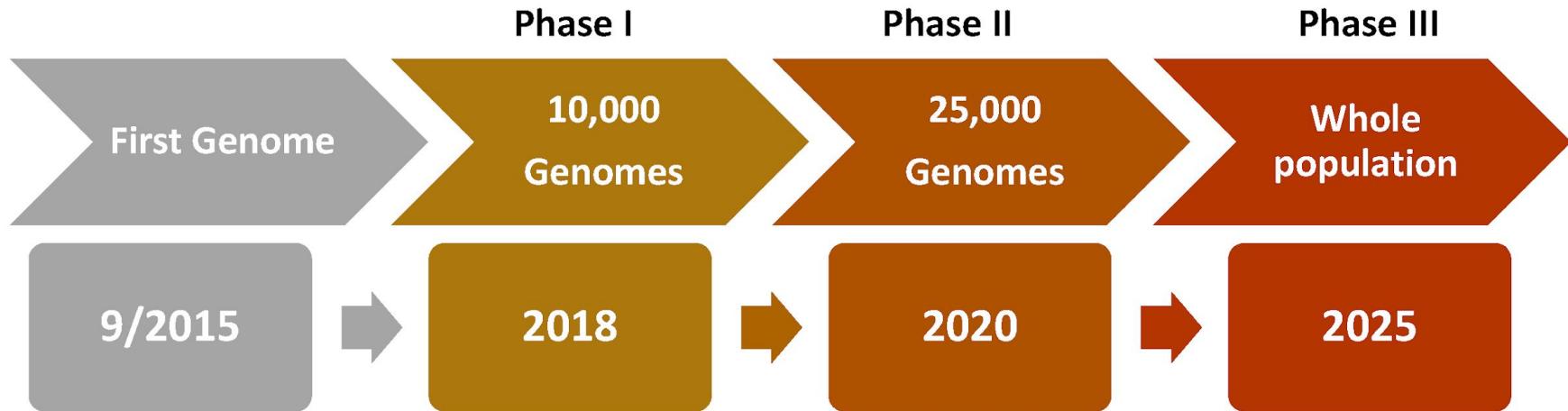
Qatar Genome Programme



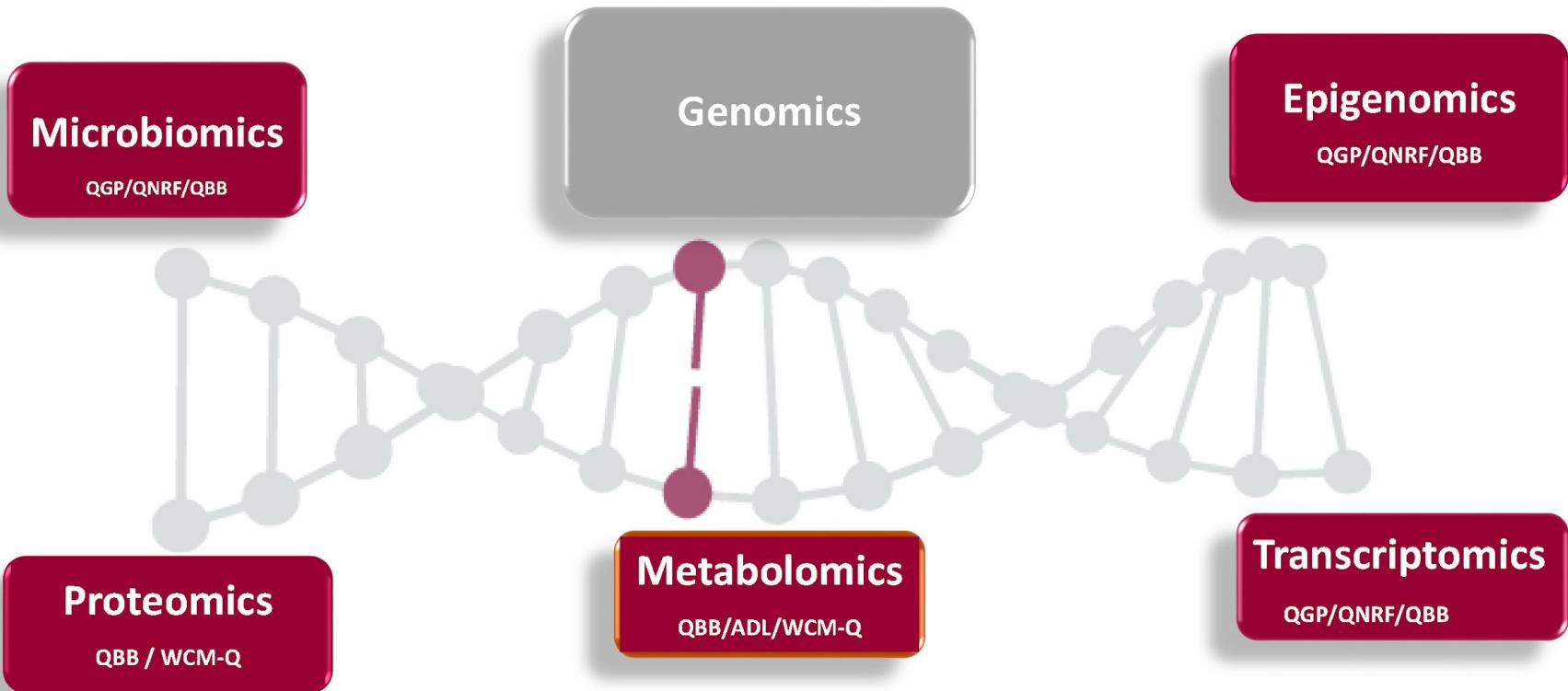


A national strategy built on “7 Pillars”

Time frame:



Multi Omics



The “7 Pillars”

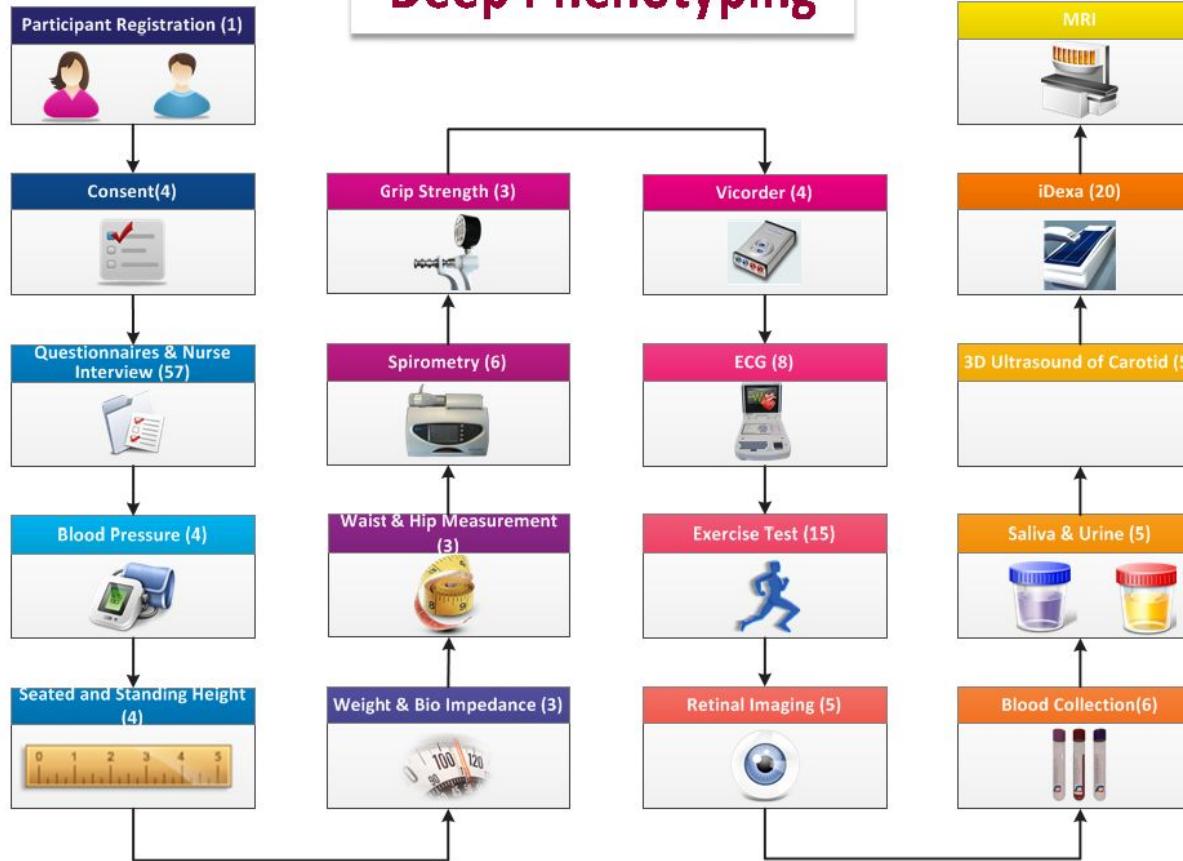
1. Qatar Biobank



Comprehensive **Phenotypic** data

1. Qatar Biobank

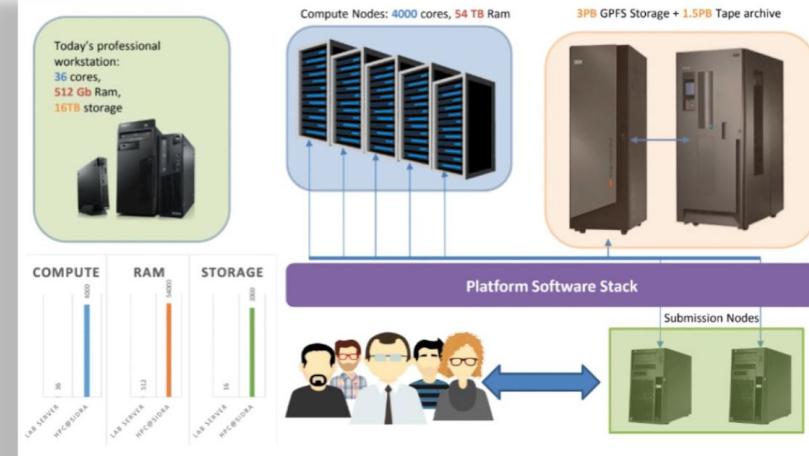
Deep Phenotyping



2. Genomics/Bioinformatics Infrastructure



State of the art setup:



Sequencing

Bioinformatics

3. Fostering Genomic Research



QGP Consortium

More than 150 local researchers with international partners



All Local Institutes are involved



PPM Awards

The Pathway To Personalized Medicine

Launched in Partnership between QGP and QNRF

QGP's arm to encourage and foster PIs driven research proposals



Member of *Qatar Foundation*



Member of *Qatar Foundation*

4. Policies, Regulations and Ethics



**Policy and Guidelines for the Design, Ethical Review, and Conduct
of Genomic Research in Qatar**



**Ministry of Public Health
Department of Research**



GENOMICS IN THE GULF REGION AND ISLAMIC ETHICS

A Special Report in Collaboration with
the Research Center for Islamic Legislation and Ethics

Mohammed Ghaly (editor)*
Eman Sadoun
Fowzan Alkuraya
Khalid Fakhro
Mai Zawati
Said Ismail
Tawfeq Ben-Omrani

*After the editor, authors are arranged in
alphabetical order of their names.



PRECISION MEDICINE A GLOBAL ACTION PLAN FOR IMPACT

Report of the WISH Precision Medicine Forum 2016

Victor Dzau
Geoffrey S Ginsburg
Elizabeth Finkelman
Celynne Balatbat
Kelsey Flott
Jessica Prestt



5. Building Human Capacity



MSc/PhD program in Genomic and Precision Medicine:

- Initiated in collaboration with HBKU
- Launched in August 2017

جامعة
حمد بن خليفة
HAMAD BIN KHALIFA
UNIVERSITY



MSc program in Genetic Counseling:

- Initiated in collaboration QU
- Launched in August 2018



Community outreach:

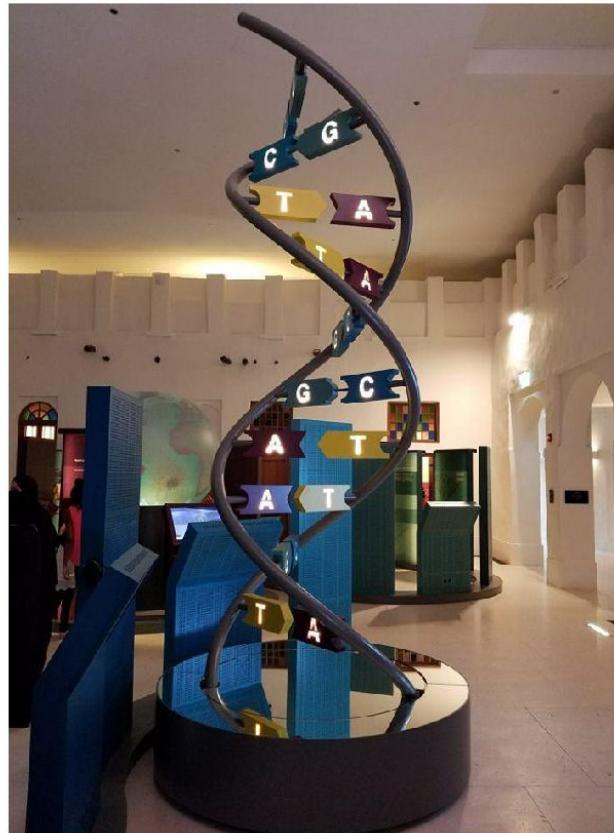
- DNA Museum in Musheireb:

Introducing Genomics to:

- Schools
- Families

- QGP Also has an Internship

Program



6. National Data Hub

Integrating Genomic Data in the
National Health care e-records

Provide access to genomic data for:

- Doctors
- Researchers
- Patients

QBB



Researchers



HMC



Sidra



Patients

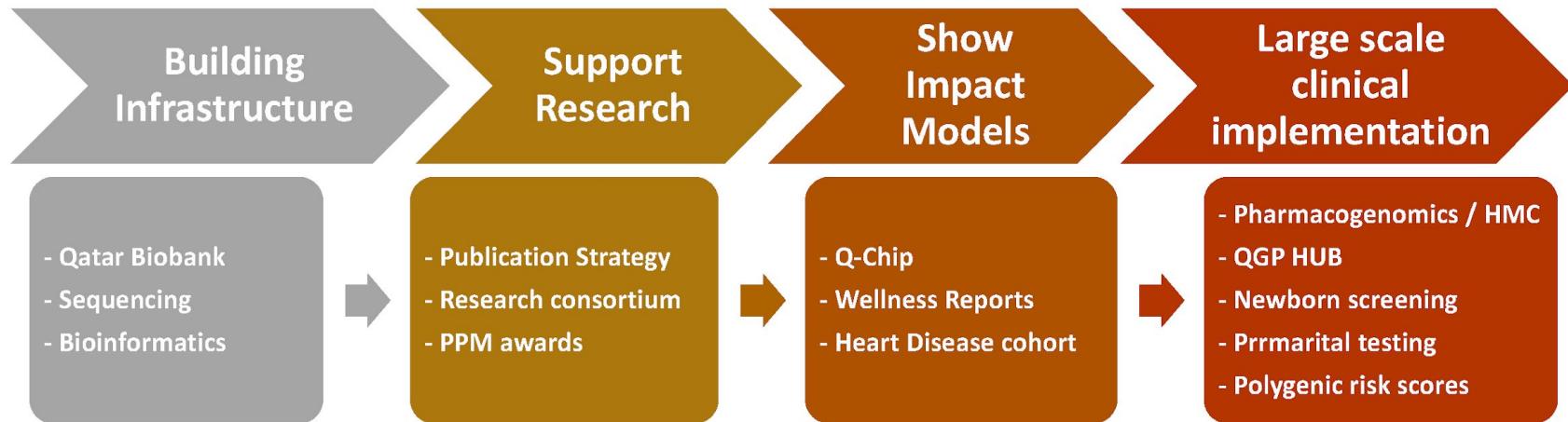


Doctors



7. Clinical Implementation

Stepwise approach:



Clinical impact models: The Low hanging fruits

- 1. The Q-Chip:** Version 1 (> 450,000 variants)
- 2. Genomic reports:** General health (wellness) traits (QBB participants)
- 3. Pharmacogenomics:** Working with HMC (Cardiovascular drugs)
- 4. Heart disease:** 1,000 Qatari heart disease patients (WGS)

Delivering Genomic reports

Lifestyle and wellness genomics:

- Food metabolism
- Weight management
- Response to exercise
- Metabolic health and Diabetes

Pharmacogenomics:

Start with:

- CVD
- Diabetes
- Pain management

Polygenic risk scores !



Personal Genomic Report

Participant Name: Radja Badji
QID Number: 28023123255
HC Number: 345678
Date of Birth: 9 October 1980



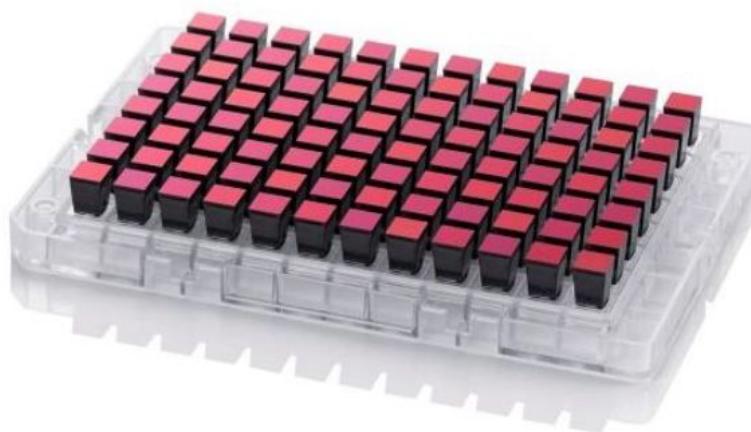
The Q-Chip

Gene Array containing “Qatari” Specific mutations
More than 450,000 mutation

Will be used in:

1. Research
2. Diagnosis

Version 1 produced
Version 2 underway



كلية طب وايل كورنيل في قطر
Weill Cornell Medical College in Qatar



The Heart Project

1,000 Qatari Coronary Heart Disease patients

Whole Genome Sequenced

Multi-center research team

Plans to do multi-omics on same cohort

Future plans for on Familial Arrhythmias

أكثر من ١٠٠٠ مشارك في دراسة أمراض القلب

نحو علاجات مشخصنة لمرضى القلب في قطر

Towards Precision medicine
for heart diseases in Qatar



Why QGP is unique ?

1. Applicable plan:

- Small Population
- Centralized health care system
- All major stakeholders onboard
- State of the art Infrastructure

2. Qatars:

- Represent the whole of Arabia
- High consanguinity rate

3. Comprehensive Phenotyping at QBB





Member of Qatar Foundation

THANK YOU

www.qatargenome.org.qa

BIPMed

Benilton de Sá Carvalho
University of Campinas
Brazil

Presentations on Data Sharing Pilot Projects

- Genomic Knowledge Curation Toolkit for National Initiatives (15 min) - Rehm
- Clinical Data (15 min) - Stark
- Curation: PanelApp (15 mins) - McDonagh
- Genomic Data Sharing & GA4GH (15 min) - Hofmann

Developing a National Initiative Toolkit for Clinical Genomic Knowledge Sharing

Heidi Rehm

*Broad Institute of MIT and Harvard
Massachusetts General Hospital*

Domains of Clinical Genomic Knowledge Sharing



Variant interpretation sharing – aids in accurate interpretation of test results for patients

Gene-disease validity and gene-to-phenotype curation – aids in deciding which genes should be included on clinical test panels or interpreted for different indications

Rare disease gene discovery – clinical implementation of genomic sequencing (exome and genome) often requires participation in rare disease gene discovery

Variant Interpretation Knowledge Sharing



Step 1: Use standard data model for defining and annotating a variant

- Variant Representation and Variant Annotation Standards from GA4GH GKS Workstream
 - Used by ClinGen Allele Registry; incorporates HGVS nomenclature

Step 2: Apply standards for variant interpretation

- ACMG/AMP 2015 Guideline widely adopted internationally
- Additional specifications provided by the ClinGen Sequence Variant Interpretation WG and Disease-Specific Expert Panels

Step 3: Share variant interpretations with the community through ClinVar

- Countries/Labs need their own database to track their work and then they submit to ClinVar
 - Currently submission is manually triggered and periodic
 - In the future, we hope to have API-based sharing
 - However, to support API-based sharing, experience with manual ClinVar submission is critical

Step 4: Collaborate through ClinGen Expert Panels to harmonize variant interpretations

- ClinGen Variant Curation Expert Panels: Gene and/or Disease Specific

ClinGen Allele Registry

Canonical Allele Identifier: **CA321211**

Gene: NDUFS8 [HGNC](#) [NCBI](#)

Identifiers and link-outs to other resources

ClinVar Variation Id: 214835 [↗](#)

ClinVar RCV Id: RCV000196794 [↗](#) RCV000276295 [↗](#)

dbSNP Id: rs369602258 [↗](#)

gnomAD: 11:67799758 C / T [↗](#)

RCV000389629 [↗](#)

ExAC: 11:67799758 C / T [↗](#)

MyVariant Identifiers: chr11:g.67799758C>T (hg19) [↗](#)

chr11:g.68032291C>T (hg38) [↗](#)

Calculator

JSON-LD

Genomic Alleles

HGVS

NC_000011.10:g.68032291C>T , CM000673.2:g.68032291C>T

Genome Assembly

[GRCh38](#)

NC_000011.8:g.67556334C>T

[NCBI36](#)

NC_000011.9:g.67799758C>T , CM000673.1:g.67799758C>T

[GRCh37](#)

NG_017040.1:g.6675C>T

Transcript Alleles

HGVS

Amino-acid change

ENST00000313468.9:c.64C>T

[ENSP00000315774.5:p.Pro22Ser](#) [↗](#)

ENST00000526339.5:c.64C>T

[ENSP00000436287.1:p.Pro22Ser](#) [↗](#)

ENST00000531228.1:c.119C>T

[ENSP00000433054.1:p.Ser40Phe](#) [↗](#)

This allele is not present in the allele registry. To get CA identifier, please click on the "Get CA identifier" below.

Canonical Allele Identifier: [Get Identifier](#)

Gene: NDUFS8

[HGNC](#) [↗](#)

[NCBI](#) [↗](#)

ClinGen Allele Registry provides identifiers (CAID) for > 910 million variants

Allows user to quickly and easily get identifiers for new variants

Uses GA4GH Standards



ClinGen CAIDs used in key resources

<https://reg.clinicalgenome.org>

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, PhD¹, Nazneen Aziz, PhD^{2,16}, Sherri Bale, PhD³, David Bick, MD⁴, Soma Das, PhD⁵, Julie Gastier-Foster, PhD^{6,7,8}, Wayne W. Grody, MD, PhD^{9,10,11}, Madhuri Hegde, PhD¹², Elaine Lyon, PhD¹³, Elaine Spector, PhD¹⁴, Karl Voelkerding, MD¹³ and Heidi L. Rehm, PhD¹⁵, on behalf of the ACMG Laboratory Quality Assurance Committee

Benign		Pathogenic			
Strong	Supporting	Supporting	Moderate	Strong	Very Strong
Population Data	MAF is too high for disorder <i>BA1/BS1</i> OR de novo variant in controls inconsistent with disease penetrance <i>BS2</i>		Absent in population databases <i>PM2</i>	Prevalence in affecteds statistically increased over controls <i>PS4</i>	
Computational And Predictive Data	Multiple lines of computational evidence suggest no impact <i>BP4</i> Missense when only three amino acid change <i>PP3</i> Silent variant with non predicted splice impact <i>BP7</i> In-frame indels in repeat w/out known function <i>BP3</i>	Multiple lines of computational evidence support a deleterious effect on the gene /gene product <i>PP3</i>	Novel missense change at an amino acid residue where a different missense change has been seen before <i>PM5</i> Protein length changing variant <i>PM4</i>	Same amino acid change as an established pathogenic variant <i>PS2</i>	Predicted null variant in a gene where LOF is a known mechanism of disease <i>PS1</i>
Functional Data	Well-established functional studies show no deleterious effect <i>BS3</i>	Missense in gene with low rate of benign missense variants and pathogenic variants common <i>PP2</i>	Mutational hot spot or well-studied function domain without known variation <i>PM3</i>	Well-established functional studies show a deleterious effect <i>PS3</i>	
Segregation Data	Non-segregation with disease <i>BS4</i>	Co-segregation with disease in multiple affected family members <i>PP2</i>	Increased segregation data		
De novo					
Allelic Data	Observed in trans with a dominant variant <i>BR2</i> Observed in cis with a pathogenic variant <i>BP2</i>		De novo (without paternity & maternity confirmed) <i>PM6</i> <i>PS2</i>		
Other Database	Reputable source w/out shared data + a benign <i>BP6</i>	Reputable source = pathogenic <i>PP5</i>			
Other Data	Found in case with an alternate cause <i>BP5</i>	Patient's phenotype or F/H highly specific for gene <i>PP4</i>			

Pathogenic
Likely pathogenic
Uncertain
significance
Likely benign
Benign

ClinGen Sequence Variant Interpretation Working Group

1. Refine and evolve the ACMG/AMP guidelines as they are tested and deployed by the community
2. Review and harmonize gene and disease specifications provided by Variant Curation Expert Panels
3. Move the ACMG/AMP guideline towards a more quantitative framework



New ACMG/ClinGen/AMP Working Group Now Convened to Update the 2015 Guidelines

- Adopted by UK in 2016
- Published in Chinese in 2017
- Used by 95% of surveyed labs worldwide (Niehaus et al 2019)

Sequence Variant Interpretation

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

The Sequence Variant Interpretation Task Team 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 Working Group has representation from the following ClinGen curation groups: Brainmalformations Expert Panel, Cardiovascular CDWG, Hereditary Cancer CDWG, Hereditary Hearing Loss CDWG, Inborn Errors of Metabolism CDWG, Mitochondrial Expert Panel, Monogenic Diabetes Expert Panel, RASopathy Expert Panel, Biocurators WG and the Variant Curation Interface development team.

MEMBERS 



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LETTER TO THE EDITOR | Genetics inMedicine

The ACMG/AMP reputable source criteria for the interpretation of sequence variants

To the Editor: In 2015, the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) promulgated recommendations for

on assertions from reputable sources in the absence of primary evidence.

A second rationale for these two criteria was to support the efforts of the Sharing Clinical Reports Project (<https://www.clinicalgenome.org/data-sharing/sharing-clinical-reports-project-script/>), in which clinicians collected the test reports (including variant interpretation) produced by a large commercial laboratory that for the past decade has consistently declined to share underlying data or to submit assertions to ClinVar. As data for hereditary breast and

General SVI Publications

- Modeling the ACMG/AMP variant classification guidelines as a Bayesian classification framework

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)
- PP5/BP6: Recommendation for reputable source PP5 and BP6 ACMG/AMP criteria

SVI Approved Expert Panel Specified ACMG/AMP Variant Interpretation Guidelines

- ClinGen Cardiomyopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines
- ClinGen CDH1 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines
- ClinGen Hearing Loss Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines
- ClinGen PAH Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines
- ClinGen PTEN Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines
- ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines

Leadership

Leslie G. Biesecker, MD

Steven Harrison, PhD

Coordinators

Please contact a coordinator if you have questions.

Danielle Azzariti, MS, CGC
dazzarit@broadinstitute.org

Membership

Membership in this committee spans many fields, including genetics, medical, academic, and industry. [View Members](#)

For more information, please contact:
Danielle Azzariti, MS, CGC
dazzarit@broadinstitute.org

Official journal of the American College of Medical Genetics and Genomics

Open

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, MS¹, Colleen Caleshu, MS², Ana Morales, MS³, Jillian Buchan, PhD¹, Zena Wolf, PhD¹, Steven M. Harrison, PhD¹, Stuart Cook, MD⁴, Mitchell W. Dillon, MS⁵, John Garcia, PhD⁵, Eden Haverfield, PhD⁵, Jan D.H. Jongbloed, PhD⁶, Daniela Macaya, PhD⁷, Arjun Manrai, PhD⁸, Kate Orland, MS⁹, Gabriele Richard, MD⁷, Katherine Spoonamore, MS¹⁰, Matthew Thomas, MS¹¹, Kate Thomson, BSc^{12,13}, Lisa M. Vincent, PhD¹⁴, Roddy Walsh, PhD^{4,14}, Hugh Watkins, MD PhD¹⁵, Nicola Whiffin, PhD^{4,14}, Jodie Ingles, PhD¹⁴, J. Peter van Tintelen, MD PhD¹⁶, Christopher Semarians, MBBS PhD¹⁵, James S. Ware, PhD MRCP^{4,14}, Ray Herscherger, MD³ and Birgit Funke, PhD^{1,17,18}, for the ClinGen Cardiovascular Clinical Domain Working Group¹⁹

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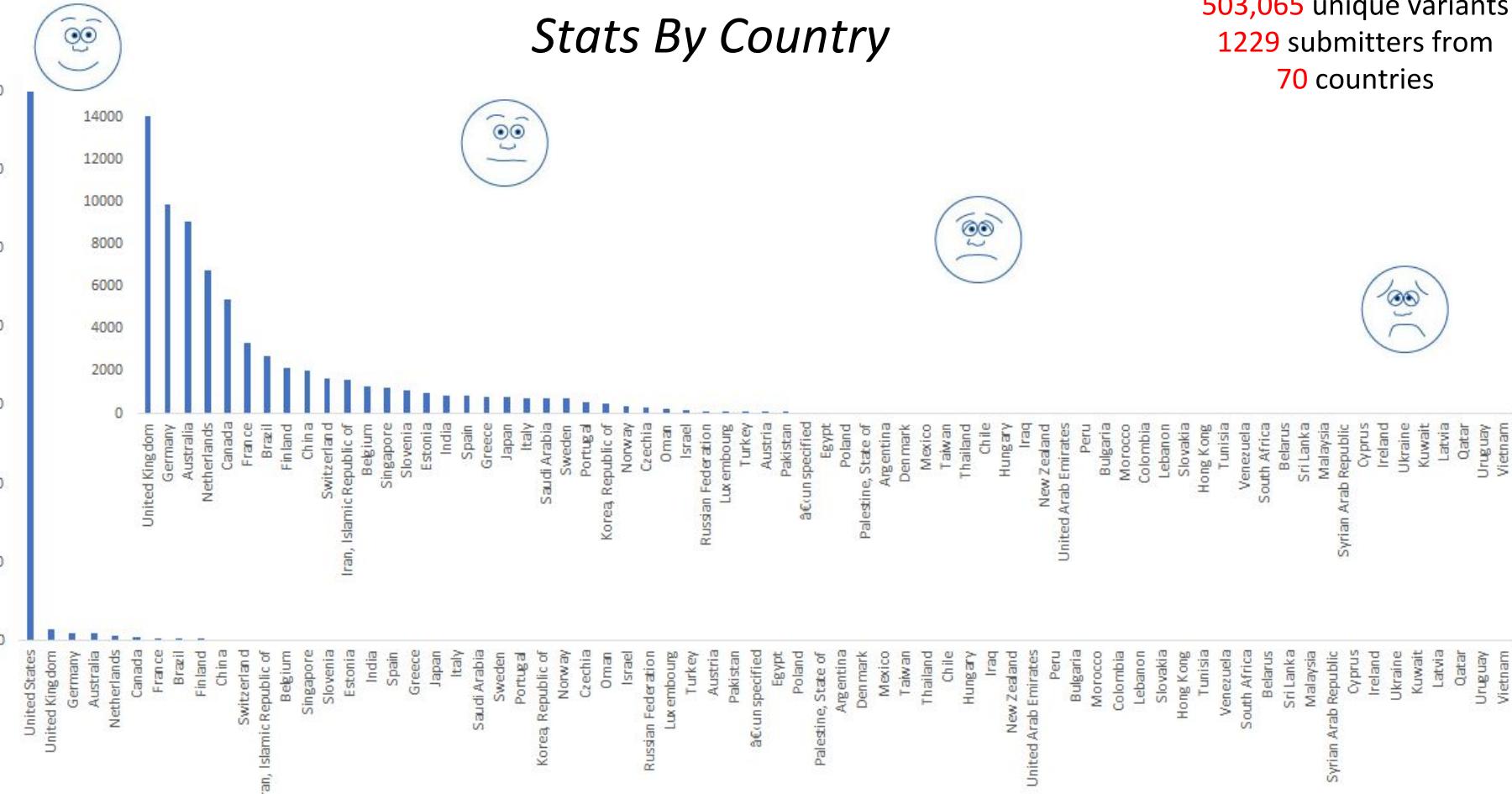
ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

ClinGen's RASopathy Expert Panel consensus methods for variant interpretation

Bruce D. Gelb, MD¹, Hélène Cavé, PharmD, PhD², Mitchell W. Dillon, MS³, Karen W. Gripp, MD⁴, Jennifer A. Lee, PhD⁵, Heather Mason-Suarez, PhD⁶, Katherine A. Rauen, MD, PhD⁷, Bradley Williams, MS⁸, Martin Zenker, MD⁹, Lisa M. Vincent, PhD⁸ and for the ClinGen RASopathy Working Group

Step 3: Submission to ClinVar

Stats By Country



794,361 submissions on
503,065 unique variants
1229 submitters from
70 countries

Each country defines arguments for sharing variant-level interpretations

Arguments for Clinical Labs:

- ✓ Improved Variant Classification
- ✓ Keep Providers Up-to-Date with Variant Knowledge
- ✓ Adds Value through Standardization and Quality Control
- ✓ Publicity as a Lab that Shares Data
- ✓ Position Your Lab with Evolving Regulatory and Medical Standards
- ✓ Data Sharing as a Business Strategy

2013



Our AMA: (1) encourages payers, regulators and providers to make clinical assures patient and provider privacy protection; and (2) encourages laboratory clinical significance of these results, into the public domain which would allow the public's health.

Position Statements

Clinical Data Sharing

2015



The National Society of Genetic Counselors phenotype and interpretation data acquired genetic and genomic testing. Timely data improve accuracy of variant interpretation, patient confidentiality and should label underlies any variant classification. By sharing variants, data-sharing allows for more laboratories. For this reason, responsibility relies on genetic testing to facilitate their plans.

Benefits of Sharing Variant Classifications and Evidence with ClinVar



Given the rarity of most variants of clinical relevance, it is imperative that genomic variant classifications and supporting evidence are shared in a public, centralized database such as ClinVar (<https://www.ncbi.nlm.nih.gov/cdinvar>) to improve both our understanding of genomic variation and patient care that relies on this information.

Improved Variant Classification

Sharing variant classifications with ClinVar allows laboratories to identify classification differences with other ClinVar submitters and work towards consensus, providing more accurate and consistent results to patients.

- ClinVar provides a broader set of clinical classifications than users may have assessed in their own laboratory. Data can be retrieved programmatically via APIs, which allows users to incorporate the information into their own workflow.
- ClinVar provides a monthly report of conflicting classifications which submitters can use to prioritize reassessment (<https://ftp.ncbi.nlm.nih.gov/pub/cdinvar/>).
- Studies of clinical laboratory ClinVar submitters have shown data sharing is a successful approach to prioritizing variant reassessment and resolving classification differences.^{1,2,3}

Keep Providers Up-to-Date with Variant Knowledge

- Classifications change over time and providers, patients and scientists in the community need to be kept up-to-date. Directing inquiries to ClinVar for current knowledge can reduce resources needed to respond to inquiries on current variant classifications.

Adds Value through Standardization and Quality Control

ClinVar adds value to submitted classifications by standardizing descriptions of variants, conditions, and terms for clinical significance.

- Variants are mapped to reference sequences and reported in HGVS. This provides a quality control check for accurate nomenclature.
- Clinical significance terms for Mendelian disorders are converted to standard ACMG-AMP categories (Pathogenic, Likely pathogenic, Uncertain significance, Likely benign, Benign), enabling comparison across laboratories.
- As many variants identified in Mendelian disease testing are extremely rare and thus unlikely to be observed, sharing variant interpretations in ClinVar can serve as an ongoing quality assurance measure for laboratory reassessment of rare variants.

Publicity as a Lab that Shares Data

- ClinGen recognizes submitters meeting minimum requirements for data sharing to support quality assurance (<https://www.clinicalgenome.org/submit>).
- Submitters receive recognition by ClinGen at meetings and conferences for sharing data (https://www.ncbi.nlm.nih.gov/cdinvar/docs/submitter_list).

Genetics
inMedicine

ACMG STATEMENT

© American College of Medical Genetics and Genomics

2017

Laboratory and clinical genomic data sharing is crucial to improving genetic health care: a position statement of the American College of Medical Genetics and Genomics

ACMG Board of Directors¹

Laboratories Meeting Minimum Requirements for Data Sharing to Support Quality Assurance

Goals:

1. To publicly recognize clinical labs who support data sharing and incentivize others to share as well
2. To provide a list of clinical labs to hospitals, healthcare providers, and insurers who wish to only order from, or reimburse, labs meeting a certain standard in data sharing and quality assurance

17 labs meet requirements – USA(15), Slovenia, Greece

www.clinicalgenome.org/lablist

Launched July 14th, 2017

Laboratory	Meets requirements	Additional Achievements			
		Submitted evidence ¹	>75% from past 5 years ²	Discrepancy resolution ³	Consenting mechanism ⁴
Ambry	✓	✓	✓	✓	✓
ARUP	✓	✓	✓	✓	✓
Athena Diagnostics Inc.	✓	✓	✓	✓	✓
Centre for Mendelian Genomics, University Medical Centre Ljubljana	✓	✓	✓	✓	✓
Center for Pediatric Genomic Medicine, Children's Mercy Hospital and Clinics	✓	✓	✓	✓	✓
Color Genomics, Inc.	✓	✓	✓	✓	✓
Counsyl	✓	✓	✓	✓	✓
EGL Genetics (Emory)	✓	✓	✓	✓	✓
GeneDx	✓	✓	✓	✓	✓
GeneKor MSA	✓	✓	✓	✓	✓
Illumina	✓	✓	✓	✓	✓
Integrated Genetics/Laboratory Corporation of America	✓	✓	✓	✓	✓
Invitae	✓	✓	✓	✓	✓
Partners Laboratory for Molecular Medicine	✓	✓	✓	✓	✓
Phosphorus Diagnostics LLC	✓	✓	✓	✓	✓
Quest Diagnostics Nichols Institute San Juan Capistrano	✓	✓	✓	✓	✓
University of Chicago	✓	✓	✓	✓	✓

Some requirements and additional achievements based on self-reported data by laboratory

¹ Most recent submission pending ClinVar posting

² Majority of submissions have evidence submitted (excludes allele-frequency classified variation)

³ >75% of classified sequence variants from past 5 years submitted

⁴ Actively working to resolve interlab interpretation differences

⁴ Laboratory actively supports use of a consenting mechanism to enable patients to directly consent to share detailed, individual-level clinical data (e.g., an internal patient registry made available for collaborative research, or report language highlighting external registries such as GenomeConnect)

Points to consider for sharing variant-level information from clinical genetic testing with ClinVar

Danielle R. Azzariti,^{1,6} Erin Rooney Riggs,^{2,6} Annie Niehaus,³ Laura Lyman Rodriguez,³ Erin M. Ramos,³ Brandi Kattman,⁴ Melissa J. Landrum,⁴ Christa L. Martin,^{2,8} and Heidi L. Rehm,^{1,5,6}

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Abstract Data sharing between laboratories, clinicians, researchers, and patients is essential for improvements and standardization in genomic medicine; encouraging genomic data sharing (GDS) is a key activity of the National Institutes of Health (NIH)-funded Clinical Genome Resource (ClinGen). The ClinGen initiative is dedicated to evaluating the clinical relevance of genes and variants for use in precision medicine and research. Currently, data originating from each of the aforementioned stakeholder groups is represented in ClinVar, a publicly available repository of genomic variation, and its relationship to human health hosted by the National Center for Biotechnology Information at the NIH. Although policies such as the 2014 NIH GDS policy are clear regarding the mandate for informed consent for broad data sharing from research participants, no clear guidance exists on the level of consent appropriate for the sharing of information obtained through clinical testing to advance knowledge. ClinGen has collaborated with ClinVar and the National Human Genome Research Institute to develop points to consider for clinical laboratories on sharing de-identified variant-level data in light of both the NIH GDS policy and the recent updates to the Common Rule. We propose specific data elements from interpreted genomic variants that are appropriate for submission to ClinVar when direct patient consent was not sought and describe situations in which obtaining informed consent is recommended.

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INTRODUCTION

The benefits of genomic data sharing (GDS), including the potential to improve clinical interpretation of genomic variants and advance genomic medicine, are widely recognized, and the practice has been endorsed by both professional societies and funding agencies (American Medical Association 2013; National Institutes of Health 2014; National Society of Genetic Counselors 2015; ACMG Board of Directors 2017). One of the aims of the National Institutes of Health (NIH)-funded Clinical Genome Resource (ClinGen) (Rehm et al. 2015) is to create a publicly available knowledge base of clinically relevant genes and variants for use in precision medicine and research. As shared genomic data help

⁶These authors contributed equally to this work.



OPEN LETTER

Genomic variant sharing: a position statement [version 1; referees: 1 approved, 1 approved with reservations]

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⁷Division of Genetics and Epidemiology, Institute of Cancer Research, UK, London, UK

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V1 First published: 05 Feb 2019, 4:22 (<https://doi.org/10.12688/wellcomeopenres.15090.1>)

Latest published: 05 Feb 2019, 4:22 (<https://doi.org/10.12688/wellcomeopenres.15090.1>)

Abstract

Sharing de-identified genetic variant data is essential for the practice of genomic medicine and is demonstrably beneficial to patients. Robust genetic diagnoses that inform medical management cannot be made accurately without reference to genetic test results from other patients, as well as population controls. Errors in this process can result in delayed, missed or erroneous diagnoses, leading to inappropriate or missed medical interventions for the patient and their family. The benefits of sharing individual genetic variants, and the harms of not sharing them, are numerous and well-established. Databases and mechanisms already exist to facilitate deposition and sharing of pseudonymized genetic variants, but clarity and transparency around best practice is needed to encourage widespread use, prevent inconsistencies between different communities, maximise individual privacy and ensure public trust. We therefore recommend that widespread sharing of a small number of individual genetic variants associated with limited clinical information should become standard practice in genomic medicine. Information robustly linking genetic variants with specific conditions is fundamental biological knowledge, not personal information, and therefore should not require consent to share. For additional case-level detail about individual patients or more extensive genomic information, which is often essential for clinical interpretation, it may be more appropriate to use a controlled-access model for data sharing, with the ultimate aim of making as much information as open and de-identified as possible with appropriate consent.

Keywords

medical genomics, variant, data sharing, data ethics

Open Peer Review

Referee Status: ? ✓

Invited Referees	
1	2
version 1	?
published 05 Feb 2019	report report

1 Gert Matthijs , KU Leuven, Belgium

2 Christa L Martin, Geisinger Health System, USA

Erin Rooney Riggs, Geisinger Medical Center, USA

Heidi Rehm, Massachusetts General Hospital, USA

Broad Institute of MIT and Harvard, USA
Brigham & Women's and Harvard Medical School, USA

Any reports and responses or comments on the article can be found at the end of the article.

When is consent required for sharing?

- Consent is **not required** for sharing **variant interpretations with summarized evidence**
- Individual consent allows more detailed sharing
- ClinGen videos in English, French, Spanish and Chinese explain the difference

English - Clinical Broad Data Sharing Consent Video

GENE	VARIANT	TOTAL	SEX	RACE/ETHNICITY	HEALTH DETAILS
BRCA1	R1495M	5	4 Female 1 Male	2 Caucasian 1 African American 2 Not specified	4 Breast cancer 1 Ovarian cancer 1 Developmental Delay



Summary Information

00:03:05:24

Consent not required

English - Clinical Broad Data Sharing Consent Video

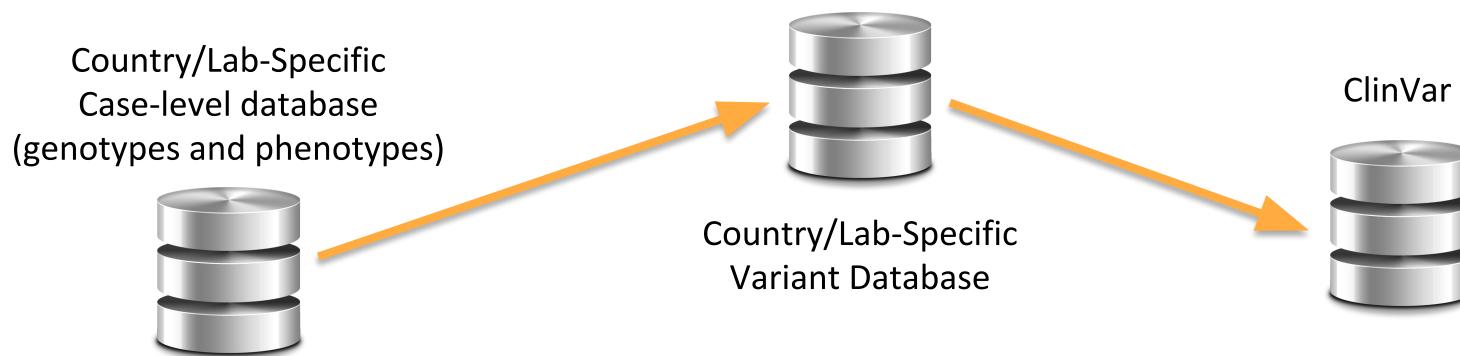
Individual Information

GENE	PARTICIPANT	SEX	AGE	RACE/ETHNICITY	HEALTH DETAILS	OTHER GENETIC CHANGES
BRCA1	343Ds2	Female	50	African American	Breast cancer	No
R1495M	574GC1	Female	35	Caucasian	Breast cancer	No
	854GE1	Female	34	Unknown	Ovarian cancer	No
	CF234H	Female	23	Caucasian	Breast cancer Developmental delay	Yes chr8:103066066-104430435 x 1 (GRCh37/hg19)
	917HB1	Male	45	Unknown	Breast cancer	No

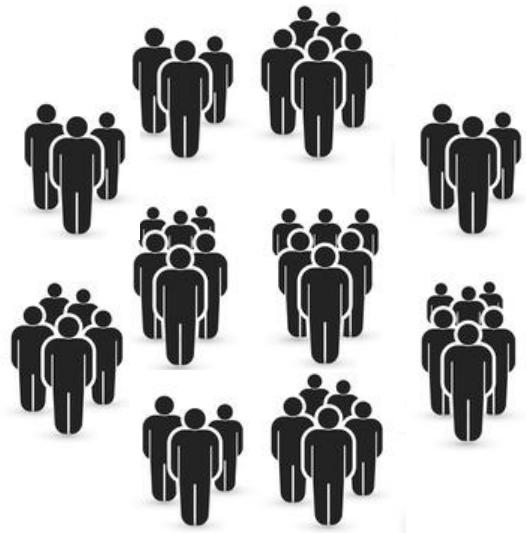
Consent required

Database Ecosystems Needed for Each Country

- Every lab/country needs a place to maintain their own variant interpretations (often with case-level data) that can be managed on a daily basis. ClinVar does not serve this purpose.
- **Case-level data** storage requires additional protections (e.g. controlled access).
- ClinVar has become the primary database for “sharing, comparing, distributing and accessing” variant interpretations with the community

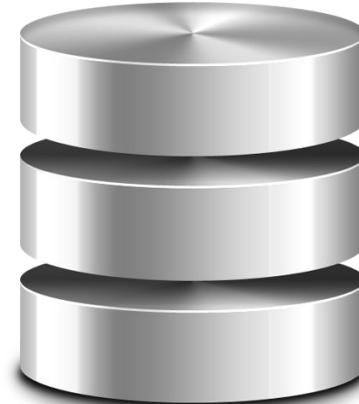
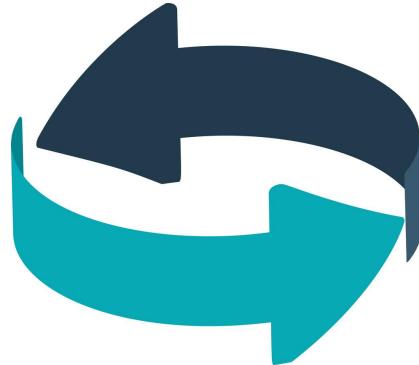


Step 4: Collaborate through ClinGen Expert Panels to harmonize variant interpretations



ClinGen

(consortium of people sharing data, developing
standards and curating knowledge)



ClinVar

(database for ingesting and sharing
variant level knowledge)

ClinGen Expert Panels (VCEPs and GCEPs)

- VCEPs create expert consensus in variant interpretation and GCEPs define valid gene-disease associations
- New members welcome!
- Enables interaction with experts in the relevant fields
- Junior members also join – excellent learning environment

Variant Curation Expert Panels

ACADVL
Brain Malformations
Cardiomyopathy
CDH1
Cerebral Creatine Deficiency Syndromes
Familial Hypercholesterolemia
FBN1
Hearing Loss
Hereditary Breast, Ovarian and Pancreatic Cancer
Hereditary Hemorrhagic Telangiectasia
KCNQ1
Mitochondrial Disease
Monogenic Diabetes
Myeloid Malignancy
Phenylketonuria
Platelet Disorder
PTEN
RASopathy
Rett and Angelman-like Disorders
Somatic/Germline
Storage Diseases
TP53
VHL

Gene Curation Expert Panels

Aminoacidopathy
Arrhythmogenic Right Ventricular Cardiomyopathy
Brain Malformations
Breast/Ovarian Cancer
Brugada Syndrome
Colon Cancer
Epilepsy
Familial Thoracic Aortic Aneurysm and Dissection
Fatty Acid Oxidation Disorders
Hearing Loss
Hemostasis Thrombosis
Hereditary Cancer
Hypertrophic Cardiomyopathy
Intellectual Disability and Autism
Long QT Syndrome
Mitochondrial Diseases
RASopathy

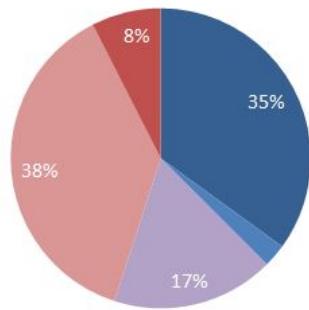
ClinGen Expert Panels Span Many Time Zones!



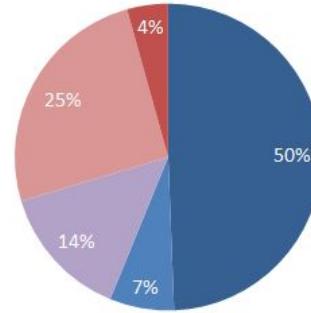
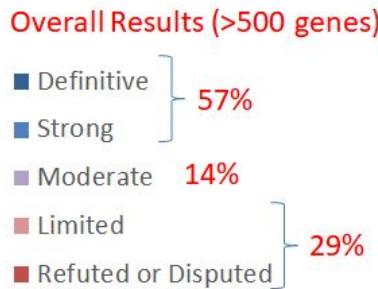
Expert Panels have Resolved 758 Conflicts in ClinVar

	ENGIMA	INSIGHT	CFTR2	RAS	MYH7	Hearing Loss	PTEN	Total
Total Submissions	7261	2405	291	233	102	49	42	10383
P/LP vs VUS/LB/B overwritten	41	55	2	6	13	3	4	124
VUS vs LB/B overwritten	416	165	0	39	12	1	1	634

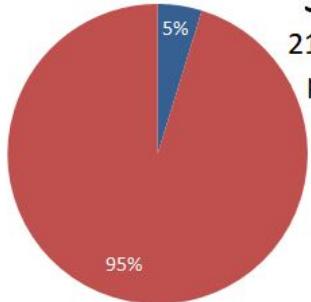
Selected Gene Curation Expert Panel Results



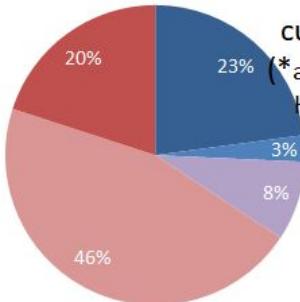
**Colorectal
Cancer**
40 gene:disease
pairs curated



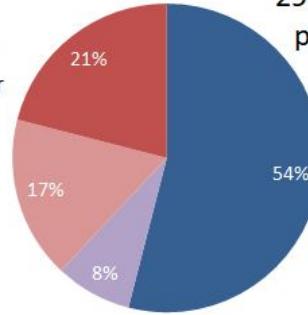
Hearing Loss
164 gene:disease
pairs curated



**Brugada
Syndrome**
21 gene:disease
pairs curated



**Hypertrophic
Cardiomyopathy**
37 gene:disease pairs
curated for isolated HCM
(*additional 18 pairs curated for
HCM as part of a syndromic
presentation)



RASopathies
29 gene:disease
pairs curated

Gene-disease validity and gene-to-phenotype curation

- aids in deciding which genes should be included on clinical test panels or interpreted for different indications

Gene
Curation
Coalition
(GeneCC)



Comparison of Terms → Delphi Survey → Harmonized

ClinGen	GDM	G2P	Orphanet	OMIM	PanelApp
Definitive	Red	Confirmed	Present	Yes	Green
Strong	Red	Confirmed	Present	Yes	Green
Moderate	Grey-Red	Probable	Absent	Yes	Amber
Limited	Grey-Blue / Grey-Red?	Possible	Candidate	?Disease	Red
No evidence	Blue	Absent	Absent	No disease claim	Red
Disputed	Grey-Blue	Absent	Candidate	?Disease	Red/Amber
Refuted	Blue	Absent	Absent (Suppressed)	Reclassified-VUS	Red



GenCC
Definitive
Strong
Moderate
Limited
Animal Model Only
No Known Disease Relationship
Disputed Evidence
Refuted Evidence

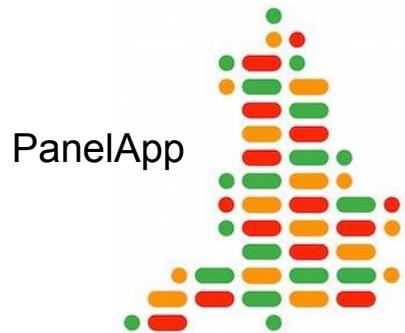
Ellen McDonagh will Provide Update on PanelApp

Gene Curation Coalition
(GeneCC)



Use defined evidence for
disease associations

Shared Resource
for Defining Panels



Rare disease gene discovery



Clinical implementation of genomic sequencing (exome and genome) often requires participation in rare disease gene discovery

For example, when you run a trio exome/genome on a patient with suspected genetic disease, and find a de novo LOF variant in a novel, constrained gene, it is important that the gene be entered into Matchmaker Exchange by the lab, or physician, or patient to find matching patients that can build evidence for causality and help diagnose the patient with a cause of their disease

Principles of Gene Matching

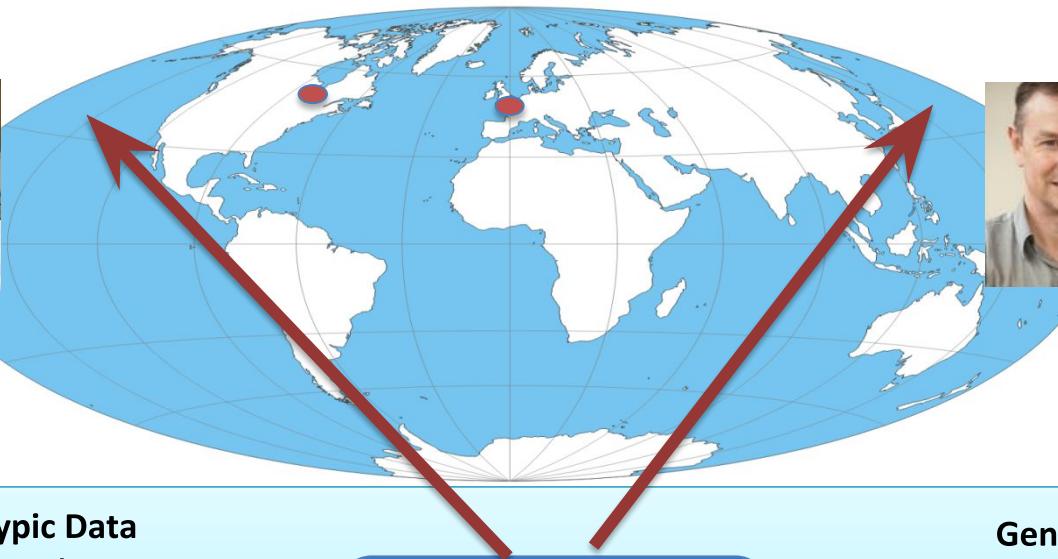
Patient #1

Clinical Geneticist #1



Patient #2

Clinical Geneticist #2



Phenotypic Data
Feature 1
Feature 2
Feature 3
Feature 4
Feature 5

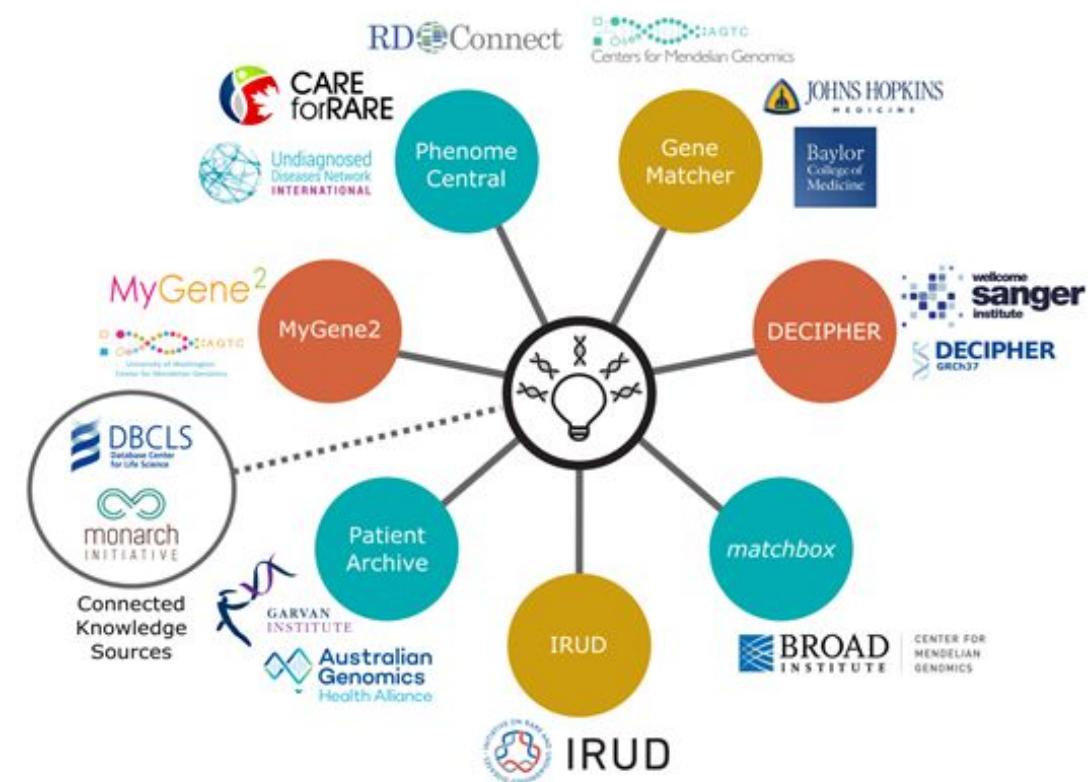
Genotypic Data
Gene A
Gene B
Gene C
Gene D
Gene E
Gene F

Genomic Matchmaker

Genotypic Data
Gene D
Gene G
Gene H

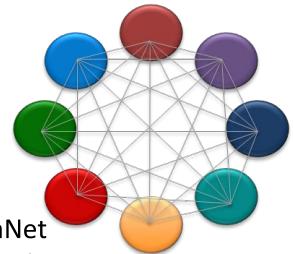
Phenotypic Data
Feature 1
Feature 3
Feature 4
Feature 5
Feature 6

Matchmaker Exchange - A Federated Network of Rare Disease Databases



API Fields

ID (Mandatory) +/- Label
Submitter (Mandatory)
Phenotypic Features and/or
Gene Names (Mandatory)
Disorders (Optional) - OMIM or OrphaNet
Sex, Age of Onset, Inheritance (Optional)



Matching typically on gene with phenotype used for ranking

Supported today:

- Match on Gene (rank by Phenotype)
 - 1 strong candidate gene (e.g. *de novo* variant in GUS)
 - 10 candidate genes each with rare variant
- Match on phenotype only
- Match case to non-human models
- Patient-initiated matching

Philippakis et al. The Matchmaker Exchange: A Platform for Rare Disease Gene Discovery. *Hum Mutat.* 2015;36(10):915-21.

Buske et al. The Matchmaker Exchange API: automating patient matching through the exchange of structured phenotypic and genotypic profiles. *Hum Mutat.* 2015;36(10):922-7

Matchmaker Exchange



Genomic discovery through the exchange of phenotypic & genotypic profiles



www.matchmakerexchange.org

Over **10,000** candidate genes

from **>130,000** patients

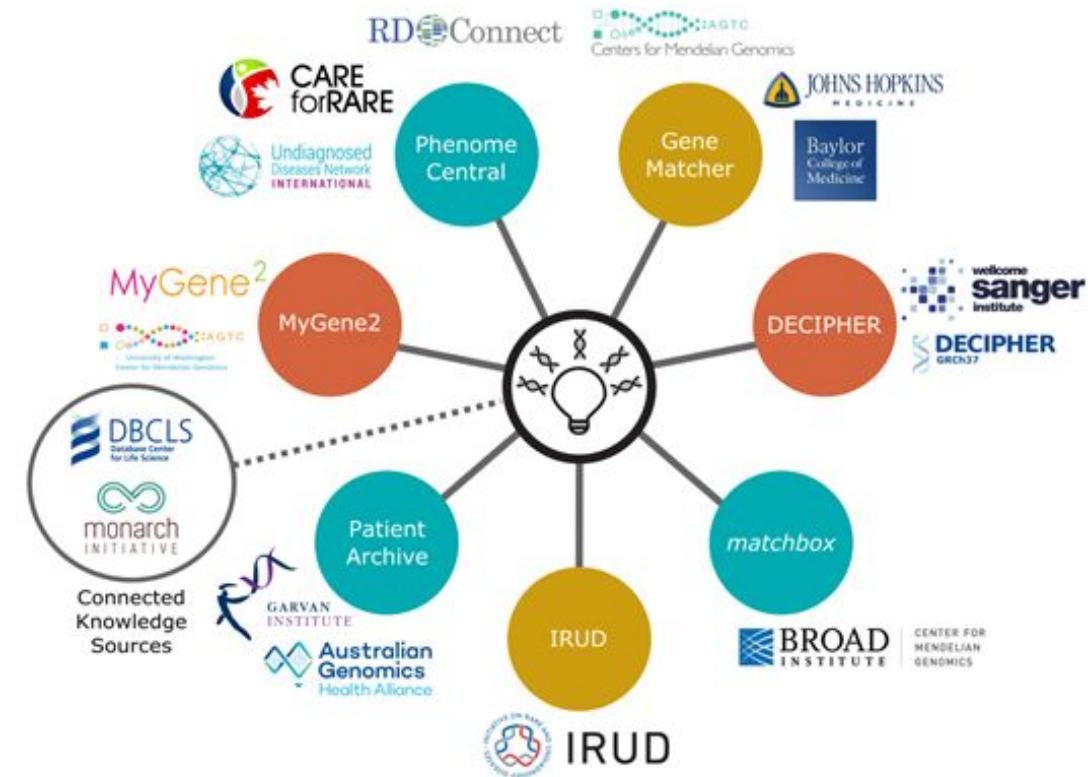
from **>4000** contributors

from 84 countries



Matchmaker
Exchange

Matchmaker Exchange



National Initiatives should either join as a new node, or make use of existing nodes (e.g. GeneMatcher most common)

USA: GeneMatcher, *matchbox*, MyGene²
Canada: PhenomeCentral
UK: DECIPHER
Australia: Patient Archive
Japan: IRUD

What's New with Matchmaker Exchange (MME)?



MME primarily matches on candidate gene.

We are now working to launch a federated network for “variant” matching.

First live system: VariantMatcher

VariantMatcher

VariantMatcher is a database open to search on genomic locations. It harbors genomic data as part of the BHCMG.

Email :

Password :

VariantMatcher (VM) created by:

- Nara Sobreira
- François Schiettecatte
- Ada Hamosh
- BHCMG Center for Mendelian Genomics

Your search included the following features:

Hypotonia, Microcephaly, Global Developmental delay, Esotropia

A submission match notification, for **your search: '6:34004293:T>C'**, was sent to the following:

BHXXXX - Patient - Affected - 6:34004293:T>C

Salmo Raskin - genetika@genetika.com.br - PUC Brazil

Bilateral Cleft

BHXXXX - Patient - Affected - 6:34004293:T>C

Hamza Aziz - haziz2@jhmi.edu - JHU

Bicuspid Aortic valve, Aneurysm, ascending aortic

BHXXXX - Patient - Affected - 6:34004293:T>C

Samantha Penney - penney@bcm.edu - Baylor College of Medicine

Encephalopathy, Ataxia, Hypotonia

BHXXXX - Patient - Affected - 6:34004293:T>C

Samantha Penney - penney@bcm.edu - Baylor College of Medicine

Ataxia, Spasticity, adult onset spinocerebellar ataxia

BHXXXX - Mother - Unaffected - 6:34004293:T>C

Filippo Vairo - fvairo@hcpa.edu.br - Hospital de Clinicas de Porto Alegre

BHXXXX - Father - 6:34004293:T>C

Daryl Scott - dscott@bcm.edu - Baylor College of Medicine

BHXXXX - Mother - 6:34004293:T>C

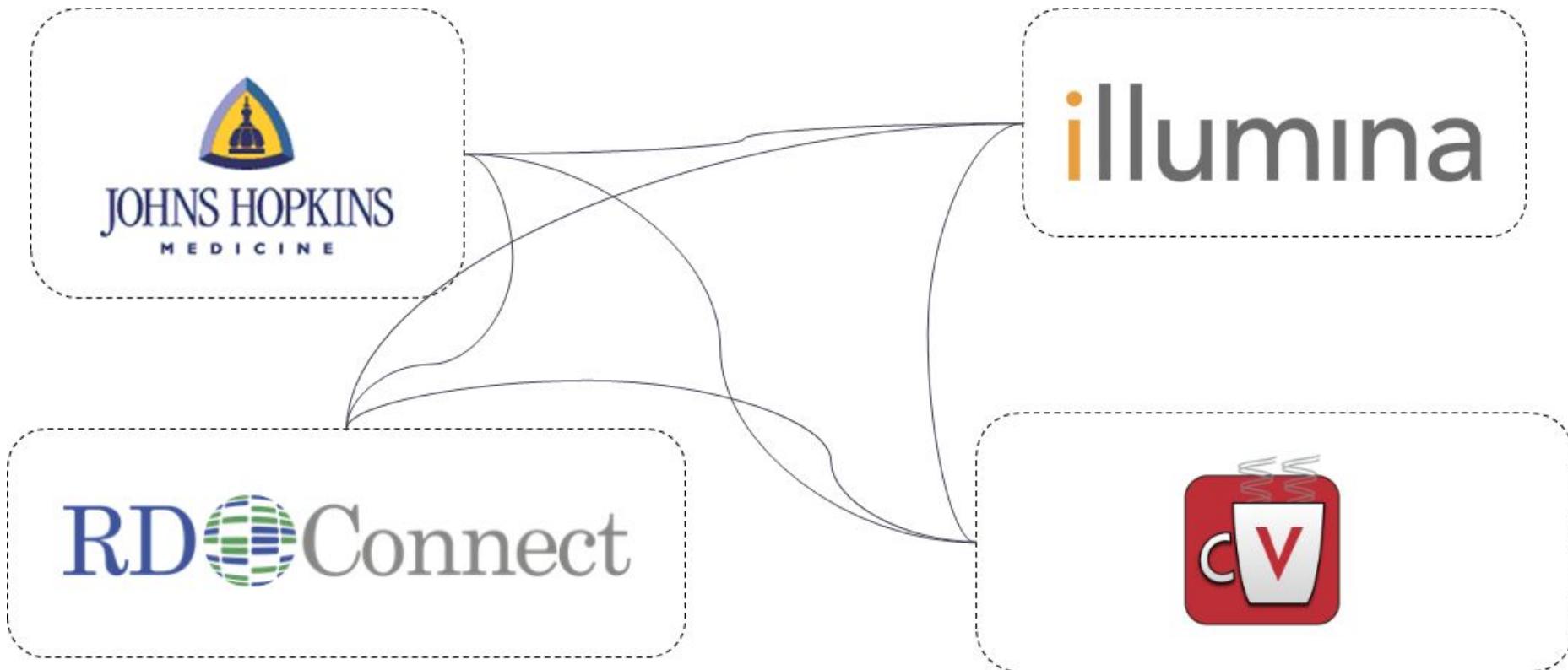
Samantha Penney - penney@bcm.edu - Baylor College of Medicine

BHXXXX - Father - 6:34004293:T>C

Samantha Penney - penney@bcm.edu - Baylor College of Medicine

Please do not reply to this email, it was sent from an unattended email address; however, you can email us at variantmatcher@jhmi.edu or use the [contact form](#).

Federated Network for Variant Matching – Test Stage



Test Version of “MME Variant”

[VariantMatcher](#) Home About Contact Us Editor Admin Help

Search Discovery Search Submission List

Discovery Search

Variants : 5:118860953 T>C 5:118792051 C>T 17:42929130 G>A

Servers : Café Variome Illumina PhenoDB Search Staging Int. RD-Connect

Response : Exists Contact Phenotype Subject Variant Gene

Search



Discovery Work Stream Search API

Not yet live!

Nara Sobreira
François Schiettecatte
Ada Hamosh

Anthony Brookes

GRCh37 chr5 118860953 Crr evnt Tg 2016000
GRCh37 chr5 118792051 Crr evnt Tg 2160000
GRCh37 chr17 42929130 Crr evnt Tg 2016000

PHENOTYPE

(D) HP:0000985

Add Remove

HP:0000103
HP:0000158
HP:0000160
HP:0000175
HP:0000179
HP:0000202
HP:0000204
HP:0000215
HP:0000218
HP:0000230

NCBI36 GRC

CV

(A OR B) AND C AND D More information

Reset Build Query

Source VariantMatcher test data Counts 1

Kyle Farh

illumina Case Log

lchr14:30095714:C:T (PRKD1)

Search

Phenotype	Mutations observed	Mutations expected	P-value (Poisson exact test)
Developmental delay	4 de novo mutations	0.038	$P < 8 \times 10^{-10}$
Congenital heart disease	3 de novo mutations	0.009	$P < 3 \times 10^{-6}$

In Summary....

Contact us if you need assistance with your clinical knowledge sharing toolkit!

1. Variant Interpretation Sharing
2. Use of Gene-level Resources
3. Matchmaker Exchange Participation

Harmonizing clinical data capture and exchange

**Zornitza Stark, Ellen Thomas, Richard Scott, Alejandro
Metke, David Hansen**

Australian Genomics/Genomics England

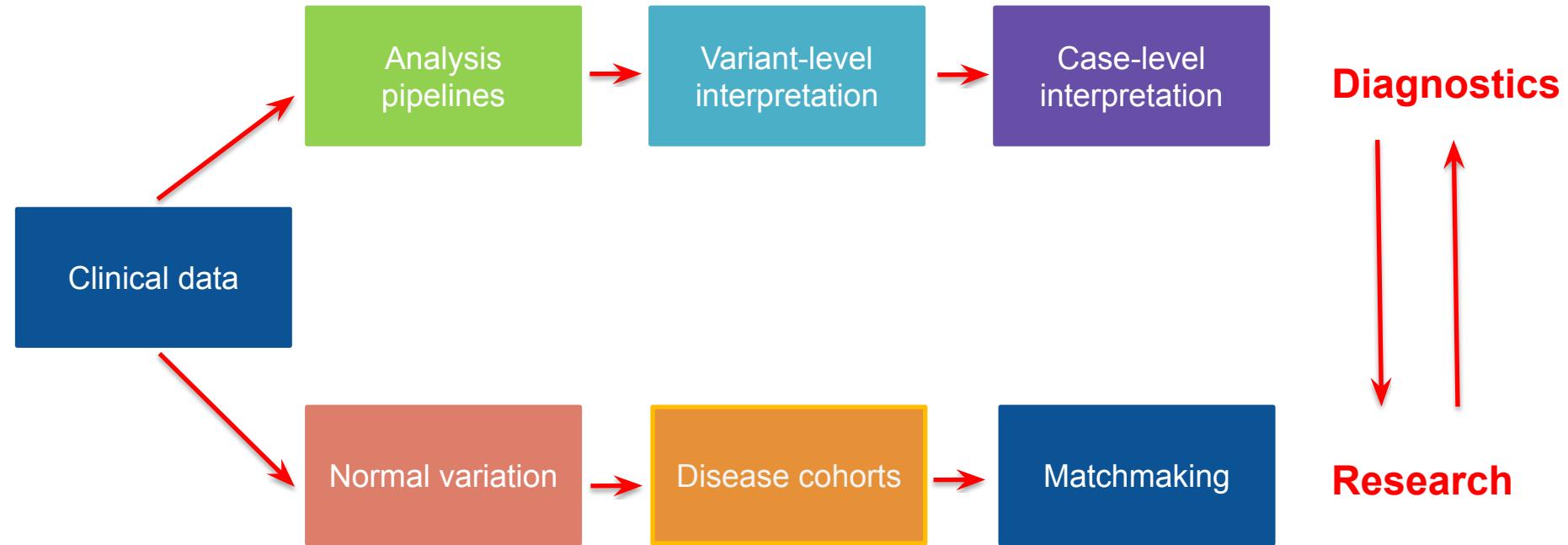


The problem



"We finished the genomic map, now we can't figure out how to fold it."

**Clinical genomic data interpretation
requires clinical information**



The problem

Relevant
High quality
Accurate
Machine-readable
Interoperable

Time
Effort
Skill
Scalability



Risk: poor quality, incomplete data
= suboptimal interpretation

Options

Custom data capture



Patient Information | Medical History | Family History | Family Charts | Prenatal/Perinatal History
Physical and Laboratory Measurement | Genotype | Gene Panels | Phenotype | Diagnosis

EMR data-driven phenotyping

Patient-driven phenotyping



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Use case: acutely unwell baby/child with genetic condition

- 5% of NICU admissions
- Compelling evidence for diagnostic and clinical utility in single centre studies
- Rapid turnaround times required
- Ready for wider implementation



Acute Paediatric Care Genomics





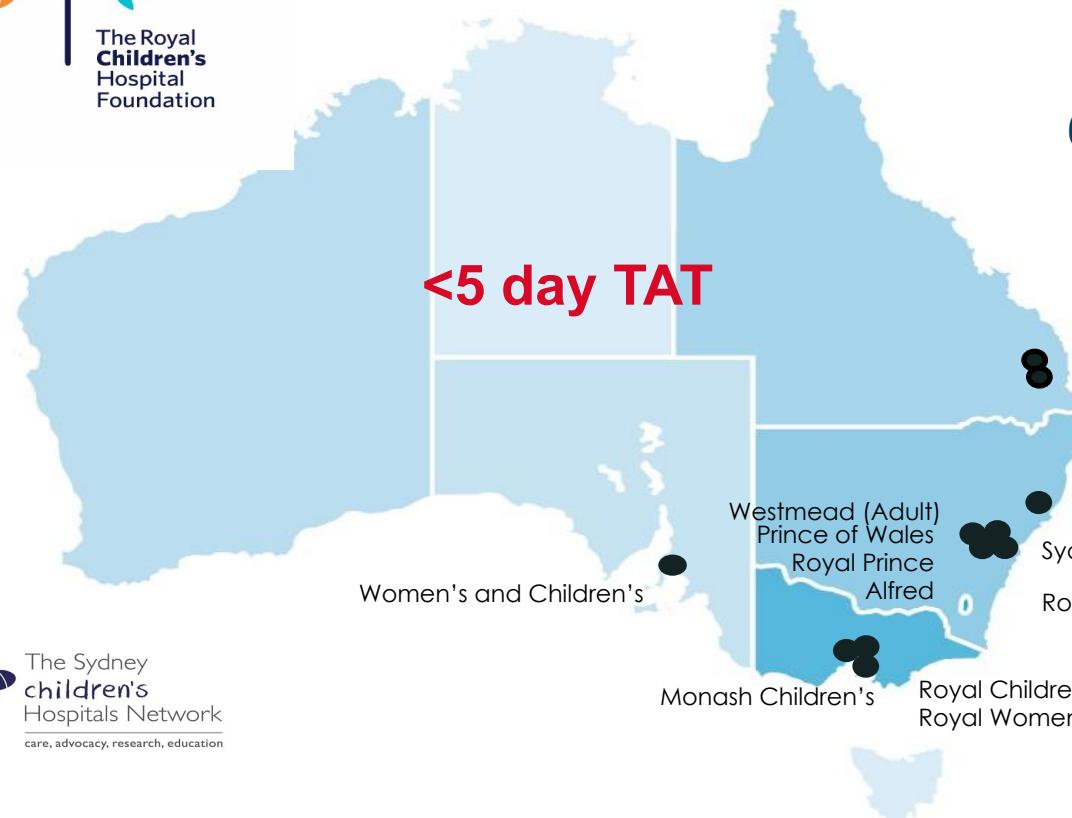
The Royal
Children's
Hospital
Foundation



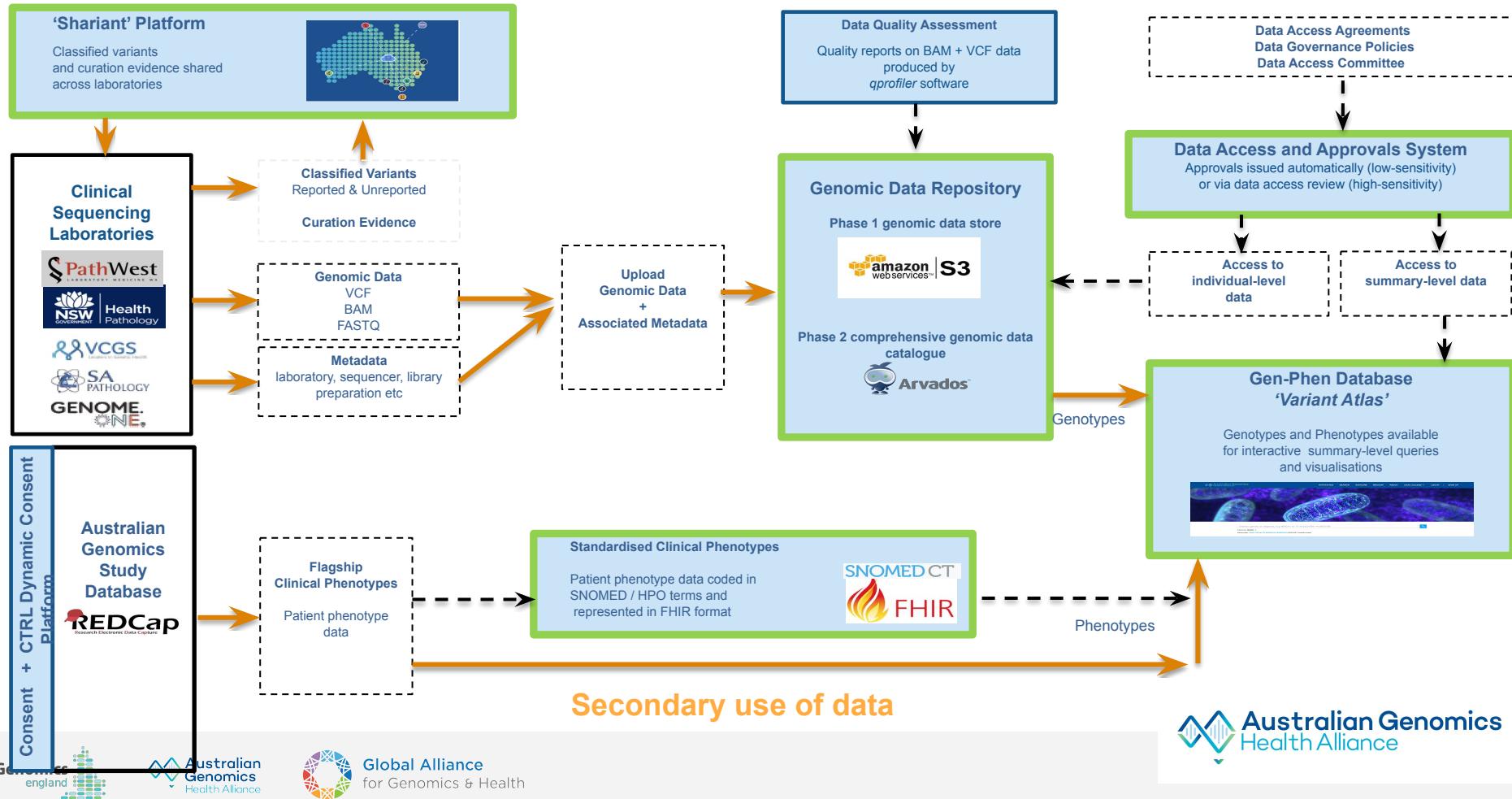
murdoch
children's
research
institute

**10 Hospitals
8 Genetic Services**

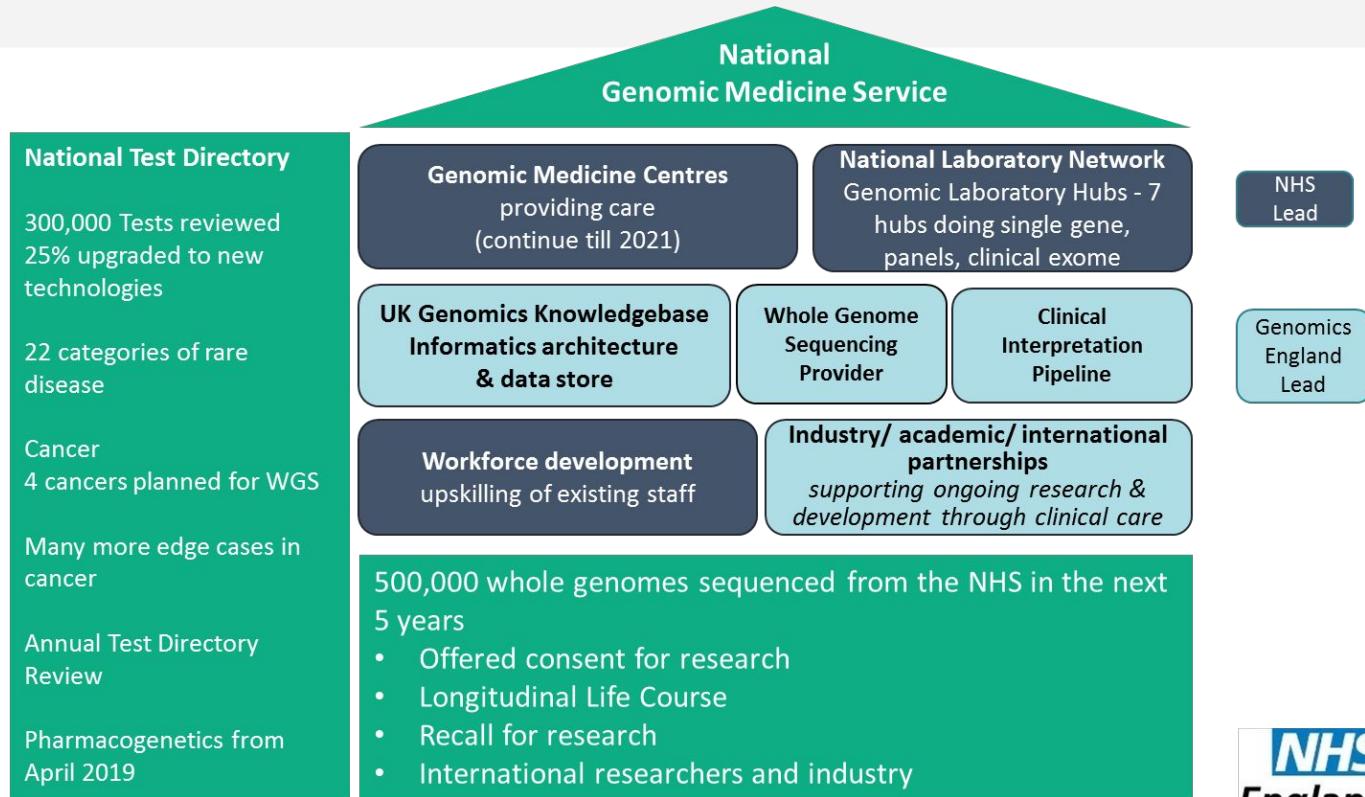
**10 NICUs (Level 3)
6 PICUs**



Program Two Data Management Work Flow and Capabilities



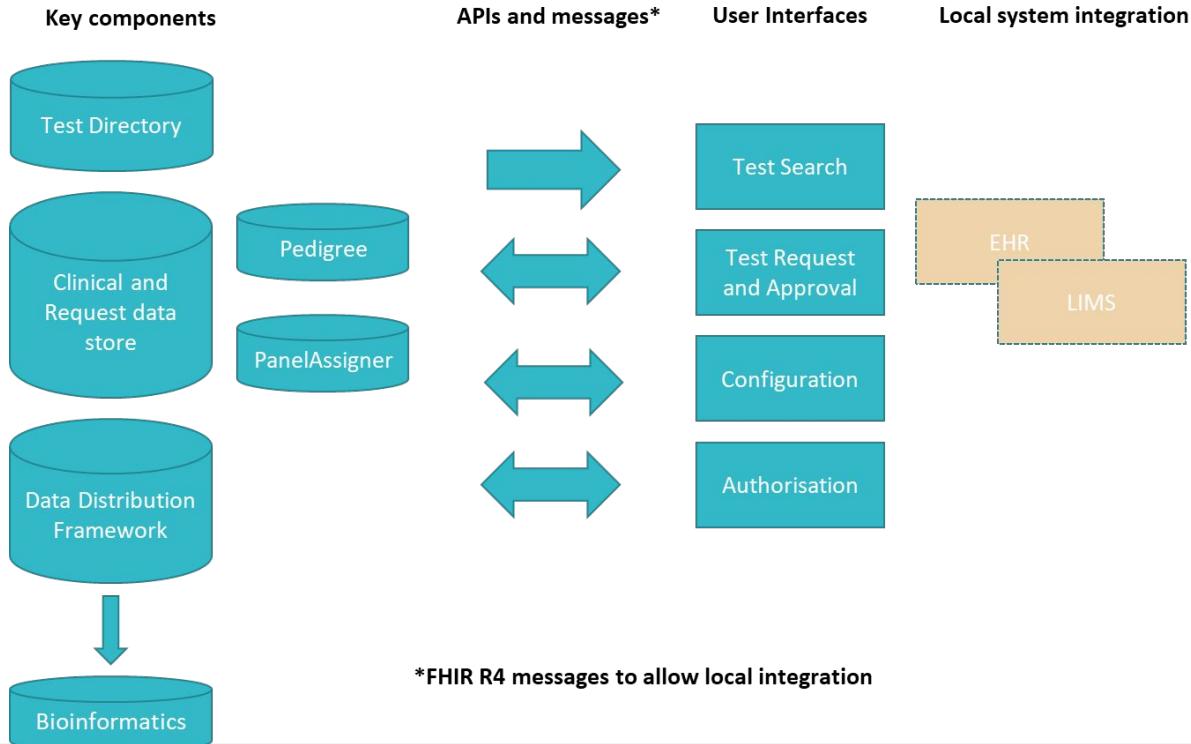
Genomics England and the NHS Genomic Medicine Service



Australian
Genomics
Health Alliance

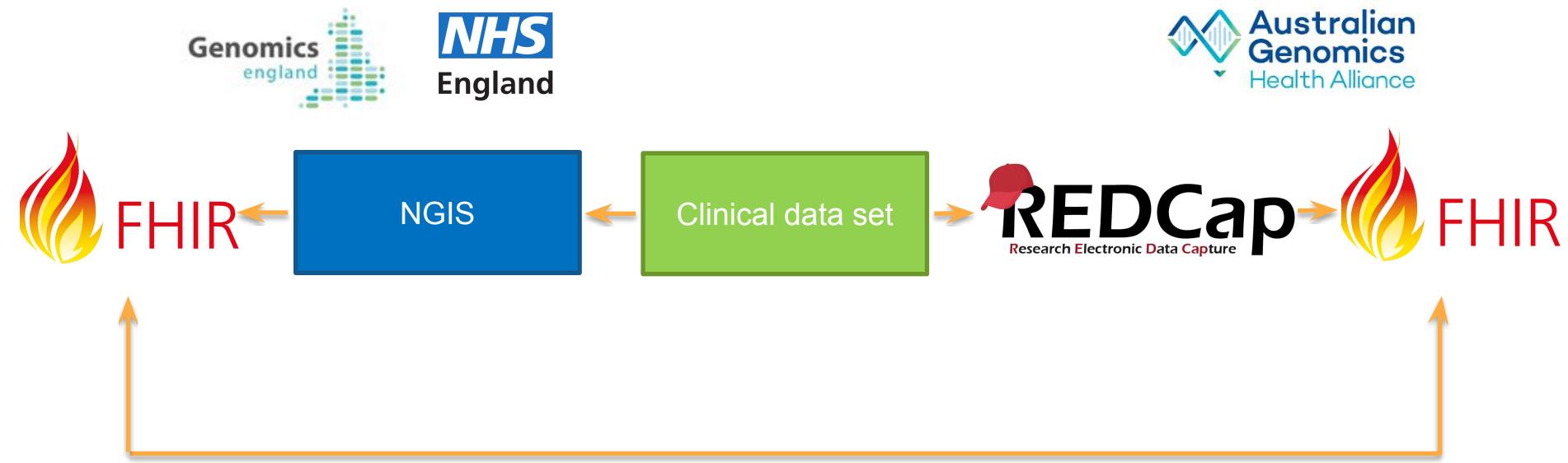
Global Alliance
for Genomics & Health

NGIS test order system overview



- Shared data model across rare disease and cancer
- Single FHIR R4 message in development for NGIS test request to allow local integration. In collaboration with NHSE and NHSE GLHs
- Dynamic content configurable for specific clinical indication e.g. acutely unwell child with suspected rare disease

Mapping, harmonization, exchange



Overlapping clinical data

Common with other tests:

- Name, surname
- DOB
- Gender: *phenotypic/karyotypic*
- Contact details
- Identifiers: study/hospital
- Referring clinician/centre/contact details



Overlapping clinical data

Unique to genetics/genomics:

- Consent status +/-additional findings, data sharing, research
- Pedigree/consanguinity
- Additional family members to be tested and affected/unaffected status/consent status
- Suspected clinical diagnosis/gene
- Gene panels for prioritized analysis



Overlapping phenotypic data

- Phenotype using standard terminology: HPO
- (Relevant prior tests: genetic and non-genetic)

Phenotype capture

Disease status
For the condition being tested for, describe patient's disease status

Disease status	Age of onset
Please select	e.g. 11

HPO phenotypes
Please provide details of the relevant clinical features.

Add HPO phenotypes
(i) Search for HPO phenotypes or codes

e.g. Ventricular fibrillation or HP:0001663

Based on what you've told us, we've suggested the following HPO phenotypes.
(i) Let us know if they're present.

Neonatal hypotonia	<input type="radio"/> Yes	<input type="radio"/> No	<input type="radio"/> Not sure	Add modifier <input type="button" value="Search"/>
EMG abnormality	<input type="radio"/> Yes	<input type="radio"/> No	<input type="radio"/> Not sure	Add modifier <input type="button" value="Search"/>
Muscle weakness	<input type="radio"/> Yes	<input type="radio"/> No	<input type="radio"/> Not sure	Add modifier <input type="button" value="Search"/>

Rare disease diagnoses
Please provide details of rare or inherited diseases that are suspected or have been confirmed

Search for diagnosis
(i) OMIM Orphanet

e.g. Myotonic dystrophy or 160900



Australian
Genomics
Health Alliance

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Phenotype capture

Acute Care: HPO terms in REDCap (via Ontoserver and REDCap Ontology Module)



Principal phenotypic features	Coarse facial features HPO terms	HP:0000280
Principal phenotypic features	Sparse hair HPO terms	HP:0008070
Principal phenotypic features	Hypertrichosis HPO terms	HP:0000998
Principal phenotypic features	Aplasia/Hypoplasia of ... HPO terms	HP:0008386
Principal phenotypic features	Dysplastic corpus callo... HPO terms	HP:0006989
Principal phenotypic features	 HPO terms	



Ethnicity



Understanding rare variation

Clinical diagnostics:

- Is this variant *actually* rare/absent?
Errors in interpretation
More VOUS, false pos, false negs
- Equity of access

Research:

Responsibility to build diverse and representative datasets



Ancestry Caucasian Eastern European Central/South American
 Western European Native American Middle Eastern Hispanic
 African American Asian Pacific Islander Caribbean
 Ashkenazi Jewish Northern European Other: _____

Ancestry Asian Black/African American White/Caucasian Ashkenazi Jewish
 Hispanic Native American Pacific Islander French Canadian
 Sephardic Jewish Mediterranean Other: _____

African-American Asian/Pacific Islander Hispanic Native American
Ashkenazi Jewish Caucasian Middle Eastern Other: _____

Ethnicity (check all that apply)

African-American
 Asian
 Caucasian/NW European
 Finnish
 Hispanic
 Jewish-Ashkenazi
 Adopted
 Other: _____

GEOANCESTRY / ETHNICITY

Ethnicity: African American Asian Caucasian Hispanic
 Jewish (Ashkenazi) Portuguese Other: _____

Ethnicity: Caucasian African-American Hispanic Asian Ashkenazi Jewish Other: _____

Patient's Ethnicity (check all that apply)

African American Ashkenazi Jewish Asian Caucasian
 Hispanic Middle Eastern Native American Other: _____

Ethnicity (check all that apply)
 African-American Asian
 Caucasian/NW European E. Indian
 Hispanic Jewish-Ashkenazi
 Jewish-Sephardic Mediterranean
 Native American Adopted
 Other: _____

Ethnicity (select all that apply):

Northern European e.g. British, German
 Southern European e.g. Italian, Greek
 French Canadian or Cajun
 Ashkenazi Jewish
 Other/Mixed Caucasian
 East Asian e.g. Chinese, Japanese
 South Asian e.g. Indian, Pakistani

Southeast Asian e.g. Filipino, Vietnamese
 African or African American
 Hispanic
 Middle Eastern
 Indigenous
 Pacific Islander
 Unknown

Race and Ethnicity: Please check ALL that apply

White Ashkenazi Jewish Hispanic Asian
 Black/African American American Indian/Native Alaskan
 Native Hawaiian or other Pacific Islander Other: _____

FIGURE 1 Screenshots of race, ethnicity, and ancestry questions on clinical laboratory requisition forms



Capturing ethnicity: current status

16 REA categories:

- *Chinese*
- *White: British*
- *White: Irish*
- *White: any other*
- *Asian or British Asian: Pakistani*
- *Asian or British Asian: Bangladeshi*
- *Asian or British Asian: Indian*
- *Asian or British Asian: any other*
- *Black or British Black: Caribbean*
- *Black or British Black: African*
- *Black or British Black: any other*
- *Mixed: x 4*



12 REA categories:

- *European (non-Finnish)*
- *European (Finnish)*
- *Sub-Saharan Africa*
- *Asian*
- *North African/Middle Eastern*
- *Other Oceanian*
- *People of the Americas*
- *Maori/Pacific Islander*
- *Aboriginal/Torres Strait Islander*
- *Australian/New Zealander*
- *Ashkenazi Jewish*
- *Sephardic Jewish*



Capturing ethnicity: a way forward?

Human Ancestry Ontology

Morales *et al.* *Genome Biology* (2018) 19:21
<https://doi.org/10.1186/s13059-018-1396-2>

Genome Biology

OPEN LETTER

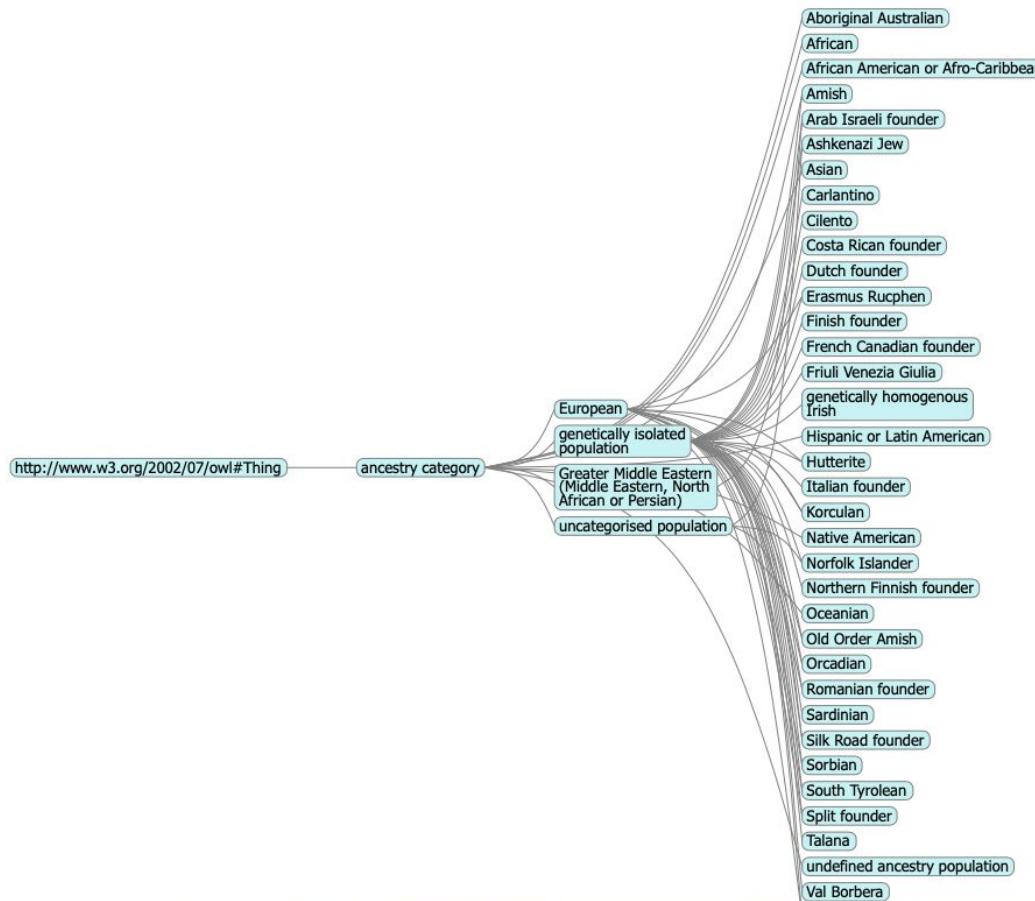
Open Access



A standardized framework for representation of ancestry data in genomics studies, with application to the NHGRI-EBI GWAS Catalog

Joannella Morales^{1*} , Danielle Welter¹, Emily H. Bowler¹, Maria Cerezo¹, Laura W. Harris¹, Aoife C. McMahon¹, Peggy Hall², Heather A. Junkins², Annalisa Milano¹, Emma Hastings¹, Cinzia Malangone¹, Annalisa Buniello¹, Tony Burdett¹, Paul Fllice¹, Helen Parkinson¹, Fiona Cunningham¹, Lucia A. Hindorff^{2†} and Jacqueline A. L. MacArthur^{1*†}





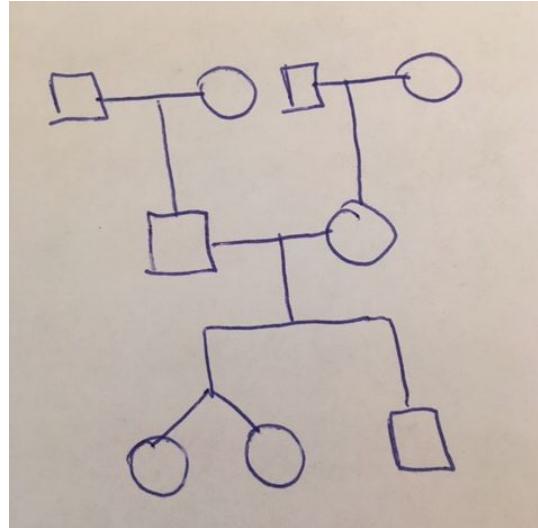
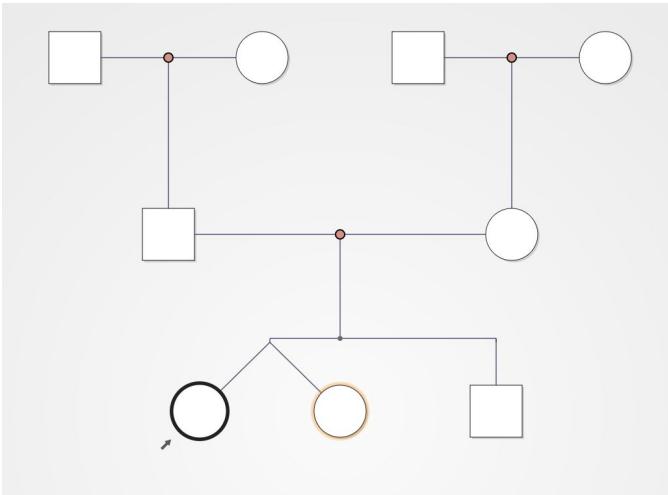
<https://genomics.ontoserver.csiro.au/fhir>
Terminology Server endpoint URL



Human Ancestry Ontology
<http://purl.obolibrary.org/obo/hancestro/releases/>

search terms

Pedigree



Consanguinity?

Affected 1st
degree relatives

Suspected mode
of inheritance

Genomics
england



Australian
Genomics
Health Alliance



Global Alliance
for Genomics & Health

Australian Genomics
Health Alliance

Clinical & Phenotypic Data Capture Work Stream

2019 Roadmap

Deliverable #1: Definition of phenotype models for different clinical domains with driver projects

Deliverable #2:
Clinical Data Exchange (FHIR)

Deliverable #3:
Pedigree representation



Update: PanelApp

Globally Sharing Curation Efforts



Ellen McDonagh

Head of Curation & Pharmacogenomics

ellen.mcdonagh@genomicsengland.co.uk @PanelAppTeam



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PanelApp: Reminder

PanelApp Panels Genes and Entities Activity Log in Register

304 panels <https://panelapp.genomicsengland.co.uk>

Compare two panels

Panel	Evaluated genes	Reviewers	Actions
Adult onset movement disorder Version 0.57	213 of 213 100%	5 reviewers	Download
	STRs: 11 Regions: 1		
Adult solid tumours cancer susceptibility Level 3: Pertinent cancer susceptibility gene panel Level 2: Cancer Programme Relevant disorders: Carcinoma of unknown primary, Other, Adult solid tumours pertinent cancer susceptibility Version 1.3	58 of 58 100%	2 reviewers	Download
Adult solid tumours for rare diseases Level 3: Tumour syndromes Level 2: Tumour syndromes Relevant disorders: Young adult onset cancer, Exceptionally young adult onset cancer, Multiple Tumours - Rare tumour predisposition syndromes		Reviewers	Download
	Regions: 1		

Rare diseases and Cancers

**crowd-sourced
expert-reviewed
evidence-based
dynamic
versioned
curated
virtual gene panels
for bioinformatics genome
analysis**

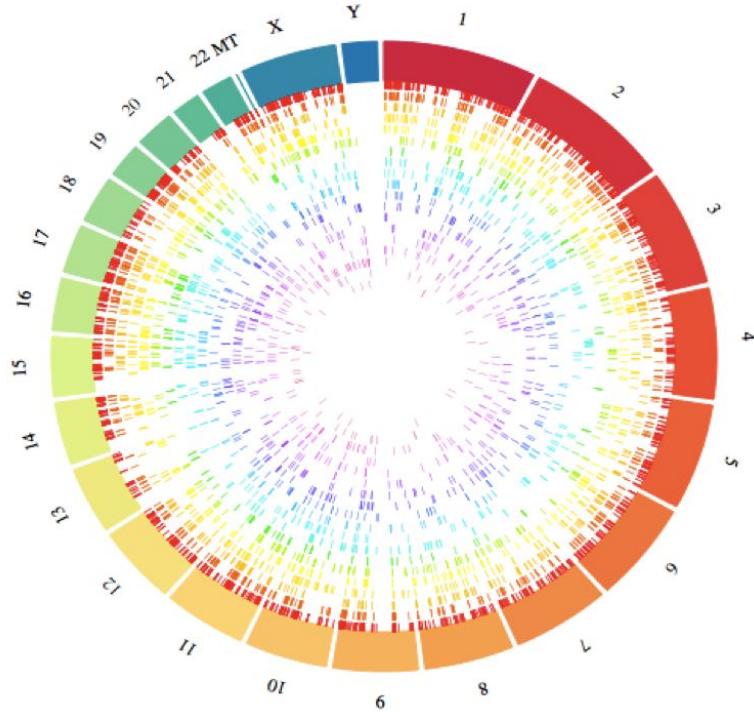
In Genomics England:

- Used to interpret the 100,000 Genomes Project participants
- Adopted as the platform for consensus panels in the NHSE Genomic Medicine Service



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PanelApp Content



5016 unique genes, 19 STRs, 62 CNVs

221 Version 1+ panels for genome analysis

304 reviewable panels

>12,000 gene-disease associations

Green genes on v1+ panels cover around **50% of OMIM Phenotypes**

PanelApp: beyond genes

+ Add a Gene to this panel + Add a STR to this panel + Add a Region to this panel

PanelApp Panels Genes and Entities Activity

Panels / Parkinson Disease and Complex Parkinsonism / HTT_CAG

Parkinson Disease and Complex Parkinsonism

STR: HTT_CAG

Green List (high evidence)

Chromosome: 4
GRCh37 Position: 3076604-3076666
GRCh38 Position: 3074877-3074939
Repeated Sequence: CAG
Normal Number of Repeats: < or = 40
Pathogenic Number of Repeats: = or > 40

HTT (huntingtin)
EnsemblGenelids (GRCh38): ENSG00000197386
EnsemblGenelids (GRCh37): ENSG00000197386
OMIM: 613004, Gene2Phenotype
HTT is in 15 panels

Reviews (2) Details History

PanelApp Panels Genes and Entities Activity

Panels / Deafness and congenital structural abnormalities / ISCA-37396-Loss

Deafness and congenital structural abnormalities

Region: ISCA-37396-Loss

15q24 recurrent region (A-D) (includes SIN3A) Loss

Green List (high evidence)

Chromosome: 15
GRCh38 Position: 72671374-75680568
Haploinsufficiency Score: Sufficient evidence suggesting dosage sensitivity is associated with clinical phenotype
Triplosensitivity Score:
Required percent of overlap: 80%
Variant types: CNV Loss

Reviews (1) Details History

1 review



ClinGen
Clinical Genome Resource

Accessing PanelApp Data

Public access

- View and download gene panels.
- View Reviewers' comments.

The image shows the PanelApp interface with two sections highlighted by dashed orange boxes. The top section, labeled "Browse PanelApp without logging in", contains a "Log in" form with fields for "Username" and "Password", and links for "I forgot my password" and "Log in". The bottom section, labeled "Register to be a reviewer", contains instructions for reviewers and a link "Register to be a reviewer". An orange arrow points from the "Public access" section towards the "Log in" form, and another orange arrow points from the "Register" section towards the "Register to be a reviewer" link.

Browse PanelApp without logging in

Log in

Username

Password

I forgot my password

Log in

Register

To review gene panels we request that you have expertise relevant to the rare diseases included in the 100,000 Genomes Project. You must have expertise in one of the following:

- a relevant disease area
- diagnostic genetic testing of a relevant disease area
- genes relevant to the diseases included in the project

A list of the diseases included in the project can be found on [Genomics England](#).

Register to be a reviewer

Register to be a Reviewer

- View and download gene panels.
- View Reviewers' comments.
- + Evaluate genes and make comments.
- + Add genes to a gene panel.

PanelApp data sharing

swagger https://panelapp.genomicsengland.co.uk/api/docs/?format=openapi Explore

PanelApp API 1

[Base URL: panelapp.genomicsengland.co.uk/api/v1]
<https://panelapp.genomicsengland.co.uk/api/docs/?format=openapi>

PanelApp API
[Terms of service](#)
[Contact the developer](#)

https://panelapp.genomicsengland.co.uk/api/docs

Schemes
HTTPS ▾

Filter by tag

activities

entities

GET /activities/

entities

GET /entities/

GET /entities/{entity_name}/

entities_read

Webservices/API

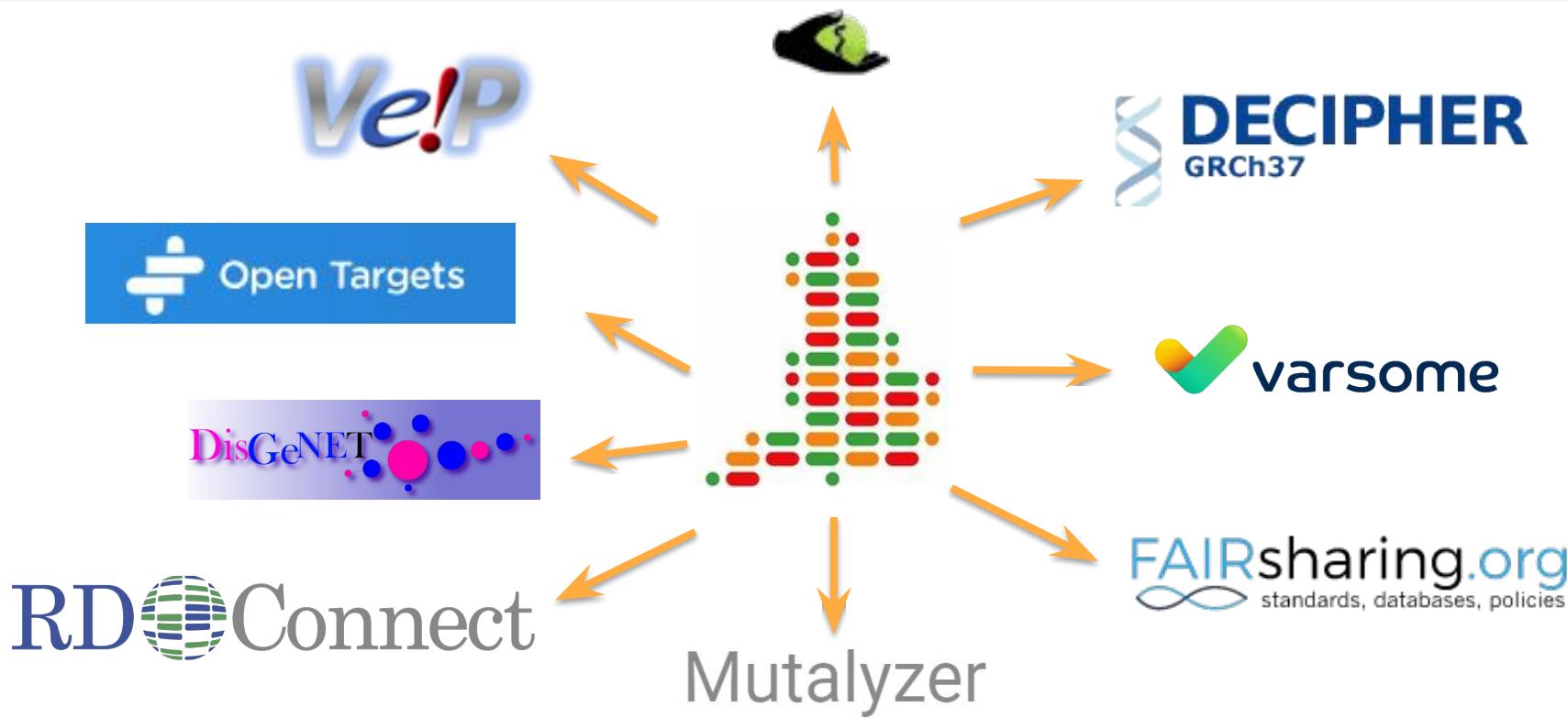
- ✓ Genome Build 38 & 37
- ✓ List panels
- ✓ Search genomic entities
- ✓ Filters

PanelApp: Global usage

3,771,779 requests
25,103 unique visitors
>700 registered reviewers



Data sharing with other databases



PanelApp: New features that will aid sharing

PanelApp Panels Genes and Entities Activity Log in Register

Panels / Paediatric disorders

Paediatric disorders (Version 3.246)

Relevant disorders: Acutely unwell children with a likely monogenic disorder, Congenital malformation and dysmorphism syndromes - microarray and sequencing

This panel contains these 9 panels:

[Intellectual disability v2.800](#)

[Skeletal dysplasia v1.151](#)

[Rare multisystem ciliopathy disorders v1.84](#)

[Inborn errors of metabolism v1.54](#)

[Familial non syndromic congenital heart disease v1.43](#)

[DDG2P v1.41](#)

[VACTERL-like phenotypes v1.23](#)

[Limb disorders v1.5](#)

[Non-syndromic familial congenital anorectal malformations](#)

Panel types: GMS Rare Disease Virtual, Super Panel



PanelApp Software is now Open Source

<https://github.com/genomicsengland/panelapp>

PanelApp Panels Genes and Entities Activity Add panel Import panel Resources - allenmodonagh Log out

Genes in panel
↑ Prev Next ↓
● AARS 1
● ADSL 4
● ALDH1A1 6
● ALG11 1
● ALG13 5
● ARHGEF9 5
● ARX 5
● ATP1A3 5
● ATP6VOA2 1
● ATRX 5
● BRAT1 1
● BSC12 1
● CACNA1D 1
● CDKL5 5
● CHD2 6
● CHRNA2 7
● CHRNA4 7
● CHRNB2 8
● CIC 1
● CLN8 5
● CLTC 1

Genetic epilepsy syndromes / ABAT

Gene: ABAT

Green List (high evidence)

ABAT (4-aminobutyrate aminotransferase)
Ensembl/GenBank (GRCh38): ENSG00000183044
Ensembl/GenBank (GRCh37): ENSG00000183044
OMIM: 137150, Gene2Phenotype
ABAT is in 21 panels

Reviews (4) Details History Review feedback

Review gene

Rating: Green Provide rating

Mode of inheritance: Autosomal dominant Provide a mode of inheritance

Mode of pathogenicity: Loss-of-function Provide exceptions to loss-of-function

Publications (PMID: 12345678): Publications (PMID: 12345678)

Phenotypes (separate using a semi-colon -): Phenotypes (separate using a semi-colon -)

Current diagnostic: Current diagnostic

Comments:

Although causing subtle abnormalities of B cell differentiation and antibody production, biallelic mutations of this gene are not linked to hypo- or α-gammaglobulinaemia to my knowledge
Sophie Hambleton (Newcastle University), 19 Oct 2015

Tags

Save changes

Rating

Reviewer	Suggestion
Louise Daugherty (Genomics England Curator)	Green List (high evidence)
Tracy Briggs (Manchester Genomic Medicine Centre)	I don't know
Peter Arkwright (Royal Manchester Foundation Trust)	Red List (low evidence)
Sophie Hambleton (Newcastle University)	Green List (high evidence)
Current	Green List (high evidence) Edit

PanelApp Panels Genes and Entities Activity Log in Register

Activity

Filter activities 3000 actions

Date	Panel	Item	Activity
26 Apr 2019	GCH1	Hereditary spastic paraparesis - adult onset v0.27	Louise Daugherty commented on gene: GCH1: Review and rating submitted by Michael Bonello (The Walton Centre NHS Foundation Trust), submitted by Diane Cairns on behalf of North West GLH for GMS Neurology specialist test group.
26 Apr 2019	GCH1	Hereditary spastic paraparesis - adult onset v0.27	Louise Daugherty Source North West GLH was added to GCH1. Mode of inheritance for gene GCH1 was changed from MONOALLELIC, autosomal or pseudautosomal, imprinted status unknown to BOTH monoallelic and biallelic, autosomal or pseudoautosomal
26 Apr 2019	GCH1	Hereditary spastic paraparesis - adult onset v0.26	Michael Bonello reviewed gene: GCH1: Rating: GREEN; Mode of pathogenicity: Publications: ; Phenotypes: Dystonia, DOPA-responsive, with or without hyperphenylalaninemia, 128230; Mode of inheritance: BOTH monoallelic and biallelic, autosomal or pseudoautosomal
26 Apr 2019	PPP2R2B_CAG	Hereditary spastic paraparesis - adult onset v0.25	Louise Daugherty edited their review of STR: PPP2R2B_CAG: Added comment: Amber rating and review from Chris Buxton (North Bristol NHS Trust), submitted by Natalie Forrester (SWGLH - Bristol Genetics) on behalf of South West GLH for GMS Neurology specialist test group.; Changed rating: AMBER
26 Apr 2019	HTT_CAG	Hereditary spastic paraparesis - adult onset v0.25	Louise Daugherty commented on STR: HTT_CAG: Green rating and review from Chris Buxton (North Bristol NHS Trust), submitted by Natalie Forrester (SWGLH - Bristol Genetics) on behalf of South West GLH for GMS Neurology specialist test group. Comment: str (Variants in this STR are reported as part of current diagnostic practice)

Crowdsourcing
Review Tools

Curation Tools

Versioning and Activity
Functionality

Gene Curation Coalition



Generating standards to enable
gene-disease validity curation
sharing efforts

Proposal for a curation network



The importance of manual scientific curation

- Vital for **evidence-based** genome analysis
- The **promise of AI** is dependent on ‘gold-standard’ databases/data sets that are manually curated as well as manual checking of NLP efforts
- Much data is still not machine-readable and requires **human interpretation** (publications, clinical notes etc...)
- The **essential link** between the Clinician and Bioinformatician

The current challenges & issues

- Manual curation is **time consuming**
- Multiple gene-disease and variant-disease curation efforts but **lack of standardised systems** to allow data sharing (vocabularies, data models, evidence frameworks)
- **Funding and support** for these resources is not globally-led/managed
- **Publication access**

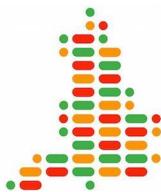
Solution?

Curation Network standard:

- Emphasis on **data sharing** between curation efforts
- Development of a standardised **data model** for curation sharing
- Development of standardised **vocabularies**
- Development on standardised **APIs** to query and disseminate curation efforts
- Support **access** to publications/data
- Support of **existing databases/curation efforts** on a global level
- Gain a **consensus view of the evidence** for genome analysis
- **Enable genome interpretation sharing and standardisation**

Curation Network User Story

Example: Gene-Disease validity



Gene A
For Disease Z
Reclassified from
Amber to Green
due to new publication

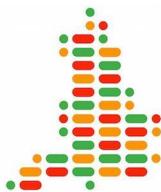


Alert
New evidence
Should a gene-disease
Status be re-evaluated
Change from Moderate
to Strong?



Alert
New evidence
Should a gene be added
to a panel?

Curation Network User Story: Challenges



Gene A
For Disease Z
Reclassified from
Amber to Green
due to new publication



Challenge 1: Gene symbol changes

Solutions: Ensembl Gene ID, HGNC Gene ID

Challenge 2: Disease or phenotype for panel/per gene

Solutions: disease/phenotype ontologies for cross-mapping

Challenge 3: Difference in term used for gene-disease validity

classification

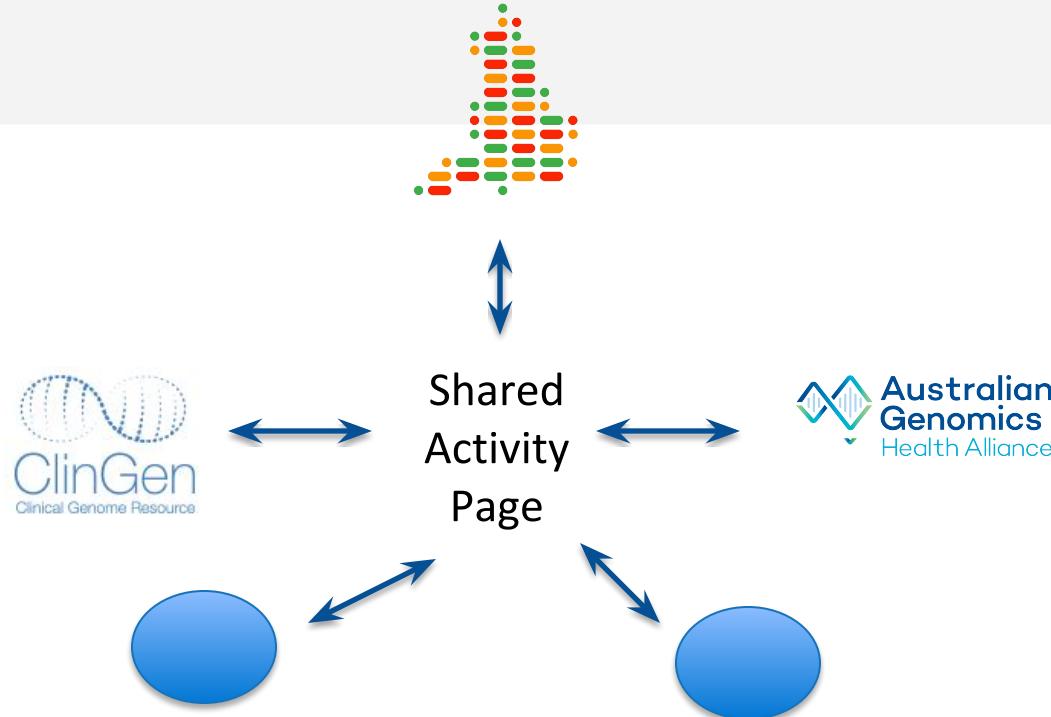
Solution: Gene Curation Coalition standardised terms

Challenge 4: Difference in the level of evidence used for

gene-disease validity classification

Solution: cross-mapping guidelines between GenCC members,
capture of number of unrelated cases/families? Publications?

Alert system



- Follow specific diseases/genes?
- Alerts for specific actions: Reclassification, new gene-disease curations

Example: PanelApp Activity page

PanelApp Panels Genes and Entities Activity Log in Register

Activity ▾

Date	Panel	Item	Activity
classified			348 actions
28 Apr 2019	Hereditary spastic paraplegia - childhood onset v1.47	DARS	Louise Daugherty Classified gene: DARS as Green List (high evidence)
28 Apr 2019	Hereditary spastic paraplegia - childhood onset v1.47	DARS	Louise Daugherty Gene: dars has been classified as Green List (High Evidence).
28 Apr 2019	Hereditary spastic paraplegia - childhood onset v1.45	GCH1	Louise Daugherty Classified gene: GCH1 as Green List (high evidence)
28 Apr 2019	Hereditary spastic paraplegia - childhood onset v1.45	GCH1	Louise Daugherty Gene: gch1 has been classified as Green List (High Evidence).
28 Apr 2019	Hereditary spastic paraplegia - childhood onset v1.44	IBA57	Louise Daugherty Classified gene: IBA57 as Green List (high evidence)
28 Apr 2019	Hereditary spastic paraplegia - childhood onset v1.44	IBA57	Louise Daugherty Gene: iba57 has been classified as Green List (High Evidence).
28 Apr 2019	Hereditary spastic paraplegia - childhood onset v1.43	KDM5C	Louise Daugherty Classified gene: KDM5C as Green List (high evidence)

Roadmap proposal

Q2
Apr, May, June

Q3
Jul, Aug, Sept

Q4
Oct, Nov, Dec

- What elements between PanelApp, ClinGen (and other dbs) data models are key for automated data sharing?
- What changes would we want to be alerted to?
- Identify how to unify/map these to enable a shared API/Activity page: establish a minimal data sharing model
- Development of PanelApp API/ClinGen API to incorporate these changes
- Development of a shared Activity Page and alert system between PanelApp, ClinGen (+ other dbs)

Genomic Data Sharing & GA4GH

Oliver Hofmann
Australian Genomics

Australian Genomics Health Alliance (AGHA)

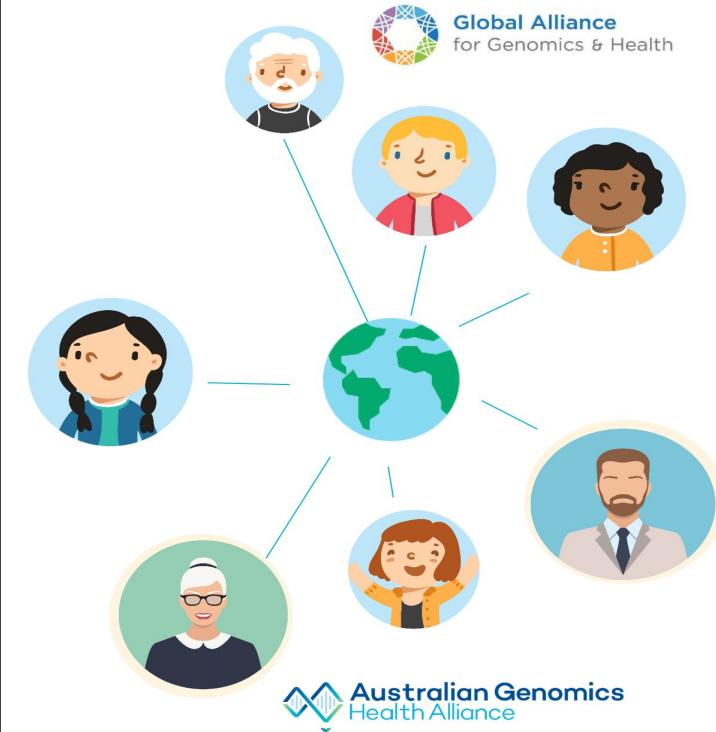
Community efforts in large scale genomics:
GA4GH and friends

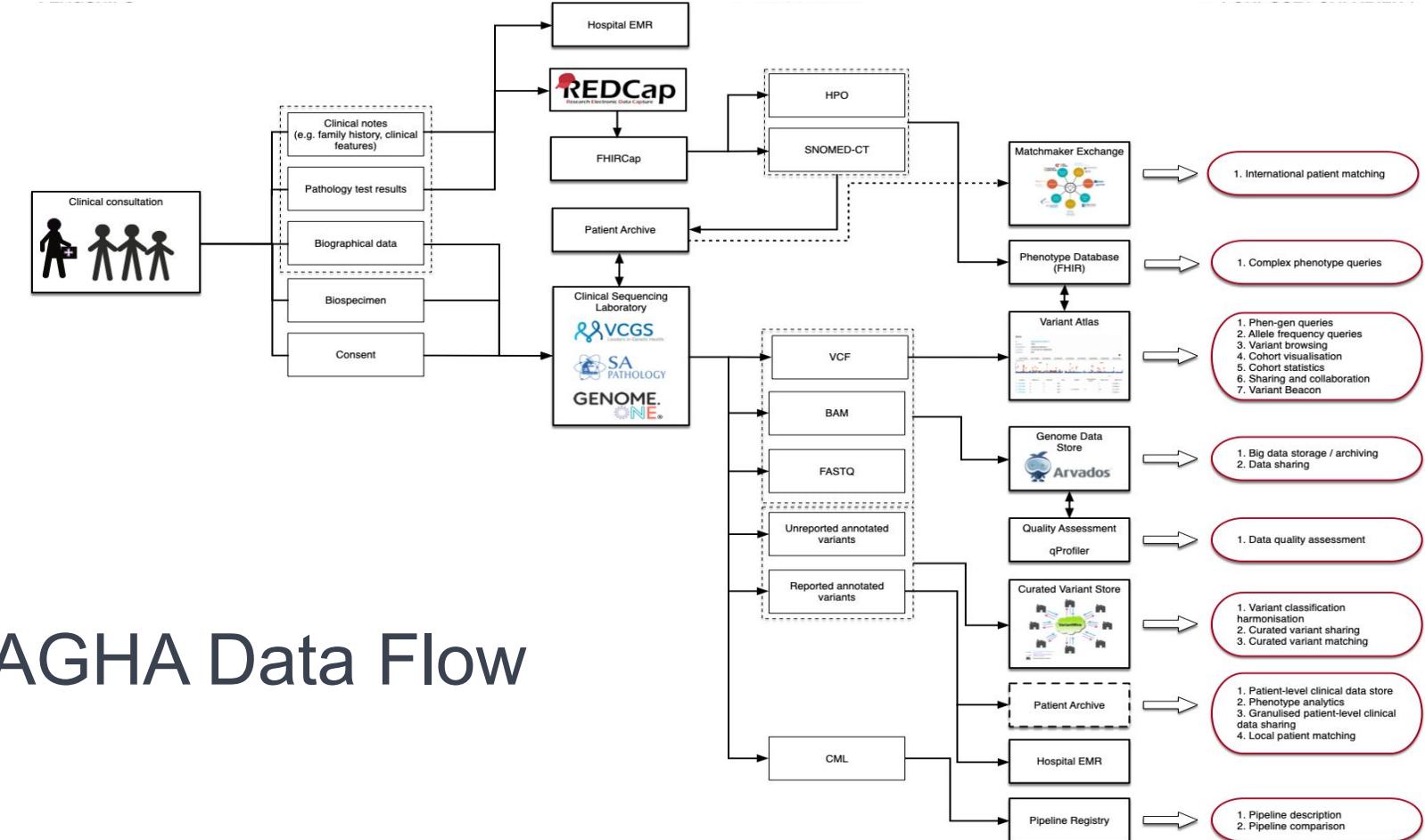


Data management & dissemination

Avoid duplication

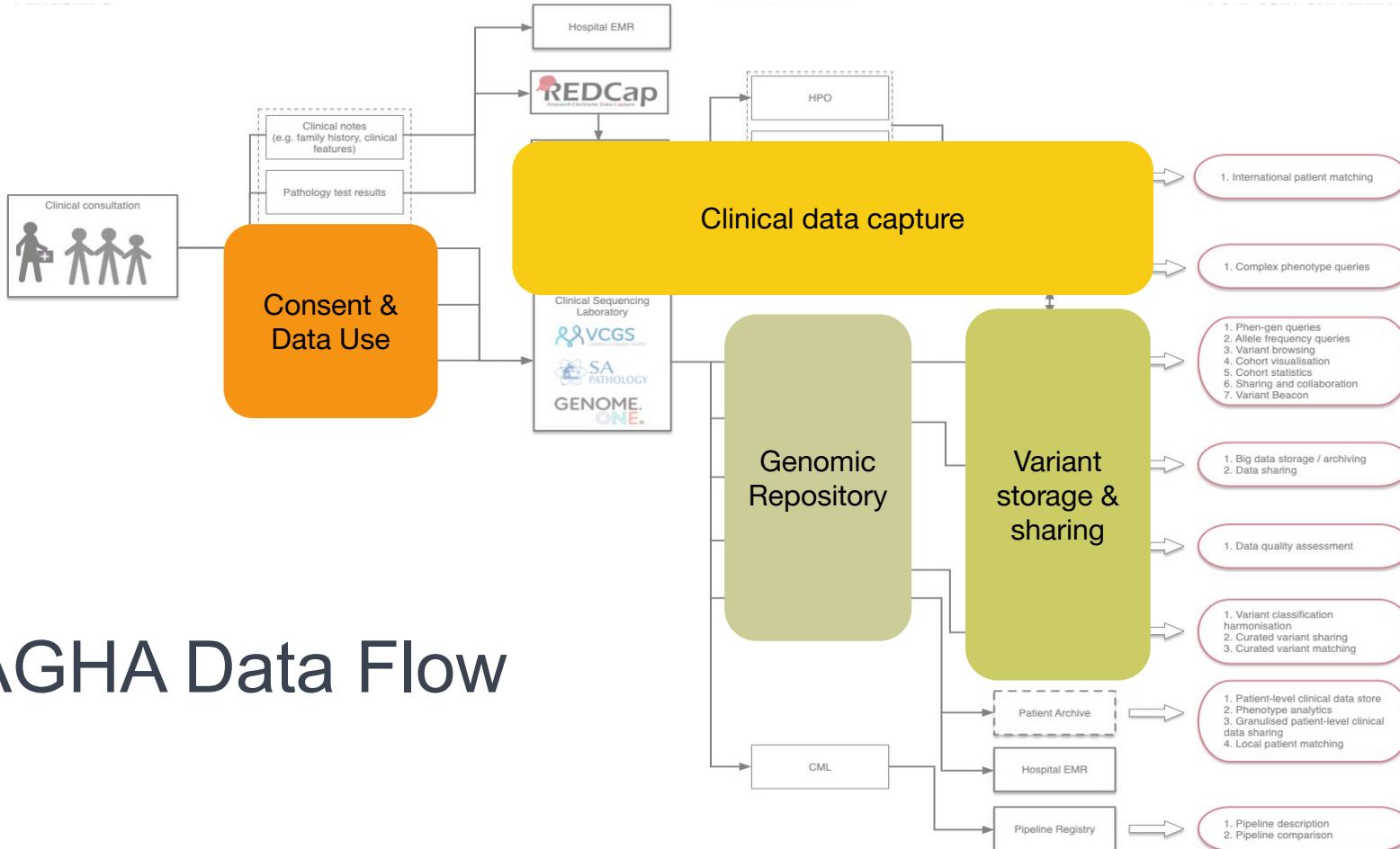
Collaborate on interfaces



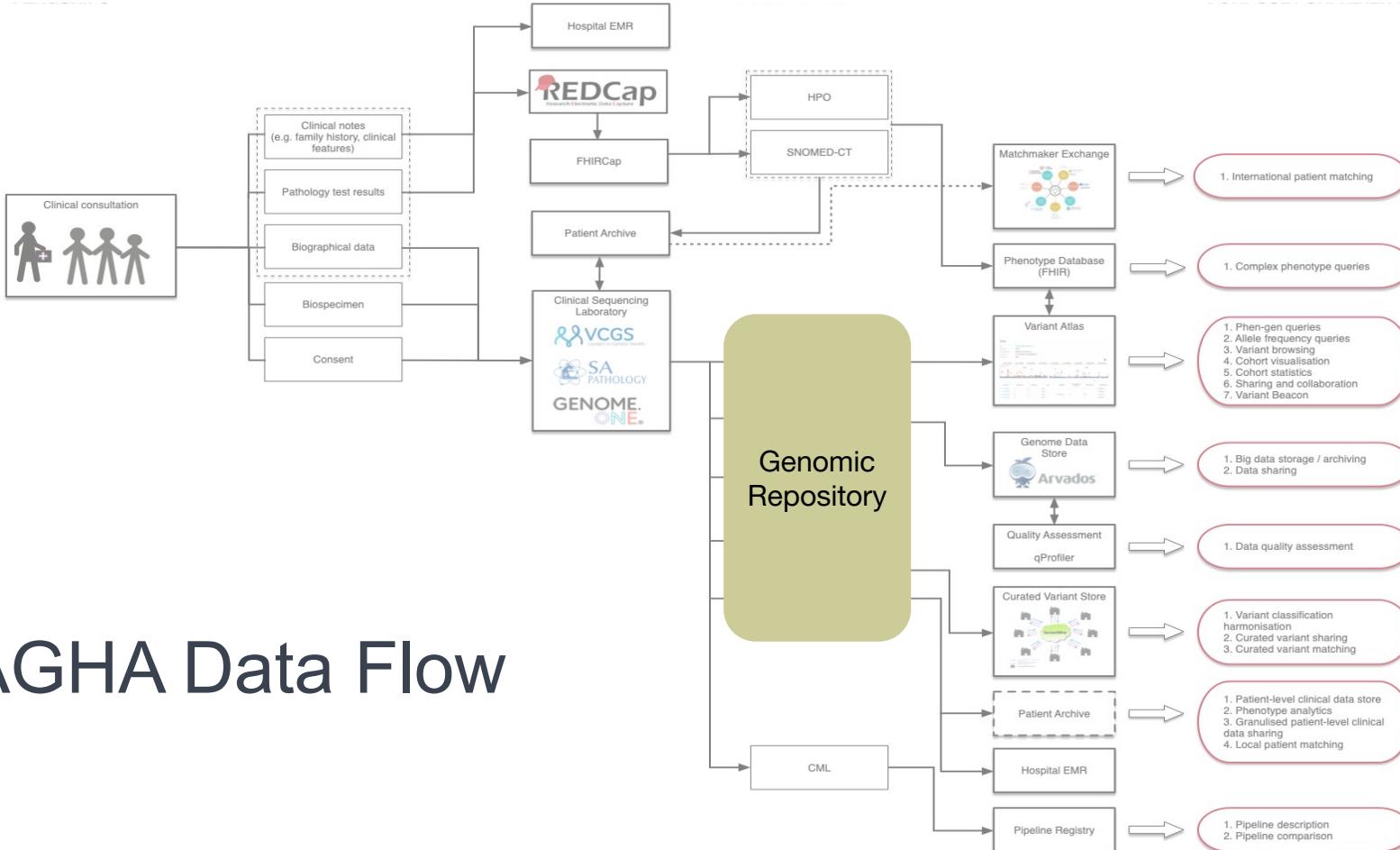


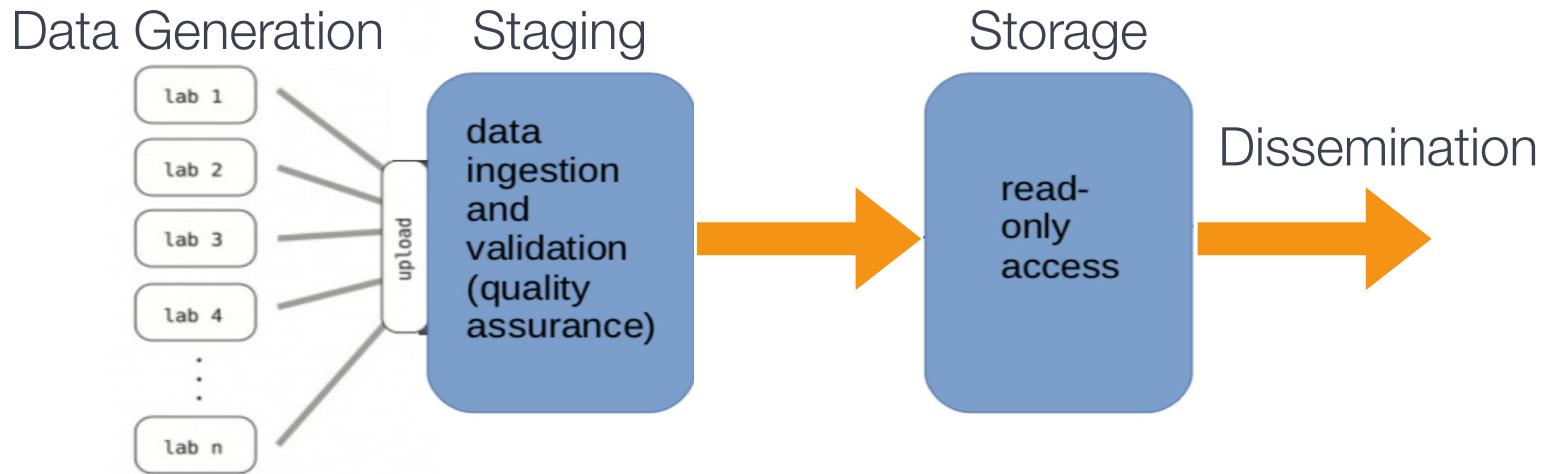
AGHA Data Flow

AGHA Data Flow



AGHA Data Flow



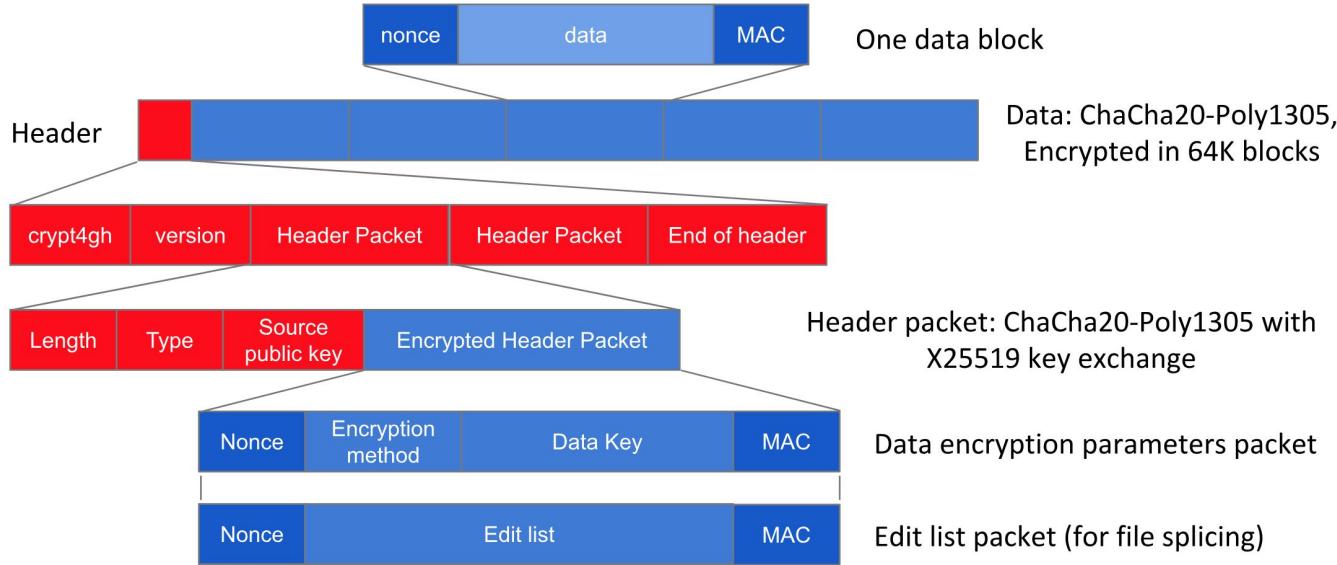


Genomic Repository



Staging: CRAM

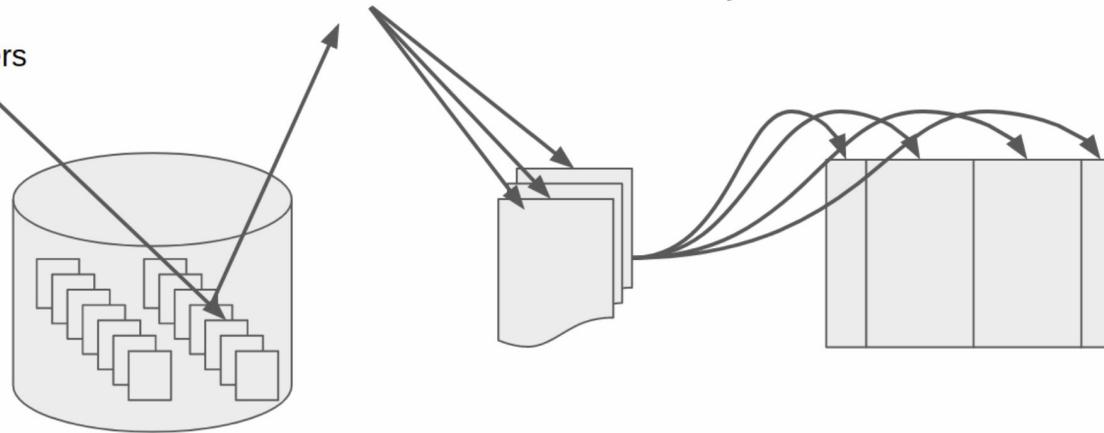
<http://ga4gh.org/cram>



Staging: Crypt4GH

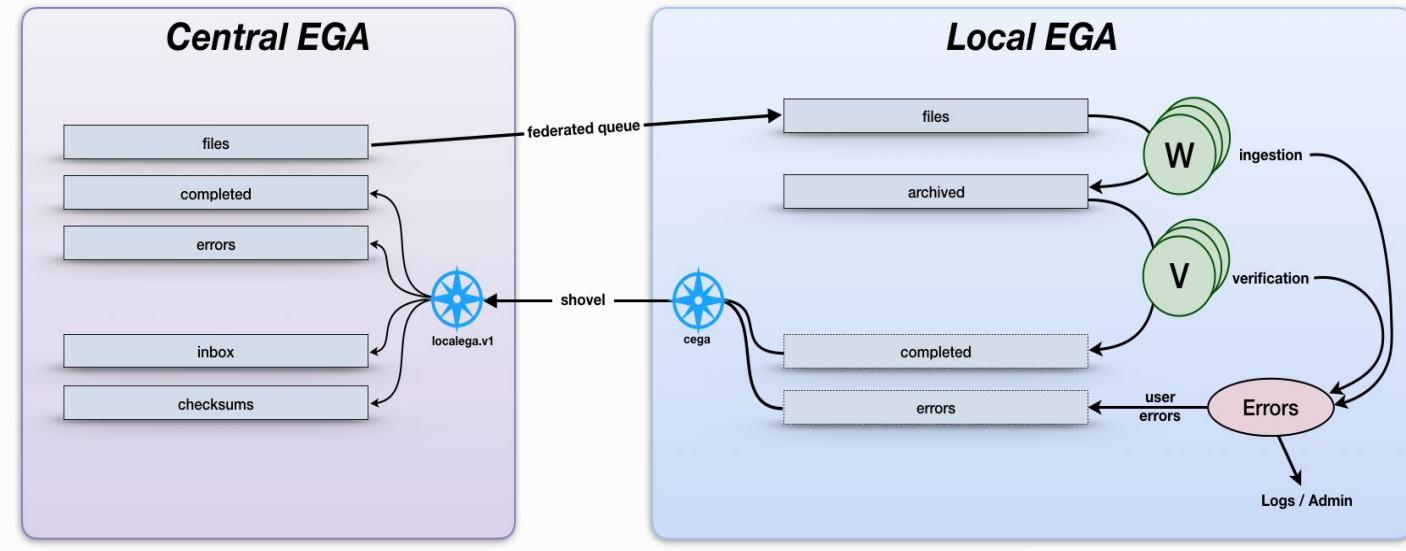
Encrypted container formats: <https://github.com/uio-bmi/crypt4gh>

- 1 Initial request (GET)**
- Identifier
 - Region
 - Format
 - Field filters
- 2 Response ticket (JSON)**
- HTTP headers
 - HTTP URLs
- 3 Fetch data (GET)**
- Download each binary data unit
- 4 Concatenate**
- Final result



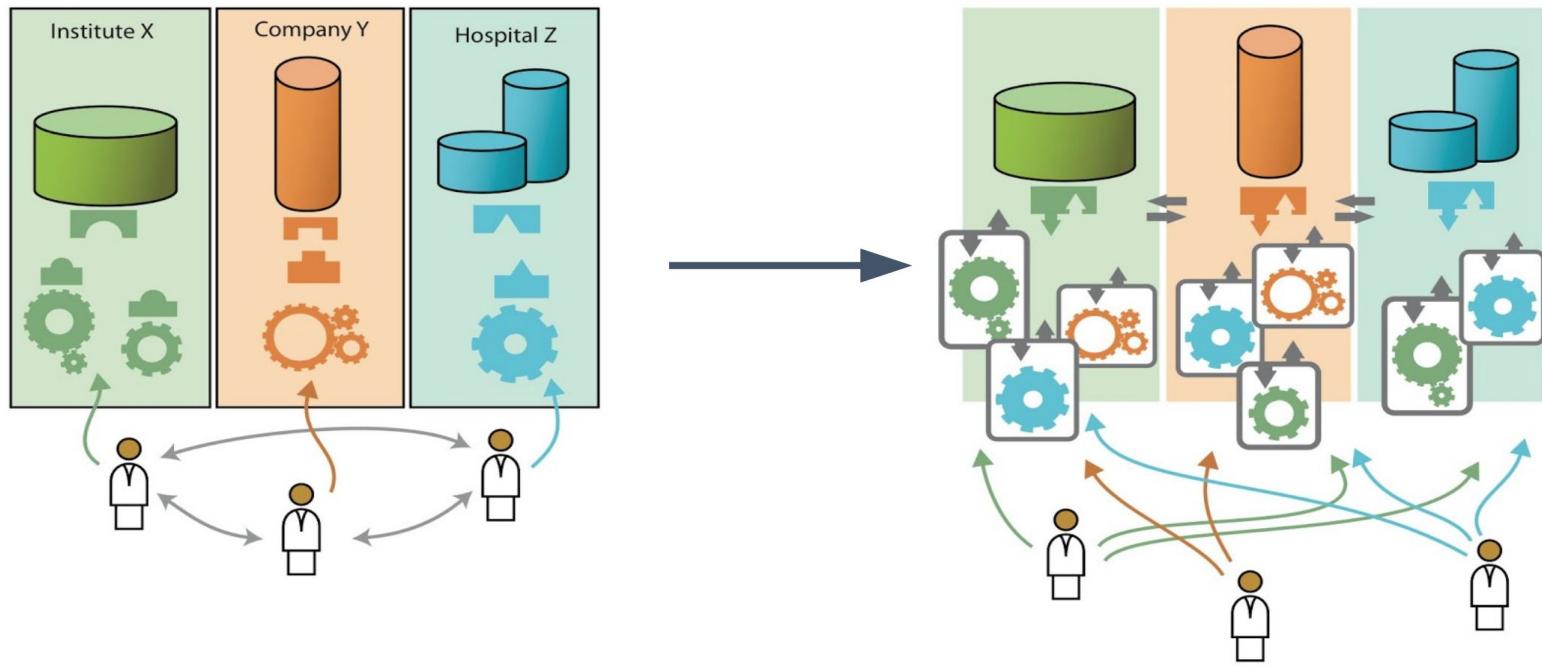
Dissemination: htsget

<http://samtools.github.io/hts-specs/htsget.html>



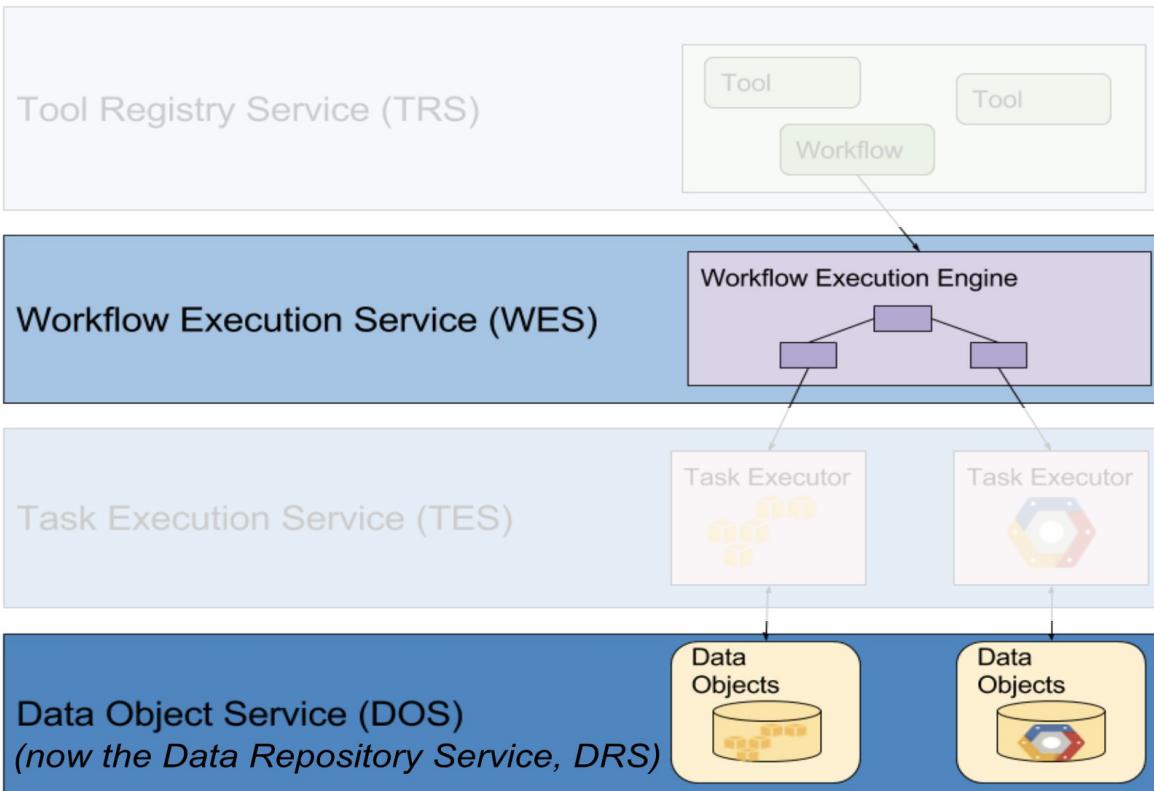
Dissemination: Local EGA

<https://localega.readthedocs.io>



Access: Workflow Execution Service

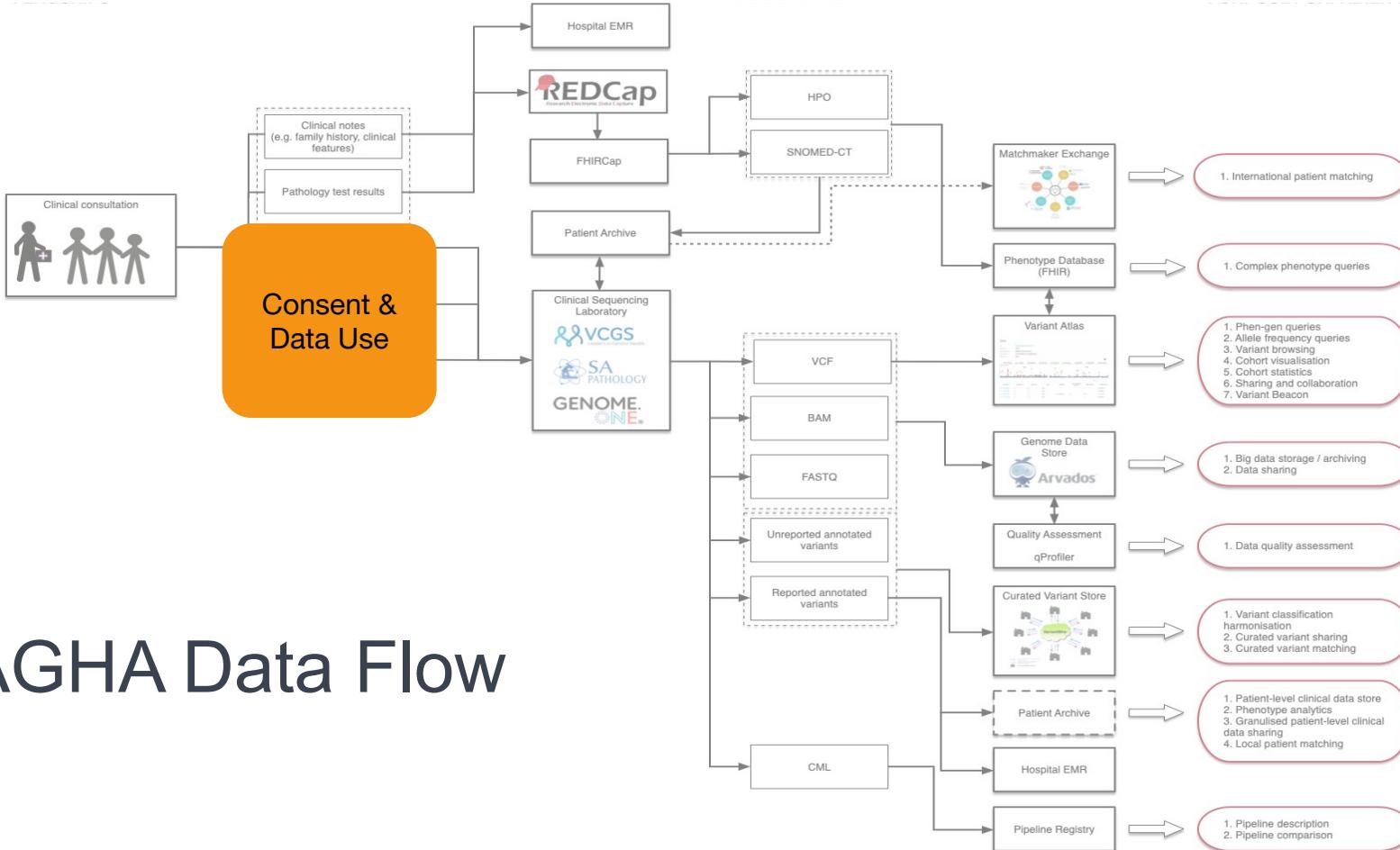
https://www.ga4gh.org/work_stream/cloud/

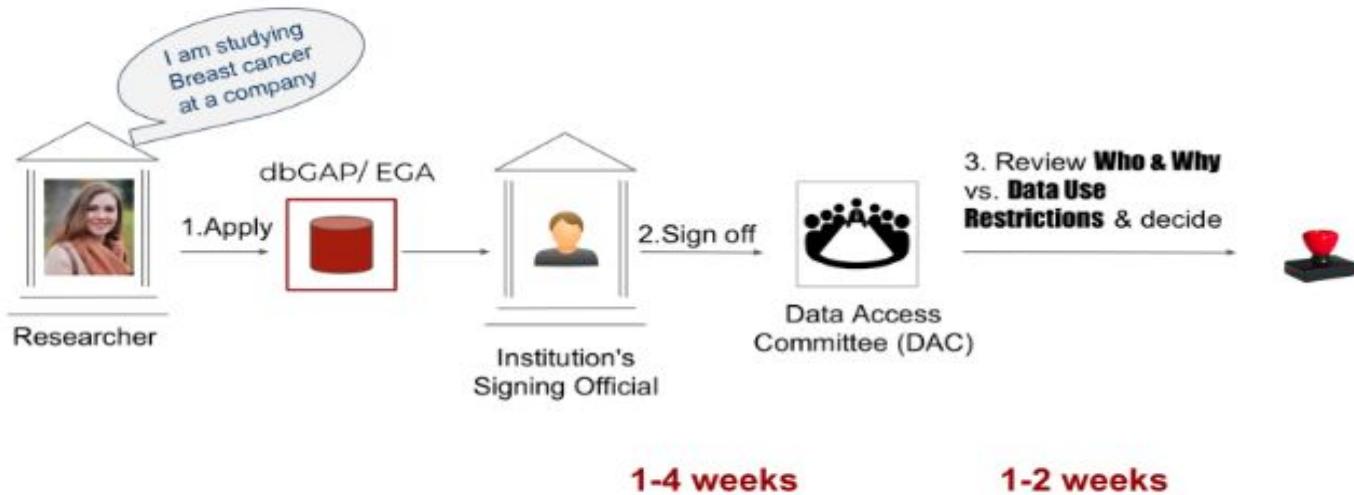


Executing
workflows

Accessing Data

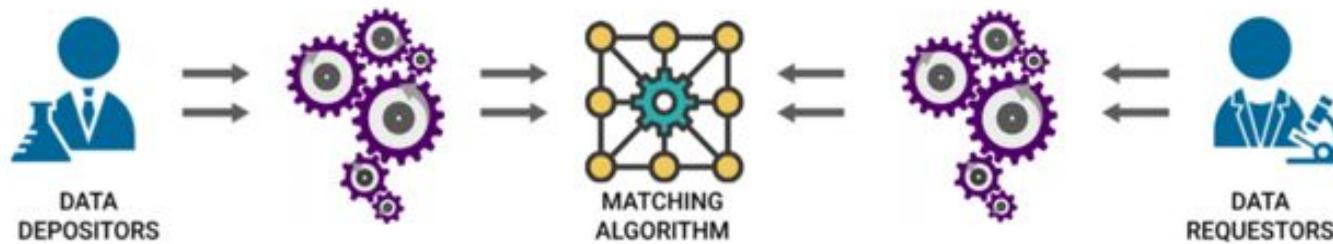
AGHA Data Flow





Access: Data Use & Researcher Identities

Simplifying data access requests



Data Use Ontology (DUO)

Automating discovery & access for controlled access data

<https://github.com/EBISPORT/DUO>

Welcome to CTRL

Consent for participating in the Australian Genomics program

Register Now

Log in

Dynamic consent

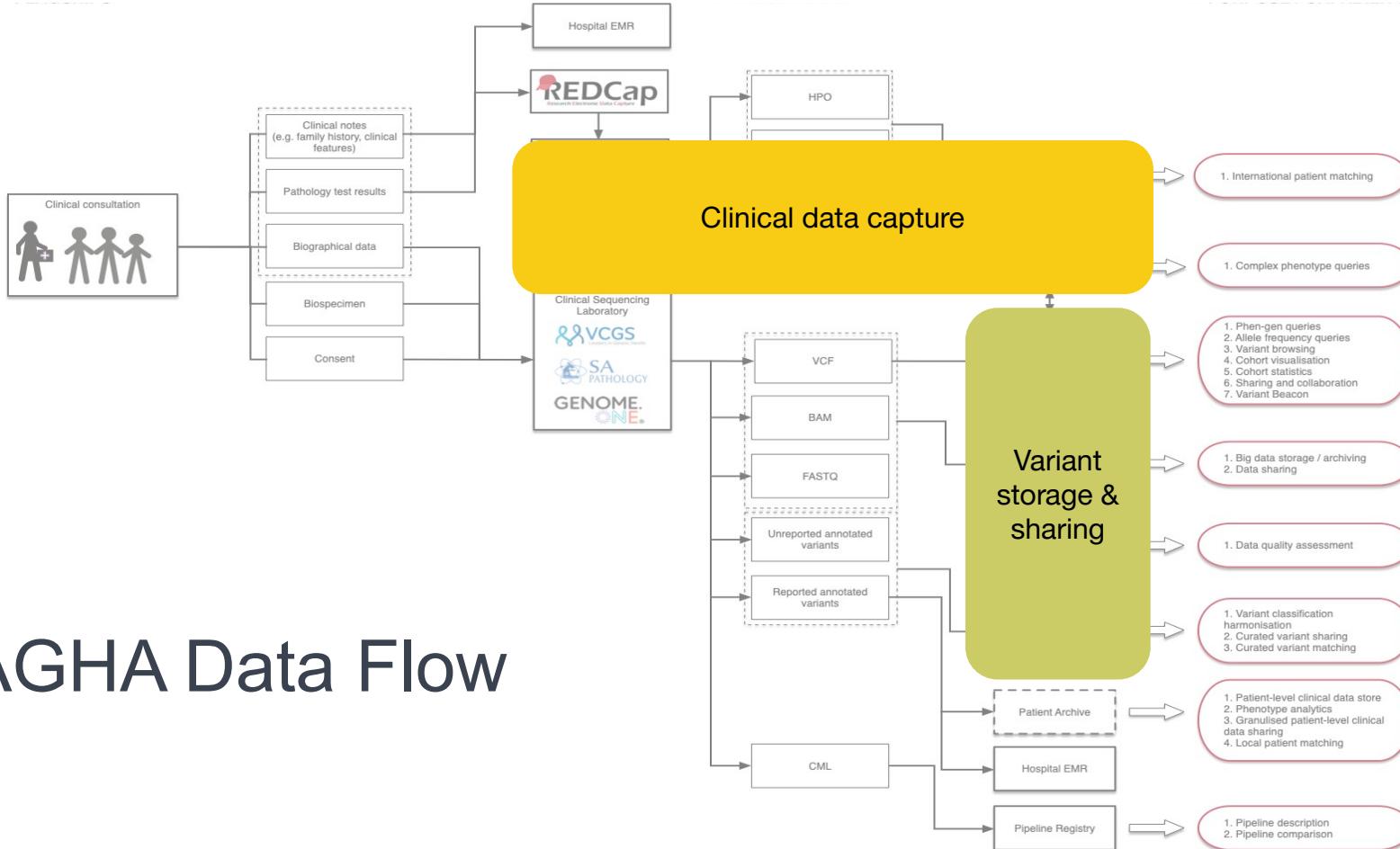
<https://demo-ctrl.australiangenomics.org.au/>



Access: Data Use & Researcher Identities

Simplifying data access requests

AGHA Data Flow

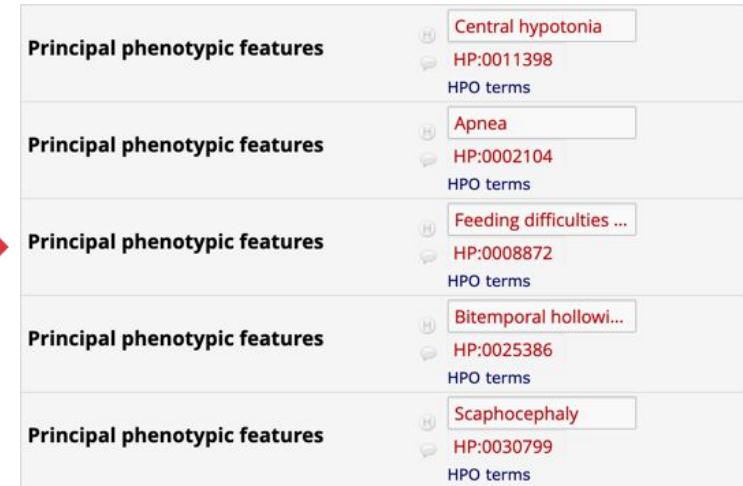


Principal phenotypic features



Central hypotonia, apnoeas,
feeding difficulties, tall forehead,
bitemporal narrowing,
scaphocephaly

Expand



Principal phenotypic features	Central hypotonia HP:0011398 HPO terms
Principal phenotypic features	Apnea HP:0002104 HPO terms
Principal phenotypic features	Feeding difficulties ... HP:0008872 HPO terms
Principal phenotypic features	Bitemporal hollowi... HP:0025386 HPO terms
Principal phenotypic features	Scaphocephaly HP:0030799 HPO terms

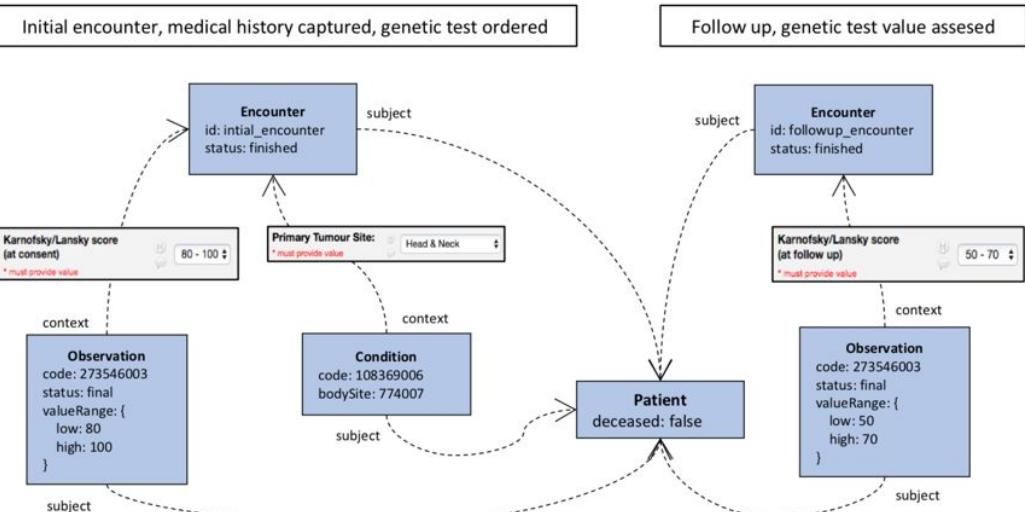
Standardise Data in REDCap

REDCap Plugin: Collecting standard terminologies via an external FHIR server, https://github.com/aehrc/redcap_fhir_ontology_provider

Ontoserver, <https://genomics.ontoserver.csiro.au/>



[condition] :
[resource_type]<[resource_id]> ->
([attribute] = [value])*



FHIRCap: REDCap to FHIR

Converting data captured in REDCap to FHIR Resources

Shariant: share variants

Australian Genomics Variant Classification Sharing Platform

Developed for [Australian Genomics](#) Program 2, Project 1: A national approach to clinical variant classification and sharing.

[About Program 2](#)

- Share clinically curated variants with structured supporting evidence and phenotypes between Australian labs
- Allow collaborative monitoring & review of curated variants
- Act as a central administrative node for submission to international databases such as ClinVar



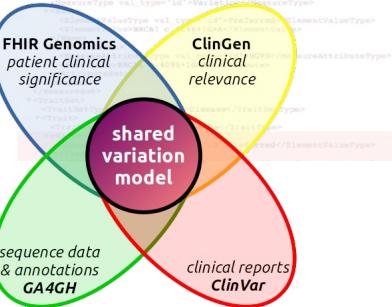
Variant Sharing

<https://shariant.org.au>

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      <Suffix>Dr</Suffix>
    </Name>
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```



Assertion and evidence details

Go to: [Clinical assertions](#) [Summary evidence](#) [Supporting observations](#)

Germline

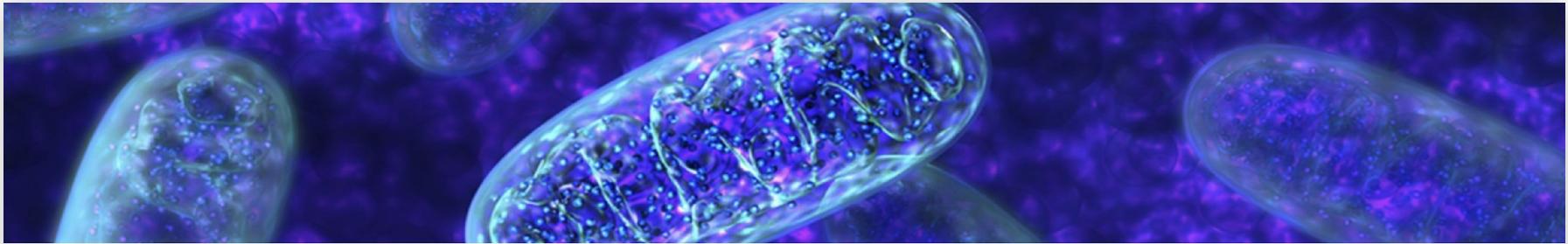
Filter:

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Submission accession
Uncertain significance (Apr 12, 2018)	reviewed by expert panel - ENIGMA BRCA1/2 Classification Criteria (2017-06-29)	curation	Breast-ovarian cancer, familial 1 [MedGen OMIM]	germline	Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) - ENIGMA Study description	SCV000783125.1	
Pathogenic (Feb 28, 2018)	criteria provided, single submitter - Causally Autosomal Dominant Disease Classification criteria (2015)	clinical testing	Breast-ovarian cancer, familial 1 [MedGen OMIM]	unknown	- PubMed (3) [See all records that cite these PMID(s)]	Causaly	SCV000786121.2

Assisted submission to ClinVar

Genomic Knowledge Standards: Variant Representation

<https://github.com/qa4gh/vmc>



Search genes or regions, e.g BRCA1 or 17:41322498-41363708



Cohorts: MGRB ▾

Examples: [FAM110C](#) or [22:46546424-46639653](#) (GRCh37 coordinates)

Medical Genome Reference Bank

Provide integrated genomic and phenotypic reference from 4000+ healthy elderly Australians.

Genomes Sequenced

3000/4000

NSW Health Genomic Medical Research Grants

Empowering researchers to translate the potential of genomic research into better health outcomes.

Genomes Sequenced

1689/2295

Genomic Cancer Medicine Program

To expedite the translation of genomic discovery into improved health outcomes for cancer patients.

Genomes Sequenced

242/2000

VariantAtlas



Genomes Sequenced

4,689



Patients and Participants

8,295



Research Projects

12



Terabytes of Data

700

<https://variantatlas.org.au/>

Search all beacons for allele

GRCh37 ▾

13 : 32936732 G > C

Cancel

Response [All](#) [None](#)

- | | |
|---|----|
| <input checked="" type="checkbox"/> Found | 5 |
| <input type="checkbox"/> Not Found | 30 |
| <input type="checkbox"/> Not Applicable | 12 |



BRCA Exchange

Hosted by BRCA Exchange

[Show Metadata](#)[Found](#)

Cafe Variome

Hosted by University of Leicester

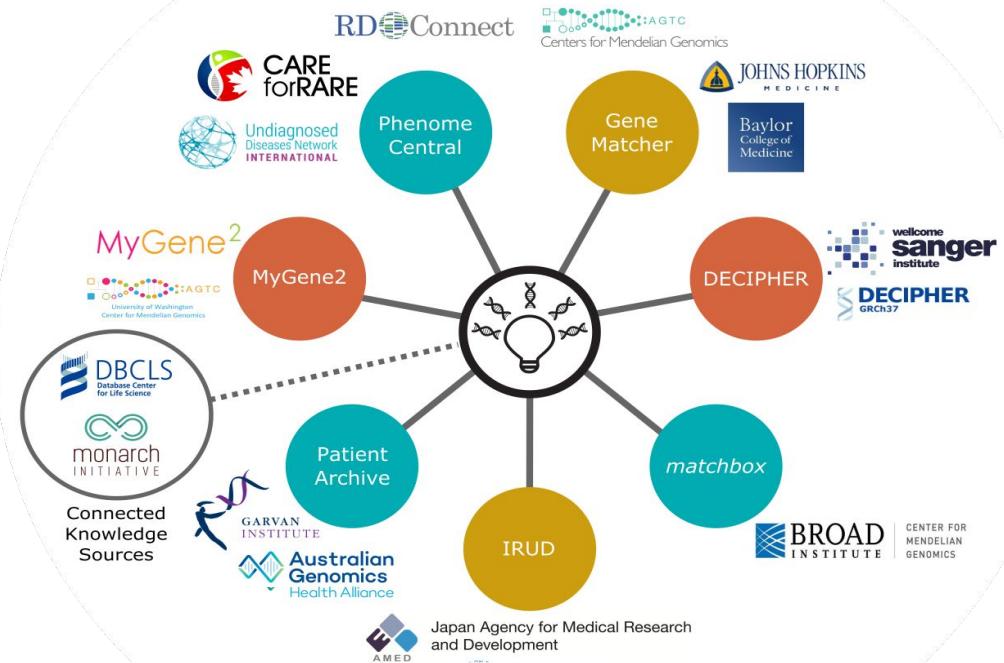
[Found](#)

Cafe Variome Central

Hosted by University of Leicester

Discovery: Beacon

<https://beacon-network.org/>



Discovery: Matchmaker & Beyond

Australian Genomics Health Alliance Patient Archive

Technical Workstreams

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

Foundational Workstreams

Data Security
Regulatory & Ethics



Global Alliance
for Genomics & Health
Collaborate. Innovate. Accelerate.

<https://www.ga4gh.org/how-we-work/workstreams/>

Program Two Membership

Leads

Oliver Hofmann UniMelb

David Hansen CSIRO

Natalie Thorne MGHA

Coordinator

Marie-Jane Brion QIMRB

Working Group

Mandy Spurdle QIMRB

John Pearson QIMRB

Nic Waddell QIMRB

Warren Kaplan Garvan

Alejandro Metke CSIRO

Emma Tudini QIMRB

James Andrews SAPath

Andre Hermanto Garvan

Shane Husson Garvan

Hugo Leroux CSIRO

Lavinia Gordon UniMelb

Roman Valls UniMelb

Tessa Mattiske AFGN

Uwe Dressel UQ

Philip Wu ANU

Sarah King-Smith SAPath

Sebastian Lunke VCGS

Allan Williams NCI

Boris Guennewig CPAlliance

David Bunker QGHA

David Lawrence SAPath

Denis Bauer CSIRO

John Christodoulou MCRI

Karin Kassahn SAPath

Ken Doig Peter Mac

Maureen Turner Biogrid

Simon Sadedin VCGS

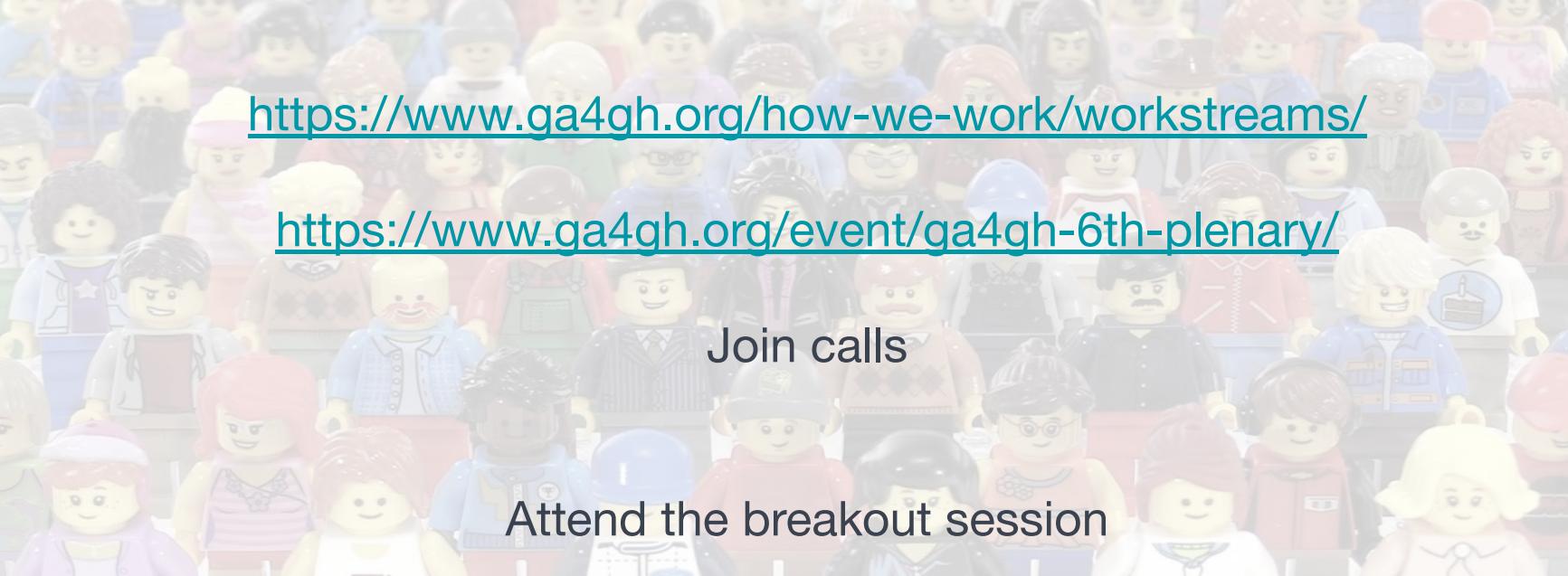
Stefanie Elbracht-Leong AG

Tiffany Boughtwood AG

CTRL Working Group Membership

Matilda Haas	Program Coordinator, Australian Genomics (Project lead)
Kirsten Boggs	Genetic Counsellor, Sydney Children's Hospital Network
David Bunker	Exec. Director, Queensland Genomics Health Alliance
Bronwyn Terril	Manager, Education and Communication KCCG
Sean Murray	CEO, Mito Foundation
Jessica Bell	Research Fellow, Melbourne Law School
Keri Finlay	Program Officer, Australian Genomics
Miranda Vidgen	Research Officer, QIMR Berghofer
Megan Prictor	Research Fellow, Melbourne Law School
Tiffany Boughtwood	Manager, Australian Genomics
Nada Mirkovic	chiLDRANZ Flagship Coordinator, Australian Genomics
Norah Grewal	PhD Student, Sydney Health Ethics, USYD
Adam Walczak	Youth Cancer Services, Canteen
Lindsay Fowles	Genetic Counsellor, Genetic Health QLD





<https://www.ga4gh.org/how-we-work/workstreams/>

<https://www.ga4gh.org/event/ga4gh-6th-plenary/>

Join calls

Attend the breakout session

Contributions welcome

LUNCH & BREAKOUT SESSIONS

BREAKOUT SESSION 1

13:50 - 15:20

Genomic Data Sharing & Access

Dale Room

Clinical Data

Burroughs Room

BREAKOUT SESSION 2

15:40 - 17:00

Curation

Dale Room

Regulatory & Ethics

Burroughs Room



Public Engagement and data sharing governance

Madeleine Murtagh, REWS Co-chair, Newcastle University
Clara Gaff, Australian Genomics
Mavis Machirori, Newcastle University

Session Rationale and Purpose

- Responsible and respectful data sharing includes alignment with societal values. So how do we know what the values are?
Public engagement.
- Goal today: share NI's experiences and lessons learnt in public engagement related to data sharing and data sharing governance
- Foster connections to inform future public engagement on data sharing by NIs
- Identify any future directions for GA4GH/REWS in this area

Dimensions of public engagement

PURPOSE



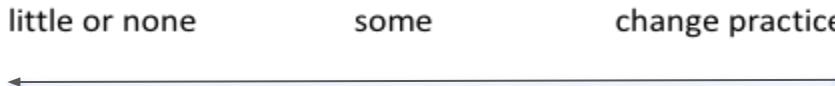
INTERACTION



APPROACH



IMPACT



CONTEXT

Multiple = research clinic, overarching governance, regulatory, society, systems, feasibility, in/equities

Workshop process: Ecouter

1. Get information
2. Analyse information
3. Construct conceptual schema
4. Feedback and iteration



ECOUTER TRIGGER QUESTIONS

- What public engagement has your initiative done?
- Why did you this public engagement?
- What worked and what didn't?

What can GA4GH do?

Group discussion



Next steps

‘Micro interview’ with each NI reps or delegates (Mavis)

To capture core information about ongoing public engagement (and contacts) in each NI

Report

Outcomes of the ECOUTER analysis

Summary of national initiatives’ public engagement activities

Contact person for each activity

DINNER

Wellcome Trust
Gibbs Building, 5th Floor
215 Euston Road