

National Initiatives Meeting

Day 2

Wellcome Collection, London
May 3, 2019

Opening Remarks

Kathryn North
Australian Genomics

Mark Caulfield
Genomics England



Breakouts Feedback

Part 1



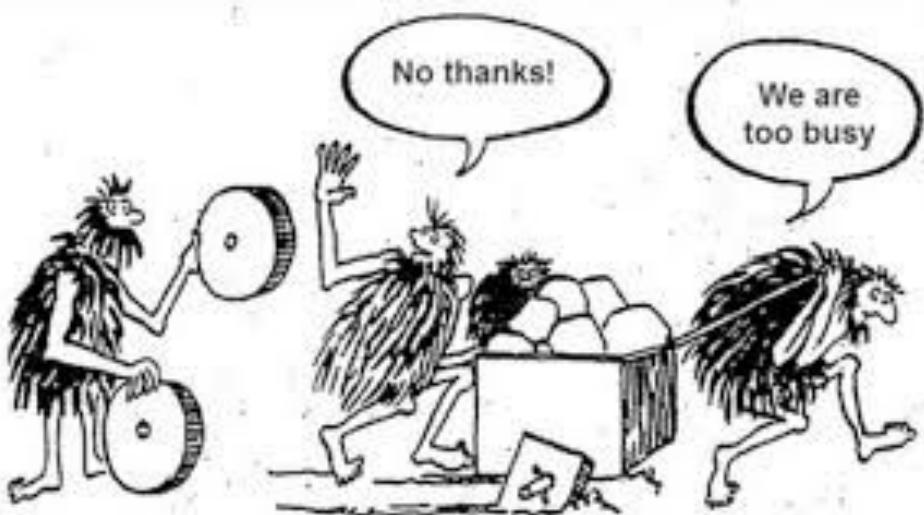
Clinical Data

Capture, Exchange, and Use in Genomic Analysis

Chairs: Zornitza Stark and David Hansen

Speakers: Ellen Thomas, James Holman, Mogomotsi Matshaba,
Kenjiro Kosaki, Robert Carroll

Goals of this Session



Look at:

- Tools/processes
- Challenges
- Solutions

What can we share?



GEM-Japan



Global Alliance
for Genomics & Health

The problem

Relevant
High quality
Accurate
Machine-readable
Interoperable



Time
Effort
Skill
Scalability

Risk: poor quality, incomplete data
= suboptimal interpretation

Ambitious → Essential



Essential data = required for the interpretation pipeline

- Disease status (bespoke)
- Pedigree data (Panogram)
- Human Phenotype Ontology

Core clinical data = wider phenotypes

- ICD10, SNOMED CT, OMIM
- Early childhood observation data
- Imaging data
- Laboratory blood tests
- Genetic Investigation
- Using established standards wherever possible

Disease

1	Disease Group	Renal and urinary tract disorders	<small>Pb</small>
2	Disease Subgroup	Syndromes with prominent renal abnormalities	<small>Pb</small>
3	Specific disease	Alport syndrome	<small>Pb</small>

Basic Phenotyping

4 Phenotype Description	5 Phenotype Identifier	6	7 Phenotype Present	Modifiers	Actions
Proteinuria	HP:0000093	<small>Pb</small>	<input checked="" type="radio"/> Unknown <input type="radio"/> Yes <input type="radio"/> No <small>Pb</small>		<small>Edit</small>
Hematuria	HP:0000790	<small>Pb</small>	<input checked="" type="radio"/> Unknown <input type="radio"/> Yes <input type="radio"/> No <small>Pb</small>		<small>Edit</small>
Nephrotic range proteinuria	HP:0012593	<small>Pb</small>	<input checked="" type="radio"/> Unknown <input type="radio"/> Yes <input type="radio"/> No <small>Pb</small>		
Renal insufficiency	HP:0000083	<small>Pb</small>	<input checked="" type="radio"/> Unknown <input type="radio"/> Yes <input type="radio"/> No <small>Pb</small>		

Pedigree diagram

A pedigree diagram illustrating inheritance across four generations. Generation I consists of a male (square) and a female (circle). They have three children in Generation II: a male (square), a female (circle), and a male (square). The female from Generation II has two sons in Generation III: one male (square) and one female (circle). The male from Generation III has a son in Generation IV (male square). The female from Generation II has a daughter in Generation IV (female circle). The male from Generation III has a daughter in Generation IV (female circle). The pedigree diagram is labeled "Pedigree diagram" at the bottom right.

Variability → Harmonization

Within and between initiatives

Harmonization algorithms



Case I: Paediatric phenotype standardization

- Curators and paediatric experts suggest if question is Essential, Optional, Recommended

	Princeton	Rehab Centers	Peninsula Associates	Beth Ingram Therapy services	IPM	GA4GH	E/R/O	Goes on CRF	PhenX	Notes	Katherine's Notes (E - Essential, R - Recommended, O - Optional)	Wording of this question in Harmonized phenotypes
Date	X			X	X		E	Yes		Is important to keep track with the questions that are followed up each	Important	E
Relationship to child (parent, teacher, etc) of the person completing the form	X			X			E	Yes		I think if we get the relationship in the previous	I agree with Lyndon on this	
Referrer details Name Contact details					X (is it the same as person completing the	R	No			Only in longitudinal studies	O	
Consent Confirmation obtained Additional findings Data sharing Research					X	E	Yes			E - I think this is becoming increasingly necessary as we move to sharing		
General & Family information	X	X	X	X	X	X					Important	
Name	X	X	X	X	X	X	E	No	Change name by identifier	Identifier required	PID only	"Current Age 1. What is your birthdate? DD/MM/YYYY _____; [] Don't Know [ask follow-up question]; 2. [Follow-up question if "don't know"] About how old are you? Age _____ DD; _____ WW
Date of birth	X	X	X	X	X	X	E	Yes	Current Age 1. What is your birthdate? DD/MM/YYYY _____	Important	Important	R alternatively definitely age at data collection time point - DOB at least allows one to calculate age at any given time point but it is considered a personal identifier
Ethnicity					X	E	Yes			Important	R	



9 of 32

H3Africa Phenotype Harmonization - National Initiatives Meeting - London, May 2019 - Mamana Mbjayanga



Global Alliance
for Genomics & Health

Share lessons/resources

Rare disease



Common disease



GEM-Japan



Clinical data toolbox



Clinical datasets: 150+



Data capture tools



Add information in any order

- Patient details
- Requesting organisation
- Test package
- Responsible clinician
- Clinical questions
- Family members *
- Patient choice
- Panels
- Pedigree
- Notes
- Print forms

Answer clinical questions

Disease status details

Disease status

Affected

Choose the status of the condition being tested for:

Age of onset

0 Years 6 Months

For prenatal patients, enter number of months before birth, e.g. -3

HPO phenotype details

Add HPO phenotype details

Find an HPO phenotype or code

intel

Intellectual disability, mild

Intellectual disability, profound

Intellectual disability, moderate

Intellectual disability, progressive

Intellectual disability, borderline

Intellectual disability, severe

int or Unknown if appropriate.

Modifiers

int Unknown Mid Select

int Unknown Select

REDCap Ontology Modules: HPO; Ancestry
REDCap forms mapped to FHIR Resources
REDCap dictionaries/ontologies

Archive v1.0.0 DASHBOARD GROUPS TUDOR GROZA Search

Clinical Data

- Summary
- Timeline
- Demographics
- Practitioners
- Clinical records**
- Diagnoses
- Imaging
- Tests
- Genomic features
- Attachments

Clinical Records

CLINICAL CONSULTATION **Phenotype Profile**

Annotation Sufficiency ★★★★☆

Jun 2, 2016 12 hours ago

Unexplained left ventricular hypertrophy (LVH). Occurs in non-dilated ventricle in the absence of other noticeable cardiac or systemic disease. Symptoms of breath (particularly with exertion), chest pain, palpitations, orthostasis, presyncope. No syncope. Recently developed symptoms.

Chest pain (chest pain) No Syncope (syncope) Palpitations (with pachycephaly/mild palpitations) Ventriculogram (dilated ventricle)

Diagnoses (diseases of breast) Left ventricular hypertrophy (left ventricular hypertrophy) •

CLINICAL CONSULTATION **Phenotype Profile**

Annotation Sufficiency ★☆☆☆☆

Jun 2, 2016 12 hours ago

Noninvasive cardiac imaging using echocardiography but results are unclear.

Powered By Human Phenotype Ontology and Bio-LarK CR (see PMID:25725061 and PMID:26119816)

Annotation Sufficiency ★★★★☆

Abnormality of the cardiovascular system: Palpitations (with pachycephaly) Left ventricular hypertrophy No Syncope

Abnormality of the nervous system: Ventriculogram

Abnormality of the respiratory system: Diagnoses

Abnormality of the skeletal system: Chest pain

Cross-lingual adaptation of GA4GH Standards

Translation of
Human Phenotype
Ontology into Japanese

Translation of
IRUD Exchange into
Japanese



Accelerating
phenotypic data capture and sharing

Cross-lingual adaptation of clinical data capture and exchange through translation of the HPO system

Japanese Symptoms

小頭症、
眼瞼下垂裂、
高脂血症、
広い鼻梁、
水腎症、
拘縮、
側弯症、
知的障害、
小脳低形成

Translated to English

microcephaly,
ptosis, pimpls,
hyperlipidemia,
broad nasal bridge,
hydronephrosis,
contracture,
scoliosis,
cerebellar hypoplasia

Human Phenotype Ontology

HP:0003077 | Hyperlipidemia
HP:0000508 | Ptosis
HP:0000126 | Hydronephrosis
HP:0000431 | Wide nasal bridge
HP:0001321 | Cerebellar hypoplasia
HP:0200039 | Pustule
HP:0000252 | Microcephaly
HP:0002650 | Scoliosis
HP:0001371 | Flexion contracture

HPO Japanese

Technical resources



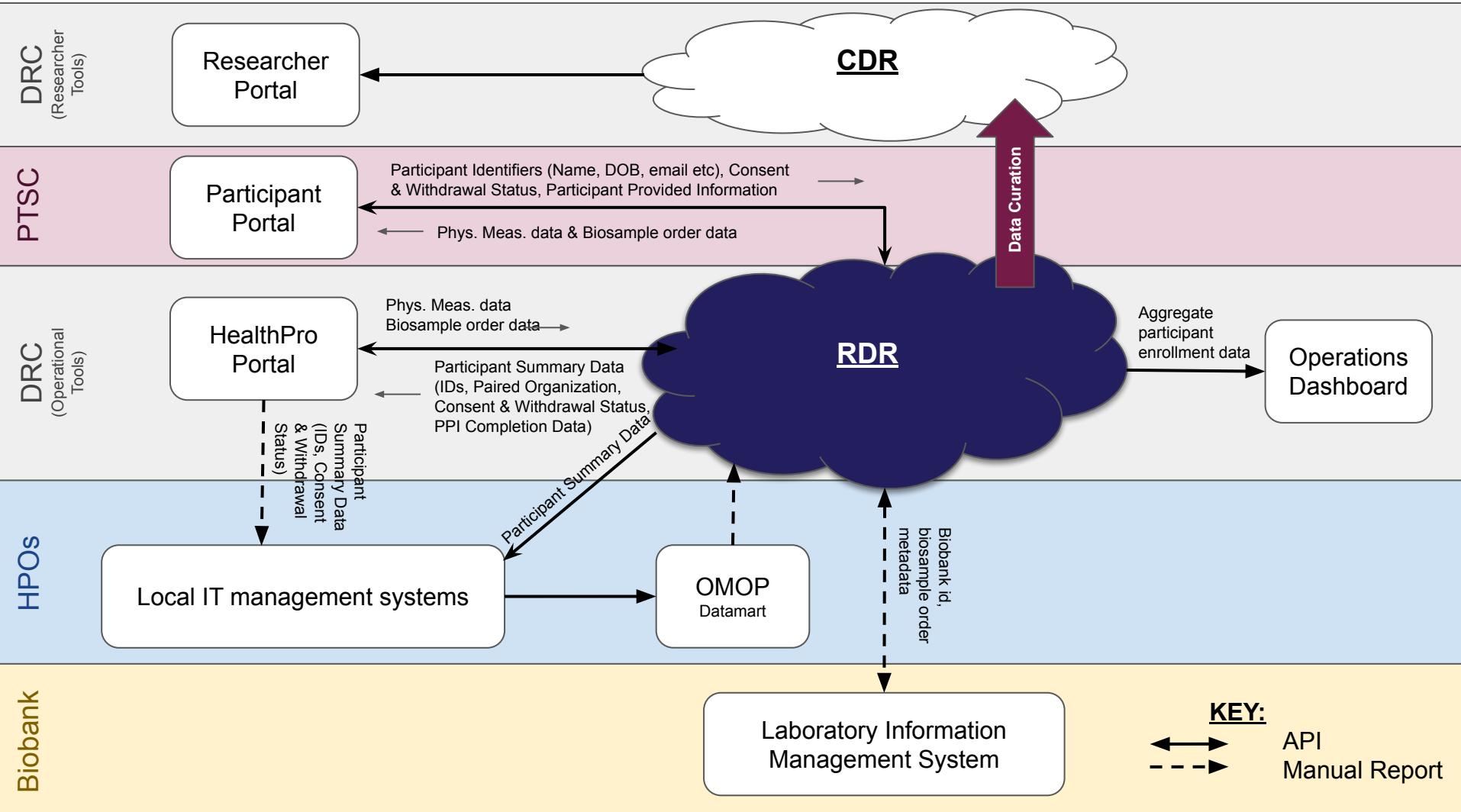
FHIR profiles
FHIR implementation guide

APIs

Common data models: OMOP

Data cleaning tools

EHR linkage





Consent

Affix identifier information here



Clinical Consent Form for Genomic Testing

It is my choice to have genomic testing. I can say yes or no to the options on this form.

I, _____ (patient and/or parent/guardian names), understand that my DNA will be tested by panel/exome/genome to look for changes in genes that may be associated with _____

About the Test

- Genomic testing is done on DNA from my blood, saliva or tissue.
- Genomic test results are based on current knowledge, which may change in the future.
- I can choose not to be told about the results.

Potential Outcomes

I understand that:

- This test may find a cause for the condition(s).
- This test may not find a cause for the condition(s).
- The result may be of '*unknown significance*', which means it cannot be understood today.

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





Global Alliance for Genomics & Health

Collaborate. Innovate. Accelerate.

Genomic Data Access & Sharing

Chairs: Oliver Hofmann, Augusto Rendon

Speakers: Thomas Keane, Ilkka Lappalainen



Genomic Data Access & Sharing: good attendance!

Genomics England

GEM-Japan

Australian Genomics

Qatar Genome Program

Genome Canada

All of Us

BIPMed

Swiss PHN

...

[H3 Africa]

ELIXIR/Nordic Countries

CanDig

Cineca

National & Other Initiatives

List incomplete!

Cohort construction kit

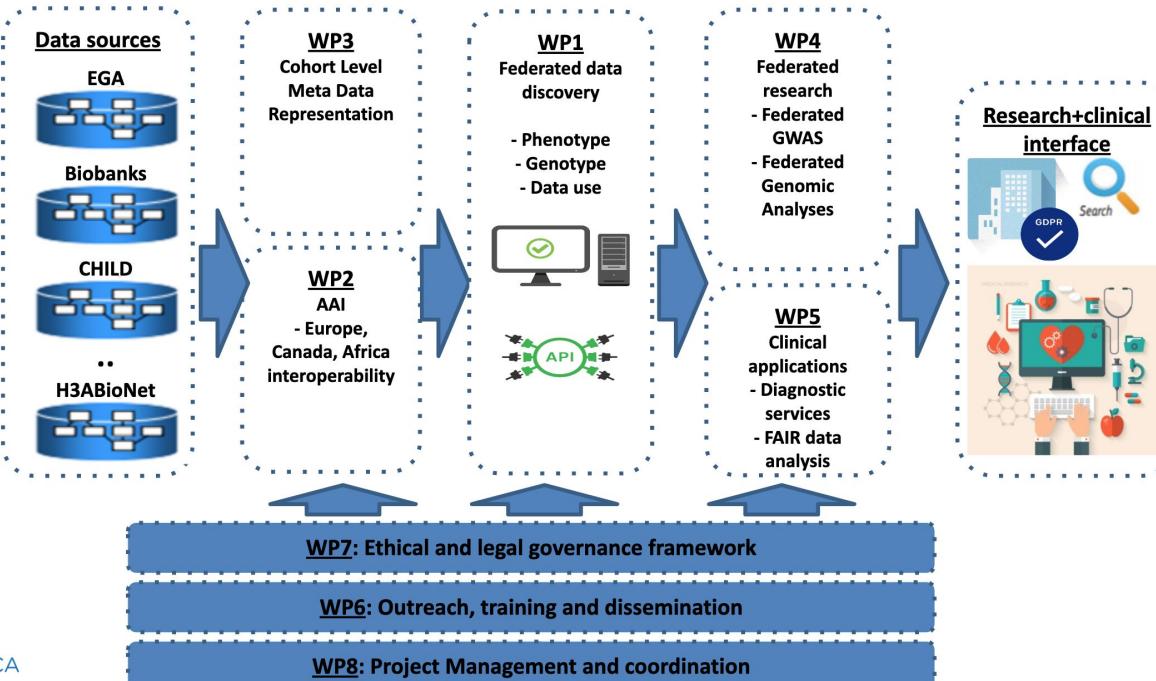
Minimum metadata set to describe cohort participant

Discovery of cohorts vs Discovery of individuals

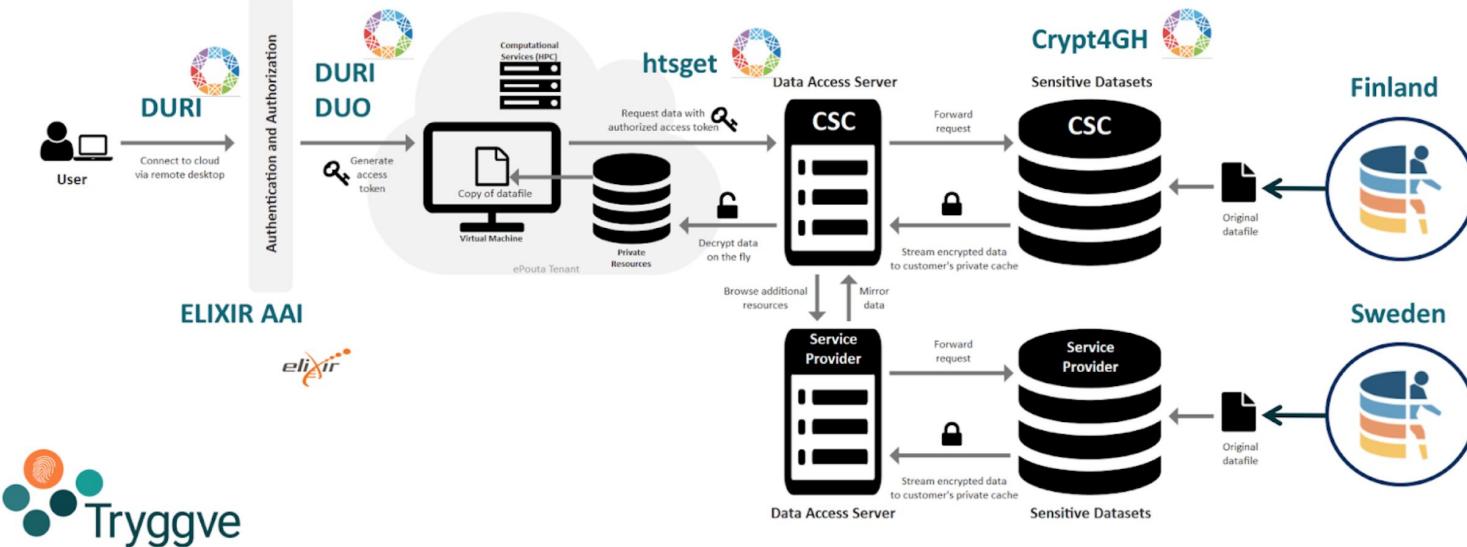
Hands-on projects

“Identify pilot projects for data sharing using specific cohorts.”

Genomic Data Access & Sharing Mandate



CINECA Overview



Tryggve Overview



No Easy Pilot Projects



Start by Taking Stock

	Authentication	Data Use	Consent
Genomics England			
GEM-Japan			
Australian Genomics			
Qatar Genome Program			
Genome Canada			
All of Us			
BIPMed			
Swiss PHN			
...			
[H3 Africa]			
ELIXIR/Nordic Countries			
CanDig			
Cineca			

Data Access

	Authentication	Data Use	Consent	...	GA4GH Standards
Genomics England					
GEM-Japan					
Australian Genomics					
Qatar Genome Program					
Genome Canada					
All of Us					
BIPMed					
Swiss PHN					
...					
[H3 Africa]					
ELIXIR/Nordic Countries					
CanDig					
Cineca					

Extend to GA4GH standards

	Authentication	Data Use	Consent	...	GA4GH Standards	...
Genomics England						
GEM-Japan						
Australian Genomics						
Qatar Genome Program						
Genome Canada						
All of Us						
BIPMed						
Swiss PHN						
...						
[H3 Africa]						
ELIXIR/Nordic Countries						
CanDig						
Cineca						

EGA-archive / crypt4gh

Code

Issues 1

Pull requests 1

Projects 1

GA4GH cryptogra

htsget: a protocol for securely streaming genomic data ⚒

[Jerome Kelleher](#), Mike Lin, C H Albach, Ewan Birney, Robert Davies, Marina Gourtovaia, David Glazer, Cristina Y Gonzalez, David K Jackson, Aaron Kemp ... [Show more](#)

Bioinformatics, Volume 35, Issue 1, 01 January 2019, Pages 119–121,
<https://doi.org/10.1093/bioinformatics/bty492>

Published: 19 June 2018 Article history ▾

Include implementation details

	Authentication	Data Use	Consent	...	GA4GH Standards	...	PanelApp	...
Genomics England								
GEM-Japan								
Australian Genomics								
Qatar Genome Program								
Genome Canada								
All of Us								
BIPMed								
Swiss PHN								
...								
[H3 Africa]								
ELIXIR/Nordic Countries								
CanDig								
Cineca								

Do not limit to GA4GH standards



Identify interfaces to internal solutions

Users

Want to...

Recommendation



- ...call variants in WGS trios.
- ...perform federated joint-joint-variant calling.
- ... find matching *cohorts* from different NIs.

BEST PRACTICE

User stories

Connecting user needs to existing / future technical solutions

Users



Want to...

- ...call variants in WGS trios.
- ...perform federated joint-joint-variant calling.
- ... find matching *cohorts* from different NIs.

Recommendation



BEST PRACTICE

Mapping existing solutions to user stories

Users



Want to...

- ...call variants in WGS trios.
- ...perform federated joint-joint-variant c
- ... find matching *cohorts* from differen
NIIs.

Recommendation



Keep track of support for federation



A different kind of Matchmaker Exchange

Gene Curation Coalition as a model



(Initiative) Engagement

The next meeting

- Smaller working groups?
- Topic-driven breakouts
 - How to scale a variant database?
 - How to use DUO
 - Remote joint calling ideas
 - ...



BREAK

30 min

Breakouts Feedback

Part 2



Curation

Chairs: Heidi Rehm, Ellen McDonagh

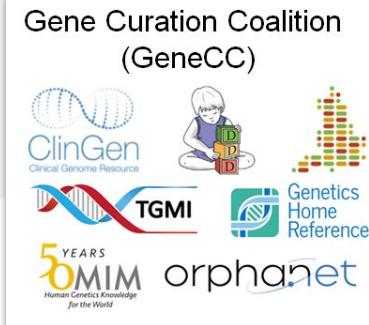
Curation Breakout Session

Three topics addressed:

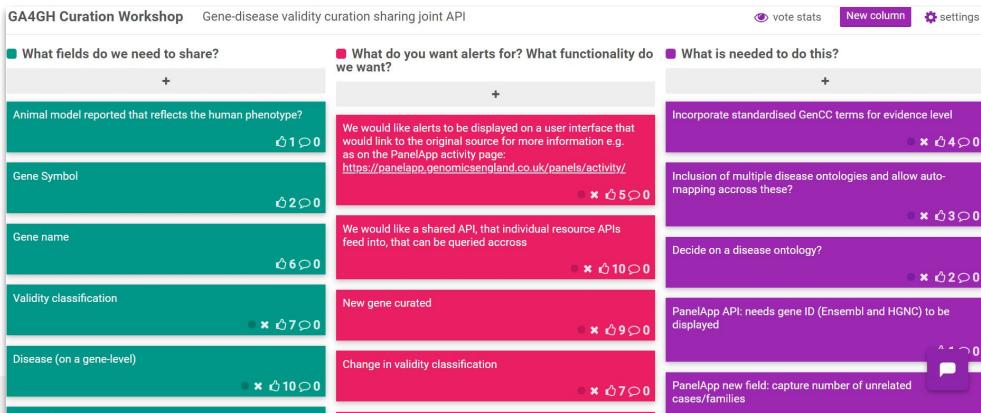
1. Exchange gene-level data (evidence, disease associations) - follow-up plans
2. Standardizing the genomic interpretation pipeline - follow-up plans
3. ClinVar Submission: Plans and Challenges - toolkit and API needed

Link to original session content: <https://docs.google.com/document/d/19EE8uB2JGH3bNMeLNrqxNO2KymHyqpeFpRcqYp6FtqM/edit>

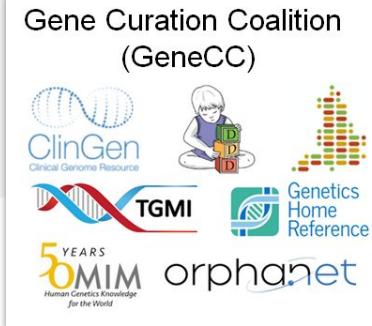
Project 1: Exchange curated gene-level data (evidence, disease associations) used for genome interpretation



- Surveyed (in the room) which countries are interested in using Genomics England PanelApp/having their own PanelApp instance (Australian Genomics, Brazil, Japan, Finland)
- Discussed the proposal of a shared activity page/shared API for updates/changes to enable sharing of gene-disease validity information between different PanelApp instances, ClinGen, ...
- Initial ideas, requirements and votes were captured here:
<https://tinyurl.com/y63kf58o>



Project 1: Exchange curated gene-level data (evidence, disease associations) used for genome interpretation



Next steps:

- Share with the other Gene Curation Coalition members for interest/requirements.
- Define a minimal requirement set for APIs from these resources for this data sharing.
- Bring for discussion with the GA4GH Discovery Work Stream as well as Genomic Knowledge Standards Workstream ...ensure capture of gene-level data in Search API and knowledge data model

Proposed Project to Define Best Practices for Genomic Interpretation

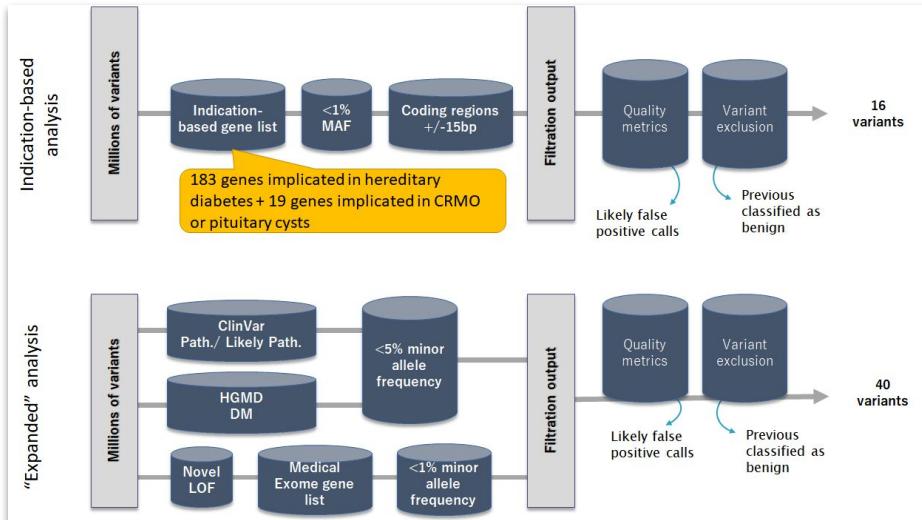
Defined a need to standardize:

Scope of Analysis?

- Panel-driven; who chooses panel?
- Phenotype-driven

What is reported?

How often to reanalyze?



THE MEDICAL GENOME INITIATIVE

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BAYLOR GENETICS BROAD INSTITUTE illumina® HUDDONALPHA INSTITUTE FOR BIOTECHNOLOGY

MAYO CLINIC Rady Children's Institute for Genomic Medicine SickKids THE HOSPITAL FOR SICK CHILDREN Stanford MEDICINE

Steering Committee Members

- Hutton Kearney, PhD, The Mayo Clinic
- Shashikant Kulkarni, PhD, Baylor Genetics & Baylor College of Medicine
- Euan Ashley, MD, PhD, Stanford University
- David Dimmock, MD, Rady Children's Institute for Genomic Medicine
- (Chairperson) Christian Marshall, PhD, The Hospital for Sick Children (SickKids)
- Heidi Rehm, PhD, The Broad Institute
- David Bick, MD, HudsonAlpha Institute for Biotechnology
- John Belmont, MD, PhD, Illumina

<https://medgenomeinitiative.org>

Rare Disease Conditions Clinical Data Models Maintenance release v1.9.0

GEL Doc [Link](#)

Functional Area	Document Owner	Status	Document Key
Document Author	Richard Scott	Version	1.9.0
Document Reviewer(s)	Andrew Devereau, Richard Scott, Ellen Ellsworth, Richard Scott	Version Date	09/04/18
Document Approval	Richard Scott, Clinical Lead for Rare Disease	Next Review Date	30/09/2018
Electronic Signature		Approval Date	09/04/2018
Impact on Competent Personnel (please choose Y/N in the boxes to the right)	<input type="checkbox"/> Read and understand <input type="checkbox"/> Re-train	Y Y	
Transaction ID			



Building a Toolkit for Knowledge Sharing

Laboratory & Clinician Data Sharing Resources

Learn how to share variant classifications and supporting observations from your clinic or laboratory with ClinVar.



About For Laboratories For Clinicians



For Laboratories

Learn how to share variant interpretations and supporting observations from your laboratory with ClinVar.

[Learn More](#)



For Clinicians

Learn how to share variant interpretations and supporting observations from your clinic with ClinVar.

[Learn More](#)

<https://clinicalgenome.org/share-your-data/>

The screenshot shows the ClinGen Allele Registry homepage. At the top, there's a header with the ClinGen logo and a search bar. Below the header, there's a large blue section with the text "ClinGen Allele Registry". Underneath this, there are several navigation links: "Allele Registry", "Pathogenicity Calculator", "Login", and "Forgot Password?". Further down, there's a search interface with fields for "Type of search" (dropdown menu with "Select One" option), "Query" (text input field), and a "Search" button. A note below the search bar says "For example: Select type of search to load examples." At the bottom of the page, there's a section titled "Search Variants in ClinGen Allele Registry" with a "Type of search" dropdown and a "Query" input field.

This is a screenshot of a research article from Wellcome Open Research. The title is "Points to consider for sharing variant-level information from clinical genetic testing with ClinVar". The authors listed are Danielle R. Azzari, Erin Rooney Riggs, Annie Nienhaus, Laura L. Rodriguez, Emily K. Miller, Brandi Kattman, Melissa J. Landrum, Christa L. Mungall, and Heidi Rehm. The journal is COLD SPRING HARBOR Molecular Case Studies, and the article type is COMMENTARY. The text discusses the importance of data sharing between laboratories, clinicians, researchers, and patients for improving and standardizing in genomic medicine, encouraging genomic data sharing (GDS) as a key activity of the National Institutes of Health (NIH)-funded Clinical Genome Resource (ClinGen). It highlights the need for clear guidance on the clinical relevance of genes and variants for use in precision medicine and research. The article notes that data originating from each of the aforementioned stakeholder groups is represented in the ClinVar database, which is the primary source of genomic data used by the medical community. The article also discusses the role of ClinGen in developing tools to support health literacy by the National Center for Biotechnology Information at the NIH. Although public access to ClinVar is limited, the article emphasizes the importance of broad consent for broad data sharing from research participants, no clear guidance exists on the level of consent appropriate for sharing data from clinical samples. The article concludes by advancing knowledge. ClinGen has collaborated with ClinVar and the National Human Genome Research Institute to develop points to consider for clinical laboratories or sharing data from clinical samples with ClinVar. These points are available online and are consistent with the Common Rule. We provide 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 required.

This is a screenshot of a research article from Wellcome Open Research. The title is "Benefits of Sharing Variant Classifications and Evidence with ClinVar". The authors listed are Danielle R. Azzari, Erin Rooney Riggs, Annie Nienhaus, Laura L. Rodriguez, Emily K. Miller, Brandi Kattman, Melissa J. Landrum, Christa L. Mungall, and Heidi Rehm. The journal is COLD SPRING HARBOR Molecular Case Studies, and the article type is COMMENTARY. The text discusses the benefits of sharing variant classifications and evidence with ClinVar, emphasizing that sharing evidence as it evolves in a public, centralized database such as ClinVar can improve both our understanding of genomic variation and patient care that relies on this information. The article highlights that sharing variant classifications and evidence with ClinVar can help providers keep up-to-date. Directing inquiries to ClinVar for current knowledge can reduce resources needed to respond to inquiries on current variant classifications.

This is a screenshot of a research article from Wellcome Open Research. The title is "Improving Variant Classification". The authors listed are Danielle R. Azzari, Erin Rooney Riggs, Annie Nienhaus, Laura L. Rodriguez, Emily K. Miller, Brandi Kattman, Melissa J. Landrum, Christa L. Mungall, and Heidi Rehm. The journal is COLD SPRING HARBOR Molecular Case Studies, and the article type is COMMENTARY. The text discusses the challenges of improving variant classification, noting that ClinVar provides a broader set of clinical classifications than may have been assessed in the original study. The article highlights the importance of using ClinVar to incorporate new evidence and update classifications. It also discusses the use of ClinVar for research purposes, noting that ClinVar provides a valuable resource for researchers who want to use it for their own studies. The article concludes by stating that studies of clinical laboratory ClinVar submissions have shown that data sharing is a successful approach to prioritizing variant measurement and resolving classification differences.^{1–3}

Keep Providers Up-to-Date with Variant Knowledge

- ClinVar allows providers to keep up-to-date with variant knowledge and provides a central place for patients and scientists in the community to keep 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 uses automated 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 mechanism for variant interpretation.
- Clinical significance terms for Mendelian disorders are converted to standard ACMG-AMP categories (Pathogenic, Likely pathogenic, Uncertain significance, benign, benign). enabling comparison across studies.
- As many variants identified in Mendelian testing are extremely rare and thus unlikely to be re-observed, sharing variant interpretations in ClinVar can serve as an ongoing quality assurance measure for the systematic assessment of rare variants.

Publish as a Lab That Shares Data

- ClinGen recognizes submitters meeting minimum requirements for data sharing to support quality assurance (<https://www.clinicalgenome.org/submitter/>).
- Submitters are encouraged to attend ClinGen meetings and conferences for sharing data.
- Submitters are displayed on the ClinGen website (<https://www.ncbi.nlm.nih.gov/clinvar/submitter.html>).

This is a screenshot of a research article from Wellcome Open Research. The title is "Wellcome Open Research". The authors listed are Caroline F. Wright, James S. Ware, Anneke M. Lucasen, Alison Hall, Anna Middleton, Nazneen Rahman, Sian Ellard, Helen V. Firth, and Heidi Rehm. The journal is Wellcome Open Research, and the article type is COMMENTARY. The text discusses the Wellcome Open Research platform, highlighting its open access, peer-reviewed nature, and the fact that it is the first open access journal to be approved by the Wellcome Trust.

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

Caroline F. Wright¹, James S. Ware², Anneke M. Lucasen³, Alison Hall⁴, Anna Middleton⁵, Nazneen Rahman⁶, Sian Ellard⁷, Helen V. Firth^{8,9}

¹Institute of Biomedical and Clinical Sciences, University of Exeter, Exeter, UK
²National Heart and Lung Institute, Imperial Centre for Translational and Experimental Medicine, London, UK
³Department of Clinical Ethics and Law, Faculty of Medicine, University of Southampton, Southampton, UK
⁴949G Foundation, Cambridge, UK
⁵Faculty of Education, University of Cambridge, Cambridge, UK
⁶Connecting Science, Wellcome Genome Campus, Cambridge, UK
⁷Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN, USA
⁸Department of Clinical Genetics, University of Cambridge Addenbrooke's Hospital Cambridge, Cambridge, UK
⁹Wellcome Trust Sanger Institute, Cambridge, UK

Open Peer Review	
Referee Status:	?
Initiated References	1 2
version 1	?
version 2	?
report	✓
report	✓
Abstract	
Sharing de-identified genetic variant data is essential for the practice of genomic medicine and is demonstrably beneficial to patients. Robust genetic diagnostic and therapeutic interventions require access to high-quality, well-curated data 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 diagnosis and treatment. ClinGen has developed a framework for the sharing of variant-level data from clinical samples, while protecting the privacy of the patient and their family members. The benefits of sharing de-identified individual genetic variants, and the harms of <i>raw</i> sharing them, are numerous and well-established. Databases readily exist to support deposition of variants, but clarity and transparency around best practices are needed to prevent inconsistencies, immunize against individual privacy and ensure public trust. ClinGen has developed a framework for the sharing of variants associated with linked clinical information that facilitates in genomic medicine. Information robustly linking clinical variants to individual patients is critical for diagnosis and treatment, and therefore should not require consent to share. For details about individual patients or more extensive genomic data, ClinGen has developed a framework for the sharing of variants that can be more controlled-access model for data sharing, with the ultimate aim of making data widely available.	
First Published: 05 Feb 2019; 2(2) 15096 (1)	
Latest published: 05 Feb 2019; 2(2) 15096 (1)	
https://doi.org/10.12691/wellcomeresources.15096.1	
Abstract	
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Report	
1	Gert Matthijs ¹ , Utrecht, Belgium
2	Christina L. Martin, Geisinger Health System, USA
3	Erin Rooney Riggs, Geisinger Medical Center, USA
4	Heidi Rehm, Massachusetts General Hospital, USA
5	Broad Institute of MIT and Harvard, USA
6	Brighton & Hove and Harwell Medical School, USA

Groups continue to express need for a ClinVar Submission API



Identifying submissions to ClinVar from your country

ClinVar Miner

Welcome to ClinVar Miner!

The content on this website is current as of April 2019. At that time, ClinVar had 793,507 submissions on 501,786 variants. When referencing data from this website, please cite the 2018 Human Mutation article "ClinVar Miner: Demonstrating utility of a Web-based tool for viewing and filtering ClinVar data".

Data exploration	Conflict exploration	High-level trends
Variants by significance	Variants in conflict by significance	Total submissions by method
Variants by gene	Variants in conflict by gene	Total submissions by country
Variants by condition	Variants in conflict by condition	Significance terms
Variants by submitter	Variants in conflict by submitter	

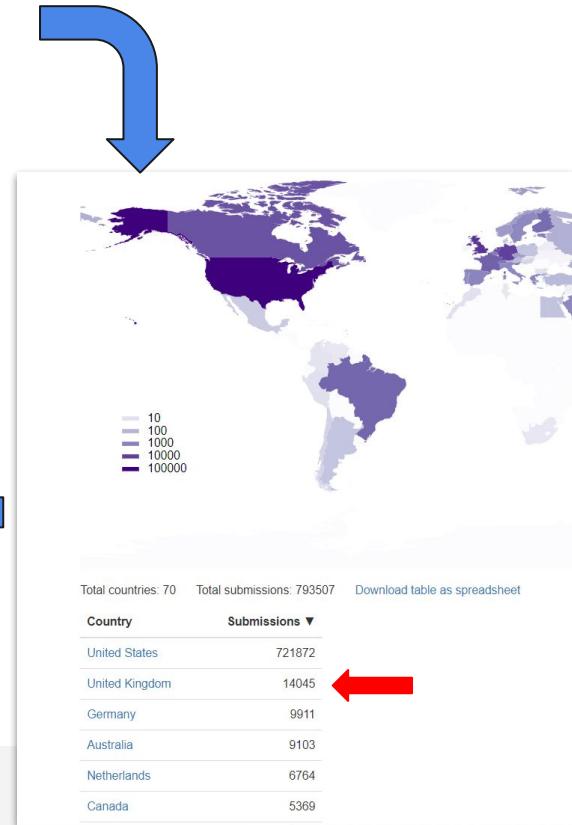
<https://clinvarminer.genetics.utah.edu>

Total submissions from United Kingdom

Minimum review status: Collection method:
Minimum conflict level:
 Apply filters ClinVar version: 2019-04

Total submitters: 55 Total submissions: 14045 [Download table as spreadsheet](#)

Submitter	Submissions
Consortium of Investigators of Modifiers of BRCA12 (CIMBA), c/o University of Cambridge	3326
International Society for Gastrointestinal Hereditary Tumours (InSiGHT)	2405
LDLR-LOVD, British Heart Foundation	1686
Tuberous sclerosis database (TSC2)	1671
Cardiovascular Biomedical Research Unit,Royal Brompton & Harefield NHS Foundation Trust	1523
Tuberous sclerosis database (TSC1)	603
NIHR Bioresource Rare Diseases,University of Cambridge	580
Medical & Molecular Genetics Group,University of Lincoln	448
Academic Unit of Haematology, University of Sheffield	383
Clinical Biochemistry Laboratory,Health Services Laboratory	318
PALB2 database	242
Centre for Genomic Medicine, Manchester,Central Manchester University Hospitals	198



Regulatory and Ethics Breakout Summary

**Bartha Knoppers
Tiffany Boughtwood
Clara Gaff, Christine Patch
Madeleine Murtagh**

International Context for Data Sharing

- EU General Data Protection Regulation (like it or not)
 - extraterritorial implications for international data sharing
- Legacy Data
 - as we move to clinical setting, new approaches necessary
- Waiver
 - distinct from research ethics waiver
 - ?? no consent required if part of 'genomic' medical care



Summary – Electronic & Dynamic Consent for Research

E-consent is not just an electronic representation of a research participant's consent documentation {enriched educational content; means of communication; mechanisms to evaluate participant comprehension of info}

Dynamic consent extends e-consent to incorporate the **means for a participant to change consent choices in real time.**

Benefits - For **patients**: more **appropriate, granular and flexible** consent options; access to better study and educational information, communication with researchers, **building trust**.

For **research organisations**: improved **consent records, retention of participants, clearer data sharing** frameworks, potentially **enriched self-reported data**.

Considerations - **Data** protection, storage and archive; **validity** of participant identification and e-signature; **administrative burden** (researcher, participant); **consent fatigue**; participant **access to technology**.

Research use of clinical data

- NHS establishing a new consent process ‘Record of Discussion’
Australia Genomics piloting a national consent form and patient info
- Evolving regulatory environment
- Variation in approach e.g. use of information for others/family
- Important to consider how consent operations will be operationalised - withdrawal/change; childhood to adult transition; converting paper into electronic information

Responsible, respectful, proportionate: graduated data access for complex, linked data

- Graduated data access; calibrated to potential data risks, sensitivity and/or ethical issues
 - Risks = privacy/disclosure, alienating participants, reputational damage to the study
 - Other ethical issues, e.g. RoR
- A mixed economy of data access governance
 - Tech mediated (potential) = Registered access; Light touch/administrative DAC;
 - Human mediated = Proportionate review; full DAC consideration
- Participant and public engagement
 - Participants involved in co-producing access policies and access decisions
 - Public communication
 - Impact = better decisions, more aligned with participant experiences, values and expectations



Next REWS steps for future genomic medicine interoperability

- Framework for the responsible sharing of genomic and health related data
- Revisiting 2015 research privacy/consent policy* templates and clauses
- Creating **generic research** privacy/consent clauses
 - To be customised as needed for clinical data collection and sharing
- Creating **generic clinical genomics** privacy/consent clauses for data collection and data sharing
- Adding terms to Lexicon (e.g GDPR terms)
- Preparing new IP policy, including considerations for open science/health

Four things for the NIs group to progress

1. Active engagement in review and revision of the REWS tools (=5 tools!)
2. Share clauses relating to use/communication to family
3. Share clauses relating to use of data/results for others
4. Share clauses relating to sharing of the data for research

Sharing Resources:

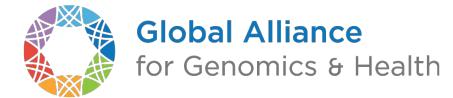
Panel discussion on moving from research into clinical care

—

Chair: Kathryn North

Speakers: Sue Hill, Peter Goodhand, Anna Middleton, Clara Gaff,
Heidi Rehm, Zornitza Stark

The world is changing



Percentage of whole genomes and exomes
that are funded by **healthcare** systems

2012

~1%

2018

~20%

2022

>80%

Areas of clinical uptake: infectious disease, cancer, rare disease,
common/chronic

How big is healthcare - worldwide



MRI – (\$400-\$4,000)

100 million scans - pa

PET/SPECT (\$1000-\$6,000) 50 million scans - pa

Opportunities



If we can enable secondary use of clinical genomic data for research we will have a >60 million virtual cohort by 2025.

Global genomic data sharing can lead to...

- Demonstrated patterns in health and disease
- Increased statistical significance of analyses
- Matching other / similar patients, leading to increased diagnoses
- ‘Stronger’ variant interpretations
- More informed clinical decisions



150+ Genomic Data Initiatives Globally



CLINICAL/GENOMIC
MEDICINE



RESEARCH



NATIONAL



COHORTS



Initiatives



Initiatives



from 15 countries



globally

HTA – Government decision making



- Geisinger/Regeneron – fund exomes and evaluate in practice
- Kaiser Permanente – very diligent HTA pre introduction
- Canadian clinical genomes for RD diagnosis or large panels for cancer
 - Several provinces - re-patriate “out-of-country tests” optics vs budget control; secondary use for research versus rather than pdf report; build the competency and capacity in hospital labs versus cost, speed, clinical certification; over capacity in research sequencing but lab not certified for clinical use
 - Other provinces no experience with clinical NGS- only research experience; ministries of health need clear, well articulated case with HTA that they will regard as valid and the competency/capacity – Pop scale 8.5 m vs ~1m or <
 - Work force, wait list, diagnostic odyssey, early identification, role of AI

Five times the diagnosis, one quarter the cost

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ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders

Zornitza Stark, MD¹, Tiong Y. Tan, MD, PhD^{1,2}, Belinda Chong, PhD¹, Gemma R. Brett, MSc, MGenCouns^{3,4}, Patrick Yao, MD¹, Maile Walsh, MD¹ Alison Yeung, MD¹, Heidi Peters, MD, PhD^{1,2,4}, Dylan Mordaunt, MD^{1,2,4}, Shannon Cowie, BSc¹, David J. Amor, MD, PhD^{1,2}, Ravi Savarirayam, MD^{1,2}, George McGillivray, MD¹, Lillian Downie, MD¹, Paul G. Ekeret, MD, PhD^{1,2}, Christiane Theda, MD, PhD^{1,2}, Richard A. James, MD, PhD^{1,2}, Joy Yapil-to Lee, MD^{1,4}, Monique M. Ryan, MD^{1,2}, Richard J. Lewinter, MD, PhD^{1,2}, Emma Creech, MGenCouns^{3,4}, Ivan Maciocca, BSc, MHSc¹, Katrina M. Bell, PhD¹, Alicia Oshlack, PhD¹, Simon Saeedan, BSc, BEng¹, Peter Georgeson, BEng, BMATH¹, Charlotte Anderson, BSc, NRke¹, Natalie Thorne, PhD^{1,2}, Melbourne Genomics Health Alliance, Clara Gaff, PhD^{1,2}, Susan M. White, MD^{1,2}

© American College of Medical Genetics and Genomics

ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of usual care overwhelmingly supports early use and reimbursement

Zornitza Stark, MD¹, Deborah Schofield, PhD^{1,2}, Khurshid Alam, PhD^{1,4}, William Wilson, PhD^{1,5}, Nessie Mupfeki, MHIM^{1,6}, Ivan Maciocca, MHS^{1,5}, Rupendra Shrestha, PhD¹, Susan M. White, MD^{1,4,5} and Clara Gaff, PhD^{1,5}

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ARTICLE | Genetics inMedicine

Does genomic sequencing early in the diagnostic trajectory make a difference? A follow-up study of clinical outcomes and cost-effectiveness

Zornitza Stark, BMBClin DM^{1,2,3}, Deborah Schofield, PhD^{1,4,5}, Melissa Martyn, PhD^{2,3}, Luke Rynehart, BEcon¹, Rupendra Shrestha, PhD¹, Khurshid Alam, PhD^{1,3,6}, Sebastian Lunke, PhD¹, Tiong Y. Tan, MBBS PhD^{1,2,3}, Clara L. Gaff, PhD^{1,2} and Susan M. White, MBBS^{1,3}

Melbourne Genomics Health Alliance

Design Gaff et al, (2017) *npj Genomic Medicine* 2: Article 16



Prospective comparison of diagnosis

- 80 children <2 years of age
- Features of known mendelian conditions
- **58% diagnosis vs 11% in standard care**

Cost effectiveness study of first 40 children

- **Cost per diagnosis \$5047 vs \$27050 std care**
- Incremental saving of \$2,181 per additional dx
- Bootstrapped & sensitivity analysis

Follow up cost utility study

- **Cost saving of AU\$1,578 per QALY gained**
- No increase in hospital service use.

Evaluation for effective education

Genetic specialists: Current practice and workforce



Other medical specialists: needs, practice, preference



Surveying medical specialists about their practice and training in genomics

Information and consent to participate

This survey is an activity of the Workforce & Education Program of the Australian Genomics Health Alliance (Australian Genomics). Australian Genomics is a NHMRC-funded national network working towards the development of genomic medicine within Australia. The Workforce & Education Program aims to investigate current and future education and training needs of the workforce in genomic medicine.

This survey has three aims:

Tools to assist genomic education design and evaluation

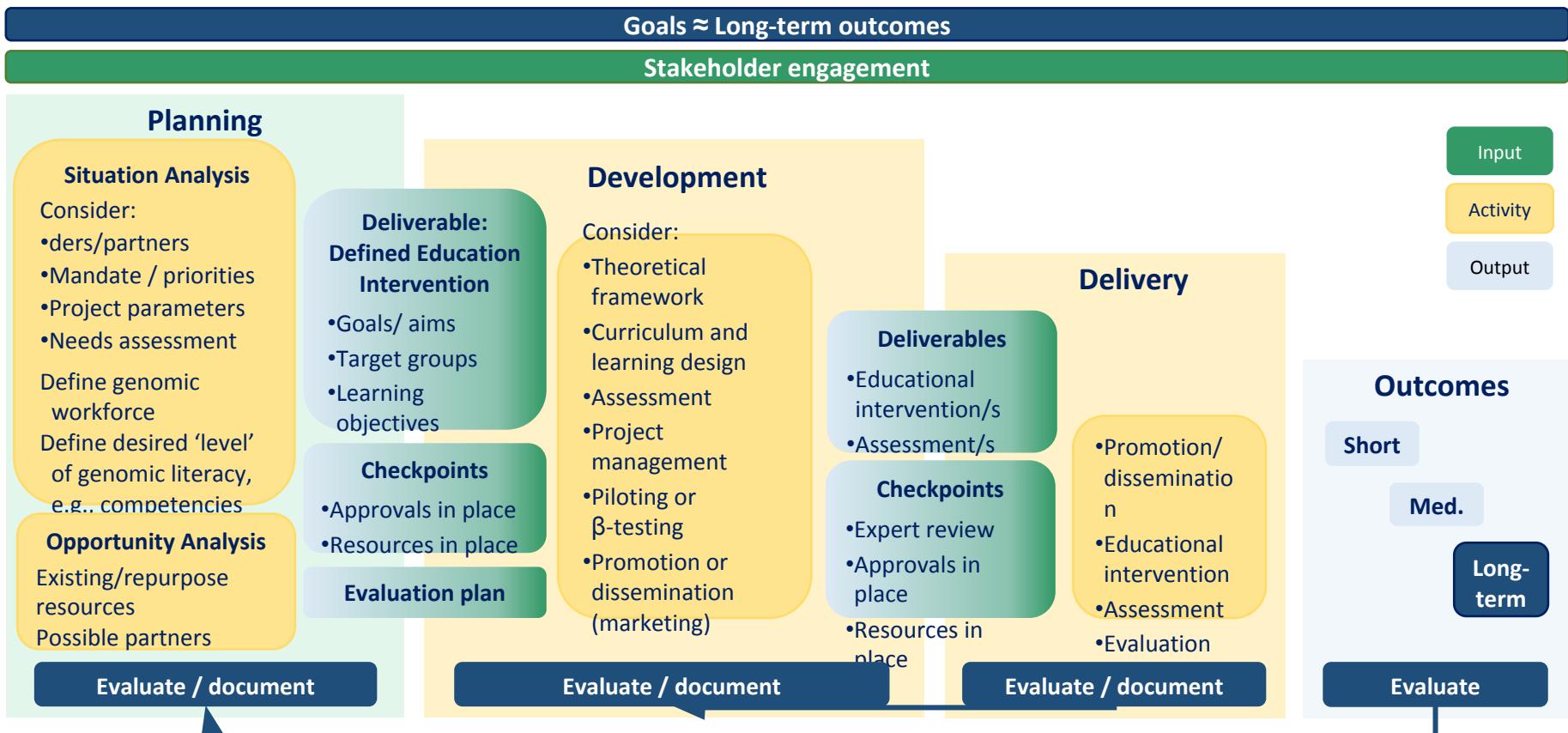


Research Topic



Educating Health Professionals in Genomic Medicine: Evidence- Based Strategies and Approaches

Program logic + evaluation framework for genomic education



100,000 Genomes Project: structured to build the approach for future care

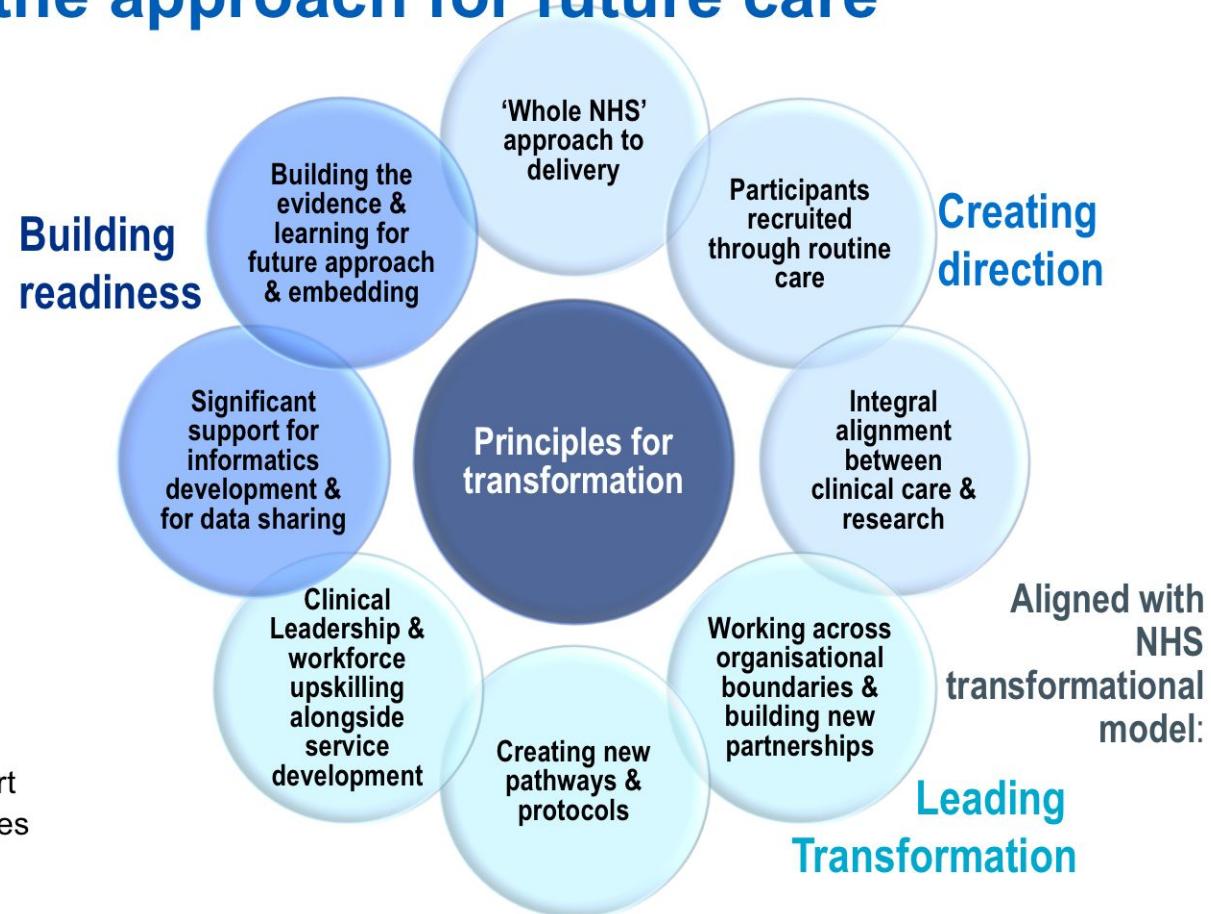
Proof of concept through
the 100,000 Genomes Project

4 principles

1. WGS extends current diagnostic scope
2. Recruitment from routine care, treated through routine channels
3. Participants consent to sharing of de-identified data for R&D & industry use & longitudinal access
4. Establishes model for transformational change

4 key legacies

1. Increased discovery of new pathogenic variants
2. Integrating advanced genomics into mainstream NHS
3. Increasing public understanding & support
4. Stimulating and advancing UK life sciences industry



Governance

Ministerial:
National
Genomics Board

NHS & GeL:
Partnership Board

NHS England:
SRO – Genomics
Programme Board

NHS England:
Service Partnership
Boards (GMC/GLH)

Five Year Forward View 2014

100,000
Genomes
Project 2013



Improving outcomes through Personalised Medicine 2016 (PM framework)

CMO: Generation
Genome 2016
(societal engagement)



Building on our
Inheritance 2012
(lab reconfiguration)



Policy & Strategy Alignment

National Genomic
Healthcare
Strategy
to come 2019

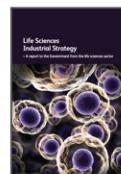


NHS Interim
Workforce Plan 2019
(implementing LTP
inc genomics req'mts)



NHS Long Term Plan 2019
(500k WGS; improved cancer offer; CVD)

Life Sciences Industry
Strategy 2017



NHS England Board:
Genomic Medicine
Service 2017
(approval for service)



CMO: Better
Health Within Reach 2018
(data-led healthcare)



(500k WGS; improved cancer offer; CVD)

Making the case for genomics



COST/BENEFIT

- Understanding cost of multiple sequential testing/ unwarranted variation & establishing activity
- Replacement of outmoded technologies – enhanced diagnostic yield above SoC
- Made clinical & economic case for both non-WGS & 500K WGS in mainstream care & mechanism for annual review & prioritisation
- Gained tripling of investment in genomics over next 5 years & centralisation of budgets

QUALITY & OUTCOMES

- Improving care in key national clinical priority areas (Cancer/ Rare Disease/CVD/Acute Care)
- Supporting and linking with personalisation/ medicines optimisation & ADR reduction (*NHS drugs budget £17bn pa*)
- Established principle & buy in for single national approach, protocols, standards, datasets, data sharing, IG, metrics & scrutiny (quality dashboard) *inc National Genomics Testing Service & National Genomics Test Directory*

DELIVERY & SERVICE MODEL

- Established WGS deliverability and requirements for whole infrastructure (inc non-WGS) with NHS informatics and data developments
- Service & human cost of diagnostic odyssey
- Reducing inequity and unmet clinical need
- Demonstrated value of new models of care and how existing services could be consolidated & networked

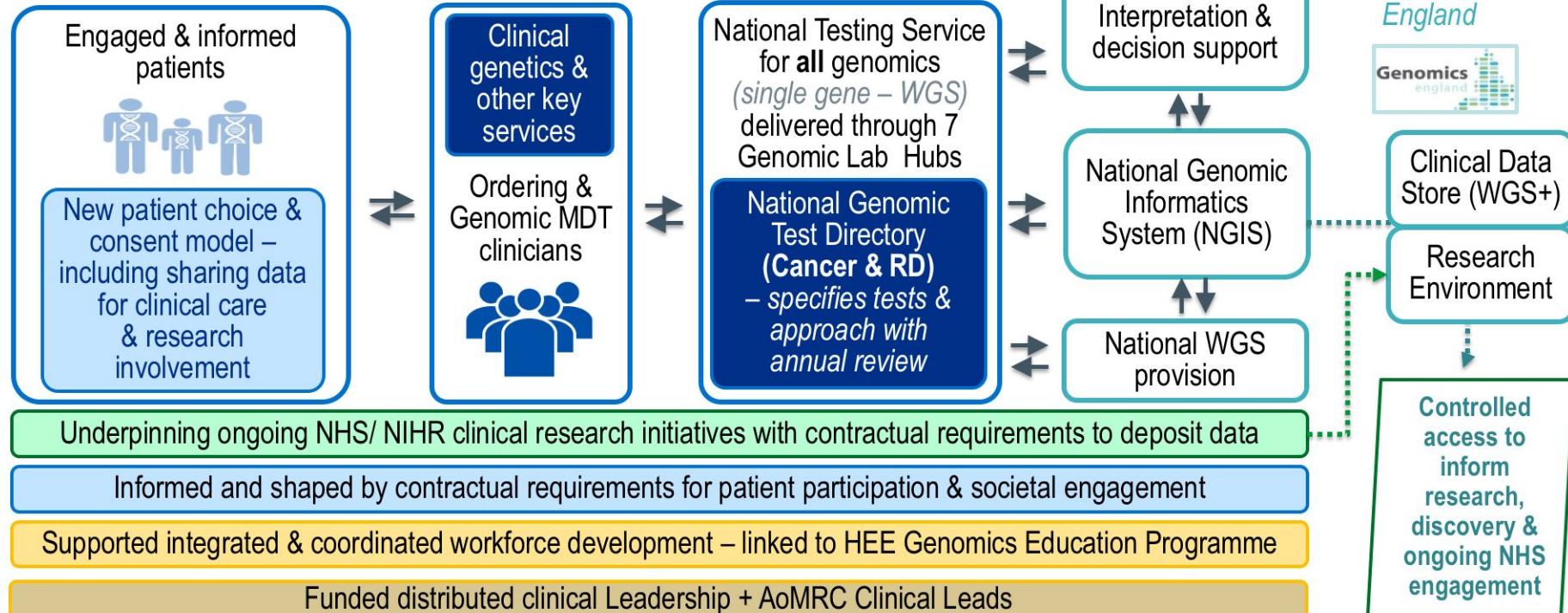
The new national genomic infrastructure



System Contracts & Budgets, Strategic Planning & Coordination, Standards, Clinical Policies, Assurance, Delivery & Improvement



Coordination, engagement & networks through contracted NHS Genomic Med Centres til 2023/4



Developing the health system workforce alongside service transformation



The Genomics Education Programme was established in 2014 to run alongside the developments in genomic medicine services to driving training and upskilling for the **entire 1.3 million NHS** workforce

The GEP provides a wide range of free-to-access resources to provide an '**anytime, anywhere, anywhere**' approach to education – tailored to suit the range of professional requirements, the extent and time available for learning & the immediate need for education

Central to the programme is the multiprofessional **Masters in Genomic Medicine** (& associated CPD modules) and specialist commissioned training places (eg Bioinformatics & genomic counselling) + undergraduate & postgraduate training curricula



Resources and material at genomicseducation.hee.nhs.uk and www.futurelearn.com

Resources show huge reach

50,000+ total staff reached

1400+ Masters framework places

1.5million+ web page views

460,000+ resource views

34,440 course registrations

19,600+ MOOC registrations

Public Engagement

Prof Anna Middleton

Wellcome Genome Campus, Cambridge, UK

www.wgc.org.uk/ethics

Public engagement is **not** education

It is:

Making a connection, Building a bridge

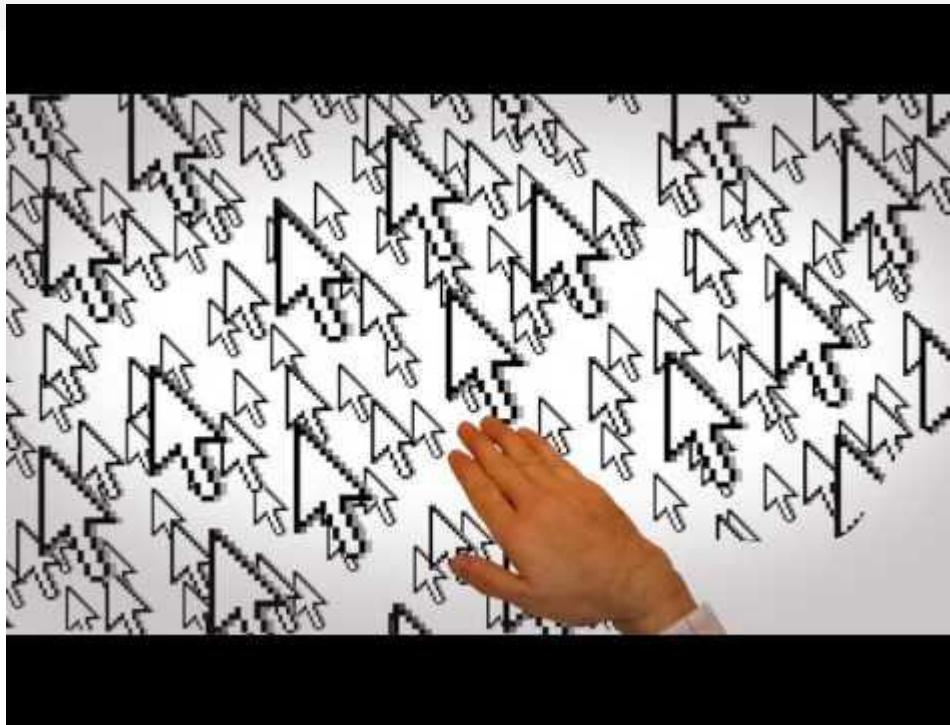
No scientific jargon, but culturally acceptable metaphors

Different engagement for publics and patients

We already have 50+ GA4GH films on genomic data sharing, translated into 14 languages, plus 20 other films in English (incidental findings, genetic counselling terms etc)

Light touch, google search as a metaphor for sequencing

Prof Anna Middleton
Wellcome Genome Campus, Cambridge, UK
www.wgc.org.uk/ethics

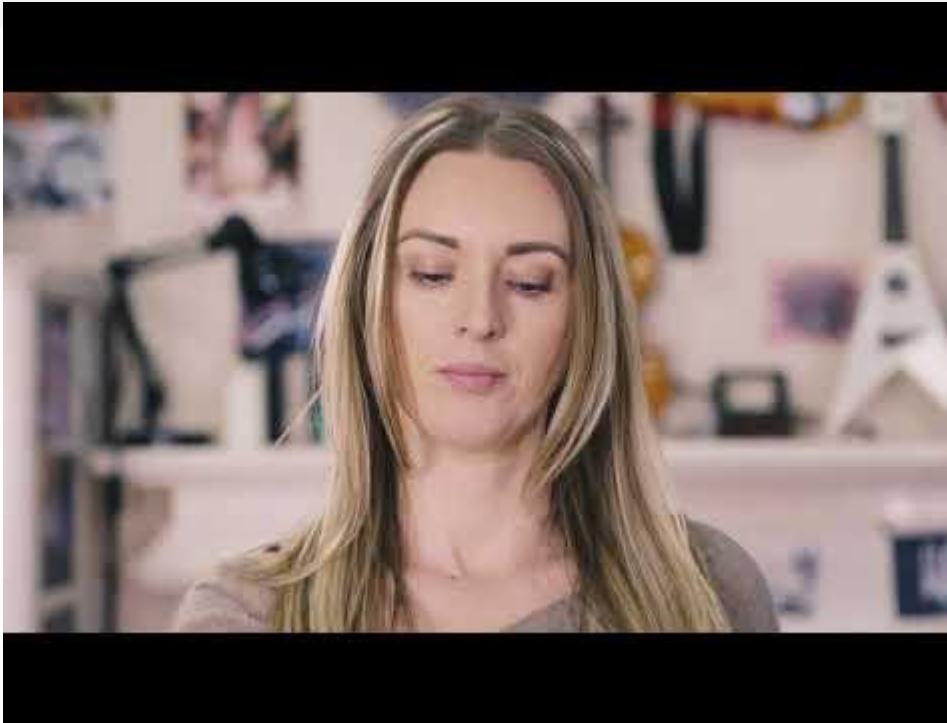


Global Alliance
for Genomics & Health



Deeper connection, dominant inheritance, used within clinic

Prof Anna Middleton
Wellcome Genome Campus, Cambridge, UK
www.wgc.org.uk/ethics



Global Alliance
for Genomics & Health



Closing Remarks

Kathryn North
Australian Genomics

Mark Caulfield
Genomics England



Breakout leads: Priority Toolkit Inclusions



- Clinical Data Capture and Exchange
Zornitza Stark
- Genomic Data Access and Sharing
Oliver Hofmann
- Curation
Heidi Rehm
- Regulatory and Ethics
Clara Gaff



GA4GH 7th Plenary Meeting

Boston, USA

Oct 21 - 24, 2019

bit.ly/GA4GH2019



GA4GH Connect Implementation Meeting

Germany

March 25 - 27, 2019



GA4GH 8th Plenary Meeting

Melbourne, Australia

Sep 30 - Oct 2, 2020