GENOMICS IN HEALTH
IMPLEMENTATION FORUM

Opening Remarks: Day 2

Kathryn North and Mark Caulfield

Agenda – Day 2

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

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

We encourage you to participate!

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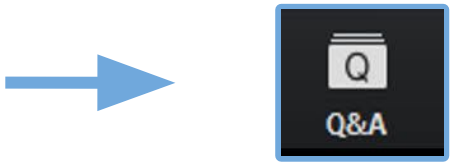
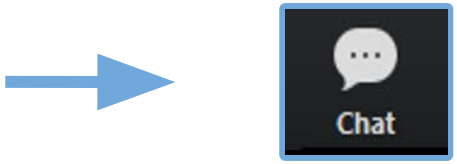
Please use **Q&A** to ask questions during plenary sessions



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

Continue discussions using **Chat**

Please ensure your message is set to “All panelists and attendees”



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Clinical Data Exchange - Pedigree and Family Health History

Global Alliance
for Genomics & Health

Collaborate. Innovate. Accelerate.

Genomics in Health Implementation Forum 2021

Clinical and Phenotypic Data Capture & Exchange –

Pedigree & Family Health History

Intro to the GA4GH Pedigree Standard and Upcoming Connectathon

Grant Wood, Orion Buske

A Recommendation for a Minimum Data Set for Family Health History

Global Alliance for Genomics & Health

Background – The original peer-reviewed paper was published in December 2008

GA4GH driver projects and other interested parties in GA4GH have expressed interest in a pedigree standard that supports their wide-ranging use cases

A recommendation to follow for the development of new data collection tools, storage, and solutions

Builds upon existing standards like PED and HL7 FHIR

Support the community of GA4GH (which includes healthcare, research, patient advocacy, life science, and information technology), in expanding their collection, study, use, and especially sharing, of FHH information.

A Recommendation for a Minimum Data Set for Family Health History

Global Alliance for Genomics & Health

Data Elements: Pedigree

Element Name	**R**equired **O**ptional	PED column	FHIR name	Notes
Family ID (Pedigree ID)	R	Col. 1 Family ID	FamilyMemberHistory. identifier	This is used when distinct family records are defined then shared. Also can be thought of as the Pedigree ID.
Proband ID	O / R		Patient <id value = "proband" Or New extension to include a Proband type	Only required when the pedigree is used to focus on heritable risk for a specific person in the pedigree. For other use cases such as research, a Proband type may be needed. The FHIR resource ResearchSubject.identifier includes the following status choices: follow-up, ineligible, not-registered, off-study, on-study, on-study-intervention, on-study-observation, pending-on-study, potential-candidate, screening, and withdrawn.
Pedigree Source metadata	O		FamilyMemberHistory. Meta Or FamilyMemberHistory. reasonCode	Possible uses are, but not limited to, where did the pedigree come from, tool or method used, clinical or patient entered, research identifier.
Status	O		FamilyMemberHistory. status	From FamilyHistoryStatus choices are: partial, completed, entered-in-error, and health-unknown.
Language	O		FamilyMemberHistory. language	The codes SHOULD be taken from Common Languages.
Narrative	O		FamilyMemberHistory. text	A human-readable narrative that contains a summary of the resource and can be used to represent the content of the resource to a human. Resource definitions may define what content should be represented in the narrative to ensure clinical safety.
Date of FHH data collection	O		FamilyMemberHistory. date	Date should be the latest date of when any data is updated.

A Recommendation for a Minimum Data Set for Family Health History

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Data Elements: Individual

Element Name	Required Optional	PED column	FHIR name	Notes
Individual ID	R	Col. 2 Individual ID	Need to add to FamilyMemberHistory	An 'Individual type' (not type of ID) may be needed. This could include the individual's electronic medical record identifier, genealogical record identifier, could be the person is only represented via their lab sample identifier, or person information is missing or unknown (just have a relationship), or person information is private/hidden based on a consent choice, or the same individual and/or Individual ID is found in other pedigrees.
Father ID	R	Col. 3 Paternal ID	FamilyMemberHistory. extension:Parent	Must be an Individual ID
Mother ID	R	Col. 4 Maternal ID	FamilyMemberHistory. extension:Parent	Must be an Individual ID
Biological Sex	R	Col. 5 Sex	FamilyMemberHistory. sex	This element should ideally reflect whether the individual is genetically male or female (chromosomal sex). See AdministrativeGender and Patient Gender and Sex.
Person Gender	O		Person.gender	The gender might not match the biological sex as determined by genetics, but the individual's preferred identification.
Human Name Given	O		FamilyMemberHistory. name	Datatype is HumanName, includes Given name, and subsequent Given names for middle names.
Human Name Family	O		FamilyMemberHistory. name	Datatype is HumanName, includes Family name
Relative Relationship	O		FamilyMemberHistory. Relationship	See HL7 v3 Value Set FamilyMember and CodeSystem: RoleCode

The table shown is a subset - Also includes elements like individual age, disease, disease age of onset, disease contributed to death, adoptive status, multiple birth status, consanguinity, etc.

Issues on collecting Race, Ethnicity, or Ancestry

- Multiple ontologies to choose from that match specific use cases
- US based ontology has long list of native American tribes
- Another ontology is geographically based
- In South Africa they combined a tribe with a language
- We need codes for the different ontologies

Multiple formats and methods exist for the capturing of these data elements

- General or disease specific (e.g., cancer, etc.), clinical, research, or patient-facing
- Form, survey, or questionnaire
- Graphical creation of a pedigree. These tools follow the genealogical method of building a family tree, but then add medical histories for each family member on that tree.
- The Pedigree Standardization Work Group (PSWG) of the National Society of Genetic Counselors (NSGC) developed a system for a clinical pedigree nomenclature.
- Pedigree derived from the patient electronic medical record
- Chatbot technology has been applied to the questionnaire format to guide people in gathering a complete history.

A Recommendation for a Minimum Data Set for Family Health History

Global Alliance for Genomics & Health

Other Data Elements to Consider (listing some examples)

- *Data sharing status* - interoperability capability with other systems

- *Consent status or record* - may be required in some use cases, especially if names and DOB's are shared

Other Data Elements to Consider (listing some examples)

- Representation of marital or partner status and other relationship qualities (e.g., estranged, close, household member)
- *Extension.extension:Source (FHIR)* - In what way the disease, condition, race, ethnicity, ancestry is reported (e.g., patient reported, genetic test, EMR record, public records like death certificate or disease registries, clinical trial or research, other, unknown).
- *FamilyMemberHistory.condition.outcome (FHIR)* - Indicates what happened following the condition. If the condition resulted in death, the deceased date is captured on the family member.

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Other Data Elements to Consider (listing some examples)

- *Genetic observations* – General genomic reporting, Variant reporting, Pharmacogenomic reporting, Somatic reporting (FHIR profiles)
- *Pedigree analysis results* – Analysis result, Probability, Percentage risk, Relative risk (HL7 Version 3, needs to be developed as a FHIR profile)

Why PED is not enough

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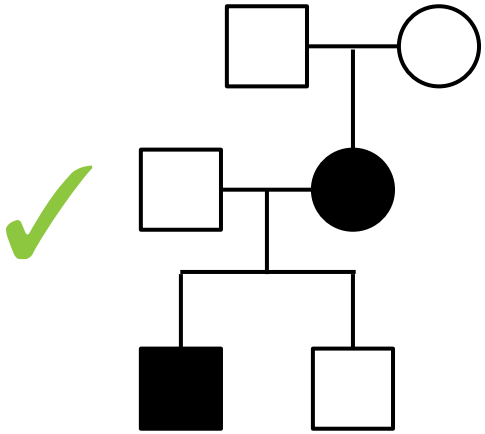

- basic parent-child

- twins
- adoption
- separation, donors
- consanguinity
- pregancy/fetus/miscarriage
- alive/deceased
- multiple phenotypes
- data provenance

Necessary for **counseling**, **risk assessment**, and **genomic interpretation**

Standardizing collection and interoperability

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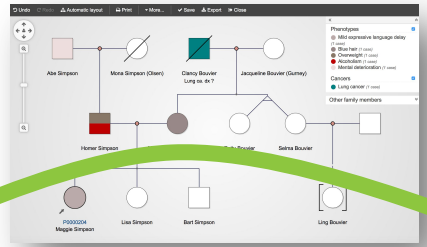
Self-reported by patient/family

or

Genetics consult

Collection tools



PHENOTIPS

monarch INITIATIVE
DISEASE DISCOVERY & DIAGNOSIS

hpo

REDCap
Research Electronic Data Capture

Australian Genomics Health Alliance

EHR/EPR

Clinical decision support

Genetic testing

Graph-based conceptual model

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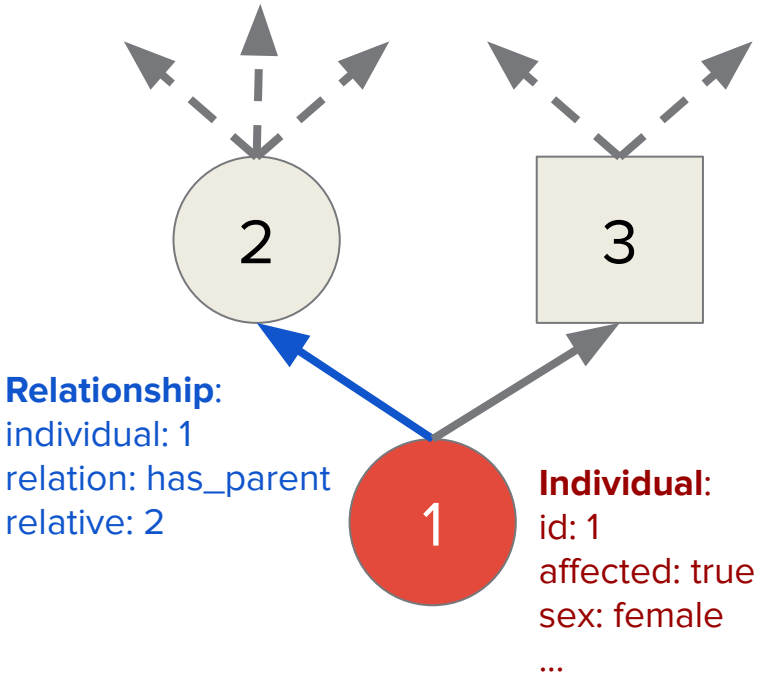
Directed graph: nodes are individuals and arrows are relationships



1. Superset of 6-column **PED format**
2. Optional genderless **relationship vocabulary** distinguishes biological and social relationships
3. Graph structure allows specifying arbitrary relationships
4. Easy-to-use **within the context of other standards** such as FHIR or Phenopackets
5. Simplifies converting a genetic family history from **one proband to another**

Use by related standards

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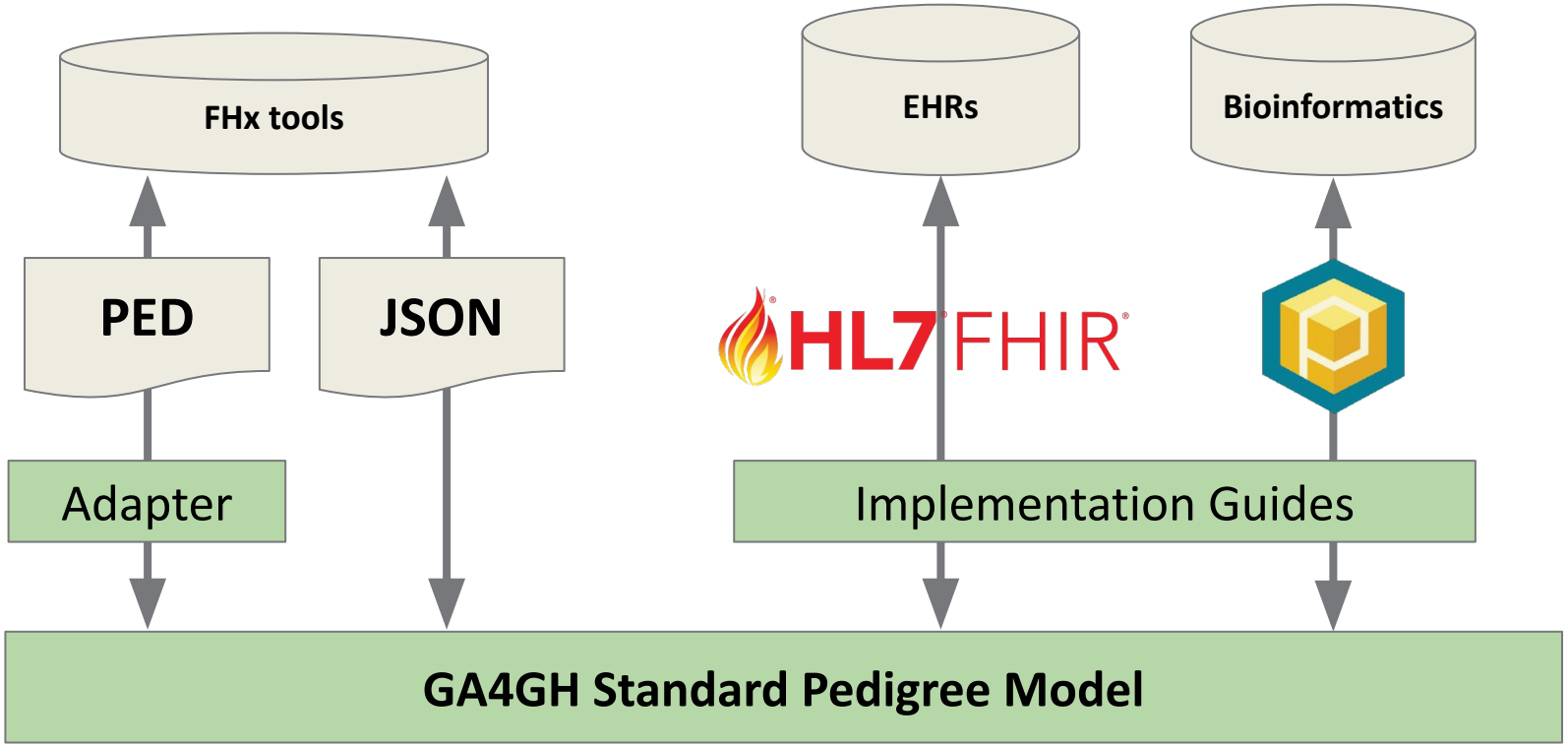

Learn More

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Participate in the Pedigree Connectathon to test interoperability with Phenopackets v1.1, HL7 FHIR: April 1 @ 19:00 UTC

Registration: bit.ly/PedigreeConnect

GitHub: https://github.com/ga4gh-cp/pedigree (proposal is PR)

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Clinical Interoperability of Variant Evidence

Alex Wagner (VICC/Nationwide) &
Larry Babb (Broad Institute)

Precision Medicine

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Assayed DNA

Clinical Genomic Variant Report

Patient Care

The Interpretation Bottleneck

Problem: NGS has been largely automated but **clinical interpretation of genomic alterations remains a major bottleneck** for realizing precision medicine

Variant Centric

Variant Evidence Collection

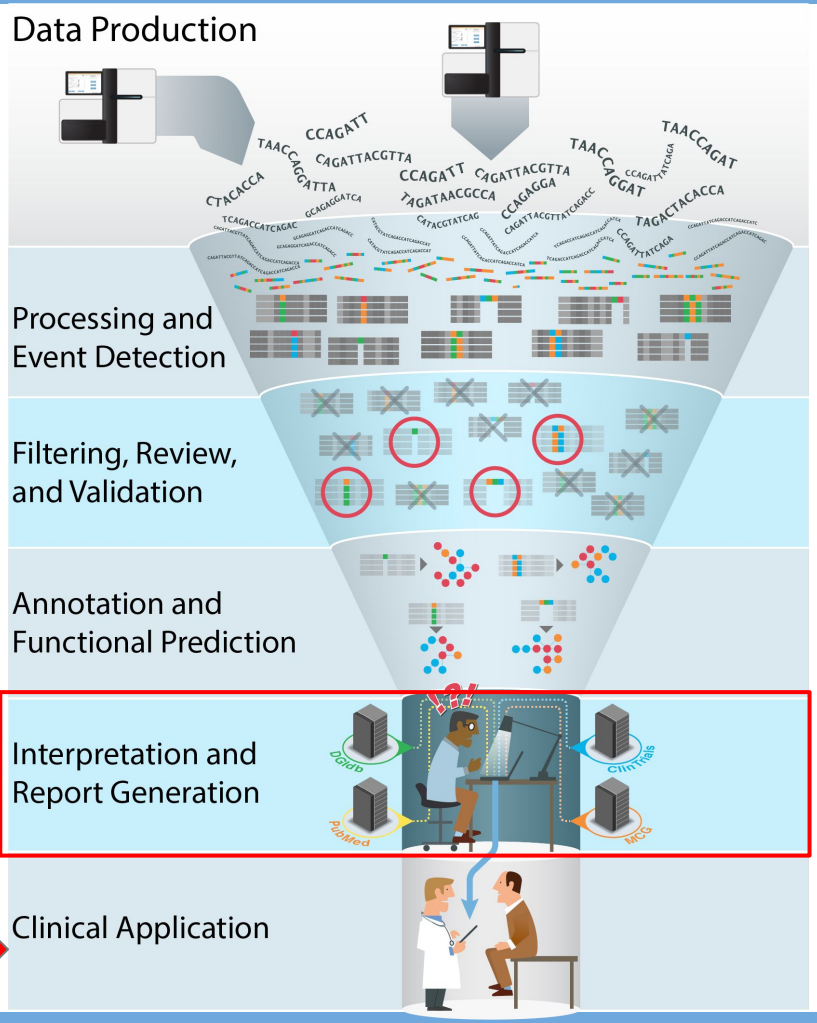
Variant Classification

Case Centric

Observed Variant Findings

Variant Interpretation

Knowledge Update Alerting



Good BM, Ainscough BJ, McMichael JF, Su AI†, Griffith OL†. 2014. Genome Biology. 15(8):438.

ClinGen + VICC Driver Project Initiative

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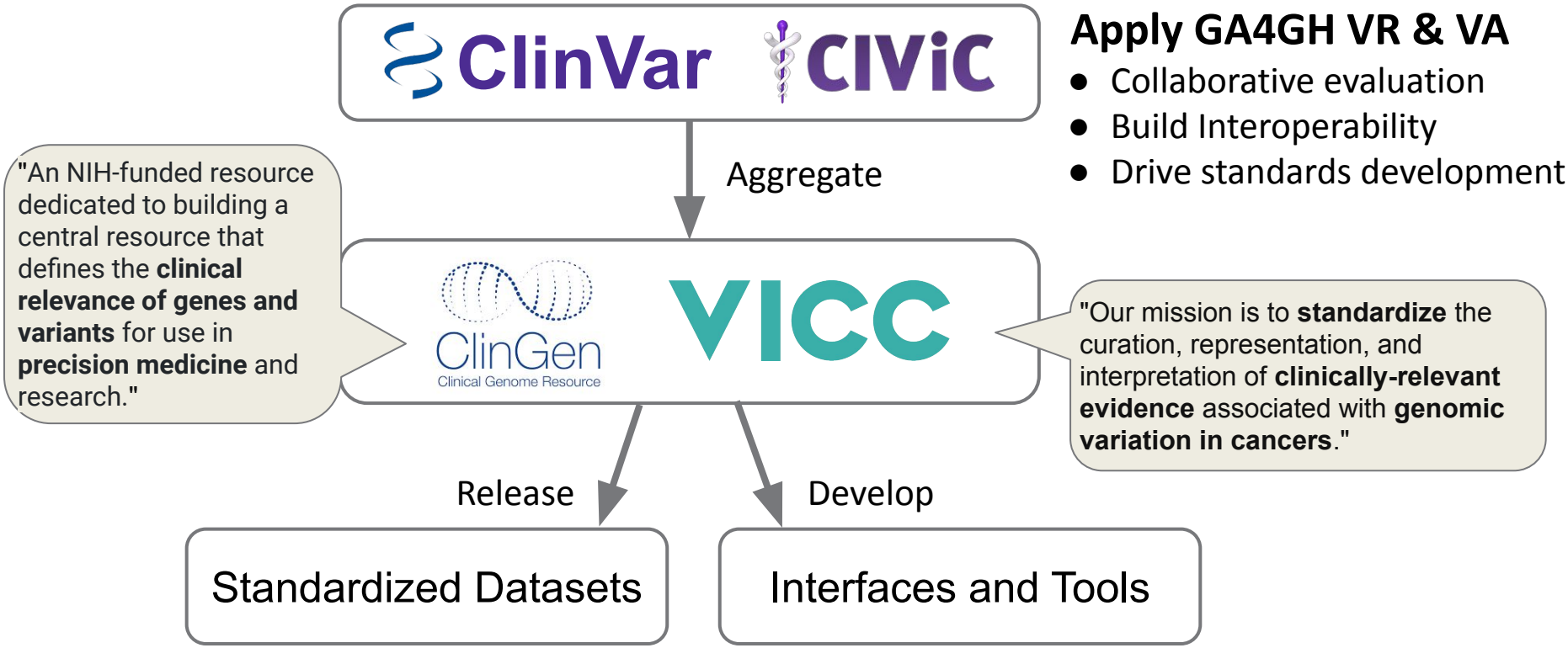
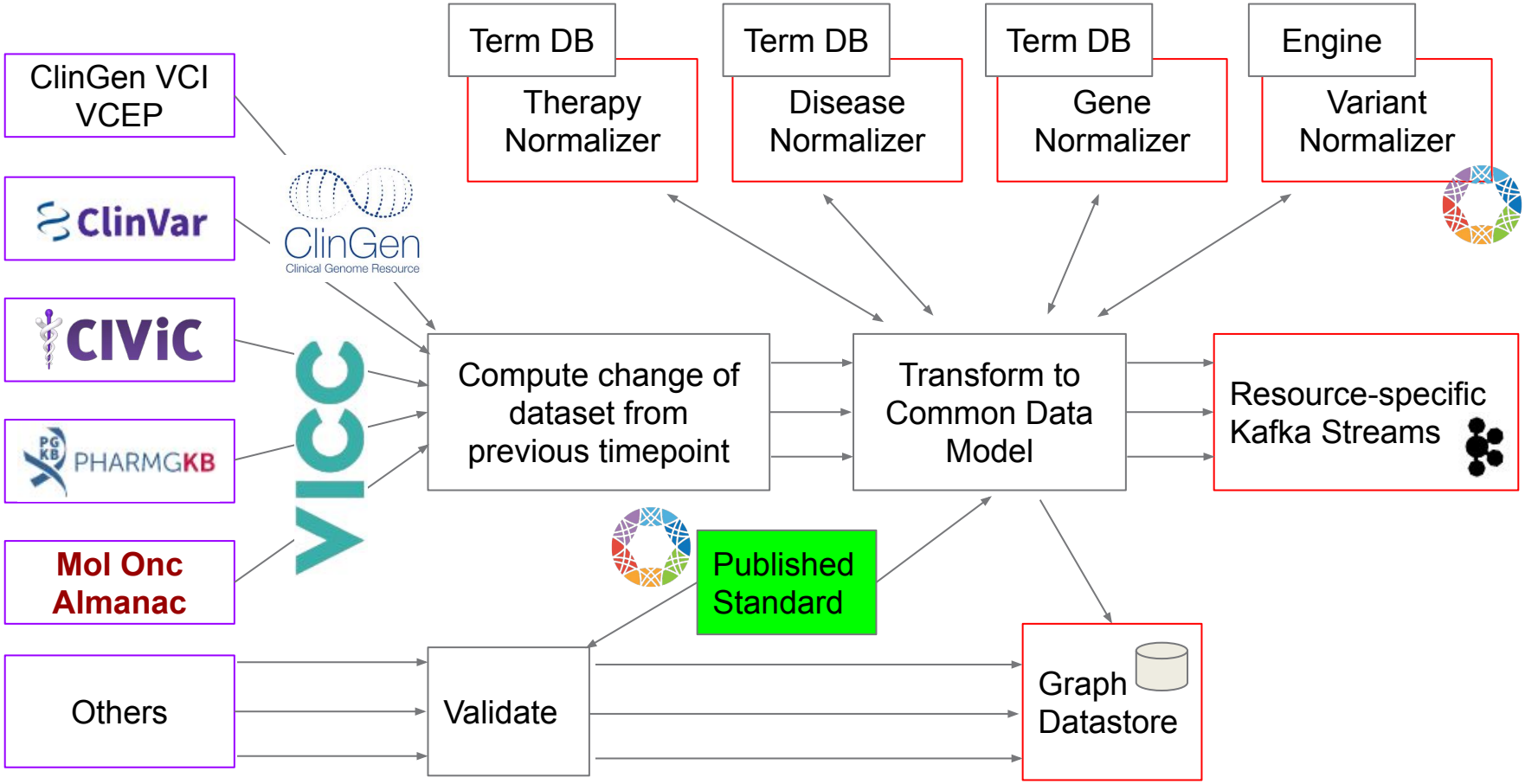


Apply GA4GH VR & VA

- Collaborative evaluation
- Build Interoperability
- Drive standards development


ClinGen VCI VCEP
ClinVar
CIViC
PHARMGKB
Mol Onc Almanac
Others
ClinGen
Clinical Genome Resource
VICC
Term DB
Therapy Normalizer
Term DB
Disease Normalizer
Term DB
Gene Normalizer
Engine
Variant Normalizer
Compute change of dataset from previous timepoint
Transform to Common Data Model
Resource-specific Kafka Streams
Published Standard
Validate
Graph Datastore

So why is it so hard?

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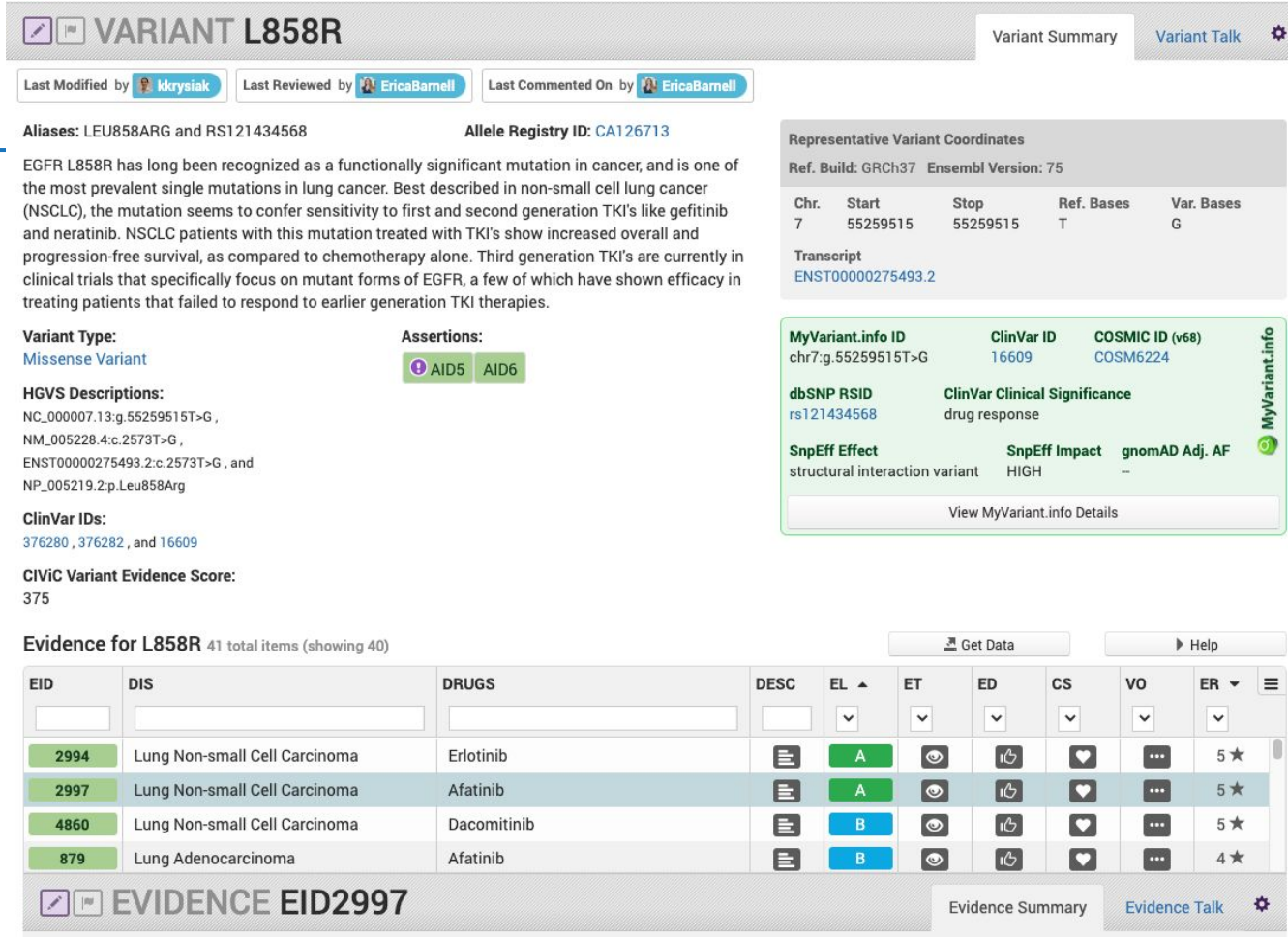
Let's take a look at interoperability between

CIViC and **ClinVar**

variant representations

to demonstrate the complexities

CIViC Record



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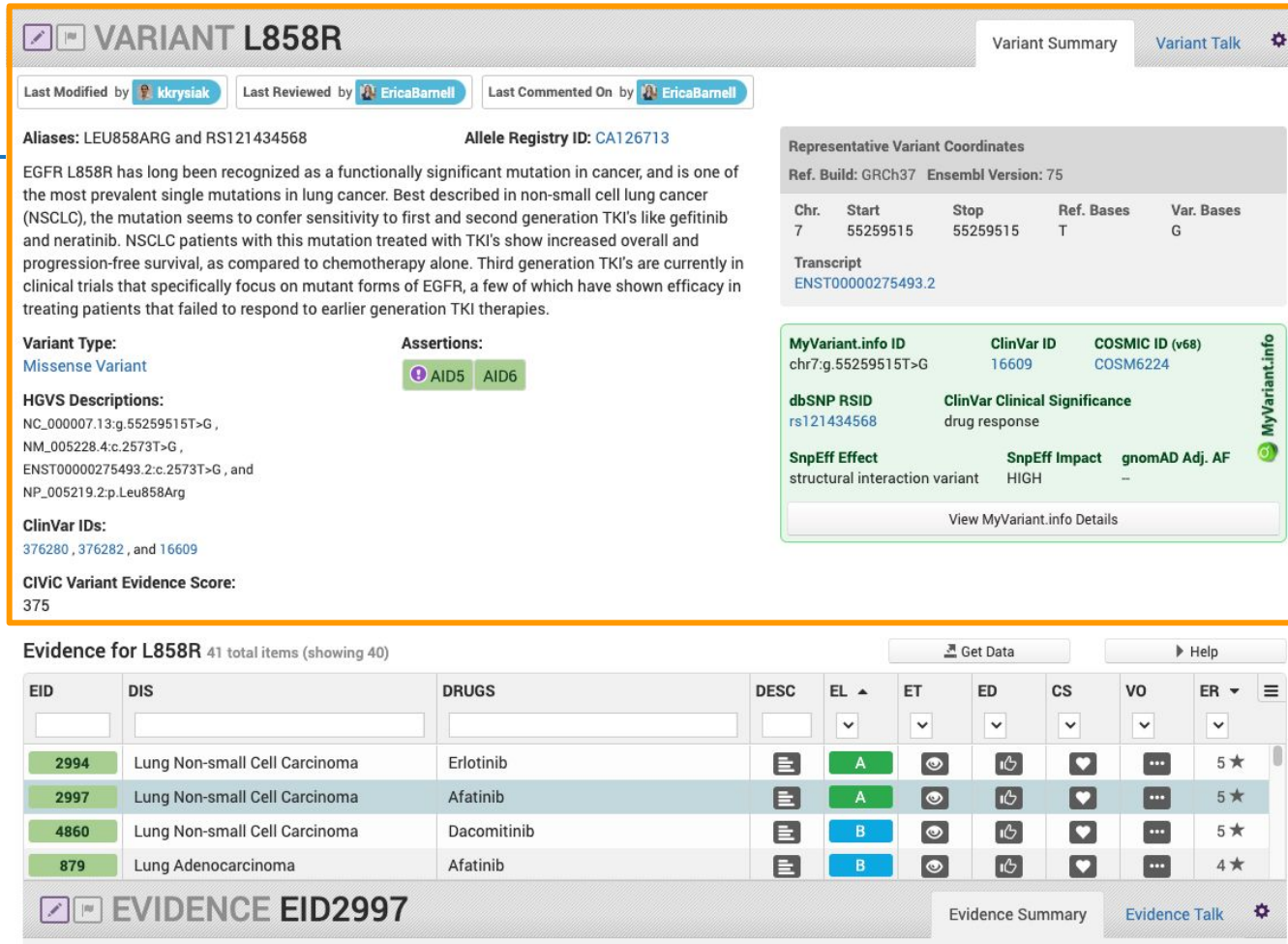

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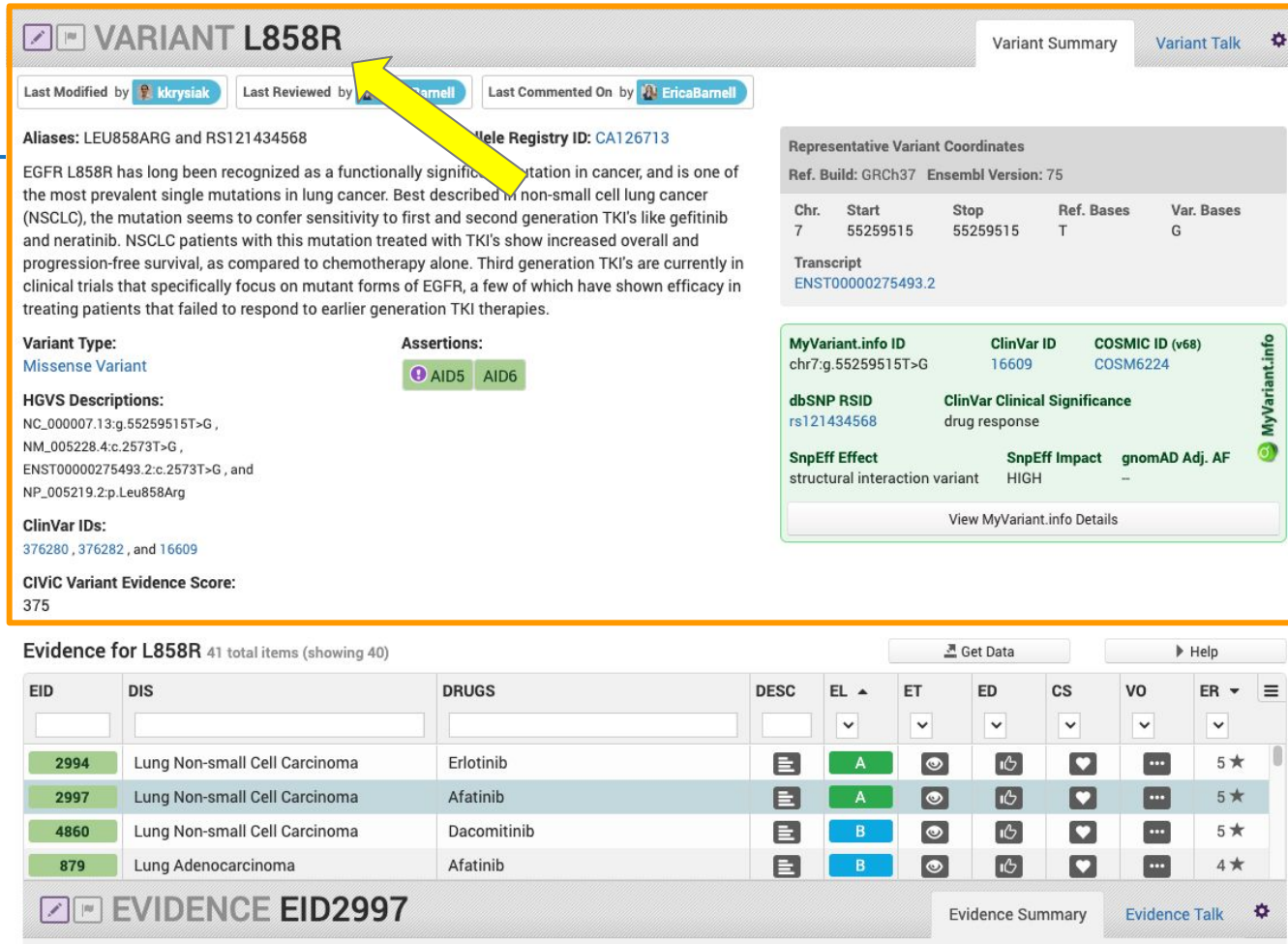

Evidence for L858R 41 total items (showing 40)

Get Data | Help

EID	DIS	DRUGS	DESC	EL	ET	ED	CS	VO	ER
2994	Lung Non-small Cell Carcinoma	Erlotinib		A					5 ★
2997	Lung Non-small Cell Carcinoma	Afatinib		A					5 ★
4860	Lung Non-small Cell Carcinoma	Dacomitinib		B					5 ★
879	Lung Adenocarcinoma	Afatinib		B					4 ★

EVIDENCE EID2997 — Evidence Summary | Evidence Talk

https://civicdb.org/links/evidence/2997

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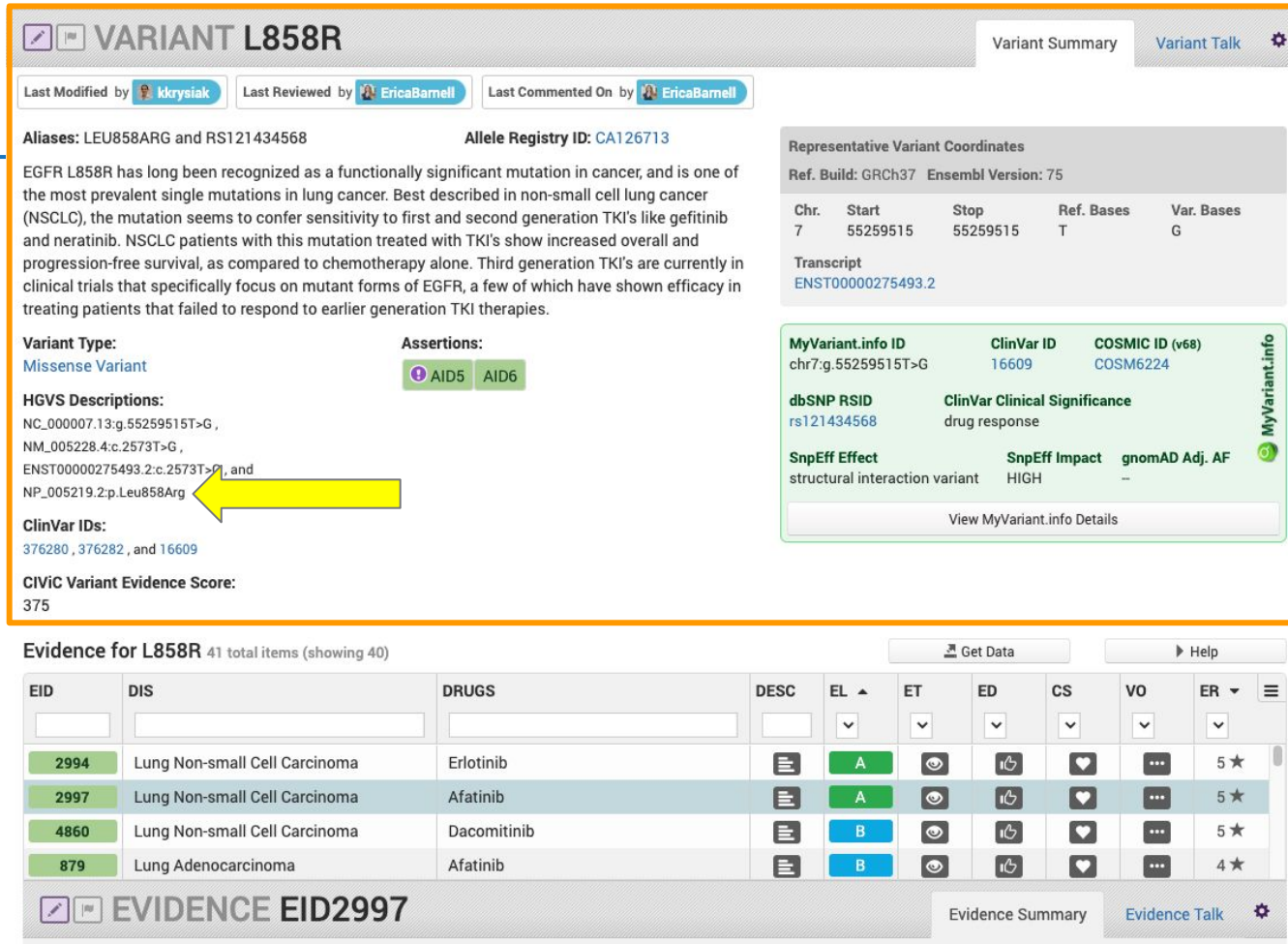

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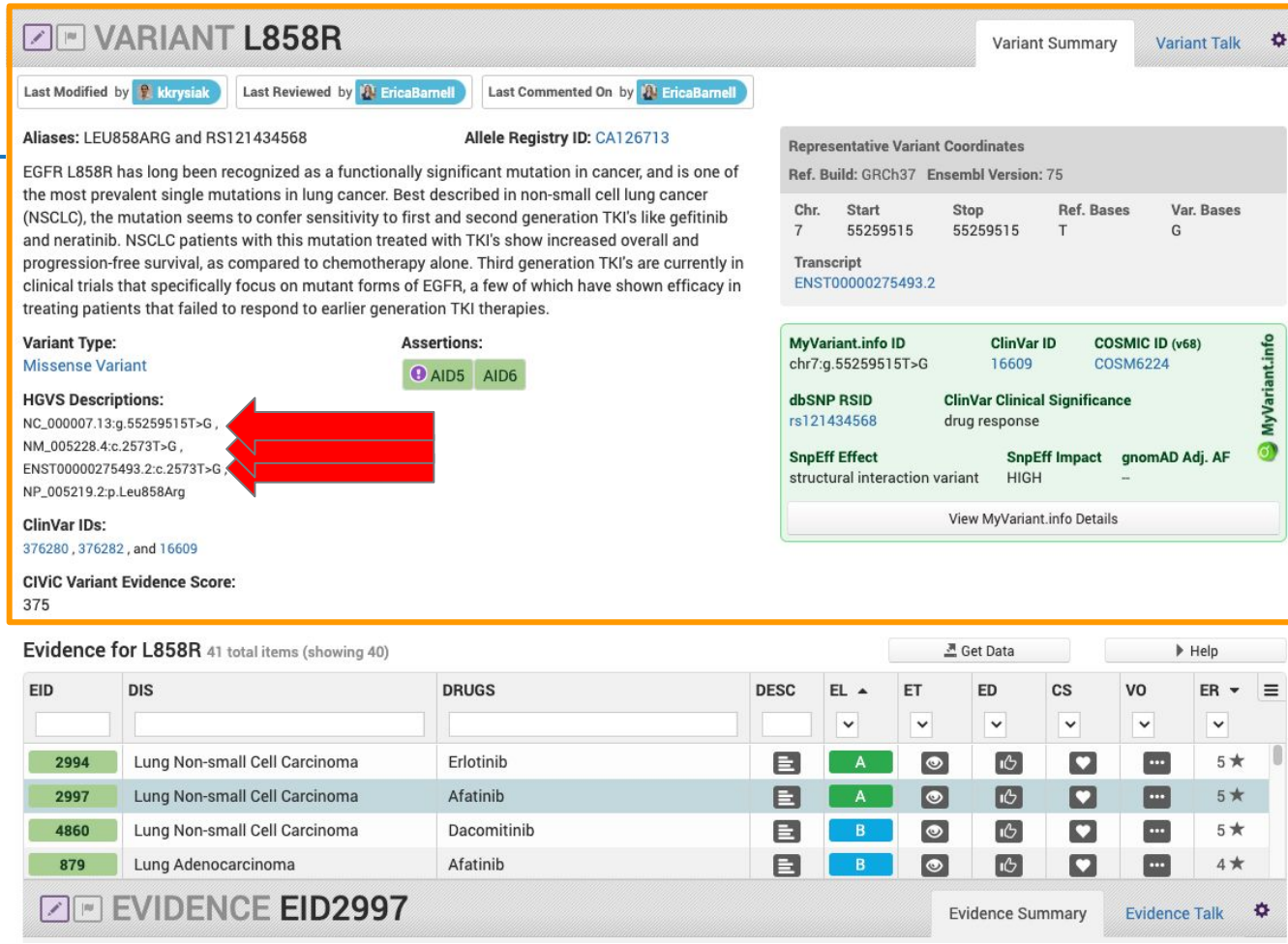

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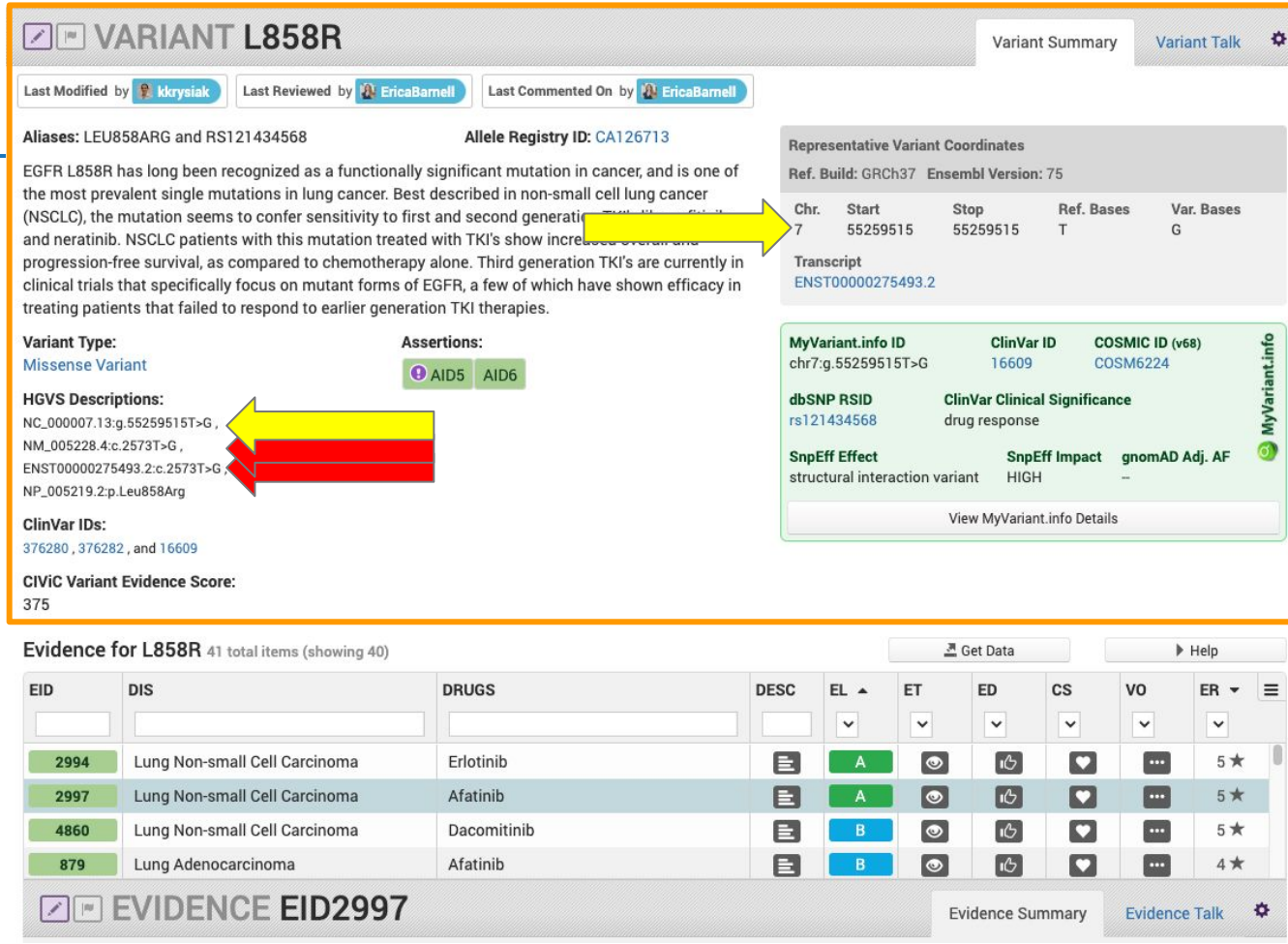

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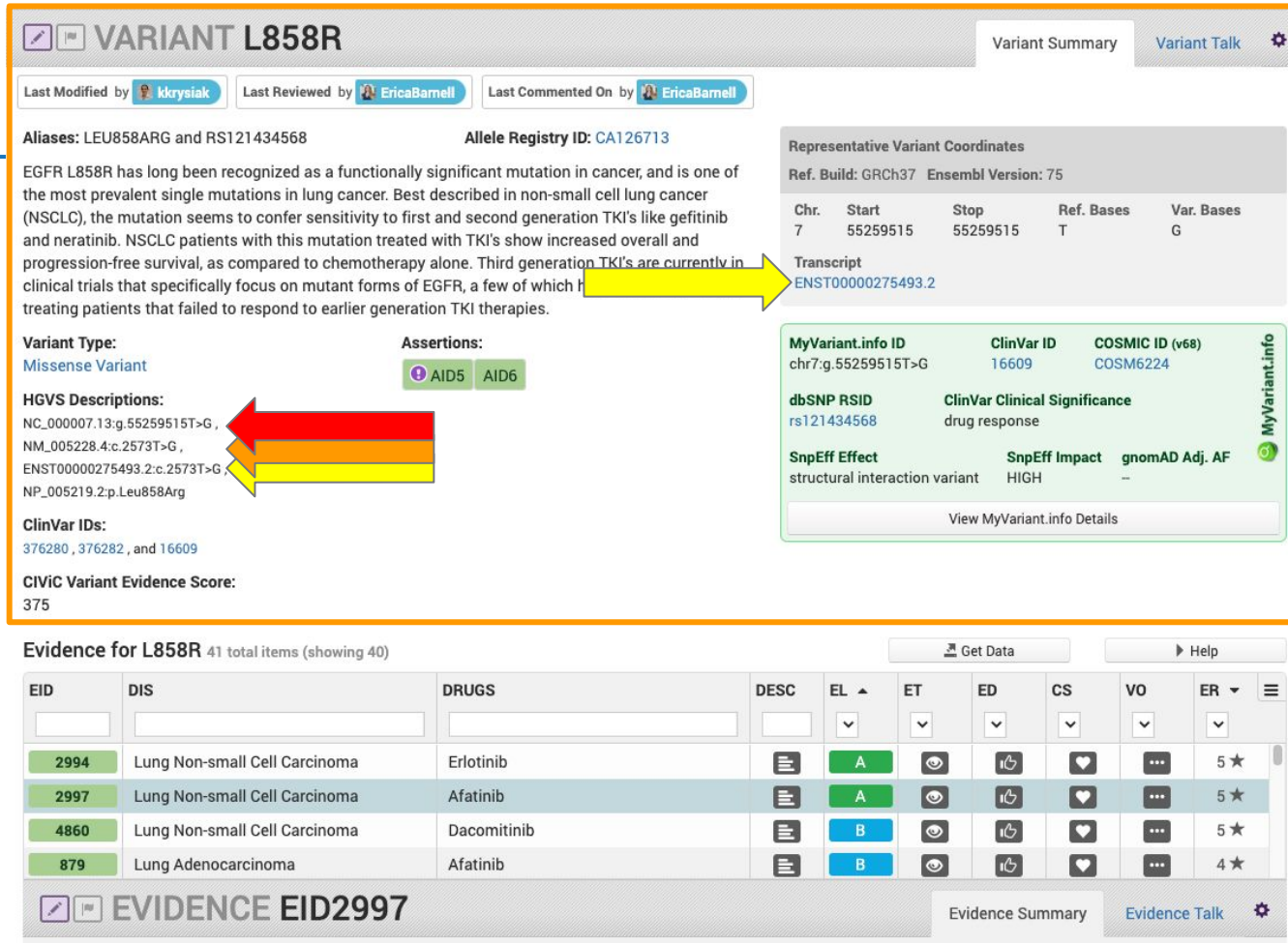

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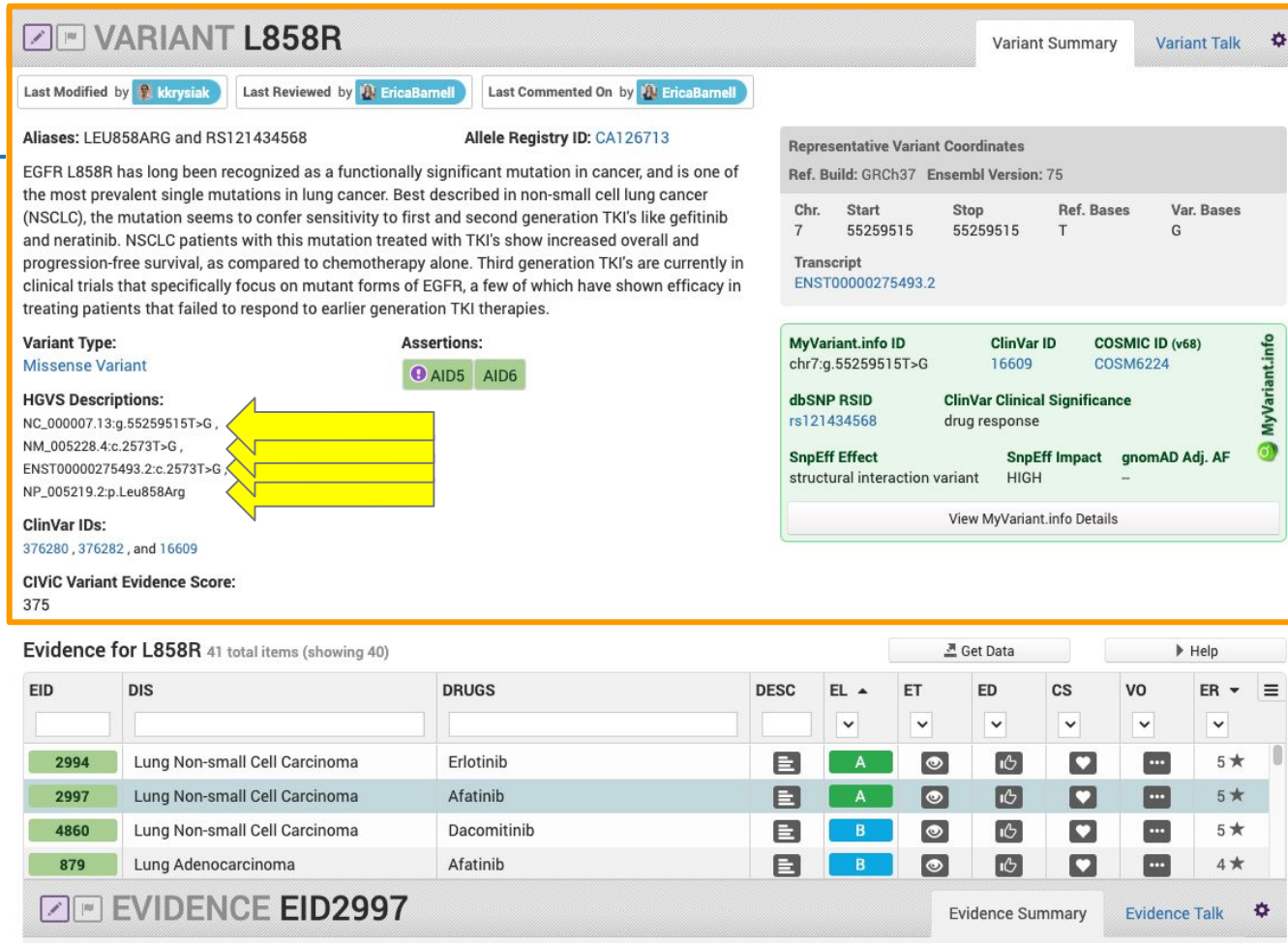

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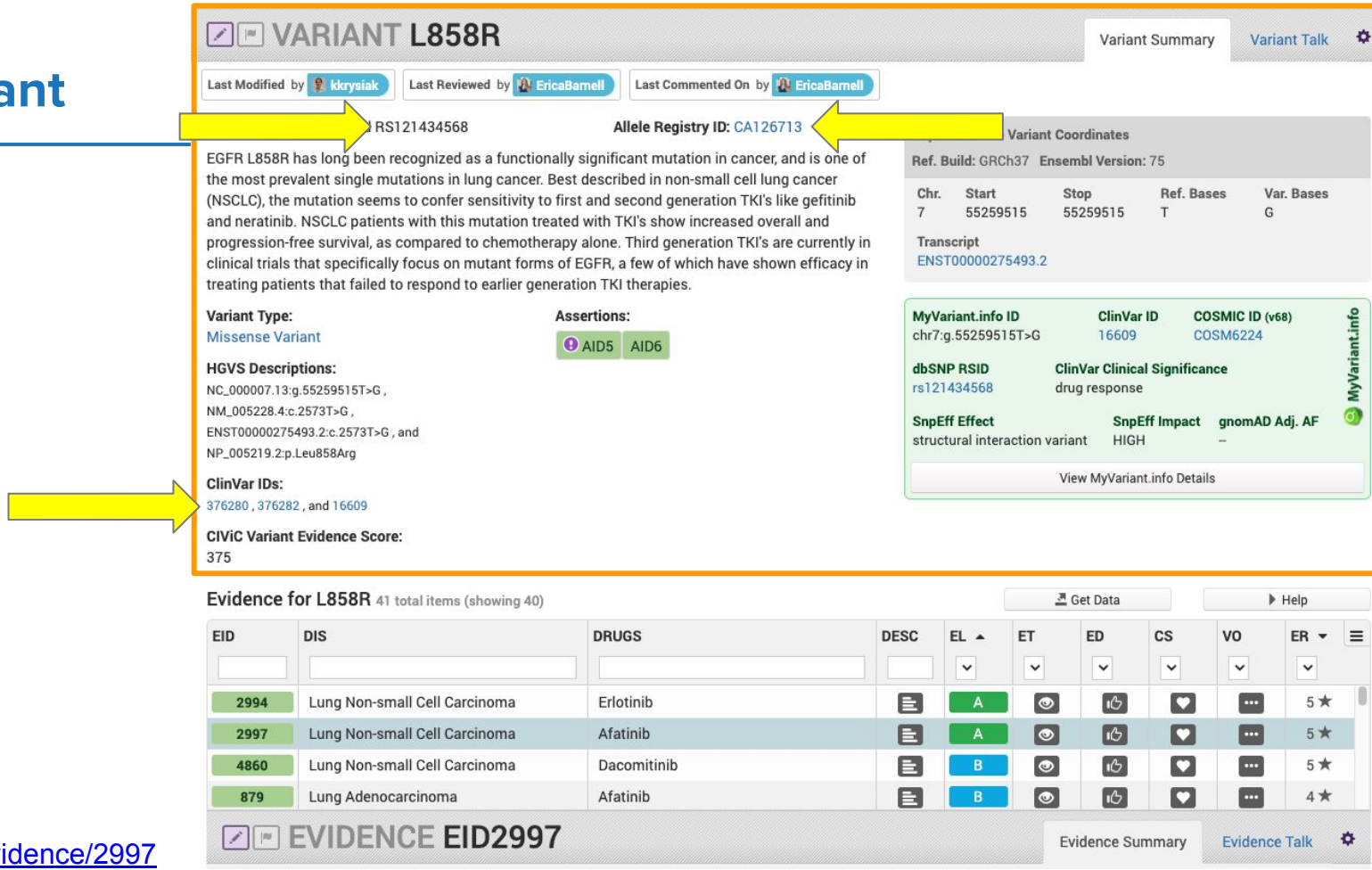

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CIViC Variant

ClinVar Display Names:

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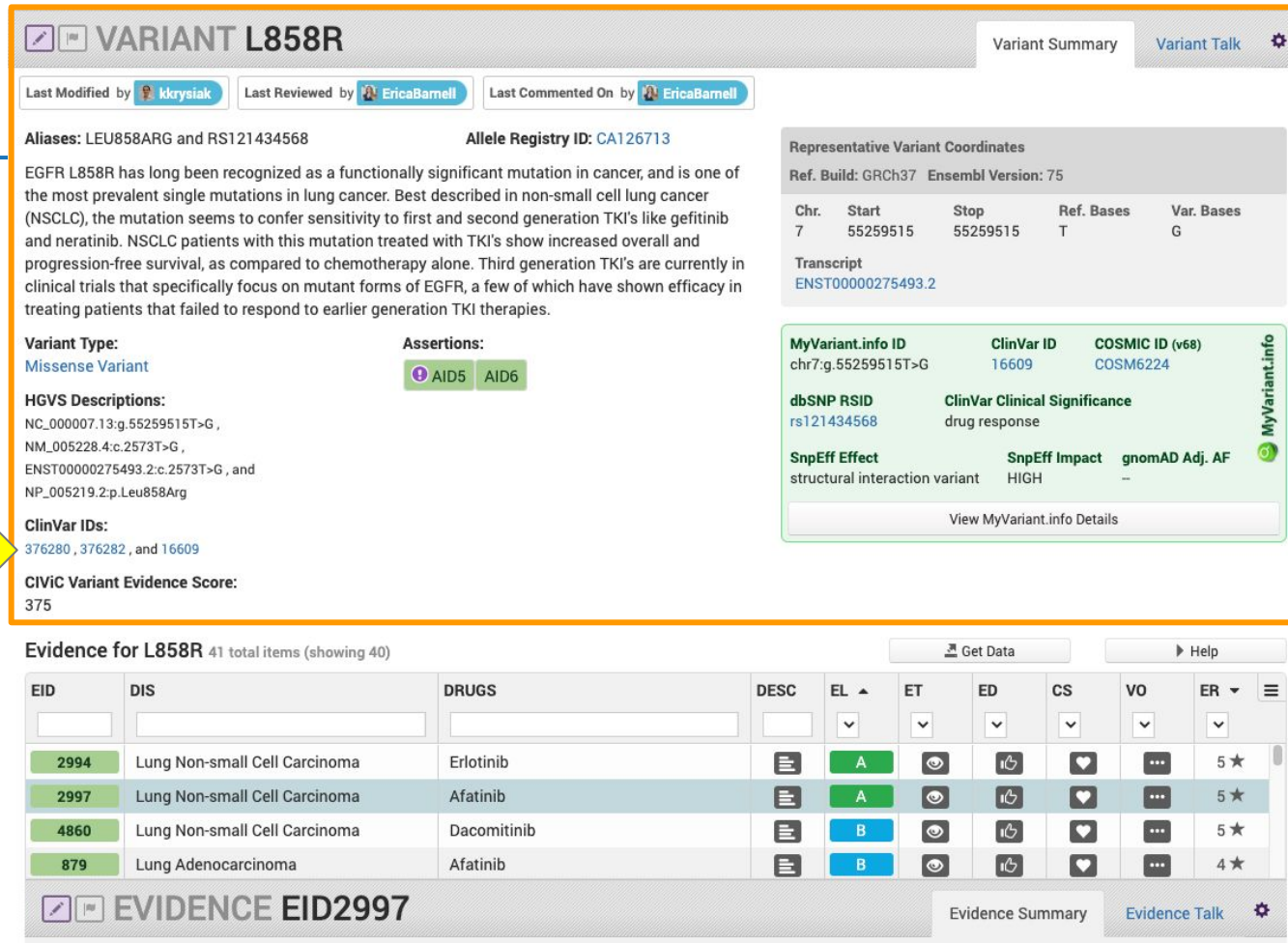
376280: c.2572_2573inv

376282: c.2573_2574delinsGT

16609: c.2573T>G



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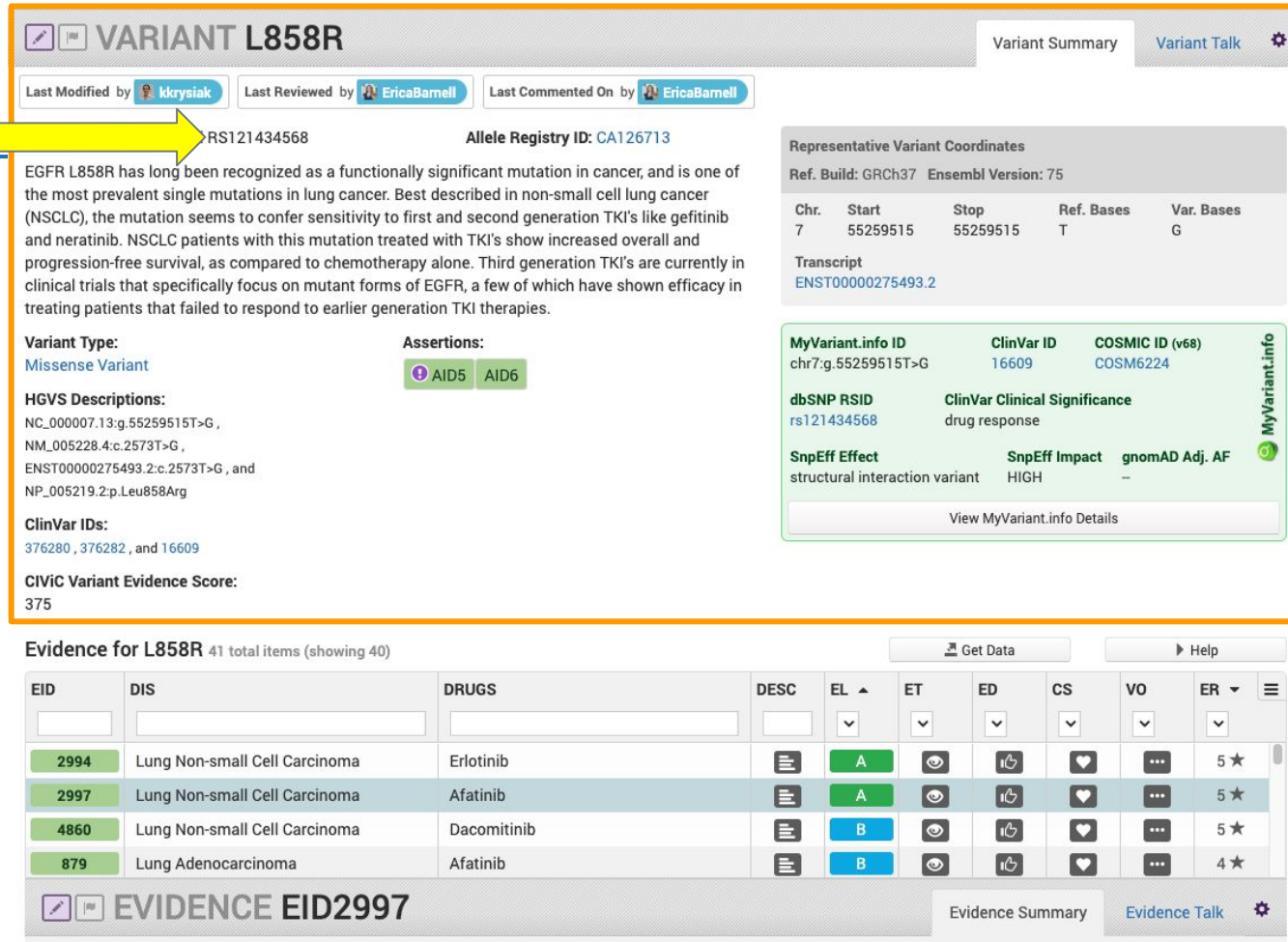

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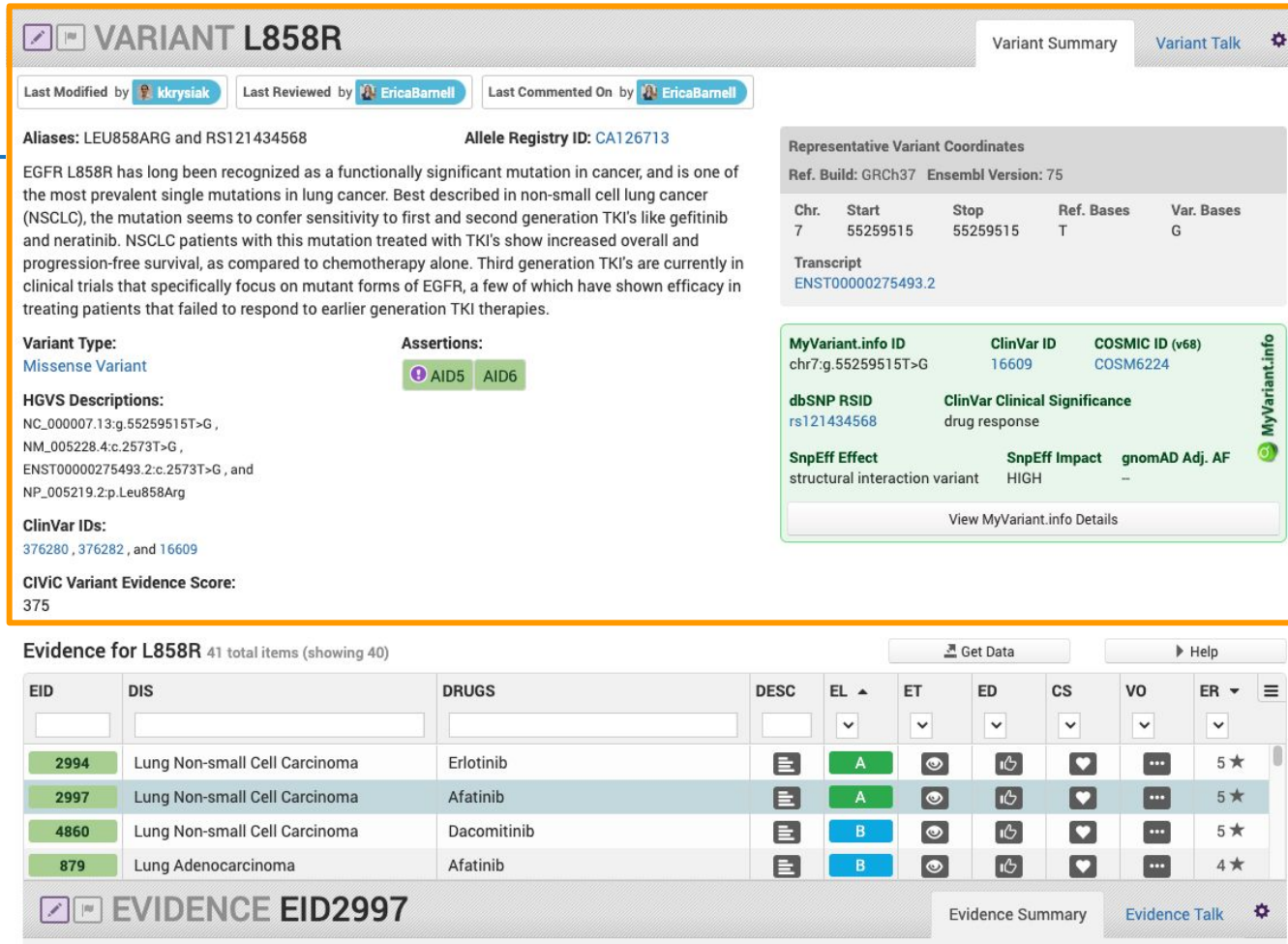

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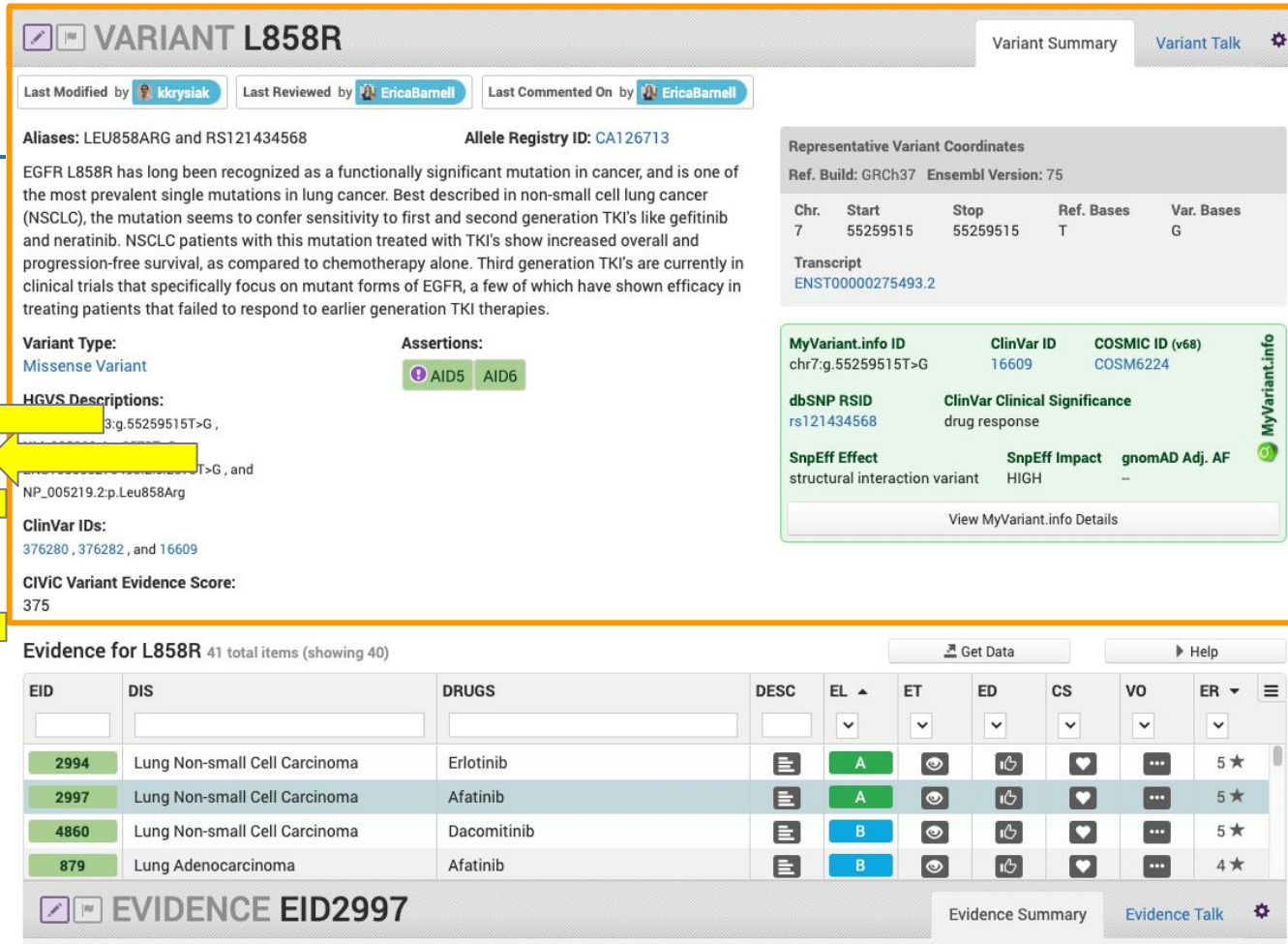

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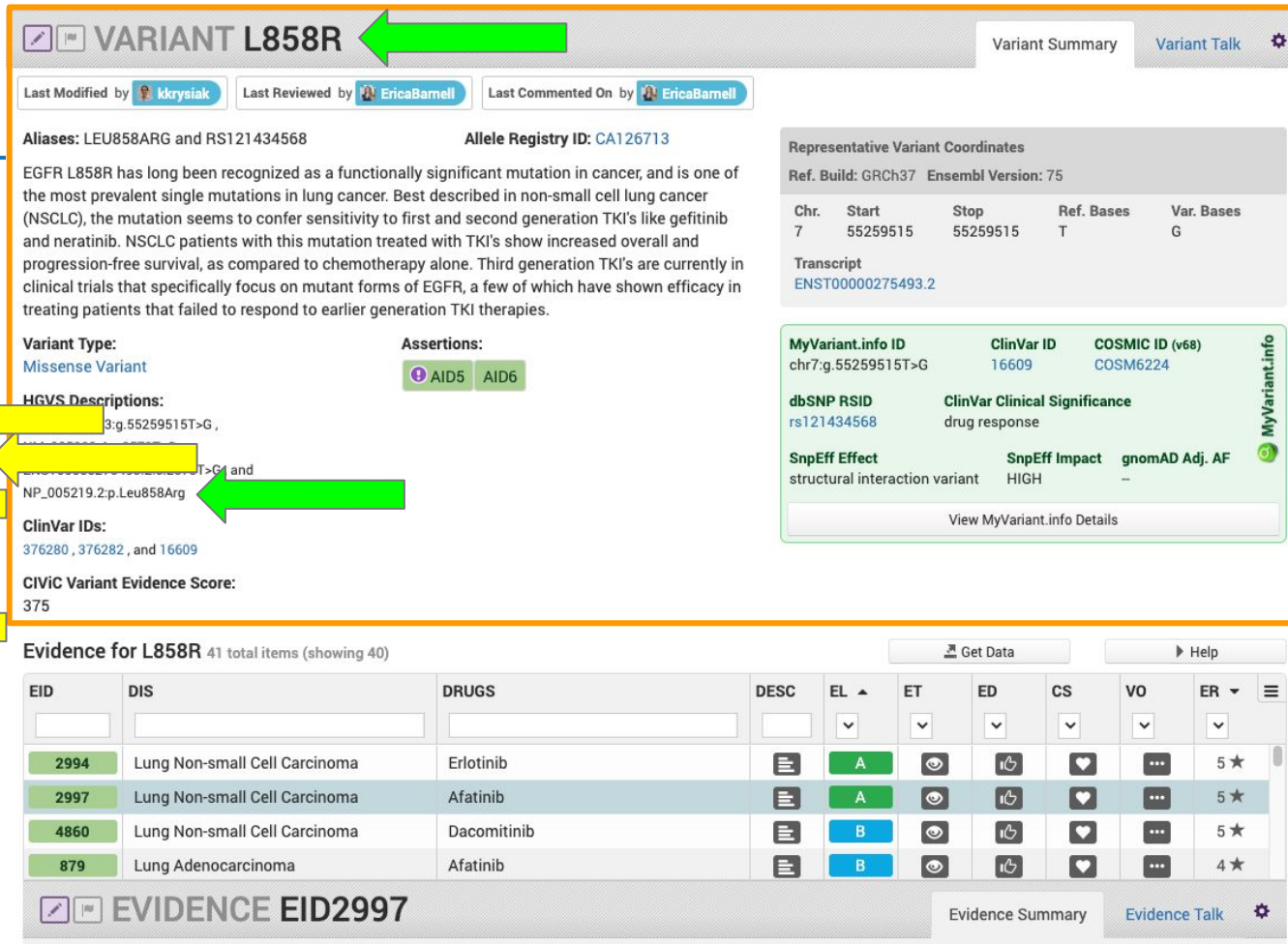

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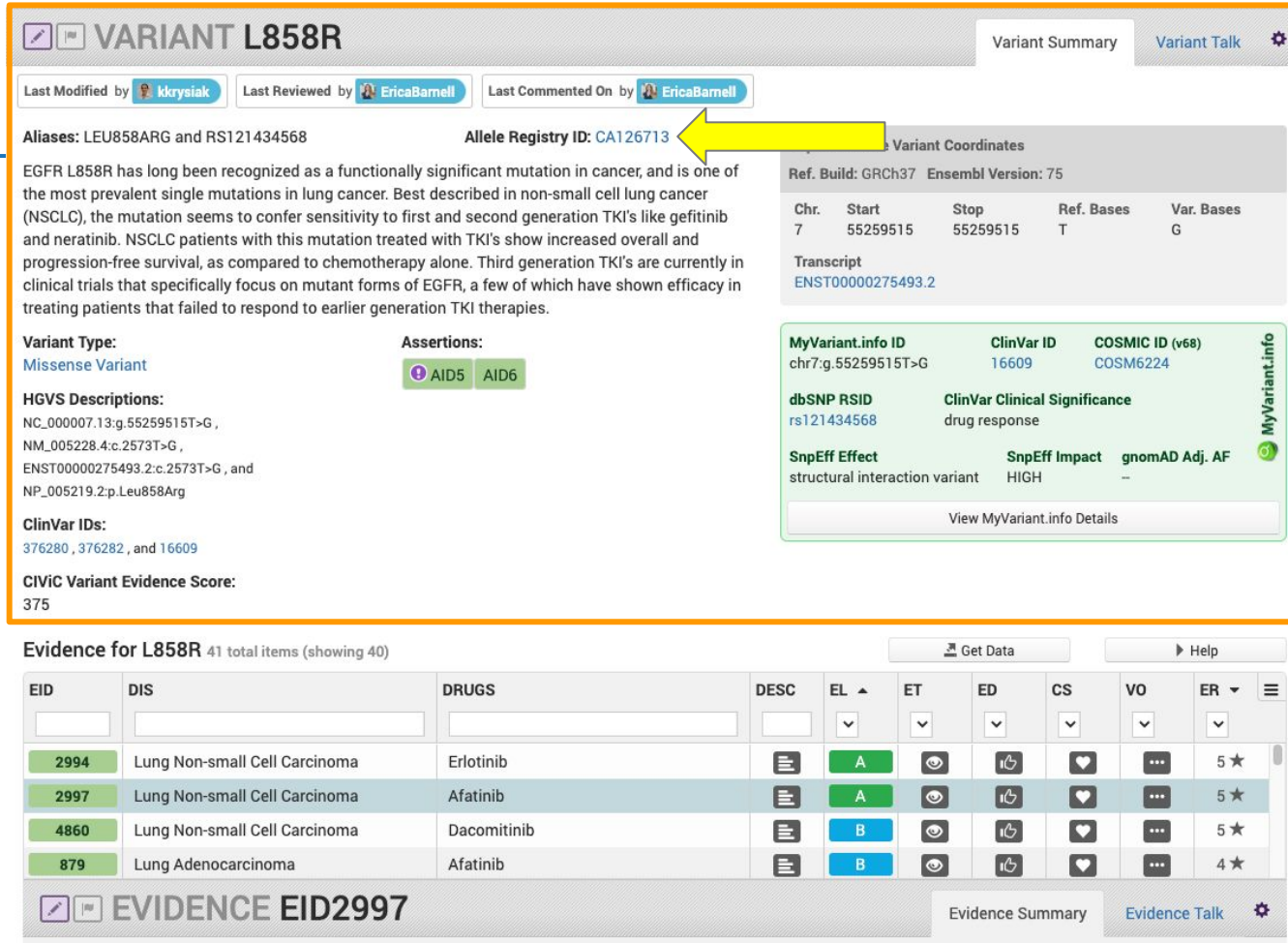

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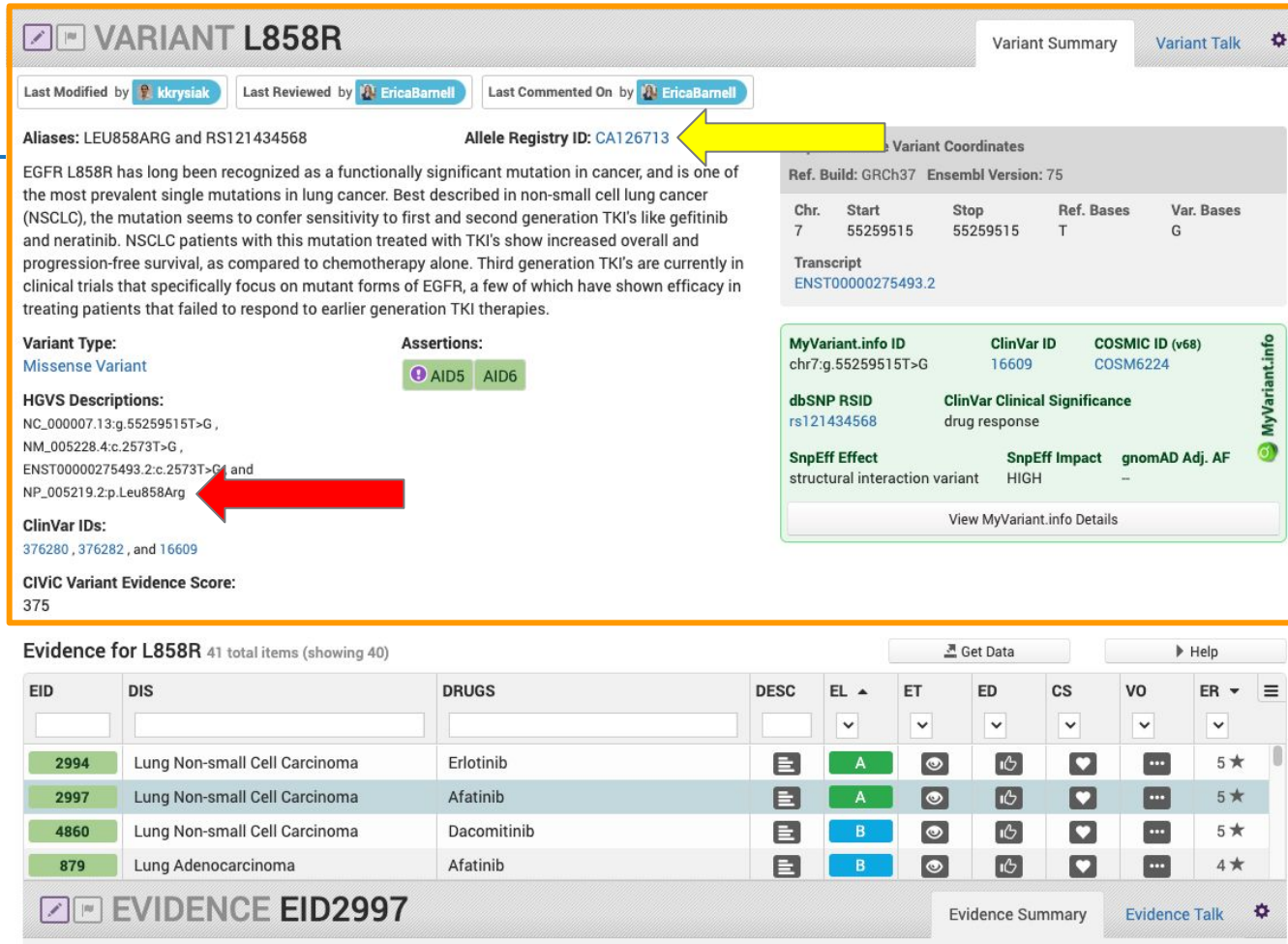

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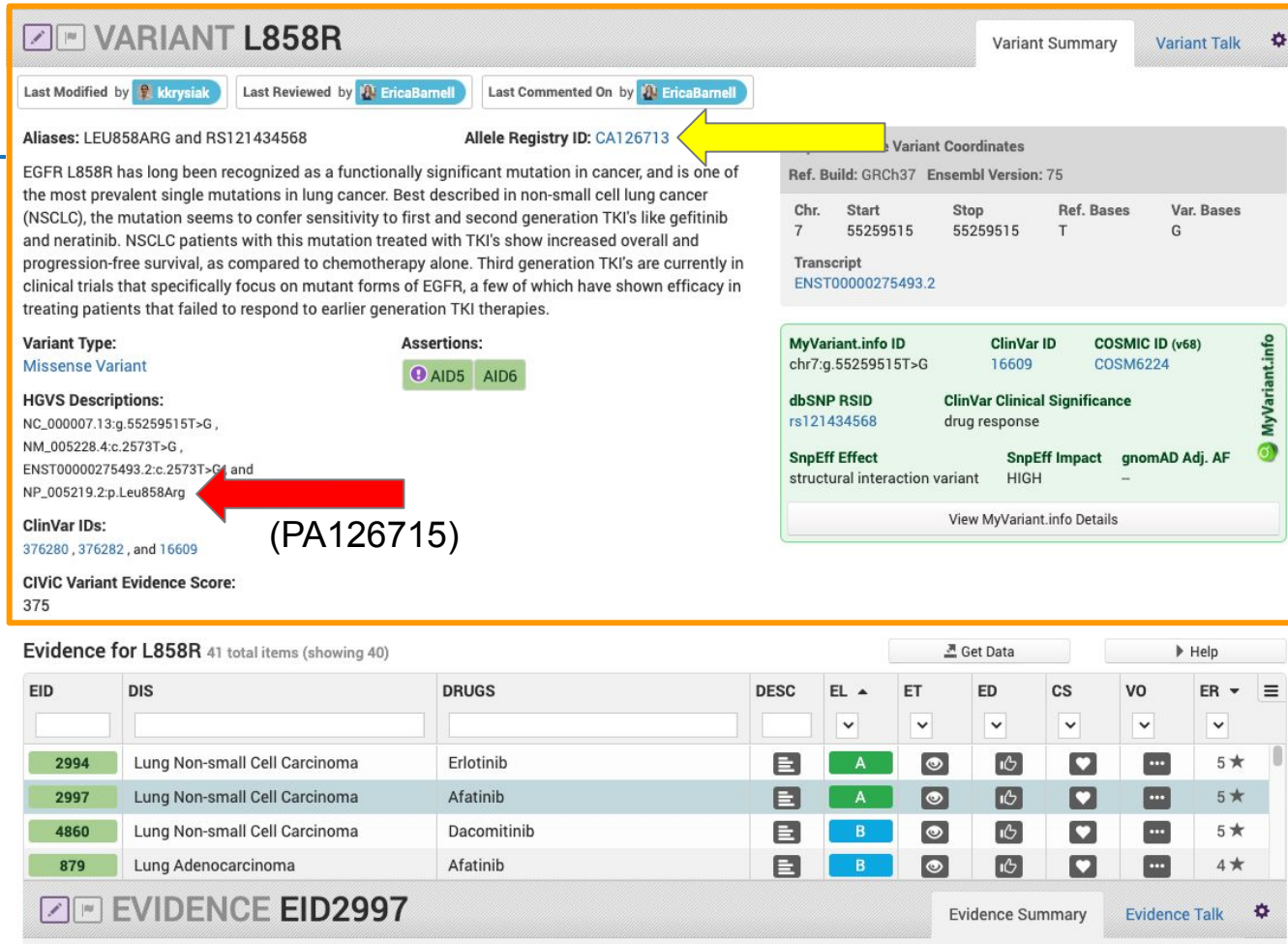

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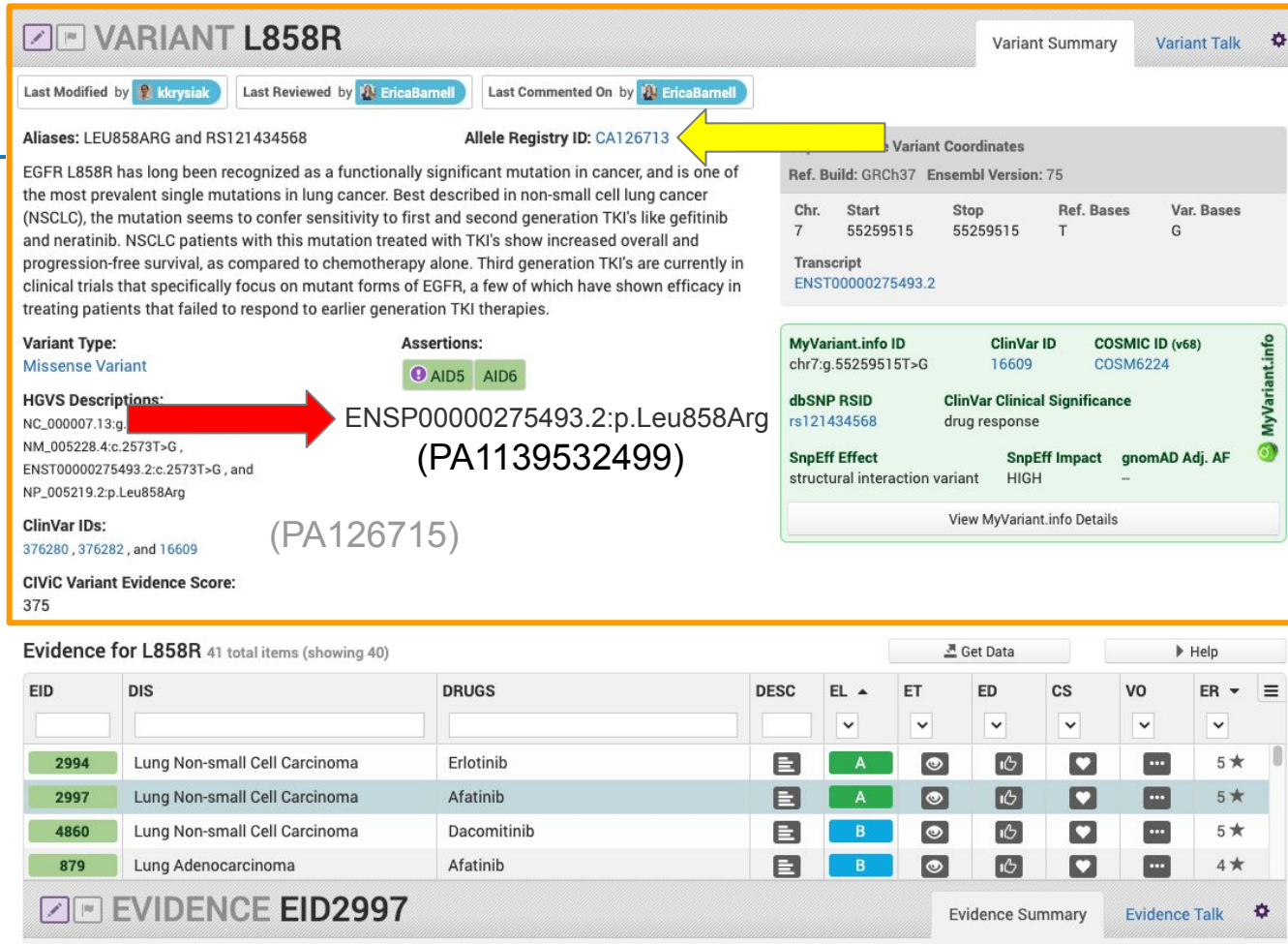
NC_000007.13:

g.55259515T>A

g.55259515T>G

https://civicdb.org/links/evidence/2997



Variant Complexity in Other Resources

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

ClinVar Display Names:
NM_005228.5(EGFR)
376280: c.2572_2573inv
376282: c.2573_2574delinsGT
16609: c.2573T>G

dbSNP rs121434568:
NC_000007.13:
g.55259515T>A
g.55259515T>G

Variant Complexity in Other Resources

GENOMICS IN HEALTH
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dbSNP rs121434568:
NC_000007.13:
g.55259515T>A
g.55259515T>G

...this represents an ***oversimplification***

ClinVar Variant 16609

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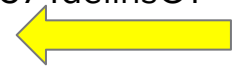
IMPLEMENTATION FORUM

ClinVar Display Names:
NM_005228.5(EGFR)
376280: c.2572_2573inv
376282: c.2573_2574delinsGT
16609: c.2573T>G 

dbSNP rs121434568:
NC_000007.13:
g.55259515T>A
g.55259515T>G

https://www.ncbi.nlm.nih.gov/clinvar/variation/16609/

ClinVar Variant 16609

ClinVar Display Names:
NM_005228.5(EGFR)
376280: c.2572_2573inv
376282: c.2573_2574delinsGT
16609: c.2573T>G

dbSNP rs121434568:
NC_000007.13:
g.55259515T>A
g.55259515T>G

https://www.ncbi.nlm.nih.gov/clinvar/variation/16609/

NM_005228.5(EGFR):c.2573T>G (p.Leu858Arg)

Allele ID: 31648
Variant type: single nucleotide variant
Variant length: 1 bp
Cytogenetic location: 7p11.2
Genomic location: 7: 55191822 (GRCh38) GRCh38 UCSC
7: 55259515 (GRCh37) GRCh37 UCSC

HGVS:

Nucleotide	Protein	Molecular consequence
NC_000007.13:g.55259515T>G		
NC_000007.14:g.55191822T>G		
NM_005228.5:c.2573T>G MANE SELECT	NP_005219.2:p.Leu858Arg	missense
NM_001346897.2:c.2438T>G	NP_001333826.1:p.Leu813Arg	missense
NM_001346898.2:c.2573T>G	NP_001333827.1:p.Leu858Arg	missense
NM_001346899.1:c.2438T>G	NP_001333828.1:p.Leu813Arg	missense
NM_001346900.2:c.2414T>G	NP_001333829.1:p.Leu805Arg	missense
NM_001346941.2:c.1772T>G	NP_001333870.1:p.Leu591Arg	missense
LRG_304t1:c.2573T>G		
LRG_304:g.177791T>G		
NG_007726.3:g.177791T>G		
	P00533:p.Leu858Arg	

... less HGVS

Protein change: L858R, L591R, L805R, L813R
Other names: -
Canonical SPDI: NC_000007.14:55191821:T:G
Functional consequence: -
Global minor allele frequency (GMAF): -
Allele frequency: -
Links: ClinGen: CA126713
Genetic Testing Registry (GTR): GTR000560812
UniProtKB: P00533#VAR_019298
OMIM: 131550.0002
dbSNP: rs121434568
PharmGKB Clinical Annotation: 981420042
PharmGKB Clinical Annotation: 981475838
PharmGKB Clinical Annotation: 981475880

Not Just CIViC and ClinVar

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Not Just CIViC and ClinVar

GENOMICS IN HEALTH
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CIViC

dbSNP

ClinVar

ClinGen
Clinical Genome Resource

Allele
Registry

Not Just CIViC and ClinVar

GENOMICS IN HEALTH
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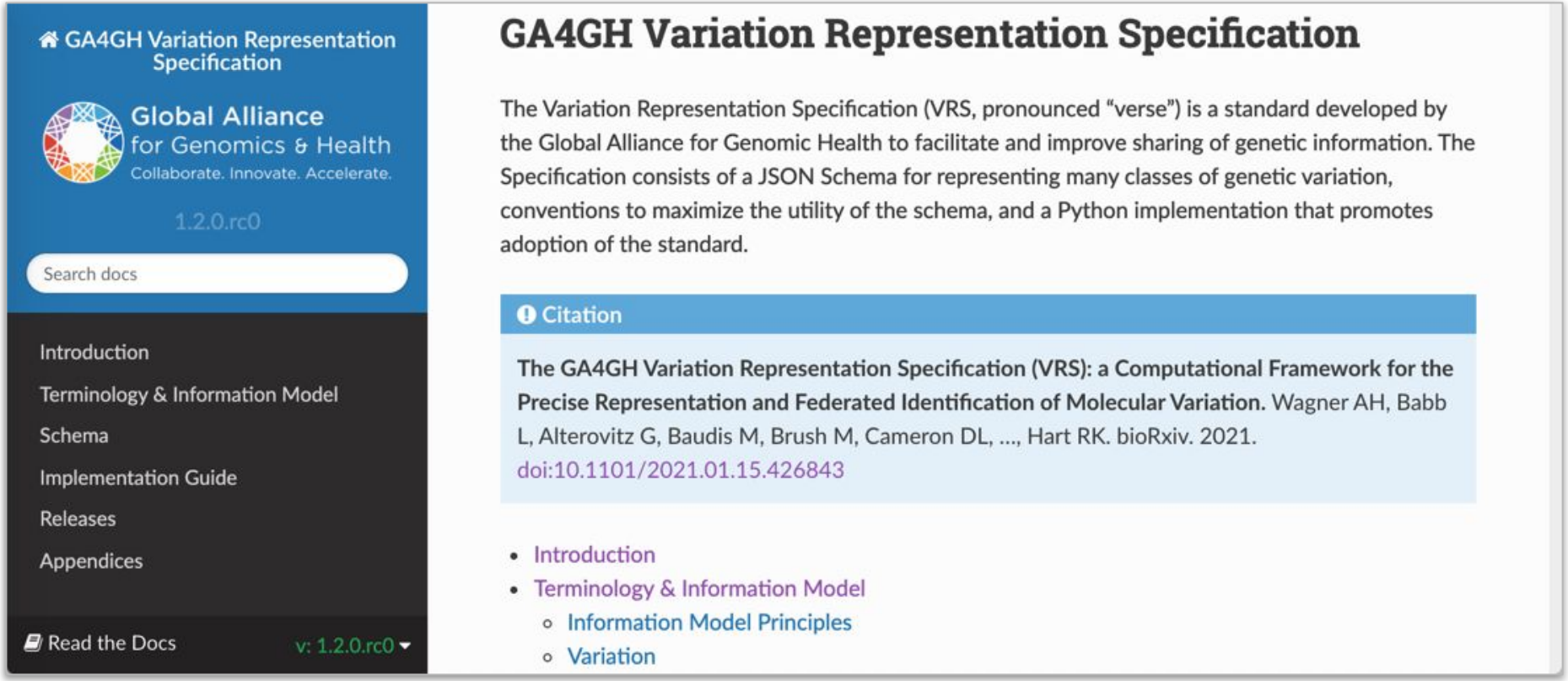
Allele
Registry



https://vrs.ga4gh.org/en/1.2.0.rc0/

Extensible Information Model (v 1.2 and going)

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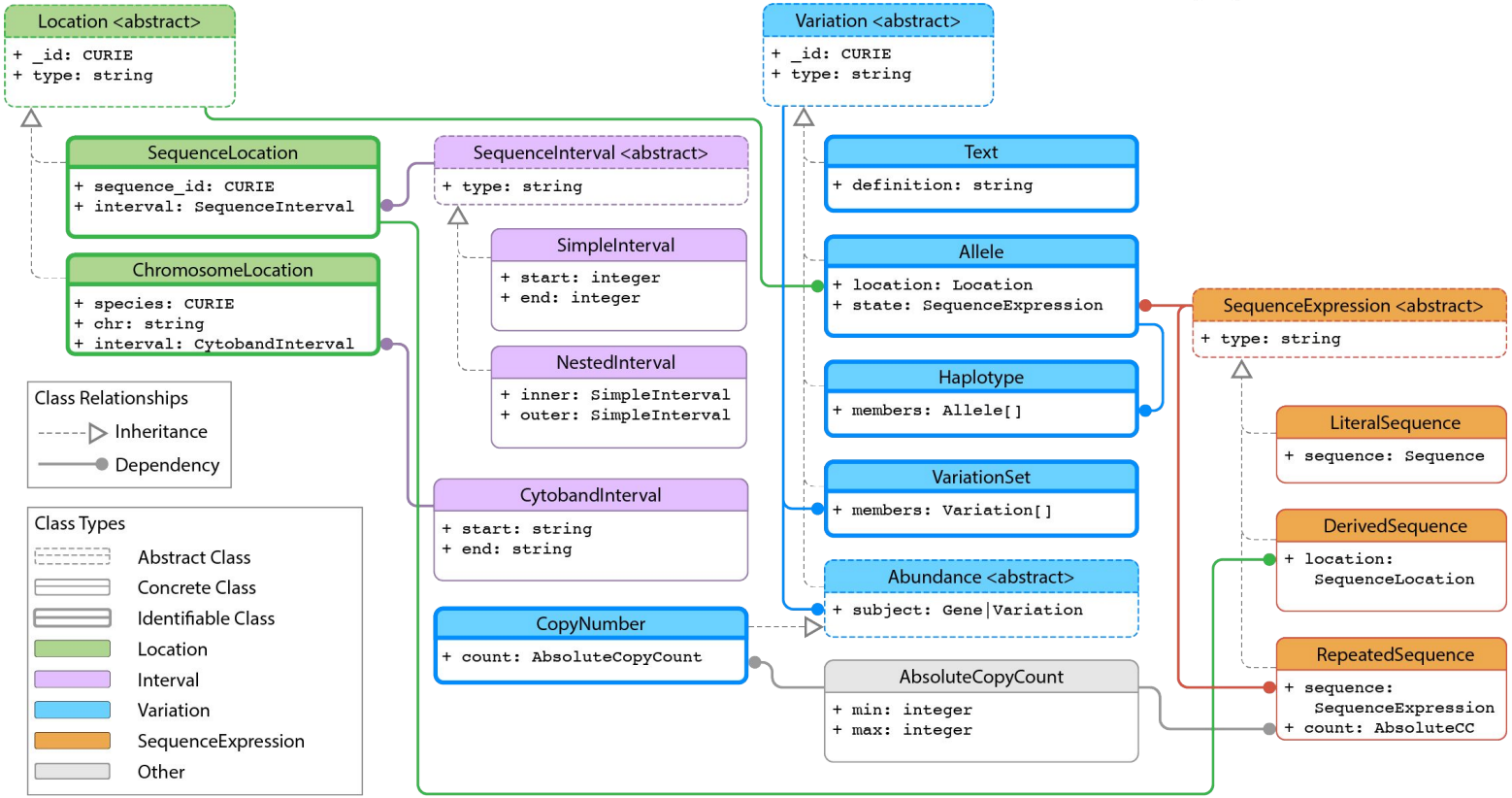

VRS Objects are minimal Value Objects

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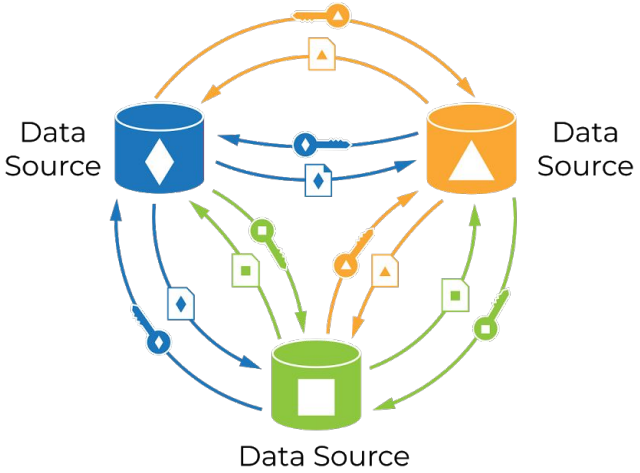
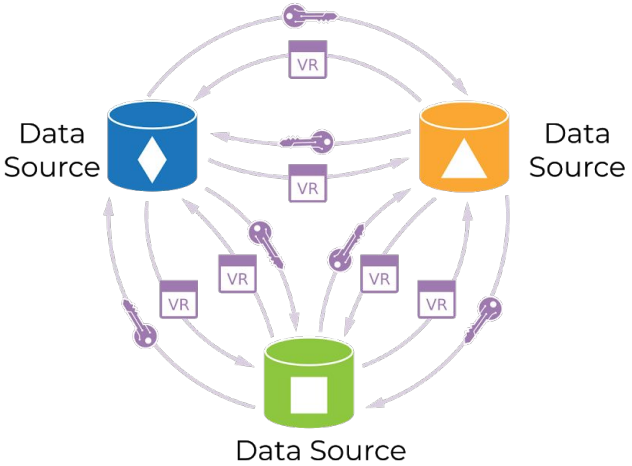
CURRENTLY...



PAIRS OF SYSTEMS COORDINATE KEYS AND FORMATS IN ORDER TO SHARE VARIATION DATA. ADDING A NEW SYSTEM IS DIFFICULT.

WITH THE VR SPECIFICATION...



SYSTEMS USE A COMMON IDENTIFIER, COMPUTED FROM THE DATA ITSELF, AND A COMMON DATA FORMAT. ADDING A NEW SYSTEM IS MUCH EASIER.

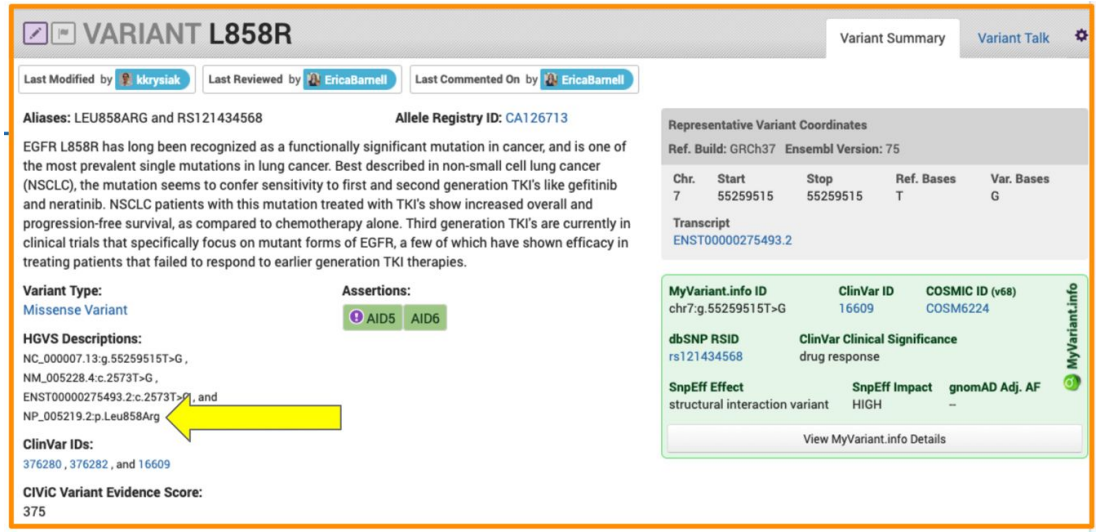
Rendering by
Stephanie Li

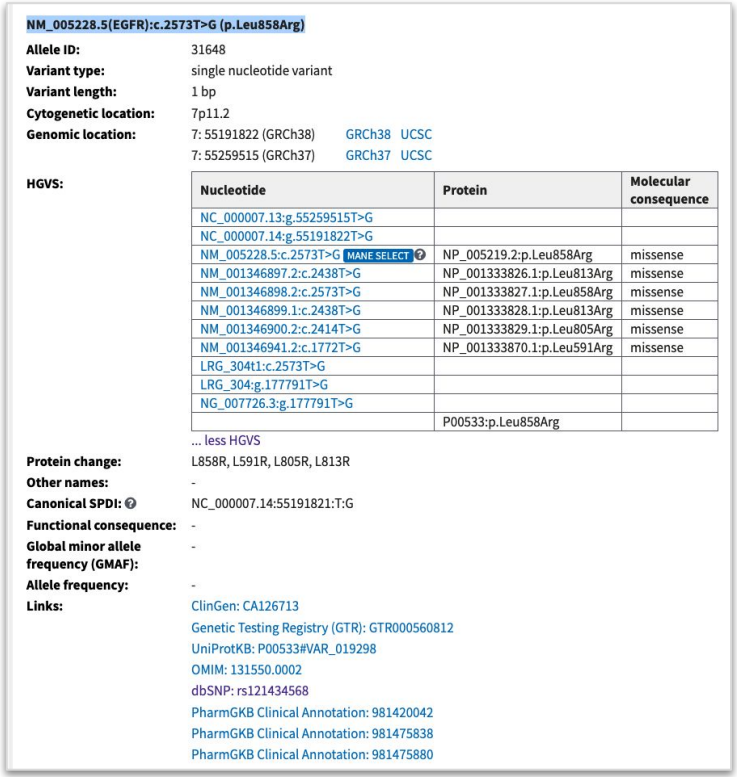
Sounds good, but what about ...

GENOMICS IN HEALTH IMPLEMENTATION FORUM

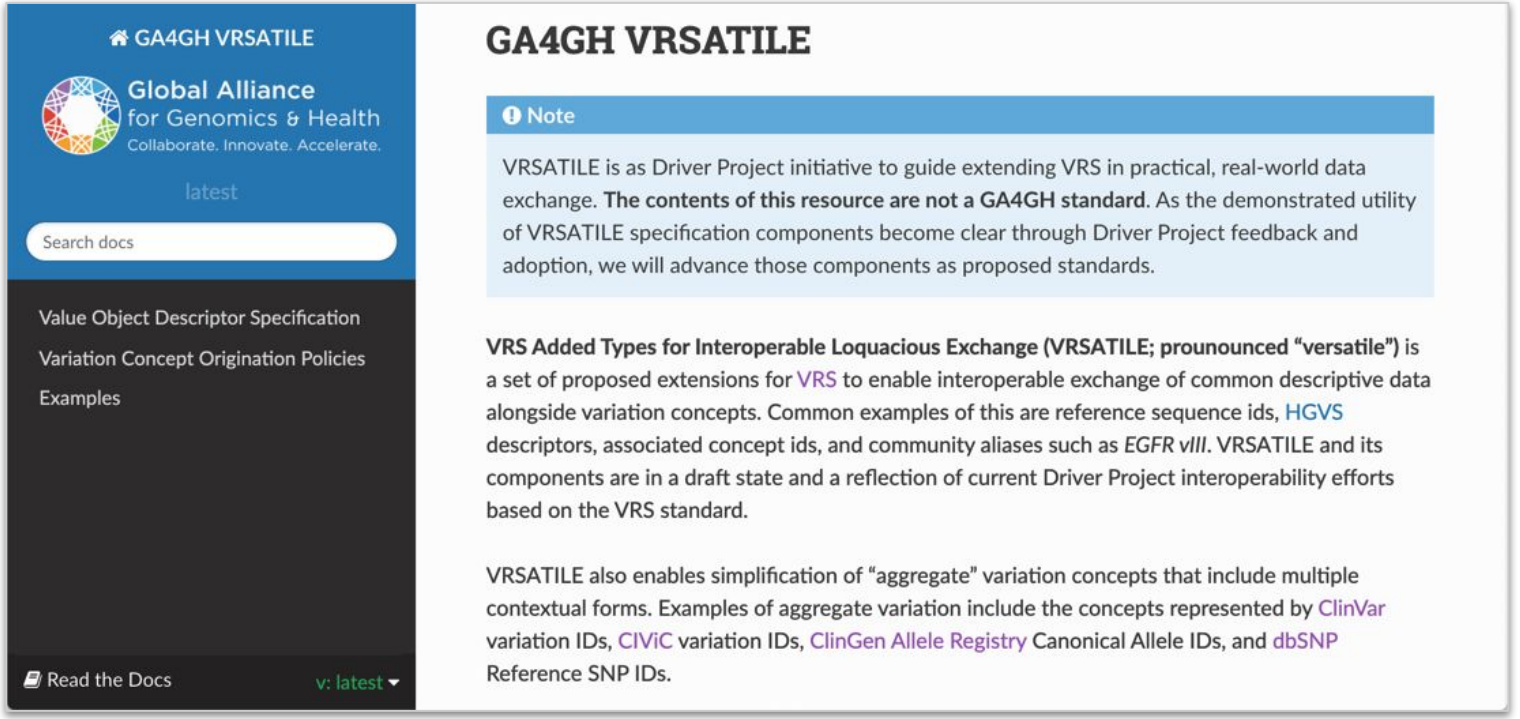
... sharing the non-minimal variant elements ?

... clarifying the originating variant context ?





VRS
Added
Types for
Interoperable
Loquacious
Exchange



Reproducible and **descriptive** normalization of variation concepts to VRS through resource-defined VCOPs.

https://vrsatile.readthedocs.io

Real world, practical application of VRS

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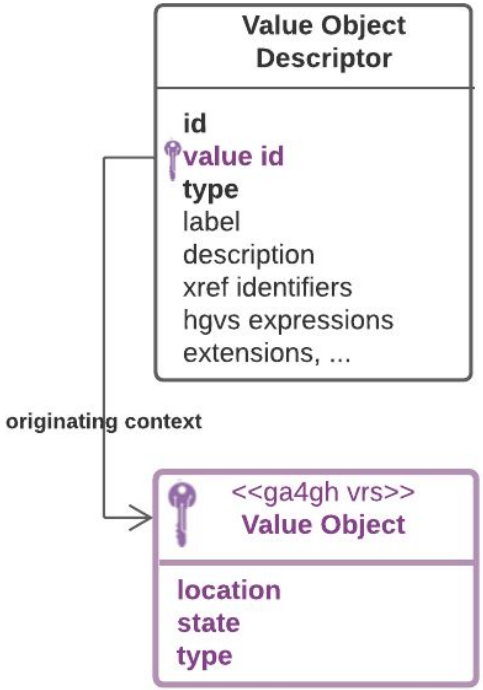
- VRS value objects **define** the variation
- **Descriptors are flexible transfer mechanisms** that reduce refactoring costs and enable VRS standards use.
- The Variation Concept Origination Policy (**VCOP**) **clarifies the originating context** variation from 3rd party resources.
    - e.g. CIViC, ClinVar, ClinGen A/R, MetaKB, ...



Computationally identifying the Variation

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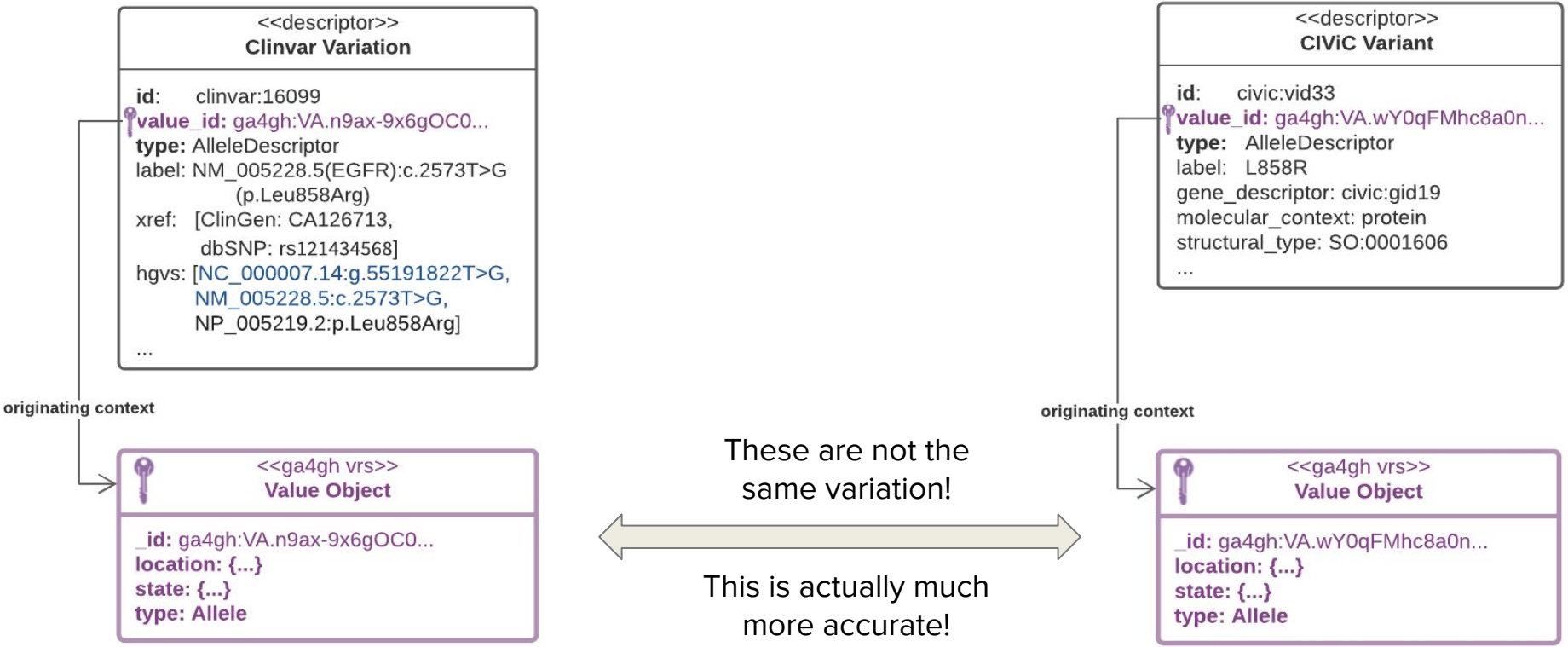

Computationally identifying the Variation

GENOMICS IN HEALTH
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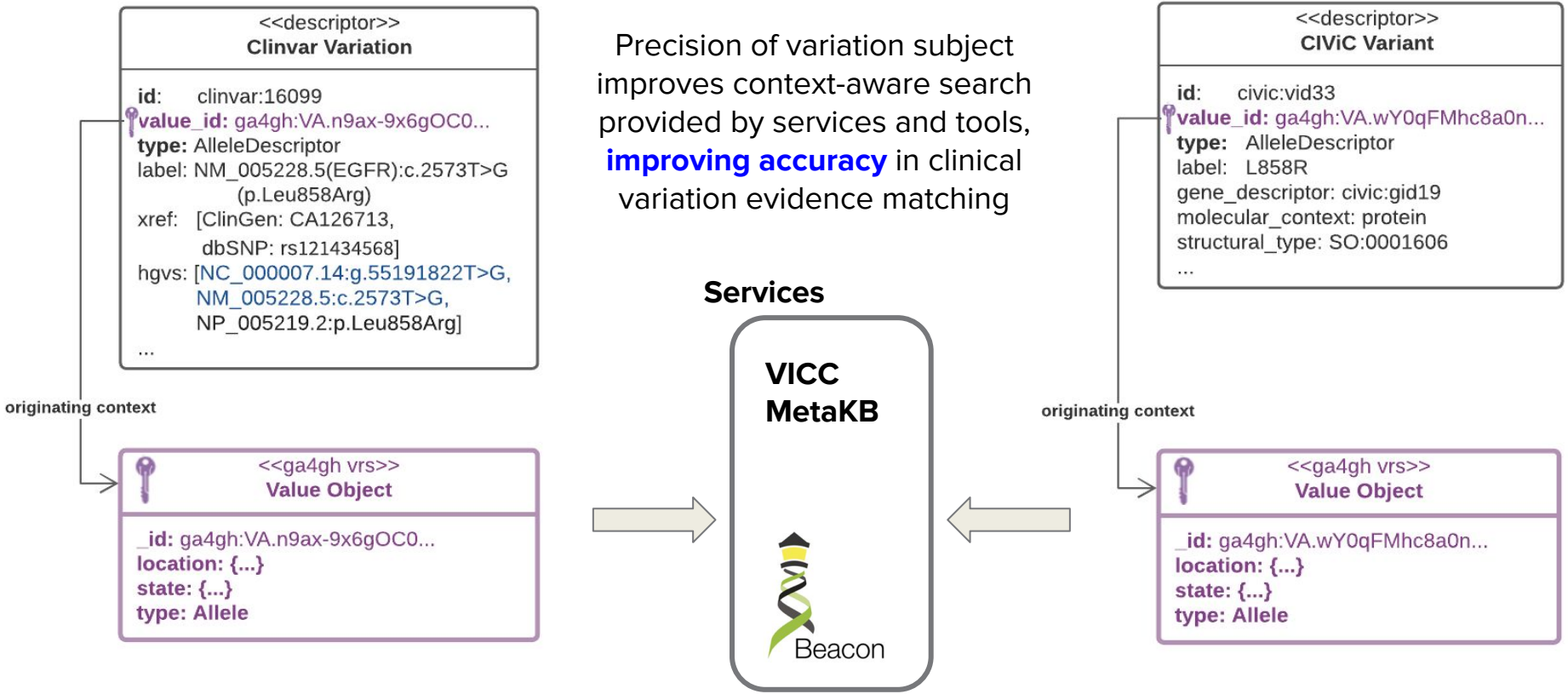

Learn More

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IMPLEMENTATION FORUM

VRS Webinar / Workshop in June 2, at 19:00 UTC

- **How-to** transform clinical evidence to the GKS framework
- **Survey** of available tools and services
- **Demonstration** using example datasets

Sign up for the webinar at http://bit.ly/vrs-webinar-registration !

Acknowledgements

ClinGen Data Platform

Tristan Nelson

Kyle Ferriter

Terry O'Neill

VICC MetaKB Team

Brian Walsh

Xuelu "Jeff" Liu

Kori Kuzma

James Stevenson

Jiachen Liu

GA4GH GKS WS

Reece Hart

Robert Freimuth

Matthew Brush

Melissa Cline

Helen Shuilenburg

...and many others!

U41 HG006834, U41 HG009649
U41 HG009650, K99 HG010157

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

Getting Clinic Ready

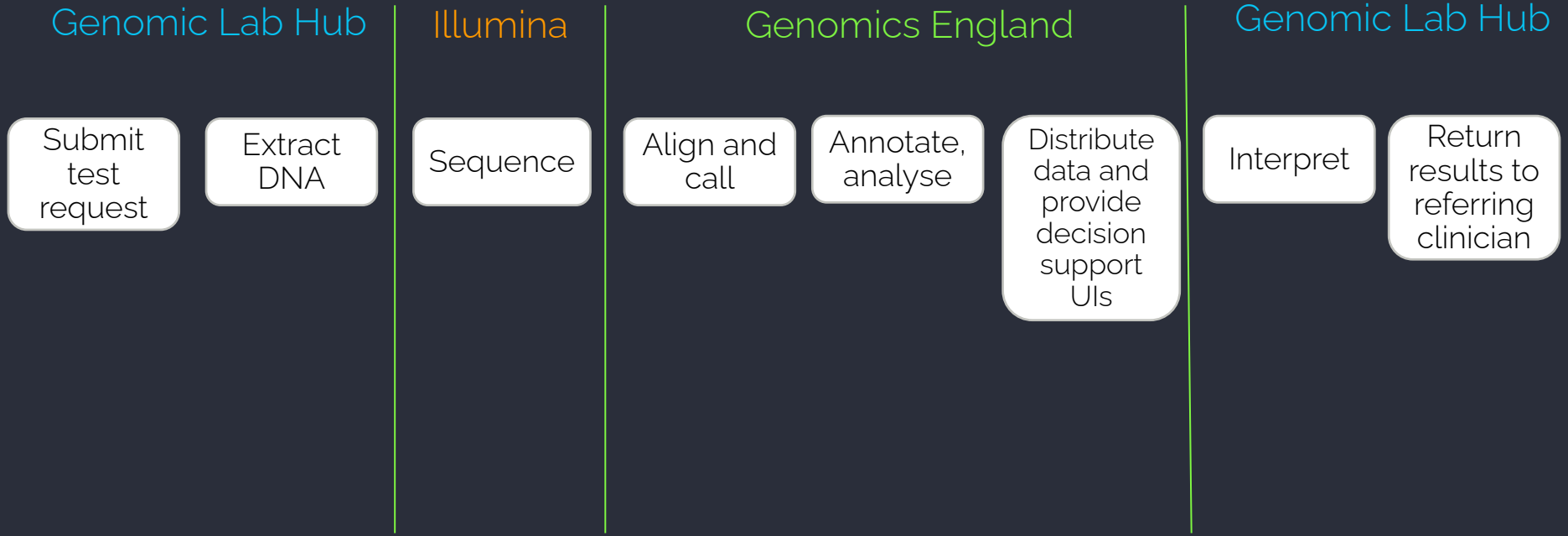
Genomics in Health Implementation Forum 10 03 2021

Accrediting Whole Genomes for Patient Care

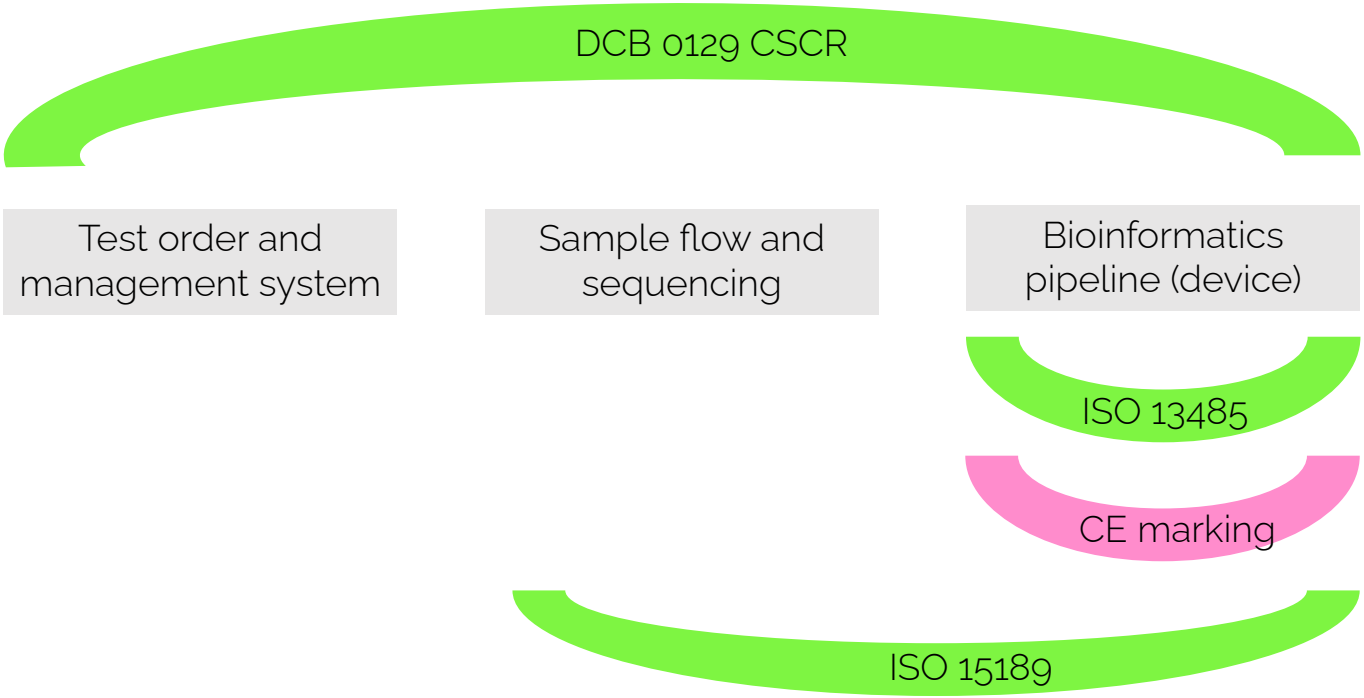
Dr Ellen Thomas
Clinical Lead for Rare Disease and Clinical Safety Officer, Genomics England
Clinical Advisor, Genomics Unit, NHS England and Improvement
Consultant in Clinical Genetics, Guy's and St Thomas' NHS Trust

Genomics england

Genomics England's place in the genomic diagnostic ecosystem



Overview of regulatory ecosystem



Areas of focus

DCB 0129 is an NHS Digital standard

- Focuses more on test order system / front end of the National Genomic Information Service (NGIS)

ISO 15189 – audited by UK Accreditation Service

- Assesses GEL as a diagnostic laboratory

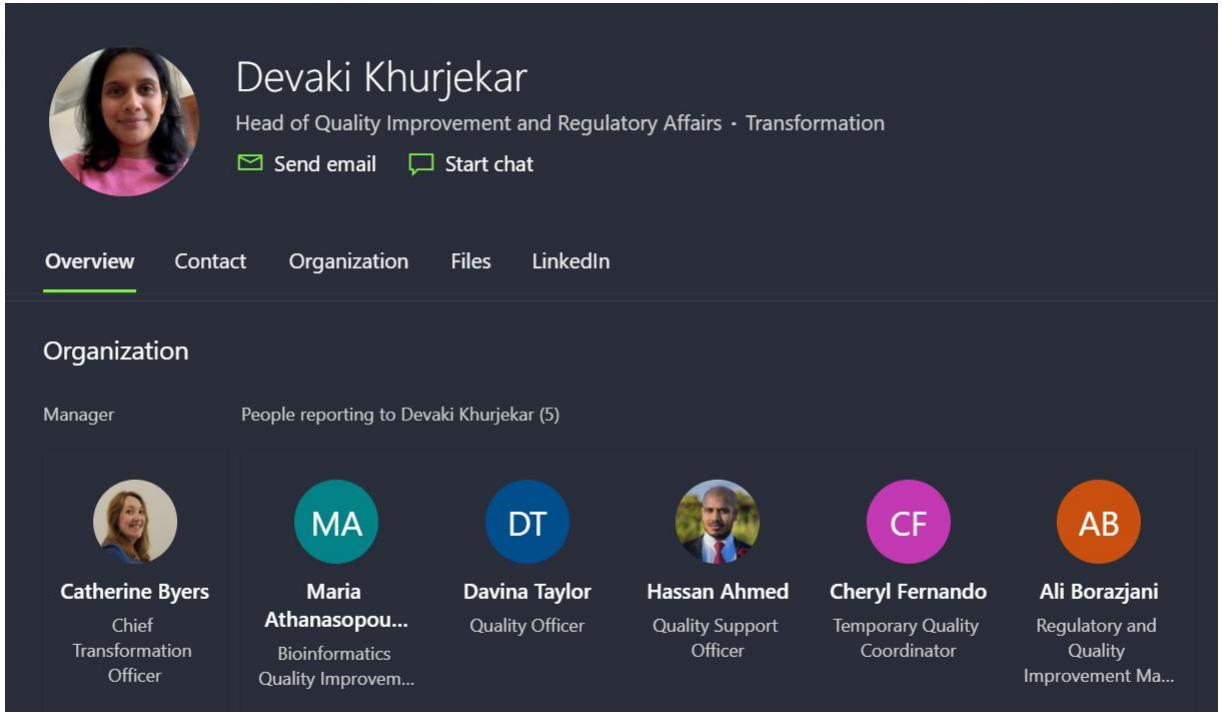
ISO 13485 – audited by British Standards Institution

- Focuses on development of software as a medical device

CE / UKCA marking – working towards self-certification

- Relevant to the bioinformatics pipeline as a medical device

Staffing quality management and regulatory compliance

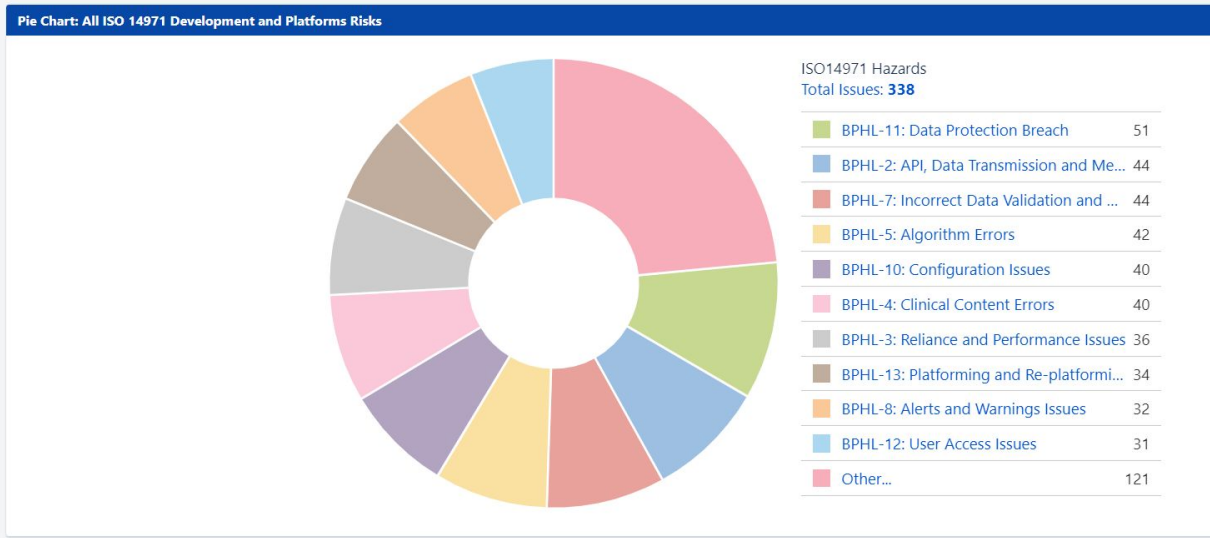


This is the (crucial!) tip of the iceberg – all 82 members of the Healthcare Tribe contribute to our accreditation work

Common themes across all schemes

- Quality management system – designed to meet requirements of all accreditations and applicable regulations
- Documentation standards – versioning, authorization
- Training management – competency demonstration
- Hazard identification and risk management system
- Incident tracking, root cause analysis and corrective and preventive actions
- Rolling internal audit programme tracking compliance with each standard's requirements – also used with 3rd party suppliers
- Participation in relevant EQA schemes (some adaptation sometimes needed)

Risk management system



Consequence Category	Interpretation
Catas	
Major	

CIP-API / CIPAPI-811 Health checks on replica database for prod / CIPAPI-8

Health checks on replica database for prod a

Edit | Comment | Assign | More | Open | Discarded (2) | CSO

Details

Type:	ISO Risk Assessment
Priority:	3. Medium
Affects Version/s:	None
Component/s:	None
Labels:	None
Software Safety Classification:	B: possibility of indirect harm to patient
Sprint:	InterPlat 15.3 (2/12-15/12)
Existing Controls:	Replicadb is using a postgresdb instance rather than a weka file so we already have a replica(slave) database.
Treatment:	Mitigate
Treatment plan:	Update health check endpoint in cipapi-test. Update cipapi-test to have a weka based replica db. Shut off the weka replica db. Show that haproxy returns 503 and a datadog error appears.
Treatment Evidence:	DR report with health check and haproxy shutting down shown here:
Failure Effect:	Currently, without the weka/haproxy PR, there is no 503 service unavailable. This change will make the product inaccessible.
Failsafe:	None
Probability:	Likely (< 1 month)
Impact:	Major
Residual Probability:	Rare (<1 year)
Residual Impact:	Major
Exposure:	4
Residual Exposure:	2

onal	0	1 / E	1 / E	1 / E	2 / D	2 / D
e (<	0	1 / E	1 / E	1 / E	1 / E	1 / E
	0	0	0	0	0	0
	Nil	Minor	Significant	Considerable	Major	Catastrophic

Accreditation challenges in genomic medicine

Accreditation at the cutting edge:

- Genomics is constantly evolving, often lacks certainty, and one size never fits all
- Accreditation is founded on standardization, truthsets, and painstaking change management

When do you introduce a new discovery or technology for diagnostic use?

Subject to changes in the wider environment, e.g. Brexit has led to changes in the CE / UKCA certification process

Addressing these challenges

- Develop internal truthsets, e.g. validation using known diagnoses from the 100,000 Genomes Project
- Employ or contract an experienced quality team, familiar with your national regulatory environment
- Keep evolving and learning from non-conformities, incidents and risk assessments
- Ensure the whole organization buys into the accreditation process
  - Leadership support crucial for resourcing
  - Safety systems stand or fall on those who operate all elements daily

Conclusions

In preparation for offering diagnostic services to the NHS, GEL has invested heavily in accreditation

Accreditation is all about the quality of output, to serve patients as well as we can throughout all our activities

Compliant ways of working have led to major improvements in our quality of communication and efficiency

Questions?

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Application of CLIA/CAP standards to genomic testing

David Bick, M.D.

Application of CLIA/CAP standards to genomic testing

Global Health
Implementation Forum
3-10-21

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

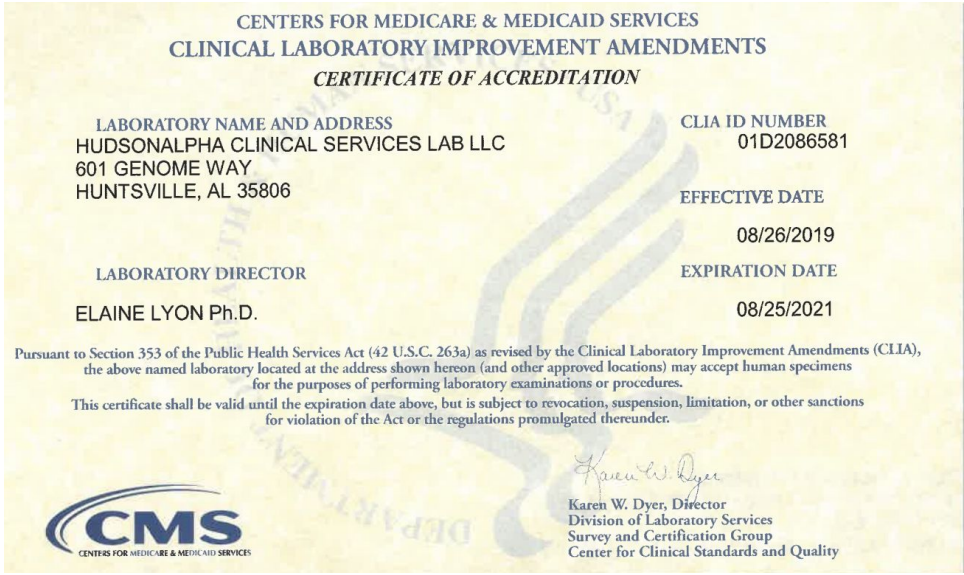
David Bick, M.D.
Smith Family Clinic for Genomic Medicine
HudsonAlpha Clinical Services Laboratory
HudsonAlpha Institute for Biotechnology

Disclosures:

- Chief Medical Officer and Faculty Investigator, HudsonAlpha Institute for Biotechnology
- Medical Director, The Smith Family Clinic for Genomic Medicine, LLC
- Associate Director, The HudsonAlpha Clinical Services Laboratory, LLC
- Member, Genomics England Science Advisory Committee
- Consultant, Northwestern Mutual Life Insurance Company
- Director, iRepertoire Molecular Laboratories, Inc

U.S. clinical laboratory regulation: CLIA and CAP

- Clinical Laboratory Improvement Amendments of 1988 (CLIA)
  - Congress amended Public Health Services Act
  - Federal program for certification and oversight of clinical laboratory testing
  - Applies to all laboratory testing (except research) performed on humans in the U.S
- Centers for Medicare & Medicaid Services (CMS) responsible for CLIA
  - Approximately 260,000 laboratory
  - Every lab required to have a certificate
- College of American Pathologists (CAP) Laboratory Accreditation Program
  - CMS granted the CAP deeming authority
  - A CAP inspection substitute for CMS inspection
  - CAP accreditation is optional



CENTERS FOR MEDICARE & MEDICAID SERVICES
CLINICAL LABORATORY IMPROVEMENT AMENDMENTS
CERTIFICATE OF ACCREDITATION

LABORATORY NAME AND ADDRESS
HUDSONALPHA CLINICAL SERVICES LAB LLC
601 GENOME WAY
HUNTSVILLE, AL 35806

CLIA ID NUMBER
01D2086581

EFFECTIVE DATE
08/26/2019

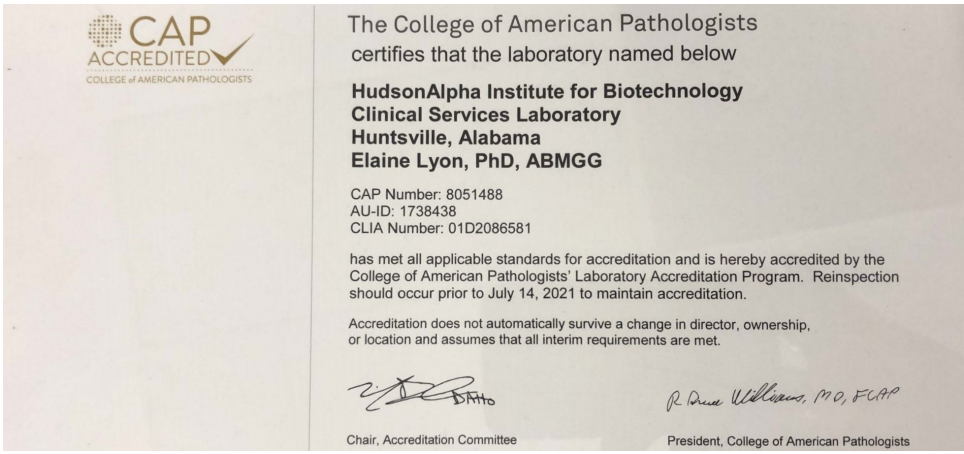
EXPIRATION DATE
08/25/2021

LABORATORY DIRECTOR
ELAINE LYON Ph.D.

Pursuant to Section 353 of the Public Health Services Act (42 U.S.C. 263a) as revised by the Clinical Laboratory Improvement Amendments (CLIA), the above named laboratory located at the address shown hereon (and other approved locations) may accept human specimens for the purposes of performing laboratory examinations or procedures.
This certificate shall be valid until the expiration date above, but is subject to revocation, suspension, limitation, or other sanctions for violation of the Act or the regulations promulgated thereunder.

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

Karen W. Dyer, Director
Division of Laboratory Services
Survey and Certification Group
Center for Clinical Standards and Quality



CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

The College of American Pathologists
certifies that the laboratory named below

HudsonAlpha Institute for Biotechnology
Clinical Services Laboratory
Huntsville, Alabama
Elaine Lyon, PhD, ABMGG

CAP Number: 8051488
AU-ID: 1738438
CLIA Number: 01D2086581

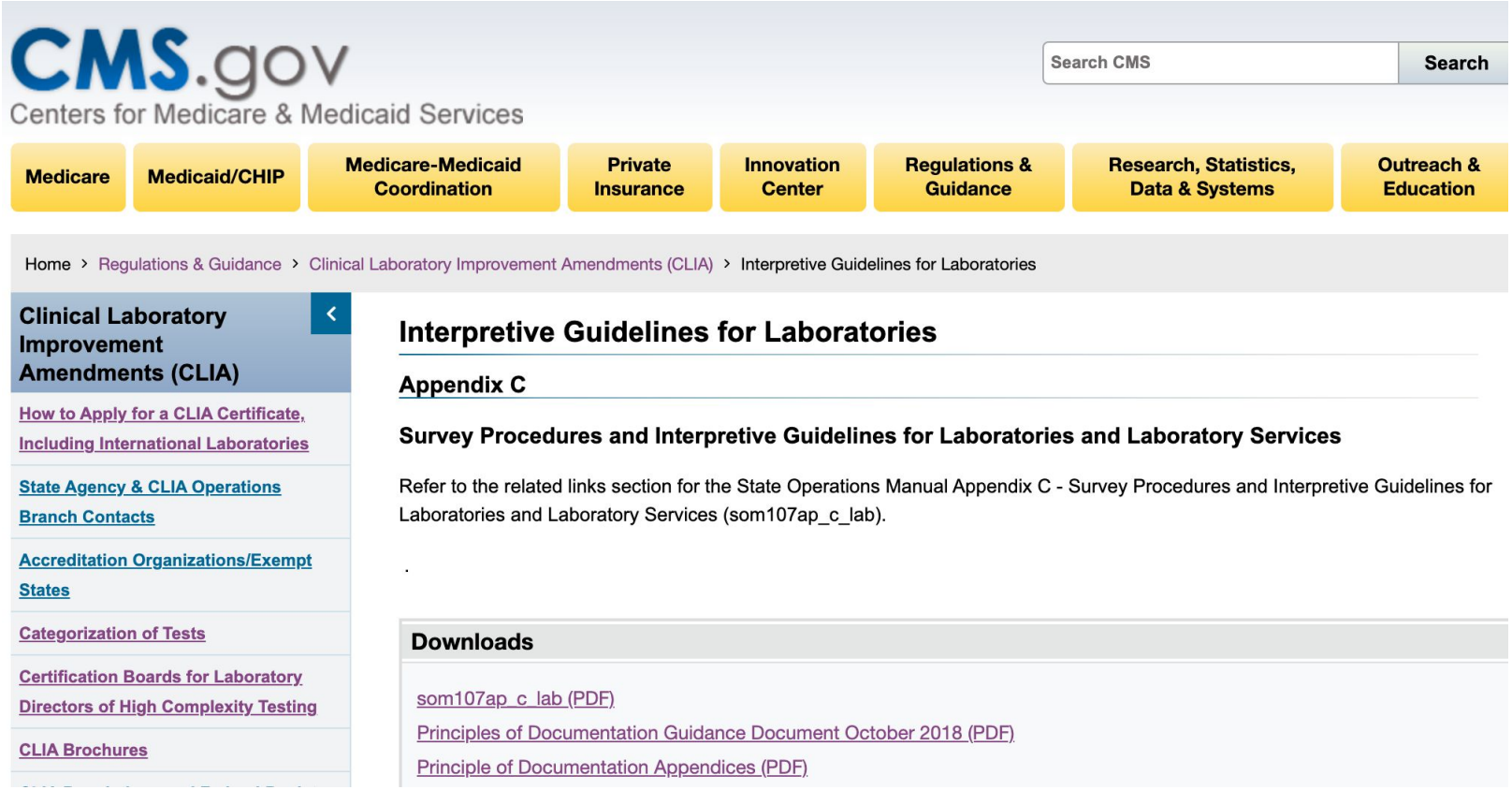
has met all applicable standards for accreditation and is hereby accredited by the College of American Pathologists' Laboratory Accreditation Program. Reinspection should occur prior to July 14, 2021 to maintain accreditation.

Accreditation does not automatically survive a change in director, ownership, or location and assumes that all interim requirements are met.

Chair, Accreditation Committee

R. Dirk Williams, MD, FCAP
President, College of American Pathologists

CLIA – onsite inspection



- Onsite inspection every 2 years – Each state performs inspections
- International Laboratory CLIA Certification Process
- Laboratory directors must meet education, training and experience requirements

State Operations Manual
Appendix C - Survey Procedures and Interpretive Guidelines for Laboratories and Laboratory Services

Table of Contents
(Rev. 166, 02-03-17)

https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/som107ap_c_lab.pdf

CLIA – inspection process

- 418-page manual describes inspection process
  - Inspect facility
  - Interview staff
  - Review lab records & proficiency testing
  - Systems quality assessment
- Set of standards for assessment

EXAMPLE

§493.1235 Standard: Personnel competency assessment policies

As specified in the personnel requirements in subpart M, the laboratory must establish and follow written policies and procedures to assess employee and, if applicable, consultant competency.

Interpretive Guidelines §493.1235

Refer to §§493.1413(b)(8) and 493.1451(b)(8) for specific testing personnel competency requirements and refer to §493.1407(e)(12) and §493.1445(e)(13) for establishing policies to monitor each individual's competency and identify remedial training or continuing education needs. Cite deficiencies at this location when the laboratory has developed but is not following personnel competency policies and procedures. Competency assessment applies to all persons that perform patient testing and/or report patient test results, including but not limited to, technical and clinical consultants, technical supervisors, general supervisors and other laboratory staff.

CAP Laboratory Accreditation Program

All Common

- Proficiency testing
- Procedure manuals
- Specimen collection and handling
- Quality management
- Reporting of results
- Reagents
- Instruments and equipment maintenance/function checks
- Thermometers and temperature-dependent equipment
- Pipettes and analytical balances
- Waived test implementation
- Test method validation/verification–nonwaived tests
- Individualized quality control plan

Laboratory General

- Quality management
- Specimen collection
- Chain-of-custody specimen collection and handling
- Direct-to-consumer testing
- Result reporting
- Quality of water
- Laboratory computer services
- Telepathology and remote data assessment
- Whole slide imaging
- Personnel
- Physical facilities
- Laboratory safety
- California laboratory licensure requirements

Director Assessment

- Laboratory director qualifications
- Laboratory director responsibilities

Molecular Pathology

- Clinical molecular genetics testing, including oncology, inherited disease, pharmacogenomics, HLA tying, forensic identity, and relationship testing applications
- Molecular assay validation
- Methods, such as electrophoresis, PCR, arrays, FISH, and ISH, digital image analysis, and sequencing
- Next-generation sequencing, including noninvasive screening of maternal plasma to detect fetal trisomy
- Hematopoietic progenitor cell engraftment monitoring

- CAP uses CLIA standards but adds granularity & specificity
  - Onsite inspection every other year like CLIA but with self inspection between onsite inspections
- Clinical genomics laboratory
  - Our lab performs whole genome sequencing, tumor molecular testing, microarray, Sanger sequencing, qPCR
  - 4 CAP checklists: All Common, Director Assessment, Laboratory General, Molecular Pathology
  - Molecular Pathology is one of 21 discipline-specific accreditation checklists
  - Total of 517 checklist items on the 4 lists

Example CAP checklist item

Approved **MOL.36118** NGS Lower Limit of Detection

Under Clinical Services Lab (2021 On-Site Inspection) Pre-Inspection Phase » Molecular Pathology

MOL.36117 MOL.36123

Available actions for this item

Phase	2
Requirement	Testing is performed during assay validation to establish the lower limit of detection for sequencing performed on mixed populations.
Evidence of Compliance	* Records of validation used to establish lower limit of detection for sequencing performed on mixed populations AND * Written approval of validations, revalidations and/or confirmation studies AND * Records of review of referral laboratory validations, if applicable
Note	The NGS limit of detection (LOD) for variants consists of two data points: 1) the minimum required depth of coverage at the variant site and 2) minimum variant allele fraction. Determination of the LOD is relevant to several clinical diagnostic scenarios. These include, but are not limited to, detection of somatic variants in tumor samples and cell free DNA, germline variant detection in chimerism and mosaicism, maternal blood screening for fetal trisomy, detection of antimicrobial resistance mutations, microbiome analyses, identification of pathogens by targeted or metagenomic approaches, and identification of the presence/absence of clinically relevant microbial genes. Lower limit of detection for variants may vary based on variant type (eg, single nucleotide variants, indels, copy number variants and other structural variants, such as translocations and inversions) or target characteristics. In the case of microbial testing, LOD may be influenced by organism genome size. During validation, determination of LOD is required for each variant and microbial target type that the assay is intended to detect. For antiviral drug resistance testing, determination of LOD must take into account the virus load and variant allele fraction. Validation of LOD requires inclusion of samples whose variant allele fraction or percentage has been determined by orthogonal methods. Cell line mixtures, plasmid spike in studies, and the use of in silico NGS data sets may augment, but not supplant, the use of patient samples.

Training, competency documentation

User	Documentation Type	Status	Assigned On	Completed On	Expiration Date	Files
Bick, David	ABMGG Certification	Completed	8/11/2020	1/1/2020 Date entered by user	n/a	David Bick - ABMGG Certification
Bick, David	Annual HIPAA Training Record	Completed	8/11/2020	8/27/2020	n/a	David Bick - HIPAA Training Record
Bick, David	Annual Safety Training	Completed	8/11/2020	9/2/2020 Date entered by user	n/a	David Bick - Safety Training
Bick, David	CITI Training Records	Completed	8/11/2020	9/7/2020	2/2/2022	David Bick - CITI Training Records
Bick, David	CSL HIPAA Compliance Program Agreement	Confirmed	5/17/2017	2/28/2018	n/a	CSL HIPAA Compliance Program Agreement
Bick, David	Curriculum Vitae/Resume	Completed	8/12/2020	2/25/2021	n/a	David Bick - CV David Bick - CV/Resume
Bick, David	Diploma/Transcript	Confirmed	5/17/2017	6/5/2017	n/a	Academic Diploma
Bick, David	Hepatitis B Vaccination Form	Completed	8/12/2020	8/27/2020	n/a	David Bick - Hepatitis B Vaccination Form
Bick, David	Job Description	Completed	2/8/2021	2/8/2021	n/a	David Bick - Job Description (Associate Clinical Laboratory Director) David Bick - Job Description (Clinical Consultant)
Bick, David	Letter of Delegation	Completed	8/12/2020	6/4/2020 Date entered by user	n/a	David Bick - Letter of Delegation
Bick, David	Licensure and Certification	Completed	3/16/2020	10/5/2020	n/a	Alabama License (expires 2020-12-31) Wisconsin License (expires 2021-10-31) ABMGG Certificate 2020 Tennessee License (expires 2021-05-31) Alabama Controlled Substance License (expires 2020-12-31) NYSDOH Certification 2020-21 (expires 9/2021)
Bick, David	Metrics Report Review Training Checklist	Completed	8/11/2020	1/17/2020 Date entered by user	n/a	David Bick - Training Checklist - Metrics Report Review
Bick, David	Safety Orientation	Completed	8/12/2020	6/6/2017 Date entered by user	n/a	David Bick - Safety Orientation
Bick, David	Supervisor Competency Assessment Report	Completed	8/13/2020	6/2/2020 Date entered by user	n/a	David Bick - Supervisor Competency Assessment (2018-06-12) David Bick - Supervisor Competency Assessment (2020-06-02)
Bick, David	Tertiary Analysis Training & Competency Assessments	Completed	8/11/2020	6/4/2020 Date entered by user	n/a	David Bick - Training Experience - Tertiary Analysis David Bick - 6-Month Competency Assessment - Tertiary Analysis David Bick - Annual Competency Assessment - Tertiary Analysis David Bick - Annual Competency Assessment - Tertiary Analysis

Quality Management System

Quality Management System(QMS) program provides, manages, and secures quality laboratory testing services that will ensure accurate patient results and will meet customer requirements

Quality Management System

Program

- Quality Policy, Goals, and Objectives
- Quality System Essentials Focus
  - QSE 1 – Organization
  - QSE 2 – Personnel
  - QSE 3 – Purchasing and Inventory
  - QSE 4 – Equipment
  - QSE 5 – Process Control
  - QSE 6 – Documents and Records
  - QSE 7 – Nonconforming Event Management
  - QSE 8 – Assessment
  - QSE 9 – Continual Improvement
  - QSE 10 – Service and Satisfaction
  - QSE 11 – Facilities and Safety
  - QSE 12 - Information Management
- Quality Management
- Quality Records

Quality Management program

Policies

- Quality Management Committee (QMC)
- Personnel
- Quality Control
- Quality Assurance
  - Turnaround time (TAT) monitoring
  - Reagent phase-In and new lot testing
  - Event Reporting
  - Accessioning
  - NGS/Bioinformatics
  - Tertiary Analysis
  - Global Screening Array
  - TaqMan
  - Pharmacogenetic Variant Panel
  - Sanger Sequencing
  - IT
- Quality Improvement (QI) Programs
- Proficiency Testing

Quality Assurance program

Procedures

- Quality Indicators
- Pre-Analytical Metrics
- Analytical Metrics
  - General Analytical Metrics
  - Genome Sequencing Analytical Metrics
  - Global Screening Array Analytical Metrics
  - TaqMan Analytical Metrics
  - Sanger Sequencing Analytical Metrics
- Post-Analytical Metrics
  - General Post-Analytical Metrics
  - Genome Sequencing Post-Analytical Metrics
  - Global Screening Array Post-Analytical Metrics
  - TaqMan Post-Analytical Metrics
  - Sanger Sequencing Post-Analytical Metrics
- Quality Indicator Report

Effort/cost associated with CAP/CLIA maintenance

- 1/3 of one individual's time to CAP/CLIA tasks
- Cost of proficiency testing program
- Personnel time spent in ongoing training (safety, HIPAA..) and competency
- Preparation for CAP/CLIA inspection this year:
  - 2 hour meeting each week for 3 months
  - 3 directors and 6 other lab staff
  - Additional time 'between meeting' for the staff to create policies, procedures etc...

Molly Schroeder, PhD. perfectly summed up the clinical laboratory regulatory framework

"CAP is a lifestyle"

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

Building a Framework for the Adoption of GA4GH Standards

Creating a European Maturation Model through GA4GH Standards

Melissa Konopko (Melissa.Konopko@elixir-europe.org)

Scientific Product Manager

www.elixir-europe.org

Access 1M genomes across borders

- Coordinated, secure, federated environment will enable population scale genomic, phenotypic, and biomolecular data to be accessible across international borders to support personalised medicine
- Lessons learned & solutions developed should be taken from existing infrastructures and ongoing data sharing efforts in cancer, population genetics & rare disease areas
- This will rely on a suite of interoperable standards…

nature REVIEWS GENETICS

Roadmap | Published: 27 August 2019

Leveraging European infrastructures to access 1 million human genomes by 2022

Gary Saunders, Michael Baudis, […] Serena Scollen

Nature Reviews Genetics (2019) | Download Citation

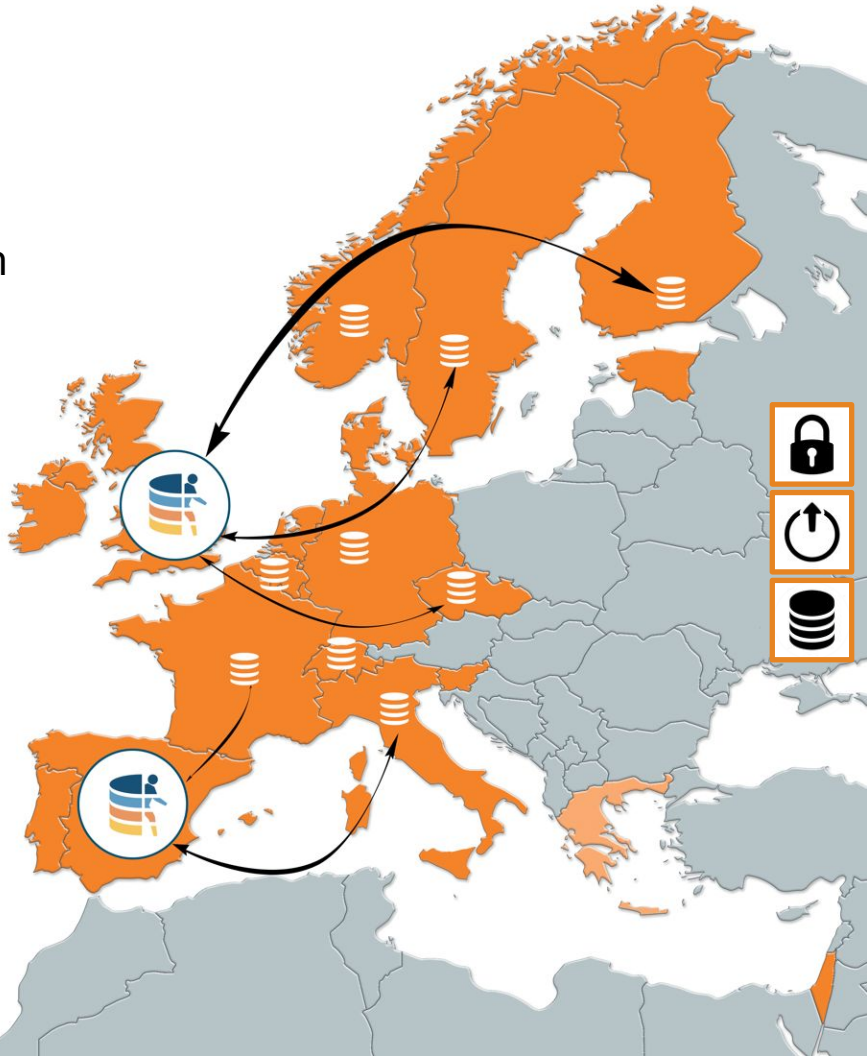
Abstract

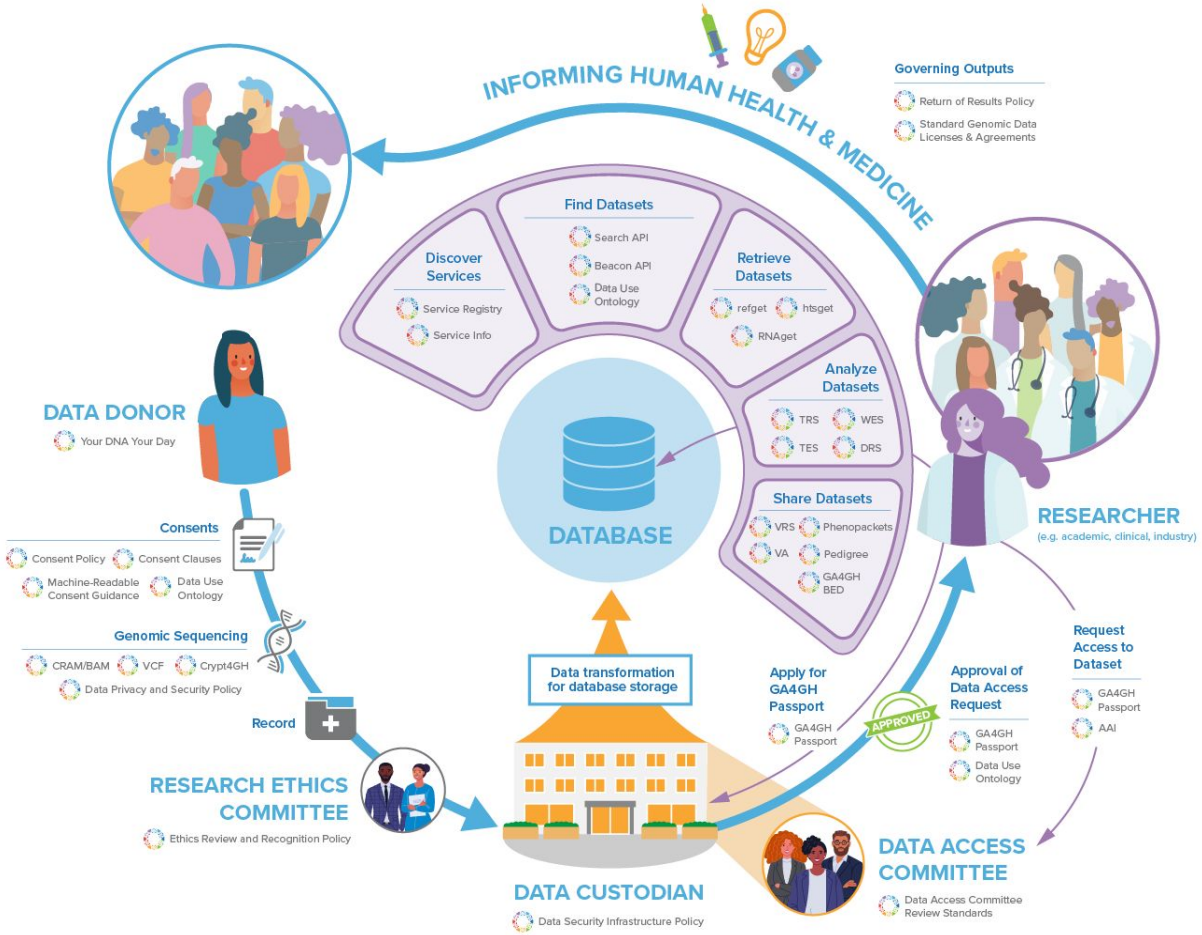
Human genomics is undergoing a step change from being a predominantly research-driven activity to one driven through health care as many countries in Europe now have nascent precision medicine programmes. To maximize the value of the genomic data generated, these data will need to be shared between institutions and across countries. In recognition of this challenge, 21 European countries recently signed a declaration to transnationally share data on at least 1 million human genomes by 2022. In this Roadmap, we identify the challenges of data sharing across borders and demonstrate that European research infrastructures are well-positioned to support the rapid implementation of widespread genomic data access.

https://t.co/87fYMyPlGO

Federation of human genome data

- Many national datasets from human research participants needs to be **stored locally**
- ELIXIR developing a federated infrastructure
- Based the GA4GH suite of interoperable, reusable, adopted, and fit-for-purpose **standards**



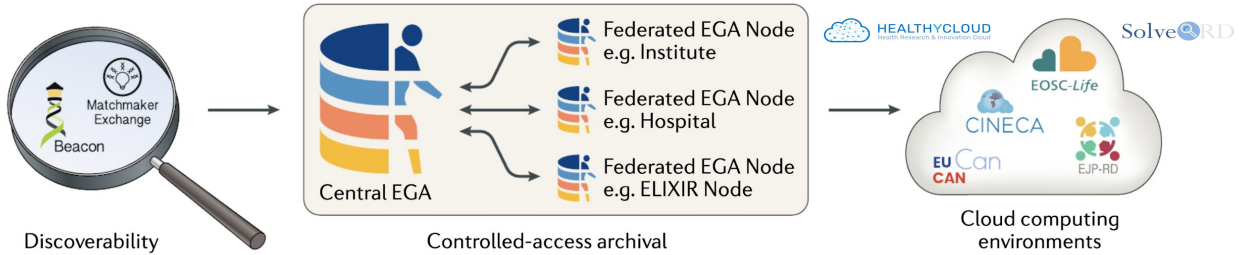

INFORMING HUMAN HEALTH & MEDICINE
Governing Outputs
Return of Results Policy
Standard Genomic Data Licenses & Agreements
Find Datasets
Search API
Beacon API
Data Use Ontology
Discover Services
Service Registry
Service Info
Retrieve Datasets
refget
htsget
RNAget
Analyze Datasets
TRS
WES
TES
DRS
Share Datasets
VRS
Phenopackets
VA
Pedigree
GA4GH BED
DATABASE
DATA DONOR
Your DNA Your Day
RESEARCHER
(e.g. academic, clinical, industry)
Consents
Consent Policy
Consent Clauses
Machine-Readable Consent Guidance
Data Use Ontology
Genomic Sequencing
CRAM/BAM
VCF
Crypt4GH
Data Privacy and Security Policy
Record
RESEARCH ETHICS COMMITTEE
Ethics Review and Recognition Policy
Data transformation for database storage
DATA CUSTODIAN
Data Security Infrastructure Policy
Apply for GA4GH Passport
GA4GH Passport
APPROVED
Approval of Data Access Request
GA4GH Passport
Data Use Ontology
Request Access to Dataset
GA4GH Passport
AAI
DATA ACCESS COMMITTEE
Data Access Committee Review Standards

Connecting Europe via Standards-Based Federation

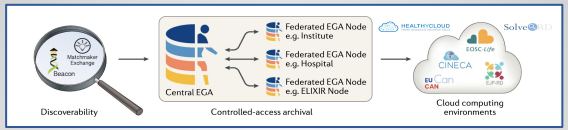
GA4GH Standards

European Projects

Beacon	DUO	TRS
Phenopackets	Read file formats	WES
AAI	AAI	DRS
	htget	TES
	refget	



Connecting Europe via Standards-Based Federation



B1MG Beyond one Million Genomes

High-Level & Technical Maturity Models

elixir CONVERGE

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

Standards Maturity Model

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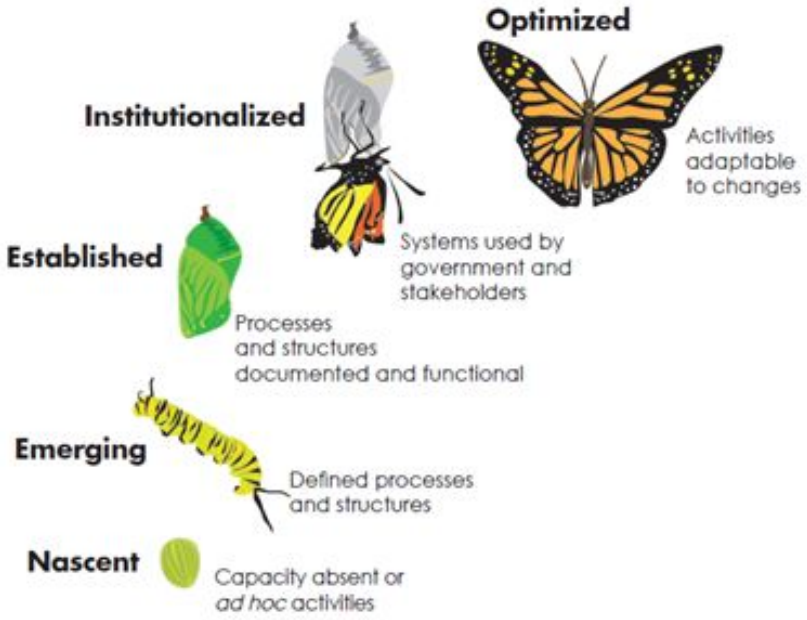
Maturity Model Concept

- A maturity level model is an instrument to **assess and continually improve organizational processes**
- Concept of the maturity level models consists of a **sequence of discrete maturity levels for specific domains**
- Maturity level models are indicators of progress, identifying weaknesses to **generate an improvement plan**



from: https://www.measureevaluation.org/resources/tools/health-information-systems-interoperability-toolkit

Slide Courtesy of Astrid Vincente

Maturity Model Basic Format

Functional Area	Level			
	Level 1	**Level 2**	**Level 3**	**Level 4**
Security	DSIP	Breach Response	Crypt4GH	Malfeasance Detection
Policy	The Framework	DACReS	Conse Policy	Familial Consent Clauses
Data Storage	VCF	SAM, BAM	CRAM	
Discoverability	Beacon DUO		Search	
Data Access	DUO	Pa sports	AAI	Machine Readable Consents
Retrieval & Analysis	Phenopackets	HTSget	TRS WES VRS	VA RNAget DRS

A sample of potential functional areas and levels with associated standards.

B1MG vs ELIXIR:GA4GH Maturity Models

High-Level Maturity Model

- Focused on Health Care Sector
- Covers ELSI & Technical domains
- High level view without defining specific solutions
- Intended for decision-makers at the national or regional level

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Collaborate. Innovate. Accelerate.

Standards Maturity Model

- Intended for both Health Care & Research sectors
- Mainly Technical with some Policy standards
- Specific & detailed to provide technical guidance and encourage international interoperability
- Intended for technical implementers who need to turn high level decisions into action

elixir

ELIXIR:GA4GH Maturity Model

- Supports technical implementers by
  - Translating organisational genomic and associated metadata sharing goals into clear standards requirements
  - Linking out to guidance such as the GA4GH Starter Kit and standards documentation
  - Plans to include costing information for organisational planning and grant writing
- Standards chosen and leveled by
  - Inclusion in ELIXIR implementations, potentially by version
  - Interdependency and connection from the GA4GH Connection Demos (FASP) and Starter Kit projects
  - Alignment to B1MG, FAIRplus, ELIXIR CONVERGE, and HealthyCloud maturity models
- Aligns to the future vision of a pan-European (and global) federated human health data network to connect across ELIXIR Nodes and beyond

ELIXIR:GA4GH MM: What's New?

- Broadened alignment across projects: B1MG, ELIXIR Converge, HealthyCloud & FAIRplus
- Planned interface with the GA4GH FASP and Starter Kit projects to provide guidance from policy level all the way down to detailed implementation guidance

- Clarified user experience goals: Technical solutions to policy demands
- Expect to present a draft on GA4GH Plenary

Any Questions?

bit.ly/ELIXIRGA4GHSurvey

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

End-to-End Implementations of GA4GH Standards

@ZornitzaS
@AusGenomics

Acute Care Genomics

GA4GH Real World Implementation: Australian Genomics

Zornitza Stark

Australian Genomics Health Alliance

Acute Care Genomics 2018-23:
Piloting a national approach

400 infants and children

Trio whole genome sequencing

Time to report 3.0 days

~50% diagnostic yield

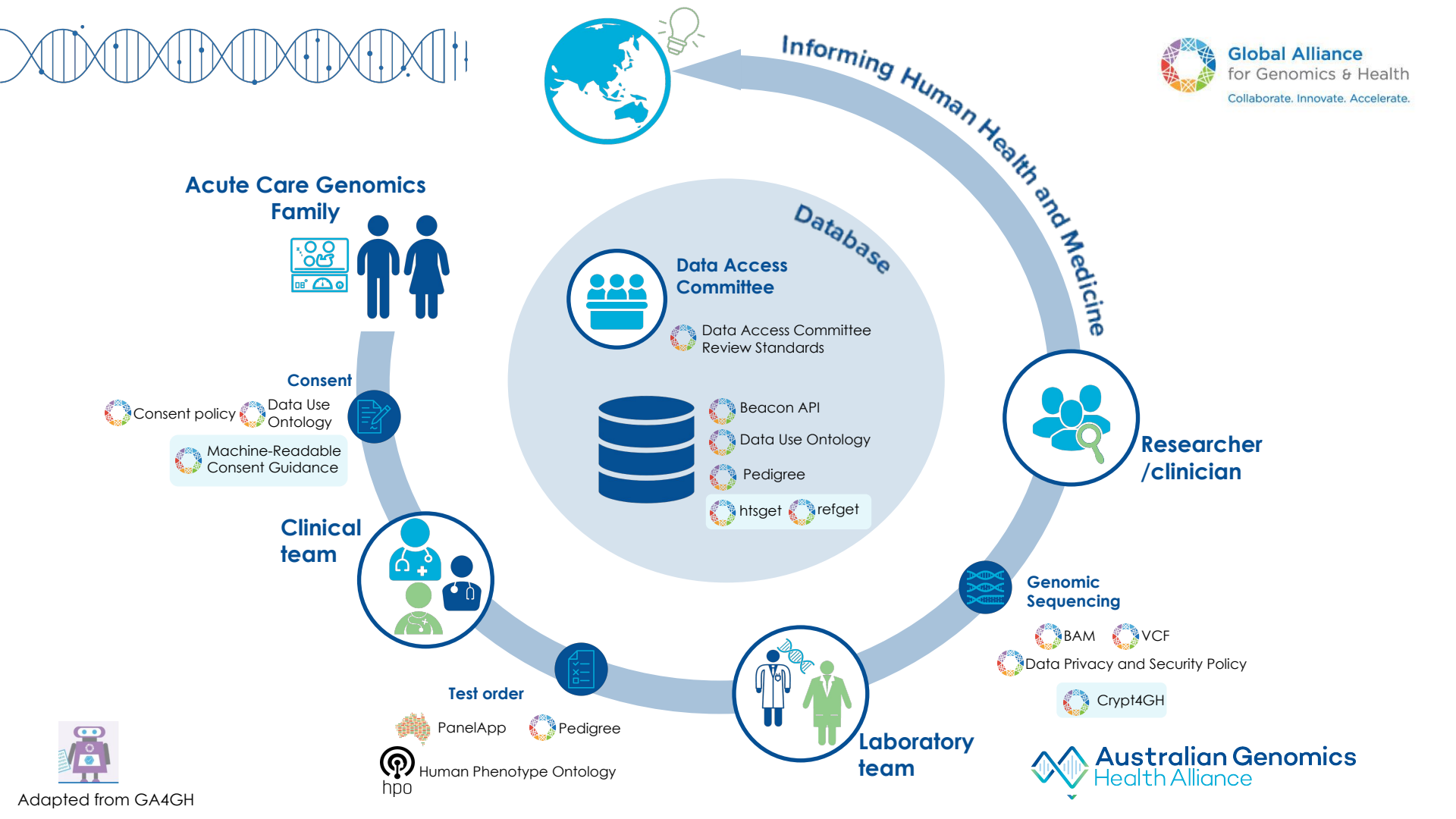
Research

JAMA | Original Investigation

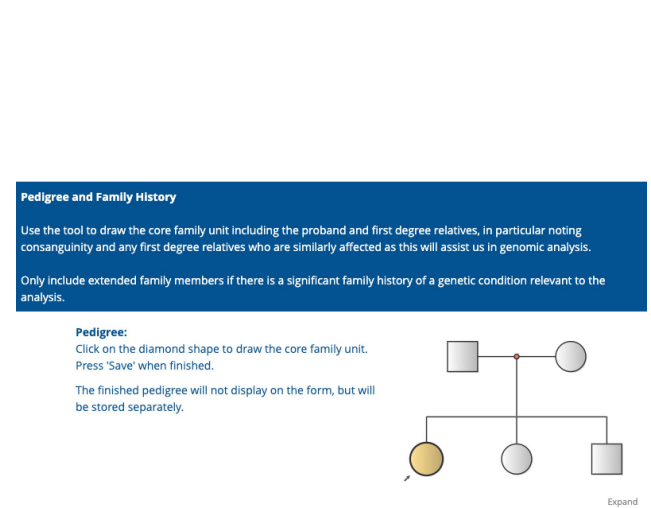
Feasibility of Ultra-Rapid Exome Sequencing in Critically Ill Infants and Children With Suspected Monogenic Conditions in the Australian Public Health Care System

Australian Genomics Health Alliance Acute Care Flagship

Australian Genomics Health Alliance

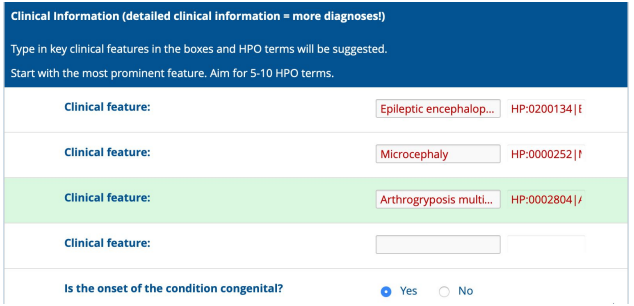

Global Alliance for Genomics & Health
Collaborate. Innovate. Accelerate.
Informing Human Health and Medicine
Acute Care Genomics Family
Database
Data Access Committee
Data Access Committee Review Standards
Beacon API
Data Use Ontology
Pedigree
htsget
refget
Consent
Consent policy
Data Use Ontology
Machine-Readable Consent Guidance
Researcher /clinician
Clinical team
Genomic Sequencing
BAM
VCF
Data Privacy and Security Policy
Crypt4GH
Test order
PanelApp
Pedigree
Human Phenotype Ontology
hpo
Laboratory team
Australian Genomics Health Alliance
Adapted from GA4GH

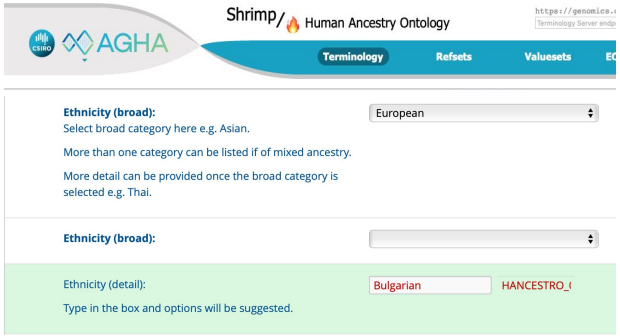
E-test order for Rare Disease



Pedigree

hpo



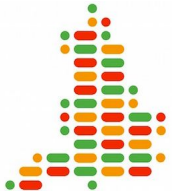


REDCap Pedigree
Plugin: https://github.com/aehrc/redcap_pedigree_editor
FHIR OWL (supports Human Ancestry Ontology in REDCap): https://github.com/aehrc/fhir-owl
REDCap FHIR Terminology Server
Plugin: https://github.com/aehrc/redcap_fhir_ontology_provider

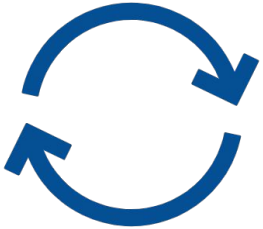
FHIR

E-test order for Rare Disease

Australian Genomics Health Alliance



ClinGen
Clinical Genome Resource



GenCC
The Gene Curation Coalition

Acute Care Genomics Test Order

Virtual Panels for this Analysis

Please select relevant virtual panels to guide the analysis.

All patients will have Mendeliome analysis, including analysis for copy number variants and variants in the mitochondrial genome.

For details on the gene content of panels, please go to PanelApp Australia.

Virtual Gene Panel 1:	Genetic Epilepsy
Virtual Gene Panel 2:	Microcephaly
Virtual Gene Panel 3:	Arthrogryposis

Supporting evidence-based diagnostic practice

Australian Genomics Health Alliance

E-consent for Rare Disease

Australian Genomics Health Alliance

Acute Care Genomics Test Order

CONSENT FORM FOR GENOMIC TESTING AND PARTICIPATION IN RESEARCH

Please select each box to indicate that you have read each point.

About the Test

- Genomic test results are based on current knowledge, which may change in the future.
- If I change my mind, I can choose not to be told about the result.

* must provide value

I agree with the points above

Potential Outcomes

- This test might find a cause for the condition(s).
- This test might not find a cause for the condition(s).
- The result might be of *'unknown significance'*, which means it cannot be understood today.
- There is a chance that genomic testing could find other medical conditions (incidental findings).
- Genomic testing may show unexpected family relationships.
- Further testing or information sharing may be needed to finalise the result.

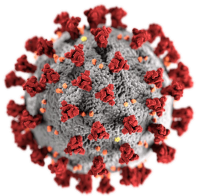
* must provide value

I agree with the points above

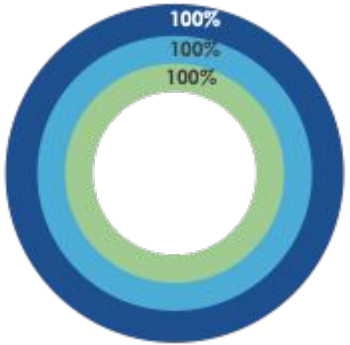
Australian Genomics Health Alliance

Improved clinical data capture

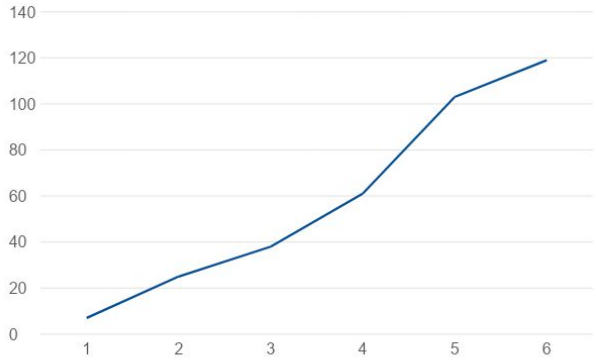
4min 35sec



Telegenomics



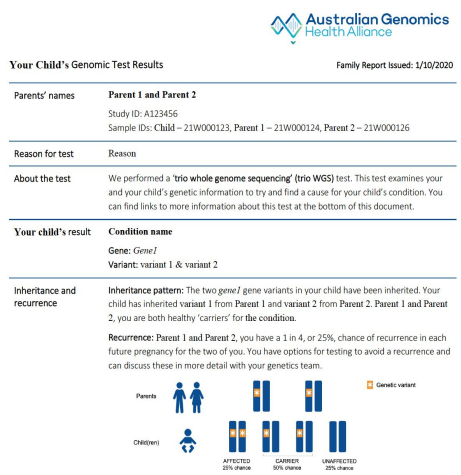
Data completeness



Australian Genomics Health Alliance

Data sharing and secondary use

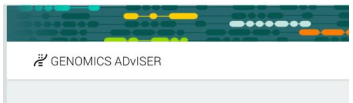
Lab report



Family report

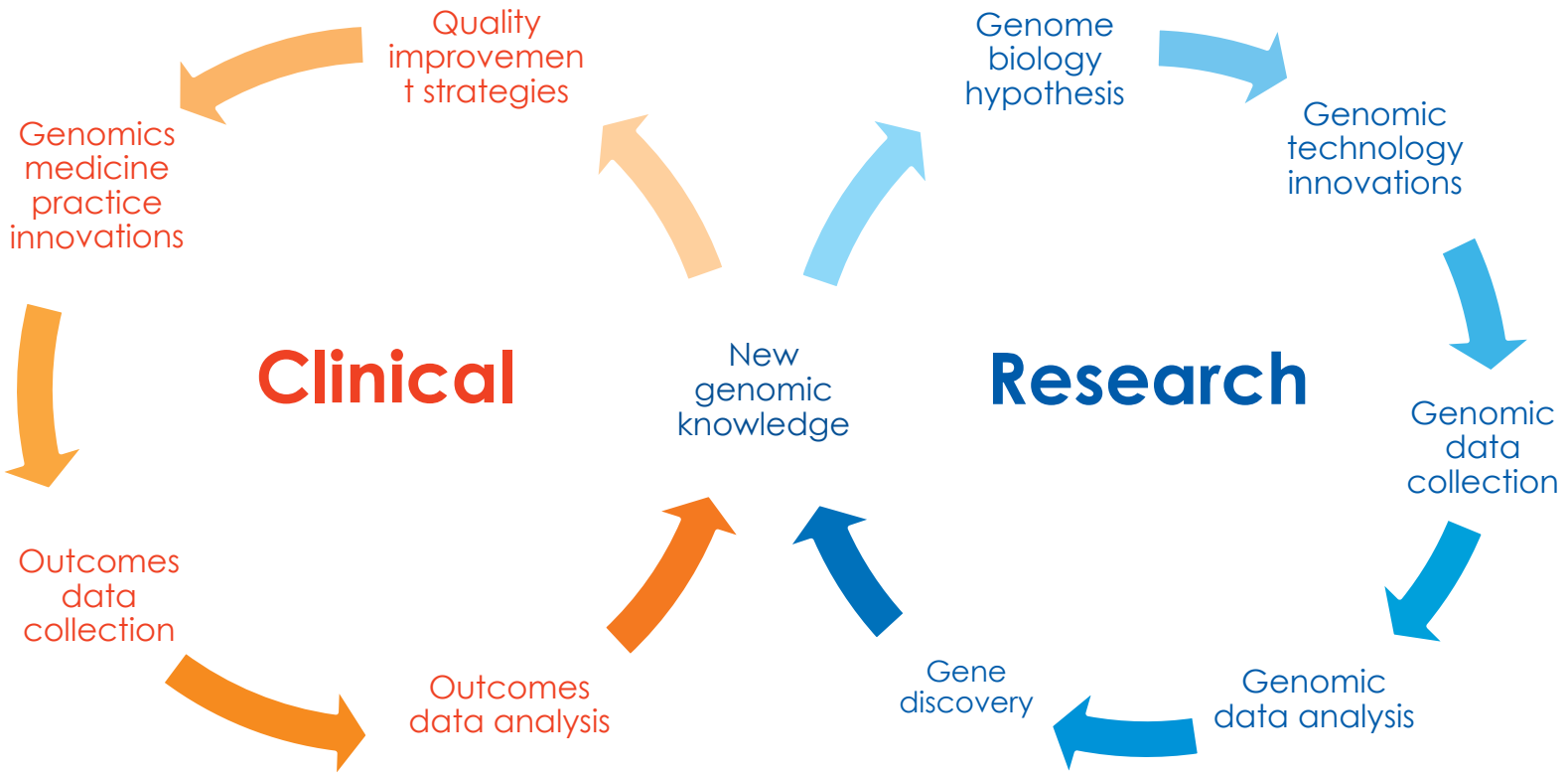
ClinVar
Clinically relevant variation

EUROPEAN GENOME-PHENOME ARCHIVE



Australian Genomics Health Alliance

Improving health outcomes



Adapted from Green *et al.* (2020) Nature

Australian Genomics Health Alliance

Learning from scaling up ultra-rapid genomic testing for critically ill children to a national level

Stephanie Best[1,2✉], Helen Brown[3], Sebastian Lunke[4,5], Chirag Patel[6], Jason Pinner[7], Christopher P. Barnett[8], Meredith Wilson[9,10], Sarah A. Sandaradura[9,11], Belinda McClaren[2,5], Gemma R. Brett[4,5], Jeffrey Braithwaite[1] and Zornitza Stark[2,4,5]

RAPID COMMUNICATION

WILEY HGVS

Biallelic loss of function variants in *PPP1R21* cause a neurodevelopmental syndrome with impaired endocytic function

Parental experiences of ultrarapid genomic testing for their critically unwell infants and children

Gemma R. Brett, MGenCouns, MSc[1,2], Melissa Martyn, PhD[2,3,4], Fiona Lynch, MGenCouns[2,4,5], Michelle G. de Silva, MGenCouns, PhD[1,2,4,5], Samantha Ayres, MGenCouns[1,5], Lyndon Gallacher, MGenCouns[1,2], Kirsten Boggs, MGenCouns[5,6,7], Anne Baxendale, GradDipGenCouns[5,8], Sarah Schenscher, MGenCouns[5,8], Sarah King-Smith, PhD[5,9], Lindsay Fowles, MSc(GenCouns), PhD[5,10], Amanda Springer, MGenCouns[11,12], Sebastian Lunke, PhD[1,2,5], Anand Vasudevan, MD[13], Emma Krzesinski, MBChB, MMed[11,12], Jason Pinner, MD[6], Sarah A. Sandaradura, MBChB, PhD[7,14], Christopher Barnett, MBBS[8], Chirag Patel, MD[10], Meredith Wilson, MD[7] and Zornitza Stark, BMBCh, DM[1,2,5]

Rapid exome sequencing and adjunct RNA studies confirm the pathogenicity of a novel homozygous *ASNS* splicing variant in a critically ill neonate

Lauren S. Akesson[1,2,3] | Adam Bournazos[4,5] | Andrew Fennell[3,6] | Emma I. Krzesinski[3,6] | Kenneth Tan[6,7] | Amanda Springer[3,6] | Katherine Rose[3,6] | Ilias Goranitis[8,9] | David Francis[1] | Crystle Lee[1] | Fathimath Faiz[10] | Mark R. Davis[10] | John Christodoulou[1,2,9,11] | Sebastian Lunke[1,9,12] | Zornitza Stark[1,2,9] | Matthew F. Hunter[3,6] | Sandra T. Cooper[4,5,13]

Genetic counseling in pediatric acute care: Reflections on ultra-rapid genomic diagnoses in neonates

Samantha Ayres[1,2,3] | Lyndon Gallacher[1,3,4] | Zornitza Stark[1,3,4] | Gemma R. Brett[1,2,3,4]

The expanding *LARS2* phenotypic spectrum: HLASA, Perrault syndrome with leukodystrophy, and mitochondrial myopathy

Lisa G. Riley[1,2] | Joëlle Rudinger-Thirion[3] | Magali Frugier[3] | Meredith Wilson[4,5] | Melissa Luig[6] | Thushari Indika Alahakoon[7] | Cheng Yee Nixon[8,9] | Edwin P. Kirk[9,10] | Tony Roscioli[10] | Sebastian Lunke[11,12,13] | Zornitza Stark[11,13,14] | Klaas J. Wierenga[14,16] | Sirish Palle[15] | Maie Walsh[17] | Emily Higgs[17] | Susan Arbuckle[18] | Shalini Thirukeswaran[14,19] | Alison G. Compton[14,19] | David R. Thorburn[11,14,19] | John Christodoulou[2,11,13,14,19]

Rapid Challenges: Ethics and Genomic Neonatal Intensive Care

Christopher Gyngell, BA/BSc, MA, PhD[a,b] Ainsley J. Newson, BSc, LLB, PhD[c] Dominic Wilkinson, MBBS, DPhil[d,e] Zornitza Stark, MA, BM BCh, MBioeth, DM[e,f,g] Julian Savulescu, B Med Sci, MA, MB BS, PhD[b,e]

BRAIN

A JOURNAL OF NEUROLOGY

LETTER TO THE EDITOR

IREB2-associated neurodegeneration

Monica S. Cooper[1,2,3] Zornitza Stark[1,3,4] Sebastian Lunke,[1,3,4] Teresa Zhao[1] and David J. Amor[1,2,3,4]

Rapid acute care genomics: Challenges and opportunities for genetic counselors

Fiona Lynch[1,2,3] | Amy Nisselle[1,2,3] | Clara L. Gaff[1,2,3,4] | Belinda McClaren[1,2,3]

RESEARCH ARTICLE

Human Mutation HGVS WILEY

Missense variants in *TAF1* and developmental phenotypes: Challenges of determining pathogenicity

Clinical genomic testing: what matters to key stakeholders?

Stephanie Best[1,2] · Zornitza Stark[2,3,4] · Peta Phillips[2] · You Wu[5] · Janet C. Long[1] · Natalie Taylor[6,7] · Jeffrey Braithwaite[1] · John Christodoulou[4,8] · Ilias Goranitis[2,5]

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European Journal of Human Genetics
https://doi.org/10.1038/s41431-019-0477-3

ESHG

ARTICLE

Early diagnosis of Pearson syndrome in neonatal intensive care following rapid mitochondrial genome sequencing in tandem with exome sequencing

Lauren S. Akesson[1,2,3] · Stefanie Eggers[1] · Clare J. Love[1] · Belinda Chong[1] · Emma I. Krzesinski[3,4] · Natasha J. Brown[1,2] · Tiong Y. Tan[1,2] · Christopher M. Richmond[1] · David R. Thorburn[1,2,3] · John Christodoulou[1,2,5,6] · Matthew F. Hunter[3,4] · Sebastian Lunke[1,6,7] · Zornitza Stark[1,2,6]

Attitudes of Australian health professionals towards rapid genomic testing in neonatal and paediatric intensive care

Zornitza Stark[1,2,3] · Amy Nisselle[1,2,3] · Belinda McClaren[1,2,3] · Fiona Lynch[1,2,3] · Stephanie Best[4] · Janet C. Long[4] · Melissa Martyn[2,3,5] · Chirag Patel[6] · Luregn J. Schlapbach[7,8,9,10] · Christopher Barnett[11] · Christiane Theda[5,3,12] · Jason Pinner[13] · Marcel E. Dinger[14,15,16] · Sebastian Lunke[1,2,3] · Clara L. Gaff[1,2,5,17]

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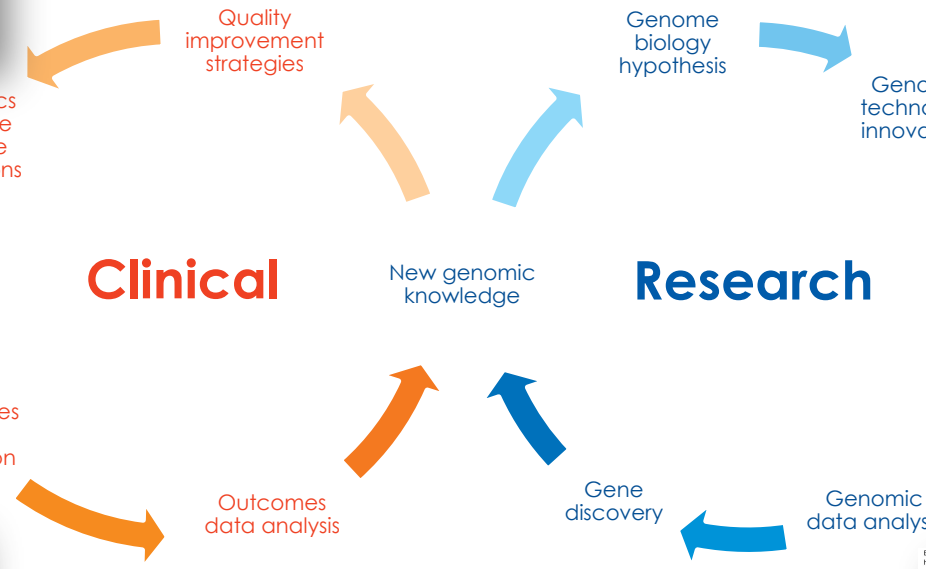
JAMA | Original Investigation

Feasibility of Ultra-Rapid Exome Sequencing in Critically Ill Infants and Children With Suspected Monogenic Conditions in the Australian Public Health Care System

Australian Genomics Health Alliance Acute Care Flagship



Australian Genomics Health Alliance

Adapted from Green *et al.* (2020) Nature

Acute Care Genomics Team

Clinical Lead: Zornitza Stark
Project Officer: Sophie Bouffler

VIC: Zornitza Stark, Matthew Hunter, Anand Vasudevan, Michelle de Silva, Gemma Brett, Sam Ayres, Lyndon Gallacher, Amanda Springer

NSW: Sarah Sandaradura, Jason Pinner, Meredith Wilson, Himanshu Goel, Kirsten Boggs

QLD: Chirag Patel

SA: Christopher Barnett, Anne Baxendale

NT: Tiong Tan

WA: Ben Kamien

TAS: Mathew Wallis

ACT: Mary-Louise Freckmann

Sub-specialists: Christiane Theda, John Christodoulou, Katherine Howell, Ben Gelbart

Laboratory Lead: Sebastian Lunke

VCGS Pathology: Sebastian Lunke, Simon Sadedin Belinda Chong

NSW Laboratory Lead: Bruce Bennetts

SA Laboratory Lead: Karin Kassahn

QLD Laboratory Lead: Ben Lundie

Evaluation:
Implementation Science: Stephanie Best, Janet C Long, Jeffrey Braithwaite

Education: Clara Gaff, Belinda McClaren, Amy Nisselle, Melissa Martyn, Fran Maher, Giulia McCorkell

Additional Findings: Clara Gaff, Elly Lynch, Melissa Martyn, Martin Delatycki, Lil Downie, Ling Lee

Health Economics: Ilias Goranitis

Ethics: Julian Savulescu, Chris Gyngell, Danya Vears, Lynn Gillam

Australian Genomics:

Tiffany Boughtwood

Matilda Haas, Dorothy Illing, Merryn Pearce

State/Territoy Project Officers: Alessandra Bray, Michael Quinn, Matilda Jackson, Denise Howting, Tessa Mattiske, Keri Finlay

Data Management: David Hansen, Alejandro Metke, Stefanie Elbracht-Leong, Sarah Casauria, Vana Madelli, Oliver Hofmann

Australian Genomics Health Alliance

GHIF 10th March 2021

Genomics England - Diagnostics

Richard Scott – Clinical Director, Genomics England

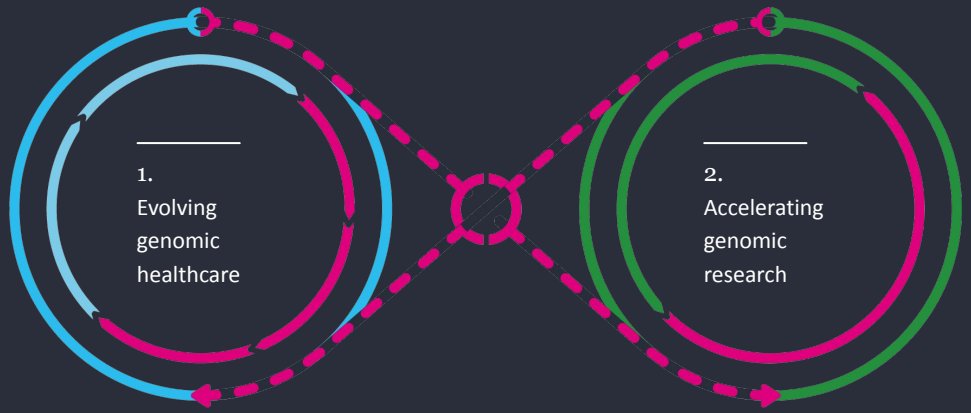
How we're changing

…now we are changing our approach and focus:

Project → Platform

Our mission is to refine, scale and continually evolve our ability to enable others to deliver healthcare and conduct genomic research

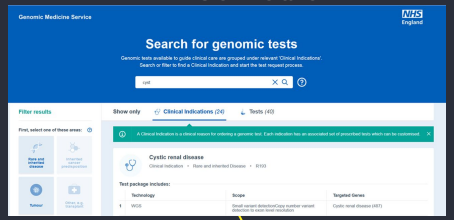
The Infinity Loop



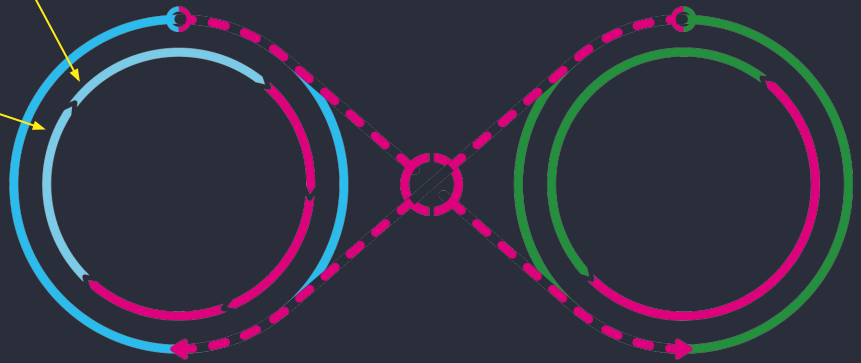
Making “the Loop” work as an efficient, robust and scalable system will help…

- …patients, as we enable dialogues on consent, diagnosis, prognosis and treatment
- …healthcare teams, as we provide reliable genomic insights that are easy to request and interpret
- …researchers, as we accelerate research by providing data, infrastructure, insights and environment to collaborate and accelerate fundamental and translational research

2. Test ordering
NHS clinicians



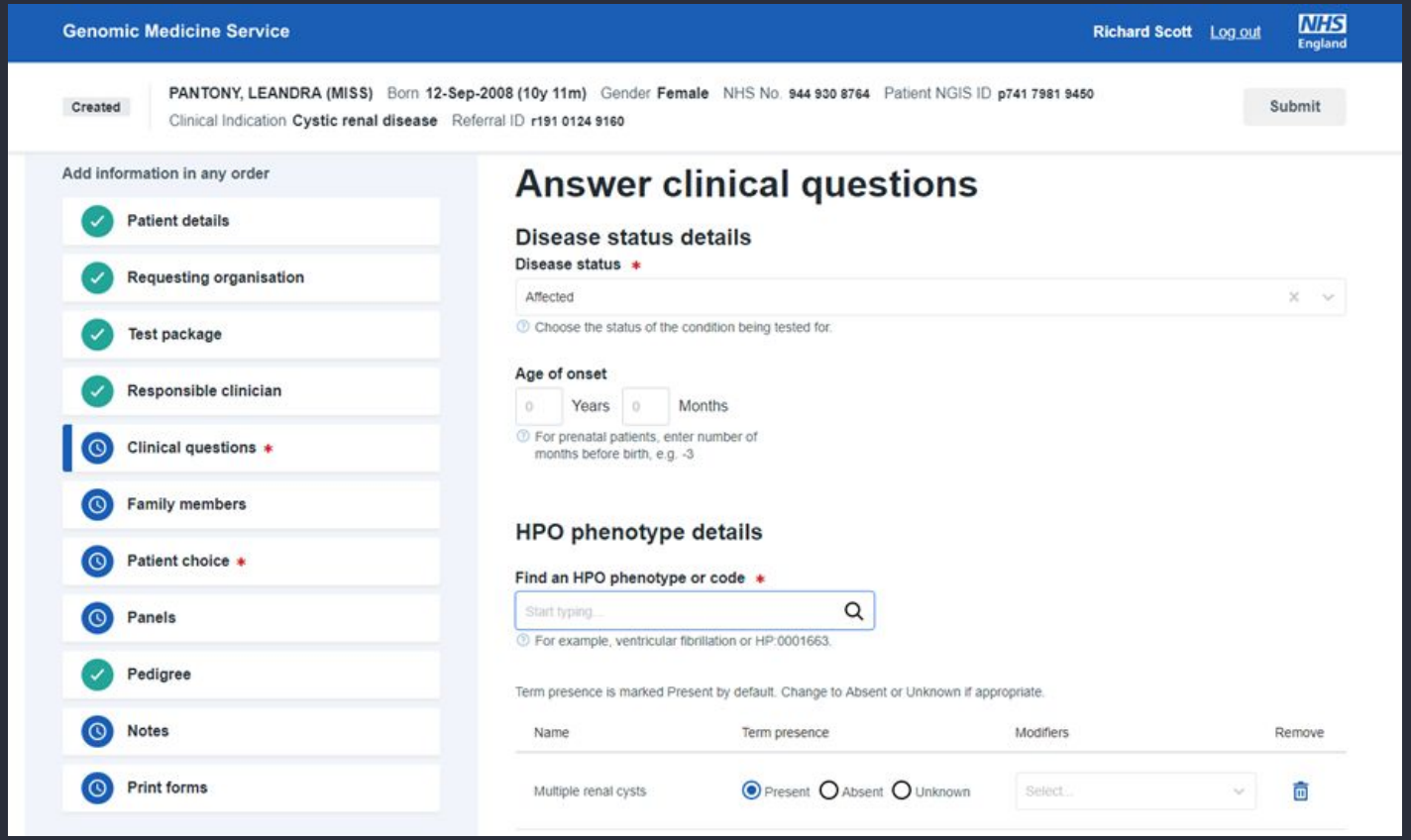
1. Consultations, decision to test
Patients, NHS clinicians



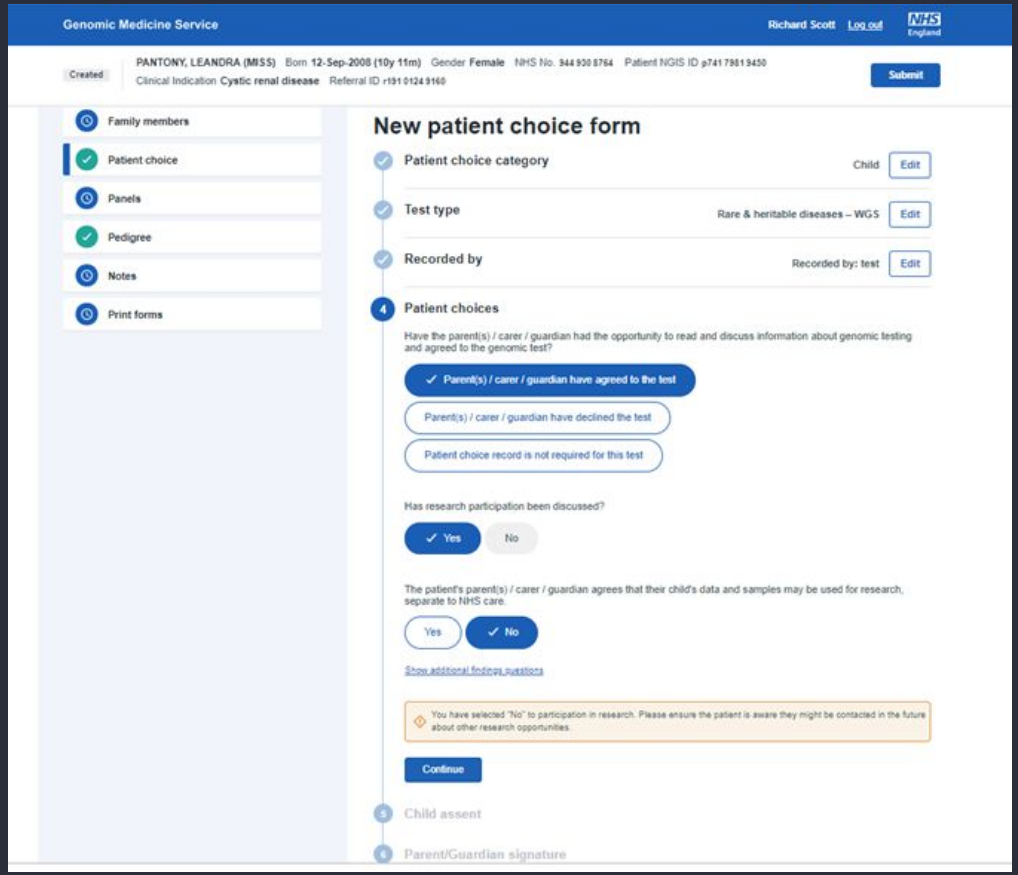
- Whole genome sequencing commissioned according to NHS England Genomic Test Directory
  - 20 rare disease indications, with focus on developmental and complex disorders
  - Paediatric cancers, Sarcoma and Acute Leukaemia

https://www.england.nhs.uk/publication/national-genomic-test-directories/

Standardised clinical data collection



Patient choice – covering diagnostics AND research



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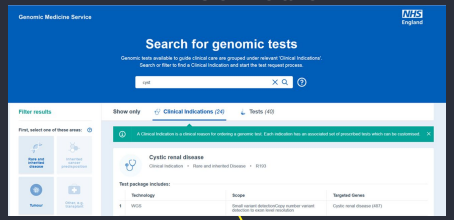

3. DNA extraction and QC
NHS labs (GLHs)

4. Sequencing
illumina

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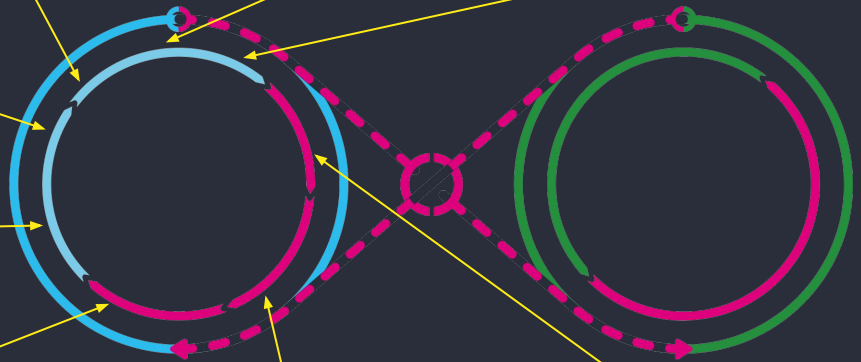
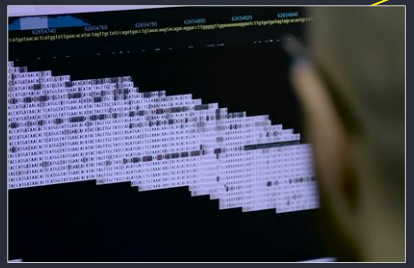
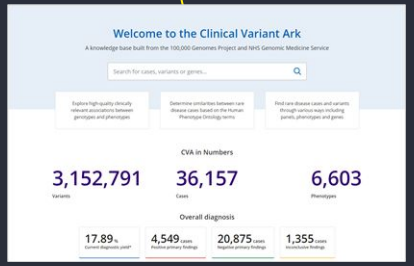


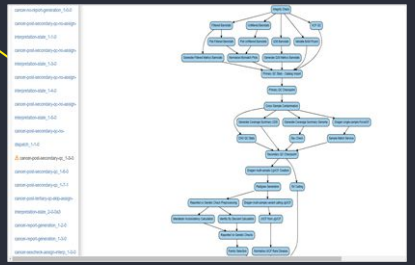
8. Return of results to patient
Patients, NHS clinicians



6. Interpretation and reporting
NHS labs (GLHs)

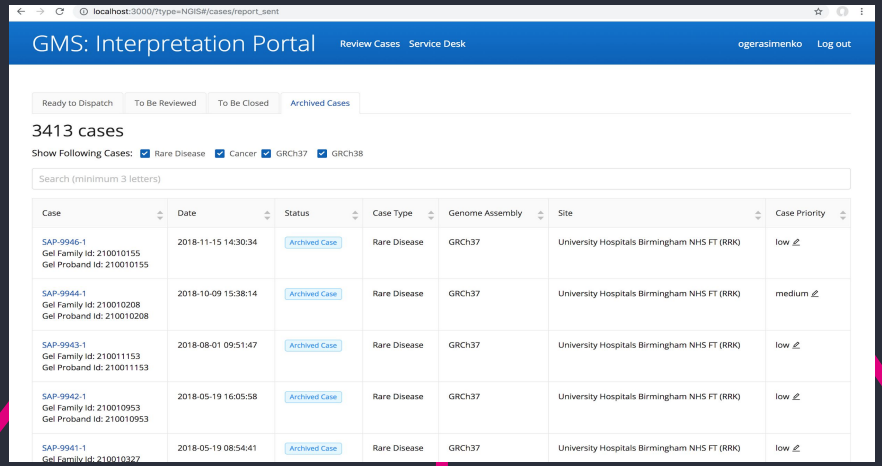


7. Knowledge exploration
NHS labs (GLHs)

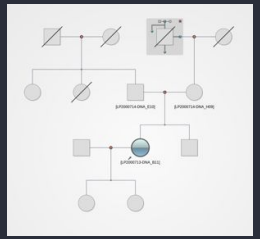


5. Genome Analysis
Genomics England

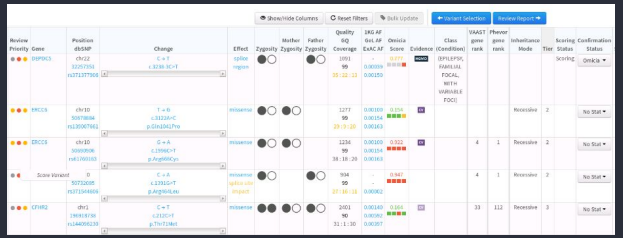
Interpretation platform



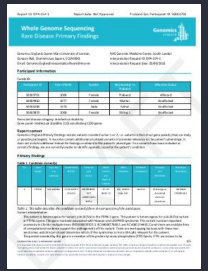
1. View family pedigree



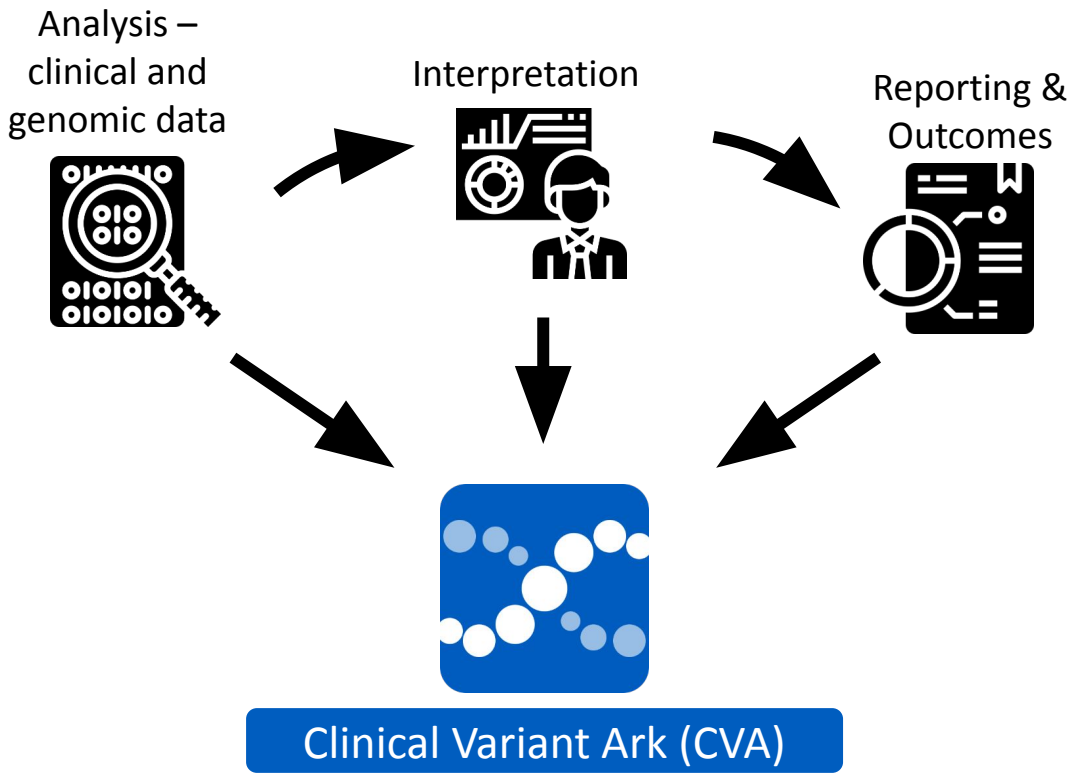
2. Review variants and close case



3. Download the report



Accruing genomic data to produce actionable knowledge

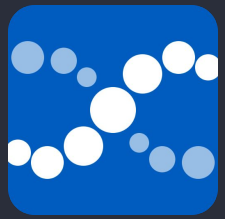


Genomic data and knowledge infrastructure

PanelApp

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

Clinical Variant Ark



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

OpenCGA

Population scale database of all variant phenotypes and all phenotypes

All open source

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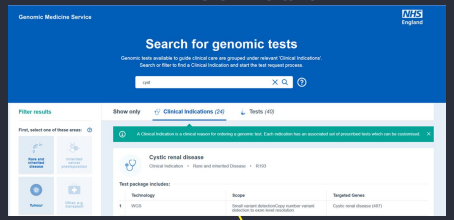
NHS clinicians



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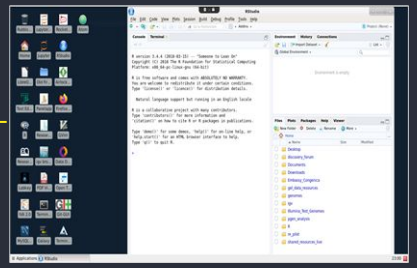
9. Research Environment
Researchers, GEL R&D



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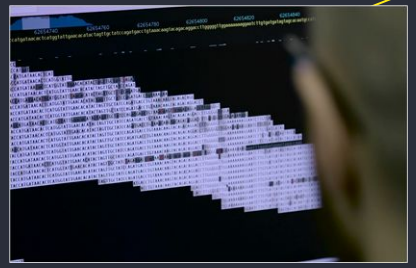

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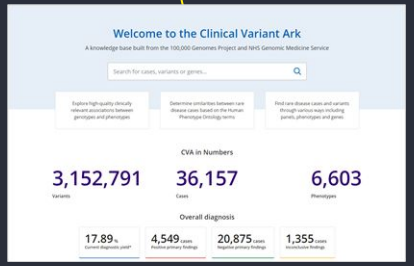

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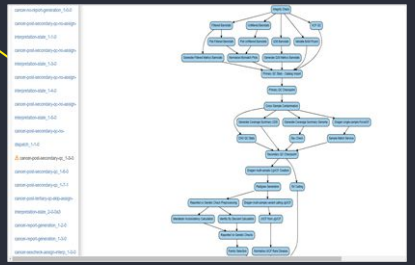

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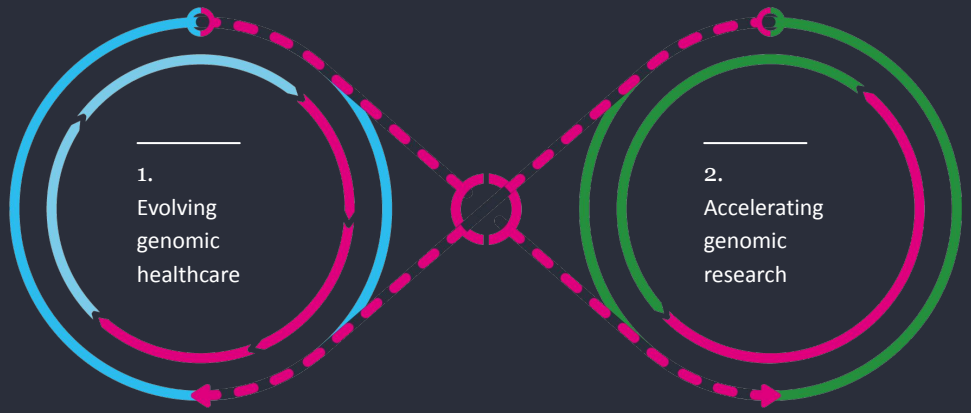

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Thank you and do get in touch:

hello@genomicsengland.co.uk
@GenomicsEngland
@rich_genomics

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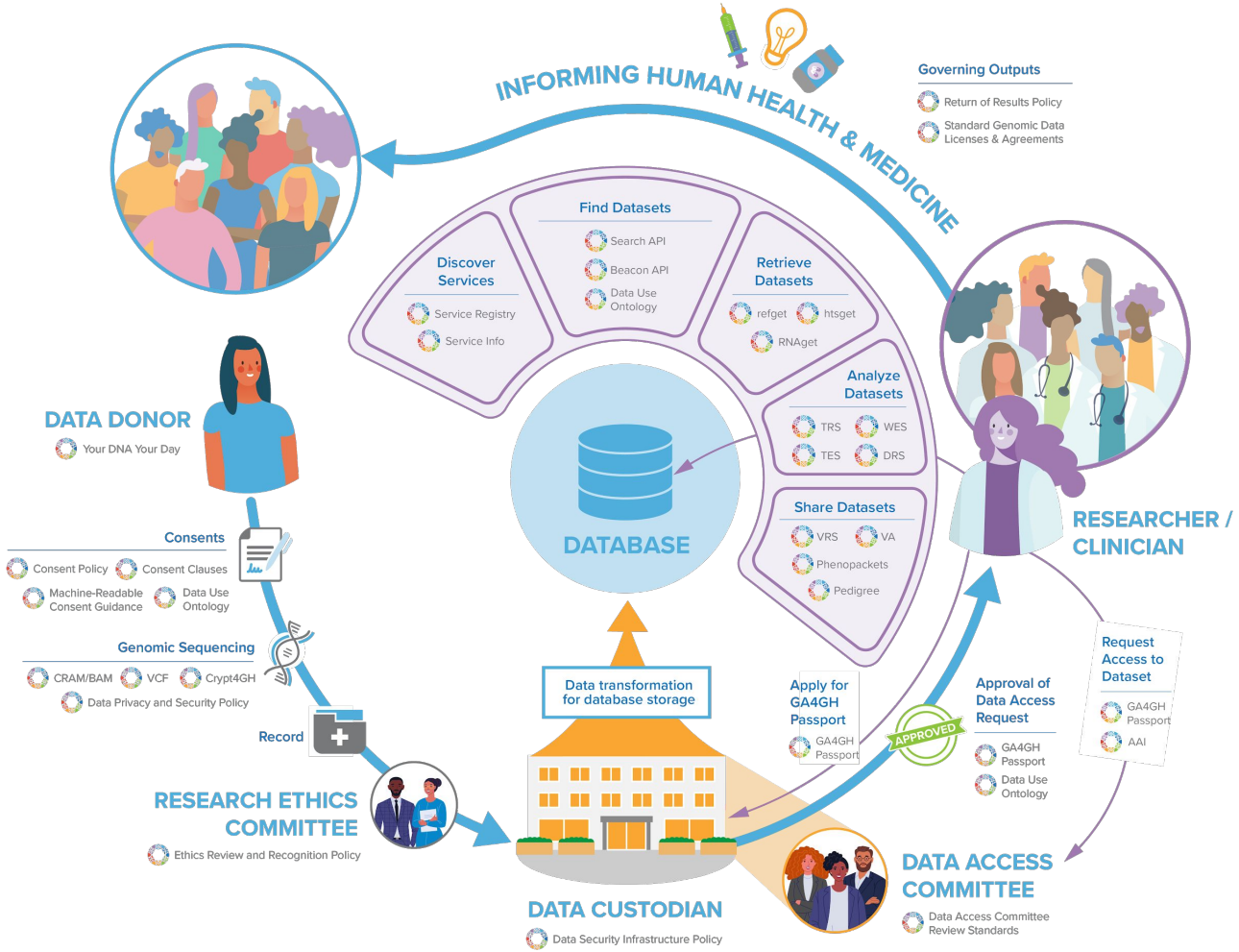
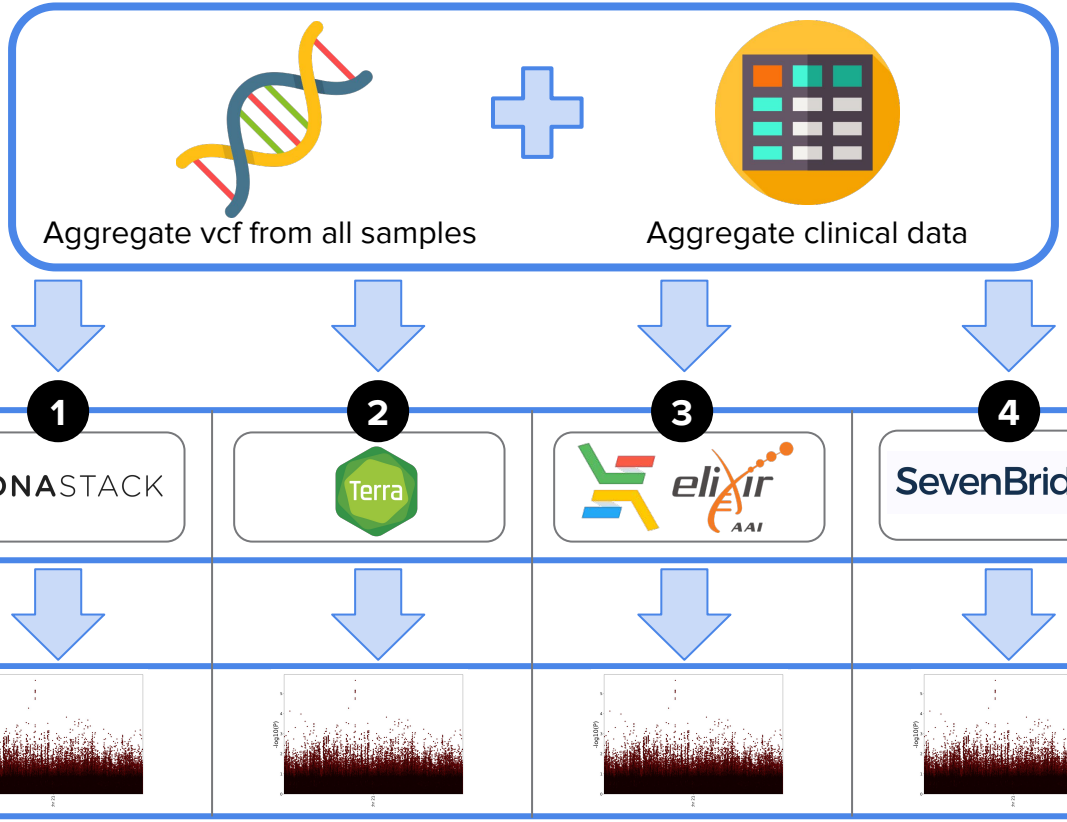
GA4GH Connections Demo

Jeremy Adams


INFORMING HUMAN HEALTH & MEDICINE
Governing Outputs
Return of Results Policy
Standard Genomic Data Licenses & Agreements
Discover Services
Service Registry
Service Info
Find Datasets
Search API
Beacon API
Data Use Ontology
Retrieve Datasets
refget
htsget
RNAget
Analyze Datasets
TRS
WES
TES
DRS
Share Datasets
VRS
VA
Phenopackets
Pedigree
DATABASE
DATA DONOR
Your DNA Your Day
Consents
Consent Policy
Consent Clauses
Machine-Readable Consent Guidance
Data Use Ontology
Genomic Sequencing
CRAM/BAM
VCF
Crypt4GH
Data Privacy and Security Policy
Record
RESEARCH ETHICS COMMITTEE
Ethics Review and Recognition Policy
Data transformation for database storage
DATA CUSTODIAN
Data Security Infrastructure Policy
Apply for GA4GH Passport
GA4GH Passport
APPROVED
Approval of Data Access Request
GA4GH Passport
Data Use Ontology
Request Access to Dataset
GA4GH Passport
AAI
DATA ACCESS COMMITTEE
Data Access Committee Review Standards
RESEARCHER / CLINICIAN

2020 Horizontal Demo

GENOMICS IN HEALTH
IMPLEMENTATION FORUM



2020 Vertical Demo

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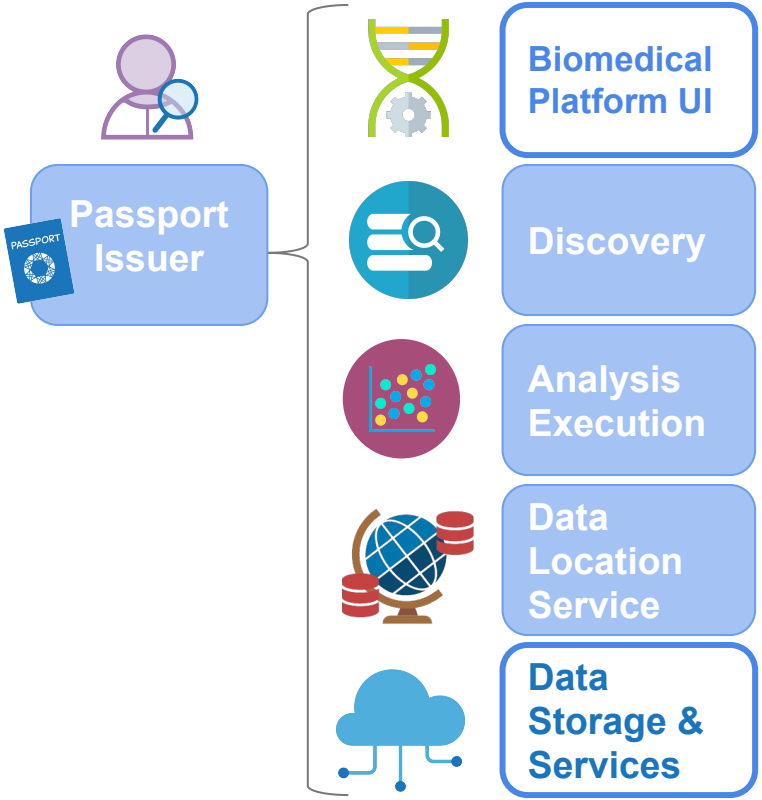


Combines **many standards** to cover a **whole use case**

GA4GH Passports for federated authorization

Single vendor

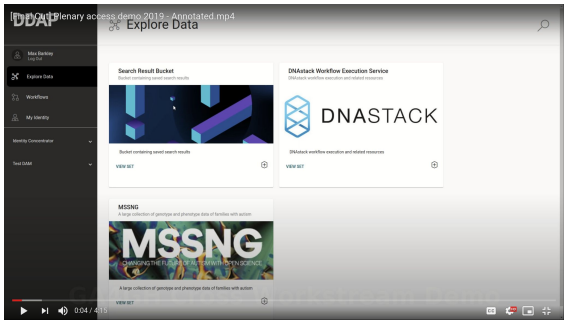
API Feedback

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

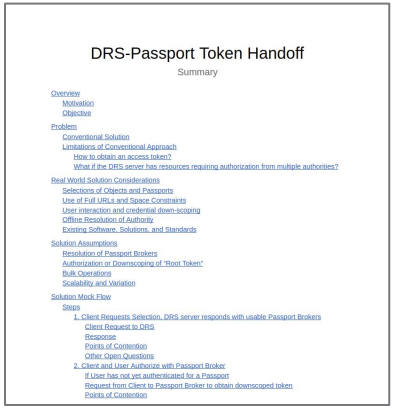
Driver Projects

Implementers

GA4GH Implementation Demo



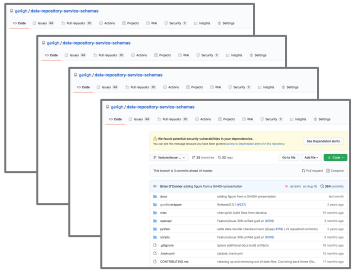
API Feedback Documentation



DRS-Passport Token Handoff

Summary

Specification updates



DRS & Passports Token Handoff

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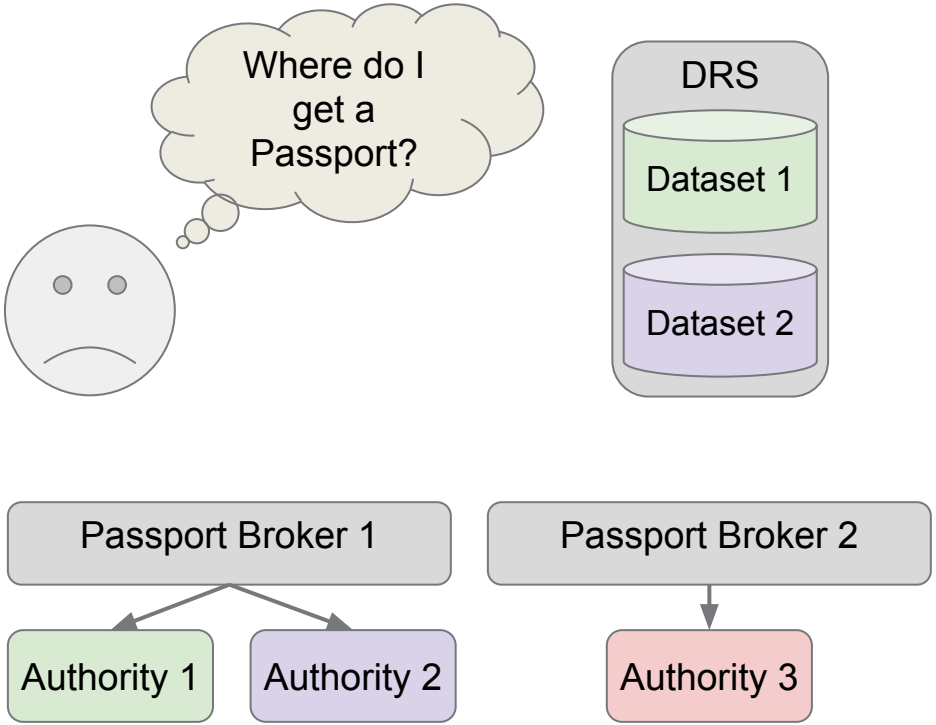
DRS server objects from **multiple datasets**

Datasets have **different authorities** granting access

Need a passport with **particular visas signed by particular authorities**

Possibly also from **particular broker**



DRS & Passports Token Handoff

GENOMICS IN HEALTH
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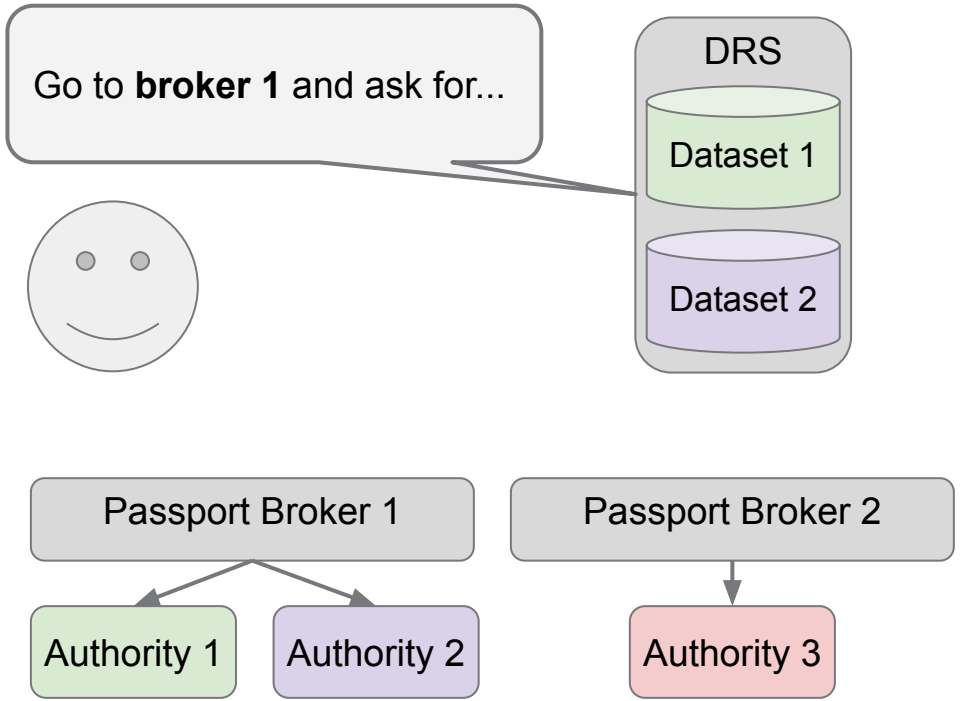
We need to expand the API so a client knows where to go for passports



Connection Demo Implementers

GENOMICS IN HEALTH IMPLEMENTATION FORUM

CANCER GENOMICS CLOUD
SEVEN BRIDGES

CAVATICA

NIH NATIONAL CANCER INSTITUTE
Cancer Research Data Commons

dbGaP
GENOTYPES and PHENOTYPES

Terra

elixir

DNASTACK

EUROPEAN GENOME-PHENOME ARCHIVE

BioData CATALYST
Powered by Gen3

ISB-CGC
Cancer Genomics Cloud

NCBI Sequence Read Archive (SRA)

The AnVIL

BigQuery

Useful Links

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

Connection Demos overview: bit.ly/GA4GHdemos

FASP update at Connect 2021: bit.ly/FASP-Connect21

FASP Breakout session at 8th Plenary: FASP-8thPlenary

Questions? Email secretariat@ga4gh.org

GENOMICS IN HEALTH
IMPLEMENTATION FORUM

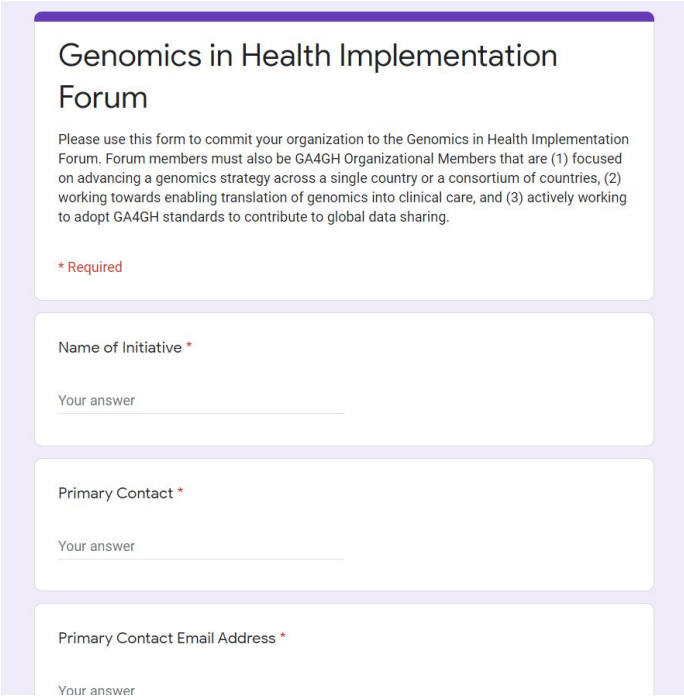
Closing Remarks

Becoming a GHIF Member

GENOMICS IN HEALTH IMPLEMENTATION FORUM

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

- Linked on the GA4GH Website - Implementation Tab



Genomics in Health Implementation Forum

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

* Required

Name of Initiative *

Your answer

Primary Contact *

Your answer

Primary Contact Email Address *

Your answer

GA4GH-GHIF Webinar Series

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