



ASCPT 2018

ANNUAL MEETING

MARCH 21 - 24, 2018 • HILTON ORLANDO • ORLANDO, FL

Knowledge Representation Standards for Translational Genomics

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Mayo Clinic

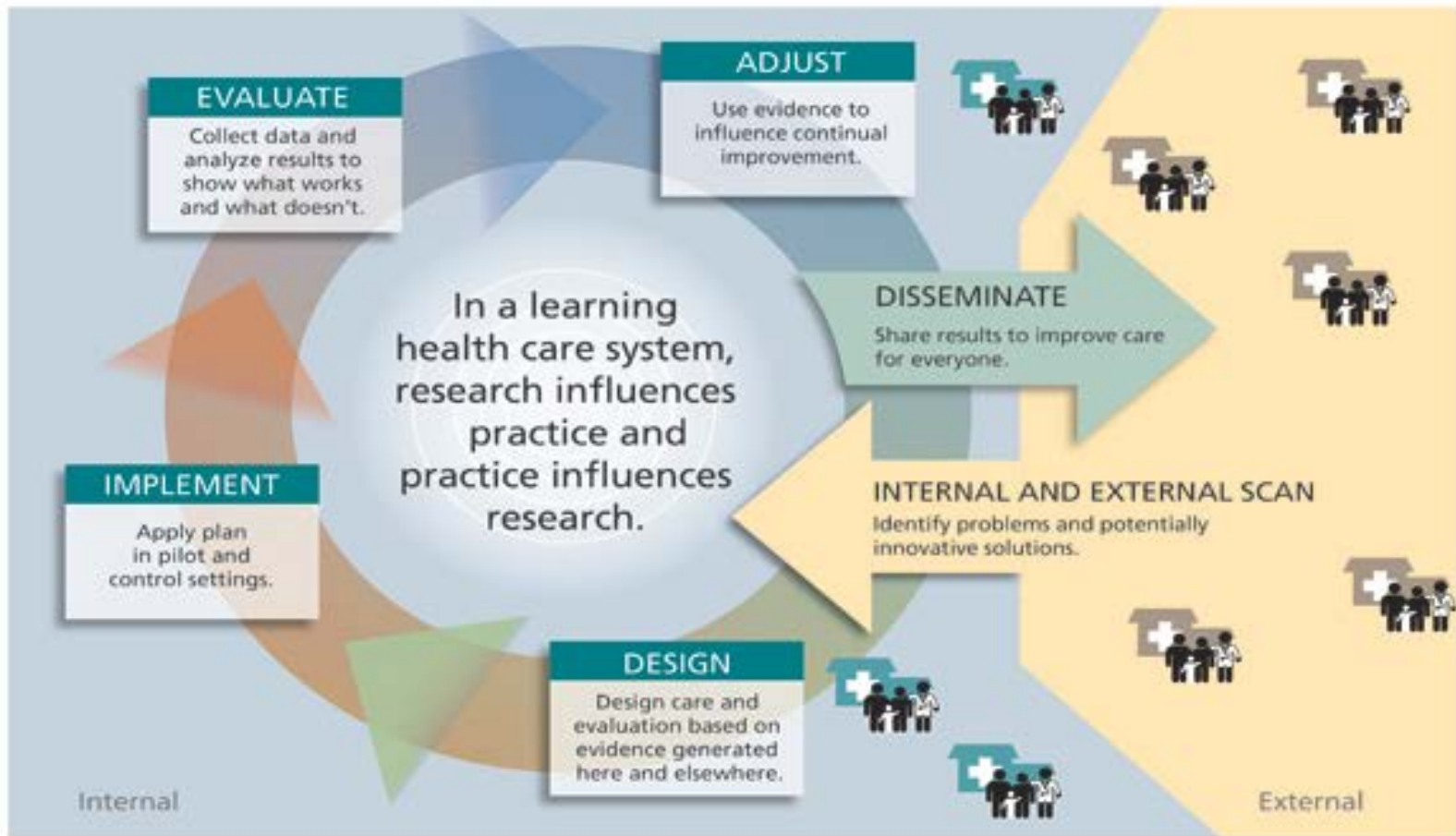
March 23, 2018



Disclaimer

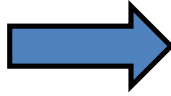
This will *not* be comprehensive!





Clinical Pharmacogenetics Implementation Consortium Guidelines for *HLA-B* Genotype and Abacavir Dosing: 2014 Update

MA Martin¹, JM Hoffman², RR Freimuth³, TE Klein⁴, BJ Dong⁵, M Pirmohamed⁶, J K Hicks⁷, MR Wilkinson², DW Haas⁸ and DL Kroetz¹



Laboratory Service Report

1-800-533-1710

Patient Name TESTINGRNV.2C19B ATLAS REPORT	Patient ID SA00234474	Age 32	Gender M	Order # SA00234474
Ordering Phys CLIENT CLIENT	Account Information		Report Notes	
Client Order # SA00234474	C7028846-DLMP Rochester		DOB 03/26/1983	
Collected 10/18/2015 00:00	SDSC 2 - Client Support			
Printed 11/02/2015 15:54	Rochester, MN 55901			

Test	Flag	Results	Unit	Reference Value
CYP2C19 Genotype, B				
CYP2C19 Phenotype		Poor metabolizer		
CYP2C19 Star Alleles		2/2		
CYP2C19 Interpretation		This individual is likely a poor CYP2C19 metabolizer. Caution should be exercised when treating with drugs metabolized by CYP2C19 as follows:		
		If this patient is taking a prodrug that is activated by CYP2C19, such as Clopidogrel, reduced activation of the drug is expected which may result in decreased efficacy of the drug.		
		If this patient is taking a drug that is inactivated by CYP2C19, such as citalopram, reduced inactivation is expected which may result in higher blood levels of the drug and potential side effects.		
		Consideration should be given to using drugs not metabolized by CYP2C19.		

MICS Decision Support System

MICS Decision Support System

Pharmacogenomics Alert: Cytochrome P450 Enzyme(s)

Metabolizer CYP2D6 Ultra Rapid

Recommendation

Based on this patient's CYP450 enzyme phenotype(s) and unissued medication order(s):

Acetaminophen-Codeine Tab PO and Metabolizer CYP2D6 Ultra Rapid: Avoid codeine due to potential for toxicity. May consider avoiding tramadol.; see [AskMayoExpert \(Codeine\)](#) for details.

If this alert is an error or you have questions send an email to micspgx@mayo.edu

OK

- *Data must be discrete, normalized, and unambiguous*
- *Knowledge must be computable*

Standards Needed for Clinical Genomics



- Data Standards
 - Genetic data (observed result)
 - Test metadata
- Process Standards
 - Variant & haplotype interpretation
 - Genotype-phenotype translation rules
- Terminology Standards
 - Coded results and interpretations
 - Molecular phenotype
- Message/Interface Standards
 - Reporting



Standards Development

- SDOs
 - HL7, CDISC
- Government
 - ONC, FDA
- Consortia
 - CPIC, GA4GH
- Academia
 - Research Networks
 - eMERGE, ClinGen
 - Individual Researchers

Formal

*International
(voluntary effort)*

Formal or
Semi-Formal

*National
(often mandated)*

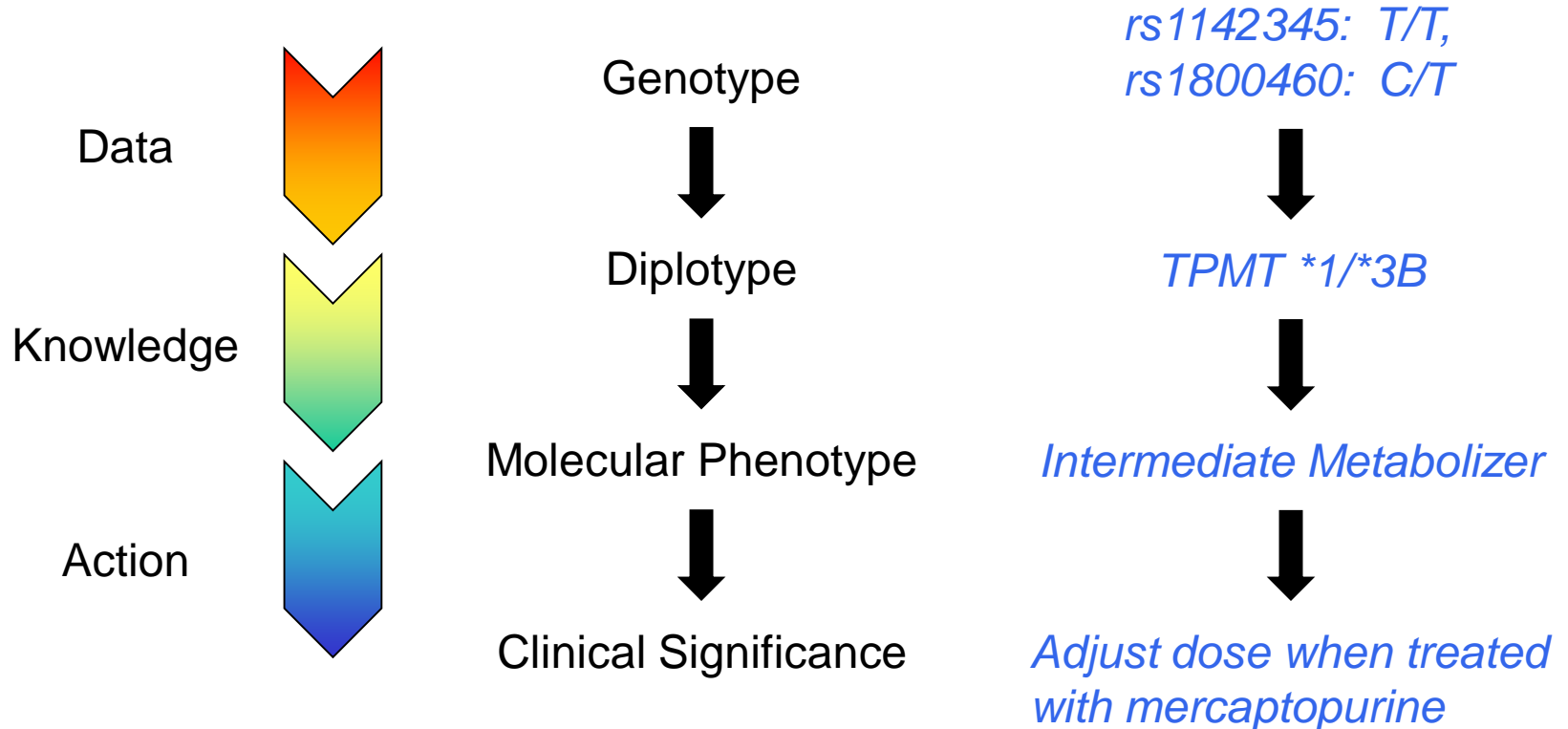
Semi-Formal

*Domain
(de facto std?)*

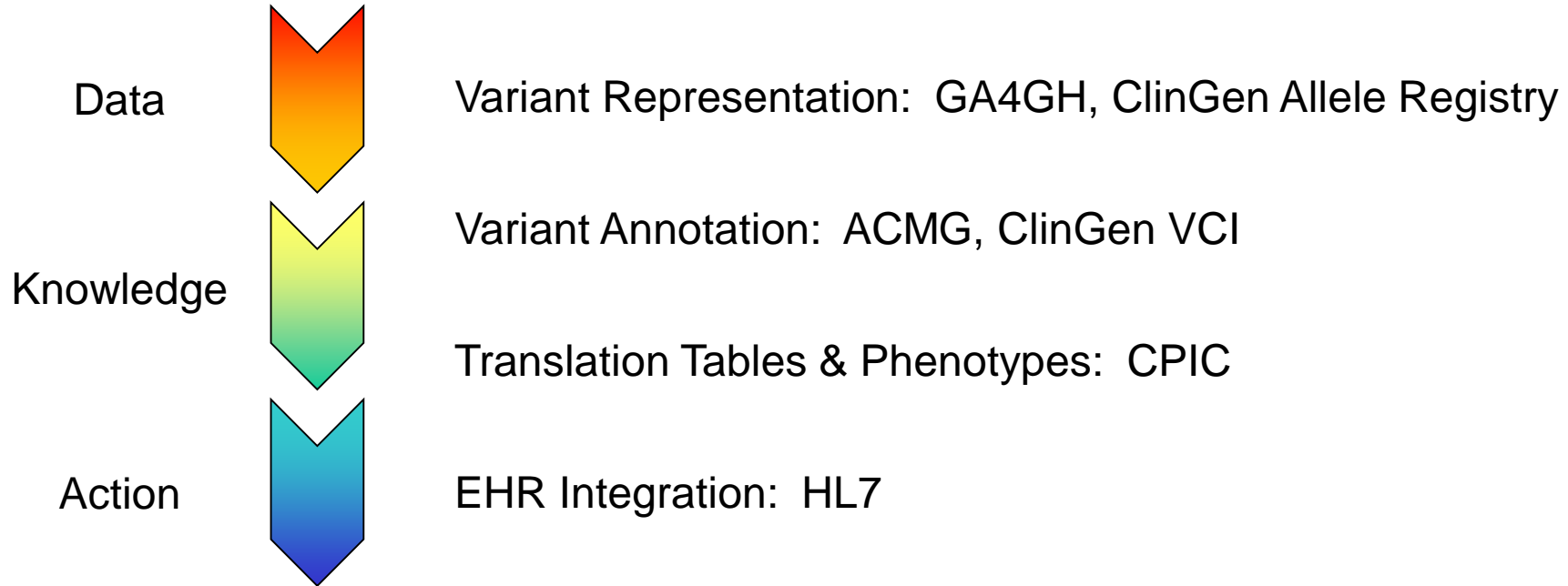
Informal or
Semi-Formal

*Pragmatic, ad hoc
(de facto std?)*

PGx Guidelines: Translating Data to Action



Agenda: Standards for Genomic Data and Knowledge





Global Alliance

for Genomics & Health

Collaborate. Innovate. Accelerate.

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

GKS aims to develop, adopt, and adapt standards to enable the exchange of genomic knowledge

- Establish framework of standards that lower barriers to translating genomic knowledge into clinical practice
- Reusing existing knowledge is essential to future impact
- Knowledge repositories are a key component
- Collaborate with other SDOs on harmonized specifications

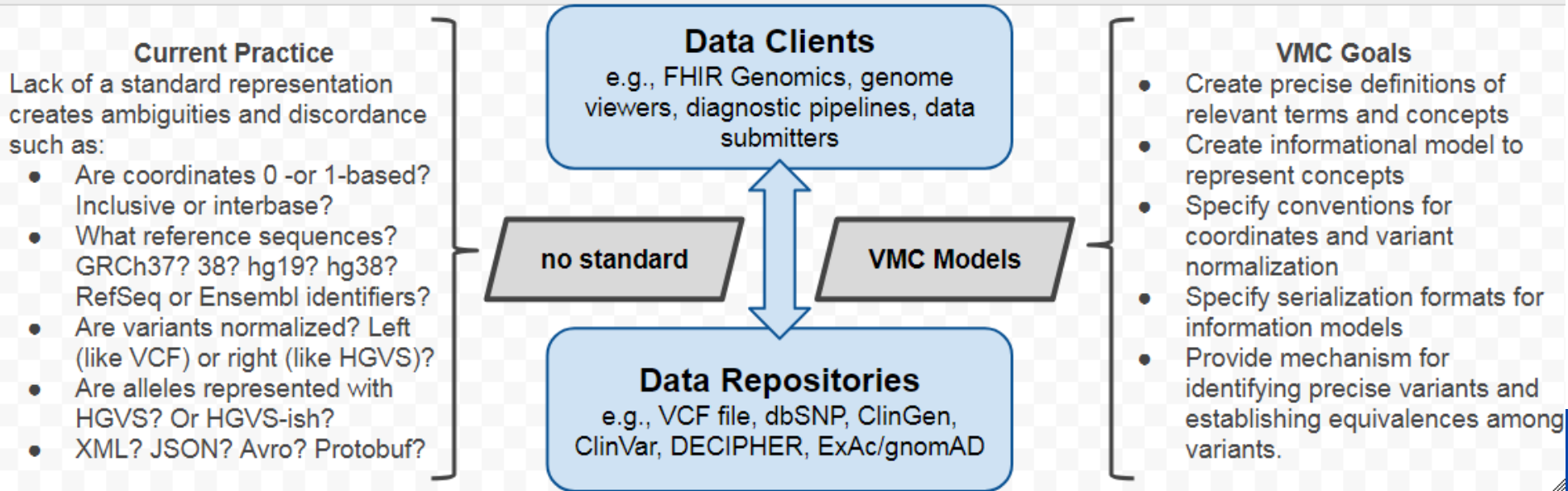
Variant Representation

- Driver Project priorities => Work Stream goal
 - Create a standard model for computer readable variant representation (definitional)
- Simple variants (VMC)
 - v 1.0 by Q4 2018
 - Peer-reviewed publication
- Complex variants (structural, CNV, imprecise ends)
 - v 0.1 by Q4 2018

Variant Modelling Collaboration (VMC)

Participants: GA4GH, HL7, ClinGen, NCBI, SO, EBI, Ensembl

Goal: to develop a technical specification for representing and communicating biological sequence variation



Focus: variation that is defined by alleles — assertions of a specific sequence at precise locations on a sequence

Entities: Sequence, Location, Allele, Haplotype, Genotype

- Terminology
- Information Model
 - Minimalistic, use as part of a given use case
- Machine-readable schema definition

ClinGen Allele Registry

Key problem for variant identification and integration:

There are different ways to describe the same variations using HGVS expressions

Indels are **defined differently using HGVS expressions**

- Reference sequence (RF1): ACTGTCGTG
- ACTG**GTC**GTG -> *RF1:c.4_6delGTC*
- ACTGT**TCG**TG -> *RF1:c.5_7delTCG*
- ACTGT**CGT**G -> *RF1:c.6_8delCGT*
- Alternate sequence: **ACTGTG**

Slide courtesy of Ronak Y Patel

Allele registry provides services to match needs of wide variety of audience

Variant interpreter/curator:

1. Search using HGVS

Type of search	Query	Q Search
HGVS	NM_002496.3:c.64_94delinsTAGT	
For example: NM_002496.3:c.64C>T, ENST00000413465.6:c.637C>T, NC_000017.10:g.7578212G>A		

2. Get identifiers if not registered in the registry

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

Canonical Allele Identifier: [Get Identifier](#) ☆

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

> 650 million variants are already registered, so likely the variant you are looking for is already registered and have a canonical allele identifier

Slide courtesy of Ronak Y Patel

How can ClinGen Allele registry help?

Resolves and provides identity to allele

Single Allele view

Canonical Allele Identifier: CA000043
Gene: TP53 [HGNC ID](#) [NCBI ID](#)

Identifiers and link-outs to other resources

ClinVar Variation Id: 186611 ↗ ExAC: 17:7572974 G / A ↗ MyVariant Identifiers: chr17:g.7572974G>A (hg19) chr17:g.7669656G>A (hg38)	ClinVar RCV Id: RCV000166233 ↗ gnomAD: 17:7572974 G / A ↗	dbSNP Id: rs749061599 ↗ COSMIC: COSM13423 ↗
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Calculator [📄](#) JSON-LD [📄](#)

Genomic Alleles

HGVs	Genome Assembly
NC_000017.11:g.7669656G>A, CM000679.2:g.7669656G>A	GRCh38
NC_000017.9:g.7513699G>A	NCBI36
NC_000017.10:g.7572974G>A, CM000679.1:g.7572974G>A	GRCh37
NG_017013.2:g.22895C>T, LRG_321:g.22895C>T	

Transcript Alleles

HGVs	Amino-acid change
ENST00000269305.8:c.1135C>T	ENSP00000269305.4:p.Arg379Cys ↗
ENST00000359597.8:n.994-3412C>T	ENSP00000352610.4:p.s
ENST00000413465.6:n.782+4525C>T	ENSP00000410739.2:p.s
ENST00000420246.6:c.*242C>T	ENSP00000391127.2:p.s
ENST00000445888.6:c.1135C>T	ENSP00000391478.2:p.Arg379Cys ↗
ENST00000455263.6:c.*154C>T	ENSP00000398546.2:p.s
ENST00000510385.5:c.*242C>T	ENSP00000478499.1:p.s
ENST00000576024.1:n.88C>T	-
ENST00000610292.4:c.1018C>T	ENSP00000478219.1:p.Arg340Cys ↗
ENST00000610538.4:c.*154C>T	ENSP00000480666.1:p.s
ENST00000610623.4:c.*154C>T	ENSP00000477531.1:p.s
ENST00000615910.4:n.1102C>T	ENSP00000482903.1:p.Arg368Cys ↗
ENST00000617185.4:c.*242C>T	ENSP00000482290.1:p.s

Canonical allele identifier
Gene

Identifiers and links
outs to various
resources
ClinVar, dbSNP, ExAC,
gnomAD, COSMIC,
myVariant.Info

Genomic HGVs

Transcript HGVs

Amino-acid
HGVs

How can ClinGen Allele registry help?

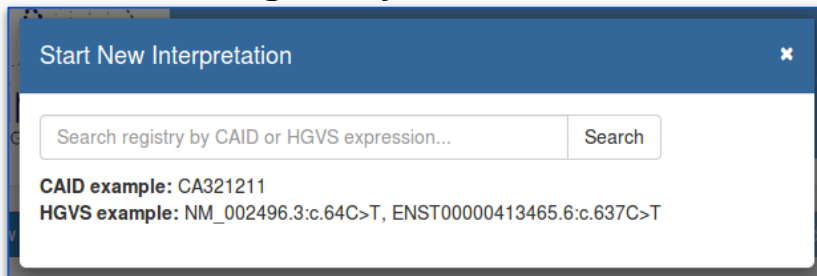
Help integrate variant annotations from various resources

- Simple, well-documented REST-APIs [Backward compatible]
- Simple GET/PUT/POST requests make it easy to integrate
- Pathogenicity Calculator/Variant curation Interface/Data exchange

ClinVar

MyVariant.info

ClinGen Pathogenicity Calculator



Start New Interpretation

Search registry by CAID or HGVS expression... Search

CAID example: CA321211
HGVS example: NM_002496.3:c.64C>T, ENST00000413465.6:c.637C>T

ClinGen Variant Curation Interface



ClinGen Allele Registry

Enter CA ID *

Retrieve from ClinGen Allele Registry

Enter a ClinGen Allele Registry ID (CA ID). The CA ID is returned when you register an allele with the ClinGen Allele Registry (example: [CA003323](#)).

Cancel Save and View Evidence

CIViC

Aliases: GLY12CYS and RS121913530

Allele Registry ID: CA122528

While the KRAS G12 region is a widely studied recurrent region in cancer, its impact on clinical action is still debated. Often associated with tumors that are wild-type for other drivers (EGFR and ALK specifically), the prognosis for patients with this mutation seems to be worse than the KRAS wild-type cohort in patients with colorectal and pancreatic cancer, however this hypothesis is in need of

May 2015

PMID 25741868

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

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

"By adopting and leveraging **next-generation sequencing**, clinical laboratories are now performing an ever-increasing catalogue of genetic testing spanning genotyping, single genes, gene panels, exomes, genomes, transcriptomes, and epigenetic assays for genetic disorders. **By virtue of increased complexity, this shift in genetic testing has been accompanied by new challenges in sequence interpretation.** In this context the ACMG convened a workgroup in 2013 comprising representatives from the ACMG, the Association for Molecular Pathology (AMP), and the College of American Pathologists to revisit and revise the **standards and guidelines for the interpretation of sequence variants.**"

2015 ACMG Guidelines: Structured Variant Data

Variant Nomenclature
(Definition) →

Variant Classification
(Causative?) ←

Disease Context

Variant Nomenclature (Definition)			Variant Classification (Causative?)		Disease Context		
YY NM_12345.6	Exon X/ Intron X/ Promoter/ UTR	c.XXX (p.XXX)	(Apparently) homozygous/ Heterozygous/ Hemizygous/ Heteroplasmic/ Homoplasmic/ Mosaic/ Somatic	Pathogenic / Likely pathogenic / Uncertain significance	Disease Z	Autosomal recessive/ Autosomal dominant/ X- linked/ Mitochondrial	Paternal/ Maternal/ De novo/ Unknown

Standardized terminology and criteria for variant classification

2015 ACMG Guidelines: Evidence Framework

Categories and Weight of Evidence

Types of Evidence

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

Criteria

ClinGen Variant Curation Interface Landing Page

ClinGen
Clinical Genome Resource

Login

ClinGen Curator Interfaces

Variant Curation • Gene Curation

Access to these interfaces is currently restricted to ClinGen curators. If you are a ClinGen curator, you may request an account at clingen-helpdesk@lists.stanford.edu [✉](#).

ClinGen is a National Institutes of Health (NIH)-funded resource dedicated to building an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research. One of the key goals of ClinGen is to implement an evidence-based consensus for curating genes and variants. For more information on the ClinGen resource, please visit the ClinGen portal at clinicalgenome.org [🔗](#).

Explore a demo version of the ClinGen interfaces at curation-test.clinicalgenome.org [🔗](#)

Variant Curation

Which changes in the gene cause disease?

The ClinGen variant curation process combines clinical, genetic, population, and functional evidence with expert review to classify variants into 1 of 5 categories according to the [ACMG guidelines](#) [🔗](#).

Pathogenic • Likely Pathogenic • Uncertain • Likely Benign • Benign

[Learn more](#)

Gene Curation

Does variation in this gene cause disease?

The ClinGen gene curation process combines an appraisal of genetic and experimental data in the scientific literature with expert review to classify gene-disease pairs into 1 of 6 categories according to ClinGen's [Gene-Disease Clinical Validity Classification](#) [🔗](#) framework.

Definitive • Strong • Moderate • Limited • Disputed • Refuted

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➔
email helpdesk to register

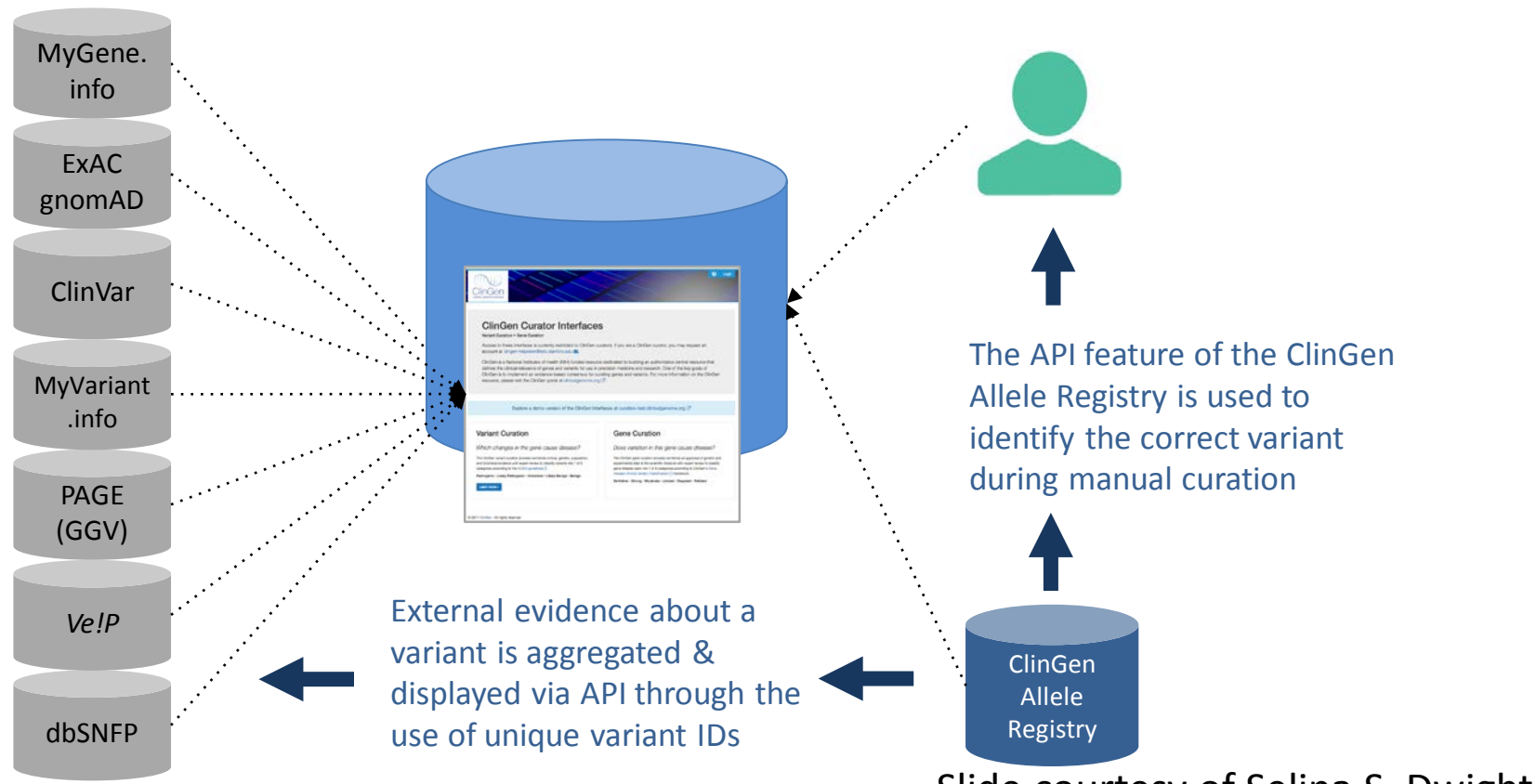
←
Login

curation.clinicalgenome.org

←
Explore demo version

Slide courtesy of Selina S. Dwight

The Variant Curation Interfaces rely on ClinGen Allele Registry and ClinVar IDs for aggregating evidence and supporting manual curation of individual variants



Interpretation Mode

3(BRCA1):c.1266T>G (p.Tyr422Ter)
Evidence View

ext All Existing Interpretations

hg19
GRCh37

Evidence View Interpretation

Predictors	Experimental	Segregation/Case	Gene-centric

ACMG criteria appear alongside relevant evidence categories

Ability to evaluate criteria at strength or modified strength

Criteria bar indicates status of each criterion (Met, Met at Modified strength, Not Met, Not evaluated)

Pathogenicity calculated “on the fly” according to ACMG rules

Variant Interpretation Record

Benign No criteria met Pathogenic Strong: 1 Supporting: 2 Calculated Pathogenicity Likely pathogenic

Basic Information Population Predictors Experimental Segregation/Case Gene-centric

Population Criteria Evaluation

BA1: Allele frequency is > 5% in ExAC, 1000 Genomes, or ESP

BS1: Allele frequency greater than expected due to disorder Disease-specific

PM2: Absent from controls (or at extremely low frequency if recessive) in ExAC, 1000 Genomes, or ESP

BA1: Not Evaluated MAF cutoff: 5 %

BS1: Not Evaluated Explanation:

PM2: Not Evaluated Met Not Met PM2_Supporting PM2_Strong

Save

Acknowledgements

GA4GH GKS

- Andy Yates
- Bob Freimuth
- Larry Babb
- Matt Brush
- Michael Baudis
- Javier Lopez
- Reece Hart

ClinGen AR

- Piotr Pawliczek
- Ronak Patel
- Lillian Ashmore
- Sameer Paithankar
- Andrew Jackson
- Neethu Shah
- Sharon Plon
- Aleks Milosavljevic

ClinGen DM WG

- Larry Baab
- Chris Bizon
- Tristan Nelson
- Bradford Powell
- Bob Freimuth
- Danielle Azzariti

ClinGen VCI

- Selina Dwight
- Matt Wright
- Jimmy Zhen



- CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy.
 - Not WHETHER tests should be ordered.
- Key Assumption:
 - Clinical high-throughput and pre-emptive genotyping will become more widespread.
 - Clinicians will be faced with having patients' genotypes available even if they did not order test with drug in mind.

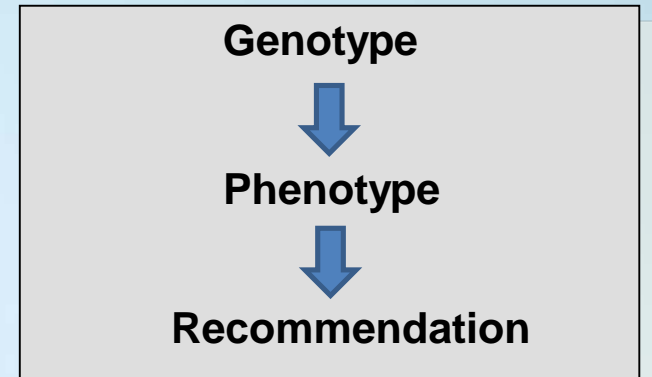
CPIC Informatics Working Group

- Growing interest in informatics aspects of CPIC guidelines and clinical implementation of pharmacogenetics
- Goal: To support the adoption of the CPIC guidelines by identifying, and resolving where possible, potential technical barriers to the implementation of the guidelines within a clinical electronic environment.
- Working group leaders
 - Bob Freimuth (Mayo Clinic)
 - James Hoffman (St. Jude)
 - Michelle Carrillo (PharmGKB)



CPIC Informatics Working Group: Initial Focus

- Create comprehensive translation tables from genotype to phenotype to clinical recommendation for CPIC guidelines
 - Define structure and process to efficiently develop and maintain in the most useful format(s)
 - Publish as part of CPIC guidelines



CPIC Translation Tables: Allele Function to Phenotype

CYP2C19 Allele	Allele Functional Status
*1	Normal function
*2	No function
*3	No function
*4A	No function
*4B	No function
*5	No function
*6	No function
*7	No function
*8	No function
*9	Decreased function
*10	Decreased function
*11	Normal function

	CYP2C19 Diplotype	Coded Genotype/Phenotype Summary ^b
1		
2	*1/*1	Normal Metabolizer
3	*1/*2	Intermediate Metabolizer
4	*1/*3	Intermediate Metabolizer
5	*1/*4A	Intermediate Metabolizer
6	*1/*4B	Intermediate Metabolizer
7	*1/*5	Intermediate Metabolizer
8	*1/*6	Intermediate Metabolizer
9	*1/*7	Intermediate Metabolizer
10	*1/*8	Intermediate Metabolizer
11	*1/*9	Likely Intermediate Metabolizer
12	*1/*10	Likely Intermediate Metabolizer



Table 1 Assignment of likely thiopurine methyltransferase phenotypes based on genotypes

Likely phenotype	Genotypes	Examples of diplotypes
Homozygous wild-type or normal, high activity (constitutes ~86–97% ^a of patients)	An individual carrying two or more functional (*1) alleles	*1/*1
Heterozygote or intermediate activity (~3–14% ^a of patients)	An individual carrying one functional allele (*1) plus one nonfunctional allele (*2, *3A, *3B, *3C, or *4)	*1/*2, *1/*3A, *1/*3B, *1/*3C, *1/*4
Homozygous variant, mutant, low, or deficient activity (~1 in 178 to 1 in 3,736 patients ^a)	An individual carrying two nonfunctional alleles (*2, *3A, *3B, *3C, or *4)	*3A/*3A, *2/*3A, *3C/*3A, *2/*2, *3B/*3B, *3C/*3C, *4/*4

The Need for Term Standardization

Term Standardization Delphi Results – Phenotype

Round 1

CYP2C19, CYP2C9, and CYP2D6

Very high function phenotype:
 Very high function, increased function, ultra-rapid function, very high activity, ultra-rapid activity, ultra-rapid metabolizer, homozygous ultra-rapid metabolizer, increased metabolizer, ultra-fast metabolizer

Normal function phenotype:
 Normal function, normal activity, homozygous wild-type, extensive metabolizer, normal metabolizer, extensive (normal) metabolizer, homozygous extensive metabolizer, wild-type

Medium function phenotype:
 Intermediate function, decreased function, reduced function, intermediate activity, decrease activity, reduced activity, heterozygous deficient, intermediate metabolizer, heterozygous extensive metabolizer, reduced metabolizer, decreased metabolizer

No function phenotype:
 Deficient function, deficient activity, low function, low activity, absent function, absent activity, no function, no activity, homozygous deficient, deficient, poor activity, poor metabolizer, slow metabolizer, poor function

CYP3A5

Normal function phenotype:
 Normal activity, homozygous wild-type, normal function, wild-type, extensive metabolizer, normal metabolizer, extensive (normal) metabolizer, homozygous extensive metabolizer, expresser

Medium function phenotype:
 Intermediate activity, decreased activity, reduced activity, intermediate function, decreased function, reduced function, heterozygous deficient, intermediate metabolizer, heterozygous extensive metabolizer, reduced metabolizer, decreased metabolizer, intermediate expresser

No allele function:
 Deficient activity, deficient function, low function, low activity, absent function, absent activity, homozygous deficient, deficient, no function, no activity, poor activity, poor metabolizer, slow metabolizer, non-expresser

DPYD and TPMT

High or normal activity phenotype:
 High function, normal function, high/normal function, normal activity, high/normal activity, homozygous wild-type

Medium activity phenotype:
 Intermediate function, decreased function, reduced function, intermediate activity, decreased activity, reduced activity, heterozygous deficient

No activity phenotype:
 Deficient function, no function, deficient activity, low function, low activity, absent function, absent activity, homozygous deficient, deficient, poor activity, no activity

UGT1A1

High function phenotype:
 Ultra-rapid activity, ultra fast metabolizer, increased metabolizer, ultra-rapid metabolizer, high function, increased function, ultra-rapid function, high activity

Normal allele function:
 Normal activity, normal function, homozygous wild-type, extensive metabolizer, normal metabolizer, extensive (normal) metabolizer, homozygous extensive metabolizer, wild-type

Medium function phenotype:
 Intermediate activity, decrease activity, reduced activity, intermediate function, decreased function, reduced function, heterozygous deficient, intermediate metabolizer, heterozygous extensive metabolizer, reduced metabolizer, decreased metabolizer

No allele function:
 Deficient function, deficient activity, low function, low activity, absent function, absent activity, no function, no activity, homozygous deficient, deficient, poor activity, poor metabolizer, slow metabolizer, poor function

CPIC Phenotype Term Standardization Project

Purpose:

- To standardize phenotype terms in the CPIC guidelines and harmonize terms with external groups (e.g., ClinGen, IOM, etc.)
 - Allele functional status terms
 - Low, absent, high, intermediate
 - Phenotype
 - UM, EM, IM, PM

Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Kelly E. Caudle, PharmD, PhD¹, Henry M. Dunnenberger, PharmD², Robert R. Freimuth, PhD³,
Josh F. Peterson, MD^{4,5}, Jonathan D. Burlison, PhD¹, Michelle Whirl-Carrillo, PhD⁶,
Stuart A. Scott, PhD⁷, Heidi L. Rehm, PhD⁸, Marc S. Williams, MD⁹, Teri E. Klein, PhD⁶,
Mary V. Relling, PharmD¹, James M. Hoffman, PharmD, MS¹

PGx in LOINC and SNOMED CT



LOINC	LOINC Component
50956-2	HLA-B*57:01
57979-7	HLA-B*15:02
79711-8	HLA-B*58:01
79712-6	HLA-A*31:01
79713-4	TPMT gene product metabolic activity interpretation
79714-2	CYP2C19 gene product metabolic activity interpretation
79715-9	CYP2D6 gene product metabolic activity interpretation
79716-7	CYP2C9 gene product metabolic activity interpretation
79717-5	CYP3A5 gene product interpretation
79718-3	UGT1A1 gene product interpretation
79719-1	DPYD gene product interpretation
79720-9	CYP2B6 gene product interpretation
79721-7	CYP4F2 gene product interpretation
79722-5	SLCO1B1 gene product interpretation

LA6576-8	Positive
LA6577-6	Negative
LA10315-2	Ultrarapid metabolizer
LA25390-8	Rapid metabolizer
LA25391-6	Normal metabolizer
LA10317-8	Intermediate metabolizer
LA9657-3	Poor metabolizer
LA25392-4	Increased function
LA25393-2	Normal function
LA25395-7	Decreased function
LA25394-0	Poor function

SNOMED International SNOMED CT Browser

© SNOMED International 2018 v1.36.5

Taxonomy Search Favorites Refset

Search

Options

Search Mode: Partial matching search mode

Active components only

Results by Language

Type at least 3 characters ✓ Example: *shou fra*

TPMT|

3 matches found in 0.294 seconds.

- TPMT poor metabolizer Thiopurine S-methyltransferase poor metabolizer (finding)
- TPMT normal metabolizer Thiopurine S-methyltransferase normal metabolizer (finding)
- TPMT intermediate metabolizer Thiopurine S-methyltransferase intermediate metabolizer (finding)

Acknowledgements - CPIC

- CPIC Leaders
 - Mary Relling
 - Teri Klein
- CPIC Coordinators
 - Kelly Caudle
 - Roseann Gammal
- PGRN
- PharmGKB
 - Russ Altman
 - Teri Klein
 - Michelle Whirl-Carrillo
- CPIC Informatics WG
 - James Hoffman
 - Michelle Whirl-Carrillo
 - Bob Freimuth





Work Groups

Active Work Groups

A

- [Affiliate Due Diligence](#)
- [Anesthesia](#)
- [Architectural Review](#)
- [Arden Syntax](#)
- [Attachments](#)

B

- [Biomedical Research and Regulation](#)
- [Board Motions](#)

C

- [CDA Management Group](#)
- [Clinical Decision Support](#)
- [Clinical Genomics](#)
- [Clinical Information Modeling Initiative](#)
- [Clinical Interoperability Council](#)

- Develops international standards for transfer of clinical and administrative data between software applications used by healthcare providers and clinical systems
- Examples
 - v2/v3 messaging
 - CDA, CCD
 - Arden Syntax
 - FHIR
- > 60 work groups

HL7 Clinical Genomics Work Group

- Goal: to facilitate the development of common standards for the exchange of clinical and translational information related to an individual's genomic data and family health history, and (its linkage to) relevant clinical information
- Organizational perspectives (not exclusive)
 - Academic medical centers, hospitals
 - Genomic testing labs
 - Public data repositories and knowledge-bases serving as references to clinical genetics/genomics
 - *Translational research programs??*

HL7 Clinical Genomics Working Group

Overview of Activities

v2

- Implementation Guides

Genetic Variation (Fully LOINC-Qualified Genetic Variation Model)

Laboratory Results Interface (LRI)

v3

- **Family History (Pedigree)**
- Genetic Variations
- Gene Expression
- CMETs defined by the Domain

CDA

- Implementation Guide for Genetic Testing Reports

FHIR STU3

- **Sequence Resource**
- **Profiles:**
 - Genetic Observation*
 - DiagnosticReport*
 - ProcedureRequest*
 - HLA Reporting*
 - Family member history for genetics analysis*

Common:

- **Domain Analysis Models for the various topics**
- **A Domain Information Model describing the common semantics**
- *Semantic alignment among the various specs*



10.6 Resource Sequence - Content

Clinical Genomics ↗ Work Group	Maturity Level: 1	Trial Use	Compartments: Not linked to any defined compartments
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Raw data describing a biological sequence.

10.6.1 Scope and Usage

The Sequence resource is designed to describe an atomic sequence which contains the alignment sequencing test result and multiple variations. Atomic sequences can be connected by link element and they will lead to sequence graph. By this method, a sequence can be reported. Complete genetic sequence information, of which specific genetic variations are a part, is reported by reference to the GA4GH repository. Thus, the FHIR Sequence resource avoids large genomic payloads in a manner analogous to how the FHIR ImagingStudy resource references large images maintained in other systems. For use cases, details on how this resource interact with other Clinical Genomics resources or profiles, please refer to implementation guidance document [here](#).

10.6.1.1 Genetic Standards and Resources include:

- Variant Databases: [dbSNP](#) [↗](#), [ClinVar](#) [↗](#), and [COSMIC](#) [↗](#)
- Reference Sequences: [RefSeq](#) [↗](#) and [ENSEMBL](#) [↗](#)



10.10 Genomics Implementation Guidance

[Clinical Genomics](#)  [Work Group](#)

Maturity Level: 1

Ballot Status: Trial Use

Table of Contents

1. [Background](#)
2. [Overview](#)
3. [Sequence Resource](#)
4. [Observation-genetics Profile](#)
5. [DiagnosticReport-genetics Profile](#)
6. [ServiceRequest-genetics Profile](#)
7. [HLA genotyping results Profile](#)
8. [Relationship among Sequence resource and genetics profiles](#)



Standards Development



Development

- Evaluate existing standards
- Gap analysis
- Define scope of new
- Develop draft spec
- Ballot (vote)
- Reconciliation
- Approval

- Implementation

Adoption

Motivation

- Define domain
- Define use cases and requirements



Global Alliance
for Genomics & Health



Standard Development – Take Home Points

- Driven by real-world use cases and implementations
- Standards are developed by those that show up
 - Nearly all participants are volunteers
- Robust standards require diverse expertise
 - Domain SMEs, modeling, technical
 - Clinical, academic, industry, government
- Standards are not perfect or perfectly comprehensive
 - Gaps in structure and/or content
 - Collaborate to extend, don't create Yet Another Standard