



Foundations of AI in Genomics and Precision Medicine

It's all about the data

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 - Mayo Clinic Center for Individualized Medicine
 - The content is solely the responsibility of the author and does not necessarily represent the official views of the NIH or Mayo Clinic
- I hold leadership roles within HL7 and GA4GH
- I have no personal financial conflicts of interest

A Vision for Genomic Medicine



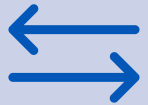
- Enables new discoveries
- Speeds up translation
- Access to the latest knowledge
 - Push notifications
- Personalized care
 - Risk and treatment
 - Adapting throughout life
- Portable across care settings
- Shareable with family members

Requirements



Consumers

Patient
Clinician
Researcher
Computer



Exchange

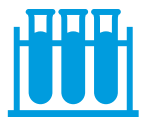
Variety of capabilities
Support for data types
Differing upgrade schedules



Interpretation and Impact

New data collected
New biomedical knowledge
New clinical guidance

Vision: Seamless Exchange of Genomic Data



Generation



Annotation



Interpretation



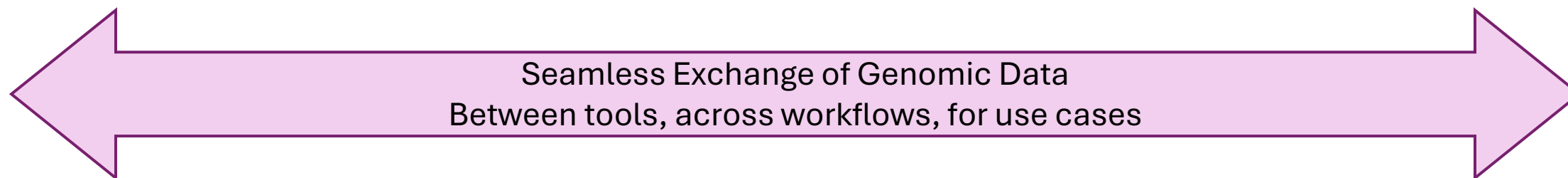
Reporting



Storage



Use



- Support entire spectrum of clinical and translational research
- Computable data, everywhere
- When transformations are necessary, they must be lossless
 - *Standards must be interoperable*

Ambiguous Semantics

“DNA Change c.-124C>T (also known as C228T)”

HBOC
COMP
COMCP

NM_198253

“c.182A>G and c.154T>G”

ACAT2

rs114493458

12 and 10 (Normal)

CYP3A5*3

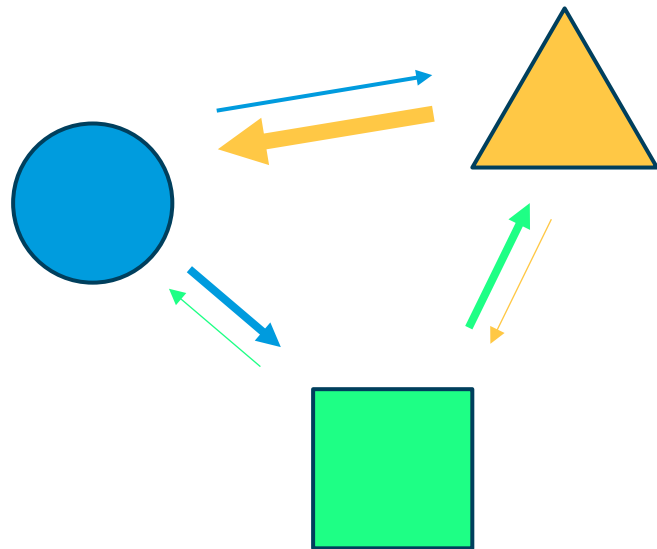
05:01, 06:01

CYP2C19 c.1016 “ref” allele

Complexity

Tesler's Law: The Law of Conservation of Complexity

For any system there is a certain amount of complexity which cannot be reduced



Grahame Grieve's Second Law of Interoperability

Complexity: you can move it around, or externalize it, but you can't make it go away

Lossy mappings = Degraded data

HOW STANDARDS PROLIFERATE:

(SEE: A/C CHARGERS, CHARACTER ENCODINGS, INSTANT MESSAGING, ETC.)



<https://xkcd.com/927/>

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Grahame Grieve's First Law of Interoperability

Interoperability: it's all about the people

“the real problems with interoperability are not technical. They’ve never been technical. It’s the people that are the problem, because IT systems are only extensions of the people who wrote them, who maintain them, who use them. If you want two IT systems to interchange data successfully, you’ve got to get alignment between the people who write them, manage them, and use them. The technical challenges the system maintainers face when making changes are miniscule compared to the problem of getting the various people to agree with each other.”

<http://www.healthintersections.com.au/2011/04/09/law-1-interoperability-its-all-about-the-people.html>

Graphs of Graphs

Clinical Guidance

Patient Data

Biomedical Knowledge



Semantically Aligned Specifications



GitHub: FHIR-MolDef-python

FHIR AlleleProfile

AlleleProfile
+ identifier (0..*) Identifier
+ description (0..1) markdown
+ molecularType (1..1) CodeableConcept
+ type (0..*) CodeableConcept
+ location (1..1) BackboneElement
+ topology (0..1) CodeableConcept
+ representation (1..*) BackboneElement

location
+ sequenceLocation (0..1) BackboneElement
+ cytobandLocation (0..1) BackboneElement
+ featureLocation (0..1) BackboneElement

sequenceLocation
+ sequenceContext (1..1) Reference(MolecularDefinition)
+ coordinateInterval (0..1) BackboneElement
+ strand (0..1) CodeableConcept

coordinateInterval
+ coordinateSystem (0..1) BackboneElement
+ start (0..1)
+ end (0..1)

coordinateSystem
+ system (0..1) CodeableConcept
+ origin (0..1) CodeableConcept
+ normalizationMethod (0..1) CodeableConcept

start
+ startQuantity (0..1) Quantity
+ startRange (0..1) Range

end
+ endQuantity (0..1) Quantity
+ endRange (0..1) Range

representation
+ focus (0..1) CodeableConcept
+ code (0..*) CodeableConcept
+ literal (0..*) BackboneElement
+ resolvable (0..1) Reference(DocumentReference)
+ extracted (0..1) BackboneElement
+ repeated (0..1) BackboneElement
+ concatenated (0..1) BackboneElement
+ relative (0..1) BackboneElement

literal
+ encoding (0..1) CodeableConcept
+ value (1..1) string



VRS Allele

Allele
+ _id: CURIE (0..1)
+ type: string (1..1)
+ location: Location (1..1)
+ state: SequenceExpression (1..1)

Location
+ _id: CURIE (0..1)
+ type: string (1..1)

SequenceLocation
+ _id: CURIE (0..1)
+ type: string (1..1)
+ sequence_id: CURIE (1..1)
+ interval: SequenceInterval (1..1)

SequenceInterval
+ type: string (1..1)
+ start: Number (1..1)
+ end: Number (1..1)

Number
+ type: string (1..1)
+ value: integer (1..1)

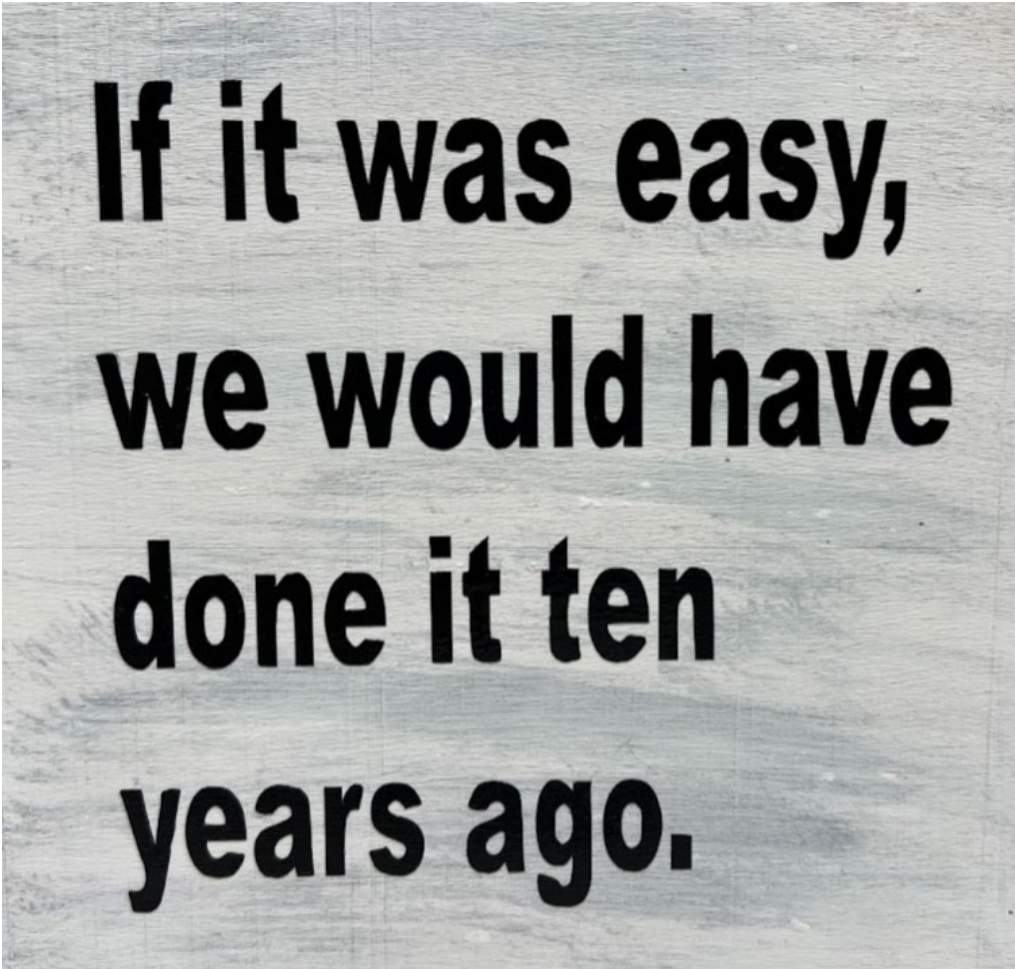
SequenceExpression
+ type: string (1..1)

LiteralSequenceExpression
+ type: string (1..1)
+ sequence: Sequence (1..1)



Isn't there an easier way?

- Can we just use AI to do it?
 - Grahame's First Law of Interoperability: it's about the people
- Robust data standards are necessary but not sufficient for interoperability
 - Agreement on semantics
 - Conformant implementations
 - Conformant usage (data)



**If it was easy,
we would have
done it ten
years ago.**

AI and Clinical Genomic Data

Reality check:

Clinical data are messy!

- Not enough time
- Not enough incentive
- It is too difficult

AI and Clinical Genomic Data

Reality check:

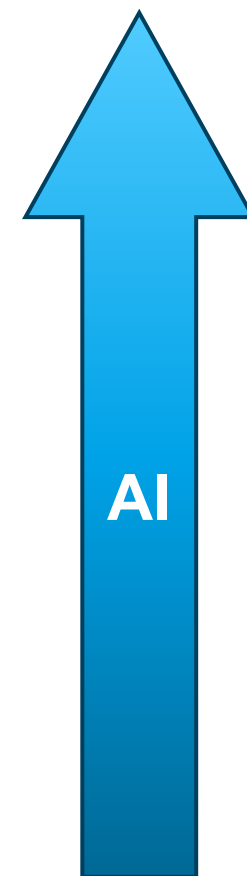
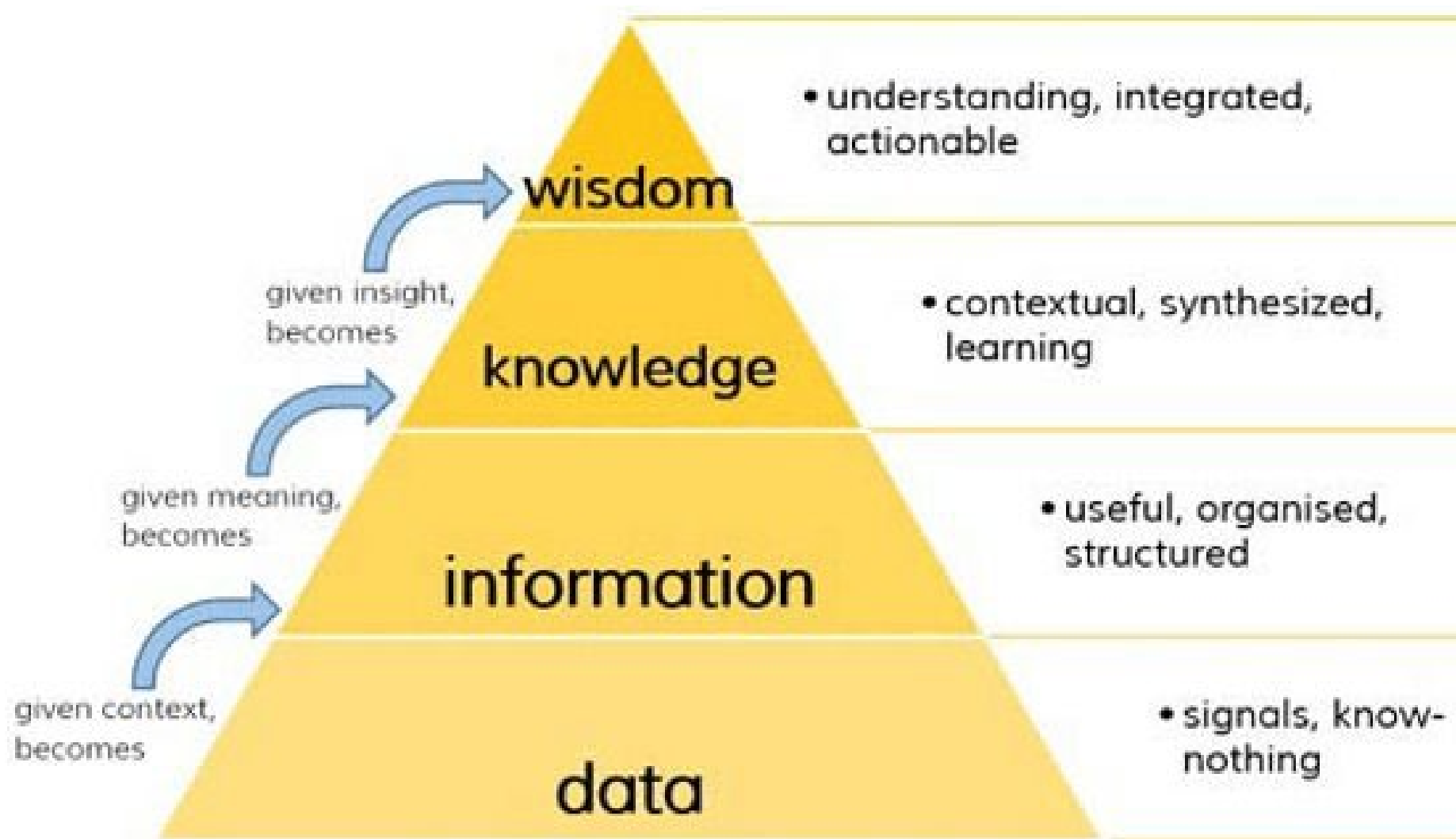
Clinical data are messy!

- Not enough time
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AI can help eliminate the toil!

- Automated QC
- Propose corrections
- Improve quality, computability, and semantic expressivity
- Rigor assured through scientific domains of medical informatics, data science, and knowledge representation

Data is Foundational



Imperatives for AI, Genomics, & Precision Medicine



Locally: Invest in data as an asset and enabling resource

Representation
Governance



Within a Community:
Prioritize robust semantics

Support complexity of the domain
AI-assisted QC and enrichment



Globally: Actively work
towards harmonization

Required for interoperability
Requires change in culture



Thank you!