

Adequate Pharmacogenomics

FHIR CG IG

11.30.2019

For comments, questions on slides refer to:

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General questions: HL7 CG WG members, FHIR community

Proposed actions

- Decide on what 'High Risk Allele' scope really is. Do we need something separate for Potential for Adverse Event.
- Vote on whether or not the increased efficiency in querying constitutes a strong imperative to change the PGx profiles to components.
- Select/Approve a group to finish selecting LOINC codes and implement switch to components.
- Vote on whether the change is important enough to be a quick version update.
- PROVIDE additional documentation on use. E.g. this power point has some textual statements that clarify how specific elements are used. Place such statements in the structure definition – not data element description.
- NOTE: level of evidence is currently adequate for the PGx use case as it allows any evidence system, such as PharmGKB's classification of evidence for PGx to be used. If a group needs to constrain then that group can do so with an implementation guide based on the CG WG implementation guide.

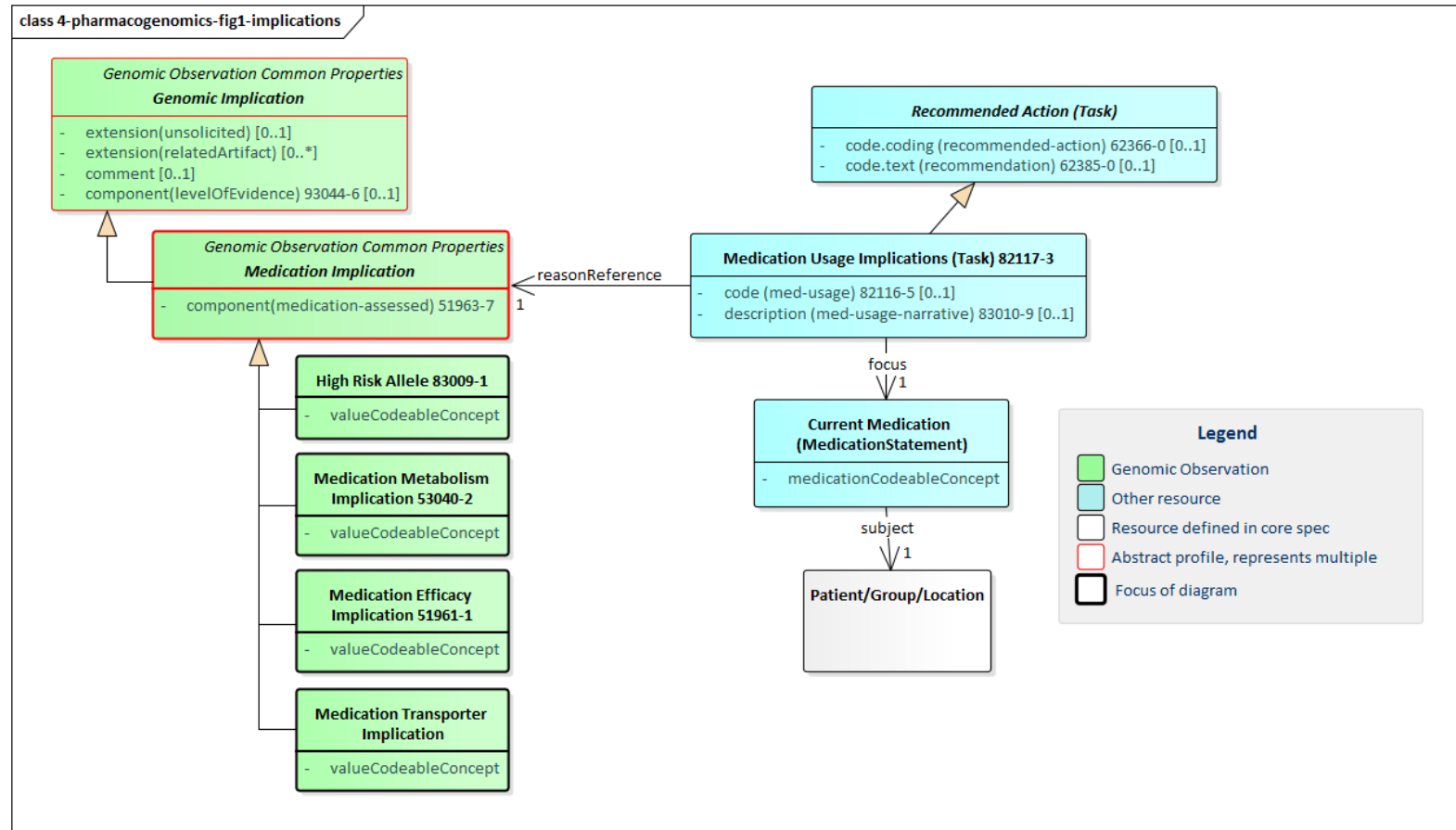
Goal

1. NOT a knowledge resource
2. NOT CDS delivery
3. NOT a guideline
4. Accommodate a variety of granular reporting of Pharmacogenomics found in current lab reports.

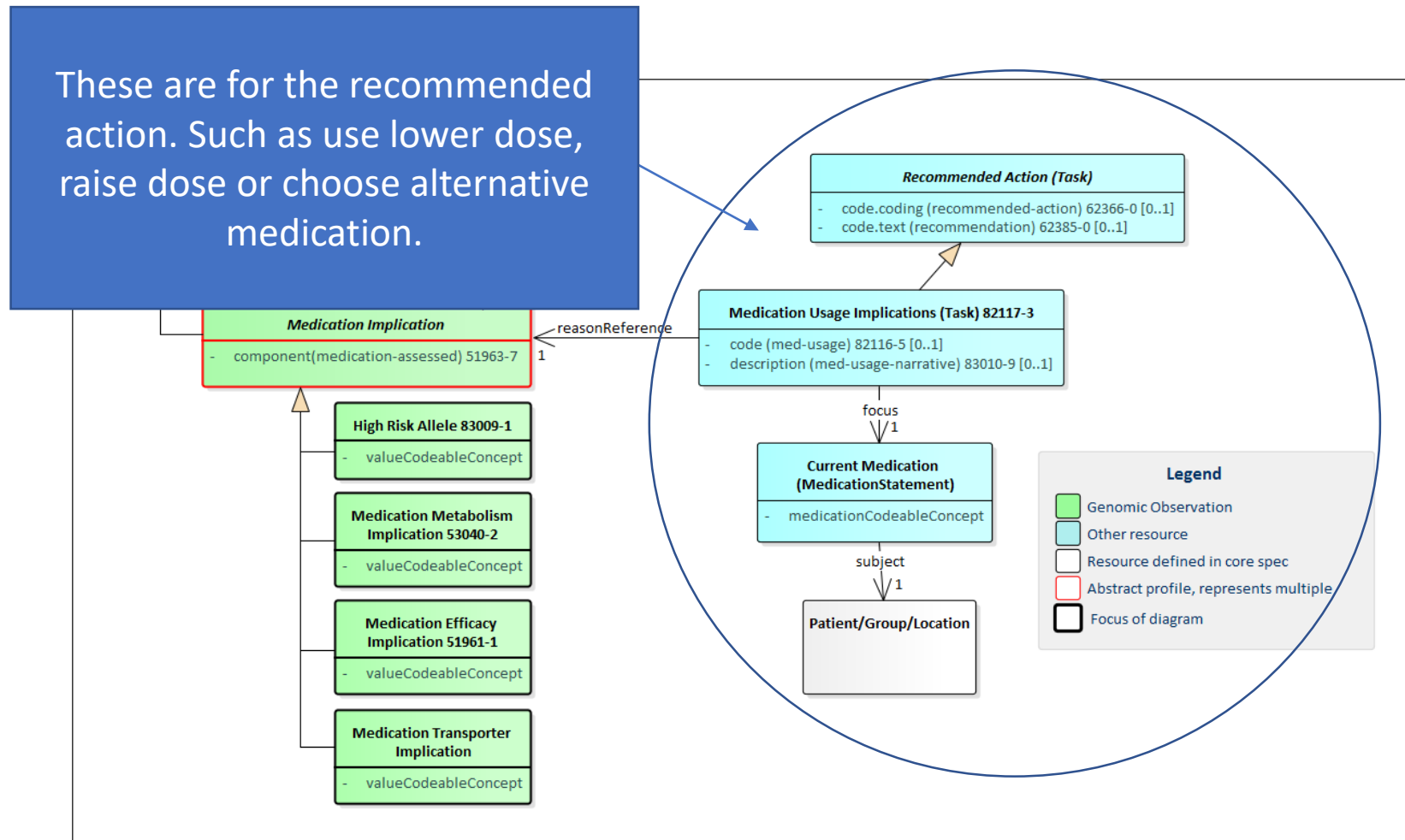
How do the current profiles differ from the existing abstract profile?

- The Medication Implication profile is an abstract profile which the current profiles are derived from
- The profile Medication Efficacy has a specific '.code' and '.value'
- The profile Medication Transporter has a specific '.code' and '.value'
- The profile Medication Metabolism has a specific '.code' and '.value'
- The profile High Risk Allele has a specific '.code' and '.value'
 - For now, suggesting using High Risk Allele for communicating Adverse Drug Event. This needs conclusive discussion
- THE PROFILES ONLY DIFFER BY USING A SPECIFIC Observation.code and value-set for Observation.value

Current Diagram



Current Diagram – note on Medication Task



Current Diagram – Med Task

For recommendation of action such as chose alternative medication, decrease dose, increase dose, Task-med-chg is used. Take note of 'intent', 'coding', 'coding.text', 'description' and 'reason reference'

intent	Σ I	1..1	code	Binding: (unbound) (example) unknown proposal plan order original-on
priority	I	0..1	code	Binding: TaskIntent (required) Fixed Value: proposal routine urgent asap stat
code	Σ I	1..1	CodeableConcept	Binding: RequestPriority (required) Task Type
id		0..1	string	Binding: TaskCode (example) Unique id for inter-element referencing
extension	I	0..*	Extension	Additional content defined by implementations
coding	Σ I	0..*	(Slice Definition)	Slice: Unordered, Open by value:url Code defined by a terminology system
coding:change	Σ I	0..1	Coding	Slice: Unordered, Open by value:system E.g. Consider alternative medication, Decrease d
id		0..1	string	Binding: LOINC Answer List LL4049-4 (preferred) Unique id for inter-element referencing
extension	I	0..*	Extension	Additional content defined by implementations
system	Σ I	1..1	uri	Slice: Unordered, Open by value:url Identity of the terminology system
version	Σ I	0..1	string	Fixed Value: http://loinc.org Version of the system - if relevant
code	Σ I	1..1	code	Symbol in syntax defined by the system
display	Σ I	0..1	string	Representation defined by the system
userSelected	Σ I	0..1	boolean	If this coding was chosen directly by the user
text	Σ I	0..1	string	Medication usage suggestion narrative
description	Σ I	0..1	string	Human-readable explanation of task
reasonCode	I	0..1	CodeableConcept	What task is setting on Why task is needed Binding: (unbound) (example)
reasonReference	I	0..1	Reference(Medication Implication)	Why task is needed

For intent use 'proposal.'

For coding.text you can put a statement like 'Change to alternative medication' in addition to the code value.

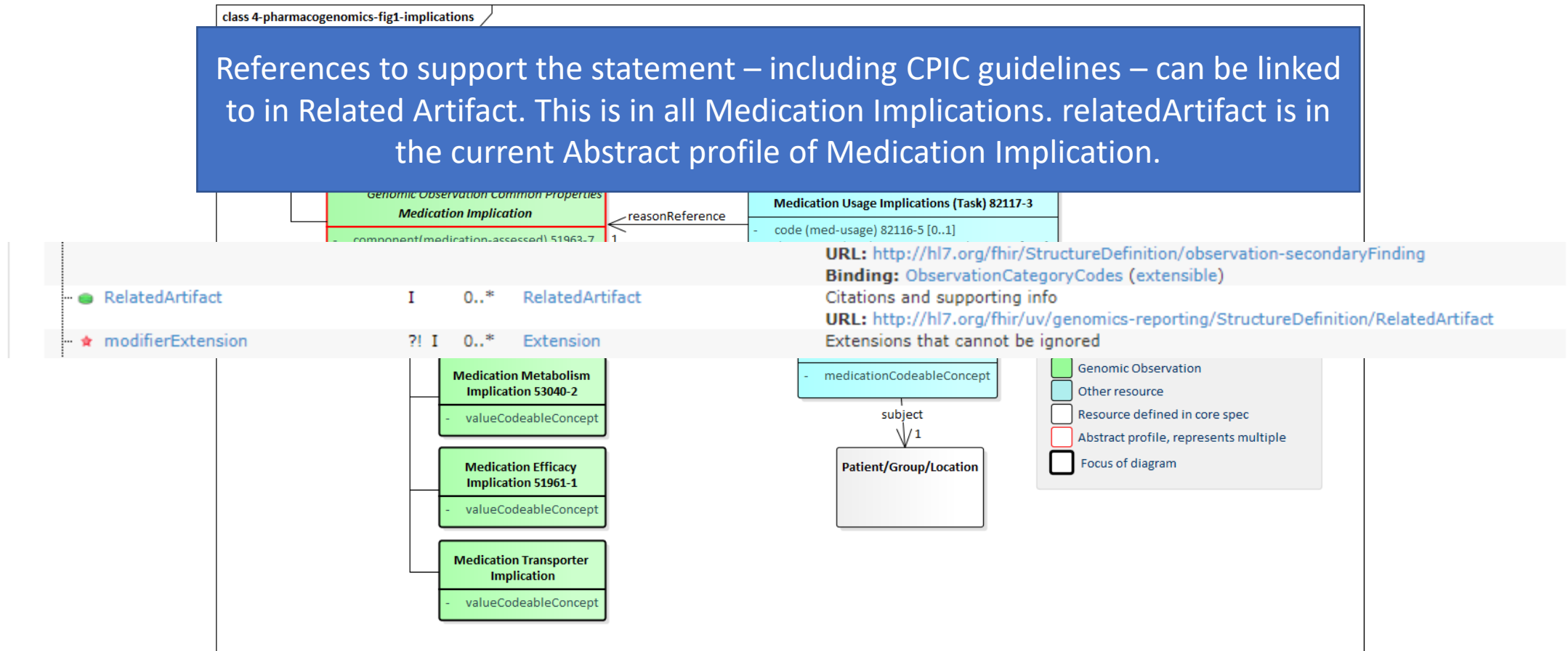
description is a useful field for human readable-text

reasonReference – this links to the Medication Implication that has a RelatedArtificat for support, such as a CPIC guideline.

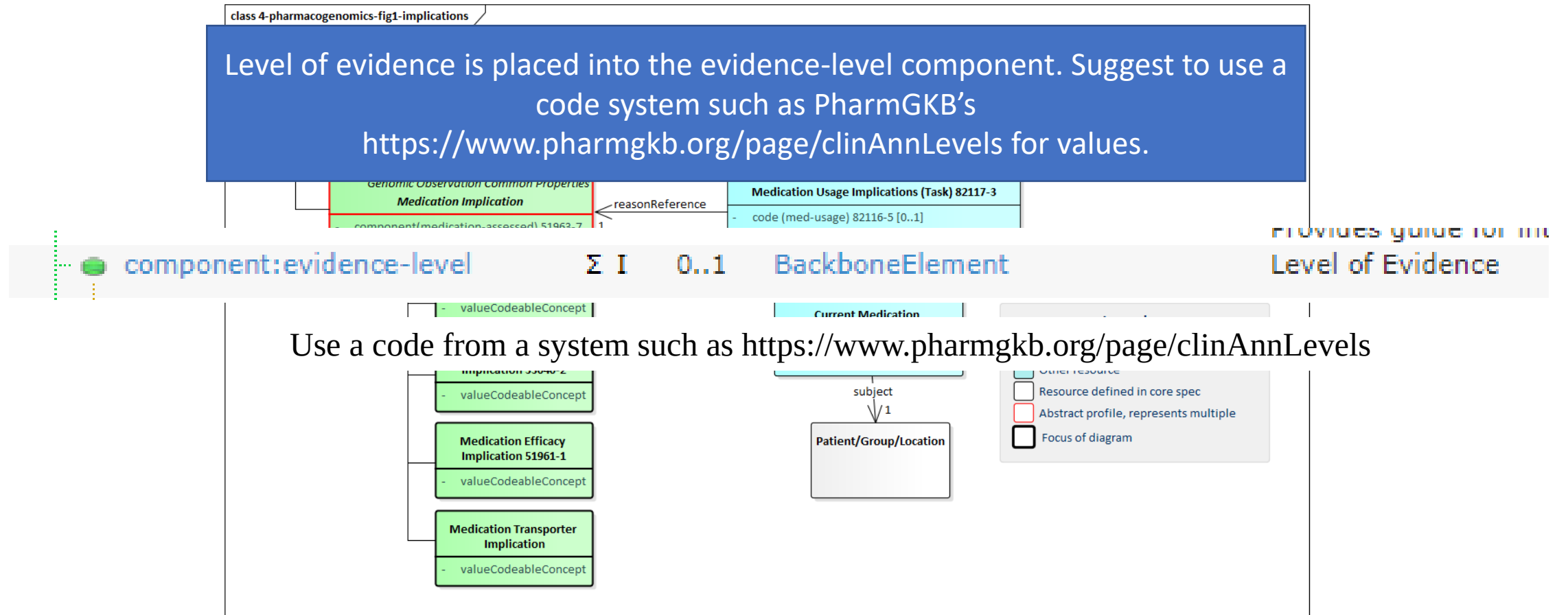
Current Diagram – note on Med assessed

class 4-pharmacogenomics-fig1-implications				
Medication-assessed – this is where the medication that the implication is about is identified. Use a code from a system such as RxNorm, SNOMED CT or LOINC				
Genomic Observation Common Properties		Medication Usage Implications (Task) 82117-3		
Medication Implication		reasonReference		
component:medication-assessed	Σ I	1..*	BackboneElement	Medication Assessed
id	0..1	string		Unique id for inter-element referencing
extension	I	0..*	Extension	Additional content defined by implementations
modifierExtension	?!	0..*	Extension	Extensions that cannot be ignored even if unrecognized
code	Σ I	1..1	CodeableConcept	Type of component observation (code / type) Binding: LOINC codes (example) Required Pattern: At least the following
id	0..1	string		Unique id for inter-element referencing
extension	0..*	Extension		Additional content defined by implementations
coding	1..*	Coding		Code defined by a terminology system Fixed Value: (complex)
id	0..1	string		Unique id for inter-element referencing
extension	0..*	Extension		Additional content defined by implementations
system	1..1	uri		Identity of the terminology system Fixed Value: http://loinc.org
version	0..1	string		Version of the system - if relevant
code	1..1	code		Symbol in syntax defined by the system Fixed Value: 51963-7
display	0..1	string		Representation defined by the system
userSelected	0..1	boolean		If this coding was chosen directly by the user
text	0..1	string		Plain text representation of the concept

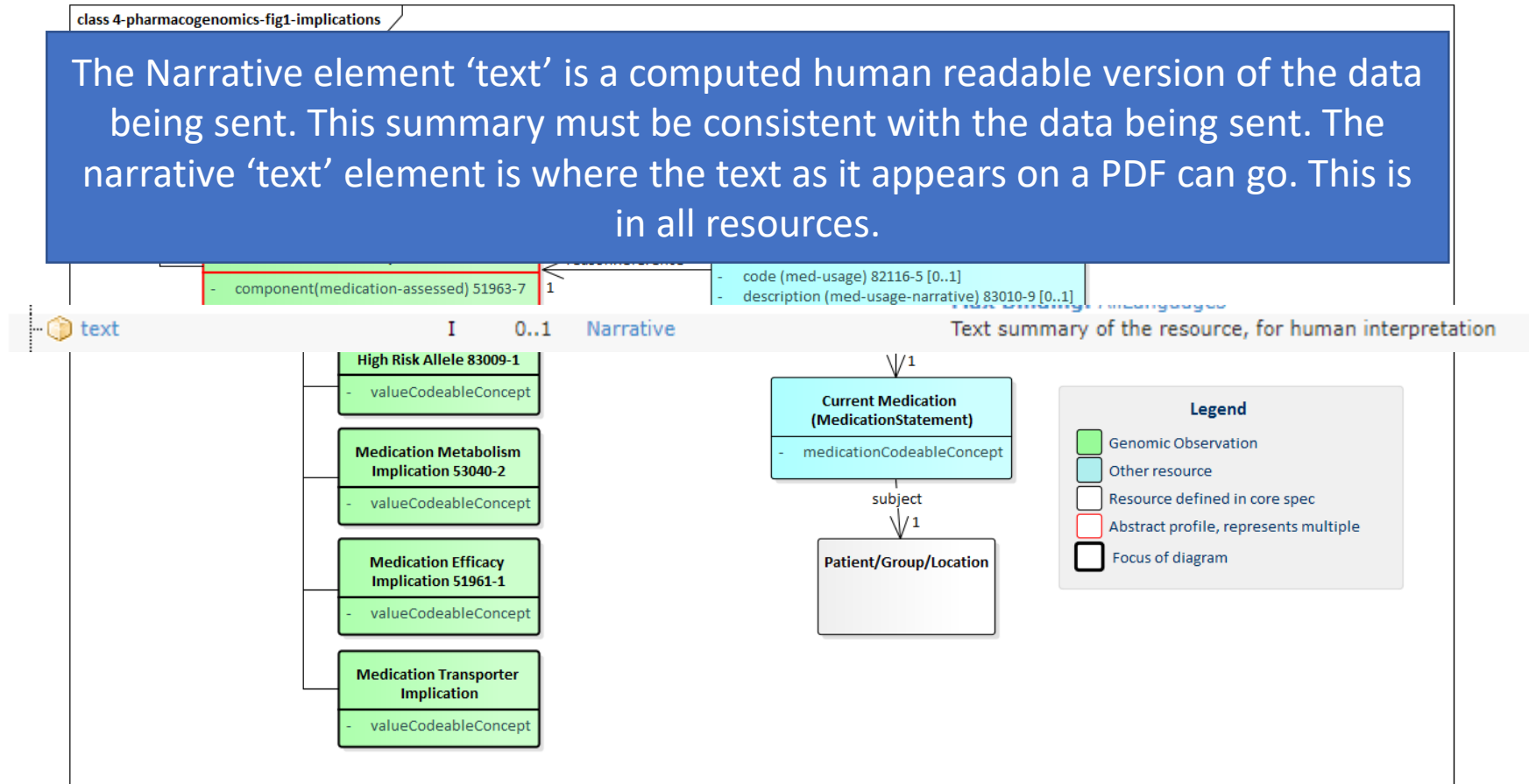
Current Diagram – note on Guidelines and Reference material



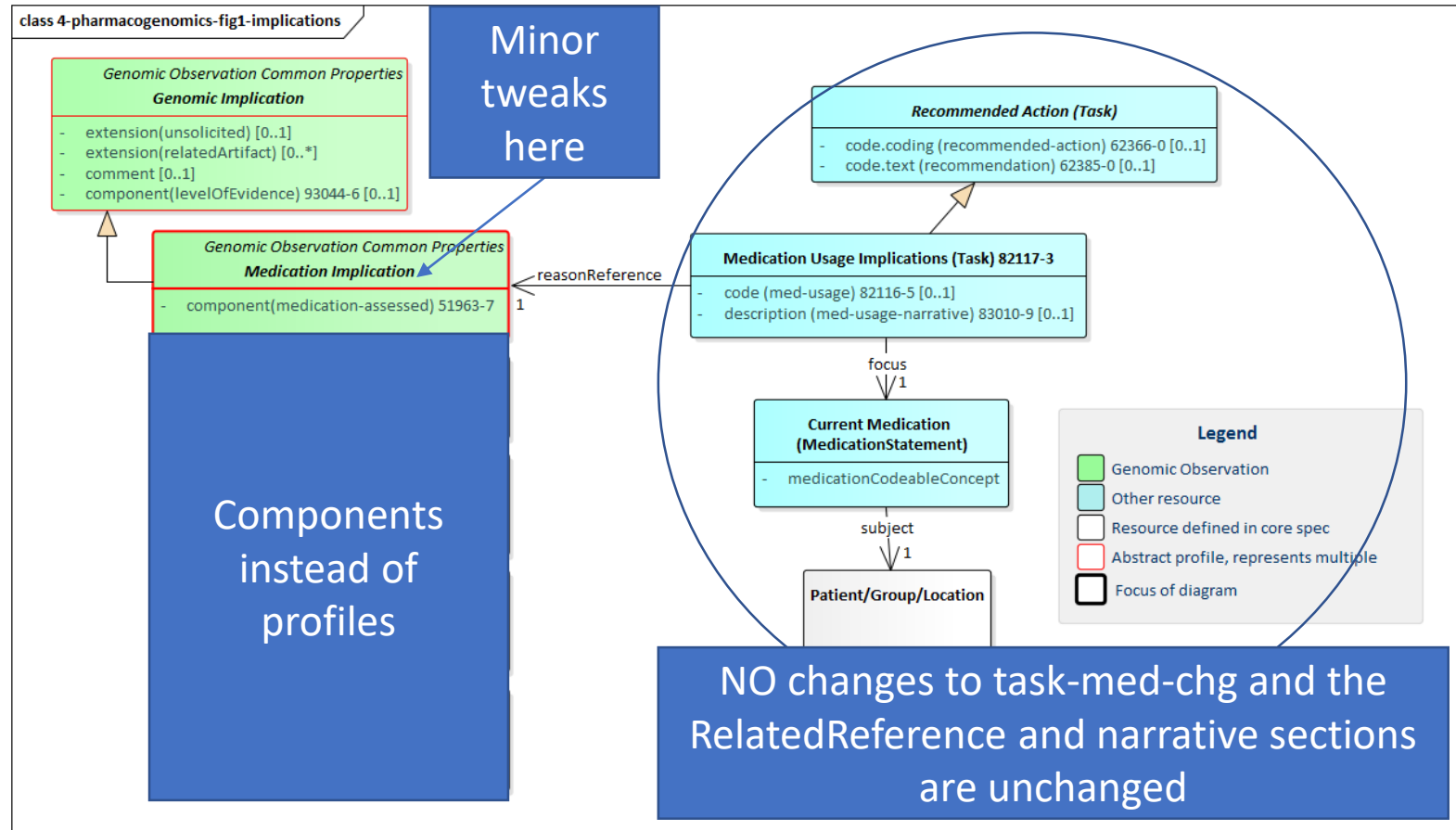
Current Diagram – note evidence level in PGx



Current Diagram – note on Narrative



Changes - diagram



Change entails

- Medication Implication profile will have:
 - Observation.code bound to LOINC code **61357-0** <https://loinc.org/61357-0/> *See the term description. Consider to request something similar or use it. Also <https://loinc.org/51965-2/>*
 - Observation.value bound to a value set of the current profile LOINC codes. Binding as 'preferred' (extensible) to 'Medication Efficacy', 'Medication Transporter', 'Medication Metabolism', 'High Risk Allele'
- Components are for providing more granular information
 - Each of 'Medication Efficacy', 'Medication Transporter', 'Medication Metabolism', 'High Risk Allele' would be a component, with a corresponding value-set (e.g. the component for the current Medication Efficacy would use the value set from the current profile)
 - Add component for Potential adverse drug event – OR use the High Risk component? I will use High Risk component (we can vote to change this) in this document
 - Suggest to add associated phenotype to the component for Potential Adverse Drug Event. So one *can* state an associated phenotype.

Think: The observation is 'what kind of variant implication does the genetic variation have' where the values are 'Medication efficacy', 'Medication transporter', 'Medication Metabolism', 'High Risk'- 'Potential Adverse Drug event.'

Second layer are the components themselves with

component.value providing a more granular statement. The component.code is used to indicate which type of implication the component.value is for (e.g. 'Medication efficacy' in component.code with component.value of 'Intermediate metabolizer')

Clinical Genomics (CG) Report and bundling – binding it all together

- The CG report structure has the variants, linked to implications, the implications linked to variants
- Task-med-chgs linked to implications and are included in the report as links for [RecommendedAction](#)
 - The implications do not have a link to task-med-chgs: so rev_include is currently necessary to find the medicine implication statements (guideline, as an example, links are in the med implication statements)

Implementation - Receiving

- Will need to capture the Medication implication profile – 1 profile to implement
- Each component may need to be handled separately
 - Not an increase in complexity – the profile based is just as complex

Implementation – Querying Efficiency

- The choice of components to handle the complexity makes querying easier. Semantically saying that the components are elements of an observation of a medication implication.
- Example query give me all implications for a patient : **‘Observation where observation.code is for Medication Implication and patient ID is X’**
- *With profiles the query is more complex and would have required each observation.code to be enumerated to find all the profiles. ‘Observation where observation.code is either Med Efficacy, Med ...and patient ID is X’*
- The component approach is less logically complex – requires less programming for system providing the data and the system querying for the data, also requires less processing at run-time.
- Getting a specific type of medication implication is possible through the observation.value E.g. ‘Observation where observation.code is for Medication Implication and observsation.value is Medication Efficacy’ would provide all the statements on medication efficacy.
- Note: task statements (e.g. lower, raise dose), supporting guidelines and variants are connected in the same manner whether components or profiles are used.

Implementation – Sending example

- Variant information is found through links to the correct variant observations.
- Molecular Phenotype example with Predicted Adverse Drug Response
 - “text interpretation”: "Individuals with **intermediate metabolizer status (IM)** have reduced metabolism of tricyclics to less active compounds when compared to extensive metabolizers; the resultant higher plasma concentrations will **increase the probability of side effects (concernCode !=A). Consider reducing the dose** by 40% and monitor nortriptyline 10-hydroxynortriptyline plasma concentrations (list of references: 8, 26, CPIC guideline).“
 - “text activity”: "Intermediate metabolizer. Two alleles showing decreased activity“
 - Confidence = ‘4’

Implementation – Sending (placing data)

Molecular Phenotype example with Predicted Adverse Drug Response

From example	Where placed in Clinical Genomics IG
“text interpretation”: “Individuals with intermediate metabolizer status have reduced metabolism of tricyclics to less active compounds when compared to extensive metabolizers; the resultant higher plasma concentrations will increase the probability of side effects.”	Narrative of Medication Implication profile instance
“Consider reducing the dose by 40% and monitor nortriptyline 10-hydroxynortriptyline plasma concentrations.”	Narrative in task-med-chg
“text activity”: “Intermediate metabolizer. Two alleles showing decreased activity”	Narrative in medication metabolism component
metabolizer status code - “IM”	intermediate metabolizer goes in value of ‘Medication Metabolism’ component.value
Confidence = ‘4’	evidenceLevel component with PharmGKB as value.code-system and value = Level 1B High
“increase the probability of side effects”, concernCode =!A	adverse Drug Event – use ‘High Risk Allele’ component with ‘High’ as value
list of references: 8, 26, CPIC guideline	in relatedArtifact of Medication Implication instance
“Consider reducing the dose”	in task-med-chg with ‘proposed’ intent

Future

- New slice on component can be made
- Additional values can be used in `Observation.value`
 - Dangerous Blessing: flexibility to accommodate future changes but can be misused
- As always, the implementer needs to use appropriate discretion. Make use of the text narrative section to provide human readable summaries. Have a clinical expert review the statements. But beware, computers need more boxes than humans. The human mind contains a model that abstracts complexity in a way not achievable with current computation. The computer needs codable concepts and labeled data elements.

The Nots – guidelines, knowledge resources, and Clinical Decision Support (CDS) delivery

- Guidelines, Knowledge Resources and Clinical Decision Support delivery should be targets for our WG in conjunction with other working groups (and a formal invitation given to genomic bodies) depending on topic.
- Knowledge resources can be found in locations such as NCBI's repository or PharmGKB documentation. For example, using the HL7 Infobutton standard as implemented by PharmGKB, <https://api.pharmgkb.org/v1/infobutton?mainSearchCriteria.v.dn=Clopidogrel> delivers a multitude of knowledge on *clopidogrel* in the context of pharmacogenomics. (aside: do we really need to create a standard for PharmGKB beyond recommending the use of the HL7 Infobutton Standard? Also, why is knowledge needing to be given in the message? Is a link sufficient?)
- My suggestion is to work on these questions with the Clinical Decision Support working group. Get a document together with the elements we think are important together and then ask the CDS working group to devise a means to communicate.

Related Topic Medication assessed - consideration

- Link to medication resource. We did not do this currently. Suggested as we need a slot for, essentially, a generic.
 - Using RxNorm as codeable concept, assumes systems will be able to traverse from RxNorm to the meds on their system. Or requires human to jump from Generic to brand etc...
 - And Drug Class is not communicated so I propose
 - ADD TO OUR MEDICATION assessed medicineClassification 0..*

medicineClassification	0..*	BackboneElement	Categorization of the medication within a formulary or classification system
type	1..1	CodeableConcept	The type of category for the medication (for example, therapeutic classification, therapeutic sub-classification)
classification	0..*	CodeableConcept	Specific category assigned to the medication

- Or use medication knowledge to provide the medication assessed using Reference.
- Ultimately, the CG WG does not have purview over Medication specific knowledge. Expect medication assessed to mature as other portions of FHIR mature. BIG CAVEAT – ***Drug Class could be considered beyond our scope.***
- <https://www.hl7.org/fhir/medication.html> one reason Medication resource is not used is to avoid confusion with actual medications the patient has. However, I think we could use the resource can be used.

<https://loinc.org/61357-0/>

61357-0 Medication pharmaceutical advice.brief DocumentActive

Component

Medication pharmaceutical advice.brief

Property

Find

Time

Pt

System

^Patient

Scale

Doc

Method

Additional Names

Short Name

Medication pharm advice.brief Doc

Term Description

This collection contains information about a) the prescription item this pharmaceutical advice is related to, b) concerns such as interactions, contraindications, and allergies, and c) changed or alternative medication information. This term was originally created for, though not limited in use to, the IHE Pharmacy Pharmaceutical Advice profile in the Community Medication Prescription and Dispense set.

Source: Regenstrief LOINC