Establishing Connectivity and Pharmacogenomic Clinical Decision Support Rules to Protect Patients Carrying HLA-B*57:01 and TPMT Variants

An Implementation Guide

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Displaying and Integrating Genetic Information Through the EHR Action Collaborative (DIGITizE AC)

Version 1.0

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Introduction

The DIGITizE Action Collaborative[1] is focused on increasing support for clinical genomics within the electronic health record (EHR) ecosystem. It is approaching this broad goal by initially focusing on creating support for a very specific set of use cases. These use cases are being used as a means to bring relevant stakeholders together to produce functionality that improves clinical care. Our intention is to use learning derived from these initial use cases to incrementally broaden support to additional areas. By doing so, we hope to create a framework for broadly expanding health information technology support for genetics and genomics.

Our initial use cases focus on two pharmacogenomic effects: the impact of a specific *HLA-B* allele on abacavir hypersensitivity and the impact of certain *TPMT* alleles on azathioprine dosing. In both cases the members of DIGITizE felt that it was optimal to ensure the patient's health record contains the specific qualified genetic observation result for the associated drug before prescribing the drug. Therefore, consistent with published Clinical Pharmacogenetics Implementation Consortium (CPIC) clinical guidelines (see reference section), we are suggesting the following Clinical Decision Support (CDS) be implemented to warn the clinician in the following situations:

- An order for abacavir or azathioprine is placed for a patient that does not have a record of the appropriate qualified genetic observation result in the EHR environment.
- An order for abacavir is placed for a patient with the specific *HLA-B* observation result stating the presence of a specific *HLA-B* allele, which would indicate whether the patient is likely to have a hypersensitivity reaction.
- An order for azathioprine is placed for a patient with the specified *TPMT* observation result indicating that the patient is an intermediate or poor metabolizer of the drug.

The goal of this guide is to specify how system developers and healthcare organizations can implement this clinical decision support. It begins with a proposed standardized process for transmitting the data needed to underlie this support and then follows with a suggestion for how the CDS rules themselves could be implemented.

[1]This implementation guide was developed by the DIGITizE action collaborative, an ad hoc activity associated with the Roundtable on Genomics and Precision Health at the National Academies of Sciences, Engineering, and Medicine (the National Academies). The implementation guide does not necessarily represent the views of any one organization, the Collaborative, the Roundtable, or the National Academies and has not been subjected to the review procedures of, nor are they a report or product of, the National Academies.

A Note Regarding Scope and Future Direction

This guide is intended to facilitate the rapid implementation of two important pharmacogenomic clinical decision support rules. While we believe the suggestions in this guide are extensible to other pharmacogenomic effects, this work has not yet been completed.

This guide does not cover the transmission of structured data describing genetic variants or positions or regions assayed in tests. These transfers are not required to implement the use cases outlined below. However, we believe these transmissions will be critical to many future use cases. For this reason, we intend to develop a guide that covers the transmission of these data. As this is done, it may make sense to update this implementation guide. Users of this guide should be aware that this future work could involve deprecating the structures and strategies proposed below.

Moving the Data

Laboratories that generate genetic test results often run different information systems than the providers who receive these results. Therefore it is important that there be a standardized method for transmitting information between these systems. The DIGITizE Standards working group has developed a process that can be used to transmit the structured data needed to underlie these clinical decision support rules. While we have primarily focused our attention on transmissions from laboratory information systems (LIS) to the EHR environment, this process could also be used to transmit needed data between EHRs or LISs.

The working group has determined the minimal set of laboratory observation results needed to support these use cases. The definition of these results and their controlled vocabulary were established by the CPIC through a consensus-based Delphi survey entitled, "CPIC Term Standardization for Clinical Pharmacogenetic Test Results." (URL provided in reference section.)

In the body of this guide we outline a method for moving the required data through HL7v2 messaging. Another emerging standard, HL7 Fast Healthcare Interoperability Resources (FHIR), can also be considered for enabling the information transfer specified in this guide (See description here: hl7.org/fhir/DSTU2/observation-genetics-cg-prf-1a.html and example here: hl7.org/fhir/DSTU2/obs-genetics-example3-mutationlist-3.json.html).

Rationale

Our current goal is to build momentum for the exchange of genetic data, provide guidance for using these data in clinical decision support, and gather information to help guide future standards and recommendations. To help achieve this goal, we've devised a basic method for collecting and exchanging information that we believe will reduce barriers to entry for organizations interested in participating. The

current method has limitations – for example, it does not support exchanging discrete variant information or other metadata. It is not intended to be a long-term solution and we plan to develop new guidance for exchanging data as this initiative progresses.

Abacavir and *HLA-B*

The CPIC Delphi survey #3 Q7, related to the *HLA-B* alleles that are strongly associated with specific adverse effects to drugs, covers the absence or presence of the lab results for 3 different *HLA-B* alleles, each with a relationship to an adverse drug reaction for a unique drug. Abacavir hypersensitivity is specifically related to the *HLA-B* allele referred to as *HLA-B**57:01.

> While this pilot project is not specifically focused on the other two *HLA-B* alleles covered by CPIC's Delphi survey Q13, which are related to different drugs, it is assumed that laboratory observation results for these other *HLA-B* allele findings could support additional CDS rules related to the specific ADRs associated with those allele findings. Refer to the last section titled "Additional Use Cases" for more information on these two *HLA-B* alleles and their association with adverse drug reactions.

The *HLA-B**57:01 [Presence] observation result is defined in the CPIC survey #3 (Q7) to provide a result from a testing laboratory of whether the *HLA-B**57:01 allele was POSITIVE or NEGATIVE in a tested subject. No further observation results are required from the testing laboratory in order to fulfill the CDS rules for the working group's initial use case surrounding abacavir.

An existing LOINC observation code used for reporting the presence or absence of the *HLA-B**57:01 allele is described in more detail in the section titled, LOINC Codes, and is expected to be integrated into the sending laboratory's HL7v2 test results and consumed by the receiving EHR's system so that it may be stored in a manner that supports the CDS pilot for abacavir.

Azathioprine and *TPMT*

The CPIC Delphi survey #4 Q4, related to the pharmacogenetic gene phenotypes, covers the controlled vocabulary to be used by labs to report the interpreted phenotype based on the results of a pharmacogenetic test performed by the lab for several genes that code for drug metabolizing enzymes. The interpreted phenotype of one of these genes, *TPMT*, drives the azathioprine use case defined by the working group. It should be noted that *TPMT* gene variants affect mercaptopurine and thioguanine to a similar extent as their effect on azathioprine, so modest changes to implementation can be used to extend this approach to all thiopurine drugs.

While this pilot project is not specifically focused on the other drug metabolizing genes included in the CPIC survey (*DPYD*, *CYP2D6*, *CYP2C9*, *CYP2C19*, *CYP3A5*, *UGT1A1*) because they are not related to azathioprine, it is assumed that laboratory observation results for these other genes could support additional CDS rules related to the specific PGx CDS rules associated with these drug metabolizing genes. Refer to the last section titled "Additional Use Cases" for more information on other drug metabolizing enzyme genes.

The TPMT Gene Product Metabolic Activity Interpretation observation is defined in the CPIC survey #4 (Q4) to provide a result from a testing laboratory of one of the specific controlled terms that represent the interpreted phenotype of *TPMT* as determined by the testing laboratory. No further observation results are required from the testing laboratory in order to fulfill the CDS rules for the initial use case surrounding azathioprine.

A new LOINC code is proposed in the following section and is expected to be integrated into the sending laboratory's HL7v2 test results and consumed by the receiving EHR's system so that it may be stored in a manner that supports the CDS pilot for azathioprine.

LOINC Codes

The individual laboratory observation result codes that enable the CDS for abacavir and azathioprine are respectively referred to as *HLA-B**57:01 [Presence] and TPMT Gene Product Metabolic Activity Interpretation.

A note about LOINC answer codes

LOINC can and does provide a special class of codes that are only used as "Answer" codes. These codes begin with the characters "LA" and will be specified within the definition of a LOINC code for which they can be used. SNOMED-CT codes are the preferred standard. In the case of the HLA-B*57:01 observation, SNOMED equivalent SNOMED-CT terms for Positive and Negative exist and are specified by this guideline as the answer codes that will trigger the associated CDS rules. However, the specific answer codes for TPMT gene product metabolic activity interpretation have not yet been established in SNOMED-CT. Follow up work may be pursued to establish these codes in SNOMED-CT and which point a modification to this guideline could be made to make use of these new codes in addition to the original LOINC answer codes. It should be noted that multiple "equivalent" codes can be sent in the OBX-5 field by separating them with a tilde "~", which should allow implementers to support one or the other or both answer codes as they become available. An example of providing the optional LOINC answer codes for the *HLA-B*57:01* allele along with the equivalent SNOMED-CT answer codes has been provided below.

*HLA-B**57:01 [Presence]

The existing LOINC code, 50956-2: *HLA-B*57:01*[Presence], is designed to communicate either the presence or absence of the specific *HLA-B**57:01 allele. Here are the details:

LOINC CD	Component	Long Common Name
50956-2	HLA-B*57:01	HLA-B*57:01 [Presence]
Part Definition/Description(s)		
Part of HLA-B57 allele family that is associated with Abacavir hypersensitivity reaction (AHSR)		
Answer List*		

	Seq #	Answer	Answer ID
	1	Positive	LA6576-8
	2	Negative	LA6577-6

When applying this observation to an HL7v2 message, 50956-2:*HLA-B**57:01 represents the observation code that would populate the OBX-3 field of a single OBX segment returned to the ordering provider system from the testing laboratory system. The observation result value associated with this same OBX segment is found in the field OBX-5 which would contain one of two ordinal values, positive or negative.

> The SNOMED-CT codes for Positive and Negative are 10828004 and 260385009, respectively. SNOMED codes are strongly recommended for accurately and precisely representing the Positive or Negative result.

The reporting laboratory is to use this LOINC code to affirm that they tested for the specific *HLA-B**57:01 allele and one of the two SNOMED codes to convey they have observed that the patient's specimen either contains it or does not contain it. If an OBX segment containing this LOINC code is not returned by a testing laboratory and stored in a manner that is available to the CDS algorithm then it cannot be assumed that the patient has been tested for the presence or absence of the *HLA-B**57:01 allele, which is directly related to the hypersensitivity of abacavir. Here's a partial OBX segment example of the key elements discussed above:

For a positive finding of the *HLA-B*57:01* allele…

OBX|1|..|50956-2^HLA-B*57:01^LN ||10828004^Positive^SCT~LA6576-8^Positive^LN-ANS |…

And, for a negative finding of the *HLA-B*57:01* allele…

OBX|1|..|50956-2^HLA-B*57:01^LN ||260385009^Negative^SCT~LA6577-6^Negative^LN-ANS |…

> NOTE: The examples above includes the equivalent SNOMED-CT (SCT) and LOINC Answer (LN-ANS) codes in each OBX-5 field. While SNOMED-CT is the preferred standard, it does not prevent the ability to provide the equivalent answer code from the LOINC Answer list. This guide does specify a requirement to use the SNOMED-CT values so that the receiving system can fulfill the CDS rules associated with this test result.

TPMT Gene Product Metabolic Activity Interpretation

A new LOINC observation code, 79713-4: TPMT gene product metabolic activity interpretation , has been created precisely to support the requirement for the azathioprine use case. The details of the LOINC code follow:

LOINC CD	Component	Long Common Name
79713-4	TPMT gene product metabolic activity interpretation	TPMT gene product metabolic activity interpretation in Blood or Tissue Qualitative by CPIC

Part Definition/Description(s)

The TPMT gene product metabolic activity interpretation is determined by the reporting lab and returned with the structured test results. It indicates the lab's interpretation of the phenotype that meets the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for reporting TPMT gene product metabolic activity (phenotype), regardless of whether the lab assay's method was genetic or enzymatic. This specific interpretation would be considered a separate observation made by the lab in addition to the primary reported results (e.g., genotype or measured activity level) and it could be included with other assay-specific observations, which would ideally support the interpretation value. [https://cpicpgx.org/resources.html]

Answer List*

	Seq #	Answer	AnswerID
	1	Ultrarapid metabolizer	LA10315-2
	2	Rapid metabolizer	LA25390-8
	3	Normal metabolizer	LA25391-6
	4	Intermediate metabolizer	LA10317-8
	5	Poor metabolizer	LA9657-3

*based on the CPIC Delphi Survey

Here is an example of a partial OBX segment to show how this LOINC code would be applied:

For an Intermediate metabolizer TPMT gene product metabolic activity interpretation observation…

OBX|1|CWE|79713-4^ TPMT gene product metabolic activity interpretation ^LN || LA10317-8^Intermediate metabolizer^LN-ANS|…

Additional Use Cases

The following list of proposed LOINC codes are provided to complete the other *HLA-B* alleles and Pharmacogenetic test results that are covered by Q7 of Survey #3 and Q6 of Survey #4 of the CPIC Delphi Survey, respectively. There is minimal additional effort in defining the LOINC codes for these additional use cases. The potential benefit is that it may allow CDS implementers and labs to easily incorporate CDS rules similar to abacavir and azathioprine for these additional use cases providing benefit to additional patient populations.

Additional *HLA-B* Allele Findings from Q7 of the CPIC Delphi Survey #3 results.

1. Carbamazepine and phenytoin cutaneous reactions
   57979-7: HLA-B*15:02 [Presence]
2. Allopurinol cutaneous reactions
   79711-8: HLA-B*58:01 [Presence]

Additional pharmacogenetic test result codes applying to the drug metabolizing enzyme genes (Q4 of the CPIC Delphi Survey #4 results: includes *CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, and UGT1A1*. For example, the *DPYD* gene product metabolic activity interpretation code would be modeled after the code that is proposed for TPMT in the section above.

1. 79719-1: DPYD gene product metabolic activity interpretation

Establishing the Clinical Decision Support Rules

> Information provided below is intended to help implementers establish specific forms of clinical decision support. However, this implementation guide should not be considered a guideline. Each site must appropriately review and validate its content prior to implementation. We hope that this guide serves as a useful template but we encourage implementers to edit our proposed text and rules as they deem appropriate.

Abacavir Ordering Pharmacogenomic Support

Trigger Condition

Each order for abacavir for a patient

Query to be Run on Trigger Condition

All records within the patient record containing the LOINC observation code: 50956-2^HLA-B*57:01^LN . (The query result.)

Check 1: Determine if the System Should Intervene

If the query result contains no records an intervention should trigger. This intervention could take the form of an alert. An alert should have at least two parts:

1) A high level concise description of the issue in a format similar to a drug allergy or interaction alert.

2) A more detailed description potentially based on the 2014 CPIC guidelines:

> A *HLA-B**57:01 genotype test is recommended before prescribing abacavir per the FDA's black box warning regarding the risk of serious hypersensitivity reactions in patients that carry this allele. A *HLA-B**57:01 genotype test does not appear to have been ordered for this patient. Please do the following to order the *HLA-B**57:01 genotype test <<insert dialogue boxes here to order clinical *HLA-B* test>>

Implementers who have the ability to detect if a test has been ordered that could supply these results once it is

completed may choose to tailor the detailed message above to provide this information.

Each institution must determine whether its clinicians should be allowed to acknowledge the alert and continue with the drug order or if they should be prevented from ordering the drug. In making this decision, it is important to consider how situations where a patient has previously tolerated abacavir should be handled. Please refer to FDA's black box warning specifically stating that prior tolerance of the medication doesn't predict future ADR in individuals who carry the *HLA-B**57:01 allele. Implementers can also consider making the ordering of the test mandatory if evidence of the test result is not available in the record and the clinician does not indicate that they have access to the test result through another source. Some implementers may want to consider facilitating or automating the test ordering process.

Check 2: Determine if the user should be alerted to the potential sensitivity

If the query result contains records with conflicting statuses – one "**10828004^Positive^SCT**" the other "**260385009^Negative^SCT**", the clinicians should receive an alert saying:

> There are two conflicting results for this patient. Consult with a clinical pharmacist or laboratory professional to resolve the conflict.

If the conflicting results alert above was not raised and any record in the query result contains the value "**10828004^Positive^SCT"** raise an alert. This alert should be formatted in a manner that is consistent with a drug allergy or interaction alert with the following textual explanation from the 2014 CPIC guidelines:

> The *HLA-B**57:01 allele is present in this patient. This allele is associated with high risk of severe hypersensitivity to abacavir. *HLA-B**57:01 positive patients should NOT be prescribed abacavir. Please choose an alternate antiretroviral. For more information, please consult a <<recommended clinical professional for consultation, for example some institutions might direct to a clinical pharmacist>>.

If the CDS capability exists, the clinician should be presented a list of acceptable alternative drugs to simplify the proper replacement of the order.

Azathioprine Ordering Pharmacogenomic Support

Trigger Condition

Each order for azathioprine for a patient

Query to be Run on Trigger Condition

All records within the patient's set of observations containing the LOINC code: 79713-4^ TPMT gene product metabolic activity interpretation ^LN.

For each of the checks below each institution must determine:

1) If its clinicians should be able to override the alerts and continue with the drug order.
2) Whether clinicians should be able to suppress alerts for future orders on the same patient.
3) Whether to establish a dosage threshold below which they will not alert. (This is not recommended for situations where a "poor metabolizer " genotype could be present.)

Check 1: Determine if the user should be alerted to order a test

If the query result is empty (return 0 records) raise an alert formatted similarly to a drug allergy or interaction alert with the following explanation:

> *TPMT* test is recommended before using a thiopurine (mercaptopurine, thioguanine, and azathioprine). A *TPMT* genotype test does not appear to have been ordered for this patient.

Implementers who have the ability to detect if a test has been ordered that could supply these results once it is completed may choose to tailor the detailed message above to provide this information.

Check 2: Determine if the user should be alerted that the dose may be too high

If the query result contains records with conflicting statuses – for example, one result of "**LA25391-6^Normal Metabolizer^LN-ANS**" and another of "**LA10317-8^Intermediate Metabolizer^LN-ANS** or **LA9657-**

3^Poor Metabolizer^LN-ANS", the clinicians should receive an alert saying:

> There are two or more conflicting TPMT results for this patient which must be resolved. Consult a clinical pharmacist or laboratory professional to resolve.

If the query result contains the value "**LA10317-8^intermediate metabolizer^LN-ANS"** the user should be warned.

The user could be warned through this high level message:

> Testing has been performed and indicates that this patient is at INCREASED risk for myelotoxicity with standard dosing of thiopurine therapy

and this explanation:

> Based on a test result, this patient is predicted to be an intermediate TPMT metabolizer. The patient is at risk for myelosuppression with normal doses of azathioprine. A normal starting dose of azathioprine (e.g. 2-3 mg/kg/day) should be reduced to 0.6 – 2 mg/kg/day. Please consult a <<recommended clinical professional for consultation, for example some institutions might direct to a clinical pharmacist>>. [The alert may also refer the user to additional information within the system.]

This text could be augmented by graphical displays depicting the patient's risk level to convey more information to clinicians. Calculations of the likelihood of myelosuppression at different doses could also be used to enhance this text if the system can provide this support.

If the most recent record in the query result contains the value "**LA9657-3^Poor metabolizer^LN-ANS"** the user should be warned.

The user could be warned through this high level message:

> Testing has been performed and indicates that this patient is at VERY HIGH risk for myelotoxicity with standard dosing of thiopurine therapy

and this explanation:

> Based on the result, this patient is predicted to have low or absent TPMT activity. The patient is at high risk for life-threatening myelosuppression with normal doses of azathioprine. Azathioprine should be avoided, or if azathioprine is given, start by reducing the does by 10-fold and administer thrice weekly instead of daily. Please consult a <<recommended clinical professional for consultation, for example some institutions might direct to a clinical pharmacist>>.. [The alert may also refer the user to additional information within the system.]

This text could be augmented by graphical displays depicting the patients risk level to convey more information to clinicians. Calculations of the likelihood of myelosuppression at different doses could also be used to enhance this text if the system can provide this support.

References

Bell, Gillian C., Kristine R. Crews, Mark R. Wilkinson, Cyrine E. Haidar, J. Kevin Hicks, Donald K. Baker, Nancy M. Kornegay et al. "Development and use of active clinical decision support for preemptive pharmacogenomics." *Journal of the American Medical Informatics Association* 21, no. e1 (2014): e93-e99.

Martin, M. A., et al. "Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and abacavir dosing." *Clinical Pharmacology & Therapeutics* 91.4 (2012): 734-738.

Peterson JF, Bowton E, Field JR, Beller M, Mitchell J, Schildcrout J, Gregg W, Johnson K, Jirjis JN, Roden DM, Pulley JM, Denny JC. "Electronic health record design and implementation for pharmacogenomics: a local perspective." Genet Med. 2013 Oct;15(10):833-41.

CPIC Term Standardization Project: https://www.pharmgkb.org/page/cpicTermProject.

SGE Marsh, ED Albert, WF Bodmer, RE Bontrop, B Dupont, HA Erlich, M Fernández-Vina, DE Geraghty, R Holdsworth, CK Hurley, M Lau, KW Lee, B Mach, WR Mayr, M Maiers, CR Müller, P Parham, EW Petersdorf, T Sasazuki, JL Strominger, A Svejgaard, PI Terasaki, JM Tiercy, J Trowsdale. "Nomenclature for factors of the HLA system, 2010." *Tissue Antigens* (2010) **75**:291-455

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