

# HITSAC Clinical Genomics Use Case: Pharmacogenomics

## Process for Integrating Results from Pharmacogenomic Testing across Electronic Health Record Systems

**DRAFT**

Version 1.0

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## Version Control

The following table contains a history of revisions to this publication.

Version	Date	Revision Description	Contact
1.0	11/10/2016	Initial Use Case Document	Joseph Grubbs, Ph.D., VITA

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# Use Case Background

## 1. Use Case ID

HITSAC Clinical Genomics Use Case: Pharmacogenomics (HITSACCG1)

## 2. Use Case Title

HITSAC Clinical Genomics Use Case: Pharmacogenomics, Process for Integrating Results from Pharmacogenomic Testing across Electronic Health Record Systems

## 3. Abstract

The HITSAC Clinical Genomics Use Case: Pharmacogenomics (HITSACCG1) defines the process for integrating results from pharmacogenomic testing across disparate electronic health record (EHR) systems. The use case has been developed by the Virginia Information Technologies Agency (VITA) at the direction of HITSAC. Partners in the development of this use case include the Virginia Department of Health (VDH), Inova Health System, Inova Translational Medicine Institute (ITMI), the Sequoia Project/eHealth Exchange, and Virginia Commonwealth University (VCH) Health System.

## 4. Description

Pharmacogenomics explores the role of genetics in drug response, focusing in particular on the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with drug absorption, distribution, metabolism and elimination and drug receptor target effects. Pharmacogenomics concentrates on single drug-gene interactions and encompasses a more genome-wide association approach, incorporating genomics and proteomics while exploring the effects of multiple genes on drug response.

Results from pharmacogenomic testing require a designated location, standardized structure and nomenclature and dedicated persistence within the EHR. Unlike other laboratory tests, such as for cholesterol or glucose level, results from pharmacogenomic testing do not change. Therefore, pharmacogenomic test results must remain with the patient and be clearly discoverable by health care providers to inform appropriate pharmacological treatment. Specific requirements for pharmacogenomic test results returned to the EHR are as follows:

- A clinical report with the results described in narrative form
  - Actions and recommendations signed off by the certified clinical and or molecular geneticists
  - Understandable information for both clinician and patient
- A discrete result of the allele variation for the specific loci being tested
  - Allows for interoperability and data sharing based on a standard set understandable across the genetic community
  - Enables alerts – both active and passive – to be generated based on the results
  - Provides for statistical and outcomes-based reporting from the results
  - Supports future reporting and alerts based on discovery of validated drug/gene interactions
- A discrete, more descriptive result of the test in the context of the test order
  - Provides for statistical and outcomes-based reporting for non-genetic purposes
  - Gives clear indication result interpretation in the context of patient point of care

The Inova Translational Medicine Institute (ITMI) is a research center established by Inova Health System, to conduct genomic research and translate findings into a clinical setting to improve quality of patient care. ITMI has implemented a pharmacogenomic testing protocol for Clopidogrel (Plavix, CYP2C19), a second-generation thienopyridine that inhibits platelet aggregation and has been designed for treatment of patients with coronary artery disease, acute coronary syndromes (ACS), and/or after

percutaneous coronary interventions (PCI). ITMI has named the test “Plavix Genotype Test” and performs the test using a kit approved by the U.S. Food and Drug Administration (FDA).

The interpretation of the Plavix Genotype Test has been standardized on the assay and ITMI’s Luminex laboratory equipment. ITMI initiated its implementation of the clinical genetic/genomics tests on these standard set FDA approved pharmacogenomics tests, as these tests have been validated and are mostly reimbursable. As the testing progresses, ITMI will implement genetic panels, targeting specific genetic markers for conditions such as cancer or supplements to standard tests such as newborn screening.

This use case has been developed by HITSAC to define the process, and associated health IT standards, for integrating results from pharmacogenomic testing across disparate EHR systems through the eHealth Exchange. The use case leverages the workflow, testing protocols, and reporting capability currently being implemented by Inova/ITMI as the Plavix Genotype Test. The ITMI Plavix Genotype Test specification has been provided in Appendix A. Specifications and requirements for integration of pharmacogenomic test results into Inova’s EPIC EHR have been provided in Appendix B.

The use case has been constrained to focus on reporting of pharmacogenomic test results – the Plavix Genotype Test – within the Inova Health System laboratory and EHR environment – and the transmittal of the results into an external EHR system through the eHealth Exchange, with the use case target being VCU Health System’s Cerner EHR. Future use cases identified by HITSAC will concentrate on generalizing from the Inova/ITMI-centric system to pharmacogenomic tests conducted on other laboratory and EHR platforms.

## 5. Stakeholders

- Inova/ITMI Pharmacogenomic Laboratory Testing
  - ITMI Laboratory Software
  - ITMI Laboratory Staff
- Inova Health System Electronic Health Record (EHR) System
  - Inova EHR System (Epic)
  - Inova Clinical Staff
- Sequoia Project/eHealth Exchange (eHealth Exchange) System
  - eHealth Exchange Software
  - eHealth Exchange Staff
- VCU Health System Electronic Health Record (EHR) System
  - VCU EHR System (Cerner)
  - VCU Health Systems Information Technology Staff

## 6. Definitions

**Pharmacogenomic Test:** A laboratory test that measures the influence of genetic variation on drug response in patients.

**Electronic Health Record (EHR):** A digital version of a patient's medical chart structured based on the Health Level 7 (HL7) Clinical Document Architecture (CDA) and Continuity of Care Document (CCD) Standards.

## Pharmacogenomic Test Result – Plavix Genotype Test

Test Title: Clopidogrel CYP2C19 Genotyping

Test Number: 511710 CPT: 81225

Specimen: Whole blood or buccal swab kit (Buccal swab collection kit contains instructions for use of a buccal swab.)

Volume: 7 mL whole blood or buccal swab kit

Minimum Volume: 3 mL whole blood or two buccal swabs

Container: Lavender-top (EDTA) tube, yellow-top (ACD) tube, or LabCorp buccal swab kit

Storage Instructions: Maintain specimen at room temperature or refrigerate at 4°C.

Causes for Rejection: Frozen or hemolyzed specimen; quantity not sufficient for analysis; one buccal swab; improper container; wet buccal swab

Use: Clopidogrel is a prodrug that is metabolized to its active component by several cytochrome P450 proteins of which CYP2C19 plays a key role. Variation in the CYP2C19 gene can result in variable metabolizer phenotypes. Among clopidogrel-treated patients, one or more loss-of-function alleles (\*2, and \*3) are associated with reduced platelet inhibition and an increased risk of cardiovascular complications, such as myocardial infarction, stroke, stent thrombosis, and/or death, as compared with homozygous (\*1/\*1) individual gene carriers. Individuals who are carriers of the \*17 allele are ultrametabolizers (UM) and may have an enhanced response to clopidogrel. Ultrametabolizers are at increased risk of bleeding. Other common drugs metabolized by the 2C19 pathway include proton pump inhibitors (omeprazole), anticonvulsants (phenytoin and diazepam), and tricyclic antidepressants (amitriptyline and nortriptyline).

Limitations: This assay detects poor metabolizer CYP2C19 alleles \*2, \*3, as well as the ultrametabolizer allele, \*17. Other rare alleles are not detected by this assay. Metabolism of drugs including clopidogrel may also be influenced by race, ethnicity, diet, and/or other medications. Results must be interpreted in the context of other test results and clinical findings. This test result does not rule out the possibility of variant alleles in other drug metabolism pathways that may impact drug efficacy and/or toxicity.

Methodology: DNA analysis of the cytochrome P450 2C19 gene (OMIM 124020, 10q24.1-10q24.3) includes the alleles \*1, \*2, \*3, and \*17 and is performed on the Tm Bioscience/Luminex Universal Array Platform using primer extension chemistry. Multiplex PCR amplifies DNA fragments containing mutations associated with the alleles mentioned above. Primer extension then generates a biotin-labeled product that hybridizes to complementary, bead-immobilized probes to permit flow-sorted detection of both normal and mutation sequences. Molecular-based testing is highly accurate, but as in any laboratory test, rare diagnostic errors may occur.

## Use Case Parameters and Transaction Workflows

**Note:** Diagrams of the transaction workflows and data flows of the integration of the ITMI Plavix Genotype Test results into Inova's EPIC EHR system have been provided in this document as Appendix D and Appendix E. Diagrams of the transaction workflows and data flows of the transmittal of the test results to the VCU Health System's Cerner EHR system through the eHealth Exchange have been provided as Appendix F and Appendix G.

### 1. Preconditions

*A set of conditions that must be met before the activities described in the use case can begin.*

1. The Inova/ITMI has conducted the Plavix Genotype Test.
2. The result from the ITMI Plavix Genotype Test has been transmitted to the patient's EHR in Inova's EPIC EHR system.
3. The ITMI Plavix Genotype Test result has been integrated into the patient's EHR in Inova's EPIC EHR system.

### 2. Post Condition

*A set of conditions that must be met after the activities described in the use case have been completed.*

The received ITMI Plavix Genotype Test becomes integrated into the patient's EHR in Inova's EPIC EHR system and transmitted into an external EHR system through the eHealth Exchange.

### 3. Priority

*Describes the importance and sequence of the use case in the overall activities of the cancer registry.*

HITSAC has defined this as a high-priority use case for immediate implementation.

### 4. Frequency of Use

*Describes how often the activities in the use case take place.*

The activities in this use case will take place each time a new or resubmitted ITMI Plavix Genotype Test result becomes transmitted into the patient's EHR in Inova's EPIC EHR system and transmitted to an external EHR system through the eHealth Exchange.

### 5. Inova Health System EHR System – EPIC Specifications

*Describes the specifications required for integration with Inova Health System's EPIC EHR System.*

## 6. Transaction Workflow

*Describes the specific steps in the workflow taken to integrate the results from the ITMI Plavix Genotype Test into the Inova EPIC EHR system.*

- 6.1 Order test in EPIC
- 6.2 SOFT registers test in LIS
- 6.3 EPIC sends a notification to SOFT to collect biospecimen
- 6.4 SOFT collects biospecimen
- 6.5 If test is external, the following steps occur:
  - 6.5a. ITMI ships biospecimen to vendor
  - 6.5b. Vendor processes the biospecimen
  - 6.5c. Vendor analyzes the biospecimen
  - 6.5d. Vendor sends results to SOFT
  - 6.5e. ITMI reviews and stores results
  - 6.5f. SOFT reviews and stores results
  - 6.5g. SOFT sends results to EPIC
  - 6.5h. EPIC associates results with MRN
  - 6.5i. EPIC stores results
  - 6.5j. EPIC records billing

If the test is not external, the workflow continues

- 6.6 ITMI processes biospecimen
- 6.7 ITMI collects workflow data and tracks workflows
- 6.8 ITMI analyzes biospecimen
- 6.9 ITMI reviews and stores results
- 6.10 SOFT reviews and stores results
- 6.11 SOFT sends results to EPIC
- 6.12 EPIC associates results with MRN
- 6.13 EPIC stores results
- 6.14 EPIC records billing

## 7. VCU Health System EHR System – Cerner Specifications

*Describes the specifications required for integration with VCU Health System Cerner EHR System.*

## 8. eHealth Exchange – Testing and Certification Specifications

*Describes the specifications required for onboarding, testing and certification onto eHealth Exchange.*

## 9. Assumptions

1. The ITMI has implemented the Plavix Genotype Test.
2. The ITMI Plavix Genotype Test results are in electronic format.
3. The ITMI Plavix Genotype Test results are encrypted pursuant to Commonwealth of Virginia standards.
4. The collection, management and transmittal of the ITMI Plavix Genotype Test results comply with applicable law.

## 10. Pilot Project Work Plan

The HITSAC Clinical Genomics Use Case: Pharmacogenomics has been used to frame a pilot project, initiated by HITSAC in September 2016. The purpose of the pilot project will be to develop and implement a process to support integration of pharmacogenomic test results into a patient's EHR to enhance quality of patient care. The pilot project will be carried out based on the following work plan:

Project Task	Description	Due Date / HITSAC Status Report
Task 1: Stakeholder Engagement	Coordination among stakeholders to level-set on use case and project objectives; trust framework execution (if required); documentation of stakeholder systems and exchange specifications	01/31/2017 / 01/19/2017
Task 2: Requirements & Specifications Analysis	Analysis of use case requirements, system specifications, performance and service specifications, and security/privacy provisions; documentation of requirements and specifications to guide project onboarding, testing, certification, and implementation ( <a href="http://sequoiaproject.org/resources/exchange-specifications/">http://sequoiaproject.org/resources/exchange-specifications/</a> )	03/31/2017 / 03/16/2017
Task 3: Onboarding, Testing, & Certification	Completion of required onboarding, testing, and certification of stakeholder systems onto the eHealth Exchange ( <a href="http://sequoiaproject.org/ehealth-exchange/onboarding/">http://sequoiaproject.org/ehealth-exchange/onboarding/</a> )	05/30/2017 / 05/18/2017
Task 4: Implementation and Production Exchange	Implementation of exchange in a production environment; ongoing monitoring and exchange refinement during project's period of performance	07/31/2017 / 07/20/2017
Task 5: Process, Data & Transaction Workflow Review	Comprehensive review of business processes, data flows, and transaction workflows in production environment; documentation of review to exchange with HL7 and other external stakeholders	09/30/2017 / 09/21/2017

## Alignment with Existing Health IT Standards

The process for integrating pharmacogenomic test results across EHR systems has been developed to comply with the following health IT standards\*:

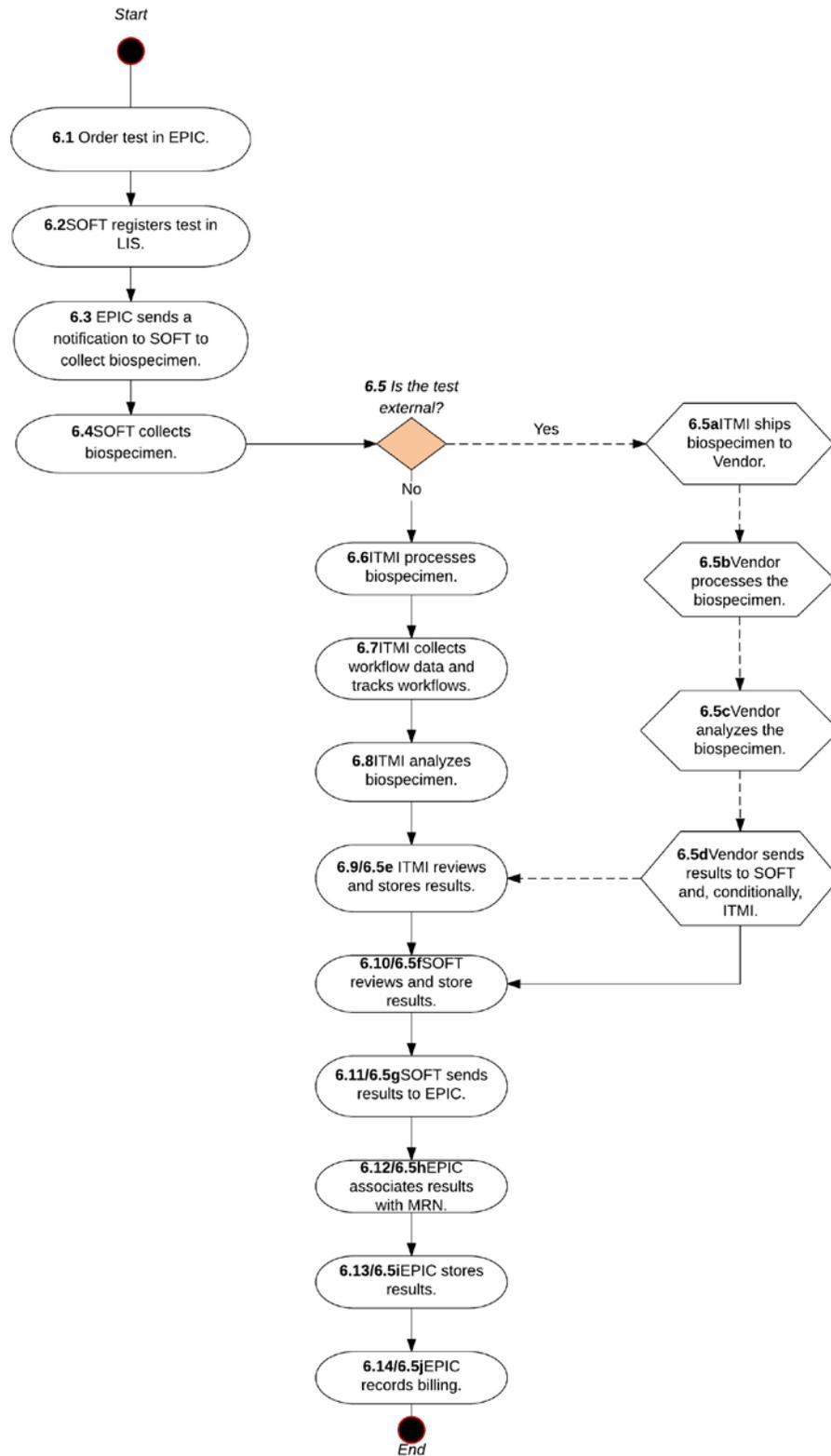
ID	TITLE	NOTES
<a href="#">EDS-R-163 (COV)</a>	HL7/Logical Observation Identifiers Names and Codes (LOINC)	LOINC #81247-9: HL7 Genetic Variant Reporting Panel (See attached panel hierarchy)
<a href="#">EDS-R-47 (COV)</a>	National Center for Biotechnology Information (NCBI) Genetic Reference Sequences	NCBI RefSeqGene
<a href="#">CAQH CORE X12</a>	Council for Affordable Quality Health (CAQH) Care Committee on Operating Rules for Information Exchange (Phase I and Phase II)	CAQH CORE X12 Document Submission Service Interface Specification v. 1, ANSI X12, required for eHealth Exchange testing, certification, and onboarding
<a href="#">NHIN WSR/WSI</a>	Nationwide Health Information Network (NHIN) Web Services Registry Web Service Interface Specification, Version 3.1	NHIN WSR/WSI Specification required for eHealth Exchange testing, certification, and onboarding
<a href="#">NHIN X12 esMD</a>	Nationwide Health Information Network (NHIN) Electronic Submission of Medical Documentation (esMD) X12 Profile, Version 1	ANSI X12 esMD required for eHealth Exchange testing, certification, and onboarding
HL7 V2IG CG LOINCENVAR R2-2013	HL7 Version 2 Implementation Guide: Clinical Genomics; Fully LOINC-Qualified Genetic Variation Model, Release 2	Ref. HL7 Version 2.5.1 Implementation Guide: Orders And Observations; Interoperable Laboratory Result Reporting To EHR (US Realm), Release 1
HL7 ORU^R01	HL7 Version 2.5.1 Implementation Guide: Orders And Observations; Interoperable Laboratory Result Reporting To EHR (US Realm), Release 1	Defines necessary specifications for clinical laboratory results reporting to EHRs for use in the U.S. Realm

\*Health IT Standards adopted for the Commonwealth of Virginia have been denoted by (COV) in the standard's identification.

## References

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# Appendix D: Pharmacogenomic Test Result-EPIC EHR Integration Transaction Workflow Diagram



## Appendix E: Pharmacogenomic Test Result-EHR Integration Data Flow

