

An ancillary genomics system to support the return of pharmacogenomic results

<https://doi.org/10.1093/jamia/ocy187>

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Luke Rasmussen
Clinical Research Associate
Department of Preventive Medicine
Northwestern University Feinberg School of Medicine

Genetic Results in the EHR

- Historical results
 - Printed & scanned
 - PDF documents
 - Labeled as "Miscellaneous"
 - Unstructured lab result
- Electronic Medical Records and Genomics (eMERGE)
 - Structured representation from genotyping facility
 - Different levels of specificity: interpretation, variant, sequence
 - Accompanying PDF report or interpretation text

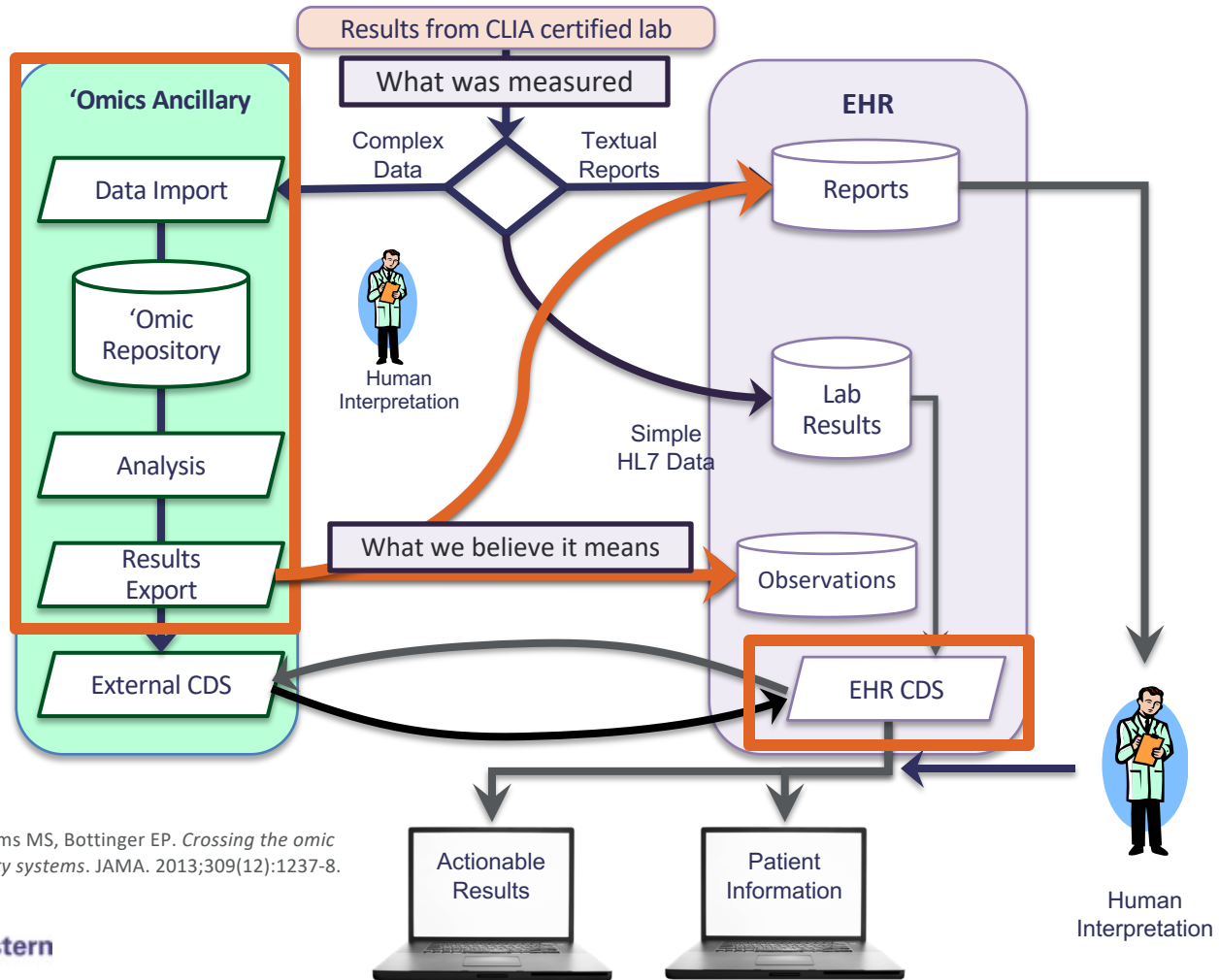
The image shows a screenshot of a genetic test result report. The report is titled "Result Information" and includes the following details:

- Exam Date and Time: 5/6/2015 8:00 AM
- Status: Final result
- Result Date and Time: 5/6/2015 11:17 AM

The report is organized into a table with the following columns:

Component Result	View	Flag	Low	High	Unit	Site
Component: Factor V Leiden						F
Value:						
Heterozygous positive for the Factor V Leiden Mutation. Heterozygous mutation for Factor V Leiden indicates increased genetic predisposition for hypercoagulability. It is recommended that all patients found to have specific genetic mutations consider genetic counseling.						
Comment:						
The LightCycler Factor V Leiden Assay allows for the detection of a single point mutation (G to A at position 169) in the human Factor V gene. The test utilizes LightCycler real time PCR to amplify a 227 bp fragment of the Factor V gene. The amplicon can be detected by fluorescence using a pair of hybridization probes that hybridize to an internal sequence within the Factor V gene. After real time detection of the Factor V gene, the internal hybridization probes will dissociate from the amplicon at different temperatures, which give us the ability to genotype. The differ-						

State-of-the-art in genomic result delivery to the EHR!

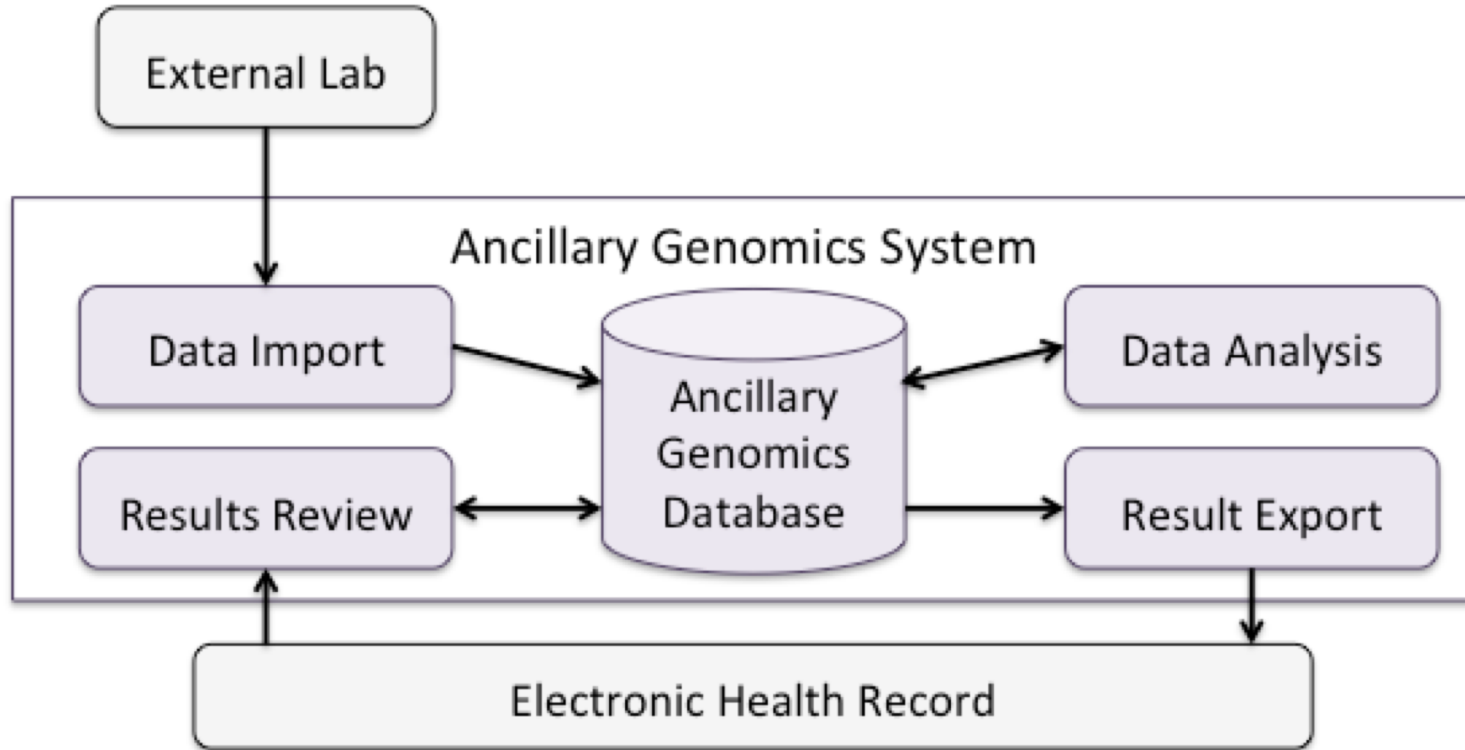


Derived from: Starren J, Williams MS, Bottinger EP. *Crossing the omic chasm: a time for omic ancillary systems*. JAMA. 2013;309(12):1237-8.

Methods

- eMERGE Pharmacogenomics Project (eMERGE PGx)
 - <https://emerge.mc.vanderbilt.edu/projects/emerge-pgx/>
- Drug-gene interactions (DGIs)
 - clopidogrel: CYP2C19
 - simvastatin: SLCO1B1
 - warfarin: CYP2C9 & VKORC1
- 750 consented subjects
- eMERGE III
 - CYP2C19, SLCO1B1, CYP2C9/VKORC1, DPYD, IFNL3, TPMT
 - ~3000 participants

Northwestern Medicine AGS Architecture



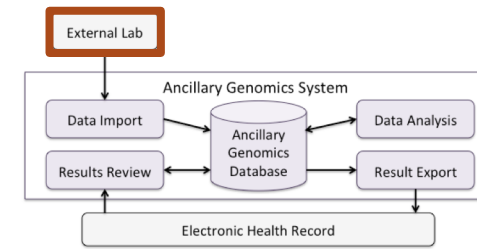
Heterogeneous Formats

Lab A

CYP2C19	CYP2C9	VKORC1	SLCO1B1
*1/*1	*1/*2	G/A	T/T
*17/*17	*1/*1	G/A	C/C

Lab B

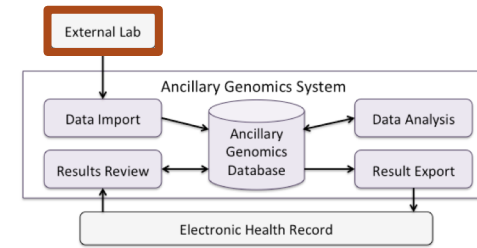
CYP2C19*17 rs12248560		CYP2C19*4 rs28399504		CYP2C19*8 rs41291556		CYP2C19*6 rs72552267	
T	Mass Array	A	Mass Array	T	Mass Array	G	Mass Array
TA	Mass Array	A	Mass Array	T	Mass Array	GA	Sequencing



Heterogeneous Formats

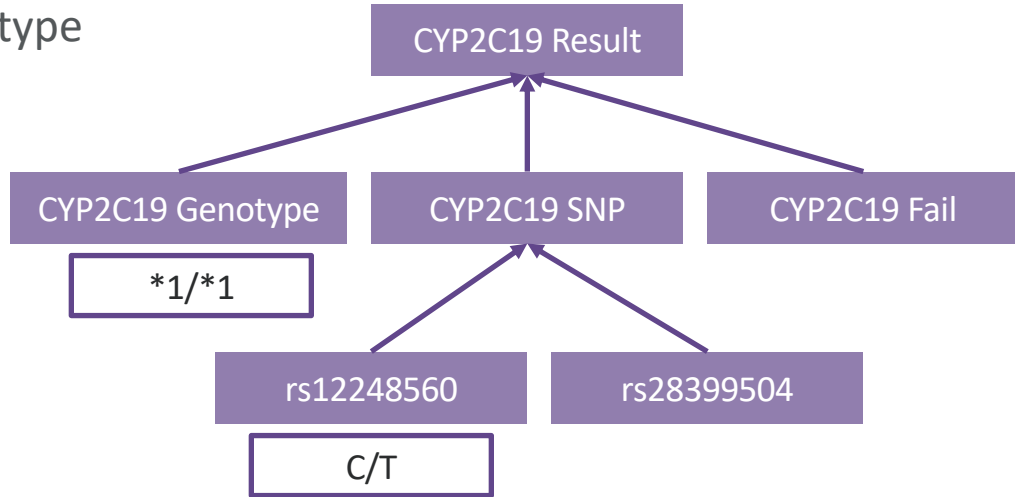
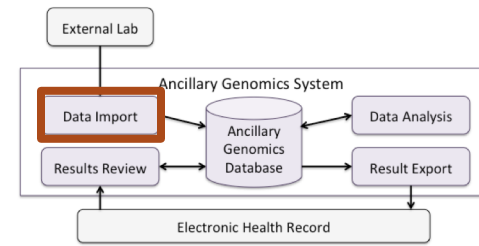
eMERGE III

```
<pgxData>
  <pgx>
    <geneSymbol>CYP2C9</geneSymbol>
    <drugs>
      <drug>warfarin</drug>
    </drugs>
    <recommendations>
      <recommendation>https://cpicpgx.org/guidelines/guideline-for-warfarin-and-cyp2c9-and-vkorc1/</recommendation>
    </recommendations>
    <interpretation>This individual is homozygous for the normal allele for the CYP2C9 gene. Based on the genotype result, this patient is predicted to have normal CYP2C9 function.</interpretation>
    <diplotype>*1/*1</diplotype>
    <phenotype>Extensive metabolizer</phenotype>
  </pgx>
  <pgx>
    <geneSymbol>IFNL3</geneSymbol>
    <drugs>
      <drug>peginterferon alfa-2a</drug>
      <drug>peginterferon alfa-2b</drug>
      <drug>ribavirin</drug>
    </drugs>
    <recommendations>
      <recommendation>https://cpicpgx.org/guidelines/guideline-for-peg-interferon-alpha-based-regimens-and-ifnl3/</recommendation>
    </recommendations>
    <interpretation>This individual is heterozygous for the rs12979860 C/T allele in the IFNL3 gene...
```



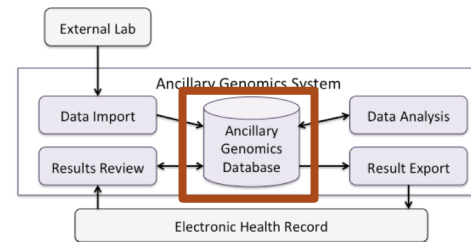
Data Import

- Custom parser for each CLIA Lab
- Mapped to result attributes
 - Manual process
 - Catch-all "Undefined" type



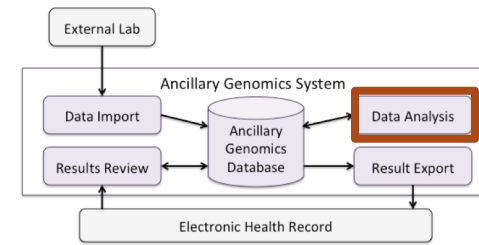
AGS Database

- Laboratory Results
 - Preserve original files
 - Result details as Entity-Attribute-Value
 - Attribute hierarchy
- Computed Observations
 - Simple relational model
 - Links to result attributes used

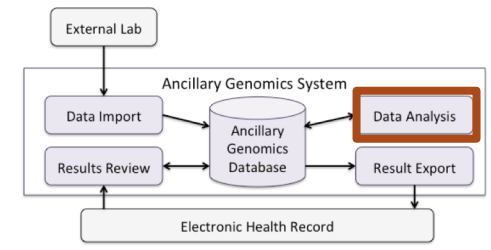
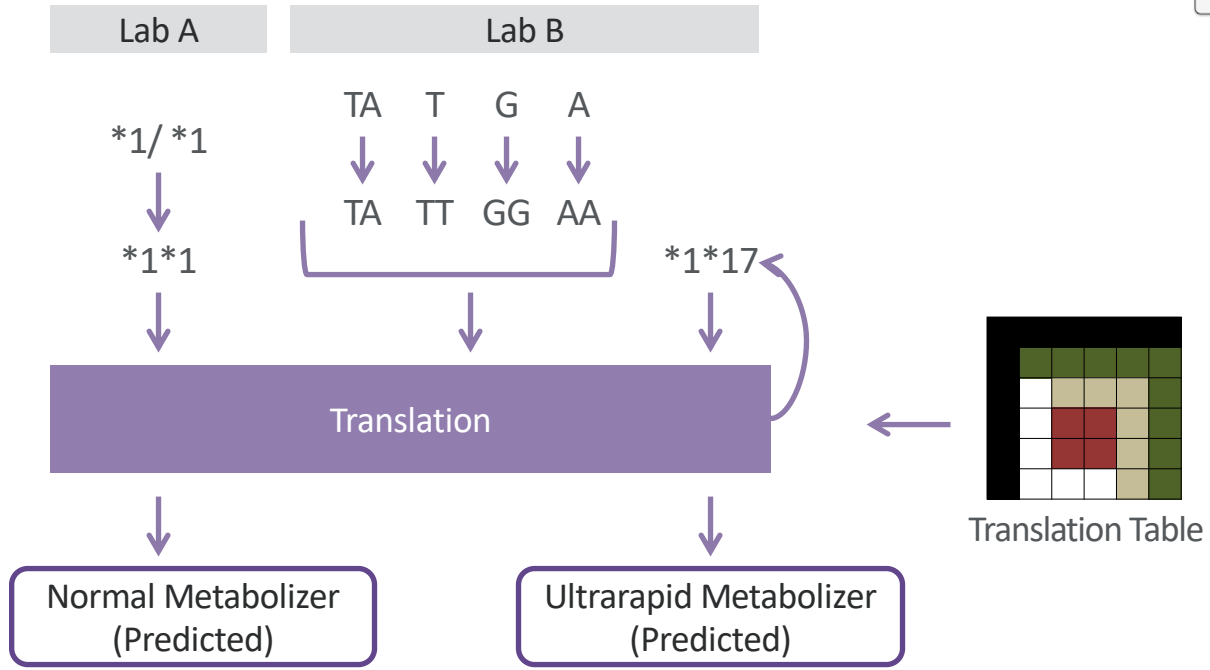


Data Analysis

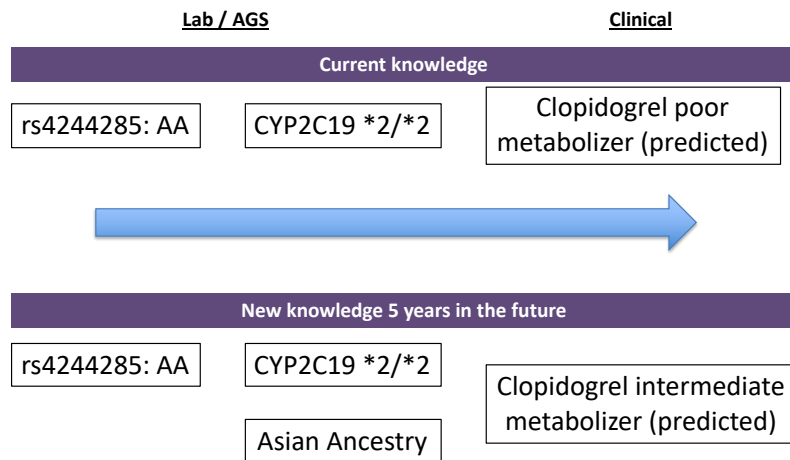
- Separate command-line EXEs
- Take result attributes and values
 - Results by category (e.g., CYP2C19 Results has star and SNP)
 - Look by date of result
 - Normalize string
 - Remove spaces
 - Split on separator character for haplotypes
 - Translation (consistent pipeline for data types)
 - SNP → Star variant → Interpretation



Example

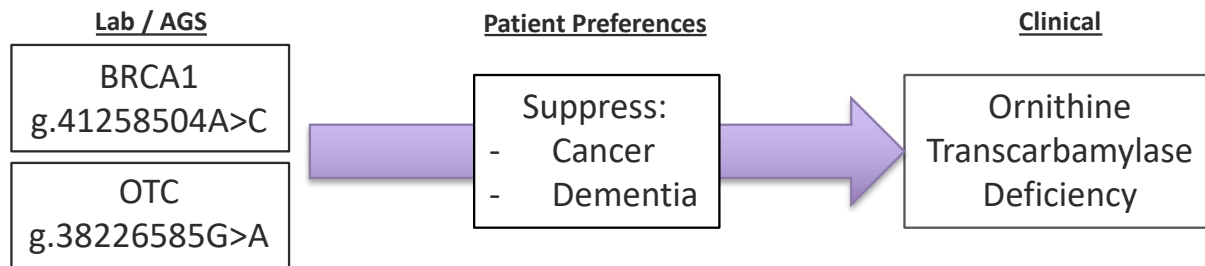


Data Analysis



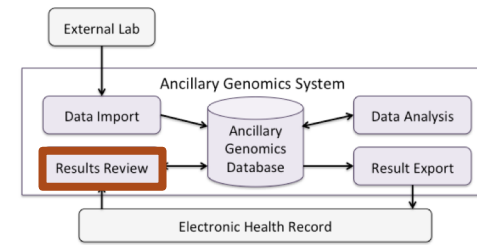
Generate “computed observations” to:

- Provide more actionable test results
- Simplify CDS rule implementation
- Generate interpretation text using template
- Links and tracing back to steps taken and data used
- *Filtering results based on preferences



Results Review (Manual)

- List of results by DGI & patient
- Worklist for release of results
 - Approval (is it accurate?)
 - Release to EHR (throttle results released per week)
- Review details
 - Confirm demographics
 - Modify report
 - Internal comments
 - View details and provenance of result



Ancillary Genomics System

DOB:

3 results displayed

Creation Date	Patient Name	DOB	MRN	Test Name	Results	
12/31/2013 10:44:20 AM	Zztest, Hamish	12/26/1961	10000084	Simvastatin Metabolism	Normal Activity (Predicted)	<input type="button" value="Details"/>
12/31/2013 10:44:21 AM	Zztest, Hamish	12/26/1961	10000084	Clopidogrel Metabolism	Ultrarapid Metabolizer (Predicted)	<input type="button" value="Details"/>
1/26/2014 10:01:56 PM	Zztest, Hamish	12/26/1961	10000084	Warfarin Dosing		<input type="button" value="Details"/>

AGS Interpretation - Report Preview

Warfarin Dosing

Value: Patient: Zztest, Hamish
Created: 01/26/2014 22:01:56 MRN: 10000084
Birth Date: 12/26/1961

Report:
RESULT
CYP2C9 *1/*2
VKORC1 (rs9923231) G/G

Use specific information below to determine the appropriate starting dose at <http://www.warfarindosing.org>.

VKORC1-1639/3673: GG (warfarin insensitive)
CYP2C9*2: CT (heterozygous)
CYP2C9*3: AA (wildtype)
CYP2C9*5: CC (wildtype)
CYP2C9*6: AA (wildtype)

INTERPRETATION
Patient carries one active and one reduced activity CYP2C9 allele and, therefore, is expected to be able to metabolize medications via CYP2C9 less effectively. Intermediate metabolizers may require non-conventional doses of medications whose major metabolic pathway is CYP2C9 or use of another drug that is not processed by CYP2C9.

Export to EHR

Drug-Gene Interaction Results Summary

Comments: These results were generated as part of a research study. Additionally, this report has been reformatted to make it easier to understand. If you would like a copy of the original report please call 312-503-6200.

If taking any of the following medications, please review summary table and detailed results below.

Medication	Drug-Gene Interaction
Warfarin	Use warfarin dosing calculator for initial dose: http://www.warfarindosing.org
Amitriptyline	Follow usual drug dosing instructions.
Azathioprine	Follow usual drug dosing instructions.
Capecitabine	Follow usual drug dosing instructions.
Citalopram	Follow usual drug dosing instructions.
Clopidogrel	Follow usual drug dosing instructions.
Escitalopram	Follow usual drug dosing instructions.
Fluorouracil	Follow usual drug dosing instructions.
Mercaptopurine	Follow usual drug dosing instructions.
Peginterferon alfa-2a	Follow usual drug dosing instructions.
Peginterferon alfa-2b	Follow usual drug dosing instructions.
Ribavirin	Follow usual drug dosing instructions.
Simvastatin	Follow usual drug dosing instructions.
Tegafur	Follow usual drug dosing instructions.
Thioguanine	Follow usual drug dosing instructions.
Voriconazole	Follow usual drug dosing instructions.

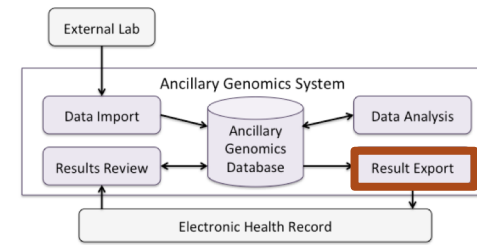
WARFARIN DOSING

VKORC1 (T/T)

DRUG RESPONSE: High sensitivity to Warfarin

THERAPEUTIC RECOMMENDATION: Consider using warfarin dosing calculator.
<http://warfarindosing.org/>

<https://cpicpgx.org/guidelines/guideline-for-warfarin-and-cyp2c9-and-vkorc1/>



- HL7 v2 result
- Includes
 - Interpretation (computed observation) as structured data value
 - Narrative report as comment

Display of Results – CDS

- Passive alerts in patient review
- Active alerts when prescribing
- Passive links (infobuttons) for additional information from alert
- Available on CDSKB.org

The screenshot shows the MyResults.org website. On the left is a purple sidebar with the following links: eMERGE PGx Pharmacogenomics, MDConsult Drug Information, MyResults.org, and Patient education. The main content area has a header with 'MyResults.org' and a navigation bar with 'Home', 'Results', 'Resources', and 'FAQs'. Below the navigation bar, there are tabs for 'Overview', 'The Test', 'Common Questions', and 'The Science'. The 'Overview' tab is selected, showing information about Clopidogrel (Plavix), including its generic name Simvastatin and other related drugs like Tegretol and Warfarin. A list of questions and answers is visible, starting with 'What is Clopidogrel?'.

Clinical Decision Support

Patient on clopidogrel, but genetic results indicate patient may be a [poor metabolizer](#). Medication may be ineffective – consider alternative.

Acknowledge Reason:



Discussed results with patient

Open SmartSet: Patient education (After Visit Summary)

[Click to review medications](#)

[View clinical references related to results](#)

[View patient materials related to results](#)

Refresh

Accept

Return of Results

- eMERGE PGx
 - Returned 2238 results for 746 patients
- eMERGE III
 - Processing results for ~2900 patients
 - Anticipate return of results starting January 2020

Discussion

- Reprocess results
 - Updated template (clarification in wording)
 - Initially unanticipated value
 - Future: changes in knowledge/interpretation
- Simplified CDS rule implementation
 - "If clopidogrel metabolism value == 'Poor Metabolizer'"
vs.
 - "If CYP2C19 == '*2/*2' or
CYP2C19 == '*2/*3' or
CYP2C19 == '*3/*3' or
rs12248560 == ..."

Discussion

- Native EHR capabilities
 - Not available at start of project
 - Evaluating as part of long-term strategy
- Computable information
 - Laboratory results
 - Underlying interpretation knowledge

Acknowledgements

NU eMERGE Team

- Dr. Rex Chisholm (co-PI)
- Maureen Smith* (co-PI)
- Dr. Justin Starren*
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- Dr. Firas Wehbe*
- Vivian Pan
- Sharon Aufox
- Cathy Wicklund
- Jennifer Pacheco*
- Tim Herr*

NM eMERGE Team

- Federico Almaraz*
- Camila Benaim
- Chris Bethman
- Johnny Bui
- Carl Christensen*
- Patrick Creamer
- Niki Drever
- Denise Hughes
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- Bob Milfajt
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- Andrew Powers
- Sameem Samad
- Michael Schachter

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luke.rasmussen@northwestern.edu
[@lrasmus](https://github.com/lrasmus)
<https://github.com/lrasmus>

<https://emerge.mc.vanderbilt.edu/>
<https://github.com/emerge-ehri>

Questions?