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An ancillary genomics system to support the return of pharmacogenomic results

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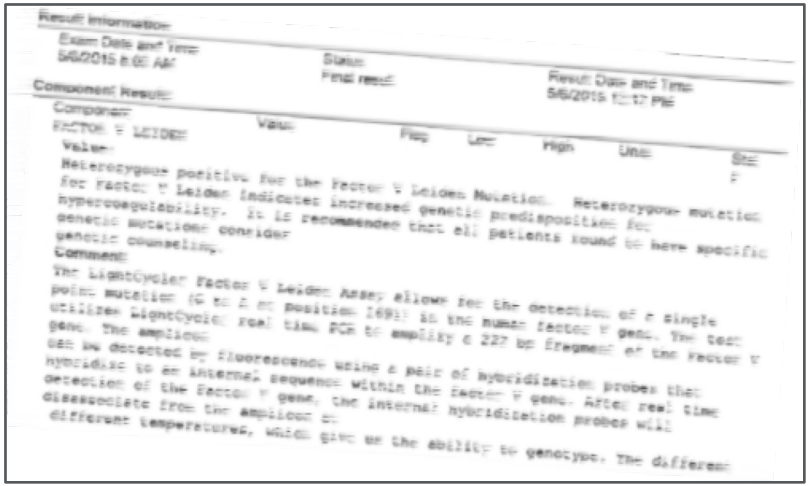
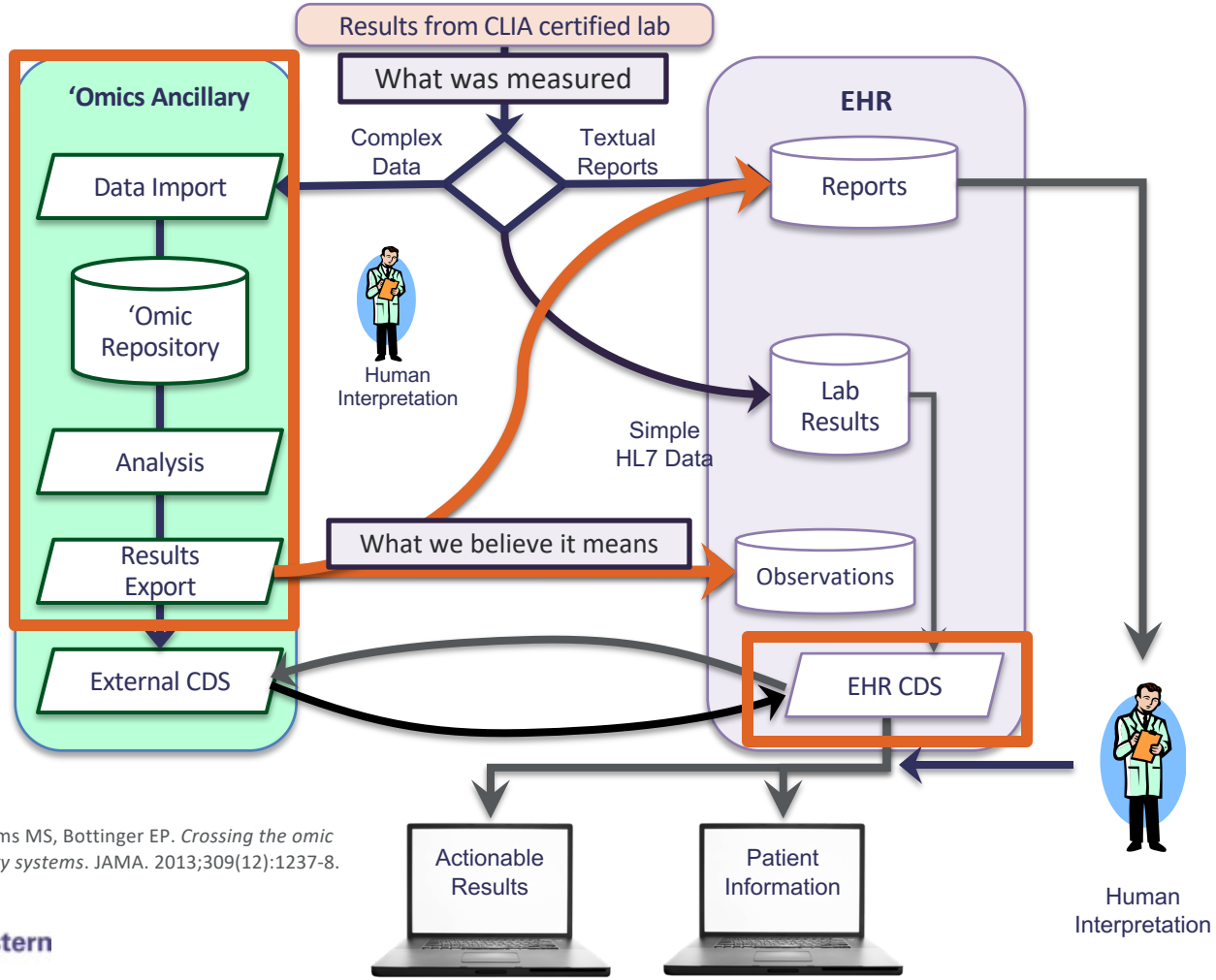
Genetic Results in the EHR

- Historical results
  - Printed & scanned
  - PDF documents
  - Labeled as "Miscellaneous"
  - Unstructured lab result



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

- Electronic Medical Records and Genomics (eMERGE)
  - Structured representation from genotyping facility
    - Different levels of specificity: interpretation, variant, sequence
  - Accompanying PDF report or interpretation text



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

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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

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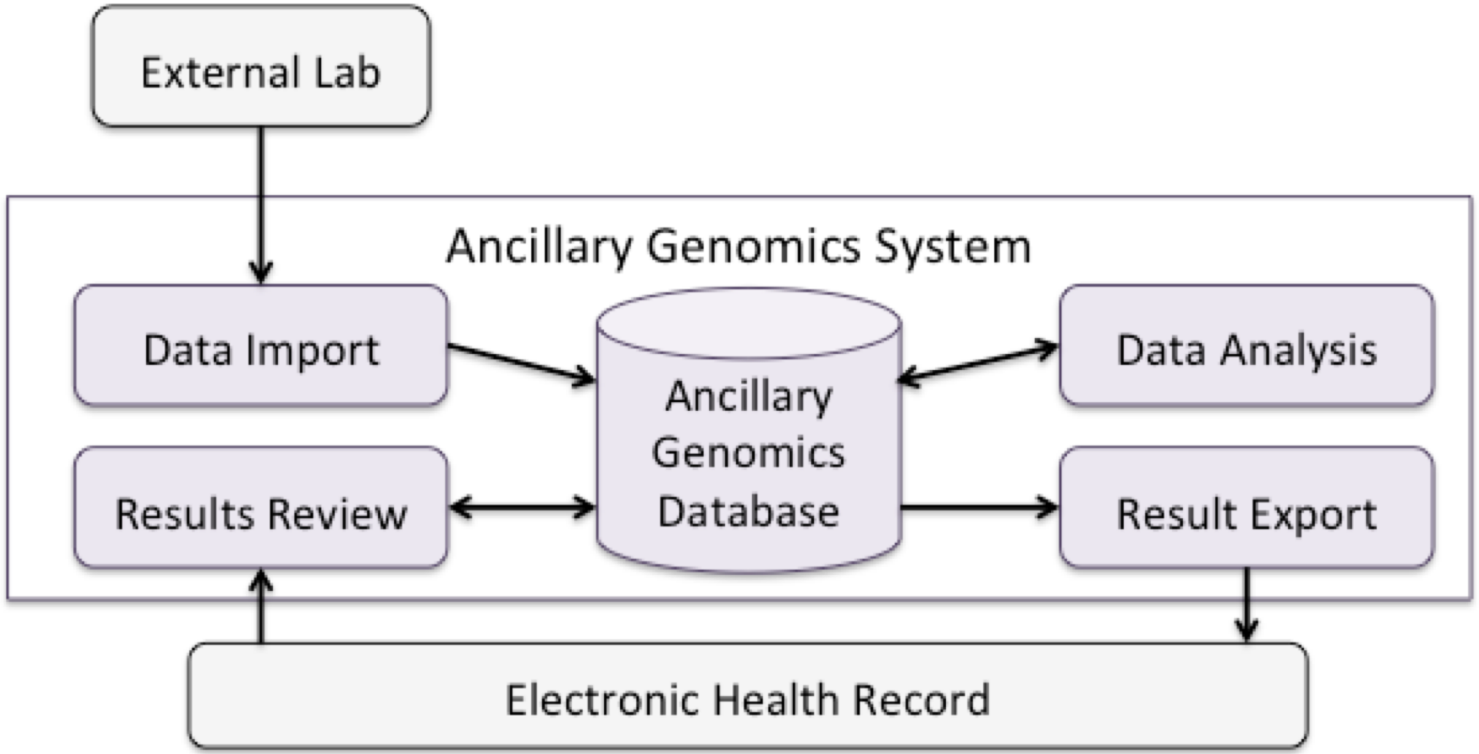
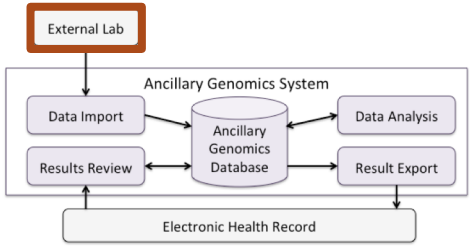


Heterogeneous Formats



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

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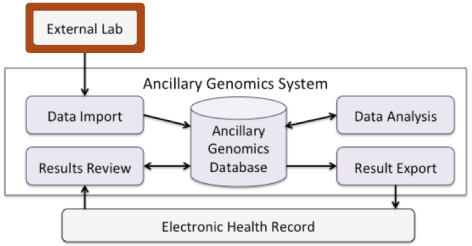
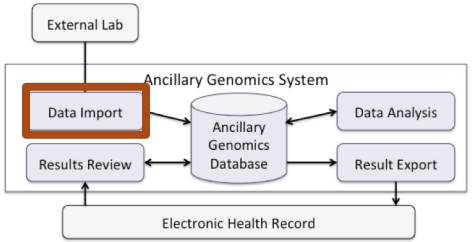
Heterogeneous Formats



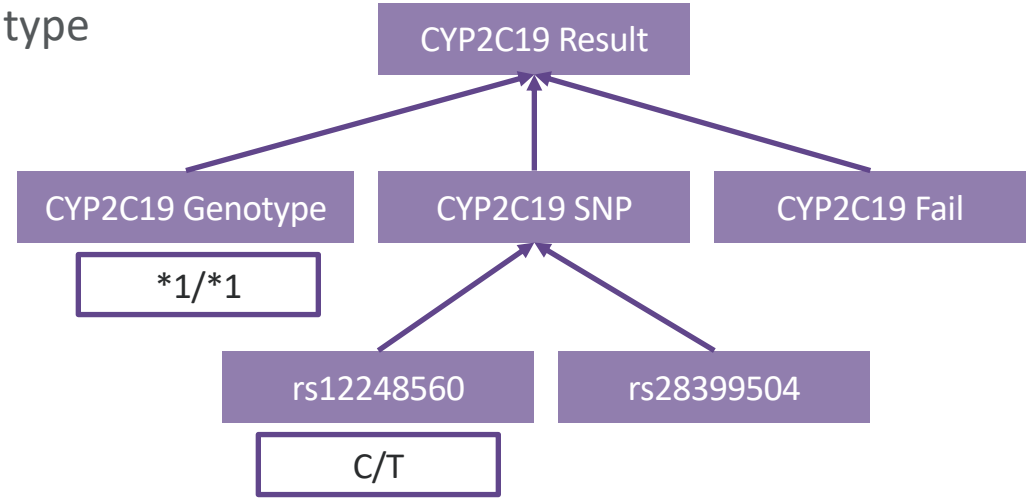
eMERGE III

```
<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



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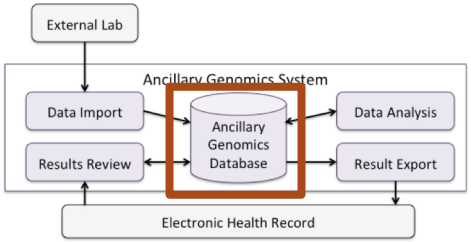
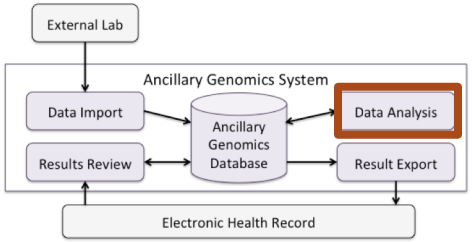
AGS Database



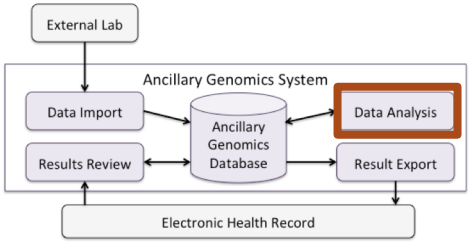
- Laboratory Results
  - Preserve original files
  - Result details as Entity-Attribute-Value
  - Attribute hierarchy
- Computed Observations
  - Simple relational model
  - Links to result attributes used

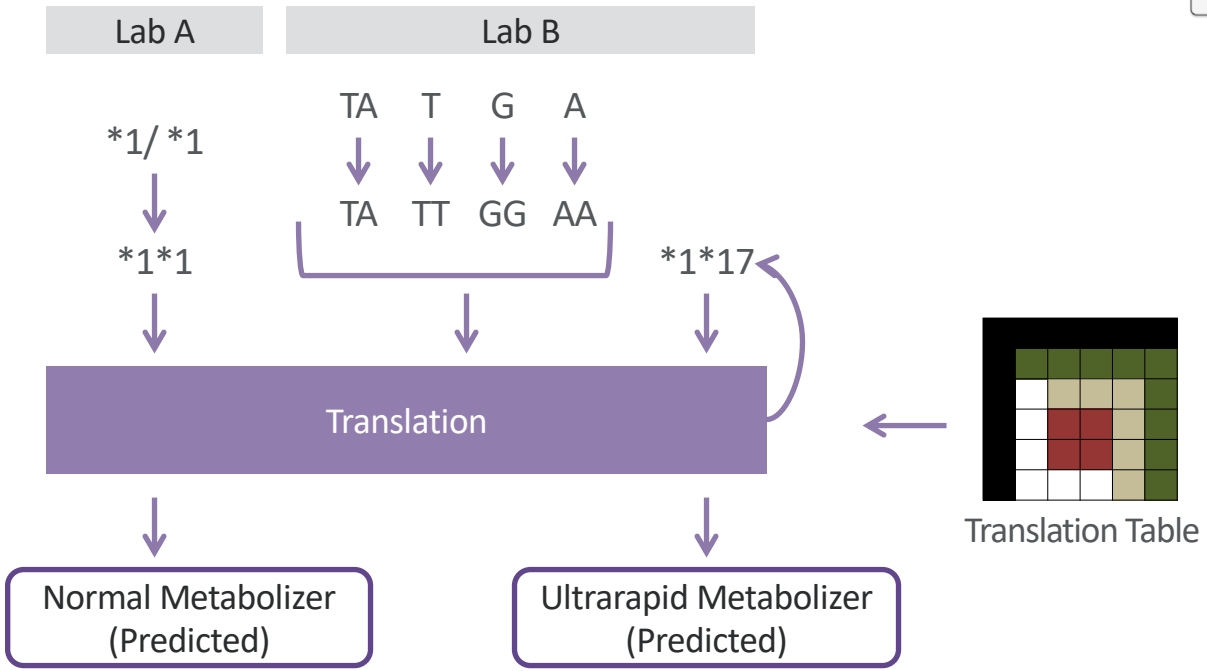
Data Analysis



- 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





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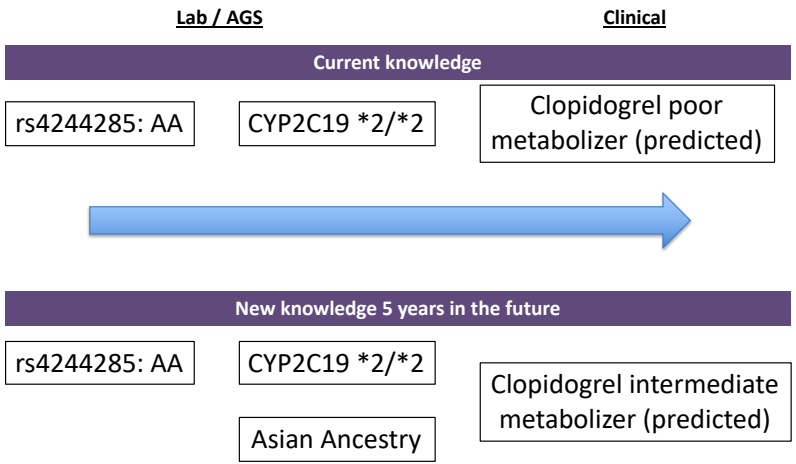
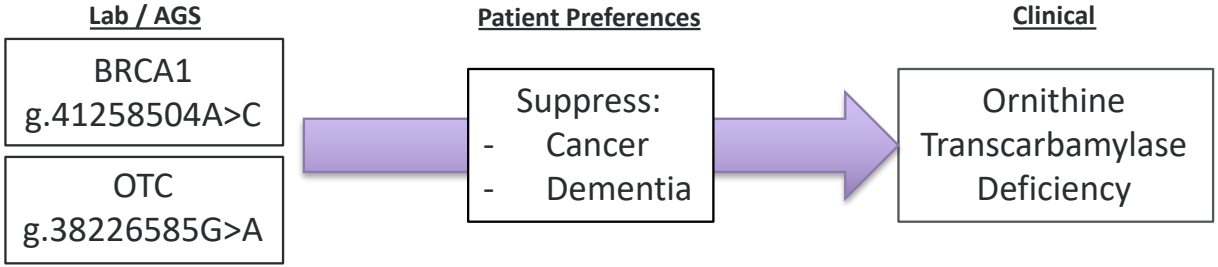
Data Analysis



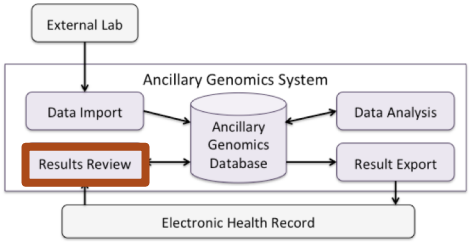
Generate "computed observations" to:

- 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



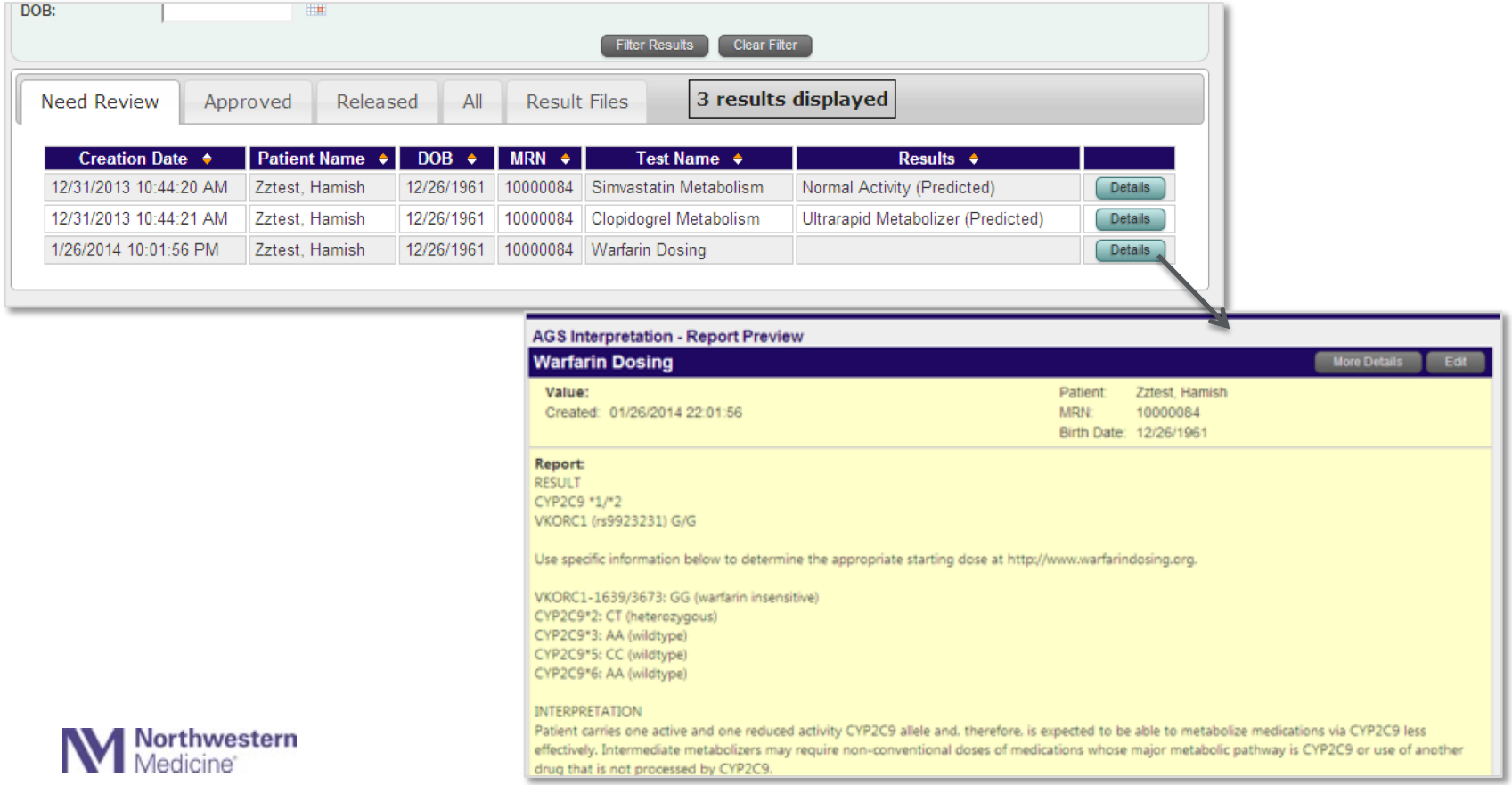
* Work done as part of eMERGE III

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



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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.

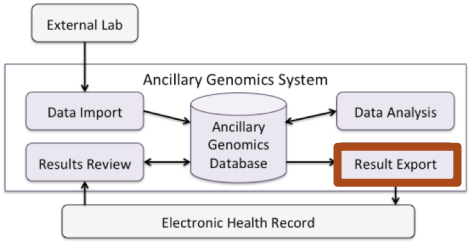
Medication	Drug-Gene Interaction
Warfarin	Use warfarin dosing calculator for initial dose: http://www.warfarindosing.org
Amitriptyline	Follow usual drug dosing instructions.
Azathioprine	Follow usual drug dosing instructions.
Capecitabine	Follow usual drug dosing instructions.
Citalopram	Follow usual 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/

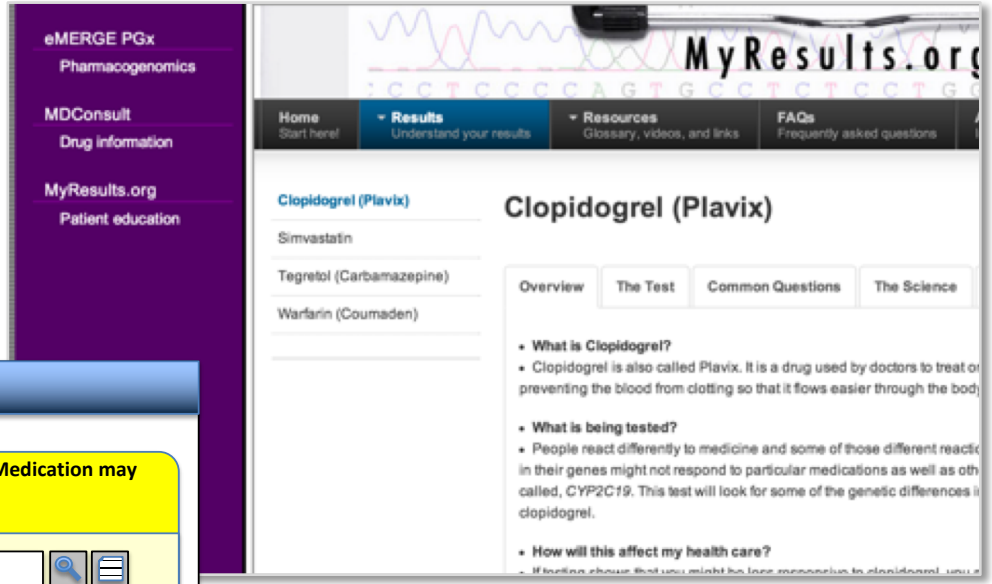
https://cpicpgx.org/guidelines/guideline-for-warfarin-and-cyp2c9-and-vkorc1/

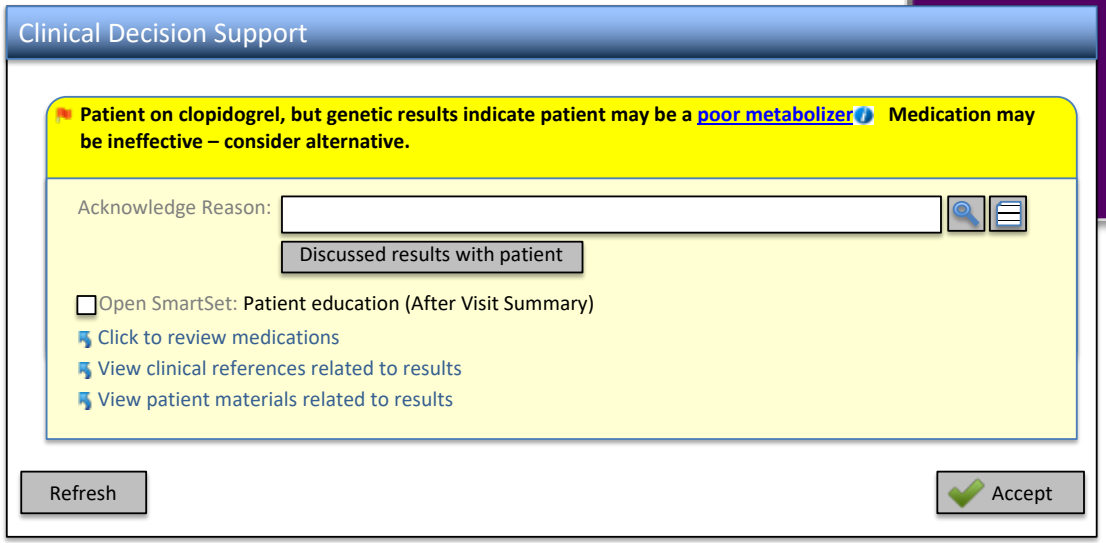


- HL7 v2 result
- Includes
  - Interpretation (computed observation) as structured data value
  - Narrative report as comment

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





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*
- Dr. Stephen Persell*
- Dr. Laura Rasmussen-Torvik*
- Dr. Firas Wehbe*
- Vivian Pan
- Sharon Aufox
- Cathy Wicklund
- Jennifer Pacheco*
- Tim Herr*

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- Niki Drever
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- Sameem Samad
- Michael Schachter

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Questions?