



# Pharmacogenetics Implementation: Focus on informatics

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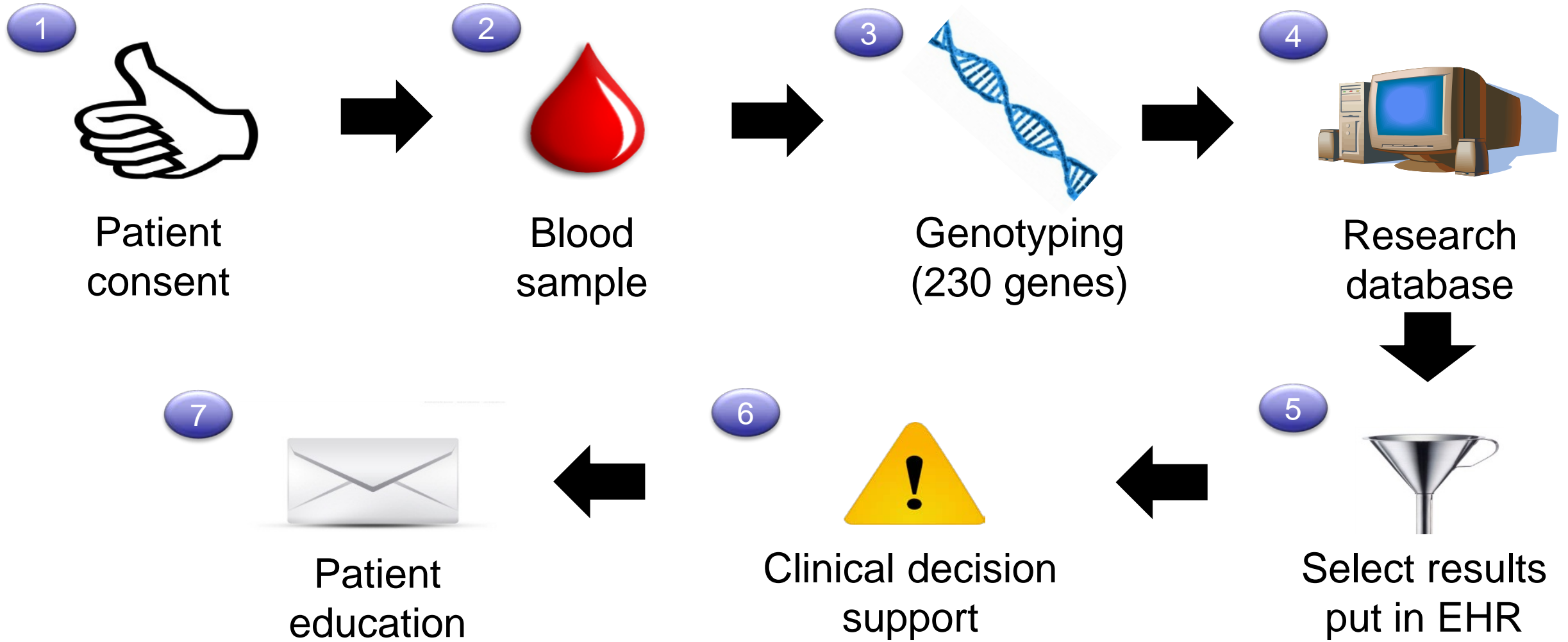


# PG4KDS: Protocol

- Goal:
  - Migrate pharmacogenetic tests from the laboratory (array-based) into routine patient care, to be available **preemptively**
    - Implement all CPIC™ level A/B gene/drug pairs
- Exclusion criteria:
  - Patients who have received a prior allogeneic stem cell transplant
  - Patient who have received a prior liver transplant



# PG4KDS: The Process



# The **PG4KDS** Process to Share and Withhold Results

Reference Laboratory



Pharmaceutical Sciences Research database (230 genes)

<i>TPMT</i>	<i>DPYD</i>	<i>CYP3A4</i>	<i>GSTT1</i>	<i>CYP4B1</i>
<i>CYP2C19</i>	<i>VKORC1</i>	<i>CYP2F1</i>	<i>NAT1</i>	<i>CYP1A1</i>
<i>ABCB1</i>	<i>SLCO1B1</i>	<i>CYP2J2</i>	<i>FMO3</i>	<i>CYP2C18</i>
<i>CYP2C9</i>	<i>G6PD</i>	<i>UGT1A1</i>	<i>CYP4F2</i>	<i>ABCC1</i>

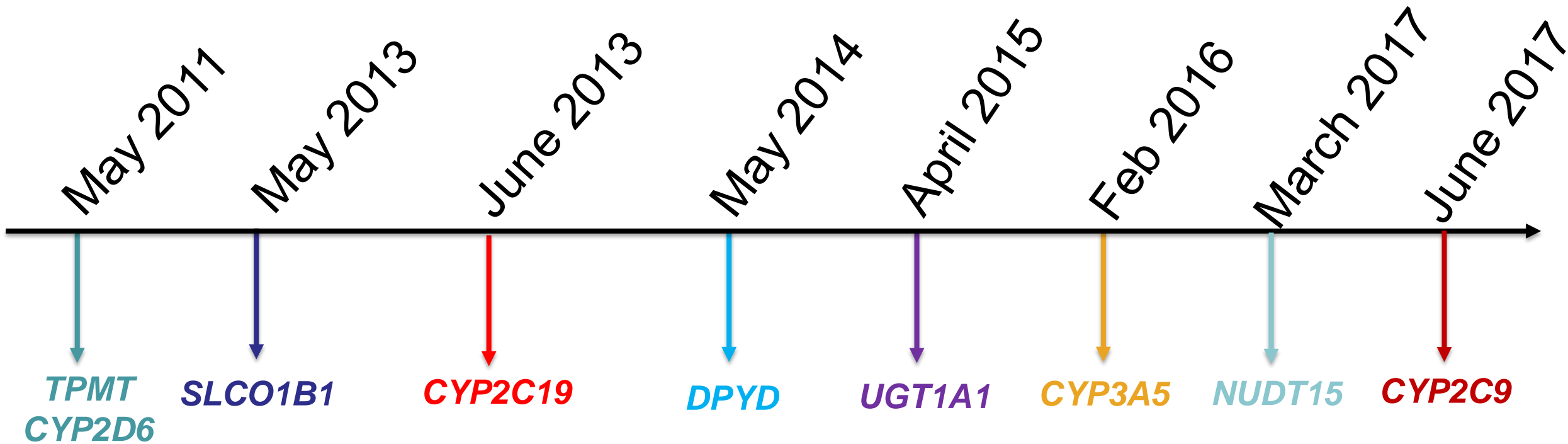
Clinical evidence



Clinical data repository into EHR (8 genes)



## Implementation Timeline





# PG4KDS: 8 Genes and 22 Drugs Implemented

- **CYP2D6 (17%)**
  - Codeine
  - Oxycodone
  - Tramadol
  - Amitriptyline, Clomipramine, Imipramine, Trimipramine
  - Doxepin
  - Fluoxetine
  - Paroxetine
  - Ondansetron
- **CYP2C19 (62%)**
  - Clopidogrel
  - Amitriptyline, Clomipramine, Imipramine, Trimipramine
  - Doxepin
  - Voriconazole
- **CYP3A5 (41%)**
  - Tacrolimus
- **SLCO1B1 (13%)**
  - Simvastatin
- **TPMT (11%)**
  - Mercaptopurine
  - Thioguanine
  - Azathioprine
- **DPYD (0.4%)**
  - Fluorouracil
  - Capecitabine
- **UGT1A1 (28%)**
  - Atazanavir
- **CYP2C9 (32%)**
  - Celecoxib

*Percentage in parenthesis denotes the % of patients enrolled on the PG4KDS protocol who have a high-risk phenotype for that gene*



Drug	Thiopurines	Codeine	Tramadol	Amirtryptiline	Fluoxetine Paroxetine	Oxycodone	Simvastatin	Ondansetron	Clopidogrel	Fluorouracil Capecitabine
Gene	TPMT	CYP2D6	CYP2D6	CYP2D6	CYP2D6	CYP2D6	SLCO1B1	CYP2D6	CYP2C19	DPYD
Adverse Outcomes	Myelo-suppression	Increased toxicity or therapy failure	Increased toxicity or therapy failure	Increased toxicity or therapy failure	Increased toxicity or therapy failure	Increased toxicity or therapy failure	Myopathy	Poor N/V control	Increased or reduced platelet inhibition	Increase d toxicity
Implementation Status	<b>Live</b>	<b>Live</b>	<b>Live</b>	<b>Live</b>	<b>Live</b>	<b>Live</b>	<b>Live</b>	<b>Live</b>	<b>Live</b>	<b>Live</b>
Clinical impact of negative outcomes significant	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Scientific evidence for drug gene effect	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient target identifiable before they receive drug	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Alternative therapy available		✓	✓	✓	✓	✓	✓	✓	✓	✓
Gene added to DMET tracker	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Gene specific look up tables created	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Consult template written	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Consult database updated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CDS language developed	✓	✓	✓	✓	✓	✓	✓		✓	✓
Patient letters	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Gene specific "Do You Know..." sheet	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient medication card	✓	✓	✓	✓	✓	✓	N/A	✓	N/A	✓
PGEN formulary table updated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Drug monograph updated in formulary	✓	✓	✓	✓	✓	✓	N/A	✓	N/A	✓
St. Jude PG4KDS webpage updated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Staff education	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Competencies	✓	✓	✓	✓	✓	✓	✓	✓		✓
POC Approval	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
P&T Communication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Go-Live Date	5/2011	5/2011	2/2012	5/2012	5/2012	5/2013	5/2013	2/2013	6/2013	5/2014



# A FOCUS ON INFORMATICS

*Finding cures. Saving children.*



# Dedicated Pharmacogenetics Section

Flowsheet

Labs/DI Quick View Vitals/Measures All Results Daily Clinical/Scanned Doc Mole Micro/Sero D

Nursing/Respiratory **Pharmacogenetics** Protocol/NPTP Documents \_Consents Consents

Flowsheet: Pharmacogenetics Level: Pharmacogenetics

Last 100 Results in the Past 99 Ye

Pharmacogenetics	10/20/2013 20:22	9/10/2013 11:01	8/29/2013 04:00	8/27/2013 00:19
<b>Pharmacogenetics</b>				
CYP2C19 PG4KDS Genotype	F *1/*1			
CYP2C19 PG4KDS Consult	F Routine			
CYP2C19 PG4KDS Letter	CYP2C19 PG4KDS			
CYP2D6 Allele 1		Negative		
CYP2D6 Allele 2		*2A		
CYP2D6 Genotype Consult		f corr Normal		
CYP2D6 PG4KDS Consult	F Routine			
CYP2D6 PG4KDS Genotype	F (*1/*2)2N			
CYP2D6 PG4KDS Letter	CYP2D6 PG4KDS			
<input type="checkbox"/> Glucose-6-Phosphate Dehydrogenase				9.2
SLCO1B1 PG4KDS Genotype	F *1a/*1b			
SLCO1B1 PG4KDS Consult	F Routine			
SLCO1B1 PG4KDS Letter	SLCO1B1 PG4KDS			
TPMT Genotype			*1/*1	
TPMT Genotype Consult			f Normal	
TPMT PG4KDS Genotype	F *1/*1			
TPMT PG4KDS Consult	F Routine			
TPMT PG4KDS Letter	TPMT PG4KDS L			
Scanned Pharmacogenetics Documents		Scanned Pharm	Scanned Pharm	



# Dedicated Pharmacogenetics Section

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CYP2D6 Allele 1		Negative		
CYP2D6 Allele 2		*2A		
CYP2D6 Genotype Consult		f corr Normal		
CYP2D6 PG4KDS Consult	F Routine			
CYP2D6 PG4KDS Genotype	F (*1/*2)2N			
CYP2D6 PG4KDS Letter	CYP2D6 PG4KDS			
<input type="checkbox"/> Glucose-6-Phosphate Dehydrogenase				9.2
SLCO1B1 PG4KDS Genotype	F *1a/*1b			
SLCO1B1 PG4KDS Consult	F Routine			
SLCO1B1 PG4KDS Letter	SLCO1B1 PG4KDS			
TPMT Genotype			*1/*1	
TPMT Genotype Consult			f Normal	
TPMT PG4KDS Genotype	F *1/*1			
TPMT PG4KDS Consult	F Routine			
TPMT PG4KDS Letter	TPMT PG4KDS L			
Scanned Pharmacogenetics Documents		Scanned Pharma	Scanned Pharma	

Each gene test result is coupled with a "consult" entry



## Interpretive Consult: Passive Alerts

Sample for CYP2D6 Genotype Obtained: 01/01/2016 08:22:00

CYP2D6 Genotype Result: (\*4/\*4)2N

CYP2D6 Phenotype: CYP2D6 Poor Metabolizer

Based on the genotype result this patient is predicted to be a poor metabolizer of CYP2D6 substrates. This patient may require either a dose adjustment of any drug metabolized by CYP2D6 or a therapeutic alternative.

This result signifies that the patient has two copies of a no function allele. This patient may be at a high risk for an adverse or poor response to medications that are metabolized by CYP2D6. To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications metabolized by the CYP2D6 enzyme pathway. If codeine is prescribed to a poor metabolizer, suboptimal analgesia is very likely; therefore a therapeutic alternative is recommended.



# High-risk pharmacogenetic phenotypes are added to the problem list

Problem List

Classification View Active Problems Change View

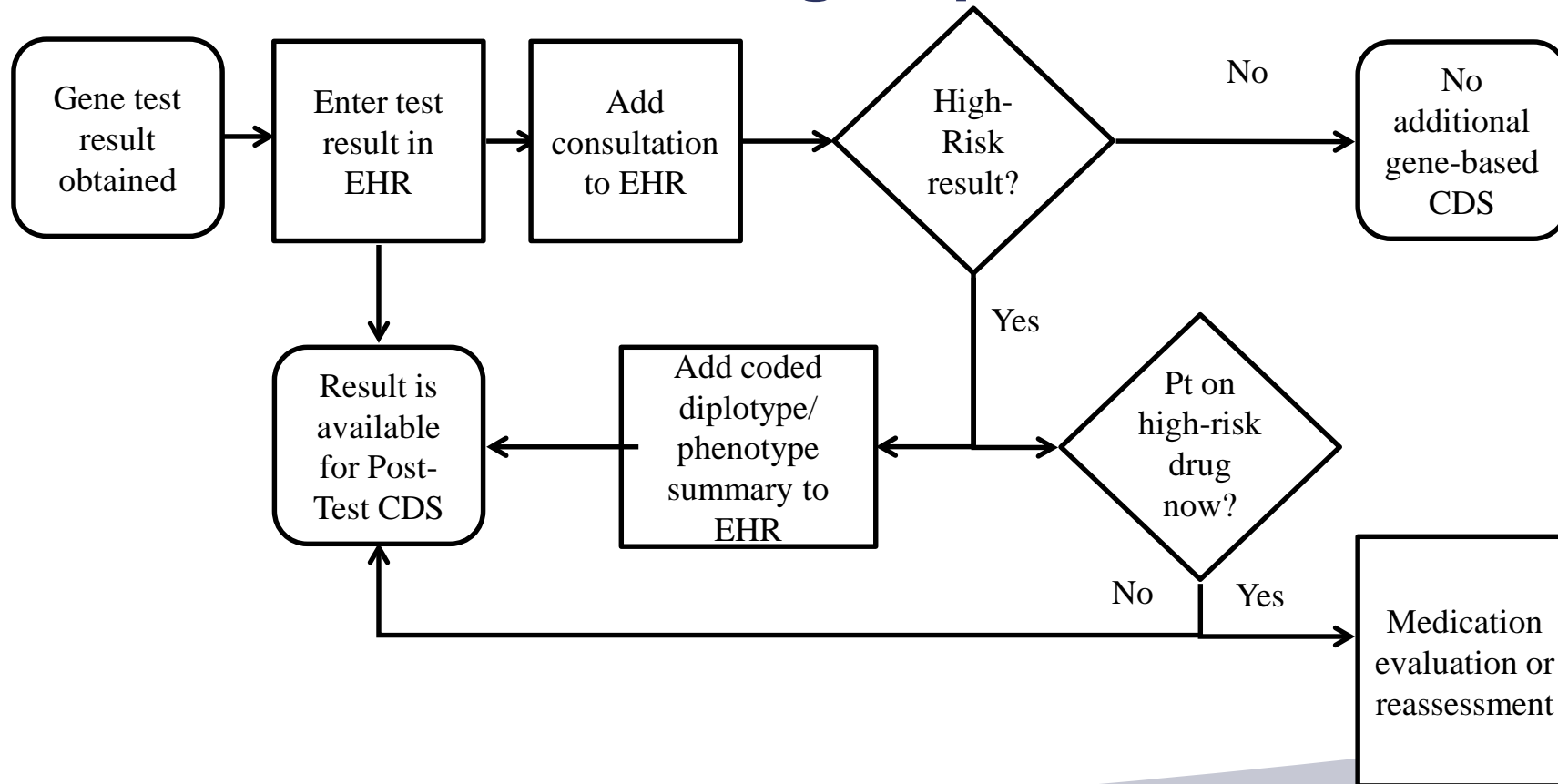
Qualifier	Name of Problem	Onset Date	Classification
<input type="checkbox"/>	<b>All Problems</b>		
	CYP2C19 ULTRA-RAPID METABOLIZER	08/20/2013	Clinical
	Hepatocarcinoma.	09/21/2012	HIMS Sum...
	HEPATOCELLULAR CARCINOMA	09/21/2012	HIMS Sum...
	HEPATOCELLULAR CARCINOMA, INV. LIVER	08/22/2013	HIMS Sum...
	HEPATOCELLULAR CARCINOMA, INV. PELVIS	12/26/2012	HIMS Sum...
	HEPATOCELLULAR CARCINOMA, INV. PERITONEUM	11/08/2012	HIMS Sum...
	HEPATOCELLULAR CARCINOMA, INVOLVEMENT LUNG	09/21/2012	HIMS Sum...
	PT. HAS SUBQPORT SINGLE	09/21/2012	Medical
	SLCO1B1 - INTERMEDIATE FUNCTION	05/16/2013	Clinical

**Problem list entries serve as the discrete data element for interruptive point of care CDS**



# Workflow for entering pharmacogenetic results in the EHR is similar to the one created by the CPIC informatics


group





# Pre-test (No-Genotype) CDS Alerts

Discern: (1 of 1)

 **WARNING**

A CYP2D6 genotype is recommended before prescribing codeine. A CYP2D6 genotype test does not appear to have been ordered for this patient. Use an alternative agent such as a non-opioid, or morphine, or HYDROmorphine (e.g.: Dilaudid®), or acetaminophen/hydroCODONE (e.g.: Lortab®, Vicodin®). Please consult a clinical pharmacist or go to [www.stjude.org/pg4KDS](http://www.stjude.org/pg4KDS) for more information.

Alert Action

Cancel  
 Continue

**Clinician has the option of ordering the genotype from the alert box**


Add Order for:

CYP2D6 Genotype -> T;N, Collect Now, Blood, Fasting Required: No, ONCE



# Post-test (High-Risk Genotype) Alerts

Discern: (2 of 2)

 **\*WARNING\***

Based on the genotype result, this patient is predicted to be a CYP2D6 ultra-rapid metabolizer. If codeine is prescribed to a CYP2D6 ultra-rapid metabolizer, adverse events are likely. Other pain medications such as morphine, HYDROMORPHONE (e.g.: Dilaudid®) or acetaminophen/hydroCODONE (e.g.: Lortab®, Vicodin®) are recommended. Please consult a clinical pharmacist, review the pharmacogenetics tab or click on the link below for more information.

**Alert Action**

Cancel entry

Continue w/order

History Add'l info OK

Phenotype

Outcome

Other recommendations

**Clinician can continue with ordering the medication or cancel order to prescribe alternative**



**As we have implemented new gene/drug pairs,  
the CDS alert rules and logic have become  
more detailed**


## CYP2C19/voriconazole

Alert take into account:

- CYP2C19 phenotype
- Route of administration
- Age of patient

Recommended dose directly ordered from alert screen

Discern: (2 of 2)



# POOR METABOLIZER

Based on the genotype result, this patient is predicted to be a **CYP2C19 POOR METABOLIZER**. If voriconazole is prescribed to a CYP2C19 poor metabolizer adverse events are likely. **For a patient 12 years of age or older and a CYP2C19 PM phenotype**, initiate voriconazole at a reduced dose of **200 mg PO Q12H** and follow up with therapeutic drug monitoring. Please consult a clinical pharmacist, review the pharmacogenetics tab or click on the link below for more information.

Alert Action

Check BELOW for age and phenotype adjusted dose


Continue with different dose

Add Order for:

Voriconazole oral -> 200 mg = PO Q12H, Routine, CYP2C19 POOR METABOLIZER. Age 12 years or above

# CYP2C19/voriconazole (CYP2C19 PM, PO formulation in patient younger than 12 yo)

Discern: (2 of 2)



## POOR METABOLIZER

Based on the genotype result, this patient is predicted to be a **CYP2C19 POOR METABOLIZER**. If voriconazole is prescribed to a CYP2C19 poor metabolizer adverse events are likely. **For a patient younger than 12 years of age and a CYP2C19 PM phenotype**, initiate voriconazole at a reduced dose of **7mg/kg PO Q12hrs** and follow up with therapeutic drug monitoring. Please consult a clinical pharmacist, review the pharmacogenetics tab or click on the link below for more information.

Alert only fires for new voriconazole prescriptions  
No voriconazole TDM

**Alert Action**

- Check BELOW for age and phenotype adjusted dose
- Continue with different dose

**Add Order for:**

- Voriconazole oral -> 7 mg/kg = PO Q12H, Routine, CYP2C19 POOR METABOLIZER. Age less than 12 years



## **CYP3A5 and tacrolimus:**

- **Route of administration**
  - **Tacrolimus TDM**
  - **Tacrolimus order**

Discern: (1 of 2)



## **DOSE ALERT**

This patient has a high-risk CYP3A5 phenotype which means the patient is at risk for lower tacrolimus whole blood concentrations at normal oral tacrolimus starting doses. Consider increasing the starting dose of ORAL tacrolimus by 1.5- 2 times the recommended dose (total dose not to exceed 0.3 mg/kg/day) and following with standard therapeutic drug monitoring. If this patient is currently receiving an azole antifungal agent, please consult a clinical pharmacist for help with determining an appropriate starting dose of oral tacrolimus. Please review the pharmacogenetics tab, or click on the link below for more information.

### Alert Action

- Cancel tacrolimus order
- Continue with current tacrolimus dose
- Modify tacrolimus dose

Add'l info

OK



**CDS alert take into  
account 2 genes  
*TPMT* and *NUDT15* for  
mercaptopurine  
dosing**

Discern: (2 of 2)



## ADJUST STARTING DOSE

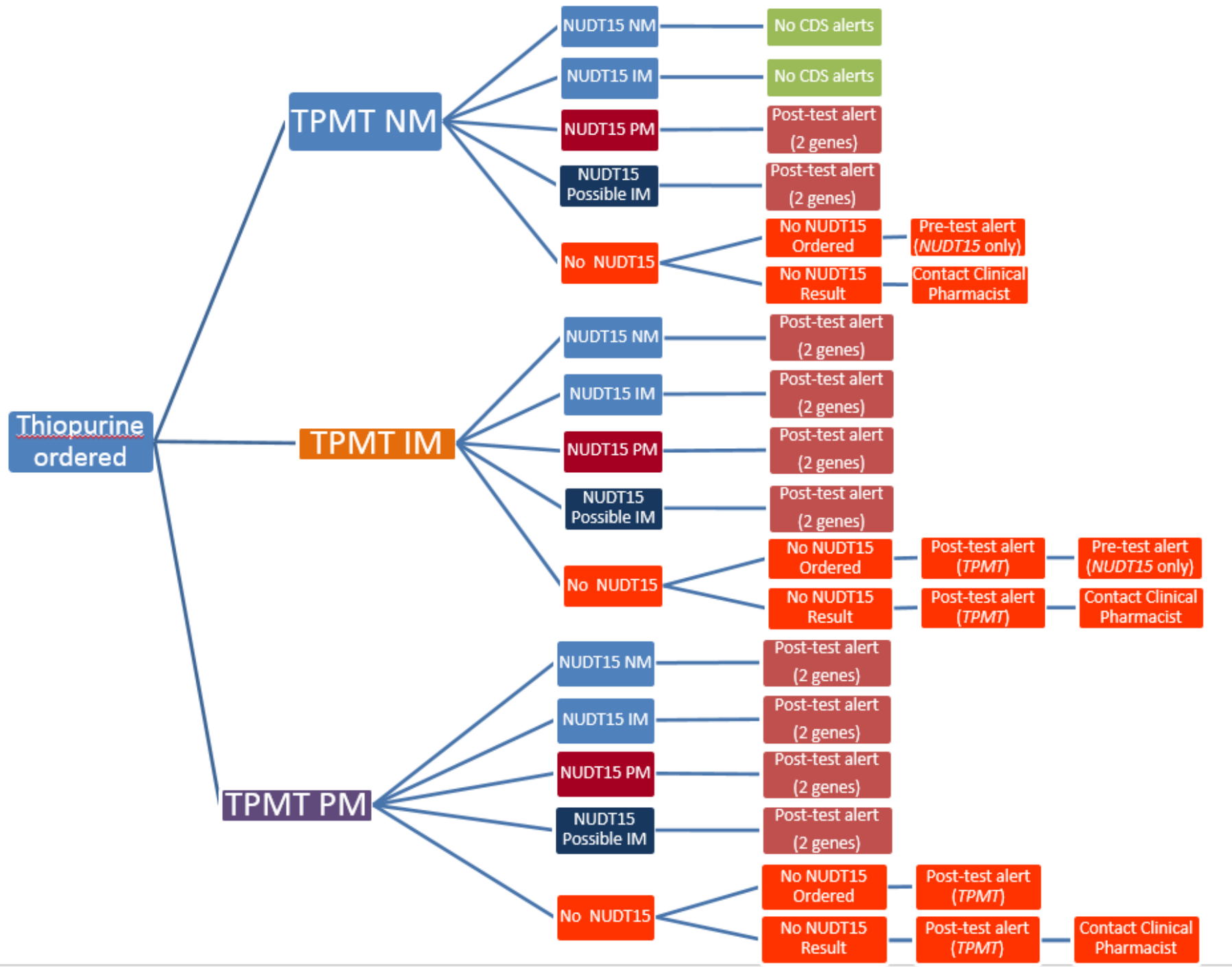
Mercaptopurine can be affected by a patient's TPMT and NUDT15 phenotype. This patient is predicted to be a TPMT NORMAL METABOLIZER and a NUDT15 POOR METABOLIZER. The patient is at risk for myelosuppression with normal doses of Mercaptopurine. Consider starting Mercaptopurine doses at 20 mg/m<sup>2</sup>/day. Please consult a clinical pharmacist, review the pharmacogenetics tab or click on the link below for more information.

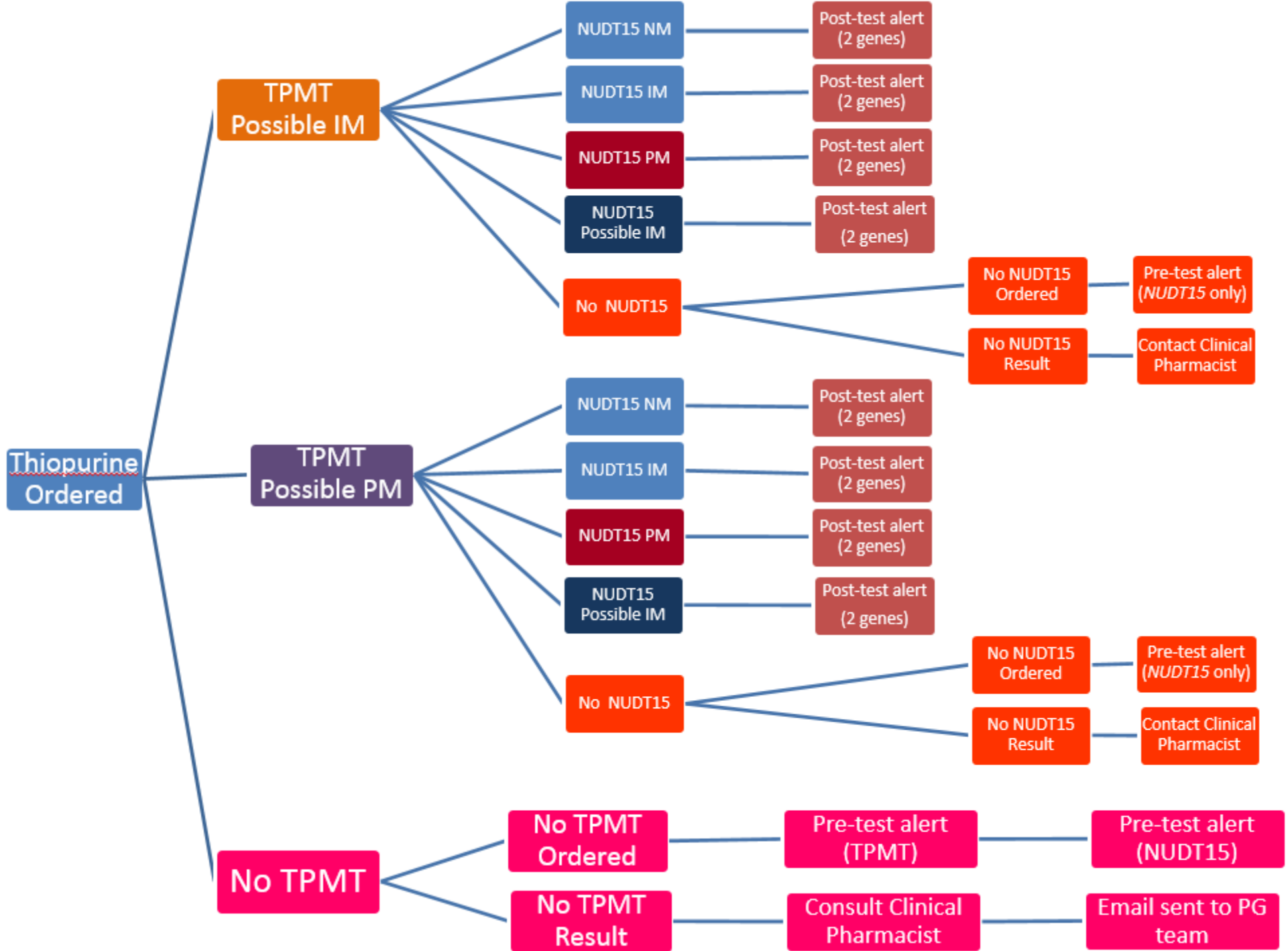
### Alert Action

- Cancel Mercaptopurine
- Mercaptopurine dose altered accordingly
- Modify Mercaptopurine order

LINK

OK







CDS alert officer created all CDS alerts: Don Baker



**Thank you!**

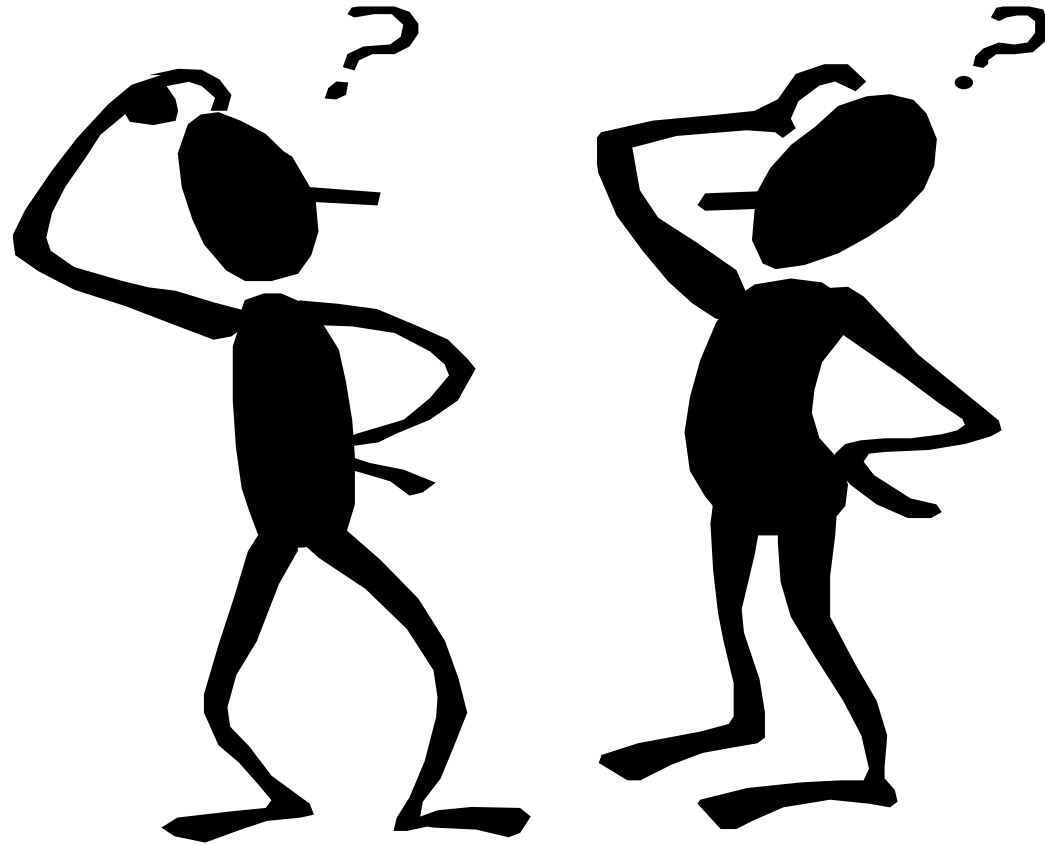


## What's next?

- Problem list entries: SNOMED codes
  - Alert logic can be shared with other users



Questions?



*Finding cures. Saving children.*