Pharmacogenetics Implementation: Focus on informatics

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February 8, 2018

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

http://www.stjude.org/pg4kds

PG4KDS: The Process

1. Patient consent
2. Blood sample
3. Genotyping (230 genes)
4. Research database
5. Select results put in EHR
6. Clinical decision support
7. Patient education

Hoffman JM, *et al*. Am J Med Genet C Semin Med Genet. 2014;166C:45-55.

The PG4KDS Process to Share and Withhold Results

Reference Laboratory

Pharmaceutical Sciences Research database (230 genes)

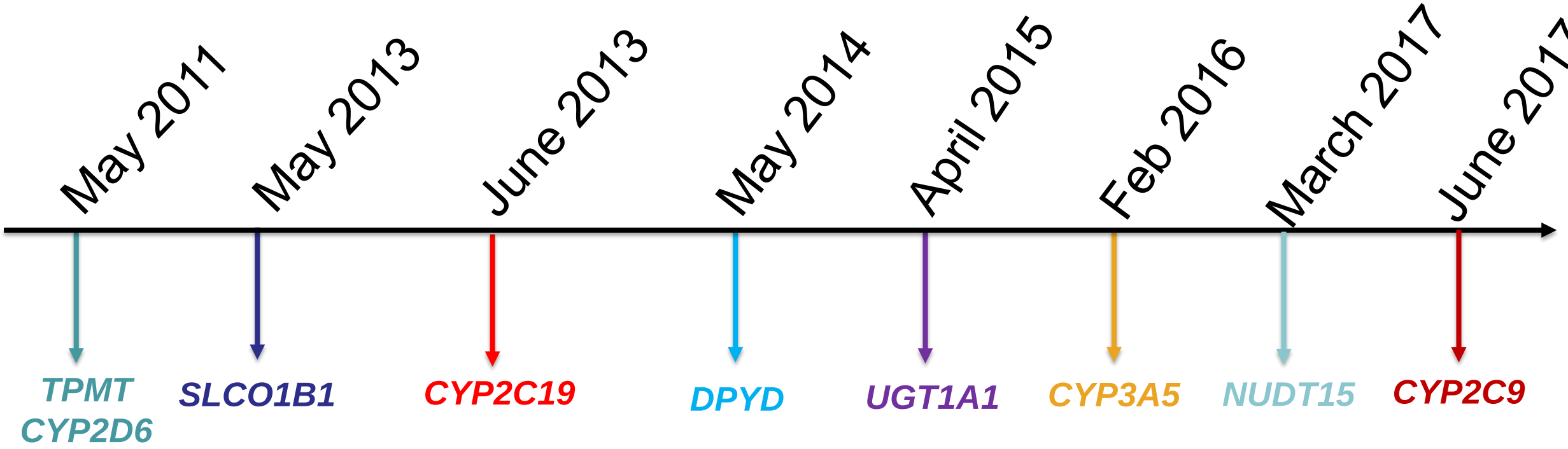
TPMT	***DPYD***	***CYP3A4***	***GSTT1***	***CYP4B1***
CYP2C19	***VKORC1***	***CYP2F1***	***NAT1***	***CYP1A1***
ABCB1	***SLCO1B1***	***CYP2J2***	***FMO3***	***CYP2C18***
CYP2C9	***G6PD***	***UGT1A1***	***CYP4F2***	***ABCC1***

Clinical evidence

CPIC™ Clinical Pharmacogenetics Implementation Consortium

Clinical data repository into EHR (8 genes)

Implementation Timeline



PG4KDS: 8 Genes and 22 Drugs Implemented

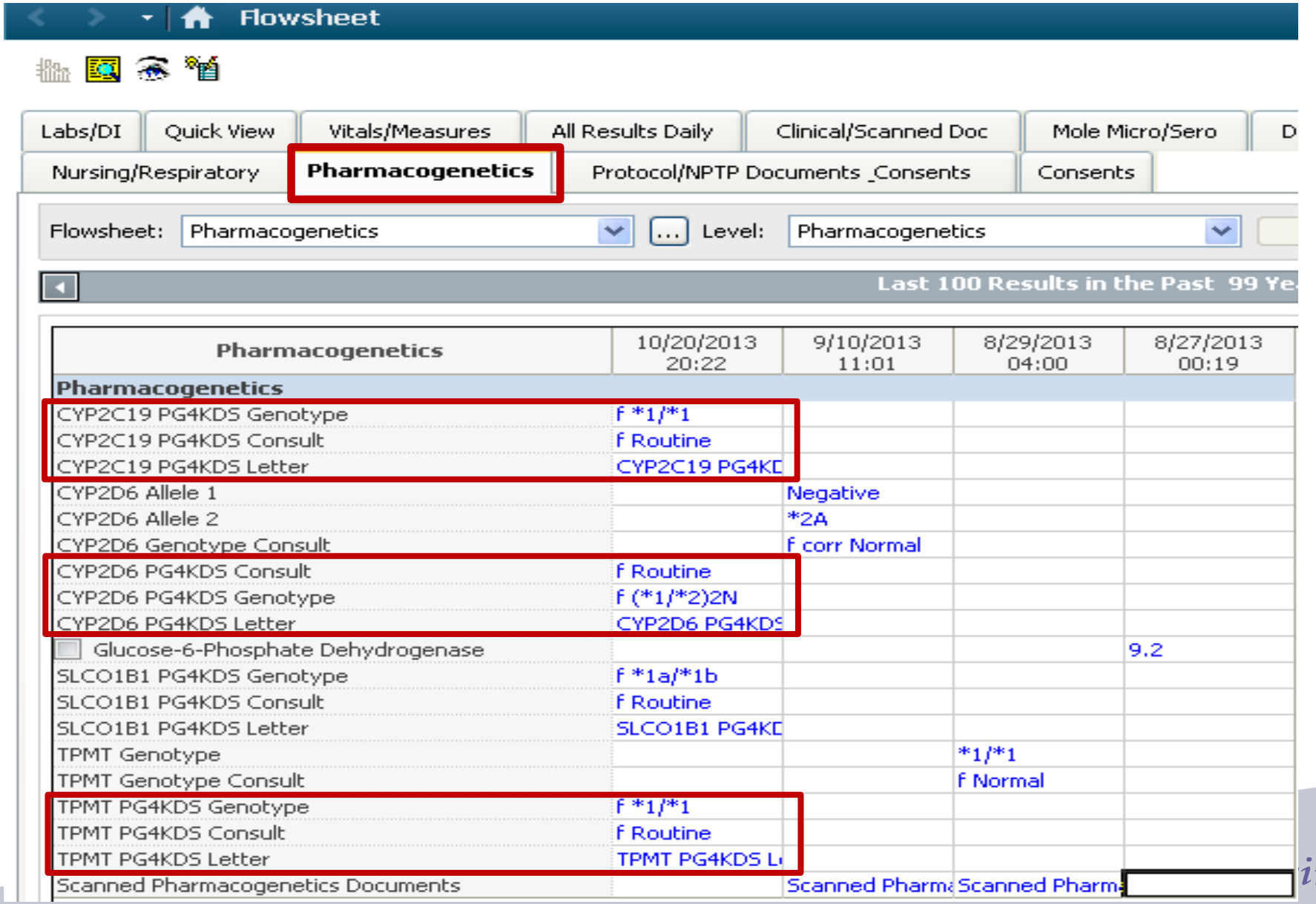
- ***CYP2D6*** *(17%)*
  - Codeine
  - Oxycodone
  - Tramadol
  - Amitriptyline, Clomipramine, Imipramine, Trimipramine
  - Doxepin
  - Fluoxetine
  - Paroxetine
  - Ondansetron
- ***CYP2C19*** *(62%)*
  - Clopidogrel
  - Amitriptyline, Clomipramine, Imipramine, Trimipramine
  - Doxepin
  - Voriconazole
- ***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	Amitryptyline	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	Increased toxicity
Implementation Status	Live	Live	Live	Live	Live	Live	Live	Live	Live	Live
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

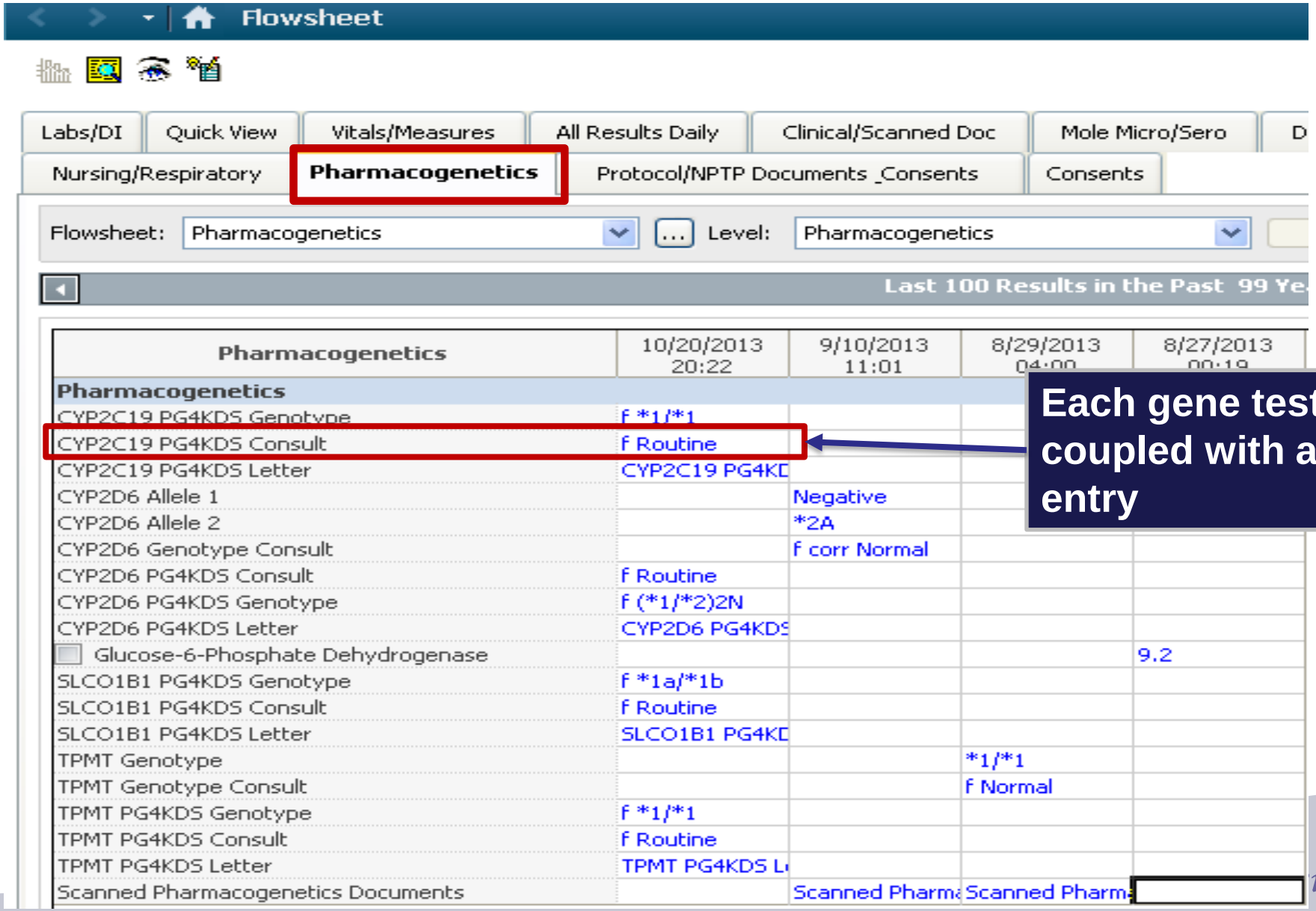
A FOCUS ON INFORMATICS

Dedicated Pharmacogenetics Section



Pharmacogenetics	10/20/2013 20:22	9/10/2013 11:01	8/29/2013 04:00	8/27/2013 00:19
Pharmacogenetics				
CYP2C19 PG4KDS Genotype	f *1/*1			
CYP2C19 PG4KDS Consult	f Routine			
CYP2C19 PG4KDS Letter	CYP2C19 PG4KD			
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			
Glucose-6-Phosphate Dehydrogenase				9.2
SLCO1B1 PG4KDS Genotype	f *1a/*1b			
SLCO1B1 PG4KDS Consult	f Routine			
SLCO1B1 PG4KDS Letter	SLCO1B1 PG4KD			
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 Pharm	

Dedicated Pharmacogenetics Section



Each gene test result is coupled with a “consult” entry

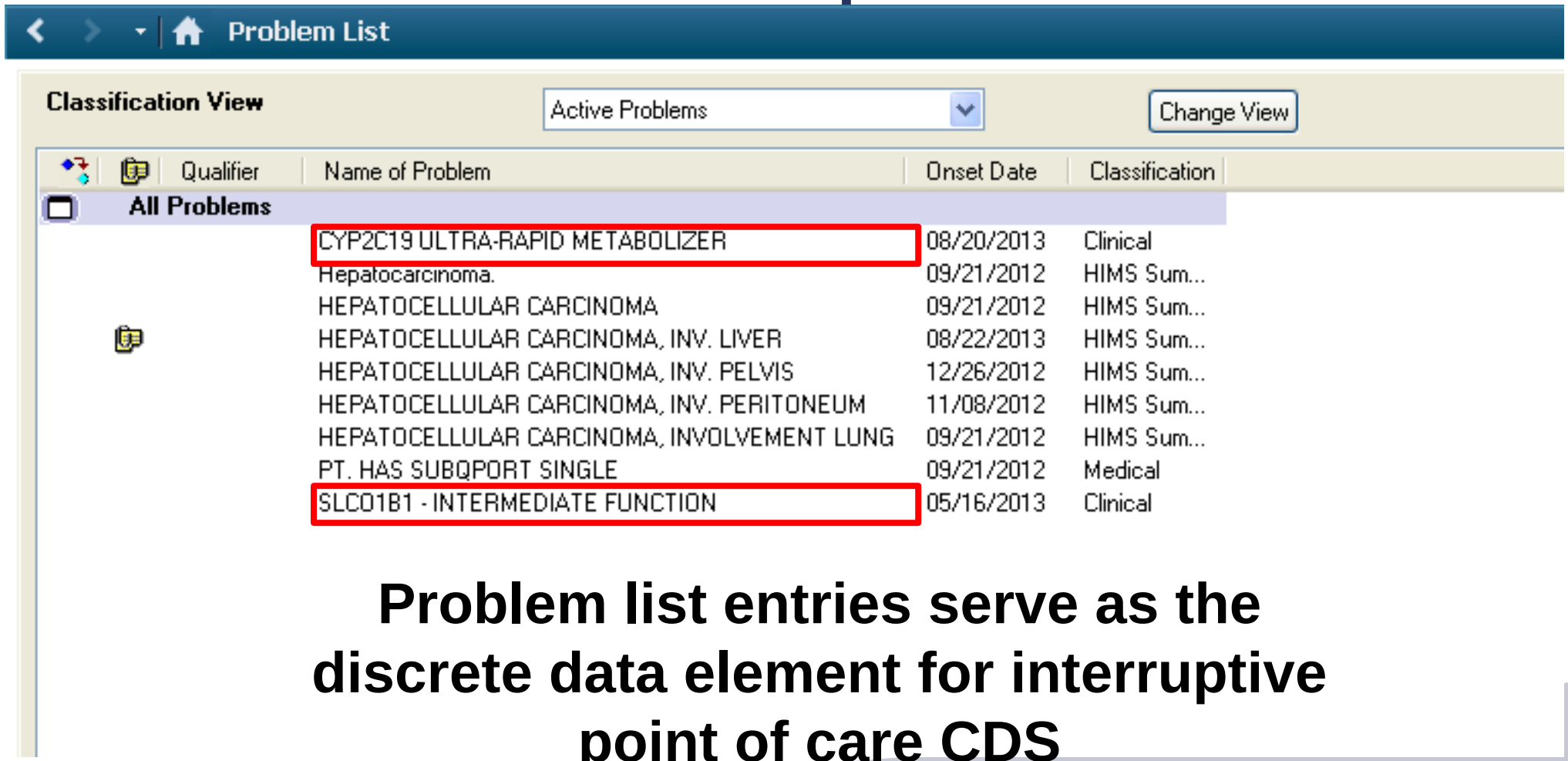
ing children.

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

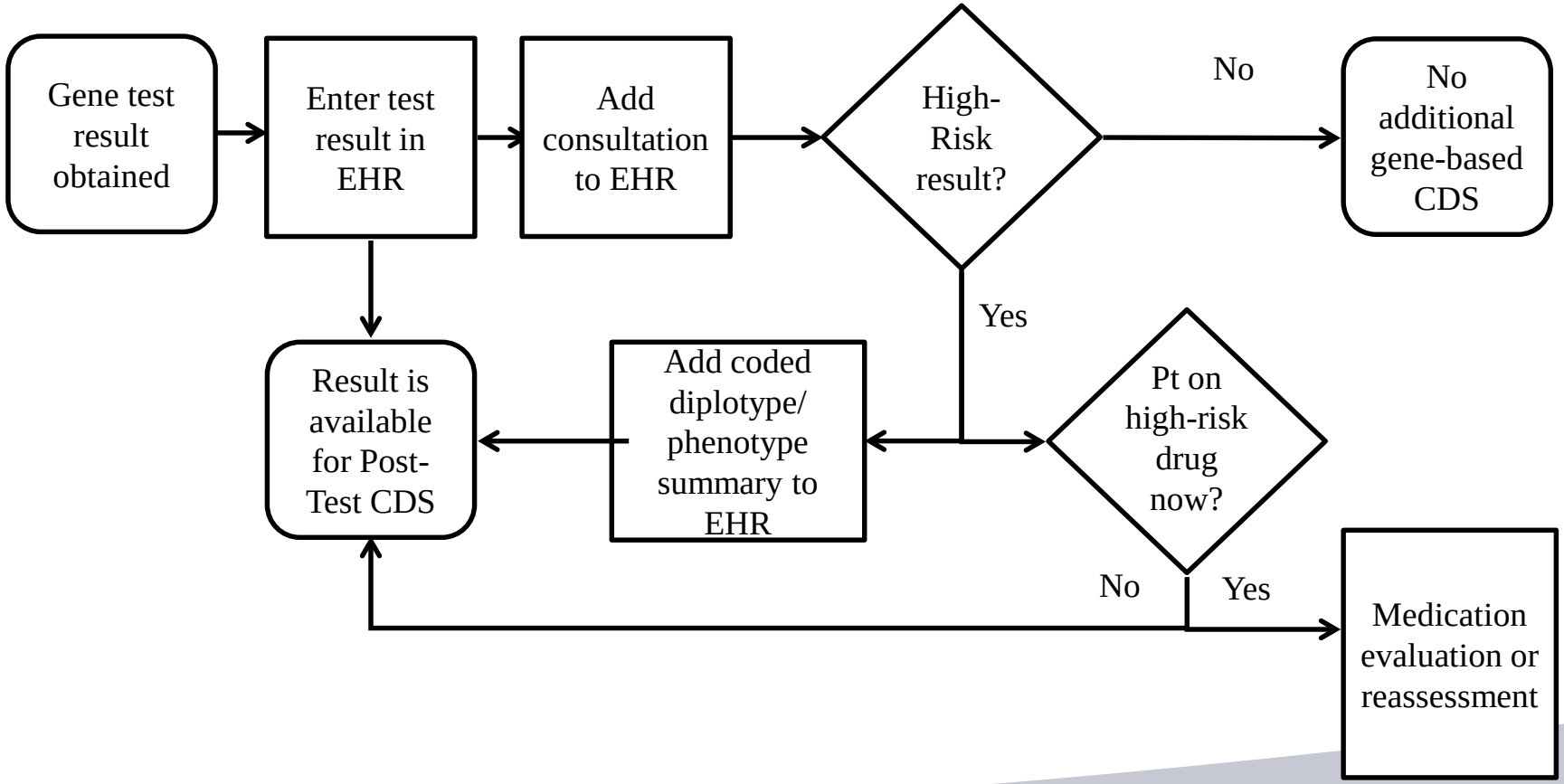
Based on the genotype result this patient is predicted to be a poor metabolizer of CYP2D6 substrates. This patient may require either a dose adjustment of any drug metabolized by CYP2D6 or a therapeutic alternative.
This result signifies that the patient has two copies of a no function allele. This patient 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

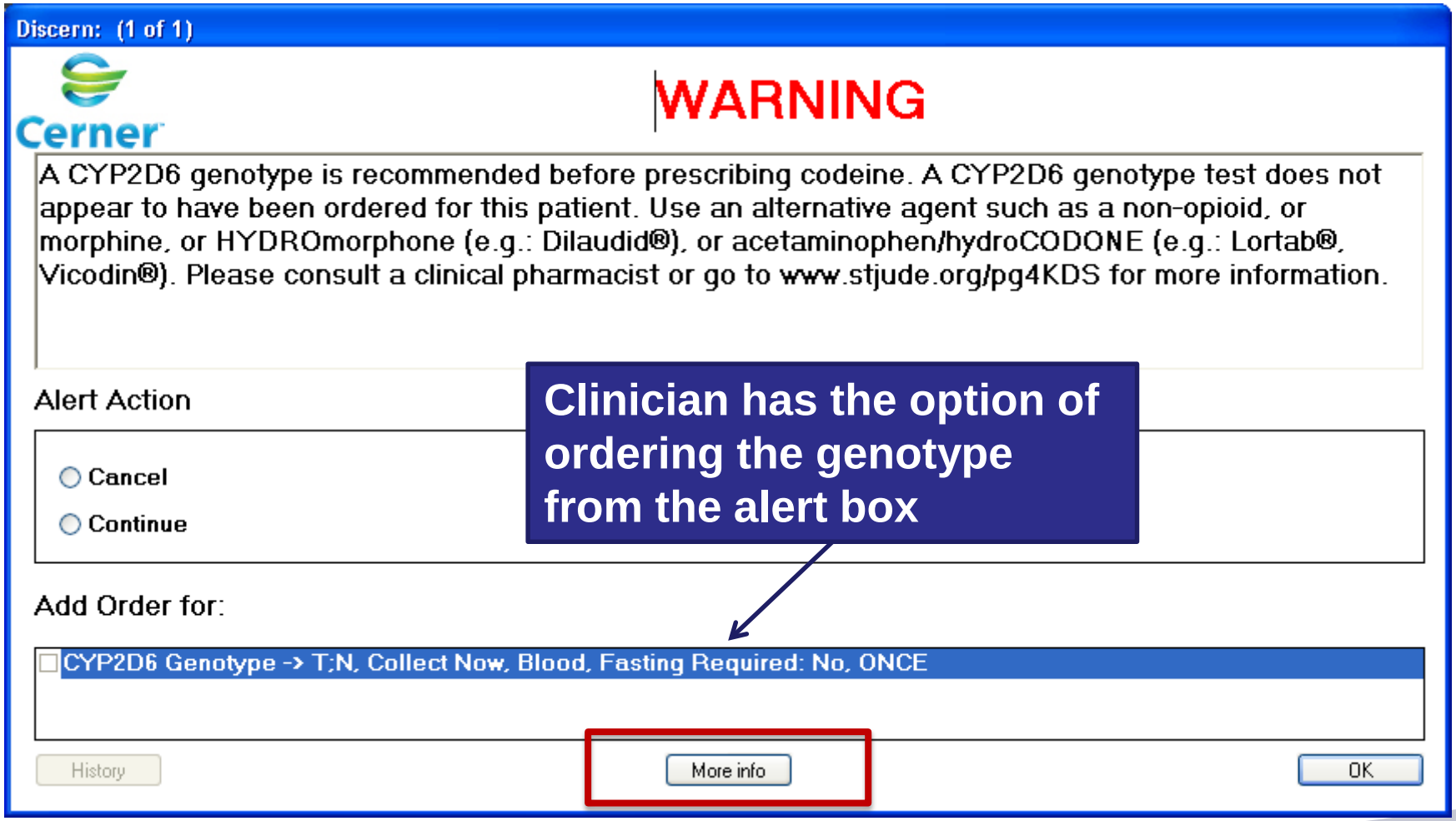


Problem list entries serve as the discrete data element for interruptive point of care CDS

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

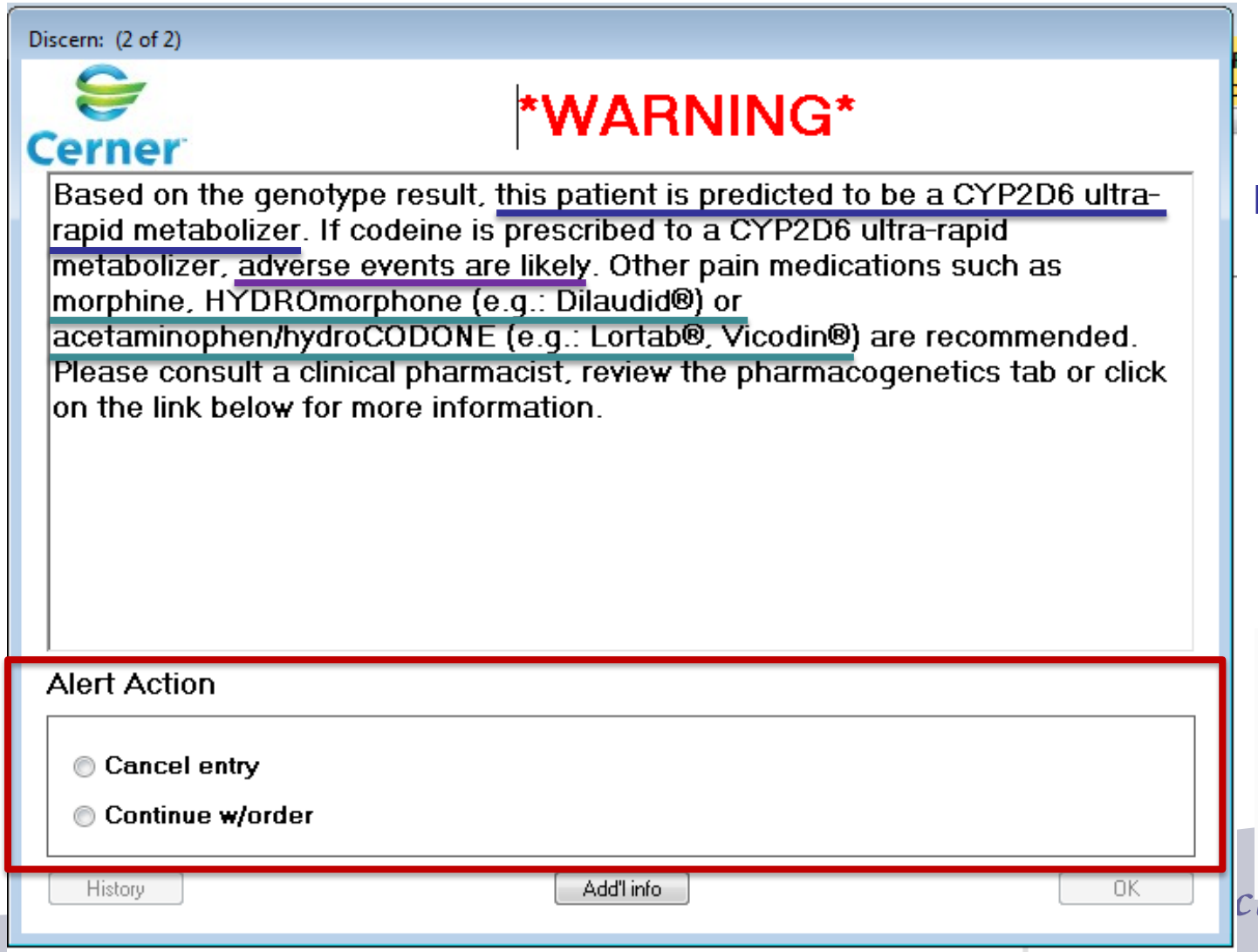


Pre-test (No-Genotype) CDS Alerts



Bell GC, et al. *J Am Med Inform Assoc.* 2014;21:e93-9

Post-test (High-Risk Genotype) Alerts



Phenotype

Outcome

Other recommendations

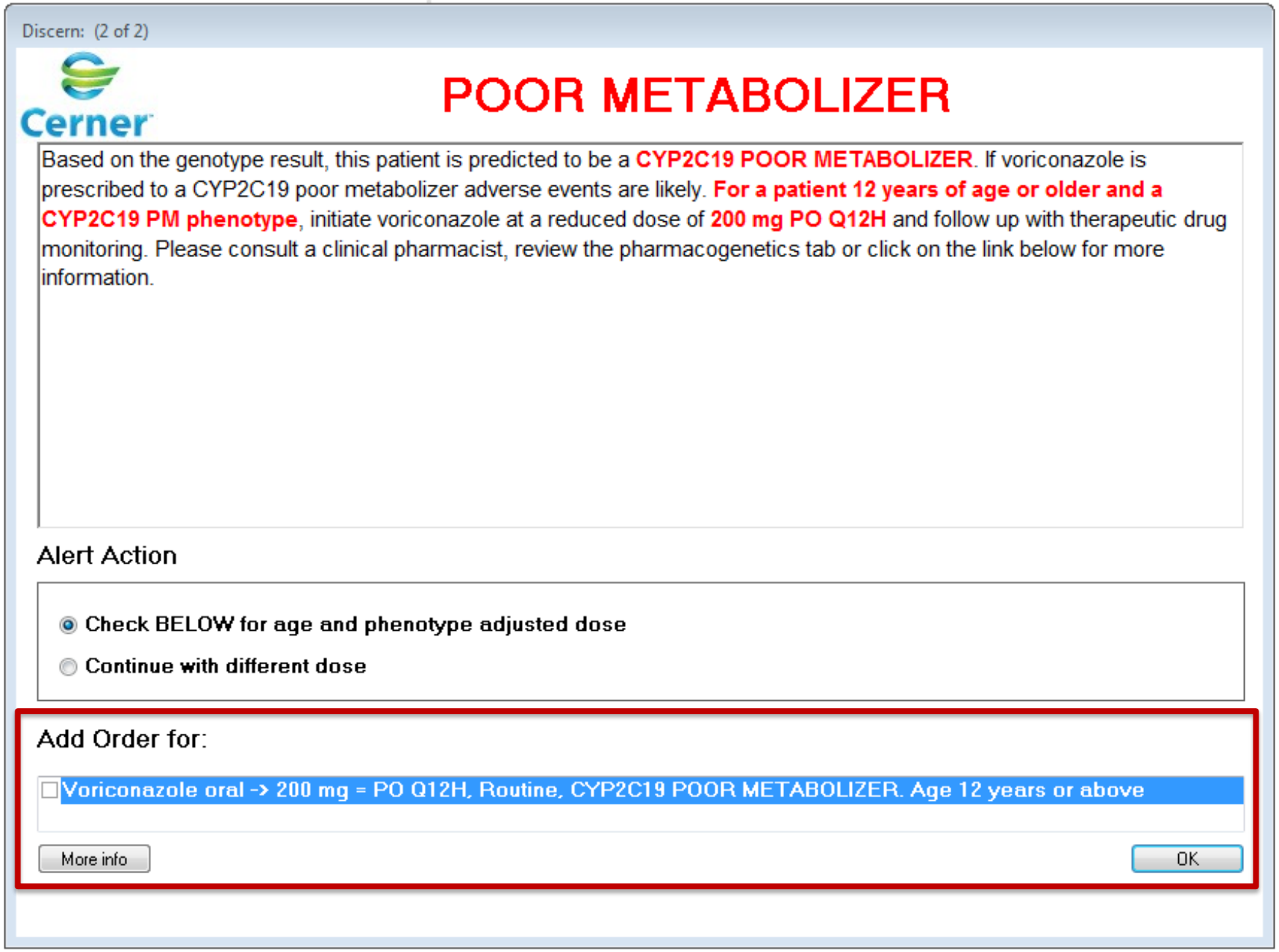
Clinician can continue with ordering the medication or cancel order to prescribe alternative

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

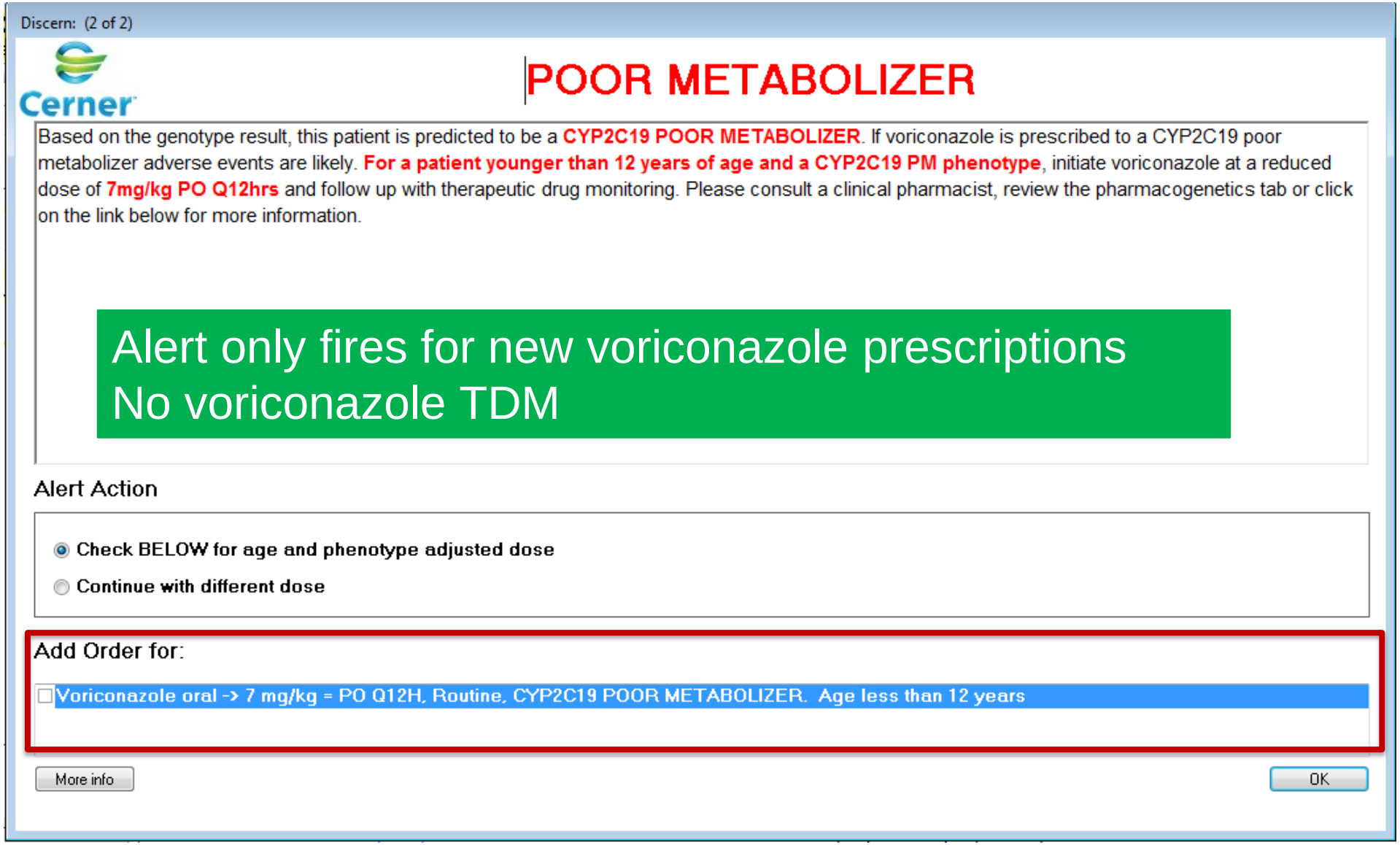
CYP2C19/voriconazole

Alert take into account:
- CYP2C19 phenotype
- Route of administration
- Age of patient

Recommended dose directly ordered from alert screen

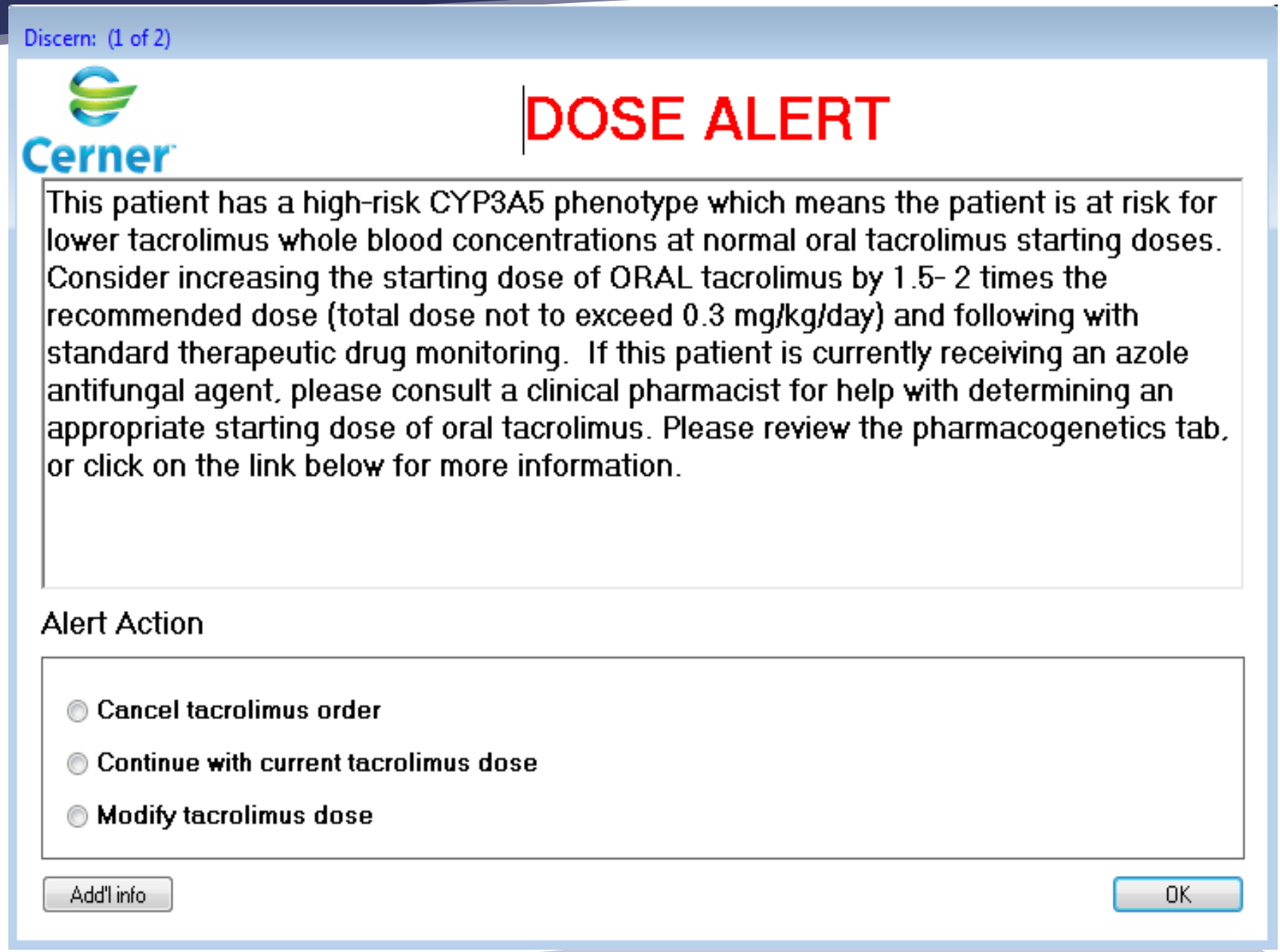


CYP2C19/voriconazole
(CYP2C19 PM, PO formulation in patient younger than 12 yo)

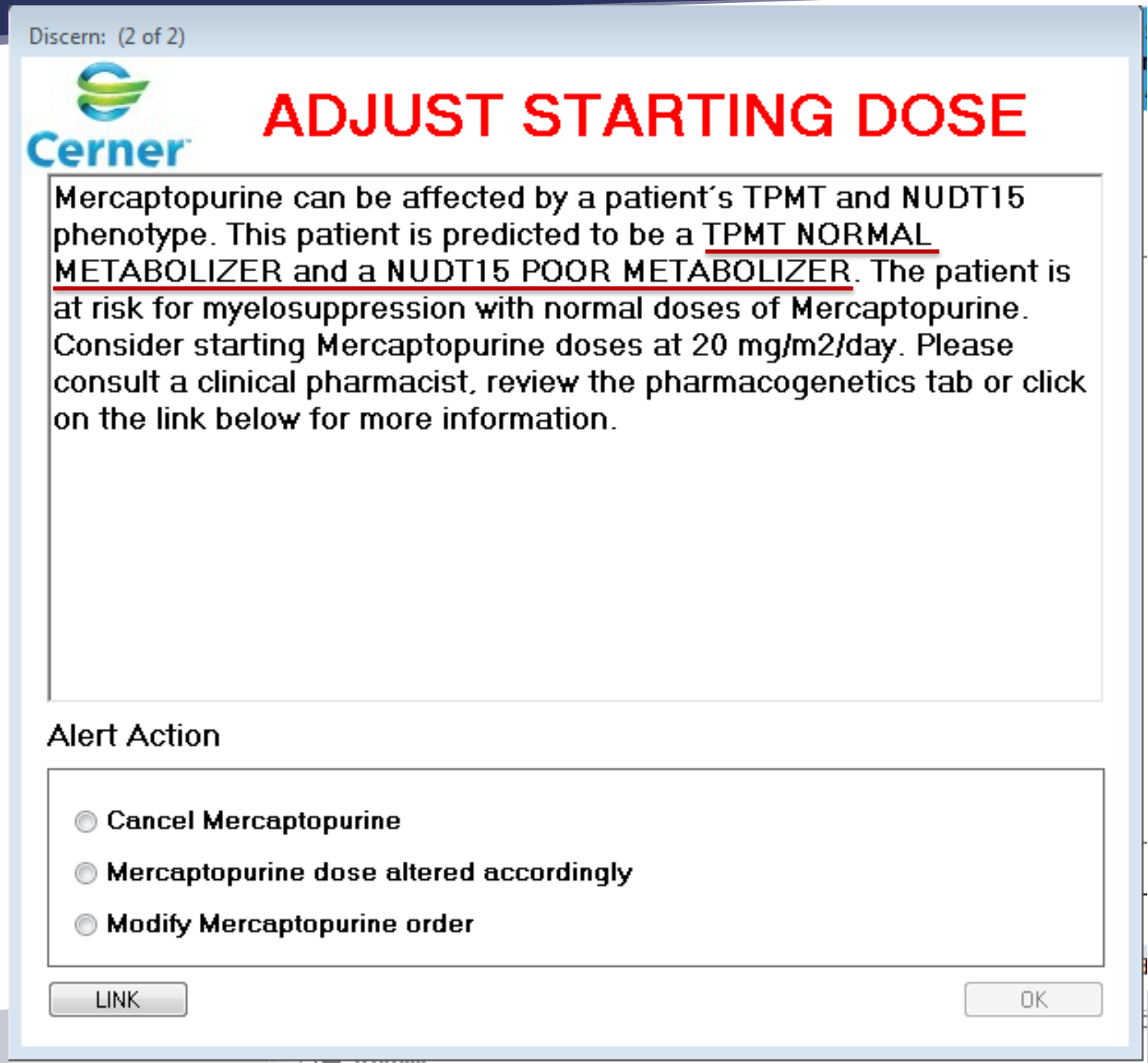


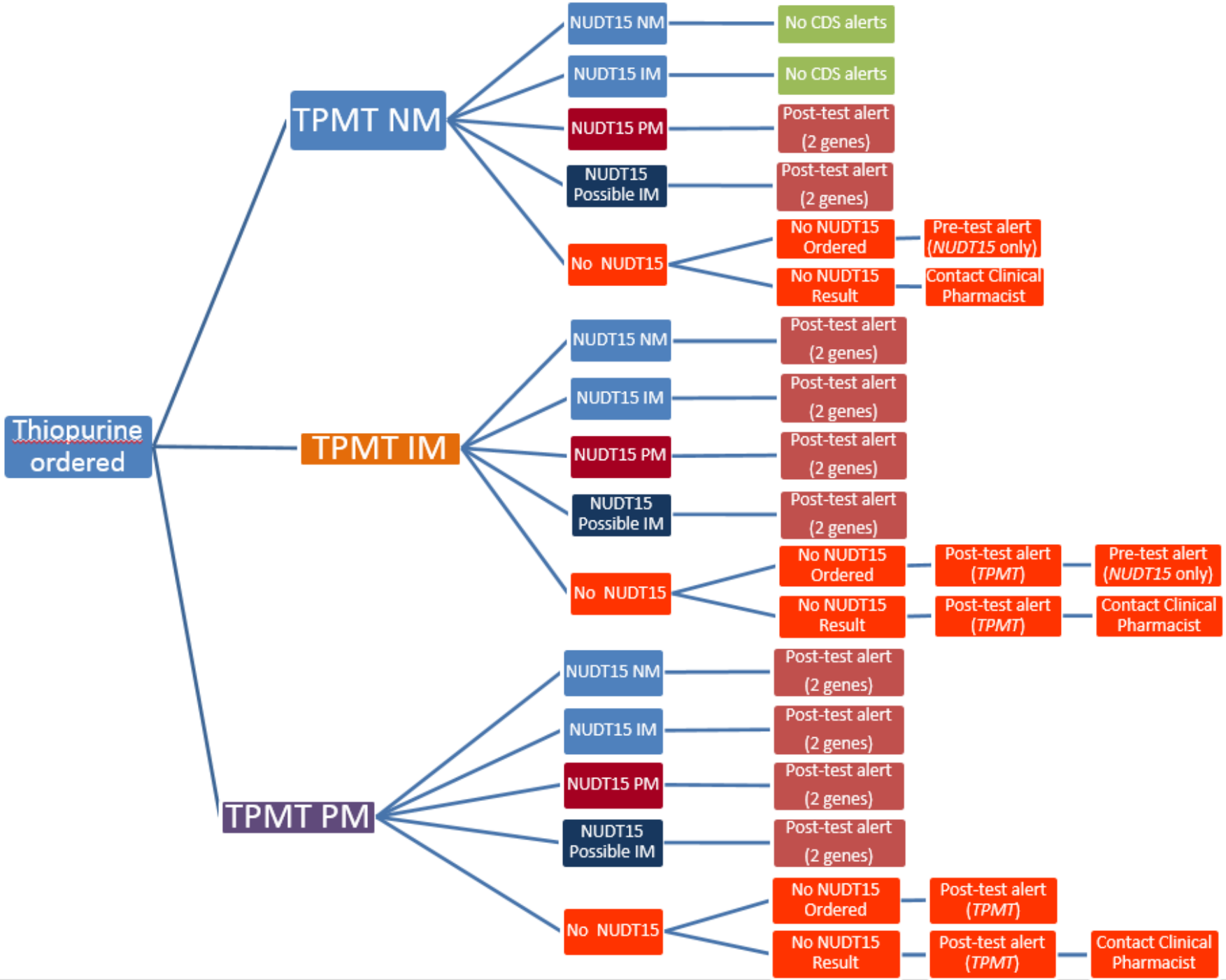
CYP3A5 and tacrolimus:

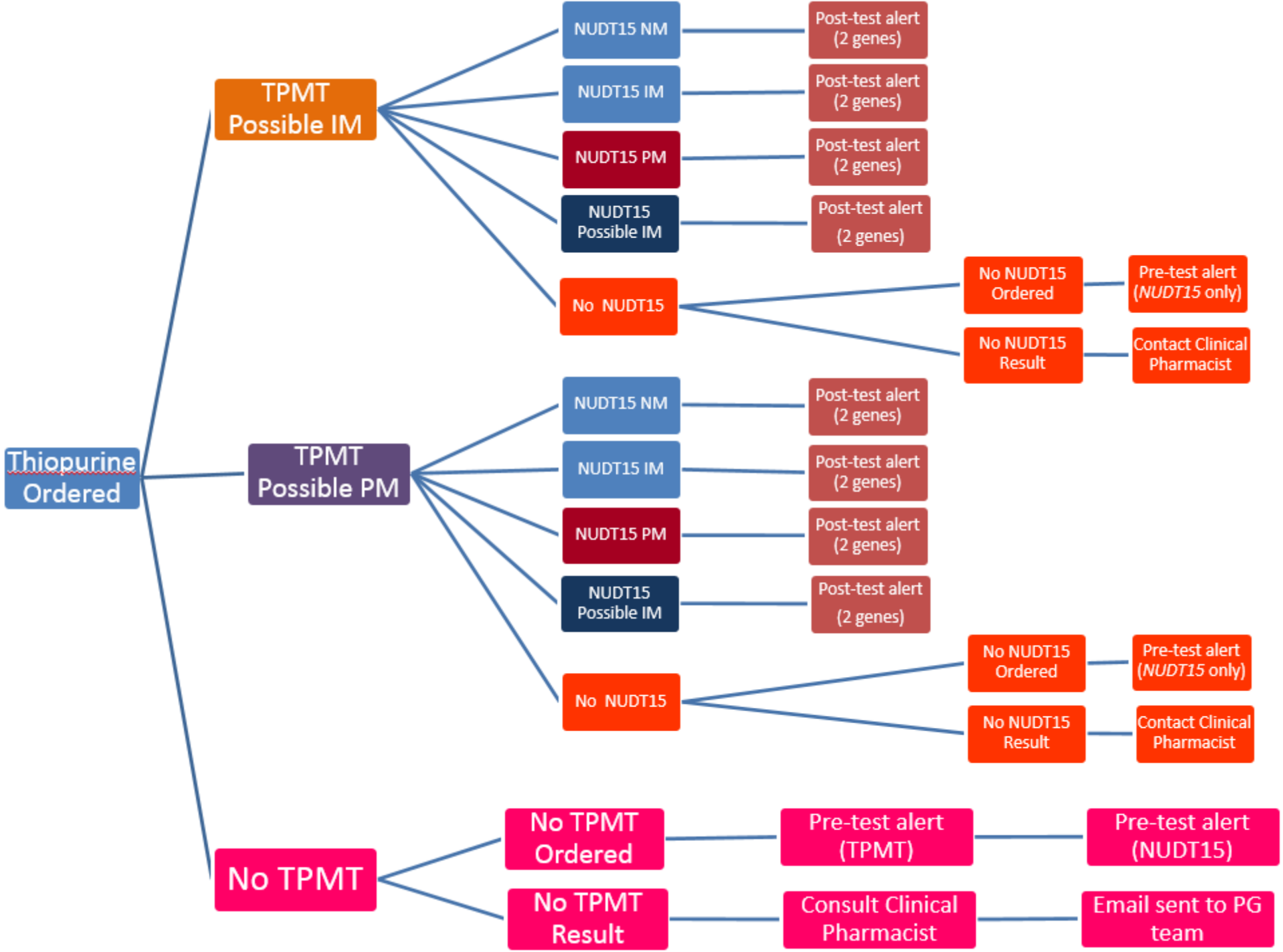
- Route of administration
  - Tacrolimus TDM
  - Tacrolimus order



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




Thiopurine ordered
TPMT NM
NUDT15 NM
No CDS alerts
NUDT15 IM
No CDS alerts
NUDT15 PM
Post-test alert (2 genes)
NUDT15 Possible IM
Post-test alert (2 genes)
No NUDT15
No NUDT15 Ordered
Pre-test alert (NUDT15 only)
No NUDT15 Result
Contact Clinical Pharmacist
TPMT IM
NUDT15 NM
Post-test alert (2 genes)
NUDT15 IM
Post-test alert (2 genes)
NUDT15 PM
Post-test alert (2 genes)
NUDT15 Possible IM
Post-test alert (2 genes)
No NUDT15
No NUDT15 Ordered
Post-test alert (TPMT)
Pre-test alert (NUDT15 only)
No NUDT15 Result
Post-test alert (TPMT)
Contact Clinical Pharmacist
TPMT PM
NUDT15 NM
Post-test alert (2 genes)
NUDT15 IM
Post-test alert (2 genes)
NUDT15 PM
Post-test alert (2 genes)
NUDT15 Possible IM
Post-test alert (2 genes)
No NUDT15
No NUDT15 Ordered
Post-test alert (TPMT)
No NUDT15 Result
Post-test alert (TPMT)
Contact Clinical Pharmacist


Thiopurine Ordered
TPMT Possible IM
NUDT15 NM
Post-test alert (2 genes)
NUDT15 IM
Post-test alert (2 genes)
NUDT15 PM
Post-test alert (2 genes)
NUDT15 Possible IM
Post-test alert (2 genes)
No NUDT15
No NUDT15 Ordered
Pre-test alert (*NUDT15* only)
No NUDT15 Result
Contact Clinical Pharmacist
TPMT Possible PM
NUDT15 NM
Post-test alert (2 genes)
NUDT15 IM
Post-test alert (2 genes)
NUDT15 PM
Post-test alert (2 genes)
NUDT15 Possible IM
Post-test alert (2 genes)
No NUDT15
No NUDT15 Ordered
Pre-test alert (*NUDT15* only)
No NUDT15 Result
Contact Clinical Pharmacist
No TPMT
No TPMT Ordered
Pre-test alert (TPMT)
Pre-test alert (NUDT15)
No TPMT Result
Consult Clinical Pharmacist
Email sent to PG team

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?