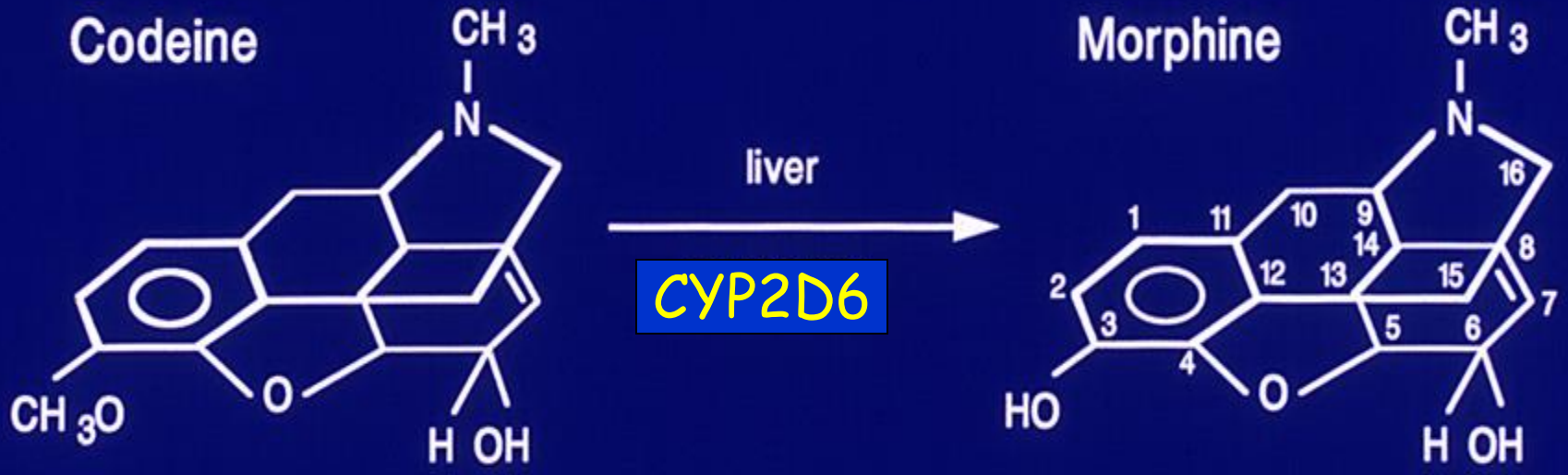
Integration of Pharmacogenetics into Clinical Practice

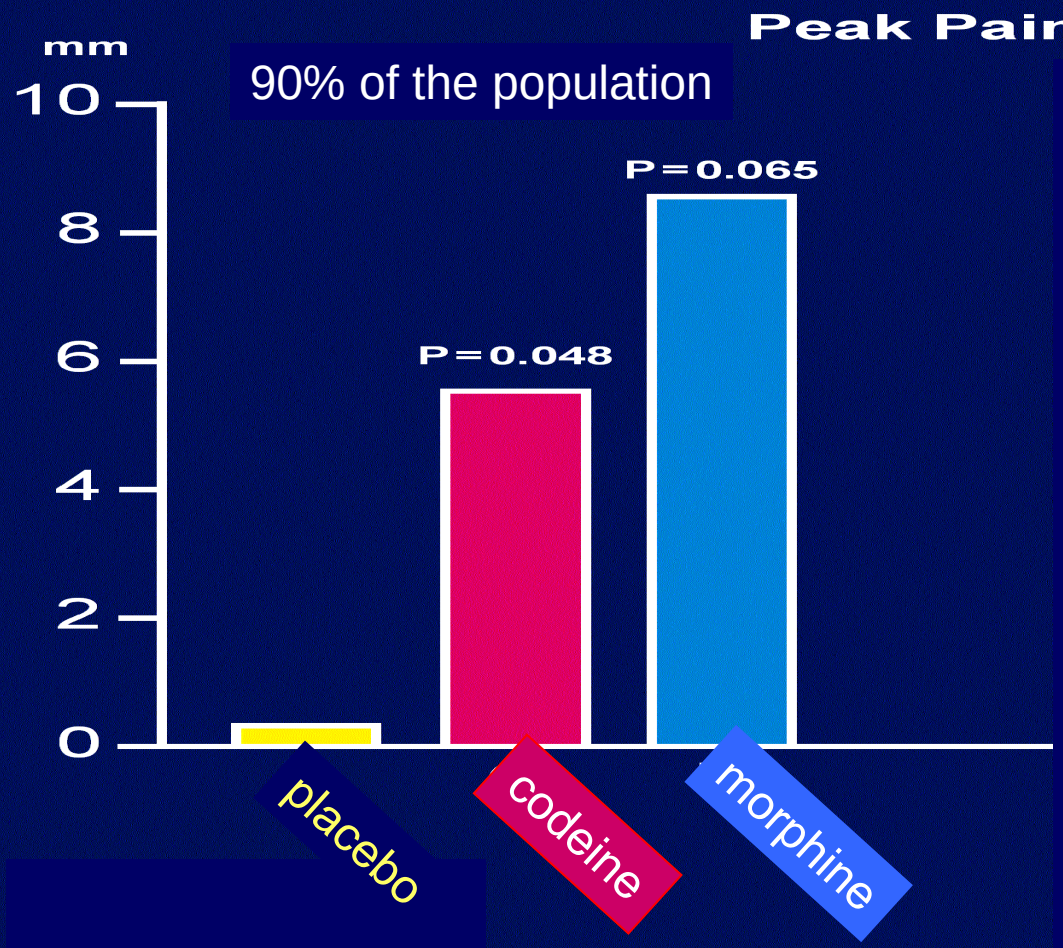
Mary V. Relling, Pharm.D.

St. Jude Children's Research Hospital and

PAAR4Kids, NIH Pharmacogenomics Research Network

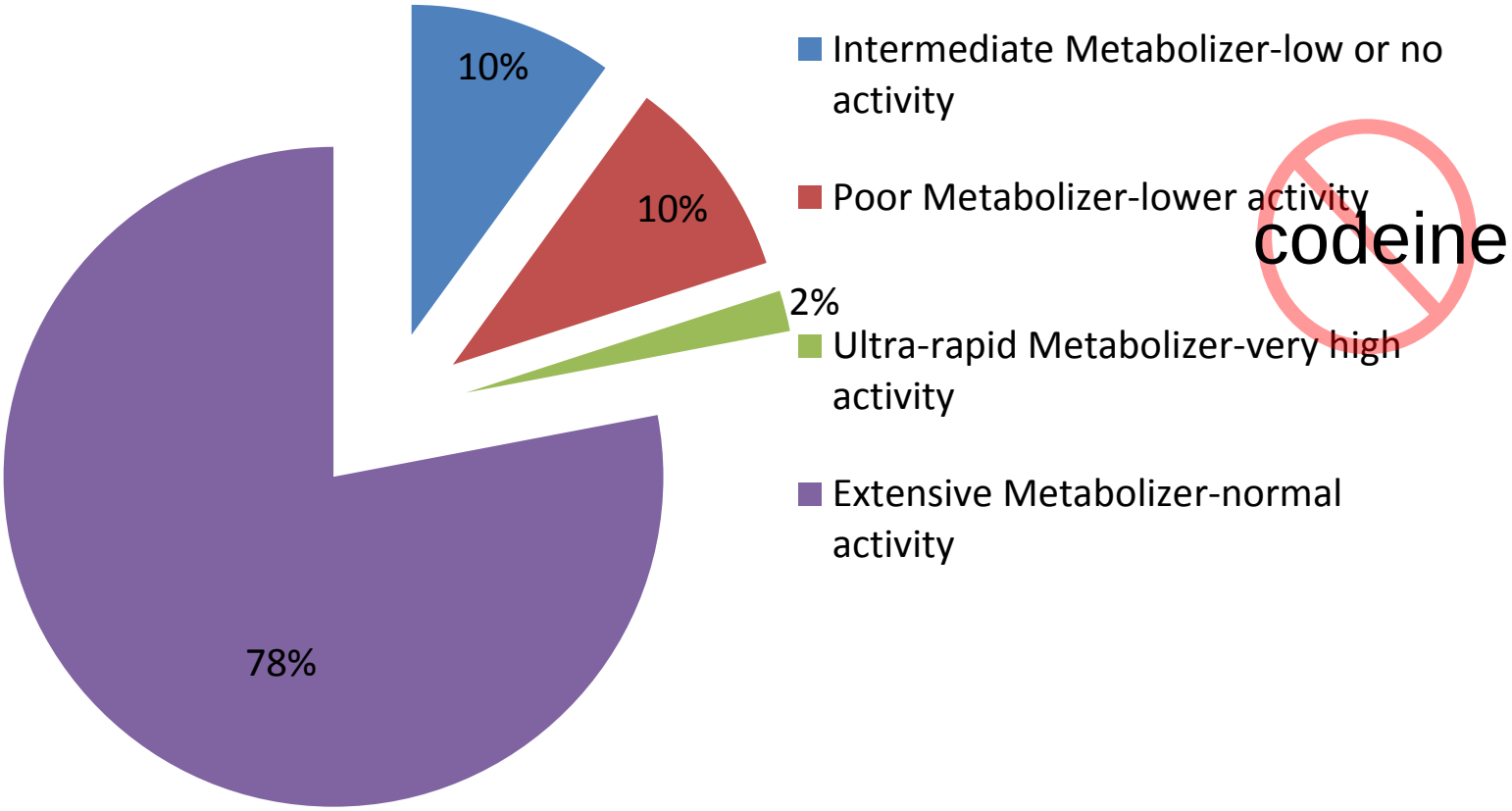

Codeine
CH 3
N
CH 3O
O
H OH
liver
CYP2D6
Morphine
CH 3
N
16
1
11
10
9
14
8
2
12
13
15
7
3
5
6
4
HO
O
H OH

Codeine is the same as placebo to 10% of the population



And too active for 1-2% of the population

CYP2D6 distribution of phenotypes



Barriers to integration of pharmacogenetic tests into clinical care

- Fragmentation of health-care systems---esp over a lifetime
- Health-care delivery system and incentive structures are focused on ‘‘sick care’’ and not disease prevention
- Lack of evidence of clinical utility or cost effectiveness--coupled with excessively high requirements
- Complexity of the underlying laboratory results
- Lack of use of computational decision support in all of medicine----including the medication process (testing, prescribing, distribution, and administration)
- Need for pre-emptive testing

At St. Jude, we can overcome (or ignore) many barriers to pre-emptive genotyping

- We cover all patient care costs
- We provide all medications for 5000 unique high-risk patients per year
  - ~ 80% have cancer
  - ~20% have sickle cell, HIV, and other life-threatening diseases
- We have a team approach to pt care
- We have an integrated, comprehensive EMR (Cerner) with customized decision support

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Ability to genotype at lots of loci on CLIA-approved array is ~~coming~~ here and allows for pre-emptive genotyping

- Affy DMET array: over 1 million features to interrogate 1900 polymorphisms in 225 genes
- For the same money we spend on 2 genes, we can interrogate 225 genes
  - Makes pre-emptive genotyping a possibility

33 "Pharmacogenetically High Risk" Drugs, 11 CPIC genes

(For 2011 Orders; Queries performed May 2012)

Abacavir	**Methylene blue**
Amitriptyline	**Metoprolol**
Aripiprazole	**Nitrofurantoin**
Aspirin	**Olanzapine**
Azathioprine	**Phenazopyridine**
Capecitabine	
Clopidogrel	
Codeine	
Dapsone	
Fluorouracil	**Sertraline**
Fluoxetine	**Sulfamethoxazole-trimethoprim**
Haloperidol	**Sulfasalazine**
Hydroxychloroquin	
Irinotecan	
Lidocaine	
Menthol	**Warfarin**
Mercaptopurine	

2023 of 4245 patients (48%) at St. Jude received orders for at least one of 33 "high-risk" drugs in a 1-yr period.

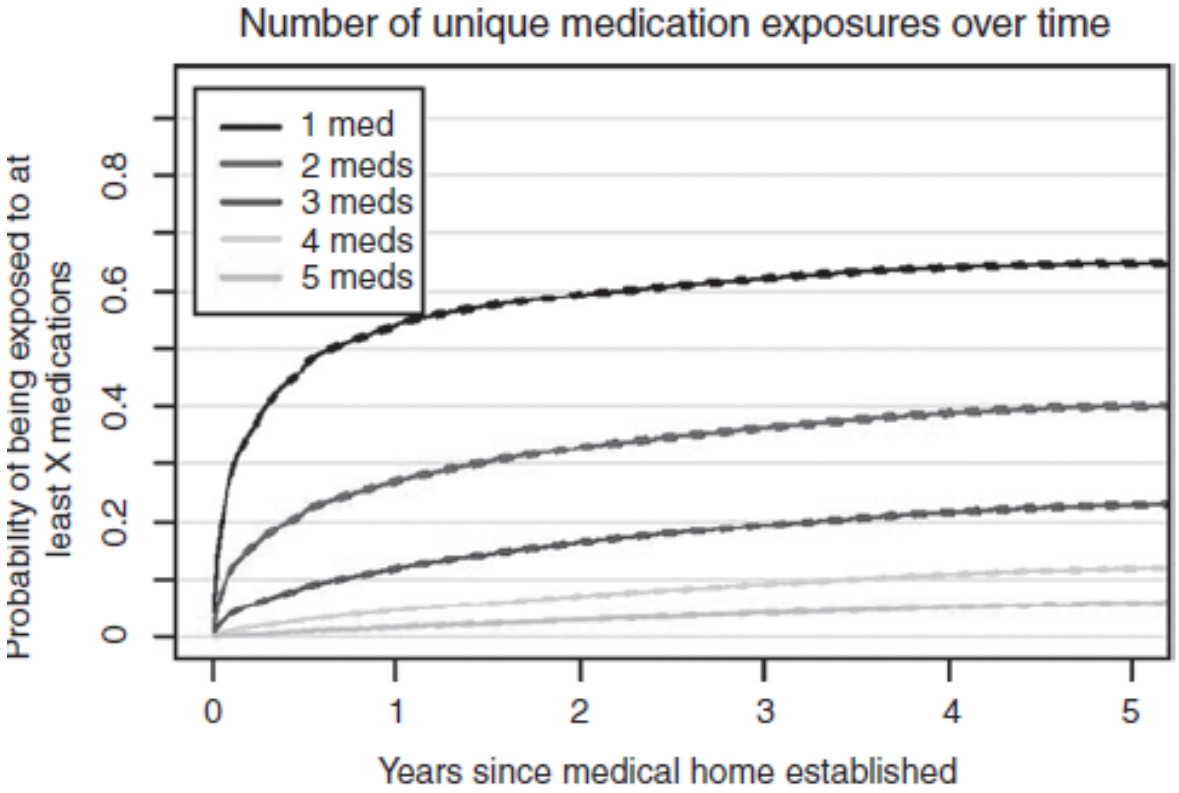
40% have high-risk genotypes with just first 3 genes (CYP2D6, TPMT, SLCO1B1)

Optimizing Drug Outcomes Through Pharmacogenetics: A Case for Preemptive Genotyping

JS Schildcrout[1,2], JC Denny[3,4], E Bowton[5], W Gregg[3,4], JM Pulley[5], MA Basford[5], JD Cowan[6], H Xu[3], AH Ramirez[4], DC Crawford[7], MD Ritchie[8], JF Peterson[3,4,9], DR Masys[3,4], RA Wilke[4,10] and DM Roden[4,5,10,11]

54% exposed to one of 56 pgen high risk drugs in one year…..

~ 75% of pts have high-risk genotypes with first 4 tests



PG4KDS : CLINICAL IMPLEMENTATION OF PHARMACOGENETICS at ST. JUDE

Goal: migrate pharmacogenetic tests from laboratory (array-based) into routine patient care, to be available preemptively

PG4KDS Protocol
Clinical Implementation of Pharmacogenetics

Principal Investigator

Mary V. Relling

Co-Investigators

Kristine Crews
James Hoffman
Shane Cross
Christine Odom
Don Baker
Jerry Shenep
Fran Greeson
Aditya Gaur
Ulrike Reiss
Sheri Ring
Lisa Walters
Paula Condy
Terri Kuehner
Alicia Huettel
Cyrine Haidar
Cheng Cheng
Amar Gajjar
Alberto Pappo
Scott Howard
Melissa Hudson
Ching-Hon Pui
Sima Jeha
William E. Evans

External Co-Investigator (Collaborating Institutions):

Ulrich Broeckel, M.D.
Medical College of Wisconsin

PGRN

PG4KDS Protocol

18 months May 20th 2011 to Jan 30th, 2013

First pt enrolled	Current clinic	n
08-Jun-2011	Neuro-oncology	165
10-Jun-2011	BMT	20
04-May-2012	After completion tx	4
21-May-2012	HIV	92
24-Apr-2012	Radiation oncology	29
24-Jun-2011	Solid tumor	189
27-May-2011	Leukemia	277
08-Nov-2012	Non-malig Hematology	180
	Total	956

Why a research protocol?

- DMET results available from CLIA lab, but process is complicated to go from lab results to clinically actionable recommendations
- Need process for withholding/sharing results
- Need consent for:
  - Withholding results
  - Incidental findings—lots of help from Ethics Committee and IRB

St. Jude Family Advisory Council (Alicia Huettel et al) educational video www.stjude.org/pg4kds

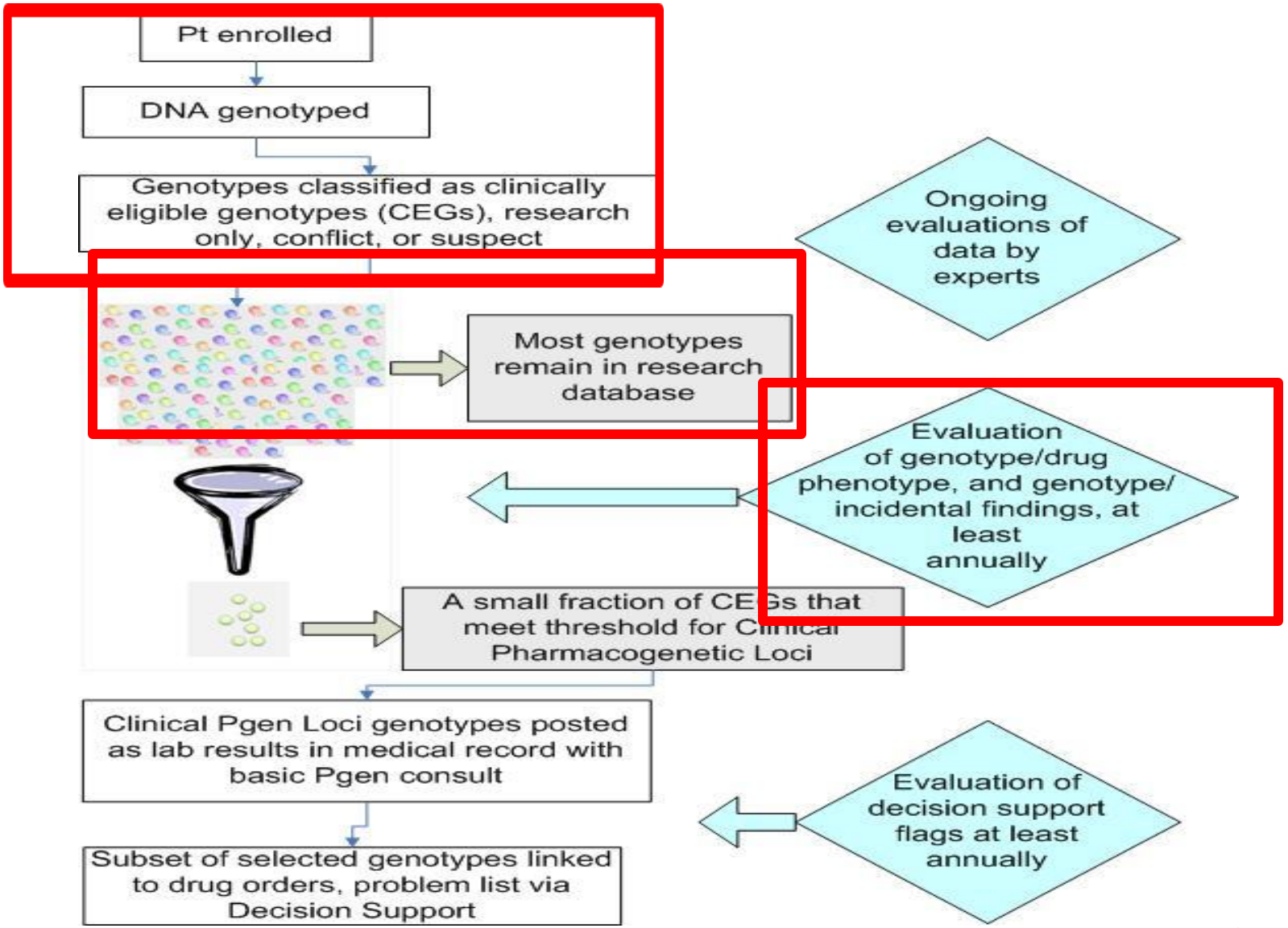
Employee Spotlight

Employees love working at St. Jude for tons of reasons—including our inspiring mission, diversity, resources, benefits and history. Each employee is a valued member of the St. Jude family, and the Employee Spotlight demonstrates how each employee's contributions support the St. Jude mission.

Melinda Wood
Pharmaceutical Sciences

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

The process

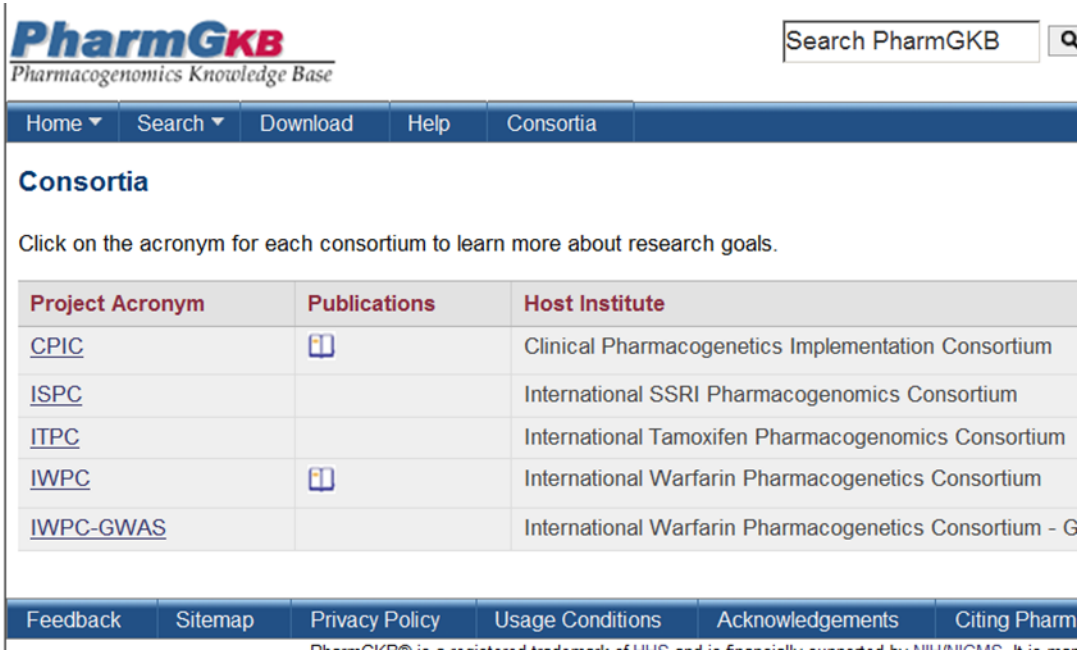


PG4Kds

CPIC: Clinical Pharmacogenetics Implementation Consortium

- Clinicians, scientists
- 60 members
- 33 institutions
- Observers: NIH and FDA
- 8 countries

CPIC: Implementing PGx
a PharmGKB & PGRN collaboration



CPIC: Implementing PGx

a PharmGKB & PGRN collaboration

- CPIC's Inherent framework: if you had the genotype result, how should you act on it?
- Consistent with preemptive, array-based genotyping

Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing

MV Relling[1], EE Gardner[1], WJ Sandborn[2], K Schmiegelow[3,4], C-H Pui[5], SW Yee[6], CM Stein[7], M Carrillo[8], WE Evans[1] and TE Klein[8]

Clinical Pharmacogenetics Implementat Consortium Guidelines for Cytochrome P450-2C19 (*CYP2C19*) Genotype and Clopidogrel Therapy

SA Scott[1], K Sangkuhl[2], EE Gardner[3], CM Stein[4,5], J-S Hulot[6,7], JA Johnson[8,9,10], DM Roden[11,12], TE Klein[2] and AR Shuldiner[13,14]

Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C9* and *VKORC1* Genotypes and Warfarin Dosing

JA Johnson[1], L Gong[2], M Whirl-Carrillo[2], BF Gage[3], SA Scott[4], CM Stein[5], JL Anderson[6], SE Kimm MTM Lee[10], M Pirmohamed[11], M Wadelius[12], TE Klein[2] and RB Altman[2,13]

Clinical Pharmacogenetics Implementation Consortium Guidelines for Human Leukocyte Antigen-B Genotype and Allopurinol Dosing

MS Hershfield[1,2], JT Callaghan[3,4,5], W Tassaneeyakul[6], T Mushiroda[7], CF Thorn[8], TE Klein[8] and MTM Lee[9,10,11]

The Clinical Pharmacogenomics Implemen Consortium: CPIC Guideline for *SLCO1B1* and Simvastatin-Induced Myopathy

RA Wilke[1,2], LB Ramsey[3], SG Johnson[4,5], WD Maxwell[6], HL McLeod[7], D Voora[8], RM Krauss[9], DM Roden[1,2], Q Feng[1,2], RM Cooper-DeHoff[10], L Gong[11], TE Klein[11,12], M Wadelius[13] and M Niemi[14]

Clinical Pharmacogenetics Implementat Consortium Guidelines for *HLA-B* Genot Abacavir Dosing

CLINICAL PHARMACOLOGY & THERAPEUTICS

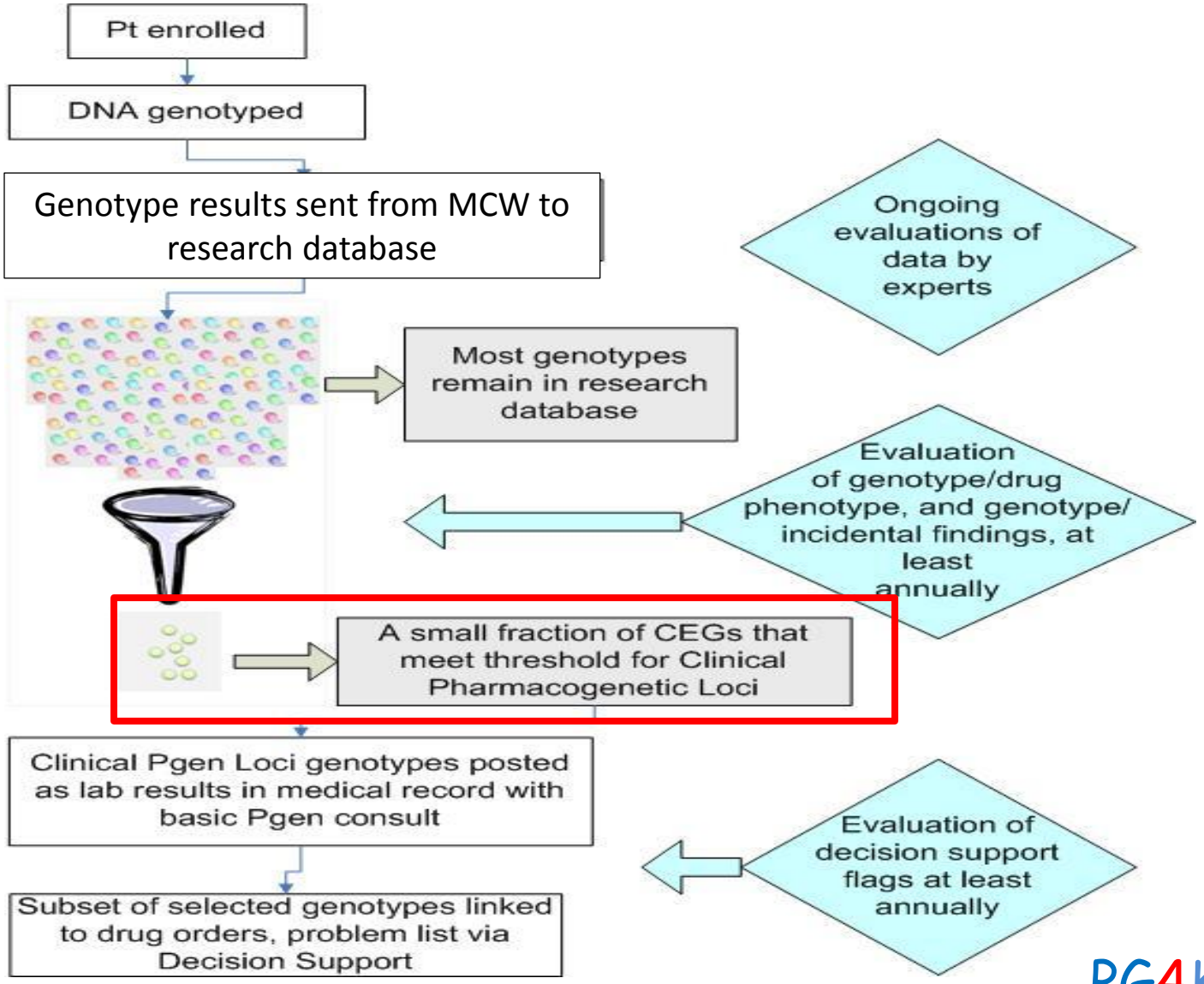
Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of *Cytochrome P450 2D6* (*CYP2D6*) Genotype

KR Crews[1], A Gaedigk[2], HM Dunnenberger[3], TE Klein[4], DD Shen[5,6], JT Callaghan[7,8], ED Kharasch[9] and TC Skaar[7]

Pharmacogenetics Oversight Committee (SJ)

- Meets quarterly
- Approves gene/drug pairs
- Approves decision support message and mechanisms
- Reports to P&T

The process



PG4KDS

Travel Route of DMET Genotyping

DMET genotyping at Medical College of Wisconsin

Pharmaceutical Sciences Research database (225 genes parsed into separate files)

TPMT	*DPYD*	*CYP3A4*	*GSTT1*	*CYP4B1*
CYP2C19	*VKORC1*	*CYP2F1*	*NAT1*	*CYP1A1*
CYP2D6	*SLCO1B1*	*CYP2J2*	*FMO3*	*CYP2C18*
CYP2C9	*G6PD*	*UGT1A1*	*CYP4F2*	*ABCC1*

Extensive quality control **Prior to upload in EHR**

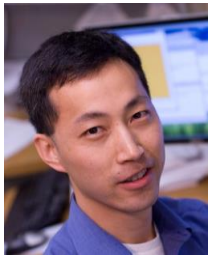
Into EHR—Clinical Data repository

TPMT, CYP2D6, SLCO1B1

DMET Tracker

Search:

Gene	DMET Diplotype	Existing Diplotype	DMET Race	Clinical Race	DMET Gender	Clinical Gender	QC Flag	Suspect QC	EMR Priority	PK Phenotype	Consult	Cross Ref	Upload Status	Approve for Upload All?
TPMT	*1/*1	None	black;	black	male?(0)	male	PASS		ROUTINE	HIGH ACTIVITY	Homozygous WT	v1	in EMR	approved by kcrews
CYP2D6	(*29/*29)1N	None	black;	black	male?(0)	male	PASS		ROUTINE	IM	2D6 IM 29/5	v1	in EMR	approved by khicks
TPMT	*1/*1	None	white;	white	female(3)	female	PASS		ROUTINE	HIGH ACTIVITY	Homozygous WT	v1	in EMR	approved by khicks
CYP2D6	(*1/*2)2N	None	white;	white	female(3)	female	PASS		ROUTINE	EM	2D6 EM Wt/Wt	v1	in EMR	approved by khicks
TPMT	*1/*1	None	white;	white	male?(0)	male	PASS		ROUTINE	HIGH ACTIVITY	Homozygous WT	v1	in EMR	approved by kcrews
CYP2D6	(*1/*4)2N	None	white;	white	male?(0)	male	PASS		ROUTINE	EM	2D6 EM Wt/NF	v1	in EMR	approved by kcrews
TPMT	*1/*8	G/G|G/G|A/A	black;	black	female(7)	female	REVIEWING	CYP2D6,TPMT	INDETERMINATE	UNKNOWN	TPMT Personalized	v1	No	---



#SJAccession=111600407B
#PatientName=Doe, Jane
#DMETfile=DNL_CLIA_272_111600407B.dmet_GT.txt
#DNL ID=DNL_272
#PatientID=33337
#SampleType=Blood
#TranslationFile=DMET_Plus.v1.20110329.translation
#AnnotationFile=DMET_Plus.v1.20110329.dc_annot.csv
#ReporterBuild=0.11.0
#VerifiedList=VerifiedbyAffy_Mar11 marker list.txt
#GeneSymbol=CYP2D6
#PharmGKBLink=http://www.pharmgkb.org/do/serve?objId=PA128&objCls=Gene
Q-PCR Determined Copy Number 2
Q-PCR Probe ID HS04502391_cn
Called Interpretation Code NC/PRA/NA
Called Diplotypes Possible *2/*6
Called Novel Diplotypes Possible *1/UNK,*2/UNK,*6/UNK,UNK/UNK
Copy Number Corrected Alleles Q-PCR Copy Number = 2, no correction needed.
Number Non-reference Probe Sets 7

Probe Set ID	Affy Verified Call	Contributes To Alleles	Genome Position Description	dbSNP RS ID	Genotype	
AM_12278	N	*29	Ch22:42525134 CYP2D6*29_1659G>A(V136I)	rs61736512	NoCall	-
AM_12276	Y		Ch22:42525086	rs5030655	T/-	Ref/Var

Parse reports for results to extract diplotypes for each gene

Quality Control Steps

Check DMET genotypes against existing genotypes, gene-by-gene

Show 10 entries

Gene	DMET Diplotype	Existing Diplotype	DMET Race	Clinical Race	DMET Gender	Clinical Gender	QC Flag	Suspect QC	EMR Priority	PK
TPMT	*1/*1	G/G|G/G|A/A	white;	white	male?(0)	male	REVIEW	snpchip	ROUTINE	HIG
CYP2D6	(*2/*6)2N	*2A/*6	white;	white	male?(0)	male	REVIEW	snpchip	ROUTINE	
TPMT	*1/*1	G/G|G/G|A/A	white;	white	female(2)	female	REVIEW	CYP2D6	ROUTINE	HIG
CYP2D6	(*10/*41)2N	*41/NEGATIVE	white;	white	female(2)	female	REVIEW	CYP2D6	ROUTINE	
CYP2D6	(*2/*2)3N	*2A/*2A	white;	white	male?(0)	male	REVIEW	CYP2D6	PRIORITY	
TPMT	*1/*3A,*3B/*3C	G/G|A/G|A/G	white;	white	male?(0)	male	REVIEW	CYP2D6	PRIORITY	INTI A
CYP2D6	(*2/*9)2N	*2A/*9	white;	white	female(3)	female	PASS		ROUTINE	
TPMT	*1/*1	G/G|G/G|A/A	white;	white	female(3)	female	PASS		ROUTINE	HIG
TPMT	*1/*1	None	white;	unknown	male?(0)	male	REVIEW	race	ROUTINE	HIG
CYP2D6	(*1/*41)2N	None	white;	unknown	male?(0)	male	REVIEW	race	ROUTINE	

Quality Control Steps

Check DMET gender against self-declared gender

Show 10 entries

Gene	DMET Diplotype	Existing Diplotype	DMET Race	Clinical Race	DMET Gender	Clinical Gender	QC Flag	Suspect QC	EMR Priority	PK
TPMT	*1/*1	G/G|G/G|A/A	white;	white	male?(0)	male	REVIEW	snpchip	ROUTINE	HIG
CYP2D6	(*2/*6)2N	*2A/*6	white;	white	male?(0)	male	REVIEW	snpchip	ROUTINE	
TPMT	*1/*1	G/G|G/G|A/A	white;	white	female(2)	female	REVIEW	CYP2D6	ROUTINE	HIG
CYP2D6	(*10/*41)2N	*41/NEGATIVE	white;	white	female(2)	female	REVIEW	CYP2D6	ROUTINE	
CYP2D6	(*2/*2)3N	*2A/*2A	white;	white	male?(0)	male	REVIEW	CYP2D6	PRIORITY	
TPMT	*1/*3A,*3B/*3C	G/G|A/G|A/G	white;	white	male?(0)	male	REVIEW	CYP2D6	PRIORITY	INTI A
CYP2D6	(*2/*9)2N	*2A/*9	white;	white	female(3)	female	PASS		ROUTINE	
TPMT	*1/*1	G/G|G/G|A/A	white;	white	female(3)	female	PASS		ROUTINE	HIG
TPMT	*1/*1	None	white;	unknown	male?(0)	male	REVIEW	race	ROUTINE	HIG
CYP2D6	(*1/*41)2N	None	white;	unknown	male?(0)	male	REVIEW	race	ROUTINE	

PG4KIDS: DMET Tracker

All Results | View by Batch | Shipping & Receiving | Weekly Specimen Manifest | Diplotype Freq | Documentation | Log out

- **Batch ID:** 44
- **Receipt Date:** Aug. 11, 2011
- **Patient Number:** [redacted]
- **Accession Number:** [redacted]
- **Tube Number:** [redacted]

- **DMET chrX hets:** 0
- **DMET call rates:** 0.995844
- **DMET vs SNPCHIP:** None

- **Clinical Sex:** male
- **DMET Race:** black;
- **Clinical Race:** multiple race (nos)

- **Gene:** CYP2D6
- **DMET Diplotype:** (*2/*2)2N [lookup]
- **Clinical Diplotype:** *2A/*2A
- **Cross Ref Version:** 1
- **EMR Priority:** ROUTINE
- **EMR Flag:** 0
- **PK Phenotype:** EM
- **Consult:** 2D6 EM Wt/Wt
- **Consult Process:** 0

- **Genotype QC FLAG:** REVIEW
  - **Passed:** CYP2D6,gender,TPMT,callrate
  - **Suspect:** race
  - **Not Available:** snpchip

- **Upload Status :** None
- **Approved By:** None
- **Approval Date:** None

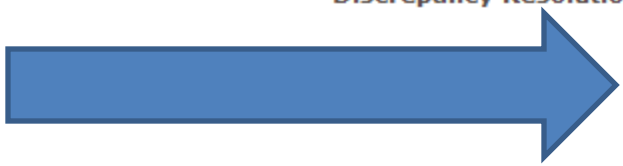
Re-calculate EMR Flag and PK Phenotype by selecting a cross-ref version (v1, 2011-10-13) and cli

Click here to compose an email about this result.

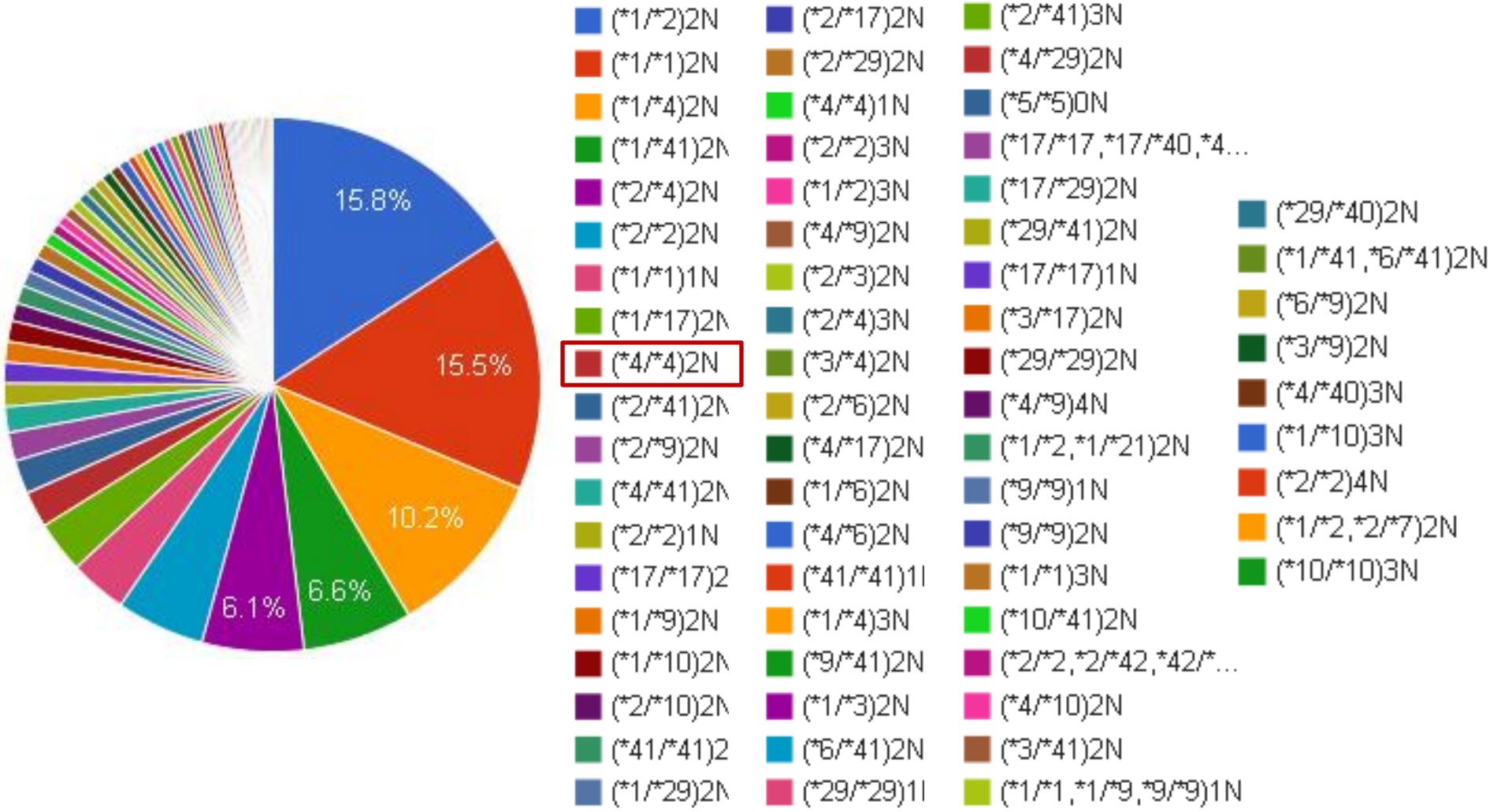
Discrepancy Resolution: None

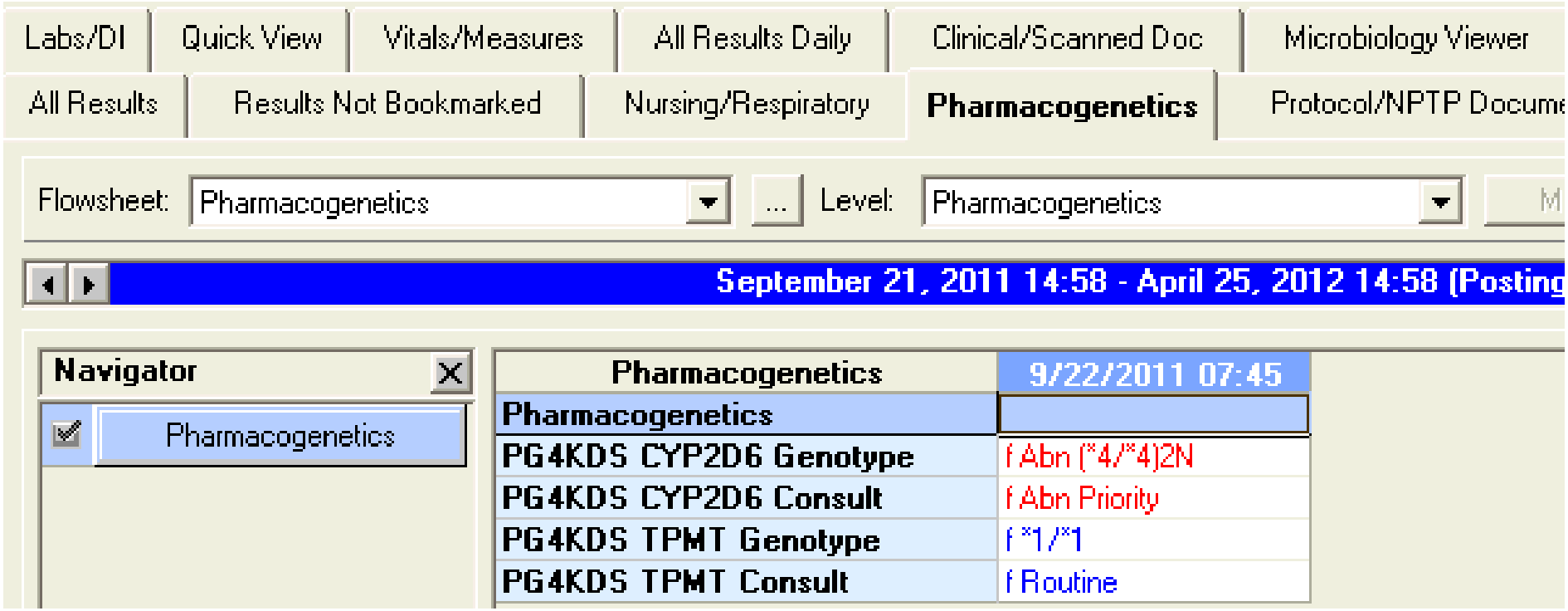
save your changes?

Discrepancy Resolution



101 unique *CYP2D6* diplotypes observed in 732 patients




Labs/DI
Quick View
Vitals/Measures
All Results Daily
Clinical/Scanned Doc
Microbiology Viewer
All Results
Results Not Bookmarked
Nursing/Respiratory
Pharmacogenetics
Protocol/NPTP Docume
Flowsheet:
Pharmacogenetics
...
Level:
Pharmacogenetics
September 21, 2011 14:58 - April 25, 2012 14:58 (Posting
Navigator
Pharmacogenetics
Pharmacogenetics
9/22/2011 07:45
Pharmacogenetics
PG4KDS CYP2D6 Genotype
f Abn (*4/*4)2N
PG4KDS CYP2D6 Consult
f Abn Priority
PG4KDS TPMT Genotype
f *1/*1
PG4KDS TPMT Consult
f Routine

Translate diplotypes into phenotypes

Diplotype in Milli (Result)	Activity Score	Phenotype	Problem List Entry
(*5/*5)0N	0.0	PM	CYP2D6 - Poor Metabolizer
(*1/*1)1N	1.0	EM	None
(*2/*2)1N	1.0	EM	None
(*1/*1,*1/*9,*9/*9)1N	1.0 or 0.5	EM or IM	CYP2D6 - Possible Intermediate Metabolizer
(*41/*41)1N	0.5	IM	CYP2D6 - Intermediate Metabolizer
(*17/*17,*17/*40,*40/*40)1N	0.5 or 0.0	IM or PM	CYP2D6 - Possible Poor Metabolizer
(*4/*4)1N	0.0	PM	CYP2D6 - Poor Metabolizer
(*1/*1)2N	2.0	EM	None
(*1/*10)2N	1.5	EM	None
(*1/*17)2N	1.5	EM	None
(*1/*2)2N	2.0	EM	None
(*1/*2,*2/*7)2N	2.0 or 1.0	EM	None
(*1/*3)2N	1.0	EM	None
(*1/*4)2N	1.0	EM	None
(*1/*41)2N	1.5	EM	None
(*1/*6)2N	1.0	EM	None
(*1/*9)2N	1.5	EM	None
(*10/*41)2N	1.0	EM	None
(*17/*17)2N	1.0	EM	None
(*2/*10)2N	1.5	EM	None
(*2/*2)2N	2.0	EM	None
(*2/*29)2N	1.5	EM	None
(*2/*3)2N	1.0	EM	None
(*2/*4)2N	1.0	EM	None

Translational Pharmacogenetics Project (TPP) Look Up Tables By Gene

The Translational Pharmacogenetics Project (TPP) is a PGRN-led initiative with the goal to operationalize the work of CPIC by translating widely accepted actionable pharmacogenetics discoveries into real-world clinical practice.

TPP creates "look up" tables by gene which contain phenotype and clinical decision support system information based on haplotypes and diplotypes. These tables are a work in progress and are offered on PharmGKB "as is" until the tables become formalized.

Gene	Table	Publication Link
CYP2D6	CYP2D6 lookup table	A Clinician-Driven Automated System for Integration of Pharmacogenetic Interpretations Into an Electronic Medical Record.
TPMT	TPMT lookup table	A Clinician-Driven Automated System for Integration of Pharmacogenetic Interpretations Into an Electronic Medical Record.
CYP2C19	CYP2C19 lookup table	

The Translational Pharmacogenetics Project (TPP) Includes:

- **St. Jude**
- **Vanderbilt University**
- **University of Florida**
- **University of Maryland**
- **Ohio State University**
- **Mayo Clinic**

Consult Builder

A Clinician-Driven Automated System for Integration of Pharmacogenetic Interpretations Into an Electronic Medical Record

JK Hicks[1], KR Crews[1], JM Hoffman[1], NM Kornegay[1], MR Wilkinson[1], R Lorier[2], A Stoddard[2], W Yang[1], C Smith[1], CA Fernandez[1], SJ Cross[1], C Haidar[1], DK Baker[3], SC Howard[3], WE Evans[1], U Broeckel[2] and MV Relling[1]

CLINICAL PHARMACOLOGY & THERAPEUTICS

Deconstruct the consult into sections; scalable to add additional diplotypes

PHARMACOGENETICS CONSULT FOR
CYP2D6 GENOTYPE

Sample for CYP2D6 Genotype Obtained: 9/22/2011
PG4KDS CYP2D6 Genotype Result: (*1/*1)2N

Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of CYP2D6 substrates.

This result signifies that the patient has two copies of a wild-type (normal function) allele. The expected phenotype suggests that there is no reason to selectively adjust the dose of most medications (including codeine) that are metabolized by the CYP2D6 enzyme pathway. The diplotype result equates to a CYP2D6 activity score of 2. For more information about specific medications metabolized by CYP2D6, please go to www.stjude.org/pg4kds.

Comments: none
Jane Smith, Pharm.D., pager 1234

Phenotype Assignment (6 versions)

Diplotype Interpretation (32 versions)

Dosing Recommendations (6 versions)

Activity Score (11 versions)

Educational Link

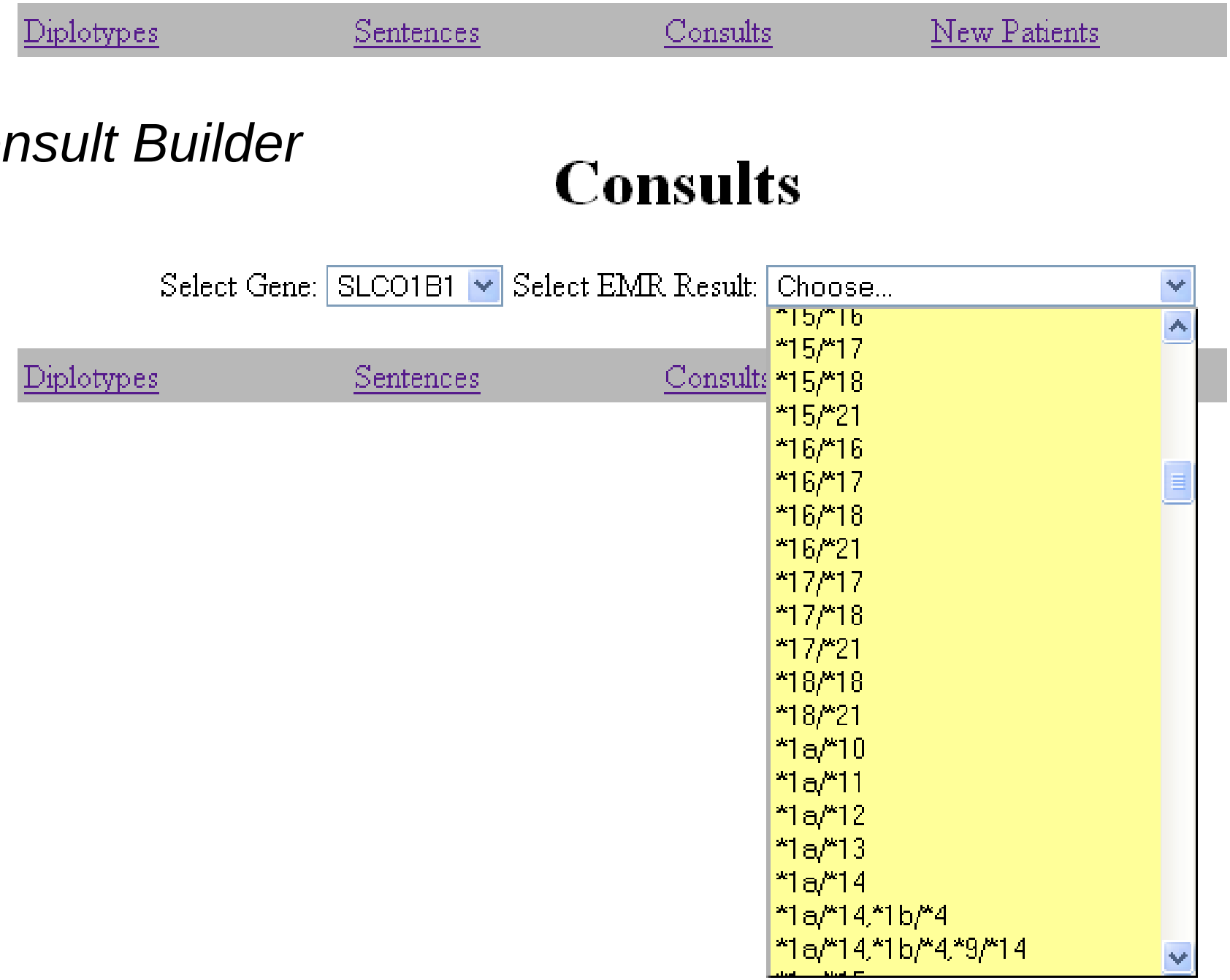
Hicks et al (CPT 2012)

Consult Builder

Diplotypes

Select Gene: CYP2D6 If a consult has a working copy, only shov

Status	Copy Nbr.	Diplotype	EMR Result	EMR Result Display	Activity Score	Phenotype	Consult Title
Approved	1	*1/*5	(*1/*1)1N	(*1/*1)1N	1.0	EM	2D6 EM 1/5
Approved	2	*1/*1	(*1/*1)2N	(*1/*1)2N	2.0	EM	2D6 EM Wt/Wt
Approved	3	*1/*1	(*1/*1)3N	(*1/*1)3N	3.0	UM	2D6 UM Wt/Wt xN
Approved	CNBD	*1/*1	(*1/*1)CNBDN	(*1/*1)CNBDN	Unknown	Indeterminate	CYP2D6 Genotype Failure
Approved	1	*1/*1,*1/*9,*9/*9	(*1/*1,*1/*9,*9/*9)1N	See Comments	1.0 or 0.5	EM or IM	CYP2D6 ambiguous result
Approved	2	*1/*10	(*1/*10)2N	(*1/*10)2N	1.5	EM	2D6 EM Wt/RF
Approved	3	*1/*10	(*1/*10)3N	(*1/*10)3N	2.5 or 2.0	UM or EM	2D6 EM/UM Wt/RF 3N
Approved	2	*1/16	(*1/*16)2N	(*1/*16)2N	1.0	EM	2D6 EM Wt/NF
Approved	2	*1/*17	(*1/*17)2N	(*1/*17)2N	1.5	EM	2D6 EM Wt/RF


Diplotypes
Sentences
Consults
New Patients
Consult Builder
Consults
Select Gene:
SLCO1B1
Select EMR Result:
Choose...
*15/*16
*15/*17
*15/*18
*15/*21
*16/*16
*16/*17
*16/*18
*16/*21
*17/*17
*17/*18
*17/*21
*18/*18
*18/*21
*1a/*10
*1a/*11
*1a/*12
*1a/*13
*1a/*14
*1a/*14,*1b/*4
*1a/*14,*1b/*4,*9/*14
Diplotypes
Sentences
Consults

Consult Builder

Consults

Select Gene: TPMT Select EMR Result: Choose...

Diplotypes Sentences Consults

- Choose...
- *1/*1
- *1/*1,*1/*2,*2/*2
- *1/*2
- *1/*24
- *1/*3A,*3B/*3C
- *1/*3B
- *1/*3C
- *1/*3D
- *1/*4
- *1/*8
- *2/*2
- *2/*3A
- *2/*3B
- *2/*3C
- *2/*4
- *24/*24
- *3A/*24
- *3A/*3A
- *3A/*3B

Diplotypes Sentences Consults New Patients

Consult Builder

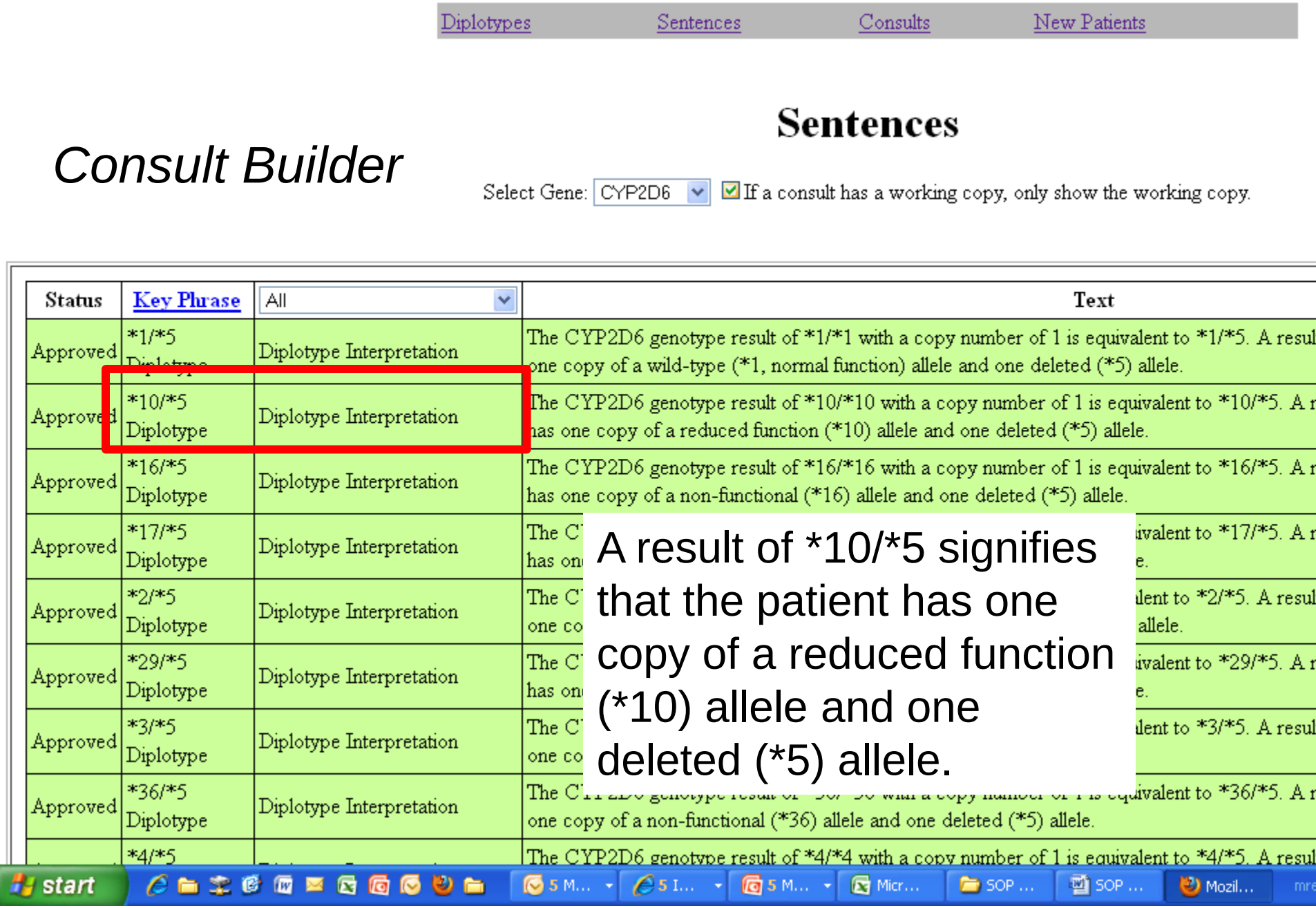
Consults

Select Gene: CYP2D6 Select EMR Result: Choose...

Diplotypes Sentences Consults

- Choose...
- (*1/*1)1N
- (*1/*1)2N
- (*1/*1)3N
- (*1/*1)CNBDN
- (*1/*1,*1/*9,*9/*9)1N
- (*1/*10)2N
- (*1/*10)3N
- (*1/*16)2N
- (*1/*17)2N
- (*1/*2)2N
- (*1/*2)3N
- (*1/*2,*2/*7)2N
- (*1/*29)2N
- (*1/*3)2N
- (*1/*36)2N
- (*1/*4)2N
- (*1/*4)3N
- (*1/*40)2N
- (*1/*41)2N

Consult Builder



A result of *10/*5 signifies that the patient has one copy of a reduced function (*10) allele and one deleted (*5) allele.

CLINICAL PHARMACOLOGY & THERAPEUTICS

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of *Cytochrome P450 2D6* (*CYP2D6*) Genotype

KR Crews[1], A Gaedigk[2], HM Dunnenberger[3], TE Klein[4], DD Shen[5,6], JT Callaghan[7,8], ED Kharasch[9] and TC Skaar[7]

Table 1. Assignment of phenotypes based on *CYP2D6* diplotypes

Likely phenotype [a]	**Activity Score**	**Genotypes**	**Examples of diplotypes**
Ultrarapid metabolizer (~1-2% of patients)	>2.0	An individual carrying more than two copies of functional alleles	**1/*1xN, *1/*2xN*
Extensive metabolizer (~77-92% of patients)	1.0-2.0	An individual carrying two alleles encoding full or reduced function; or one full function allele together with either one non-functional or one reduced function allele	**1/*1, *1/*2, *2/*2, *1/*41,*1/*4,*2/*5, *10/*10*
Intermediate metabolizer (~2-11% of patients)	0.5	An individual carrying one reduced and one non-functional allele	**4/*10, *5/*41*
Poor metabolizer (~5-10% of patients)	0	An individual carrying no functional alleles	**4/*4, *4/*5, *5/*5, *4/*6*

Tables for database for all versions of sentences for each part of the Consult

PHARMACOGENETICS CONSULT FOR
CYP2D6 GENOTYPE

Sample for CYP2D6 Genotype Obtained: 9/22/2011
PG4KDS CYP2D6 Genotype Result: (*1/*1)2N

Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of CYP2D6 substrates.

This result signifies that the patient has two copies of a wild-type (normal function) allele. The expected phenotype suggests that there is no reason to selectively adjust the dose of most medications (including codeine) that are metabolized by the CYP2D6 enzyme pathway. The diplotype result equates to a CYP2D6 activity score of 2. For more information about specific medications metabolized by CYP2D6, please go to www.stjude.org/pg4kds.

Comments: none
Jane Smith, Pharm.D., pager 1234

Phenotype Assignment (6 versions)

Diplotype Interpretation (32 versions)

Dosing Recommendations (6 versions)

Activity Score (11 versions)

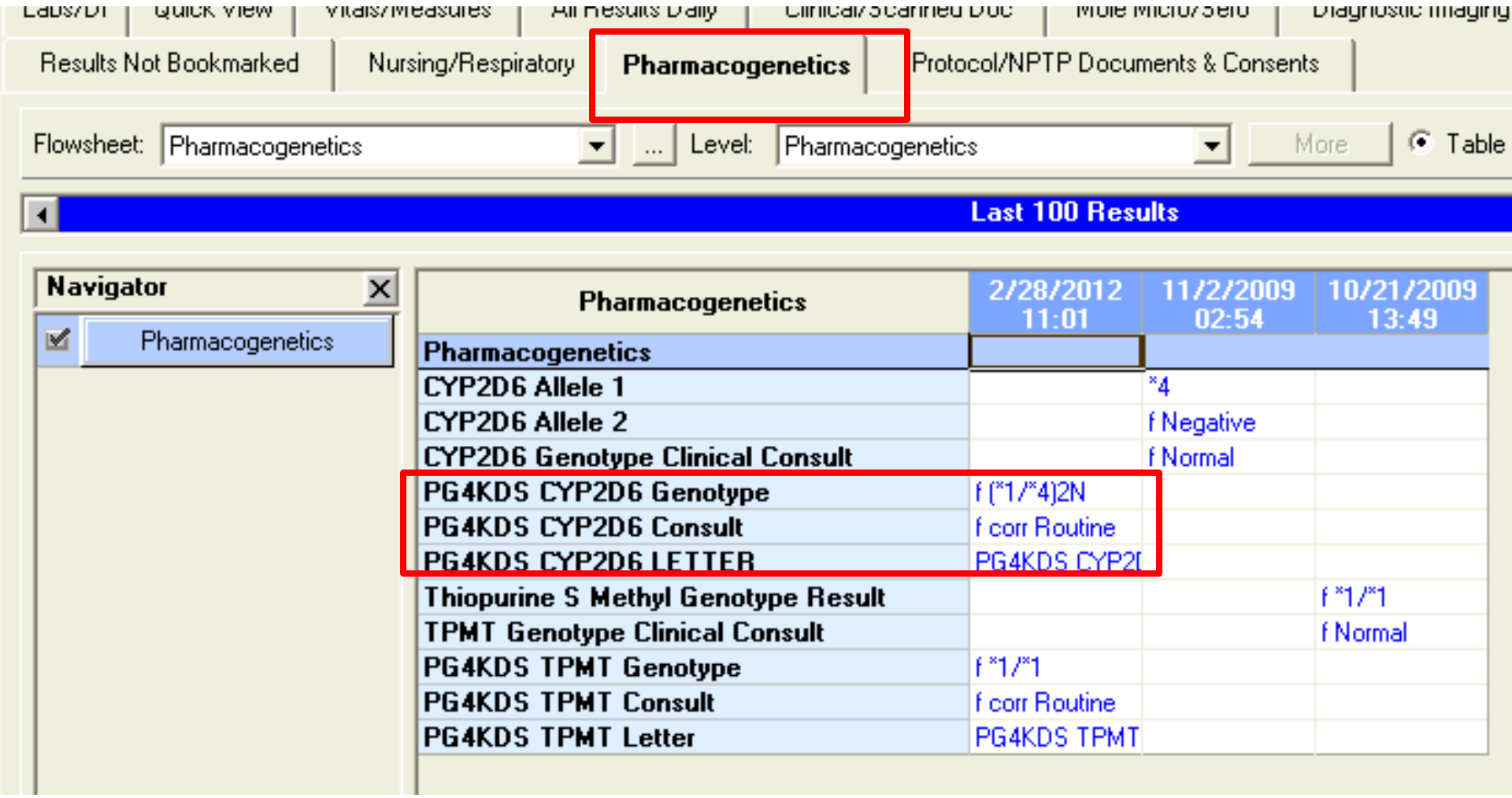
Educational Link

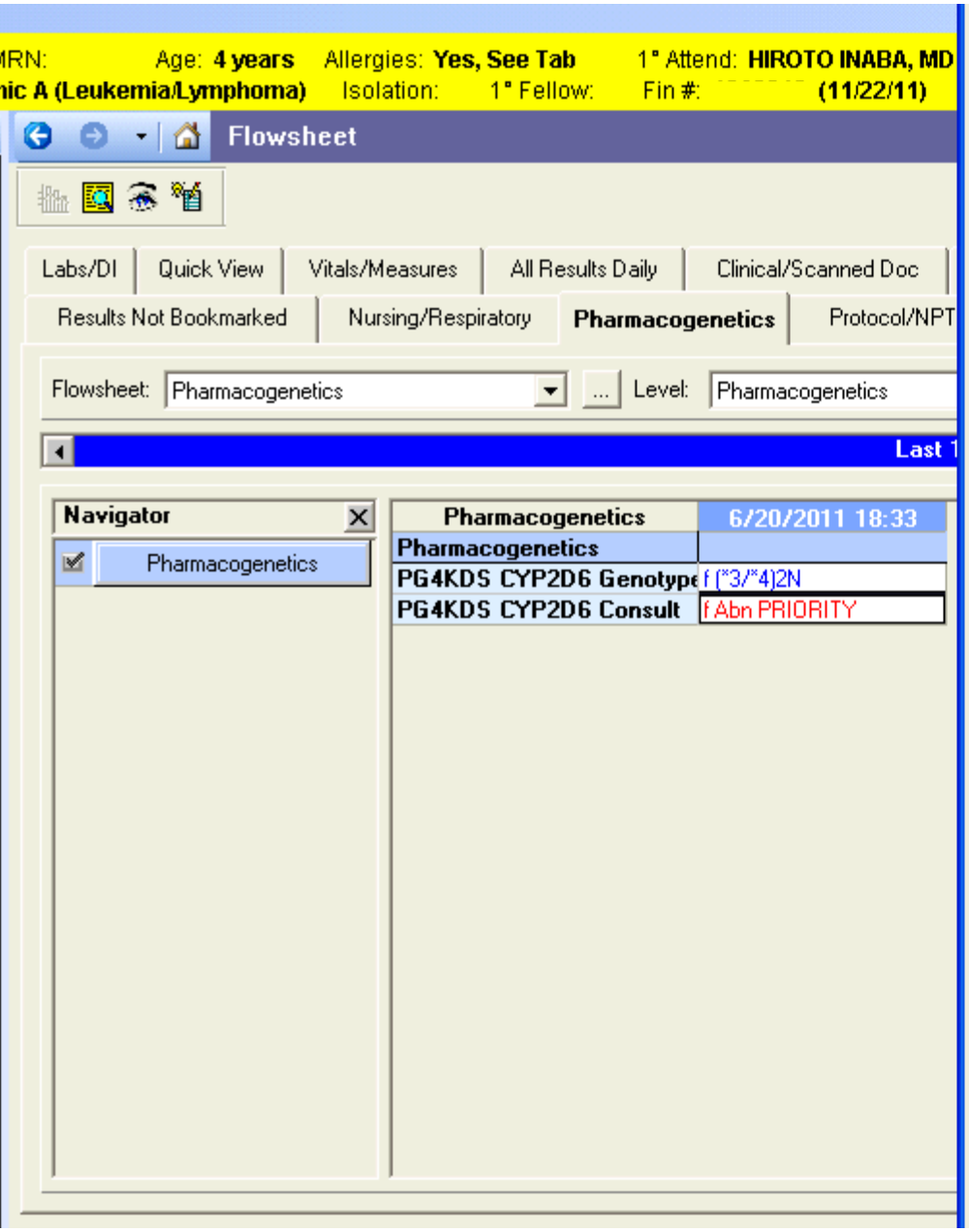
Hicks et al (CPT 2012)

CYP2D6 Look-Up Table						
Result in EMR	**Consult Type**	**EMR Flag (Color)**	**Consult Priority**	**Phenotype**	**EMR Problem List Entry**	**Modular Section Code**
(*4/*4)2N	Automatic	Abnormal	Priority	PM	CYP2D6 - Poor Metabolizer	1C, 2GG, 3U, 4R, 5CCC, 6GGG
(*1/*1)1N	Automatic	Normal	Routine	EM	None	1A, 2W, 3S, 4P,5CCC, 6GGG
(*2/*2)1N	Automatic	Normal	Routine	EM	None	1A, 2X, 3S, 4P, 5CCC, 6GGG
(*1/*1,*1/*9,*9/*9)1N	Personalized	Normal	Routine	EM or IM	None	3DDD, 5CCC, 6GGG
(*41/*41)1N	Automatic	Normal	Routine	IM	None	1B, 2CC, 3T, 4Q, 5CCC, 6GGG
(*17/*17,*17/*40,*40/*40)1N	Personalized	Abnormal	Priority	IM or PM	CYP2D6 - Possible Poor Metabolizer	3DDD, 5CCC, 6GGG
(*4/*4)1N	Automatic	Abnormal	Priority	PM	CYP2D6 - Poor Metabolizer	1C, 2FF, 3U, 4R, 5CCC, 6GGG
(*1/*1)2N	Automatic	Normal	Routine	EM	None	1A, 2E, 3S, 4N, 5CCC, 6GGG
(*1/*10)2N	Automatic	Normal	Routine	EM	None	1A, 2F, 3S, 4O, 5CCC, 6GGG
(*1/*17)2N	Automatic	Normal	Routine	EM	None	1A, 2F, 3S, 4O, 5CCC, 6GGG
(*1/*2)2N	Automatic	Normal	Routine	EM	None	1A, 2E, 3S, 4N, 5CCC, 6GGG
(*1/*2,*2/*7)2N	Personalized	Normal	Routine	EM	None	1A, 2HHH, 3S, 4XX, 5CCC, 6GGG
(*1/*3)2N	Automatic	Normal	Routine	EM	None	1A, 2G, 3S, 4P, 5CCC, 6GGG
(*1/*4)2N	Automatic	Normal	Routine	EM	None	1A, 2G, 3S, 4P, 5CCC, 6GGG
(*1/*41)2N	Automatic	Normal	Routine	EM	None	1A, 2F, 3S, 4O, 5CCC, 6GGG
(*1/*6)2N	Automatic	Normal	Routine	EM	None	1A, 2G, 3S, 4P, 5CCC, 6GGG
(*1/*9)2N	Automatic	Normal	Routine	EM	None	1A, 2F, 3S, 4O, 5CCC, 6GGG
(*10/*41)2N	Automatic	Normal	Routine	EM	None	1A, 2H, 3S, 4P, 5CCC, 6GGG
(*17/*17)2N	Automatic	Normal	Routine	EM	None	1A, 2H, 3S, 4P, 5CCC, 6GGG

Based on observed and possible reported test results 187 *CYP2D6* consultations have been built

Pharmacogenetics tab added to EMR; all clinically eligible genotypes are entered, along with a gene-specific consult and letter to patient





Value	Valid From	Valid Until
PRIORITY	11/28/2011 15:16	Current

Result | Specimen | Comments | Action List

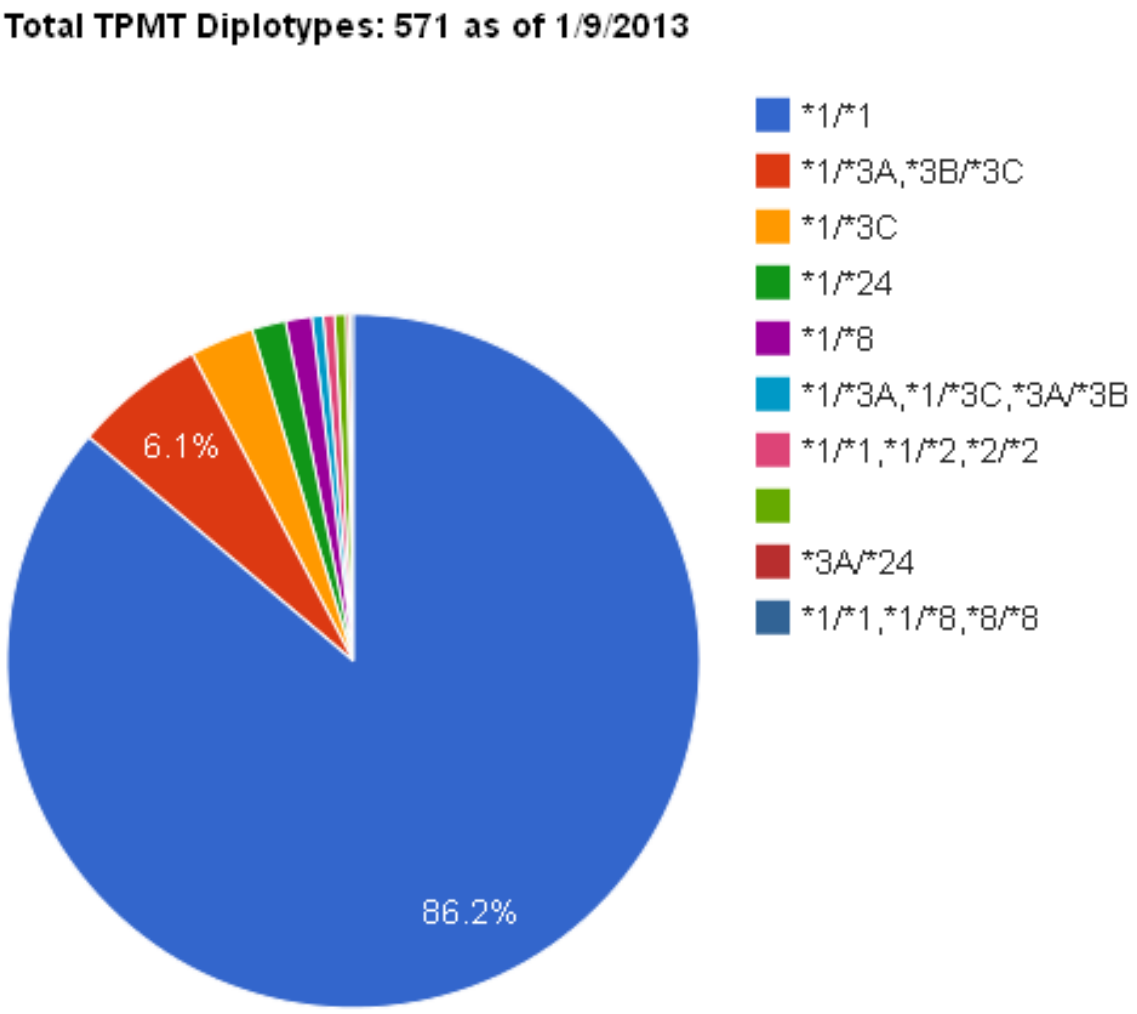
```
***PHARMACOGENETICS CONSULT FOR***
*CYP2D6 GENOTYPE*

Sample for CYP2D6 Genotype Obtained: 06/20/11
PG4KDS CYP2D6 Genotype Result: (*3/*4)2N

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 non-functional 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. The diplotype
result yields a CYP2D6 activity score of 0. For more
information about specific medications metabolized by
CYP2D6, please go to www.stjude.org/pg4kds.

Shane Cross, PharmD, pager 0920

2D6 PM NF/NF 1-20111005
```

257182899 Forward... Print... Close

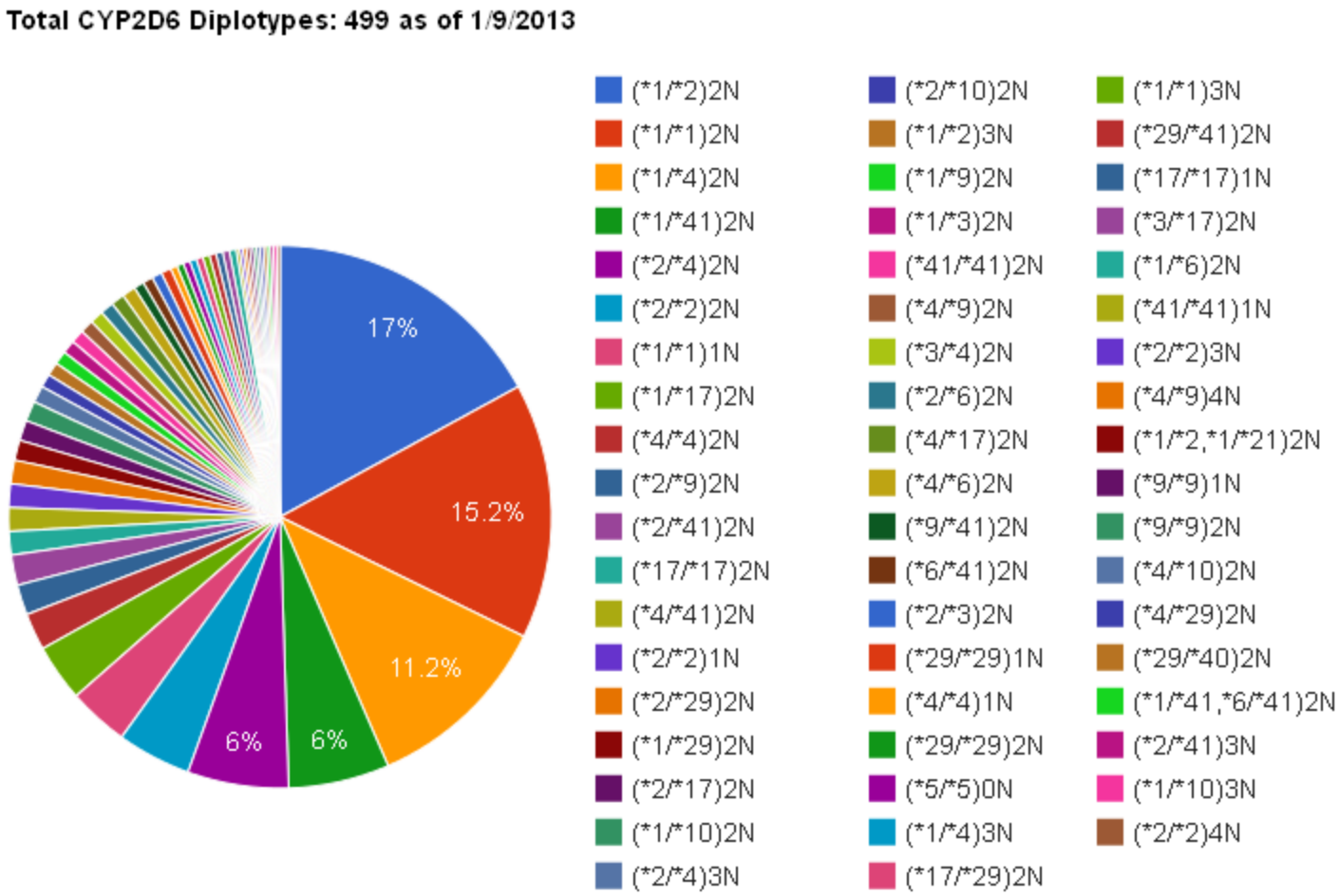
Will need to repeat this process of translation for each new gene

Name	Date modified	Size	Type
DMET_STJUDE_305_111990741B_ABCB1.txt	8/16/2011 9:51 AM	4 KB	Text Document
DMET_STJUDE_305_111990741B_ABCB4.txt	8/16/2011 9:51 AM	3 KB	Text Document
DMET_STJUDE_305_111990741B_ABCB7.txt	8/16/2011 9:51 AM	2 KB	Text Document
DMET_STJUDE_305_111990741B_ABCB11.txt	8/16/2011 9:51 AM	4 KB	Text Document
DMET_STJUDE_305_111990741B_ABCC1.txt	8/16/2011 9:51 AM	2 KB	Text Document
DMET_STJUDE_305_111990741B_ABCC2.txt	8/16/2011 9:51 AM	5 KB	Text Document
DMET_STJUDE_305_111990741B_ABCC3.txt	8/16/2011 9:51 AM	2 KB	Text Document
DMET_STJUDE_305_111990741B_ABCC4.txt	8/16/2011 9:51 AM	2 KB	Text Document
DMET_STJUDE_305_111990741B_ABCC5.txt	8/16/2011 9:51 AM	2 KB	Text Document
DMET_STJUDE_305_111990741B_ABCC6.txt	8/16/2011 9:51 AM	2 KB	Text Document
DMET_STJUDE_305_111990741B_ABCC8.txt	8/16/2011 9:51 AM	2 KB	Text Document
DMET_STJUDE_305_111990741B_ABCC9.txt	8/16/2011 9:51 AM	2 KB	Text Document
DMET_STJUDE_305_111990741B_ABCG1.txt	8/16/2011 9:51 AM	2 KB	Text Document
DMET_STJUDE_305_111990741B_ABCG2.txt	8/16/2011 9:51 AM	2 KB	Text Document
DMET_STJUDE_305_111990741B_ABP1.txt	8/16/2011 9:51 AM	2 KB	Text Document
DMET_STJUDE_305_111990741B_ADH1A.txt	8/16/2011 9:51 AM	2 KB	Text Document
DMET_STJUDE_305_111990741B_ADH1B.txt	8/16/2011 9:51 AM	2 KB	Text Document
DMET_STJUDE_305_111990741B_ADH1C.txt	8/16/2011 9:51 AM	1 KB	Text Document
DMET_STJUDE_305_111990741B_ADH4.txt	8/16/2011 9:51 AM	2 KB	Text Document
DMET_STJUDE_305_111990741B_ADH5.txt	8/16/2011 9:51 AM	1 KB	Text Document
DMET_STJUDE_305_111990741B_ADH6.txt	8/16/2011 9:51 AM	2 KB	Text Document
DMET_STJUDE_305_111990741B_ADH7.txt	8/16/2011 9:51 AM	1 KB	Text Document
DMET_STJUDE_305_111990741B_AHR.txt	8/16/2011 9:51 AM	1 KB	Text Document
DMET_STJUDE_305_111990741B_AKAP9.txt	8/16/2011 9:51 AM	1 KB	Text Document
DMET_STJUDE_305_111990741B_ALB.txt	8/16/2011 9:51 AM	2 KB	Text Document

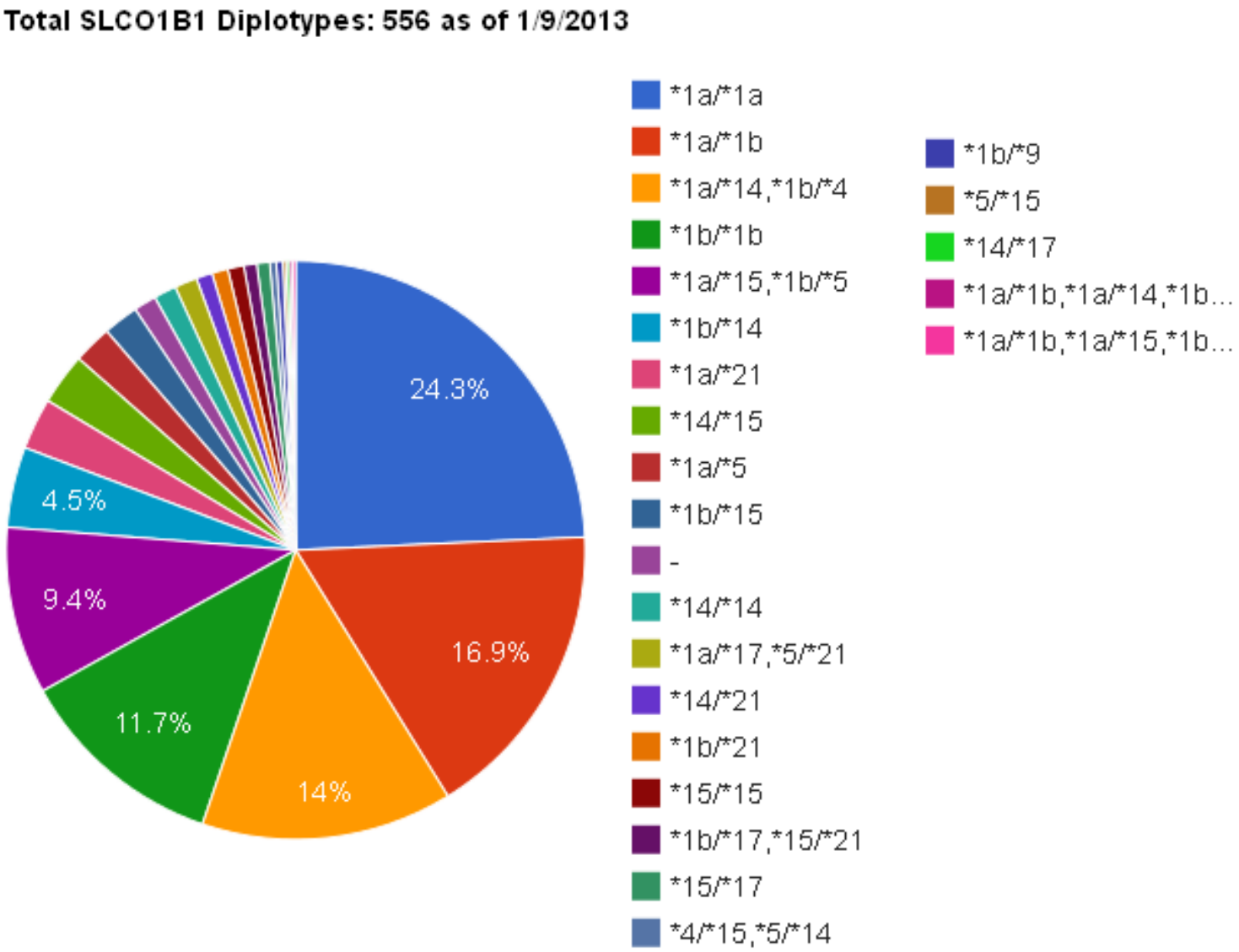
Observed TPMT Diplotypes



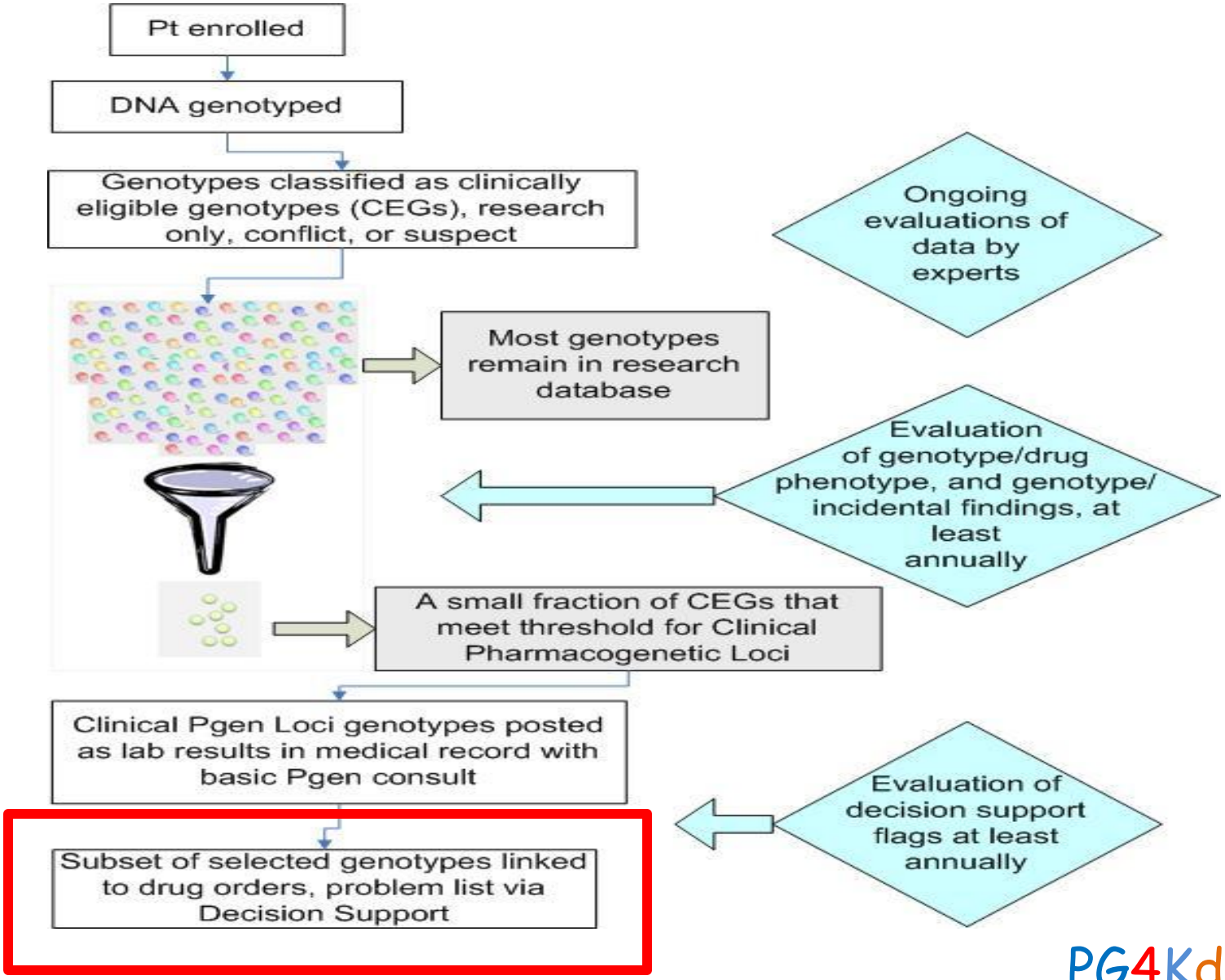
56 *CYP2D6* diplotypes in first 499 pts



SLCO1B1


Total SLCO1B1 Diplotypes: 556 as of 1/9/2013
24.3%
16.9%
14%
11.7%
9.4%
4.5%
*1a/*1a
*1a/*1b
*1a/*14,*1b/*4
*1b/*1b
*1a/*15,*1b/*5
*1b/*14
*1a/*21
*14/*15
*1a/*5
*1b/*15
-
*14/*14
*1a/*17,*5/*21
*14/*21
*1b/*21
*15/*15
*1b/*17,*15/*21
*15/*17
*4/*15,*5/*14
*1b/*9
*5/*15
*14/*17
*1a/*1b,*1a/*14,*1b...
*1a/*1b,*1a/*15,*1b...

The process



PG4Kds

CDS is both passive and active

- Translate Diplotype into phenotype
- Diplotype-specific Priority status (nl/abnl)
- Diplotype-specific Consult/interpretation

→ Passive CDS

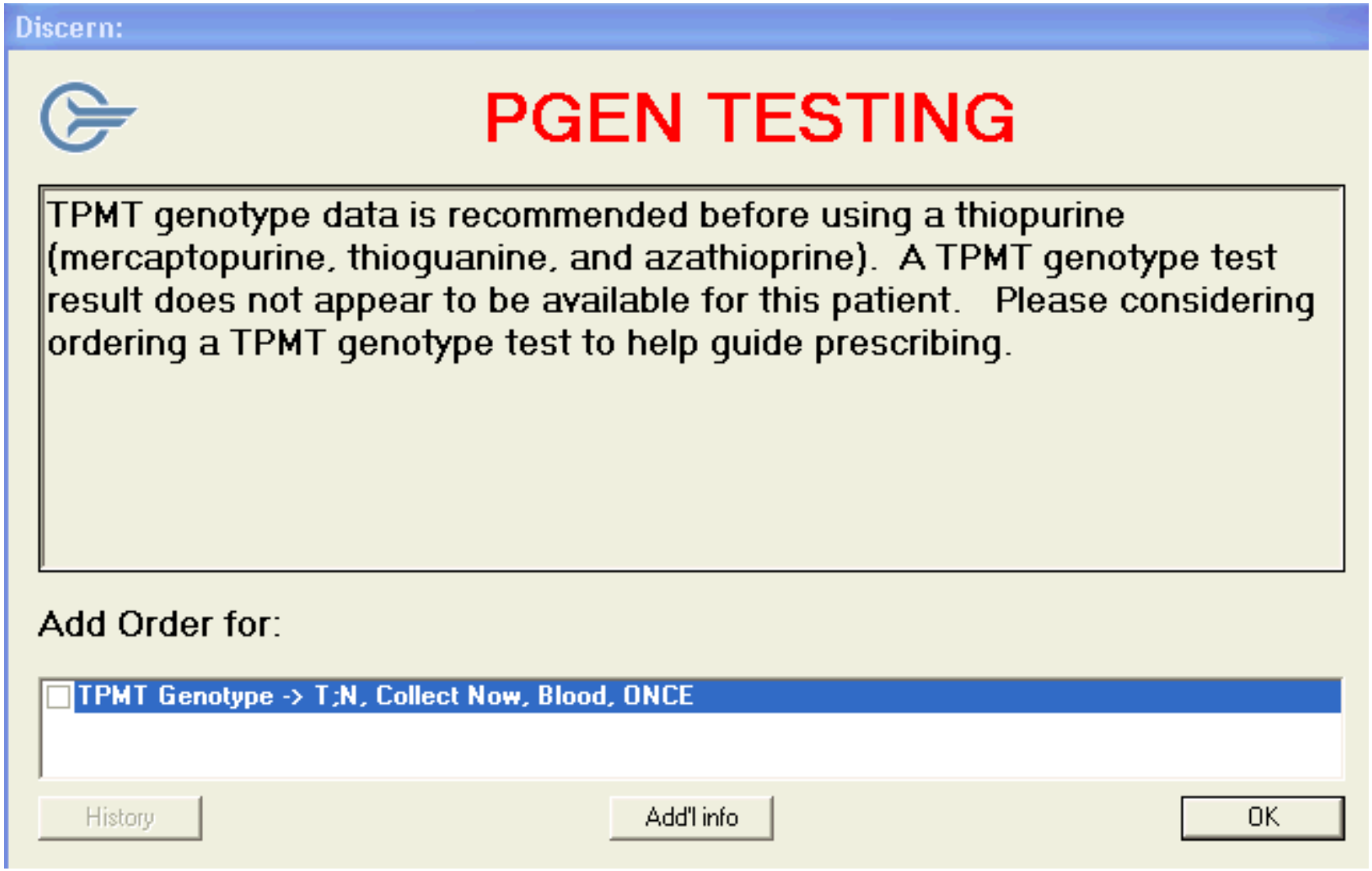
- If applicable: diplotype-specific trigger for active interruptive CDS rules to fire at point-of-care

→ active CDS

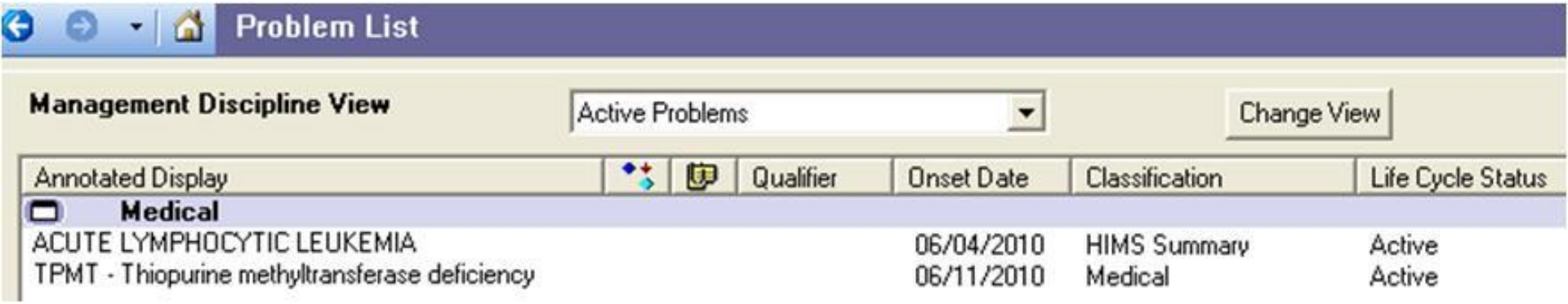
Two types of active CDS alerts delivered via alert to EMR User and/or email

- Pre-genetic test
- Post-genetic test

TPMT Pre-pharmacogenetic test warning: at point of care to prescriber



High-risk diplotypes translated to phenotype, automatically populated into Problem List of EMR



Customized Decision support "behind the scenes":

Links high-risk diplotypes to thiopurine ordering, prescribing, and administration

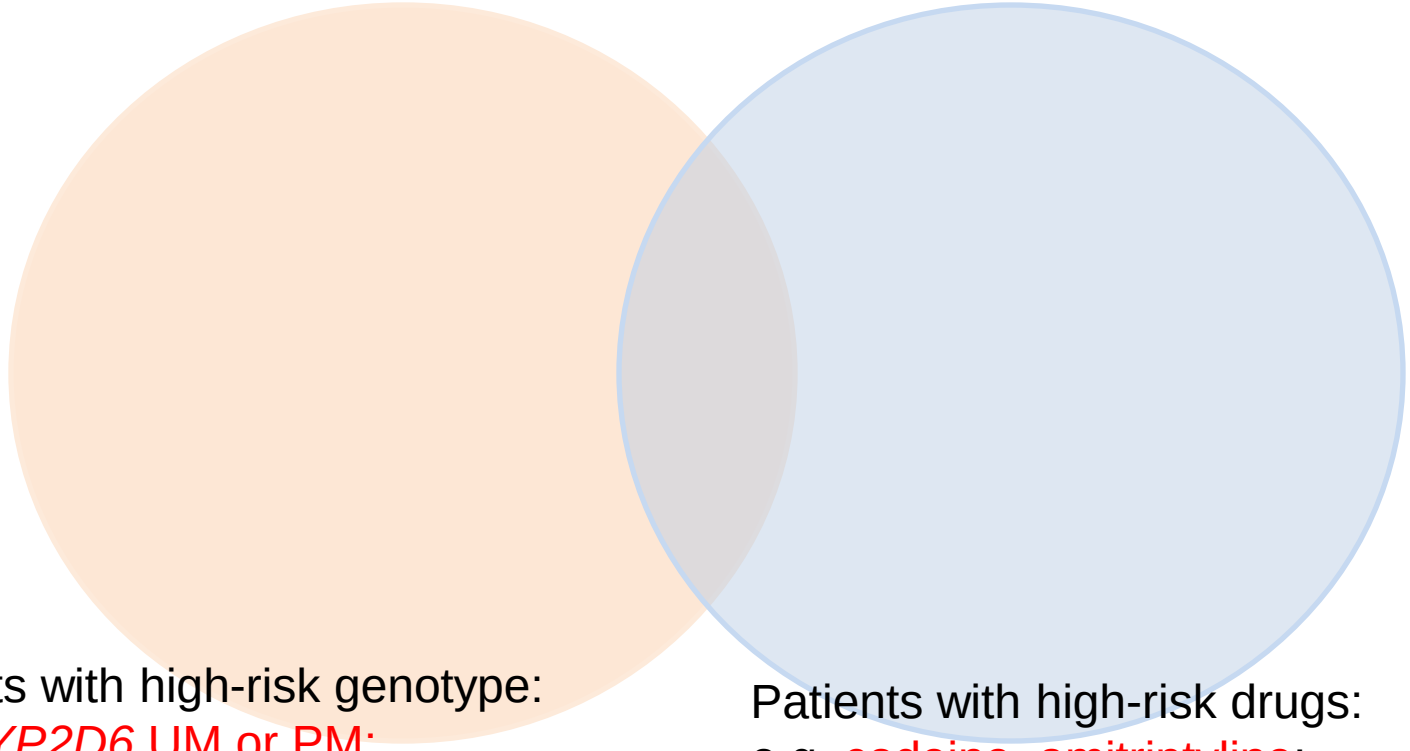
Need standard diagnostic terms

TPMT – SNOMED CT Code
Thiopurine methyltransferase deficiency

vs

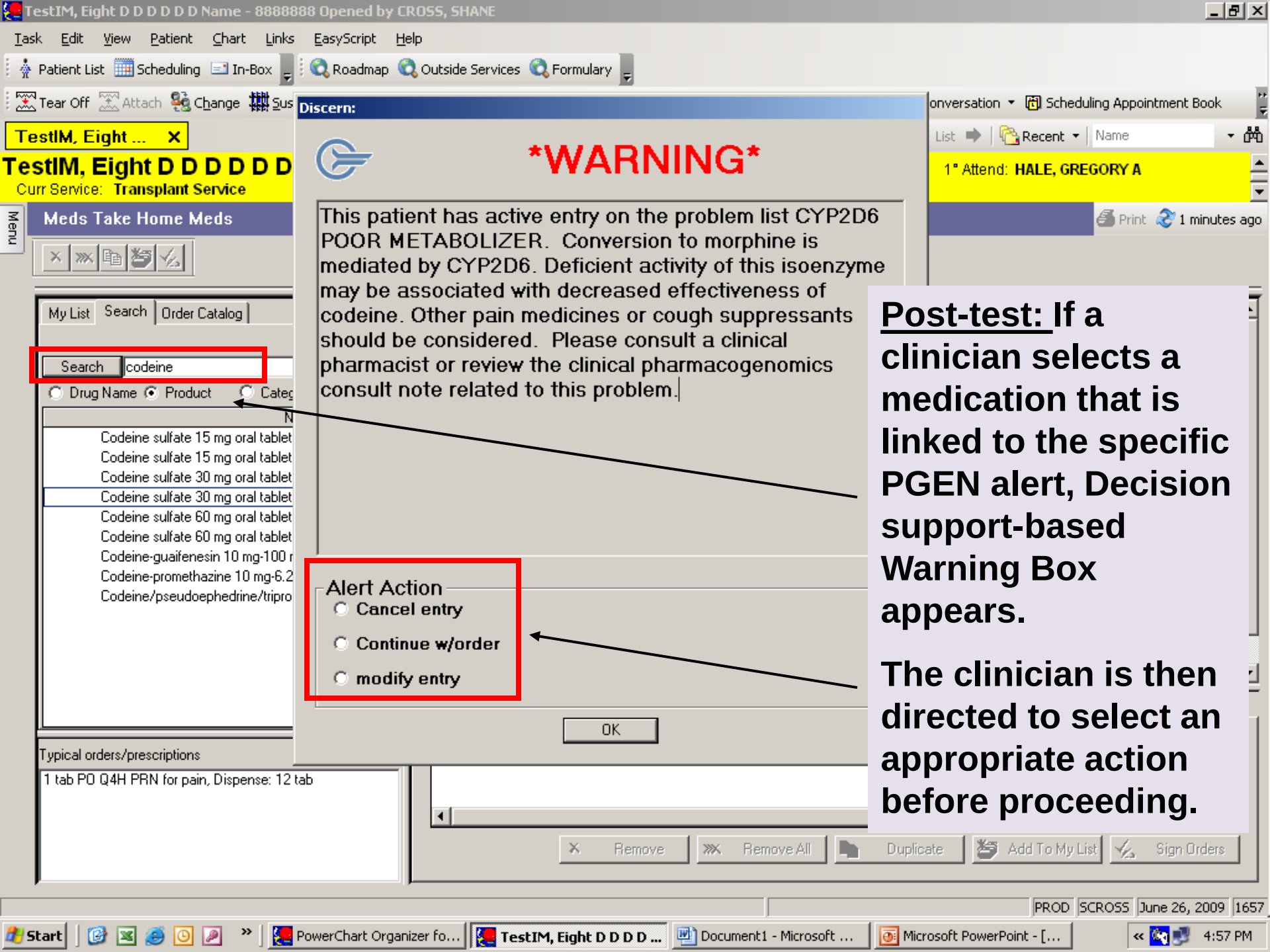
TPMT- St Jude EMR Terms
TPMT - Normal Activity
TPMT - Intermediate Activity
TPMT - Possible Intermediate Activity
TPMT - Low or absent Activity

Post-test: when a high-risk drug collides with a high-risk (priority) genotype, active CDS alerts fire at point of care



Patients with high-risk genotype:
e.g. *CYP2D6* UM or PM;
CYP2C19 PM;
TPMT heterozygote

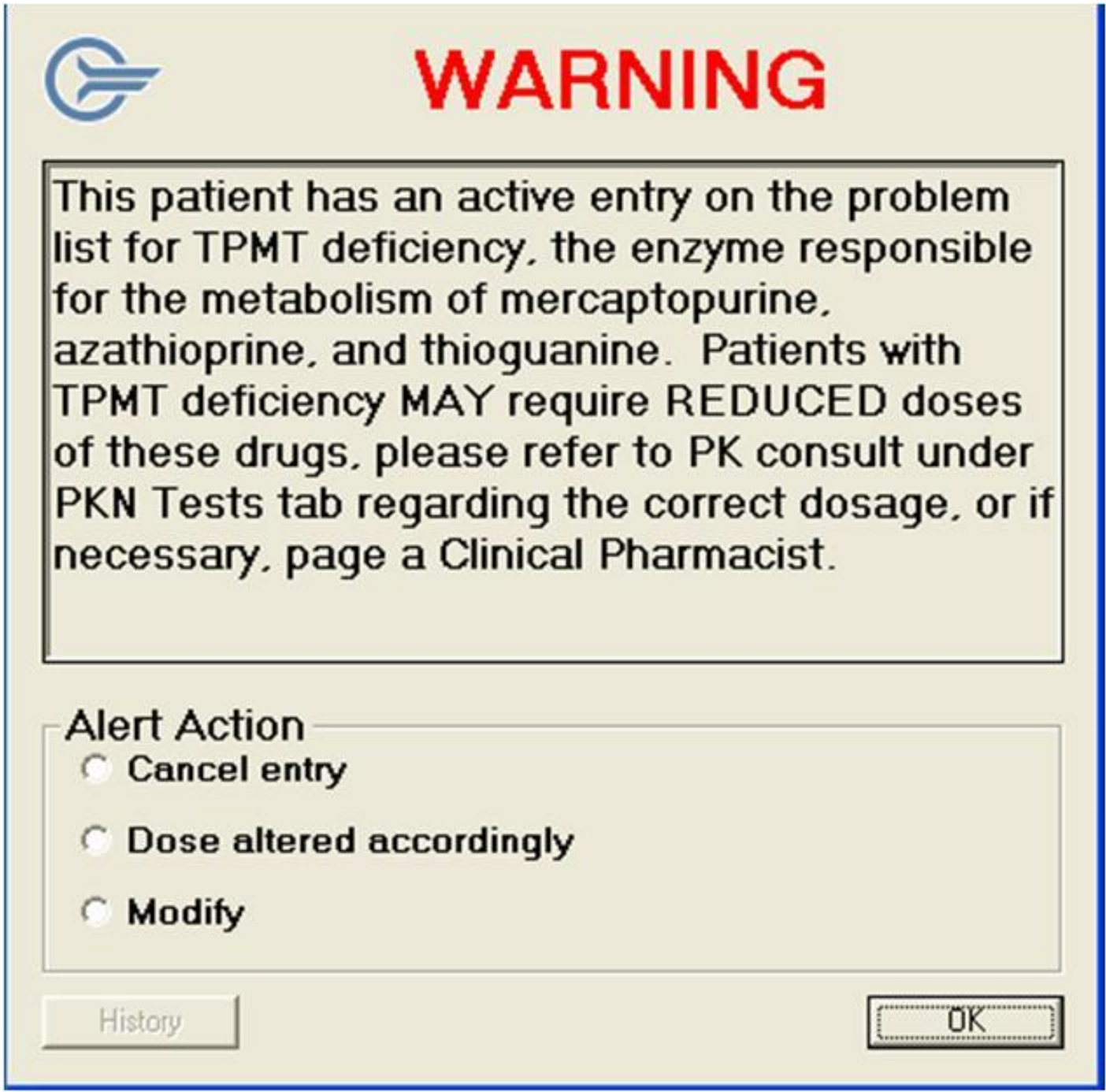
Patients with high-risk drugs:
e.g. codeine, amitriptyline;
clopidogrel
azathioprine



Post-test: If a clinician selects a medication that is linked to the specific PGEN alert, Decision support-based Warning Box appears.

The clinician is then directed to select an appropriate action before proceeding.

Orders for high-risk drugs written for those with high-risk genotype prompts an alert to fire



Delivery of Genetic Information

- Posted to EMR
  - One gene at a time
  - As each gene is prioritized, it moves to EMR for all past and future pts
- Point-of-care decision supported alerts
- Automated email to MD for high risk diplotypes
- Automated letter to participants (their choice)
- General information and video on website

PG4KDS - Priority Genes

Related Topics

Mary V. Relling, PharmD

Protocol: PG4KDS

Video: PGEN4Kids Educational Video

Updated May 2011

Thiopurine Methyltransferase (TPMT)

Thiopurine methyltransferase (TPMT) is an enzyme that breaks down (metabolizes) thiopurines. Thiopurines include three medications: 6- mercaptopurine (6-MP), 6-thioguanine (6-TG), and azathioprine. 6-MP and 6-TG are often used to treat leukemia or lymphoma. Like many drugs, their effectiveness and side effects can vary from person to person. One of the reasons why this difference occurs is because each person's ability to metabolize thiopurines is different based on variations in the TPMT gene. Every person can be classified into one of 3 possible genotype groups. We use a different starting dose of 6-MP and 6-TG for the different genotype groups. By changing the dose based on a patient's genotype, there are fewer side effects (due to low blood counts).

Priority genotypes

- **Heterozygous variant** (intermediate activity) – means there is one normal, functioning copy of the gene and one non-functioning copy of the gene. Patients have reduced TPMT activity and may require reduced doses of thiopurine medications to avoid side effects. About 1 in 10 people have this genotype.
- **Homozygous variant** (low or deficient activity) – means there are two copies of the non-functioning gene and there is no normal TPMT enzyme. These patients are at a very high risk of experiencing toxicity (low blood counts) from 6-MP or 6-TG or azathioprine. Patients should receive substantially lower doses than normal to avoid side effects of low blood counts. About 1 in 400 people have this very high risk priority genotype.

St. Jude Children's Research Hospital

Do you know...

An educational series for patients and their families

Thiopurine methyltransferase (TPMT) and medicines

Description

When you take a medicine (drug), your body has to have a way to handle the medicine. One way is for enzymes to metabolize (break down) the medicine. An enzyme called thiopurine methyltransferase (TPMT) has the ability to break down a class of medicines called thiopurines. Thiopurines include azathioprine (Imuran®), mercaptopurine (6-MP, Purinethol®), and thioguanine (6-TG, Tabloid®).

The thiopurines mercaptopurine and thioguanine are important chemotherapy agents used for the treatment of leukemia. Azathioprine is a medicine used to treat a variety of autoimmune diseases. Like many medicines, how well they work and their side effects can be different from person to person.

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Patient Medication

Codeine

Description

Codeine is an opioid medicine used to treat pain. Codeine is also used to suppress cough. It is available as 15-mg, 30-mg, and 60-mg tablets. All are taken by mouth. Codeine also can be combined with other medicines, such as:

- Acetaminophen (Tylenol® with codeine), to control pain (available in liquid and tablet form)
- Guaifenesin, to suppress cough (available in liquid form)
- Promethazine, to suppress cough (available in liquid form)

Laboratory testing

An enzyme in the body called cytochrome P450 2D6 (CYP2D6) has the ability to break down certain medicines including codeine. A genetic test can be done to determine if your CYP2D6 breaks down medicines slower or faster than normal. If your body breaks down the medicine slower or faster than normal, you should avoid taking codeine. For information about CYP2D6 and its effect on codeine, talk with your doctor or pharmacist, and see "Do you know… Cytochrome P450 2D6 (CYP2D6) and medicines." For more details, go to *www.stjude.org/pg4kds*.

St. Jude Online Formulary: linked to drugs, can also sort by gene

Drug Index: A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Abacavir

Gene	Phenotype/Allele	Dosing Recommendations
HLA-B	*57:01 Positive	HLA-B*5701 allele has been detected in this patient. This allele is associated with abacavir hypersensitivity. DO NOT prescribe aba antiretroviral. Please consult a clinical pharmacist or review the pharmacogenetics tab for more information.
HLA-B	*57:01 Negative	No dosage change.

Last updated 10/16/2012 16:09

Back To Top

Amitriptyline

Gene	Phenotype/Allele	Dosing Recommendations
CYP2D6	Ultra-rapid metabolizer	Based on the genotype result, this patient is predicted to be a CYP2D6 ultra-rapid metabolizer. If amitriptyline is prescribed suboptimal plasma concentrations of the drug and its active metabolite are likely. Other agents not metabolized by CYP2D6

PG4KDS : current results (May 2011-March 2013)

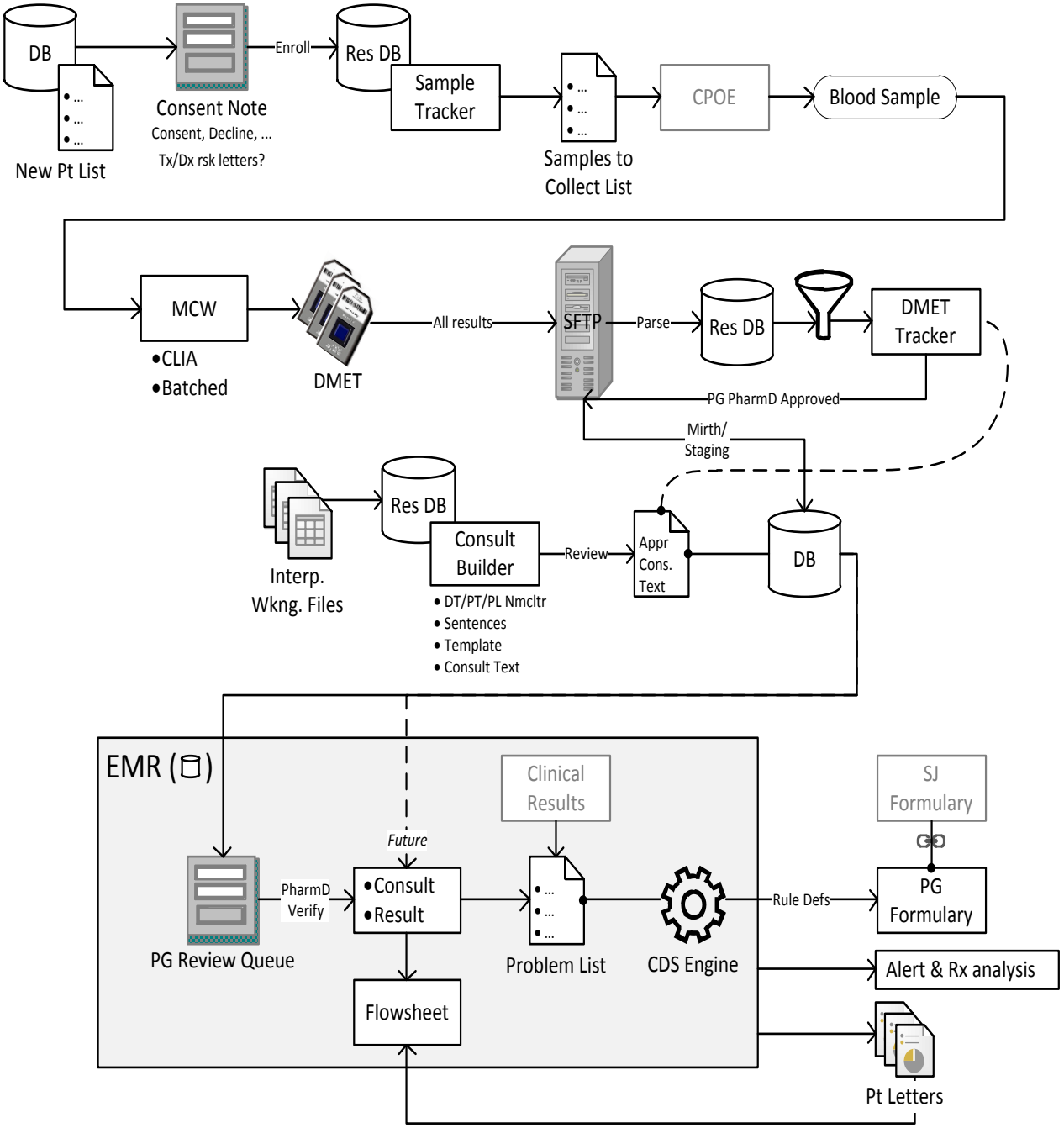
- 1074 patients enrolled
  - ~ 3% refusal rate (33/1107)
- CDS for 9 drugs:
  - CYP2D6: Codeine, Tramadol, Amitriptyline, fluoxetine, paroxetine, ondansetron
  - TPMT: MP, thioguanine, azathioprine
- Now have 36 pharmacogenomic CDS alerts in the St. Jude EHR (still just 2 genes)
  - Post-test alerts fired 596 unique times over last 12 months

PG4KDS : Why so slow?

- No genes go into EMR without adequate (and automatable) interpretation
- Each drug requires
  - gene- and diplotype-specific active (for high risk) and passive CDS (clinical decision support)
  - Update of public website
  - Update pt educational materials
  - Competencies for clinicians
  - Approval of Oversight Committee
  - Sharing with PGRN, PharmGKB, others

Pharmacogenetics Implementation Status

Drug	Thiopurines		Codeine		Tramadol	Amitriptyline	Fluoxetine	Paroxetine	Abacavir	Simvastatin	Fluorouracil	Irinotecan
Gene	TPMT		CYP2D6		CYP2D6	CYP2D6	CYP2D6	CYP2D6	HLA-B*5701	SLCO1B1	DPYD	UGT1A1
Adverse Outcomes	Myelosuppression		Increased toxicity or therapeutic failure		Increased toxicity or therapeutic failure	Increased toxicity or therapeutic failure	Increased toxicity or therapeutic failure	Increased toxicity or therapeutic failure	Hypersensitivity	Myopathy	Myelosuppression	Neutropenia
Implementation Status	Live		Live		Live	Live	Live	Live	Live	Dec-12		Live
	Clinical	PG4KDS	Clinical	PG4KDS	PG4KDS	PG4KDS	PG4KDS	PG4KDS	Clinical	PG4KDS		
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	✓	✓	✓	✓	✓	✓	✓	✓				
PGEN formulary table updated	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Drug monograph updated in formulary	✓	✓	✓	✓	✓	✓	✓	✓	✓			
St Jude PG4KDS webpage updated	--	✓	--	✓	✓	✓	✓	✓	--			--
Staff education	✓	✓	✓	✓	✓	✓	✓	✓				
Competencies	✓	✓	✓	✓	✓	✓	✓	✓				
P & T Communication	✓	✓	✓	✓	✓	✓	✓	✓				
POC Communication	--	✓	--	✓	✓	✓	✓	✓				--
Go-Live Date	1/7/2010	5/18/2011	11/7/2007	5/18/2011	2/10/2012	5/30/2012	5/30/2012	5/30/2012	10/11/2012			


DB
New Pt List
Consent Note
Consent, Decline, ...
Tx/Dx rsk letters?
Enroll
Res DB
Sample Tracker
Samples to Collect List
CPOE
Blood Sample
MCW
•CLIA
•Batched
DMET
All results
SFTP
Parse
Res DB
DMET Tracker
PG PharmD Approved
Mirth/ Staging
Interp. Wkng. Files
Res DB
Consult Builder
• DT/PT/PL Nmcltr
• Sentences
• Template
• Consult Text
Review
Appr Cons. Text
DB
EMR
Clinical Results
SJ Formulary
Future
PharmD Verify
•Consult
•Result
PG Review Queue
Problem List
CDS Engine
Rule Defs
PG Formulary
Alert & Rx analysis
Flowsheet
Pt Letters

We can deliver genetic information to our EMR, we can deliver it directly to the pt, we can deliver to outside clinicians…

- …but until we have a universal lifetime EMR, the same fragmentation that affects all of health care will affect genomic medicine as well…
  - Without seamlessness between EMRs, decision support rules must be re-created for each system
  - Without EMR, genomic information will be under-utilized

SJ Pharmaceutical

Kris Crews

Kevin Hicks

Gillian Bell

Christian Fernandez

Cyrine Haidar

Shane Cross

James Hoffman

Nancy Kornegay

Pam McGill

Emily Melton

Alejandro Molinelli

Colton Smith

William Evans

Mark Wilkinson

Wenjian Yang

Kelly Caudle

Paula Condy

Lisa Walters

Terri Kuehner

Sheri Ring

Shannon Gibbs

Margaret Edwards

SJ Biostatistics

Cheng Cheng

Deqing Pei

MCW

Uli Broeckel

Rachel Lorier

Alexander Stoddard

St. Jude

Scott Howard

Jerry Shenep

Ching-Hon Pui

Alberto Pappo

Sima Jeha

Aditya Gaur

Ulrike Reiss

Alicia Huettel

Melissa Hudson

Amar Gajjar

Information Sciences

Don Baker

Keith Kunkel

Andras Sablauer

Rajesh Parashuran

David Zhao

PGRN

Josh Peterson

Teri Klein

Alan Shuldiner

Julie Johnson

Russ Altman

Dick Weinshilboum

Wolfgang Sadee

CPIC: Implementing PGx

a PharmGKB & PGRN collaboration

PG4KDS : Initial results through March 2012

- 2 genes (*TPMT, CYP2D6*)
- 5 drugs (Codeine, Tramadol, MP, thioguanine, azathioprine)
- 201 patients genotyped
- Ten pharmacogenetic CDS rules built
    - 10 CDS rules fired 920 times from 5/18/11 to 3/31/12

St. Jude Competencies for Pharmacogenetics

- General Pharmacogenetics Competency
  - Nurses, especially research nurses obtaining consent
  - Pharmacists
  - Physicians
- Competencies to perform pharmacogenetic interpretations
  - Gene specific
  - Drug modules

Addressing the need for competencies and other educational resources for pharmacogenetics

- Leverage St. Jude experience and competencies

Vision for the Pharmacist's Leadership Role in Pharmacogenetics Recently Affirmed

ASHP Recommendation from Recent Summit on Pharmacy Practice (Pharmacy Practice Model Initiative - PPMI)

B23. The following characteristics or activities should be considered essential to pharmacist-provided drug-therapy management in optimal pharmacy practice models:

B23f. Adjustment of medication regimens based on genetic characteristics of the patient.

CASE STUDY

Implementing Proactive Pharmacogenetic Testing as a Standard of Care

Submitted by: James M. Hoffman, Pharm.D., MS, BCPS, Medication Outcomes & Safety Officer, Pharmaceutical Services, Associate Member, Pharmaceutical Sciences, St. Jude Children's Research Hospital, 262 Danny Thomas Place, MS 150, Memphis, TN 38103, (901) 595-2767, James.Hoffman@stjude.org

Photo courtesy of St Jude Children's Research Hospital

Primary Intended Outcomes

1. Facilitate the appropriate use of proactive pharmacogenomic tests as the standard of care for St. Jude patients.
2. Incorporate clinical decision support (CDS) tools linking pharmacogenetic testing to medication use, and characterize their use in the electronic medical record (EMR).

Relevant PPMI Recommendation(s)

B23. The following characteristics or activities should be considered essential to pharmacist-provided drug-therapy management in optimal pharmacy practice models:

B23f. Adjustment of medication regimens based on genetic characteristics of the patient.

Situation Analysis

Although pharmacogenetics has existed as a discipline since at least the 1950s, the adoption of genetic testing to guide the safe and effective use of medication remains the exception. While there has been considerable progress in the technical ability to perform genomic testing, various barriers exist that limit the adoption of pharmacogenetic tests as the standard of care. Examples of barriers include fragmentation of health care systems, especially for lifetime genetic results, complexity of the underlying laboratory results, and the immaturity of CDS and EMR systems to facilitate point of care use of pharmacogenetic data when making drug therapy decisions. At St. Jude, we are able to overcome many of these barriers to implementing pharmacogenetics. We provide all the medications for our patients, have decades of experience performing pharmacogenetic research, and have an integrated, comprehensive EMR with customized decision support.

Our philosophy is that pharmacogenetic tests results should be a part of the EMR prior to drug prescribing. If a genetic test is ordered at the time a drug is prescribed, clinicians must wait for the test results, which are often only available after the patient has already started therapy. A preemptive approach allows time for the reporting and interpretation of genetic test results so that

PPMI
PHARMACY PRACTICE MODEL INITIATIVE

Positioning St. Jude implementation efforts as a model for others

- 16 External Presentations in first year of PG4KDS; audience included:
  - IOM
  - NHGRI
  - Pharmacists
  - Medical Informatics
- Multiple awards for paper describing pre-PG4KDS services
- 2nd Year of only Pharmacogenetics Residency in the US; pursuing accreditation

HOPA Hematology/Oncology Pharmacy Association

Development and implementation of a pharmacist-managed clinical pharmacogenetics service

KRISTINE R. CREWS, SHANE J. CROSS, JOHN N. MCCORMICK, DONALD K. BAKER, ALEJANDRO R. MOLINELLI, RICHARD MULLINS, MARY V. RELLING, AND JAMES M. HOFFMAN

Purpose. The development and implementation of a pharmacist-managed clinical pharmacogenetics service are described.

was modeled after and integrated with an already-established clinical pharmacokinetics service. A steering committee was formed to evaluate the use of available

the leadership role that pharmacists can take in moving pharmacogenetics from research to patient care.

Conclusion. The development of and

for the genes to be tested by the clinical pharmacogenetics service. The service

positive clinician feedback. The successful implementation of this service highlights

vices; Pharmacogenetics

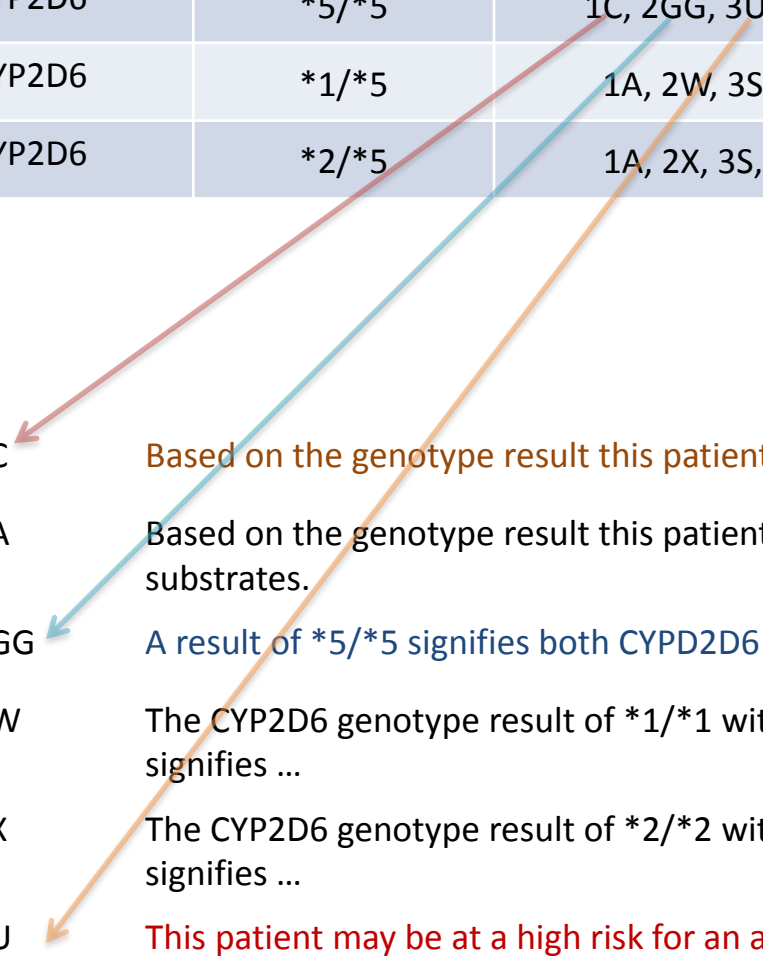
Am J Health-Syst Pharm. 2011; 68:143-50

ASHP Foundation
FOSTERING SAFE AND EFFECTIVE MEDICATION USE

Spreading PG4KDS as a model implementation of pharmacogenetics

- Summary of Outreach and Educational Efforts
  - Clinical Decision Support and other informatics tools
    - Challenging to share CDS tools for any area – not just genomics
    - Our experience is illustrating fundamental informatics limitations that will apply to any implementation (e.g. lack of thoughtful diagnostic codes)
  - Competencies and educational tools
    - General and specific
    - Pharmacists and other clinicians
  - Reaching many audiences but uniquely positioned to reach pharmacists

Gene	Diplotype	Sections codes
CYP2D6	*5/*5	1C, 2GG, 3U, 4R, 5CCC, 6GGG
CYP2D6	*1/*5	1A, 2W, 3S, 4P,5CCC, 6GGG
CYP2D6	*2/*5	1A, 2X, 3S, 4P, 5CCC, 6GGG



1C Based on the genotype result this patient is predicted to be a poor metabolizer …

1A Based on the genotype result this patient is predicted to be an extensive (normal) metabolizer of CYP2D6 substrates.

2GG A result of *5/*5 signifies both CYPD2D6 alleles are deleted in this patient.

2W The CYP2D6 genotype result of *1/*1 with a copy number of 1 is equivalent to *1/*5. A result of *1/*5 signifies …

2X The CYP2D6 genotype result of *2/*2 with a copy number of 1 is equivalent to *2/*5. A result of *2/*5 signifies …

3U This patient may be at a high risk for an adverse or poor response to medications that are metabolized by CYP2D6. …

3S This signifies the patient has an additional copy of either a wild-type (normal function) allele or a non-functional allele. …

ASHP is endorsing CPIC guidelines