Delivery of Information: Implementation of Pharmacogenomics in Clinical Practice

Mary V. Relling

St. Jude Children's Research Hospital and

PAAR4Kids, NIH Pharmacogenomics Research Network (PGRN)

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.

DMET array is CLIA-approved in at least one lab 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---but what to do with the other 223 results?
- Need process for withholding/sharing results
- Need consent for:
  - Withholding results
  - Incidental findings

PG4KDS Protocol
Clinical Implementation of Pharmacogenetics

Principal Investigator

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External Co-Investigator (Collaborating Institutions):

Ulrich Broeckel, M.D.
Medical College of Wisconsin

PGRN

PG4KDS : CLINICAL IMPLEMENTATION OF PHARMACOGENETICS at ST. JUDE

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

Which genes, which drugs should be used to inform the EMR?

- TPMT-thiopurines
- CYP2D6—codeine, ?
- G6PD---rasburicase, Septra
- CYP2C9, VKORC1---warfarin
- CYP2C19---clopidogrel, ? Voriconazole
- DPYD---5FU
- HLA—abacavir
- HLA---carbamazepine
- HLA—phenytoin
- HLA---allopurinol
- UGT1A1---irinotecan

DMET array

Non-Therapeutic Protocol

PG4KDS: Clinical Implementation of Pharmacogenetics

Type of Protocol/Clinical Study

Supportive Studies: Genetics

Description

Pharmacogenetics is the study of how genes affect a person's response to drugs. This field combines pharmacology (the science of drugs) and genetics (the study of genes and their functions) with the goal of making medications safer and more effective by tailoring medications based on a person's genetic makeup.

Gene tests are used in pharmacogenetics. Over time, scientists are discovering which of these gene tests are so important that they should move from the research lab into the patient's medical record, where they would be available to the doctors and other care givers to see the test results, and to use the information when they give the patient the drug.

The process for deciding which tests to move from the research lab into the patient medical record

Related Topics

PG4KDS - Priority Genes

Video: PGEN4Kids Educational Video

Mary V. Relling, PharmD

PG4KDS Objectives

The long term goal is to use proactive pharmacogenomic testing as the standard of care for St. Jude patients.

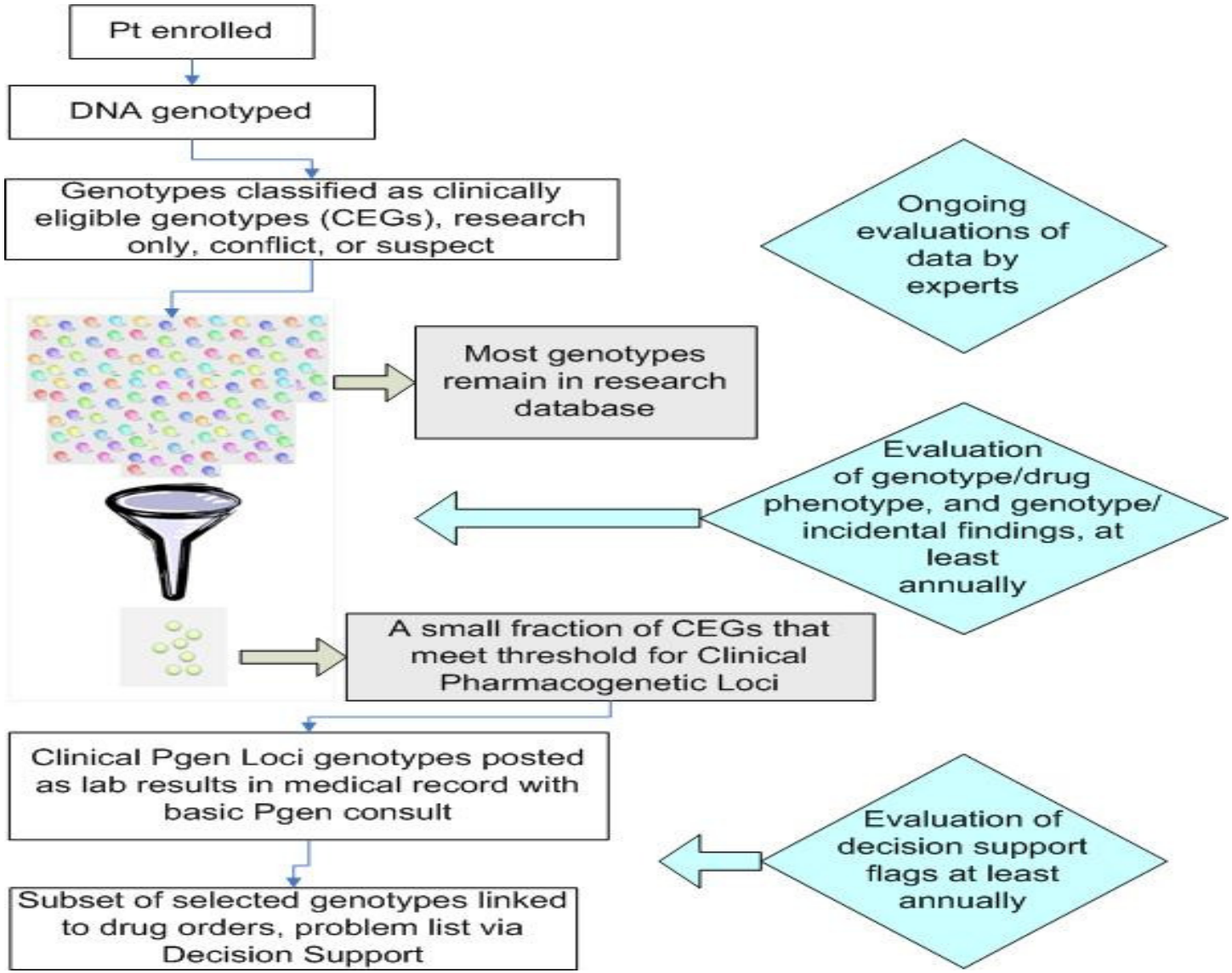
Primary Objective

Estimate the proportion of patients who have high-risk or actionable pharmacogenetic results entered in their electronic medical record (EMR) with decision support.

Secondary Objectives

- Use systematic procedures to prioritize and migrate pharmacogenomic tests to post to the EMR.
- Incorporate clinical decision support tools linking test results to medication use, and assess their level of use.
- Assess attitudes and concerns of research participants and clinicians

The process

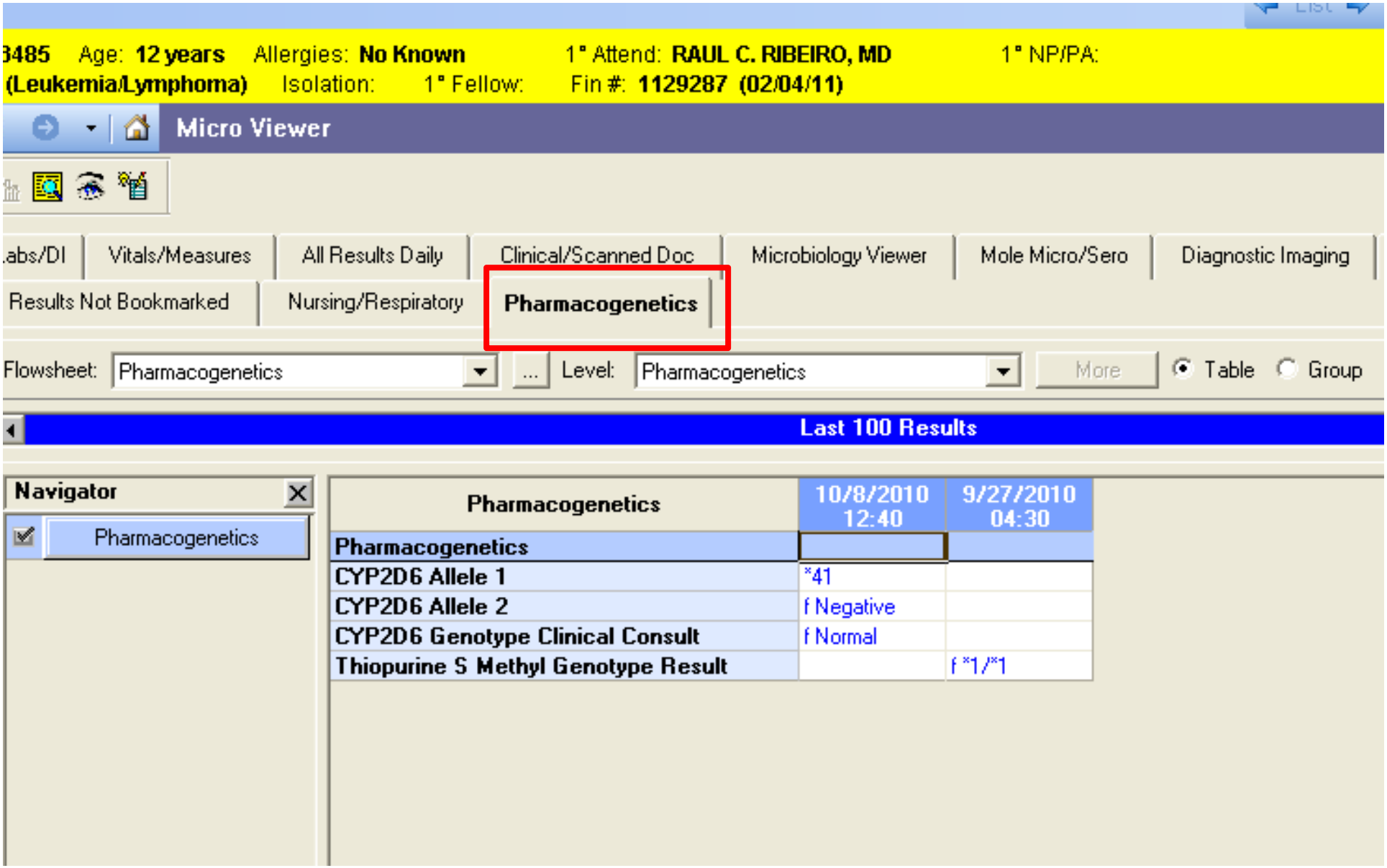


PG4KDS

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
- All participants given choice as to whether to get a “letter” (one letter for each gene)
- Only those > 18 yrs of age given choice on “incidental” findings for disease risk
- General information and video on website

Pharmacogenetics tab added to EMR; all clinically eligible genotypes are entered with a gene-specific consult



Example Pharmacogenetics Consult - TPMT

Example *TPMT* Wild-type genotype consult:

Sample for *TPMT* genotype obtained 8/31/09.

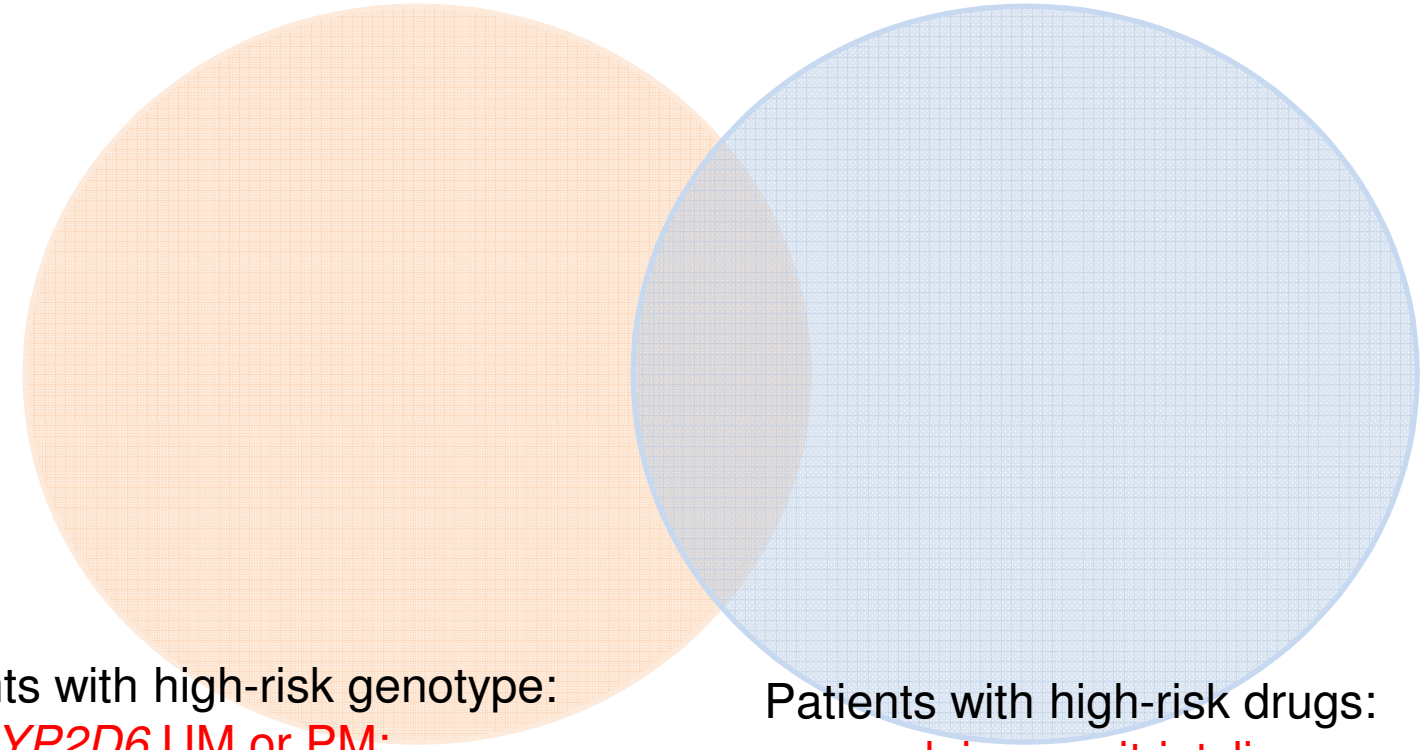
Thiopurine S Methyl Transferase Genotype Result: *1/*1.

*1/*1 means that this patient's genotype is homozygous wild-type at the three most commonly polymorphic sites; i.e., nucleotides 238, 460, and 719. Wild-type means high (normal) TPMT activity. This result suggests that there is no reason to selectively adjust 6-mercaptopurine dose in this patient. If myelosuppression occurs, consult treatment protocol for dosing adjustments for chemotherapy agents.

Time/Date of Consult: 0800/ 09/09/09

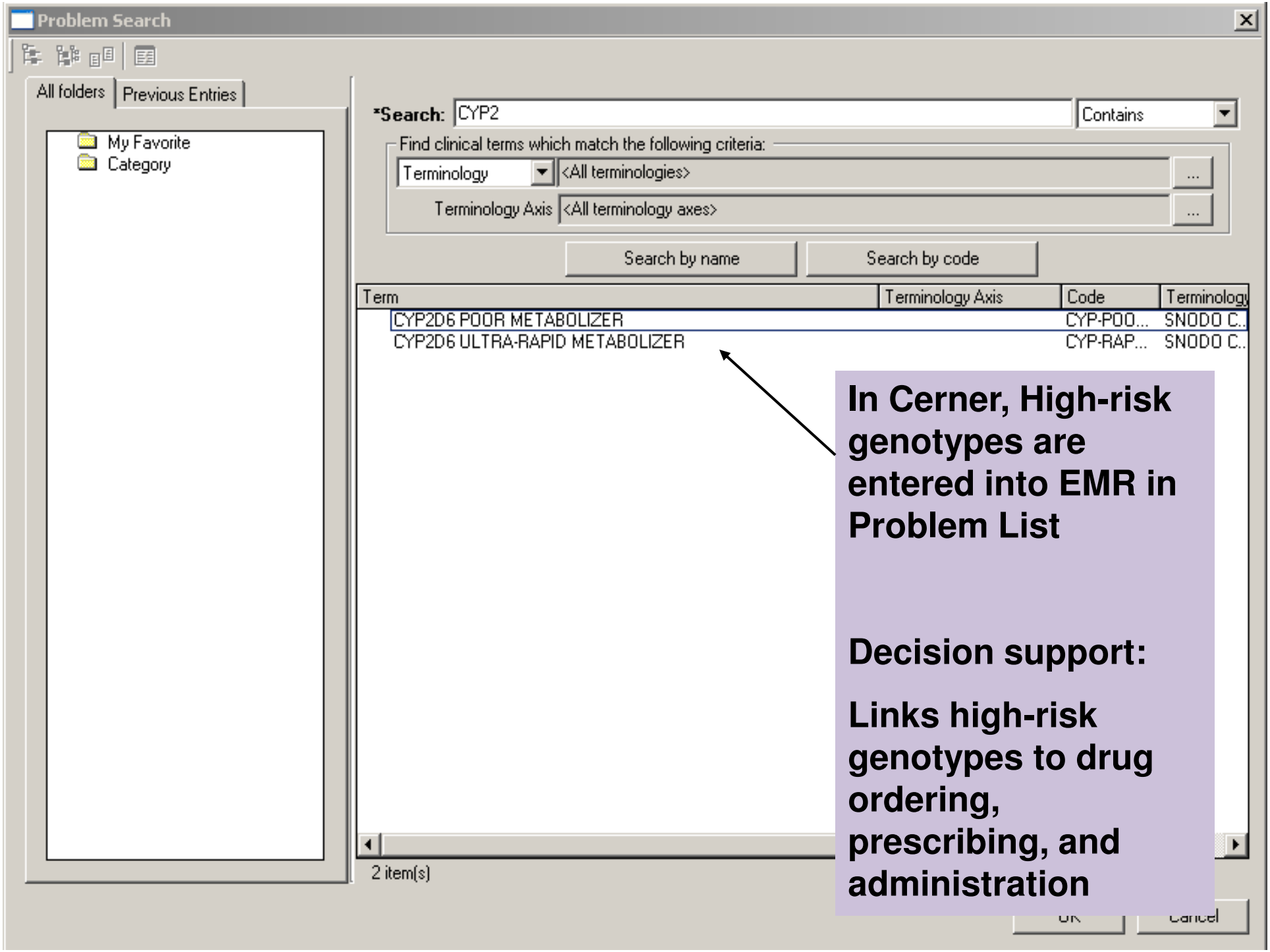
Kristine Crews, Pharm.D.

Only when a high-risk drug collides with a high-risk (priority) genotype do decision-support-based alerts fire



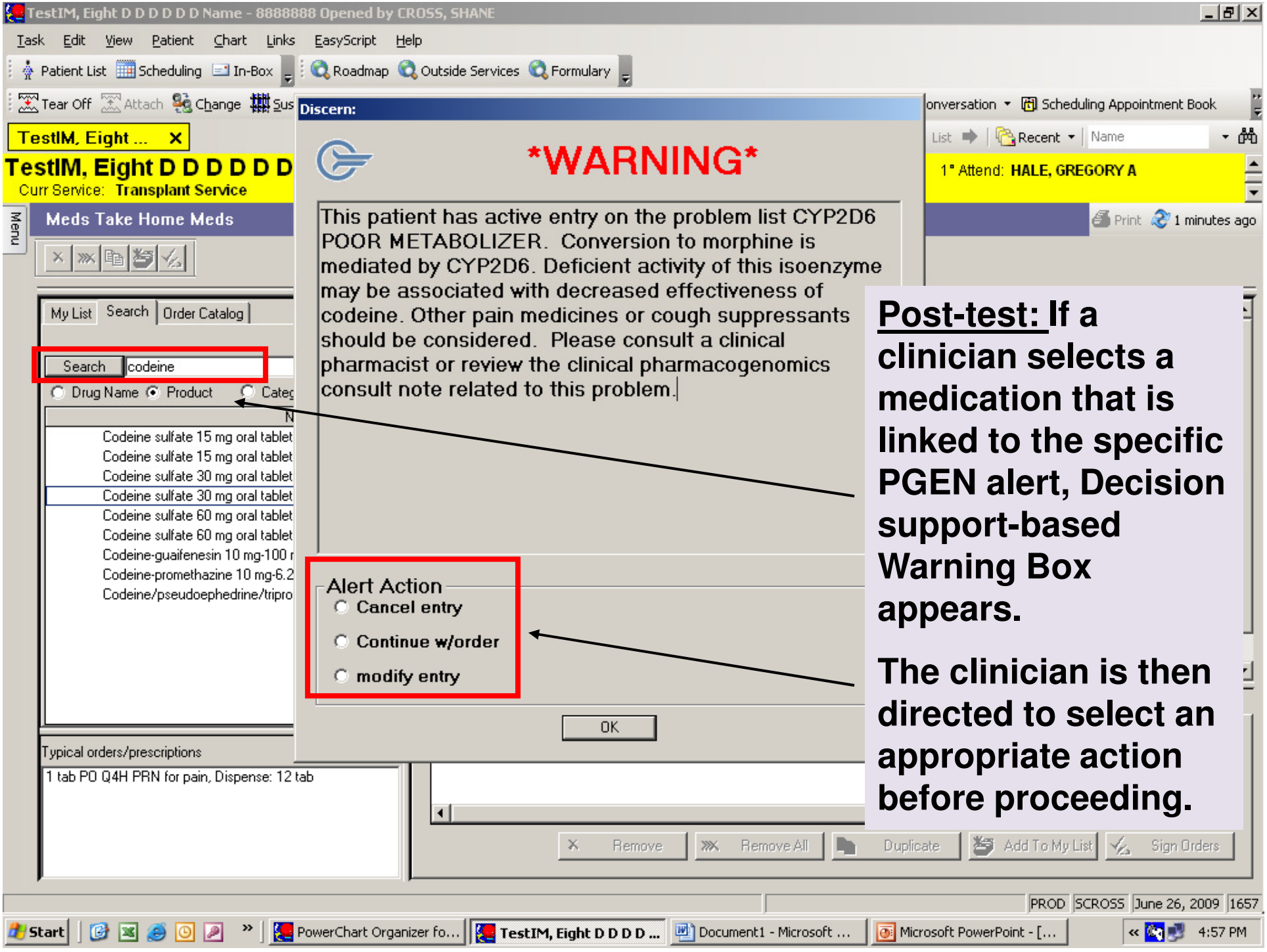
Patients with high-risk genotype:
e.g. *CYP2D6* UM or PM;
CYP2C19 PM;
TPMT heterozygote

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


Problem Search
All folders
Previous Entries
My Favorite
Category
*Search: CYP2
Contains
Find clinical terms which match the following criteria:
Terminology
<All terminologies>
Terminology Axis
<All terminology axes>
Search by name
Search by code
Term
Terminology Axis
Code
Terminology
CYP2D6 POOR METABOLIZER
CYP-POO...
SNODO C...
CYP2D6 ULTRA-RAPID METABOLIZER
CYP-RAP...
SNODO C...
2 item(s)
In Cerner, High-risk genotypes are entered into EMR in Problem List
Decision support:
Links high-risk genotypes to drug ordering, prescribing, and administration

Two types of decision support warnings

- Post-pgen test—already have high-risk genotype in EMR
- Pre-pgen test---no test results yet in EMR



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.

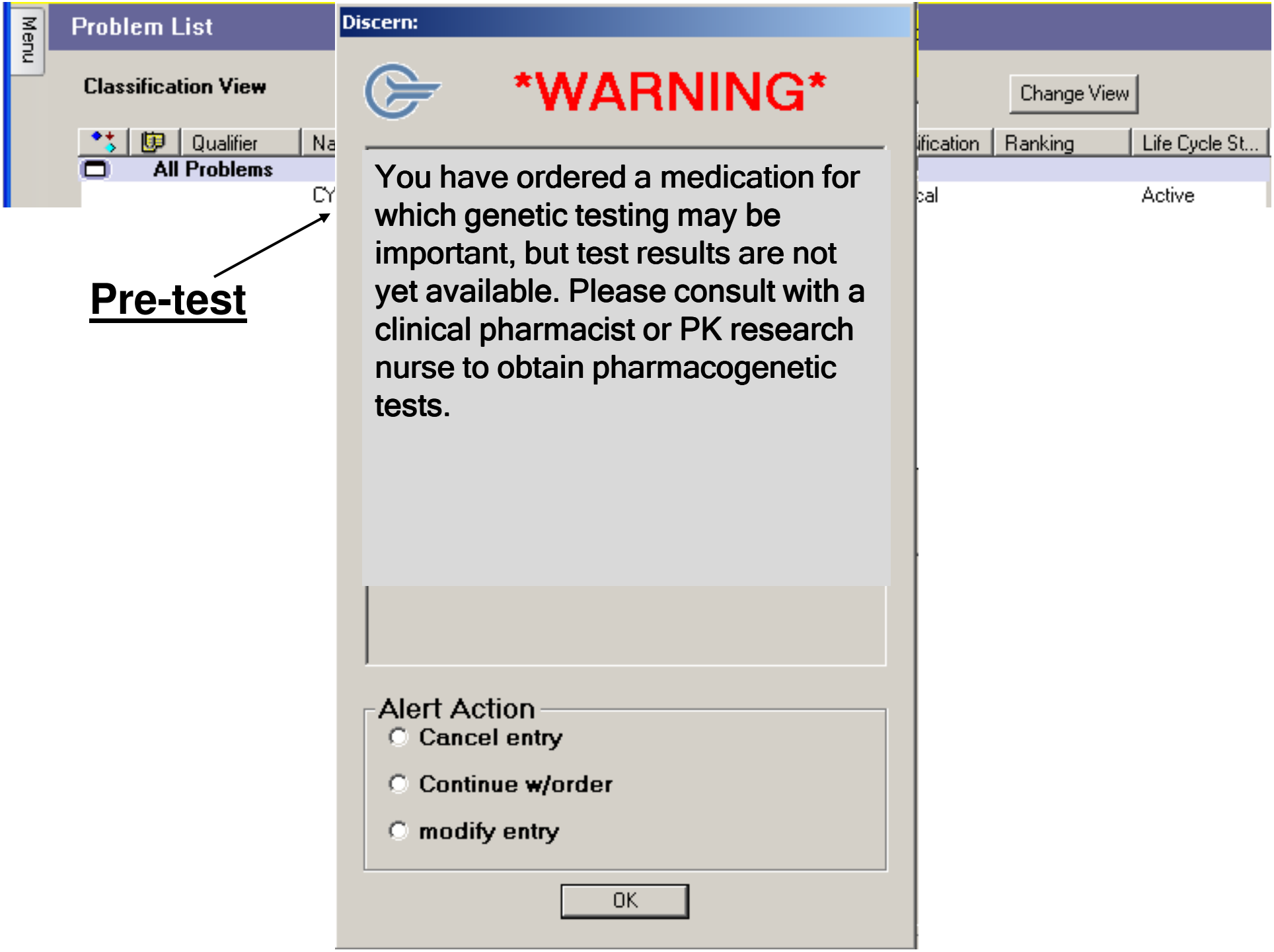
WARNING

This patient has an active entry on the problem list CYP2D6 ULTRA-RAPID METABOLIZER. Ultra-rapid metabolizers of codeine are expected to experience a higher incidence of side effects from codeine than normal. Other pain medicines or cough suppressants should be considered. Please consult a clinical pharmacist or review the clinical pharmacy consult note related to this problem.

Alert Action

- Cancel entry
- Continue w/order
- modify entry

OK


Menu
Problem List
Classification View
Qualifier
All Problems
Change View
Ranking
Life Cycle St...
Active
Discern:
WARNING
You have ordered a medication for which genetic testing may be important, but test results are not yet available. Please consult with a clinical pharmacist or PK research nurse to obtain pharmacogenetic tests.
Alert Action
Cancel entry
Continue w/order
modify entry
OK
Pre-test

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.

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

- …but until we have a universal lifetime EMR, the same fragmentation that affects all of health care will affect genomic medicine as well.

Some challenges in implementation…..

- Lack of consensus guidelines on what to recommend for high-priority/high risk diplotypes
- Must be able to update information (e.g. add drugs to genes as data accumulate)
- Many diplotypes are ambiguous
- Interpretation of diplotypes is complex and will change
- Must be mechanism for QC, sample identity and genotype reproducibility

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]

Clin Pharmacol Ther. 2011 89:387-91

Clinical Pharmacogenetics Implementation 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 PHARMACOLOGY & THERAPEUTICS

www.pharmgkb.org

Some challenges in implementation…..

- Lack of consensus guidelines on what to recommend for high-priority/high risk diplotypes
- Must be able to update information (e.g. add drugs to genes as data accumulate)
- Many diplotypes are ambiguous
- Interpretation of diplotypes is complex and will change
- Must be mechanism for QC, sample identity and genotype reproducibility

CYP2D6 metabolizes several drugs---codeine is the only one with “flag” currently

- TCAs (nortriptyline, amitriptyline)
- SSRIs (fluoxetine, paroxetine)
- Atomoxetine
- Tamoxifen
- Beta blockers (metoprolol)
- Anti-arrhythmics (propafenone, flecainide)
- Ondansetron

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DMET Diplotypes from 240 patients: many results are ambiguous

	CYP2C19	CYP2C9	CYP2D6	DPYD	TPMT	UGT1A1	VKORC1
# No Calls	1	0	5	0	0	1	3
% No Calls	0.4%	0%	2%	0%	0%	0.4%	1%
# Ambiguous	43	37	5	35	22	40	1
% Ambiguous	18%	16%	2%	15%	9%	17%	0.4%
% Called: Non-Ambiguous	81.6%	84%	96%	85%	91%	83%	98.6%

- What are the reasons for ambiguous diplotype assignments?
- Are there phenotype differences between the ambiguous diplotypes?
- Can PHASE select the most probable diplotype?

PHASE Improves Non-Ambiguous Diplotypes to Over 98% for top 7 Genes of Interest

	CYP2C19	CYP2C9	CYP2D6	DPYD	TPMT	UGT1A1	VKORC1
# No Calls	1	0	5	0	0	1	3
% No Calls	0.4%	0%	2%	0%	0%	0.4%	1%
# Ambiguous	43	37	5	35	22	40	1
% Ambiguous	18%	16%	2%	15%	9%	17%	0.4%
% Called: Non-Ambiguous	81.6%	84%	96%	85%	91%	82.6%	98.6%
PHASE Adjusted Non-Ambiguous Calls	**99.6%**	**100%**	**98%**	**100%**	**100%**	**99.6%**	**99%**

Some challenges in implementation…..

- Lack of consensus guidelines on what to recommend for high-priority/high risk diplotypes
- Must be able to update information (e.g. add drugs to genes as data accumulate)
- Many diplotypes are ambiguous
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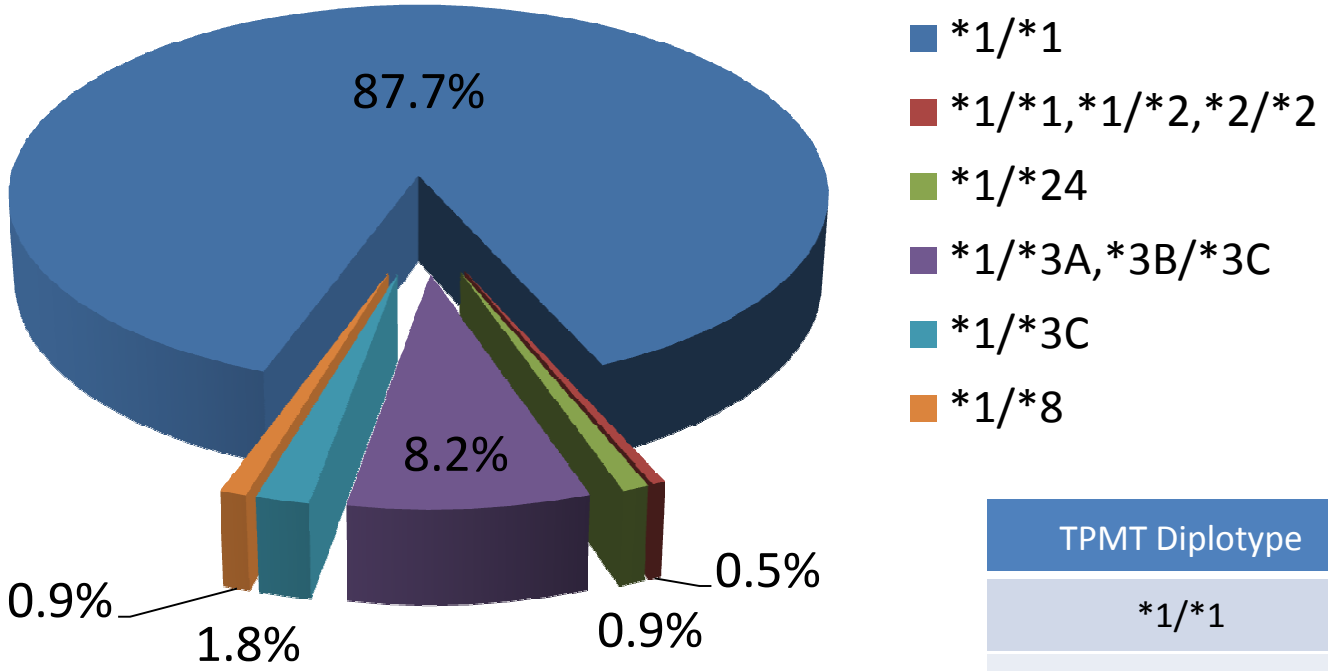
TPMT: diplotypes observed in 240 pts

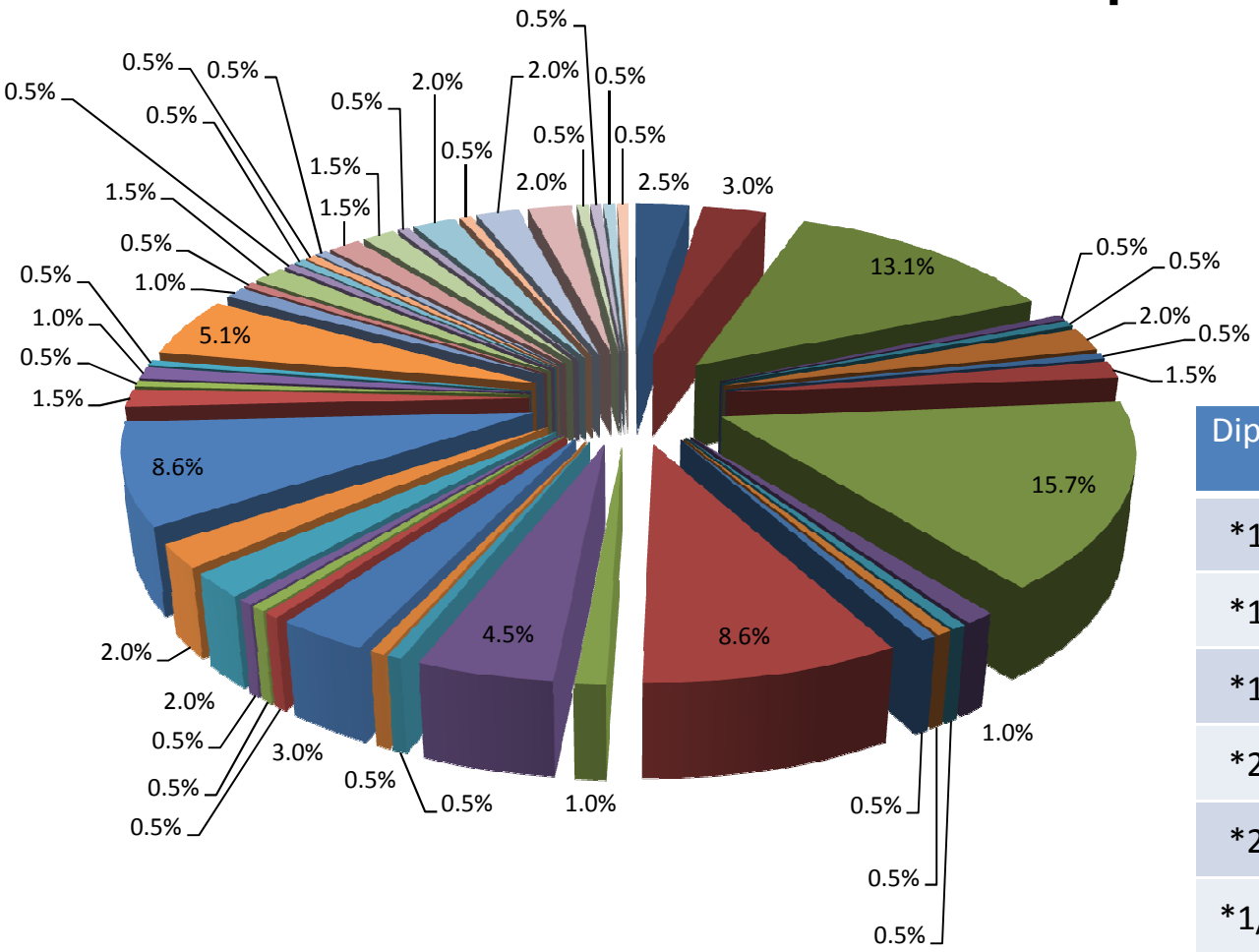


TPMT Diplotype	% Observed
*1/*1	87.7%
*1/*1,*1/*2,*2/*2	0.5%
*1/*24	0.9%
*1/*3A,*3B/*3C	8.2%
*1/*3C	1.8%
*1/*8	0.9%

Link *TPMT* diplotypes to internal review status, prioritization, lab result entry, consult template, and DS

Diplotype	Frequency	Internal Flag	EMR	Rx Consult	Link to Consult
*1/*1	193	Pass	Routine	Wild Type	wild-type
*1/*1,*1/*2,*2/*2	1	Review	Priority	Unknown	Probable wild-type
*1/*24	2	Pass	Routine	Wild Type	wild-type
*1/*3A,*3B/*3C	18	Review	Priority	Heterozygous	Heterozygous with caveat
*1/*3C	4	Review	Priority	Heterozygous	heterozygous
*1/*8	2	Pass	Routine	Wild Type	wild-type

CYP2D6: 48 diplotypes observed in first 240 pts



Diplotype & CN	% Observed
*1/*2(x2)	15.66%
*1/*1(x2)	13.13%
*1/*4(x2)	8.59%
*2/*2(x2)	8.59%
*2/*4(x2)	5.05%
*1/*41(x2)	4.55%
*1/*1(x1)	3.03%
*1/*9(x2)	3.03%

CYP2D6:

1. Generate score based on alleles called and CN

2. All “new” diplotypes must be manually reviewed

3. Translate score into phenotype

From CYP2D6 DMET results, e.g. (*1/*10)3N, the program will generate all possible combinations, e.g. (*1/*1/*10) and (*1/*10/*10).
For each possible combination, it will add up the scores; (in this case *1=1, ***10=0.5; hence [*1/*1**/*10] = 2.5; [*1/*10/*10] = 2)
For each possible score, it will check the threshold to assign PM, IM, EM, UM. (in the above case, would be UM [2.5] or EM [2]; now look at it these rules should be part of the file as well, but it’s hard coded right now…)
if score > 2 : phenotype = 'UM'
if score >= 1 and score <= 2 : phenotype = 'EM'
if score >= 0.5 and score < 1 : phenotype = 'IM'
if score < 0.5 and score >= 0 : phenotype = 'PM'

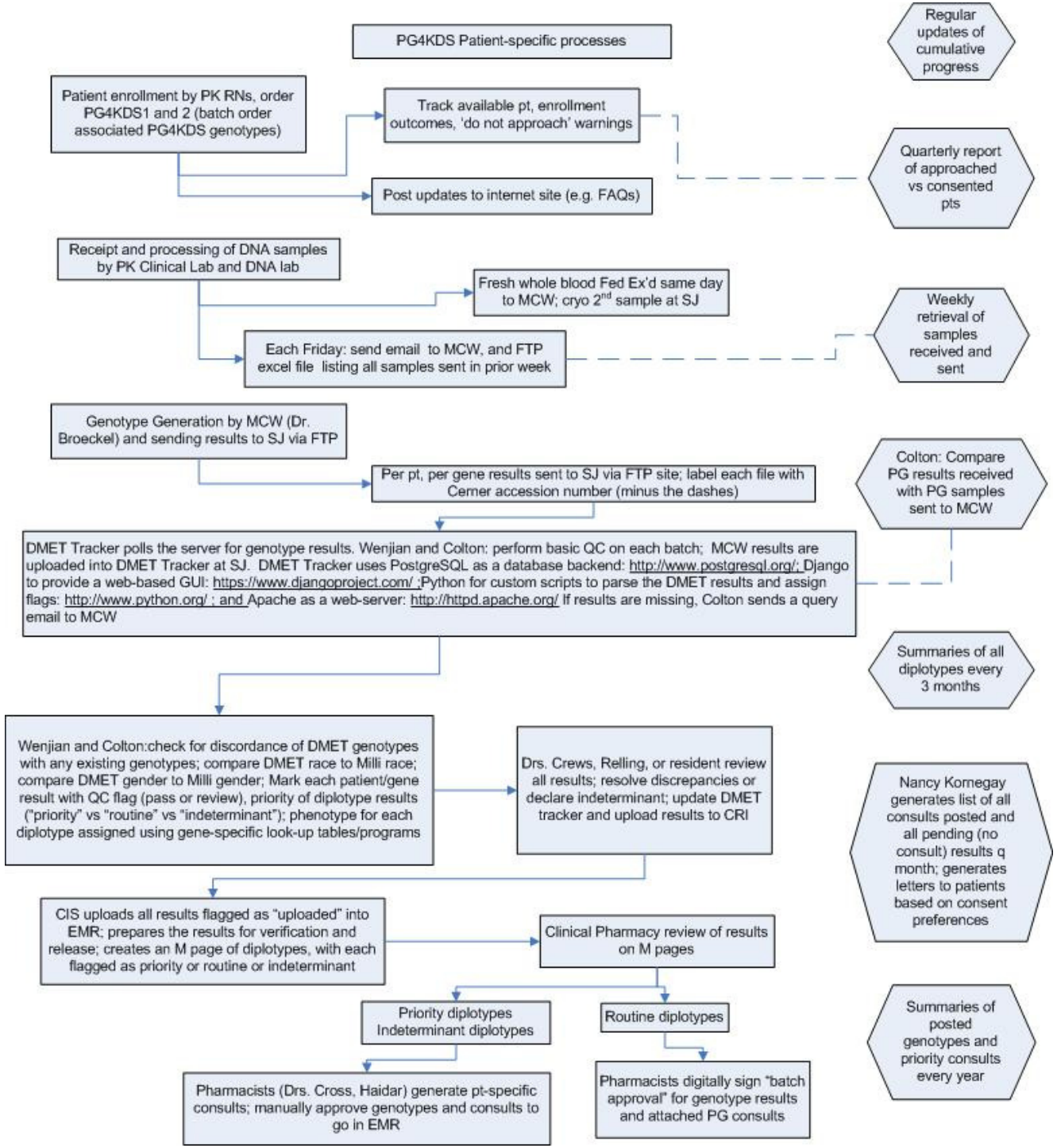
Haplotypes	Activity Score
*1	1
*2	1
*3	0
*4	0
*5	0
*6	0
*7	0
*8	0
*9	0.5
*10	0.5
*11	0
*12	0
*14A	0
*14B	0.5
*15	0
*17	0.5
*18	0
*19	0
*20	0
*21	0
*29	0.5
*38	0
*40	0
*41	0.5
*42	0
*44	0
*56A	0
*56B	0
*64	NA
*39	1
*5	0
*31	0
*36	NA
*45	1
*46	1
*49	0.5
*59	0.5
*60	0
*66	0

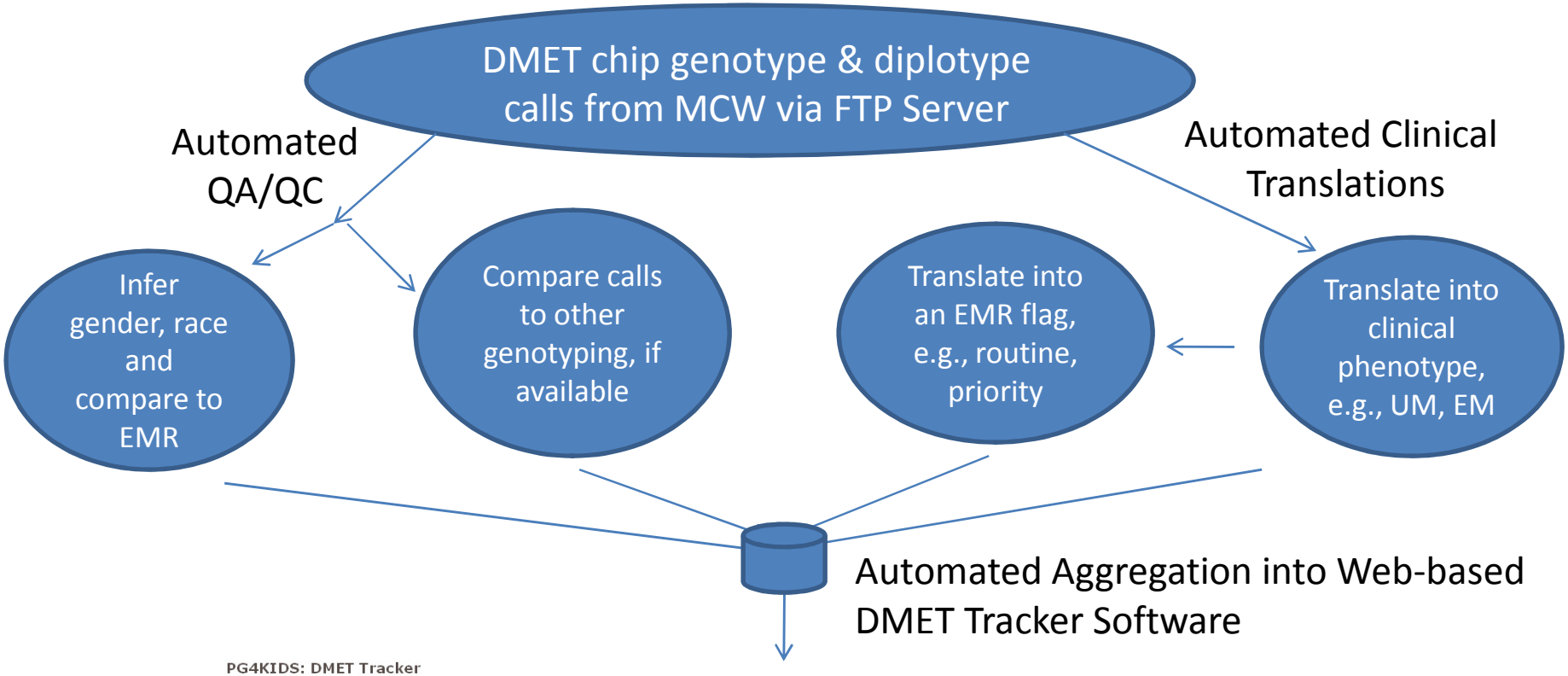
Some challenges in implementation…..

- Lack of consensus guidelines on what to recommend for high-priority/high risk diplotypes
- Must be able to update information (e.g. add drugs to genes as data accumulate)
- Many diplotypes are ambiguous
- Interpretation of diplotypes is complex and will change
- Must be mechanism for QC, sample identity and genotype reproducibility (over a lifetime)

PG4KDS

Multiple steps are involved in processing pt-specific results, from lab to EMR





Human Discrepancy Management

PG4KIDS: DMET Tracker

View Batches | Send Approved Results to CRI | Review and Upload Weekly Manifest | Documentation | Log out — Colton

[[Batch ID: 31; Receipt Date: June 14, 2011]] Submit your approvals by clicking here

Show 10 entries — Search:

Patient ID	Accession ID	Tube ID	Gene	DMET Diplotype	Existing Diplotype	DMET Race	Clinical Race	DMET Gender	Clinical Gender	QC Flag	Suspect QC	EMR Flag	PK Phenotype	Upload Status	Approve for Upload All?
17229	005-089-0580	S305	TPMT	*1/*1	None	white;	other	male?(0)	male	REVIEW	race	ROUTINE	WILDTYPE	uploaded to CRI	approved by csmith8
17229	005-089-0580	S305	CYP2D6	(*1/*2)2N	None	white;	other	male?(0)	male	REVIEW	race	ROUTINE	EM	uploaded to CRI	approved by csmith8
17454	001-249-0720	2095	TPMT	*1/*1	G/G|G/G|A/A	white;	white	male?(0)	male	PASS		ROUTINE	WILDTYPE	uploaded to CRI	approved by csmith8
17454	001-249-0720	2095	CYP2D6	(*2/*2)1N	None	white;	white	male?(0)	male	PASS		ROUTINE	EM	uploaded to CRI	approved by csmith8
17900	005-266-0670	H4869	TPMT	*1/*1	G/G|G/G|A/A	white;	white	female(3)	female	PASS		ROUTINE	WILDTYPE	uploaded to CRI	approved by csmith8
17900	005-266-0670	H4869	CYP2D6	(*10/*41)2N	None	white;	white	female(3)	female	PASS		ROUTINE	EM	No	☐
17914	005-243-0513	H4853	TPMT	*1/*1	G/G|G/G|A/A	asian;white;	white	male?(0)	male	PASS		ROUTINE	WILDTYPE	No	☐
17914	005-243-0513	H4853	CYP2D6	(*1/*1)2N	None	asian;white;	white	male?(0)	male	PASS		ROUTINE	EM	No	☐
18054	006-174-0634	H5241	CYP2D6	(*4/*4)2N	None	white;	white	male?(0)	male	PASS		PRIORITY	PM	uploaded to CRI	approved by csmith8
18054	006-174-0634	H5241	TPMT	*1/*1	G/G|G/G|A/A	white;	white	male?(0)	male	PASS		ROUTINE	WILDTYPE	No	☐

Showing 1 to 10 of 464 entries — First | Previous | 1 | 2 | 3 | 4 | 5 | Next | Last

To the EMR

DMET Tracker: place to flag genotype, race, or gender mismatches; review priority or indeterminant diplotypes; track upload from research database to clinical warehouse

entries

Search:

Accession ID	Tube ID	Gene	DMET Diplotype	Existing Diplotype	DMET Race	Clinical Race	DMET Gender	Clinical Gender	QC Flag	Suspect QC	EMR Flag	PK Phenotype	Upload Status	Approve for Upload All?
005-089-0580	S305	TPMT	*1/*1	None	white;	other	male?(0)	male	REVIEW	race	ROUTINE	WILDTYPE	uploaded to CRI	approved by csmith8
005-089-0580	S305	CYP2D6	(*1/*2)2N	None	white;	other	male?(0)	male	REVIEW	race	ROUTINE	EM	uploaded to CRI	approved by csmith8
001-249-0720	2095	TPMT	*1/*1	G/G|G/G|A/A	white;	white	male?(0)	male	PASS		ROUTINE	WILDTYPE	uploaded to CRI	approved by csmith8
001-249-0720	2095	CYP2D6	(*2/*2)1N	None	white;	white	male?(0)	male	PASS		ROUTINE	EM	uploaded to CRI	approved by csmith8
005-266-0670	H4869	TPMT	*1/*1	G/G|G/G|A/A	white;	white	female(3)	female	PASS		ROUTINE	WILDTYPE	uploaded to CRI	approved by csmith8
005-266-0670	H4869	CYP2D6	(*10/*41)2N	None	white;	white	female(3)	female	PASS		ROUTINE	EM	No	☐
005-243-0513	H4853	TPMT	*1/*1	G/G|G/G|A/A	asian;white;	white	male?(0)	male	PASS		ROUTINE	WILDTYPE	No	☐
005-243-0513	H4853	CYP2D6	(*1/*1)2N	None	asian;white;	white	male?(0)	male	PASS		ROUTINE	EM	No	☐
006-174-0634	H5241	CYP2D6	(*4/*4)2N	None	white;	white	male?(0)	male	PASS		PRIORITY	PM	uploaded to CRI	approved by csmith8
006-174-0634	H5241	TPMT	*1/*1	G/G|G/G|A/A	white;	white	male?(0)	male	PASS		ROUTINE	WILDTYPE	No	☐
006-349-0465	H5503	TPMT	*1/*1	G/G|G/G|A/A	white;	multiple race (nos)	female(3)	female	REVIEW	race	ROUTINE	WILDTYPE	No	☐
006-349-0465	H5503	CYP2D6	(*1/*2)3N	None	white;	multiple race (nos)	female(3)	female	REVIEW	race	PRIORITY	UM	No	☐

Some challenges in implementation…..

- Who's going to pay?
- Cheaper, faster, easier, more effective to genotype pre-emptively---before you even think about prescribing the drug…..

PGRN Translational Pharmacogenetics Program (TPP)

- Complete more CPIC guidelines and apply them clinically
- Measure common outcomes across clinical sites
  - accuracy of genetic testing, turn around times
  - methodologies to report results
  - suggested treatment algorithms
  - Educational programs
  - Frequency of actions taken

PGRN

SJ Pharmaceutical

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Cheng Cheng

Stan Pounds

Deqing Pei

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ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

St. Jude

Ching-Hon Pui

Dario Campana

James Downing

Susana Raimondi

Sue Kaste

Sima Jeha

Scott Howard

Jerry Shenep

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Teri Klein

Nancy Cox

Paul Scheet

Russ Altman

Dick Weinshilboum

Alan Shuldiner

Julie Johnson

Rachel Tyndale

MCW

Uli Broeckel

INITIAL PLANS FOR TRANSLATIONAL PHARMACOGENETICS PROJECT for PGRN

PGRN Group	Platform	Variant(s)	Application	Timing	Comments
PAAR 4 Kids (St. Jude) Relling	Affymetrix DMET array (225 genes) plus custom copy number assay (for CYP2D6)	TPMT and CYP2D6 now; soon CYP2C19, CYP2C9, VKORC1, DYPD, G6PD	pediatric patients receiving multiple therapies	any time while active patient at St. Jude	part of a research protocol; purpose is to develop process to move results into medical records for clinical use
PEAR (U. of FL) Johnson	Illumina ADME Core Panel	CYP2C19	cardiac catheterization laboratory; anticipating percutaneous coronary intervention (PCI)	concurrent with admission - obtain results within 24 hours to influence decision before, or within first dose of clopidogrel	additional genotypes will be stored in integrated data repository (part of CTSI and UF EMR, but not in EMR); can be pulled in as additional gene/drug pairs are added to the Personalized Medicine Program, as approved by the P&T subcommittee
PAPI (U. MD) Shuldiner	Nanosphere Verigene (point-of-care) for CYP2C19; broader panels, e.g., Illumina ADME planned	CYP2C19; more planned	cardiac catheterization laboratory	at presentation to cath lab; or earlier (if elective PCI)	
PAT (Vanderbilt) Peterson/ Roden	Illumina VeraCode ADME Core Panel	CYP2C19	preparation for angiography, anticipating percutaneous coronary	ordered and blood drawn concurrent with preparation; results obtained within 7 days	additional genotypes obtained stored electronically in secure repository separate from EMR; when appropriate drug prescribed for a drug-genome interaction, the genome is made visible in the EMR
PPI (Mayo) Pereira/ Weinshilboum	Nanosphere Varigene (point-of-care) CYP2C19 platform	CYP2C19	cardiac catheterization laboratory	point-of-care genotyping in a CLIA-approved environment	first bolus clopidogrel dose without genotype, second dose randomized to either "standard care" with clopidogrel or assignment to clopidogrel or prasugrel based on genotype; CYP2C19 information will be stored in the Mayo EMR
XGEN (OSU) Sadee	Autogenomics Infinity System at Nationwide Children's Hospital in Columbus; future use of Ilumina ADME planned	1.) CYP2C19 first; 2.) later phase in CYP2C9 and VKORC1	1.) cardiac catheterization lab of Ross Heart Hospital, anticipating PCI; 2.) subsequently, begin recruitment of orthopedic patients as part of pre-op visit	genotyping in CLIA-app lab with results available prior to surgery - goal is to have genotype information available when drug choice and dosing are to be decided	1.) results posted to EMR (EPIC) w/ alert tags & genotype compared with functional assay of clopidogrel test doses; 2.) warfarin dosing for the orthopedic population will use website with plans to incorporate algorithms directly into EMR; 3.) additional genotype information (with Illumina ADME panel) will go into OSUMC Information Warehouse, a secure depository

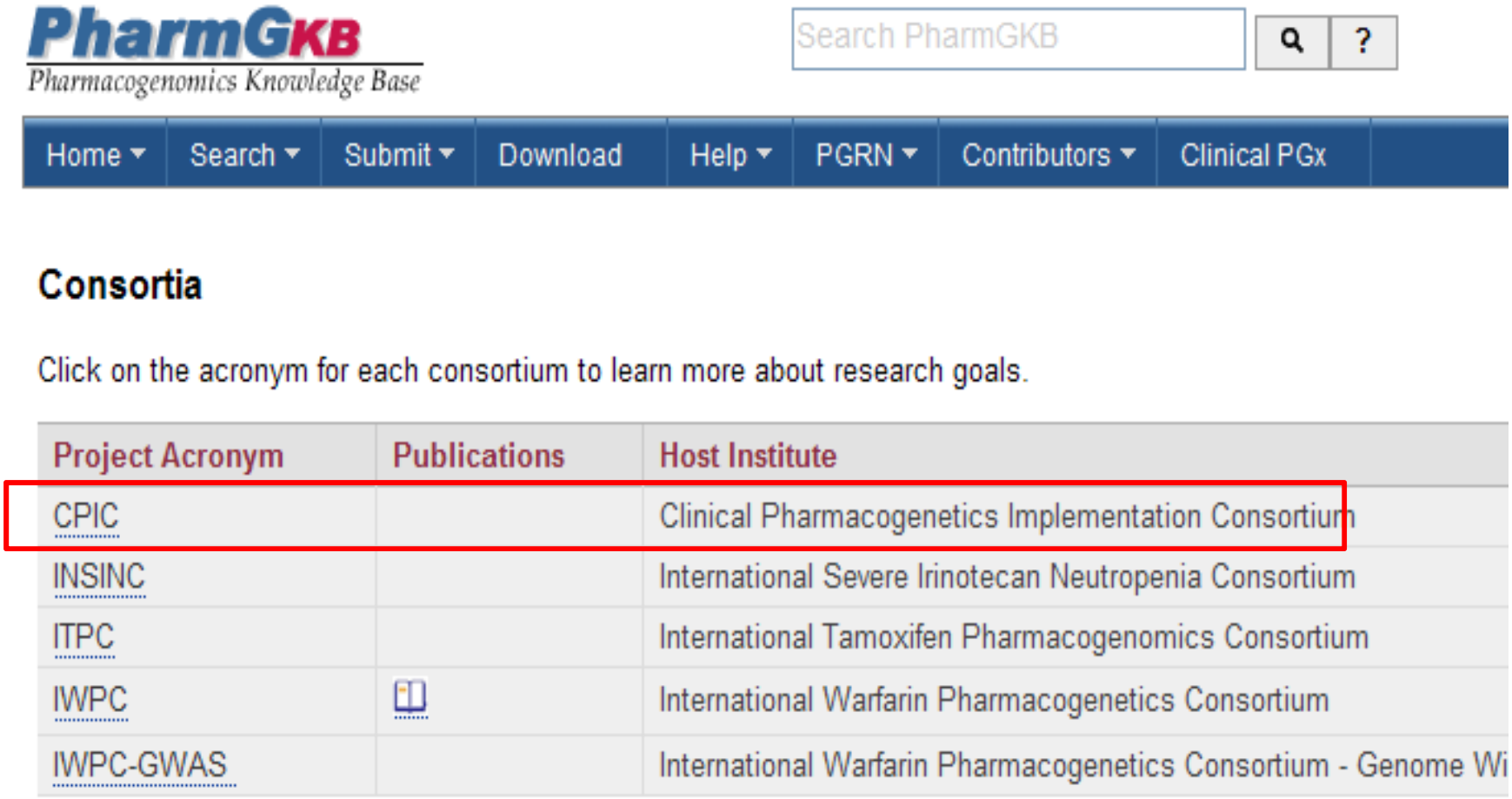
Related Projects

Rex Chisholm	Northwestern	Using pharmacogenomics evidence (from GWA genotyping) to guide prescriptions in primary care and assess risk for other conditions such as HFE/hemochromatosis
Geoff Ginsburg	Duke	• Computer-based family hx collection and CDS tool with 1-yr follow-up for perceptions, attitudes, behaviors related to thrombosis and breast, ovarian, and colon cancer • SLCO1B1*5 genotyping and statin adherence • Effect of genetic risk info on anxiety and adherence in T2DM
David Ledbetter	Geisinger	• Selection for gastric bypass surgery vs other wt loss means based on genetic variants predictive of long-term benefit from surgery • IL28B variants and response to hepatitis C treatment • KRAS and BRAF mutational analysis in thyroid cancer patients
Cathy McCarty	Marshfield	Choice of intra-ocular pressure lowering agent based on genotype
Dan Roden	Vanderbilt	Pre-emptive PGx genotyping for clopidogrel, warfarin, or high-dose simvastatin
Alan Shuldiner	U Maryland	Develop and apply evidence-based gene/drug guidelines that allow clinicians to translate genetic test results into actionable medication prescribing decisions
Dick Weinshilboum	Mayo	• PGx driven selection/dosing of antidepressants • CYP2C19 genotyping for antiplatelet rx post PCI

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

How to provide useful advice to clinicians on top gene/drug pairs?



CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network

MV Relling[1] and TE Klein[2]

- Rationale
- Format
- Grading schemes for
  - strength of recommendations
  - levels of evidence

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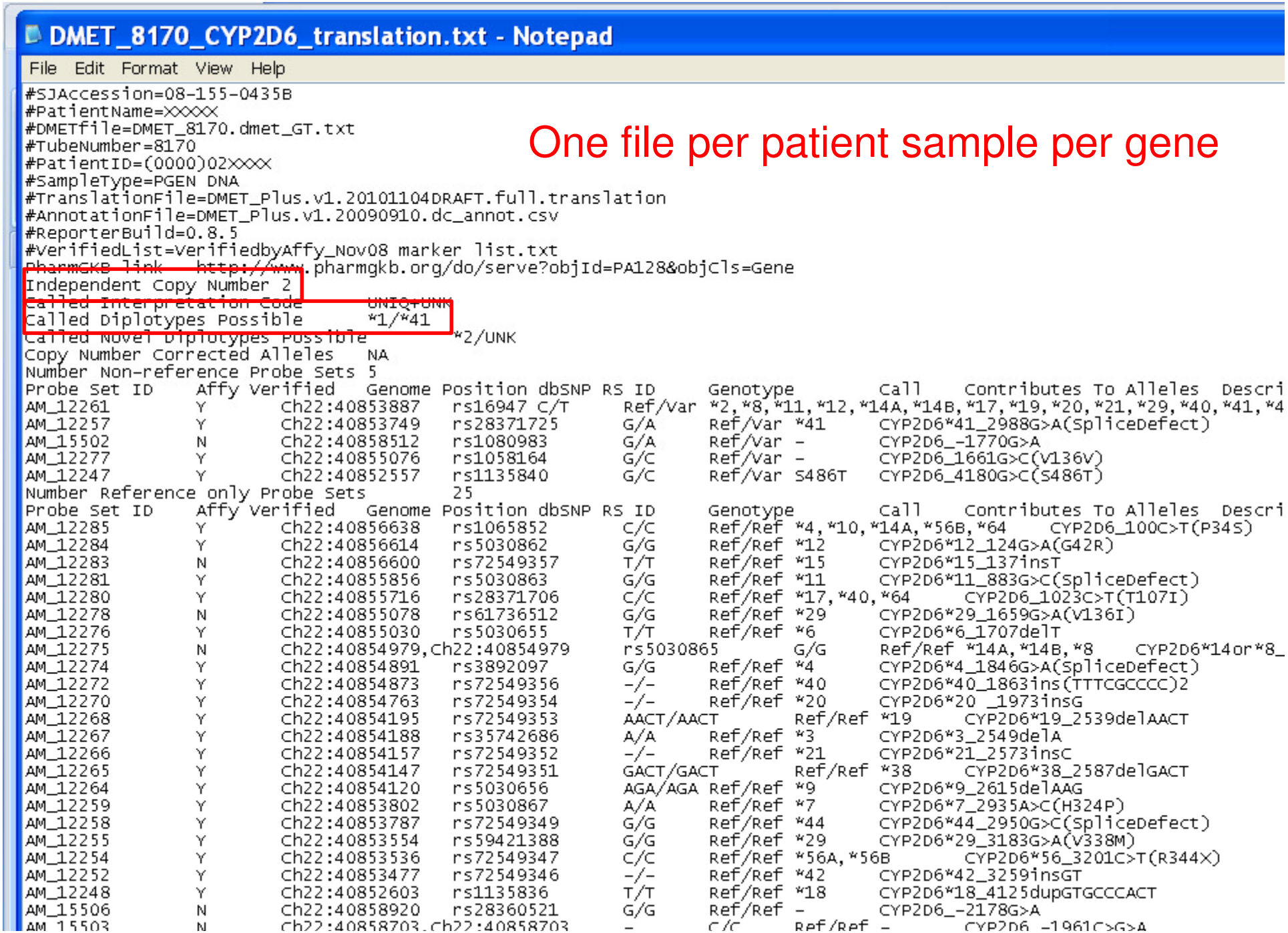
Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing

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]

Clin Pharmacol Ther. 2011 89:387-91



One file per patient sample per gene

Translate phenotypes into EMR priority status

CYP2D6 phenotype	***CYP2D6* EMR flag**
UM	priority
EM	routine
IM	routine
PM	priority
EM, IM	routine
others	marked for review