Clinical Implementation of Pharmacogenetics

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ALSAC • Danny Thomas, Founder
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CPIC™
Clinical Pharmacogenetics Implementation Consortium

NIH Pharmacogenomics Research Network

PGRN

Pharmacogenetic Discovery vs implementation

- Discovery of host and treatment risk factors for adverse outcomes in ALL: relapse and adverse drug effects (osteonecrosis)
  - Better understand mechanism and means to avoid
  - Discover and validate tests for eventual clinical use
- Implement pharmacokinetic, pharmacodynamic, and pharmacogenetic tests for patient care

Discovery of pharmacogenetic genotype/phenotype associations is ongoing----but are there pharmacogenetic tests we should be implementing in the clinic now?

When to use a test to guide prescribing?

- When getting prescribing right is important

When to use a test to guide prescribing?

- Safety: drug has a narrow therapeutic index
- Efficacy: effective treatment of disease is important
- Dosing to pharmacodynamic effects is not readily titratable via other means
- Drug that needs a test has some advantages over other drugs that don't

When to use a test to guide prescribing?

- Safety: drug has a narrow therapeutic index
  - Difference between dose of drug needed to cause intended effect is not much lower than doses that can cause serious effects
    - e.g. cytotoxic anticancer drugs vs amoxicillin or levothyroxine
  - Unpredictable, non-dose related adverse effects
    - e.g. Stevens-Johnson syndrome and carbamazepine vs drowsiness from benzodiazepines

When to use a test to guide prescribing?

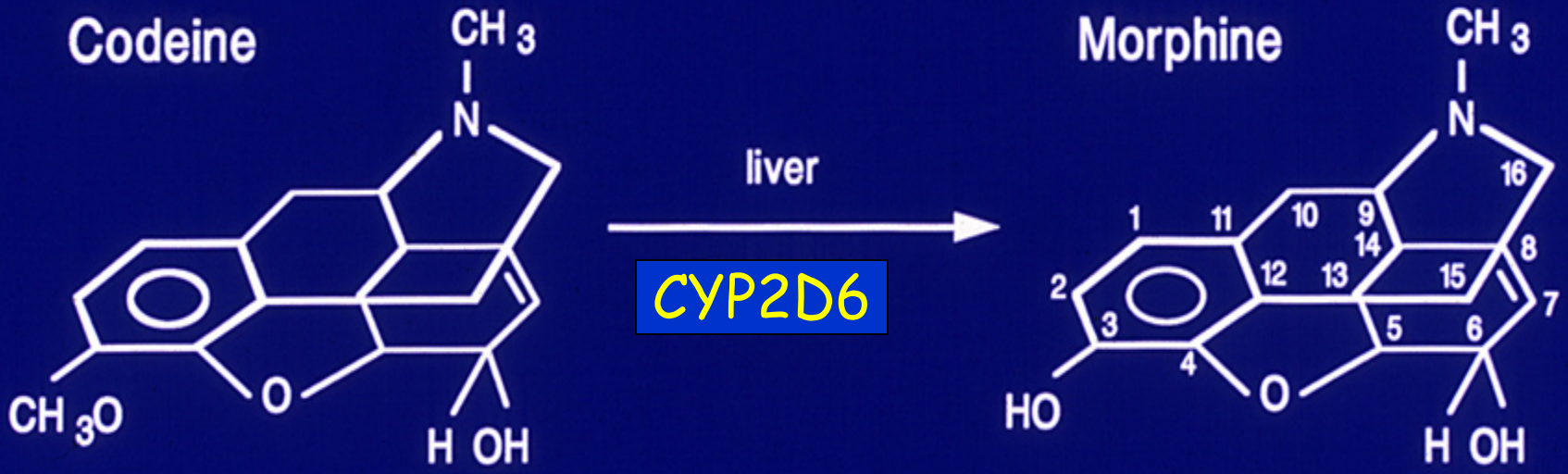
- Efficacy: effective treatment of disease is ~~important~~ life-saving
  - e.g. anticancer drugs, anticonvulsants vs antihistamines for seasonal allergies

When to use a test to guide prescribing?

- Dosing to pharmacodynamic effects is not readily titratable via other means
  - E.g. many anticancer drugs, depression, schizophrenia vs cholesterol, blood pressure, diabetes
  - Especially a problem when multiple drugs on board with overlapping toxicities

When to use a test to guide prescribing?

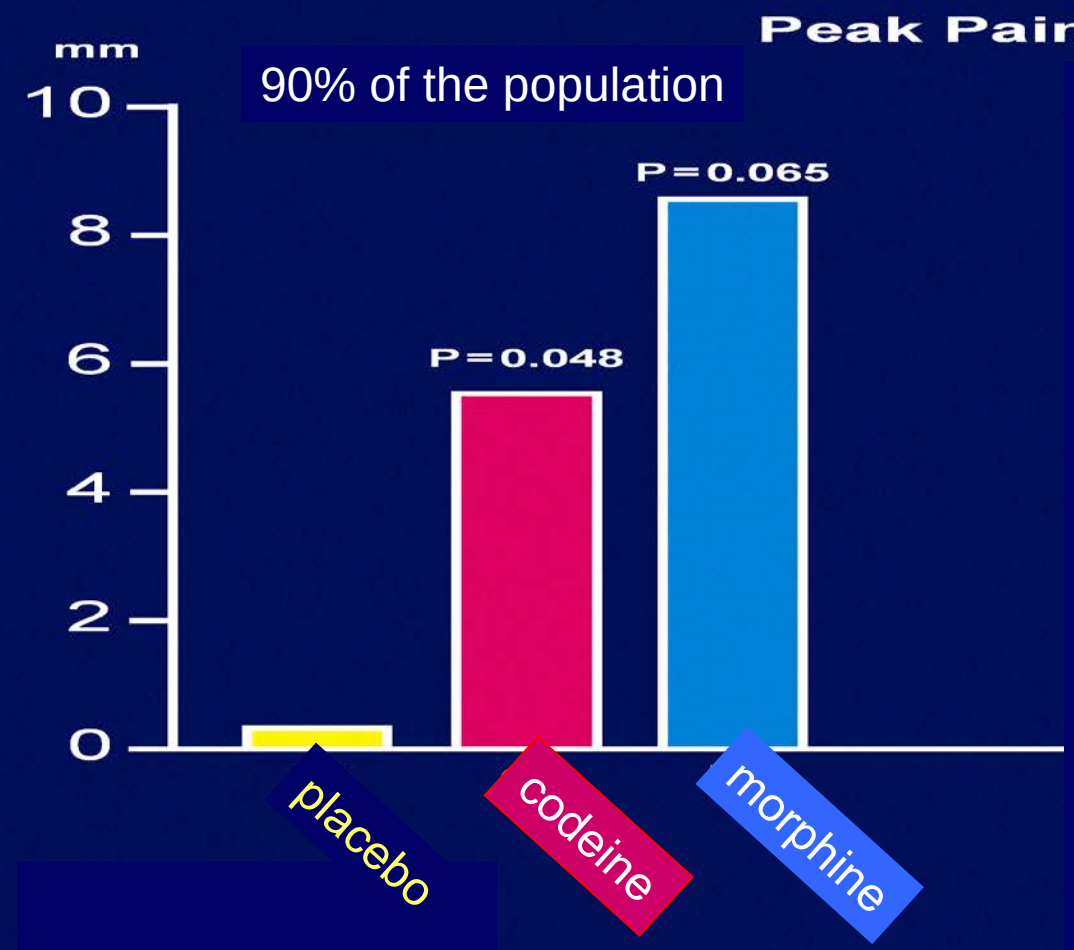
- Drug that needs a test has some advantages over other drugs that don't
  - e.g. codeine over morphine, ondansetron over granisetron



1988

Vol. 152, No. 1, 1988
April 15, 1988
BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
Pages 411-416

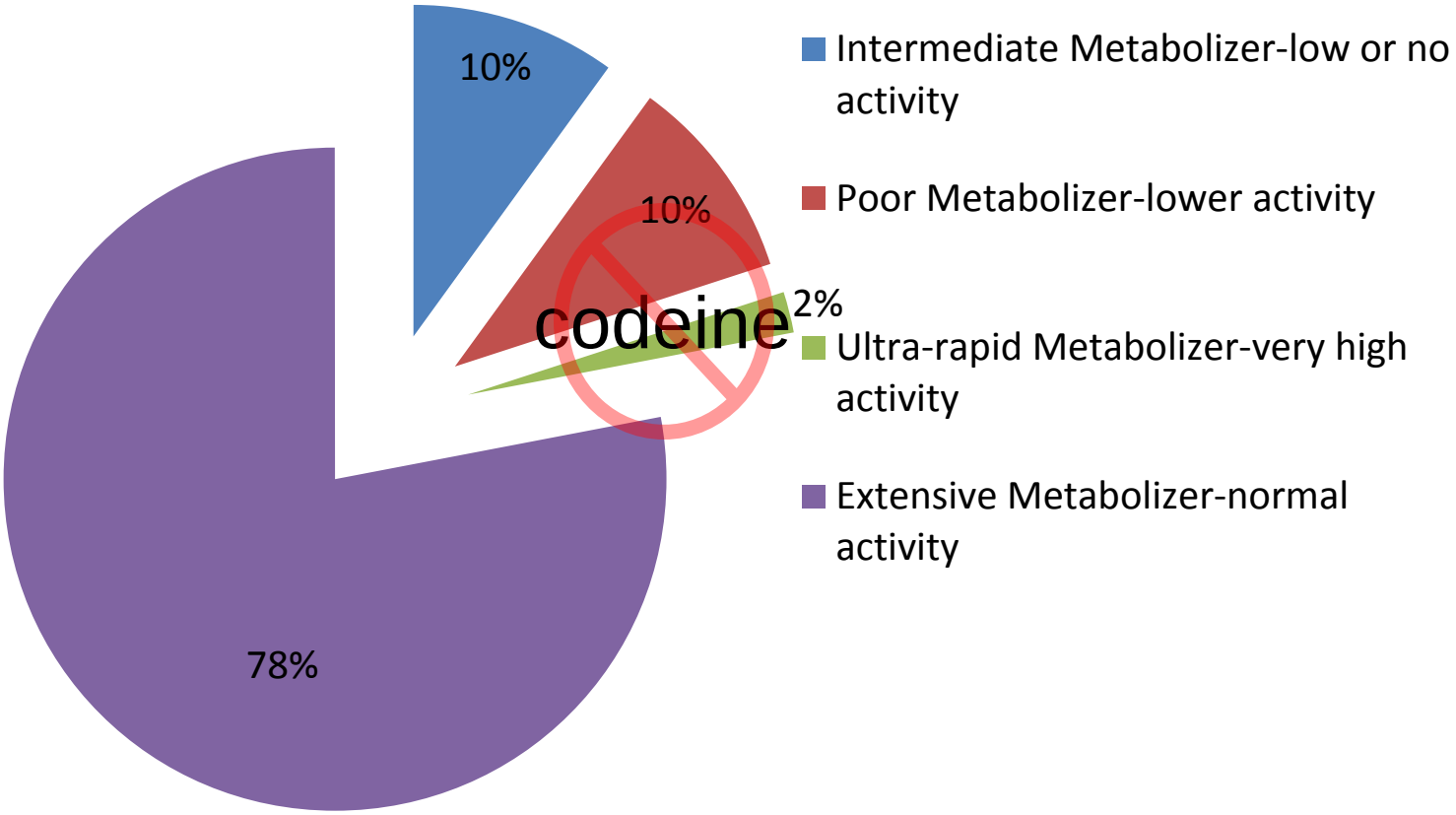
Codeine is the same as placebo to 10% of the population



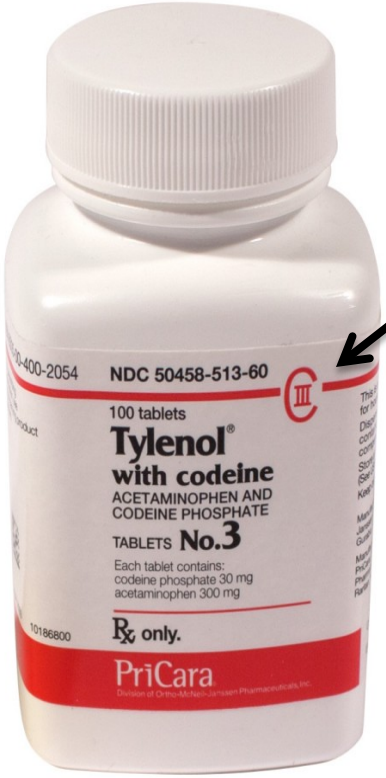
Poulsen et al *Eur J Clin Pharm* 1996;51:289-95

And too active for 1-2% of the population

12% of the population should not take codeine based on CYP2D6



Why Bother with Codeine at All?



As of 2015, only Schedule III opioid available in US

But genetic testing for this and other drugs remains extremely uncommon….

We are approaching implementation of clinical pharmacogenetics on 2 fronts

CPIC: Implementing PGx
a PharmGKB & PGRN collaboration

Clinical Pharmacogenetics Implementation Consortium

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PG4KDS Protocol

Long-term goal: preemptive pharmacogenetic testing as the standard of care… for everyone
All CPIC guidelines.

Survey: top 3 challenges to implementing pharmacogenetics in the clinic

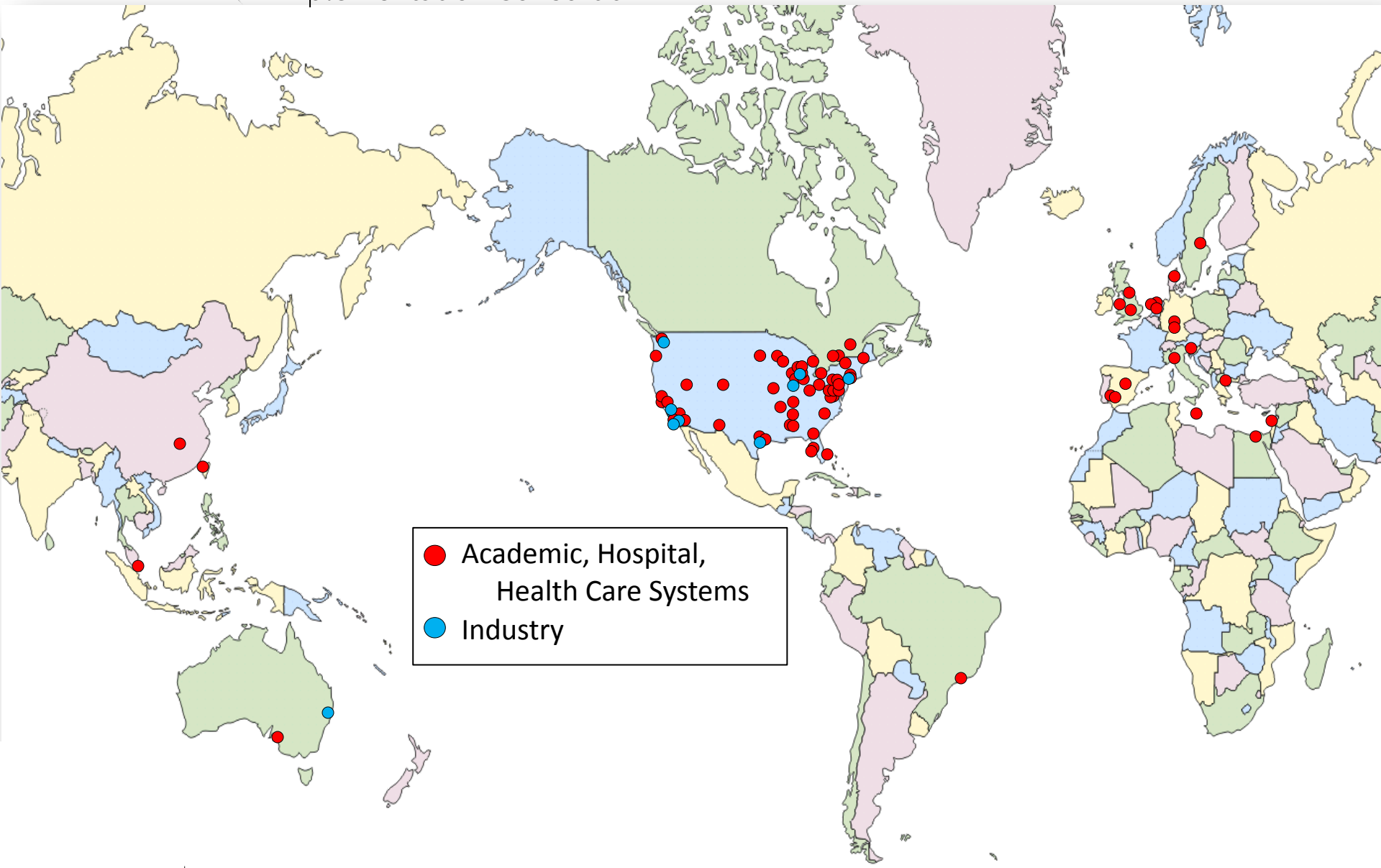
- 95% of respondents selected: “process required to translate genetic information into clinical actions”
- Next 2 responses
  - Genotype test interpretation (e.g. using genotype information to assign phenotype)
  - Providing recommendations for selecting the drug/gene pairs to implement

Clin Pharmacol Ther. 2011 89:464-7.

- formed in late 2009 as a shared project between PharmGKB and the PGRN
- CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy.
  - Not WHETHER tests should be ordered.
- Key Assumption:
  - Clinical high-throughput and pre-emptive genotyping will become more widespread.
  - Clinicians will be faced with having patients' genotypes available even if they did not order test with drug in mind.

CPIC™
Clinical Pharmacogenetics Implementation Consortium

2016 Members



CPIC level A (high or moderate actionability) guideline genes (n=14) and drugs, Feb 2016

- *TPMT*
  - MP, TG, azathioprine
- *CYP2D6*
  - Codeine, tramadol, hydrocodone, oxycodone, TCAs
- *CYP2C19*
  - TCAs, clopidogrel, voriconazole
- *VKORC1*
  - warfarin
- *CYP2C9*
  - Warfarin, phenytoin
- *HLA-B*
  - Allopurinol, CBZ, abacavir, phenytoin
- *CFTR*
  - ivacaftor
- *DPYD*
  - 5FU, capecitabine, tegafur
- *G6PD*
  - rasburicase
- *UGT1A1*
  - Irinotecan, atazanavir
- *SLCO1B1*
  - simvastatin
- *IFNL3 (IL28B)*
  - interferon
- *CYP3A5*
  - Tacrolimus
- *RYR1*
  - NM blockers

https://www.pharmgkb.org/page/cpicGeneDrugPairs

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

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

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 Implementation Consortium Guidelines for *HLA-B* Genotype and Carbamazepine Dosing

SG Leckband[1,2], JR Kelsoe[1,2], HM Dunnenberger[3], AL George Jr[4], E Tran[1], R Berger[1], DJ Müller[5,6], M Whirl-Carrillo[7], KE Caudle[3] and M Pirmohamed[8]

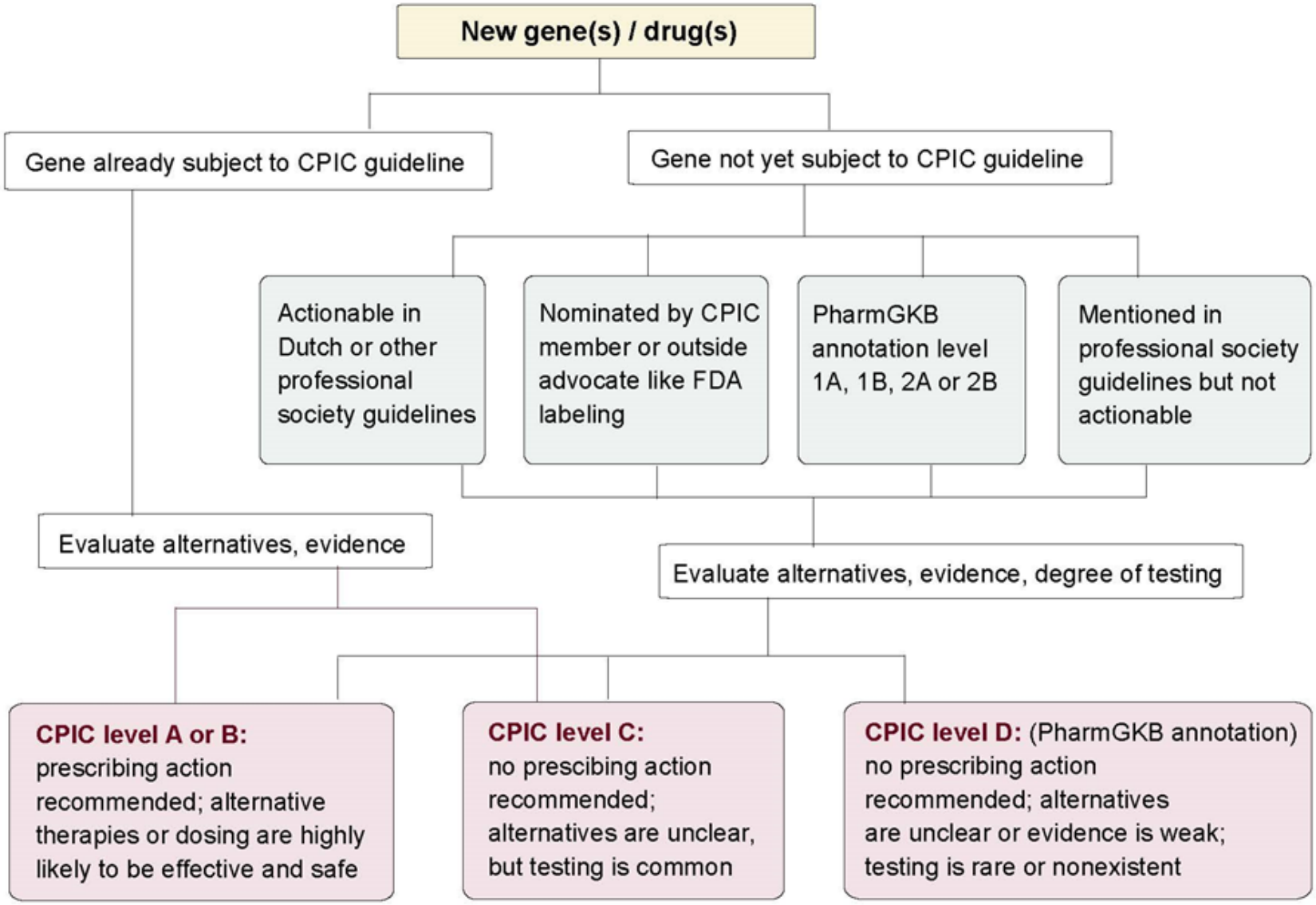
linical Pharmacogenetics Implementation onsortium (CPIC) Guidelines for Codeine herapy in the Context of *Cytochrome P450 2D6 CYP2D6*) Genotype

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

How do we impose some order on process of deciding what to implement in the clinic, and when?

Initial prioritization considerations for new gene/drug groups

(may change over time as evidence and experience accumulates)



Guidelines: 20 level A, 9 level B **20 level C** **60-100 level D**

Evidence considered for clinical implementation of pharmacogenetic testing: gene/drug specific

- Association of the genetic variation with drug effect----*GWAS can contribute here*
- randomized clinical studies of genetically-based prescribing outcomes versus "standard of care"
- pre-clinical and clinical studies linking pharmacologic effects or drug concentrations to genomic variation
- case reports
- *in vivo* PK or other functional studies
- *in vitro* functional studies

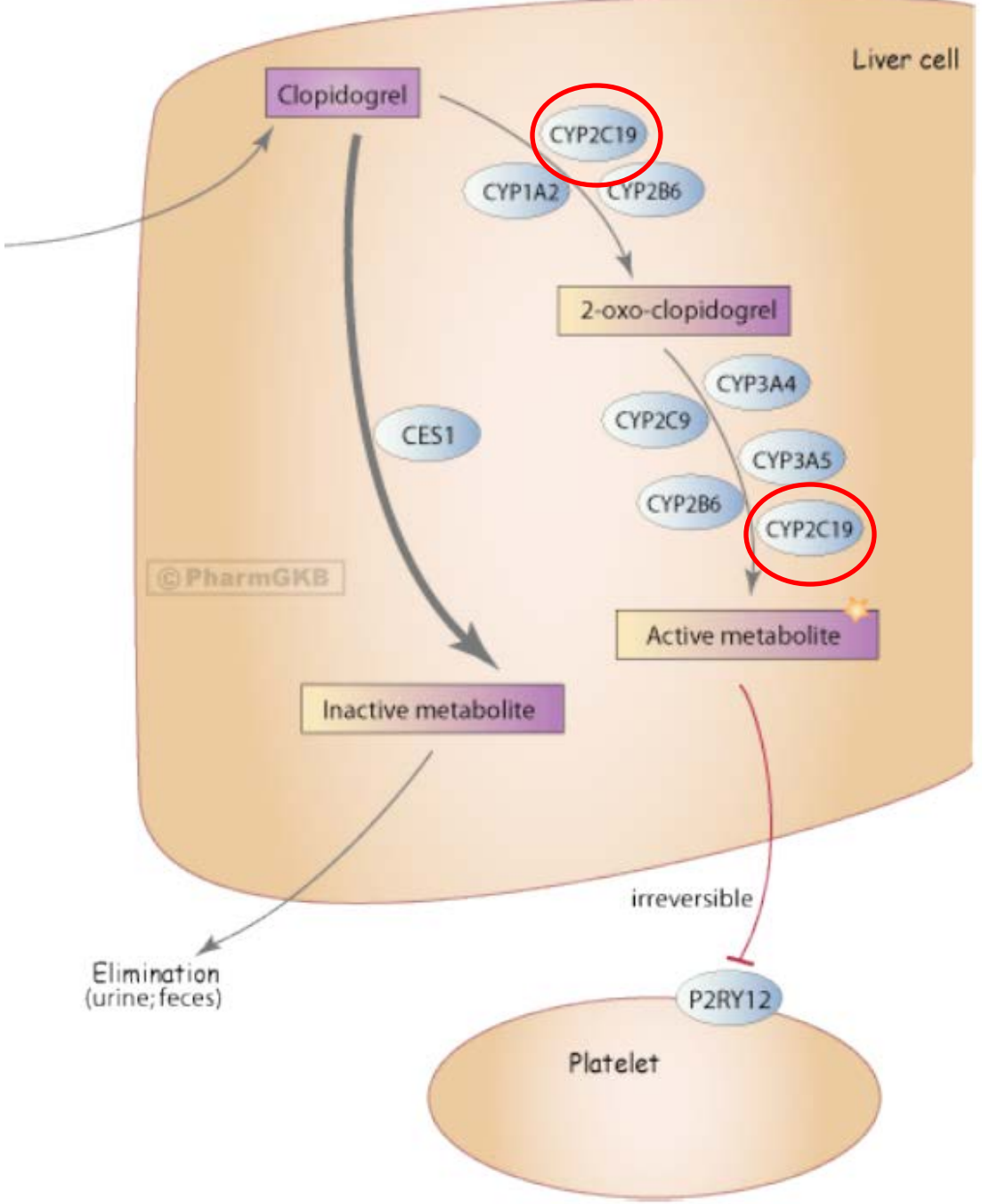
Caudle et al, *Current Drug Metab* 2014

Evidence considered for clinical implementation of pharmacogenetic testing: extra gene/drug

- therapeutic index for the drug(s)
- severity of underlying disease
- consequences of suboptimal prescribing
- availability of genetic tests
- availability of and evidence for alternative therapy

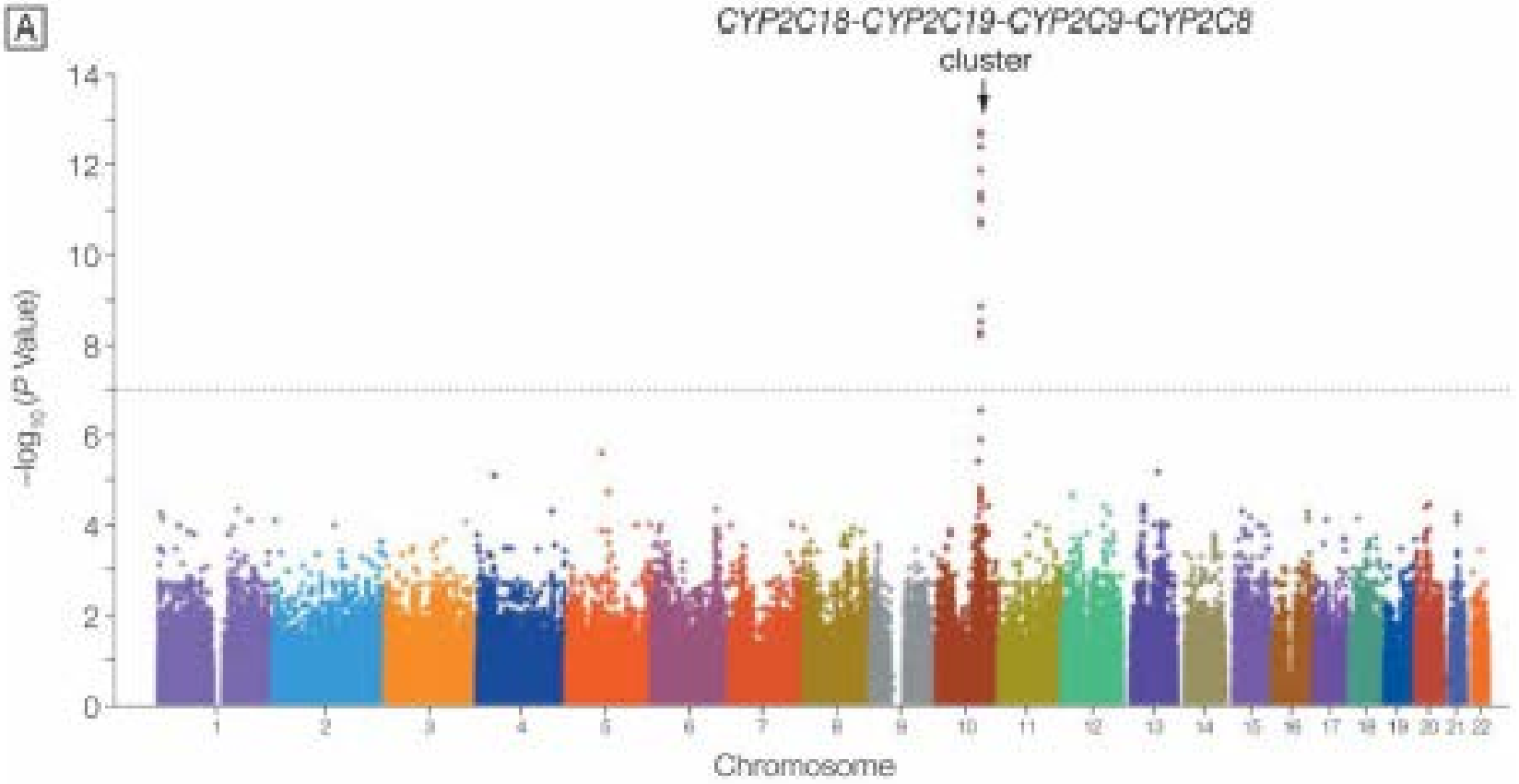
Caudle et al, *Current Drug Metab* 2014

Clopidogrel requires CYP2C19 to be activated in liver; *CYP2C19* was candidate gene for clopidogrel's antiplatelet effect



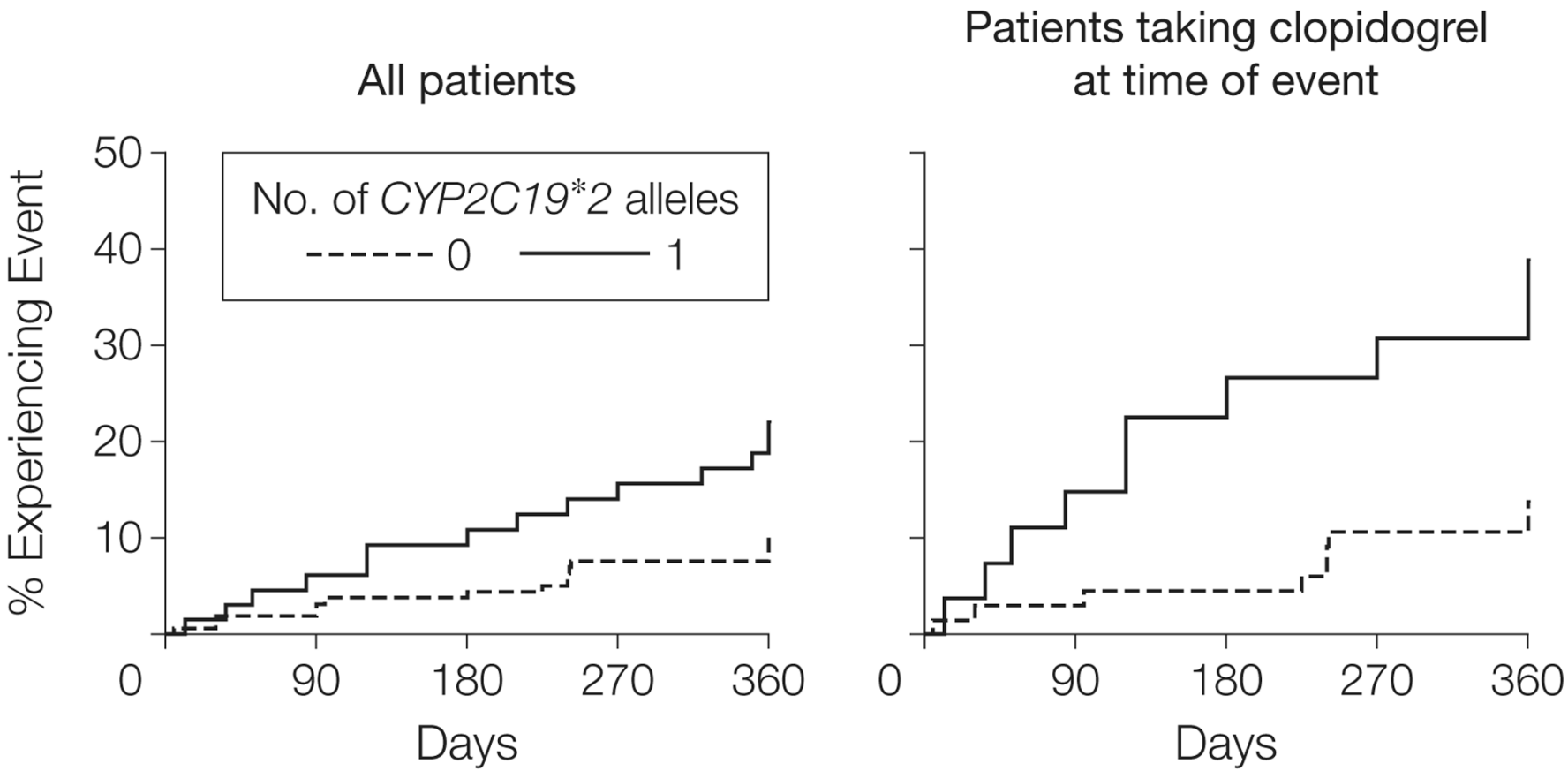
Pharmgkb.org

GWAS for platelet aggregation response to clopidogrel confirmed importance of *CYP2C19* genetic variation



Shuldiner et al JAMA 2009

More CV events in those with *CYP2C19*2* inactive alleles



Shuldiner et al JAMA 2009

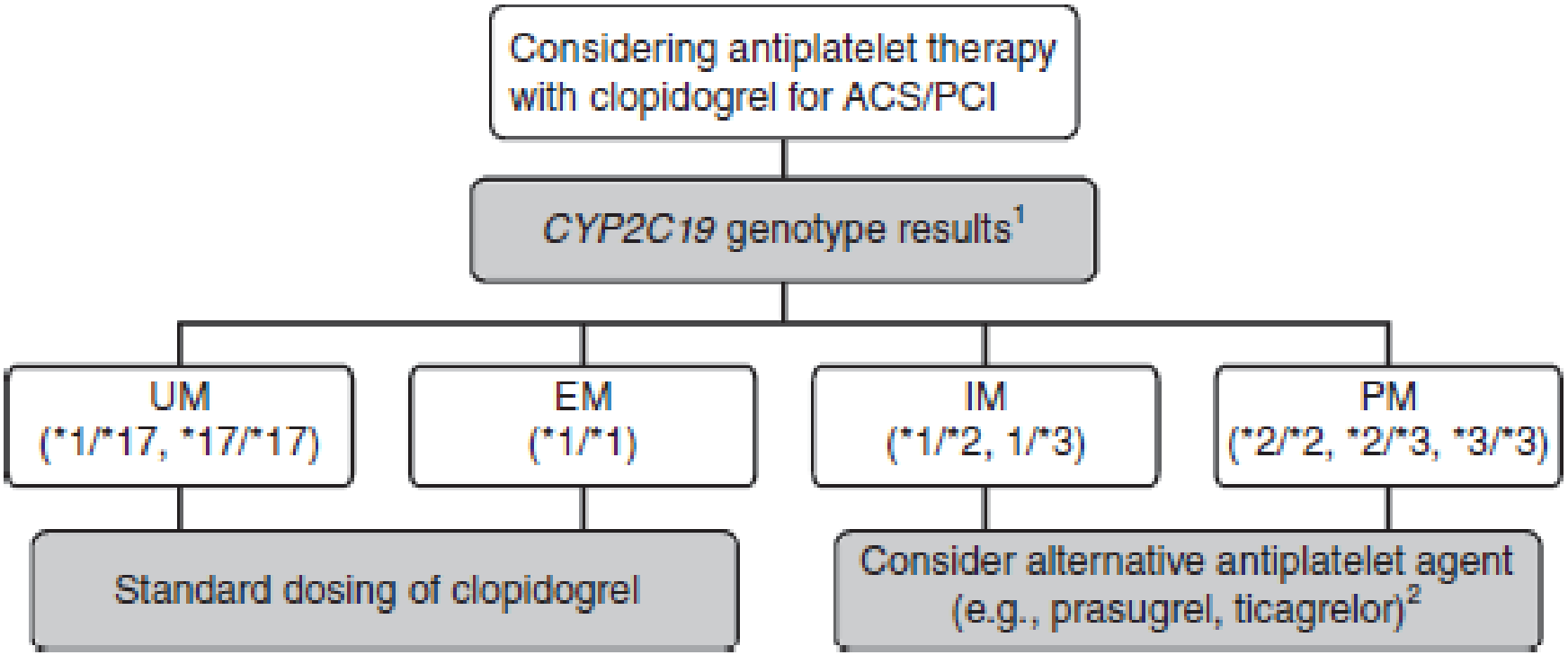
Evidence considered for clinical implementation of pharmacogenetic testing: extra gene/drug

- therapeutic index for the drug(s)
  - Bleeding vs thrombosis
- severity of underlying disease
  - Stroke, myocardial infarction
- consequences of suboptimal prescribing
  - Death, serious morbidity
- availability of genetic tests
  - yes
- availability of and evidence for alternative therapy
  - yes

Caudle et al, *Current Drug Metab* 2014

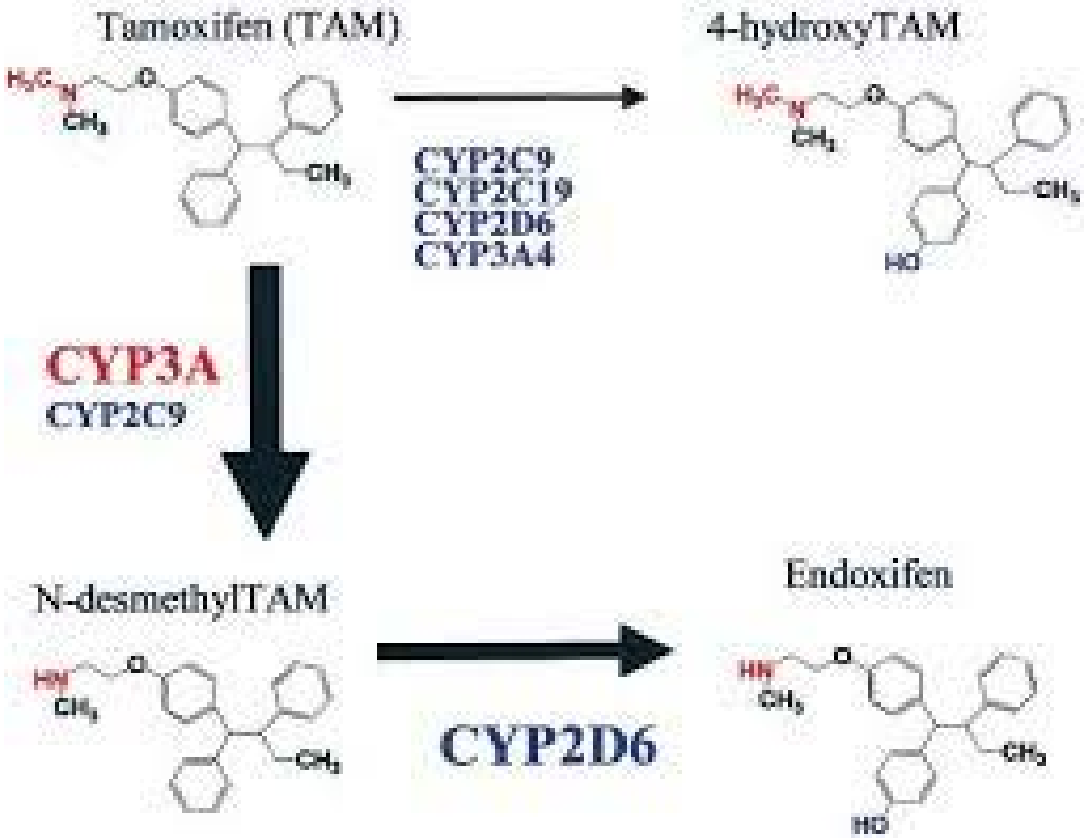
Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C19* Genotype and Clopidogrel Therapy: 2013 Update

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

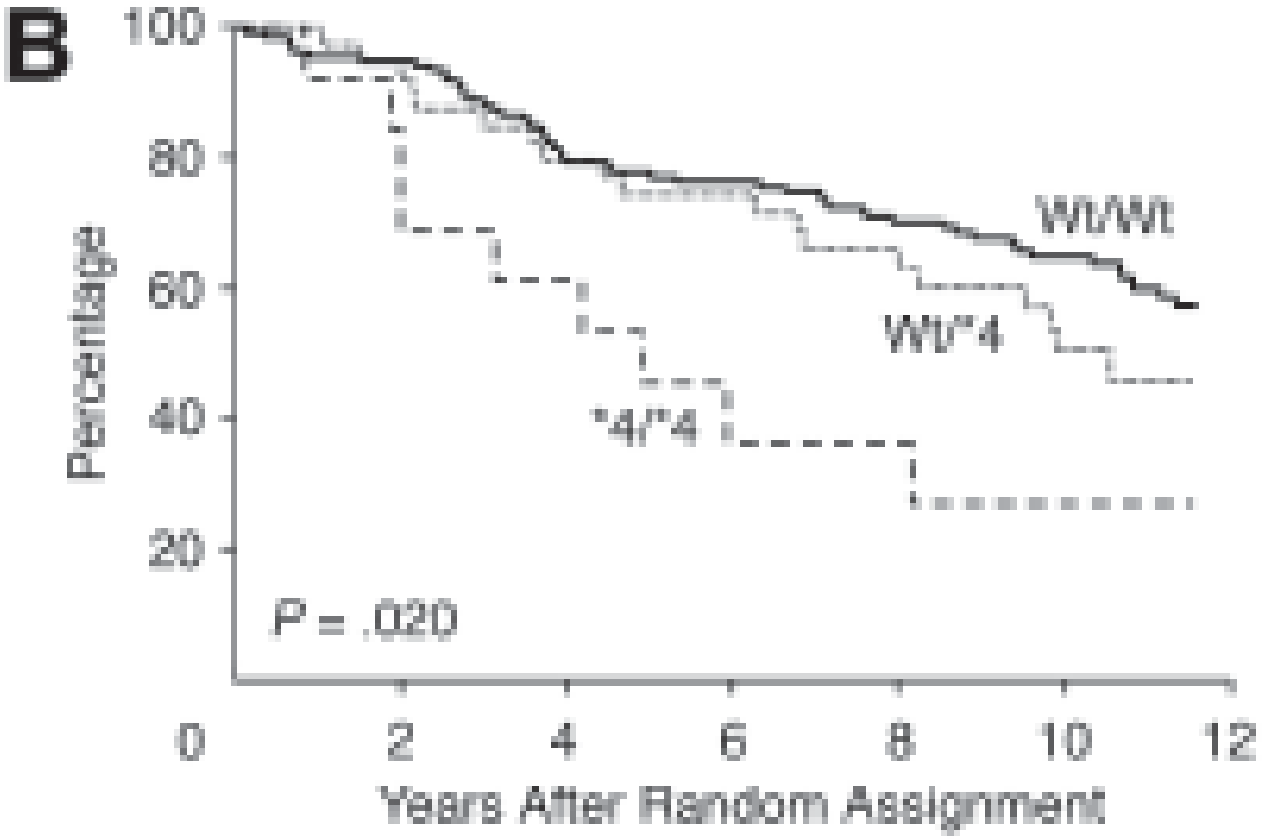


Clin Pharm Ther 2013

Alternatives may be unclear: example CYP2D6 and tamoxifen



Lower disease-free survival in pts with breast CA treated with tamoxifen with *CYP2D6* deficient genotype; but alternative therapy not clear (for some pts)



c/w tamoxifen being activated by CYP2D6

Goetz et al J Clin Oncol 23:9312-9318.

17 genes, 86 drugs with pharmacogenetically-based prescribing

Number of current and planned CPIC genes, drugs and anticipated guidelines.	Genes	Drugs	Anticipated number of unique guidelines
Strong or Moderate prescribing action-CPIC level A	14	36	20 (14 published)
Optional prescribing actions-CPIC level B	7[a]	50	9
No prescribing actions-CPIC level C	16[b]	47	20

[a]Currently this is 3 unique genes (four are already subjects of CPIC level A guidelines). [b]Currently this is 13 unique genes (three are also subject to CPIC level A or B guidelines for other drugs).

Feb 2016

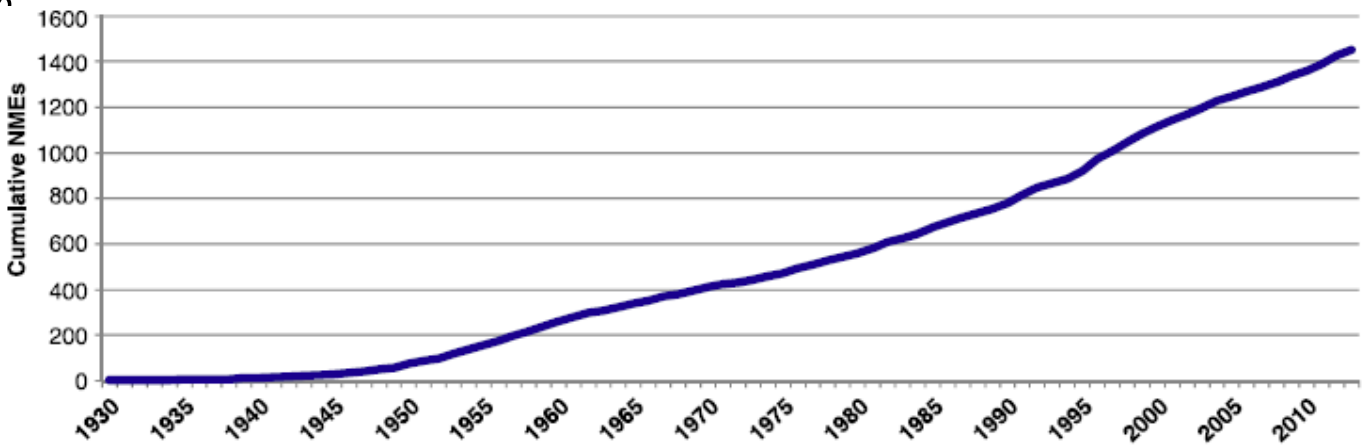
There are approximately 1200 FDA-approved medications (~1450 new drugs but ~ 250 exits)

Morphine 1827

Aspirin 1899

Food & Drug Act 1906

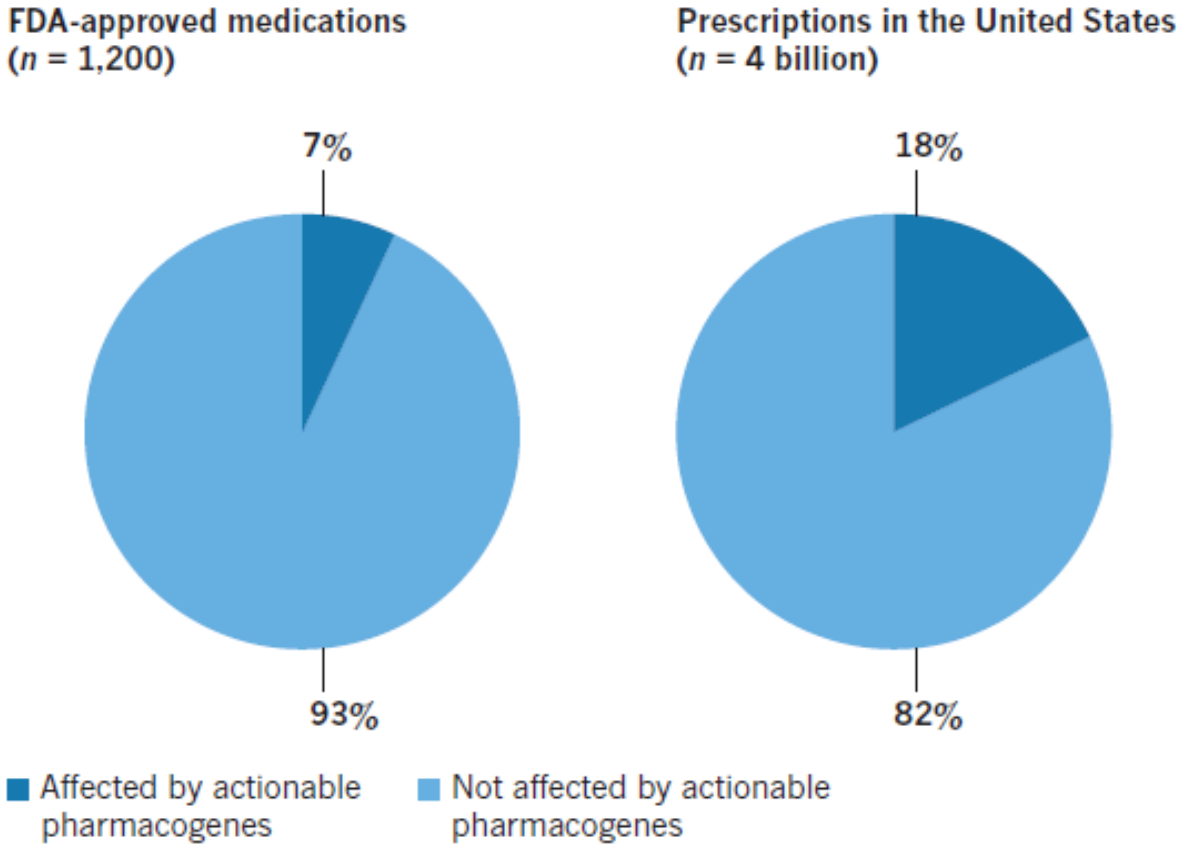
1820-1920



Kinch et al

Drug Discovery Today • Volume 19, Number 8 • August 2014

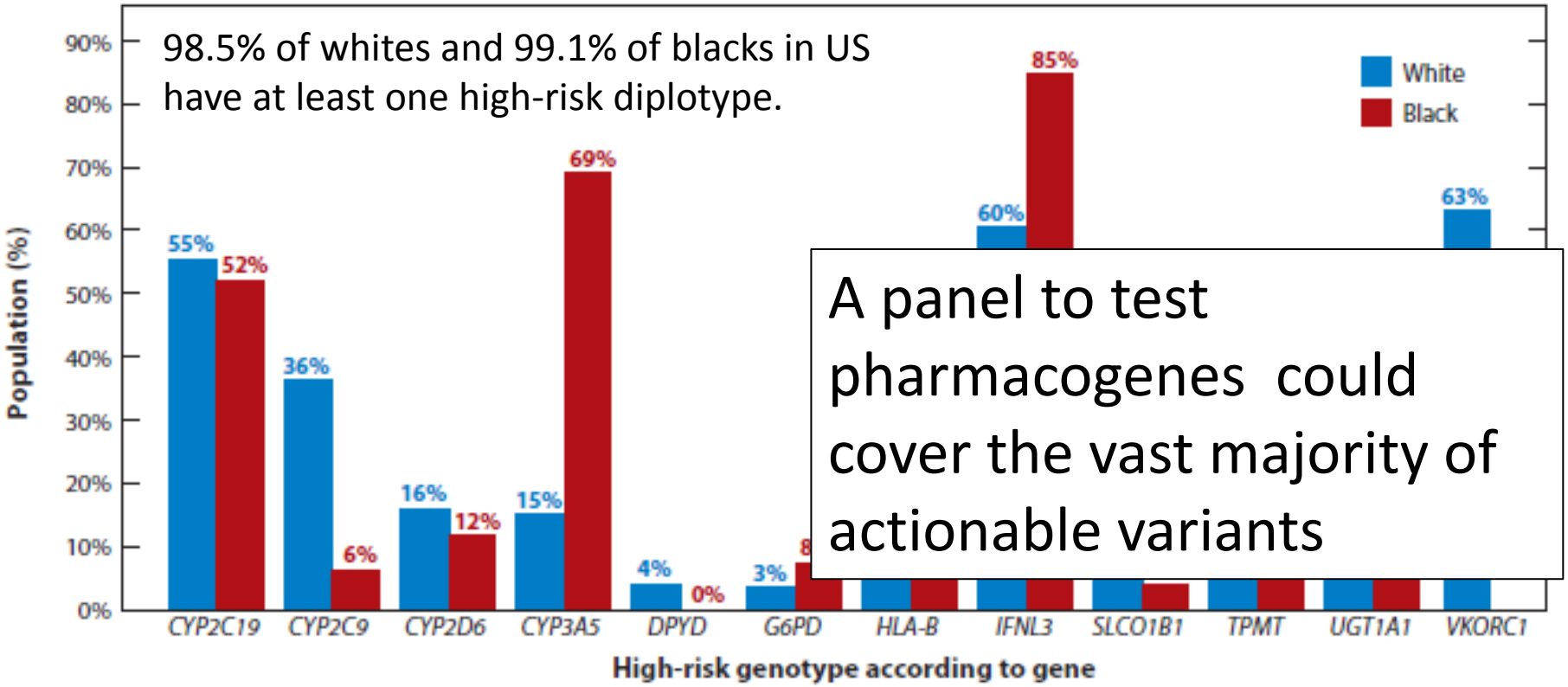
How many gene/drug pairs should be used in the clinic now?



- ~ 1200 chemical entities approved as drugs
  - http://www.pharmgkb.org/page/cpicGeneDrugPairs

Relling & Evans, *Nature,* 2015

99% of population has high-risk diplotype for at least one of 12 CPIC genes



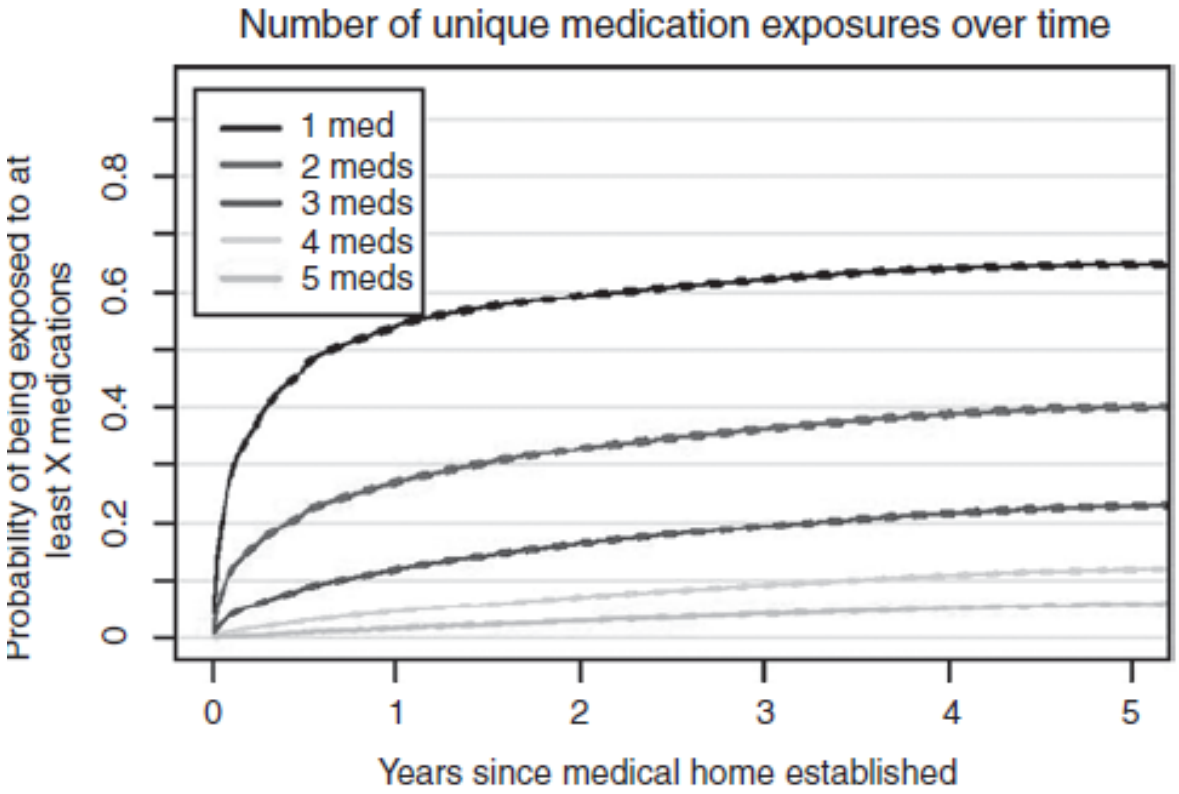
A panel to test pharmacogenes could cover the vast majority of actionable variants

Dunnenberger et al *Ann Rev Pharm Tox* 2015

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…..



CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 92 NUMBER 2 | AUGUST 2012

~ 60 “Pharmacogenetically High Risk” Drugs, 13 CPIC genes

Abacavir	Fluorouracil	Phenazopyridine
allopurinol	haloperidol	phenytoin
amitriptyline	Hydroxychloroquine	primaquine
aripiprazole	interferon	probenecid
atomoxetine	Irinotecan	propafenone
azathioprine	ivacaftor	Rabeprazole
Capecitabine	lev	
carbamazepine	me	
carvedilol	M	
Chloramphenicol	me	
chlorquine	M	
ciprofloxacin		
clopidogrel	moxiflocacin	
clozapine	nilotinib	tetrabenazine
codeine	Nitrofurantoin	Thioguanine
Dapsone	norfloxacin	thioridazine
diazepam	nortriptyline	tolterodine
Dimercaprol	ondansetron	tramadol
doxepin	oxycodone	venlafaxine
esomeprazole	paroxetine	
fluoxetine	Peg-interferon	

2023 of 4245 patients (48%) at St. Jude received at least one of 63 “high-risk” drugs in a 1-yr period.

Dunnenberger et al Ann Rev Pharm Tox 2015

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

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

- Affy DMET array: over 1 million features to interrogate 1900 polymorphisms in 230 genes
  - *CYP2D6* Copy number assay
- For less money than we spend on 1-2 genes, we can interrogate 230 genes (Fernandez et al, *Clin Pharm Ther,* 2012)
  - Makes pre-emptive genotyping a possibility
  - Includes 9 CPIC genes

PG4KDS : CLINICAL IMPLEMENTATION OF PHARMACOGENETICS at ST. JUDE

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

- Not whether to implement, but how
- Opened for patient accrual May 2011
- >3000 patients enrolled on the study
- Goal: all SJ pts, all CPIC gene/drug pairs

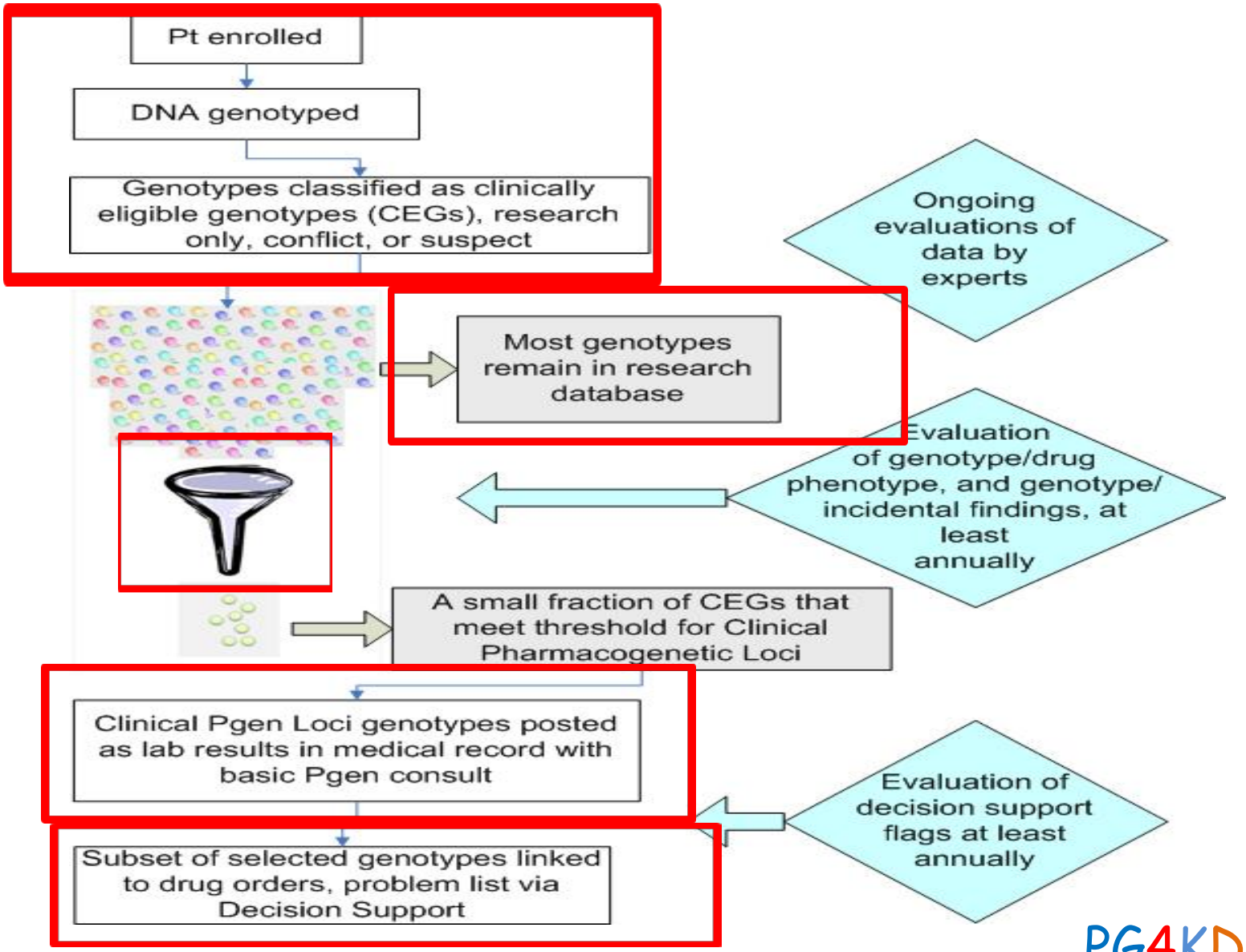
Hoffman JM, et al. Am J Med Genet C Semin Med Genet. 2014

PG4KDS : CLINICAL IMPLEMENTATION OF PHARMACOGENETICS at ST. JUDE

- Use pharmacogenetically-based array (DMET Plus + CYP2D6, Dr. Broeckel, MCW) (Fernandez CA, et al. *Clin Pharmacol Ther*. 2012 92:360-5).
- Don't put results in EHR without some computational clinical decision support (CDS) to actively guide prescribing
- Updating: once result is ready for 1 patient, migrate results for all past and future pts to EHR

Hoffman JM, et al. Am J Med Genet C Semin Med Genet. 2014

The process



PG4KDS

Some steps in PG4KDS Implementation

- QC the genotype data
- Translate into machine-readable clinical test results
- Translate diplotype into phenotype
- Translate phenotype into clinical interpretations for clinicians and pts
- Link high-risk phenotypes to actions: interruptive CDS, medication review
- Develop educational materials, competencies

#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

DMET_8170_CYP2D6_translation.txt - Notepad

File Edit Format View Help

```
#SJAccession=08-155-0435B
#PatientName=XXXXX
#DMETFile=DMET_8170.dmet_GT.txt
#TubeNumber=8170
#PatientID=(0000)02XXXX
#SampleType=PGEN DNA
#TranslationFile=DMET_Plus.v1.20101104DRAF
#AnnotationFile=DMET_Plus.v1.20090910.dc_a
#ReporterBuild=0.8.5
#VerifiedList=VerifiedbyAffy_Nov08 marker
PharmGKB link    http://www.pharmgkb.org/do
Independent Copy Number 2
Called Interpretation Code          UNIQ+UNK
Called Diplotypes Possible          *1/*41
Called Novel Diplotypes Possible          *2
Copy Number Corrected Alleles    NA
Number Non-reference Probe Sets 5
Probe Set ID    Affy Verified   Genome Pos
AM_12261        Y       Ch22:40853887   rs
AM_12257        Y       Ch22:40853749   rs28371725      G/A     Ref/Var *41     CYP2D6*41_2988G>A(SpliceDefect)
AM_15502        N       Ch22:40858512   rs1080983       G/A     Ref/Var -       CYP2D6_-1770G>A
AM_12277        Y       Ch22:40855076   rs1058164       G/C     Ref/Var -       CYP2D6_1661G>C(V136V)
AM_12247        Y       Ch22:40852557   rs1135840       G/C     Ref/Var S486T   CYP2D6_4180G>C(S486T)
Number Reference only Probe Sets        25
Probe Set ID    Affy Verified   Genome Position dbSNP RS ID     Genotype        Call    Contributes To Alleles  Descri
AM_12285        Y       Ch22:40856638   rs1065852       C/C     Ref/Ref *4,*10,*14A,*56B,*64    CYP2D6_100C>T(P34S)
AM_12284        Y       Ch22:40856614   rs5030862       G/G     Ref/Ref *12     CYP2D6*12_124G>A(G42R)
AM_12283        N       Ch22:40856600   rs72549357      T/T     Ref/Ref *15     CYP2D6*15_137insT
AM_12281        Y       Ch22:40855856   rs5030863       G/G     Ref/Ref *11     CYP2D6*11_883G>C(SpliceDefect)
AM_12280        Y       Ch22:40855716   rs28371706      C/C     Ref/Ref *17,*40,*64     CYP2D6_1023C>T(T107I)
AM_12278        N       Ch22:40855078   rs61736512      G/G     Ref/Ref *29     CYP2D6*29_1659G>A(V136I)
AM_12276        Y       Ch22:40855030   rs5030655       T/T     Ref/Ref *6      CYP2D6*6_1707delT
AM_12275        N       Ch22:40854979,Ch22:40854979     rs5030865       G/G     Ref/Ref *14A,*14B,*8    CYP2D6*14or*8_
AM_12274        Y       Ch22:40854891   rs3892097       G/G     Ref/Ref *4      CYP2D6*4_1846G>A(SpliceDefect)
AM_12272        Y       Ch22:40854873   rs72549356      -/-     Ref/Ref *40     CYP2D6*40_1863ins(TTTCGCCCC)2
AM_12270        Y       Ch22:40854763   rs72549354      -/-     Ref/Ref *20     CYP2D6*20 _1973insG
AM_12268        Y       Ch22:40854195   rs72549353      AACT/AACT       Ref/Ref *19     CYP2D6*19_2539delAACT
AM_12267        Y       Ch22:40854188   rs35742686      A/A     Ref/Ref *3      CYP2D6*3_2549delA
AM_12266        Y       Ch22:40854157   rs72549352      -/-     Ref/Ref *21     CYP2D6*21_2573insC
AM_12265        Y       Ch22:40854147   rs72549351      GACT/GACT       Ref/Ref *38     CYP2D6*38_2587delGACT
AM_12264        Y       Ch22:40854120   rs5030656       AGA/AGA Ref/Ref *9      CYP2D6*9_2615delAAG
AM_12259        Y       Ch22:40853802   rs5030867       A/A     Ref/Ref *7      CYP2D6*7_2935A>C(H324P)
AM_12258        Y       Ch22:40853787   rs72549349      G/G     Ref/Ref *44     CYP2D6*44_2950G>C(SpliceDefect)
AM_12255        Y       Ch22:40853554   rs59421388      G/G     Ref/Ref *29     CYP2D6*29_3183G>A(V338M)
AM_12254        Y       Ch22:40853536   rs72549347      C/C     Ref/Ref *56A,*56B       CYP2D6*56_3201C>T(R344X)
AM_12252        Y       Ch22:40853477   rs72549346      -/-     Ref/Ref *42     CYP2D6*42_3259insGT
AM_12248        Y       Ch22:40852603   rs1135836       T/T     Ref/Ref *18     CYP2D6*18_4125dupGTGCCCACT
AM_15506        N       Ch22:40858920   rs28360521      G/G     Ref/Ref -       CYP2D6_-2178G>A
AM_15503        N       Ch22:40858703,Ch22:40858703     -       C/C     Ref/Ref -       CYP2D6_-1961C>G>A
AM_12291        Y       Ch22:40858326   rs1080985       C/C     Ref/Ref -       CYP2D6_-1584C>G
```

Be comprehensive for those few genes:

1. define most important variants and interrogate them
2. document what was and was not interrogated
3. call gene-centric **diplotypes**—not variants

DMET_8170_CYP2D6_translation.txt - Notepad

File Edit Format View Help

```
#SJAccession=08-155-0435B
#PatientName=XXXXX
#DMETfile=DMET_8170.dmet_GT.txt
#TubeNumber=8170
#PatientID=(0000)02XXXX
#SampleType=PGEN DNA
#TranslationFile=DMET_Plus.v1.20101104DRAFT.full.translation
#AnnotationFile=DMET_Plus.v1.20090910.dc_annot.csv
#ReporterBuild=0.8.5
#VerifiedList=VerifiedbyAffy_Nov08 marker list.txt
PharmGKB link    http://www.pharmgkb.org/do/serve?objId=PA128&objCls=Gene
Independent Copy Number 2
Called Interpretation Code      UNIQ+UNK
Called Diplotypes Possible      *1/*41
Called Novel Diplotypes Possible        *2/UNK
Copy Number Interpreted Alleles    NA
Number Non-reference Probe Sets 5
Probe Set ID    Affy Verified   Genome Position dbSNP RS ID     Genotype        Call    Contributes To Alleles  Descri
AM_12261        Y       Ch22:40853887   rs16947 C/T     Ref/Var *2,*8,*11,*12,*14A,*14B,*17,*19,*20,*21,*29,*40,*41,*4
AM_12257        Y       Ch22:40853749   rs28371725      G/A     Ref/Var *41     CYP2D6*41_2988G>A(SpliceDefect)
AM_15502        N       Ch22:40858512   rs1080983       G/A     Ref/Var -       CYP2D6_-1770G>A
AM_12277        Y       Ch22:40855076   rs1058164       G/C     Ref/Var -       CYP2D6_1661G>C(V136V)
AM_12247        Y       Ch22:40852557   rs1135840       G/C     Ref/Var S486T   CYP2D6_4180G>C(S486T)
Number Reference only Probe Sets        25
Probe Set ID    Affy Verified   Genome Position dbSNP RS ID     Genotype        Call    Contributes To Alleles  Descri
AM_12285        Y       Ch22:40856638   rs1065852       C/C     Ref/Ref *4,*10,*14A,*56B,*64    CYP2D6_100C>T(P34S)
AM_12284        Y       Ch22:40856614   rs5030862       G/G     Ref/Ref *12     CYP2D6*12_124G>A(G42R)
AM_12283        N       Ch22:40856600   rs72549357      T/T     Ref/Ref *15     CYP2D6*15_137insT
AM_12281        Y       Ch22:40855856   rs5030863       G/G     Ref/Ref *11     CYP2D6*11_883G>C(SpliceDefect)
AM_12280        Y       Ch22:40855716   rs28371706      C/C     Ref/Ref *17,*40,*64     CYP2D6_1023C>T(T107I)
AM_12278        N       Ch22:40855078   rs61736512      G/G     Ref/Ref *29     CYP2D6*29_1659G>A(V136I)
AM_12276        Y       Ch22:40855030   rs5030655       T/T     Ref/Ref *6      CYP2D6*6_1707delT
AM_12275        N       Ch22:40854979,Ch22:40854979     rs5030865       G/G     Ref/Ref *14A,*14B,*8    CYP2D6*14or*8_
AM_12274        Y       Ch22:40854891   rs3892097       G/G     Ref/Ref *4      CYP2D6*4_1846G>A(SpliceDefect)
AM_12272        Y       Ch22:40854873   rs72549356      -/-     Ref/Ref *40     CYP2D6*40_1863ins(TTTCGCCCC)2
AM_12270        Y       Ch22:40854763   rs72549354      -/-     Ref/Ref *20     CYP2D6*20 _1973insG
AM_12268        Y       Ch22:40854195   rs72549353      AACT/AACT       Ref/Ref *19     CYP2D6*19_2539delAACT
AM_12267        Y       Ch22:40854188   rs35742686      A/A     Ref/Ref *3      CYP2D6*3_2549delA
AM_12266        Y       Ch22:40854157   rs72549352      -/-     Ref/Ref *21     CYP2D6*21_2573insC
AM_12265        Y       Ch22:40854147   rs72549351      GACT/GACT       Ref/Ref *38     CYP2D6*38_2587delGACT
AM_12264        Y       Ch22:40854120   rs5030656       AGA/AGA Ref/Ref *9      CYP2D6*9_2615delAAG
AM_12259        Y       Ch22:40853802   rs5030867       A/A     Ref/Ref *7      CYP2D6*7_2935A>C(H324P)
AM_12258        Y       Ch22:40853787   rs72549349      G/G     Ref/Ref *44     CYP2D6*44_2950G>C(SpliceDefect)
AM_12255        Y       Ch22:40853554   rs59421388      G/G     Ref/Ref *29     CYP2D6*29_3183G>A(V338M)
AM_12254        Y       Ch22:40853536   rs72549347      C/C     Ref/Ref *56A,*56B       CYP2D6*56_3201C>T(R344X)
AM_12252        Y       Ch22:40853477   rs72549346      -/-     Ref/Ref *42     CYP2D6*42_3259insGT
AM_12248        Y       Ch22:40852603   rs1135836       T/T     Ref/Ref *18     CYP2D6*18_4125dupGTGCCCACT
AM_15506        N       Ch22:40858920   rs28360521      G/G     Ref/Ref -       CYP2D6_-2178G>A
AM_15503        N       Ch22:40858703,Ch22:40858703     -       C/C     Ref/Ref -       CYP2D6_-1961C>G>A
AM_12291        Y       Ch22:40858326   rs1080985       C/C     Ref/Ref -       CYP2D6_-1584C>G
```

All variants tested are documented in EHR

DMET Tracker: QC, avoiding duplicates, conflicts, document problems

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	INT
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	INT 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:** 343[redacted]
- **Accession Number:** 11[redacted]
- **Tube Number:** DNI[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

At any given time, ~ 5-7% of results are in limbo

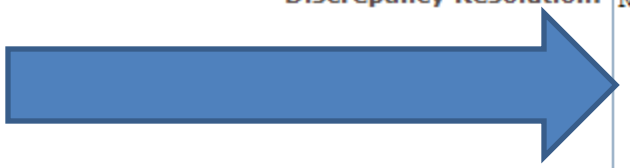
Re-calculate EMR Flag and PK Phenotype by selecting a cross-ref version (v1, 2011-10-13) and clickin

Click here to compose an email about this result.

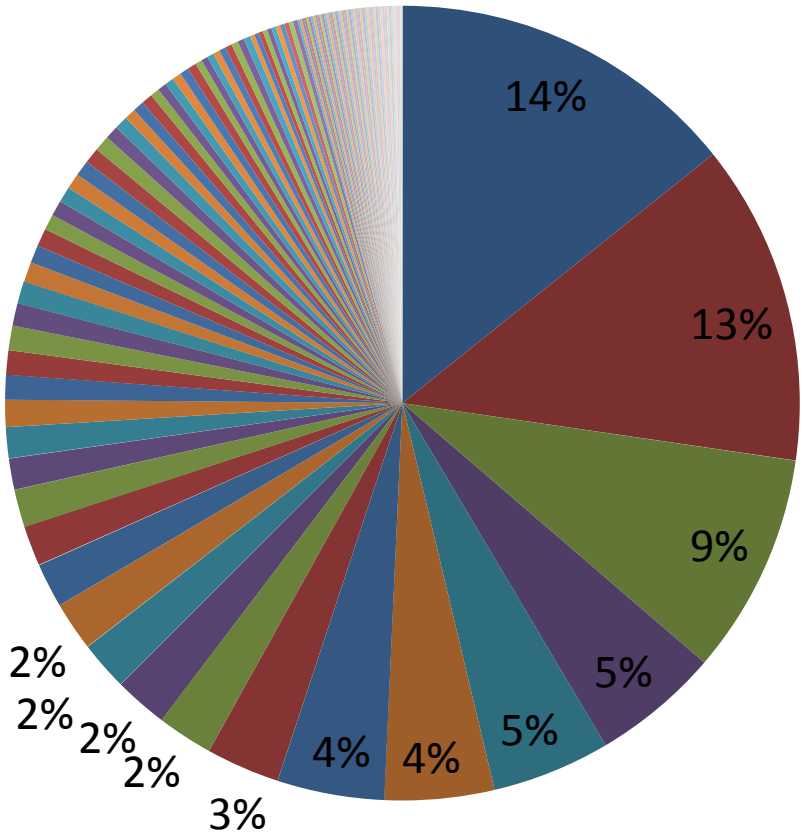
Discrepancy Resolution: None

save your changes?

Discrepancy Resolution

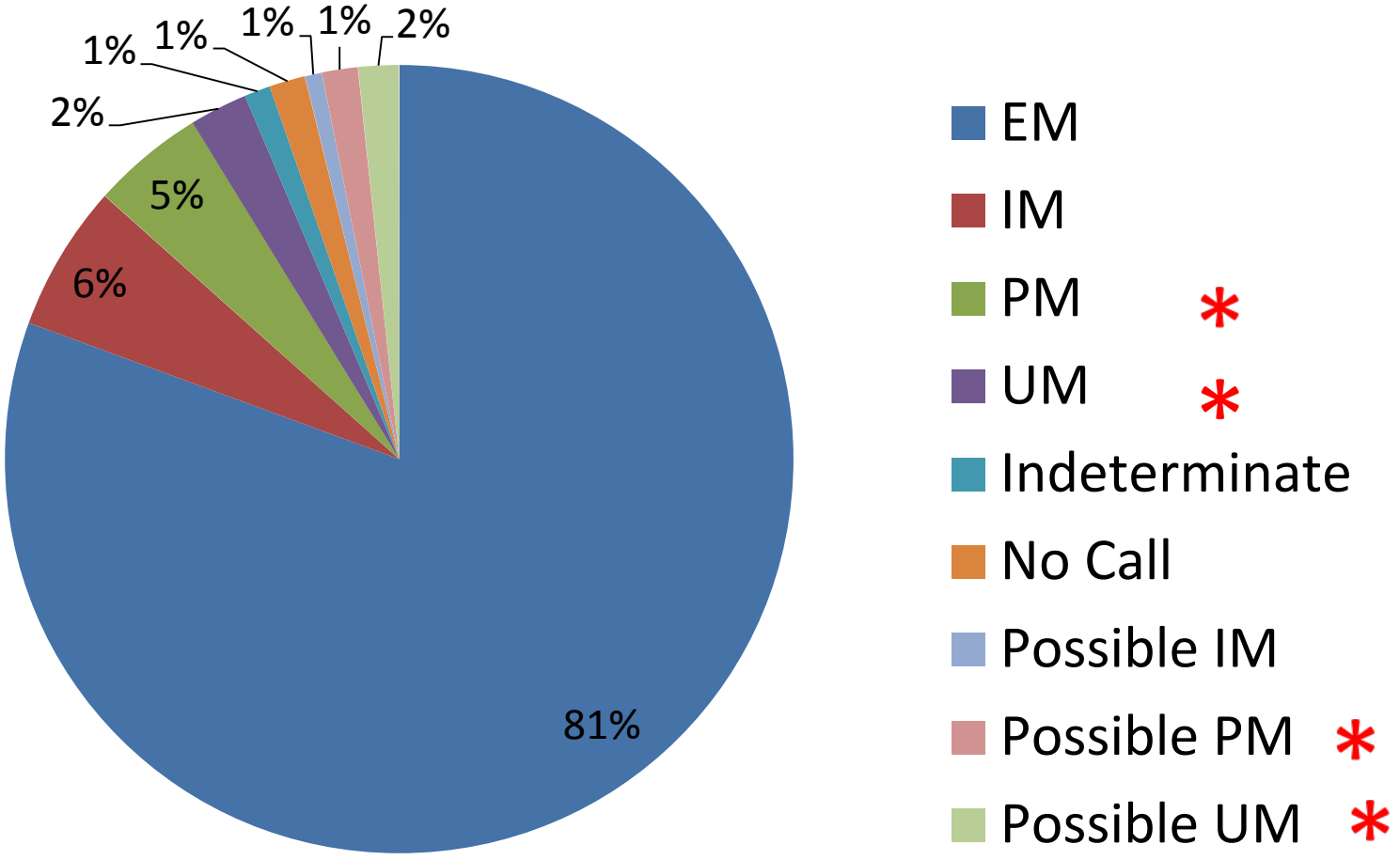


111 genotypes observed for *CYP2D6*

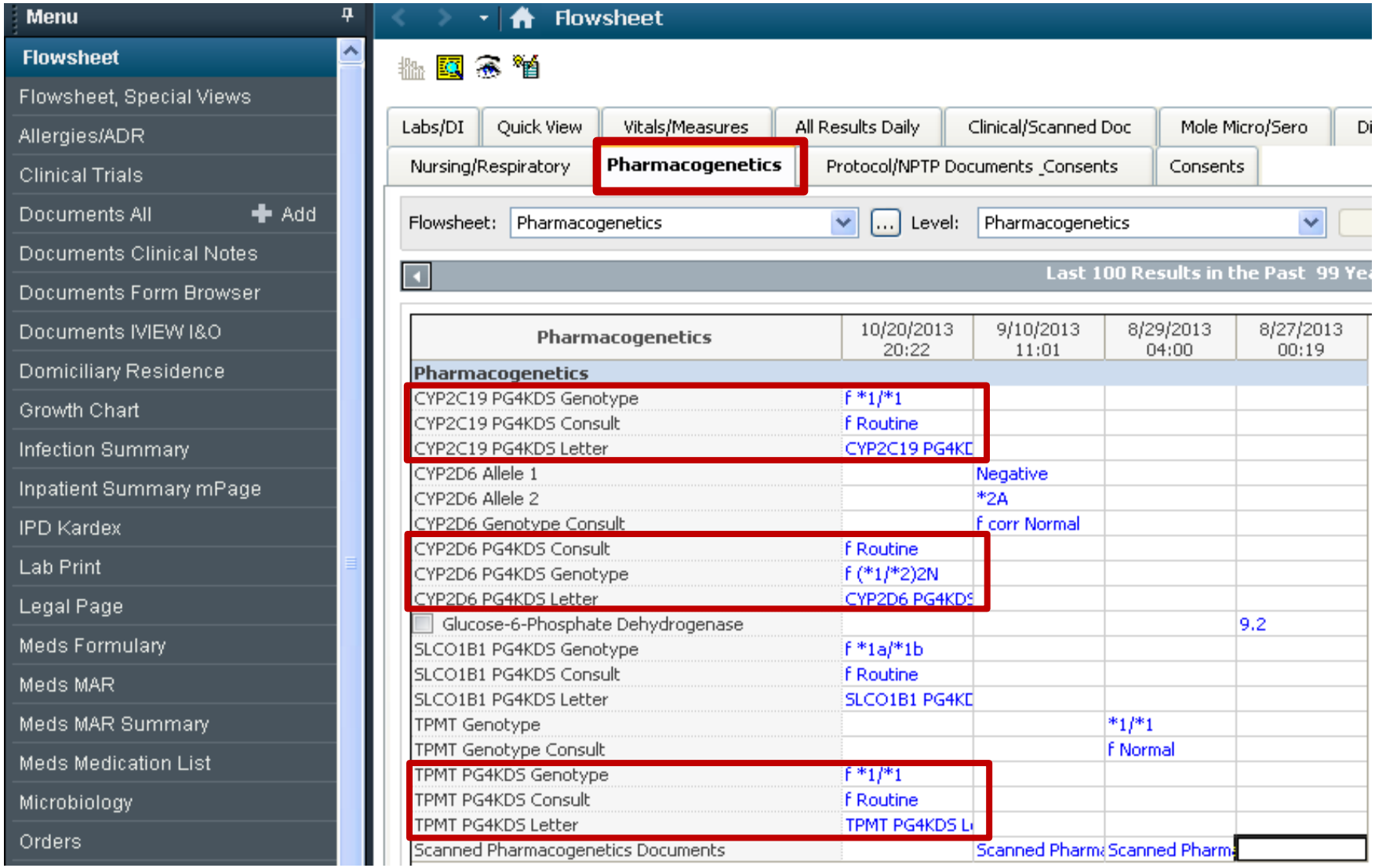


- (*1/*2)2N
- (*1/*4)2N
- (*2/*4)2N
- (*2/*2)2N
- (*4/*4)2N
- (*2/*17)2N
- (*1/*10)2N
- (*4/*41)2N
- (*17/*17)2N
- (*1/*2)3N
- (*4/*4)1N
- (*1/*4)3N
- (*17/*29)2N
- (*1/*3)2N
- (*1/*29)2N
- (*4/*10)2N
- (*2/*2)3N
- (*4/*9)2N
- (*9/*41)2N
- (*2/*6)2N
- (*2/*17,*17/*42)2N
- (*4/*6)2N
- (*5/*5)0N
- (*1/*17)3N
- (*1/*40)2N
- (*2/*41)3N
- (*9/*9)1N
- (*41/*41)1N
- (*10/*29)2N
- (*17/*40)2N
- (*4/*40,*10/*40)2N
- (*2/*2,*2/*42,*42/*42)2N
- (*9/*17)2N
- (*2/*10)2/3/2N
- (*4/*4)2/3/3N
- (*2/*2)2/3/3N
- (*2/*3,*3/*17)2N
- (*1/*2,*1/*41)2N
- (*1/*1)2N
- (*1/*17)2N
- (*1/*41)2N
- (*1/*1)1N
- (*2/*41)2N
- (*2/*29)2N
- (*2/*2)1N
- (-)2N
- (*1/*9)2N
- (*2/*9)2N
- (*2/*10)2N
- (*2/*4)3N
- (*41/*41)2N
- (*2/*3)2N
- (*17/*17)1N
- (*4/*17)2N
- (*29/*29)1N
- (*1/*1)3N
- (*6/*41)2N
- (*1/*4)2/3/3N
- (*29/*41)2N
- (*3/*4)2N
- (*2/*17)3N
- (*1/*10)2/3/3N
- (*4/*29)2N
- (*1/*6)2N
- (*2/*40)2N
- (*4/*29)3N
- (*2/*10)3N
- (*3/*17)2N
- (*29/*40)2N
- (*29/*29)2N
- (*18/*18)1N
- (*1/*4)2/2/1N
- (*1/*4)4N
- (*4/*41)3N
- (*1/*4)2/3/2N
- (*1/*6)1N

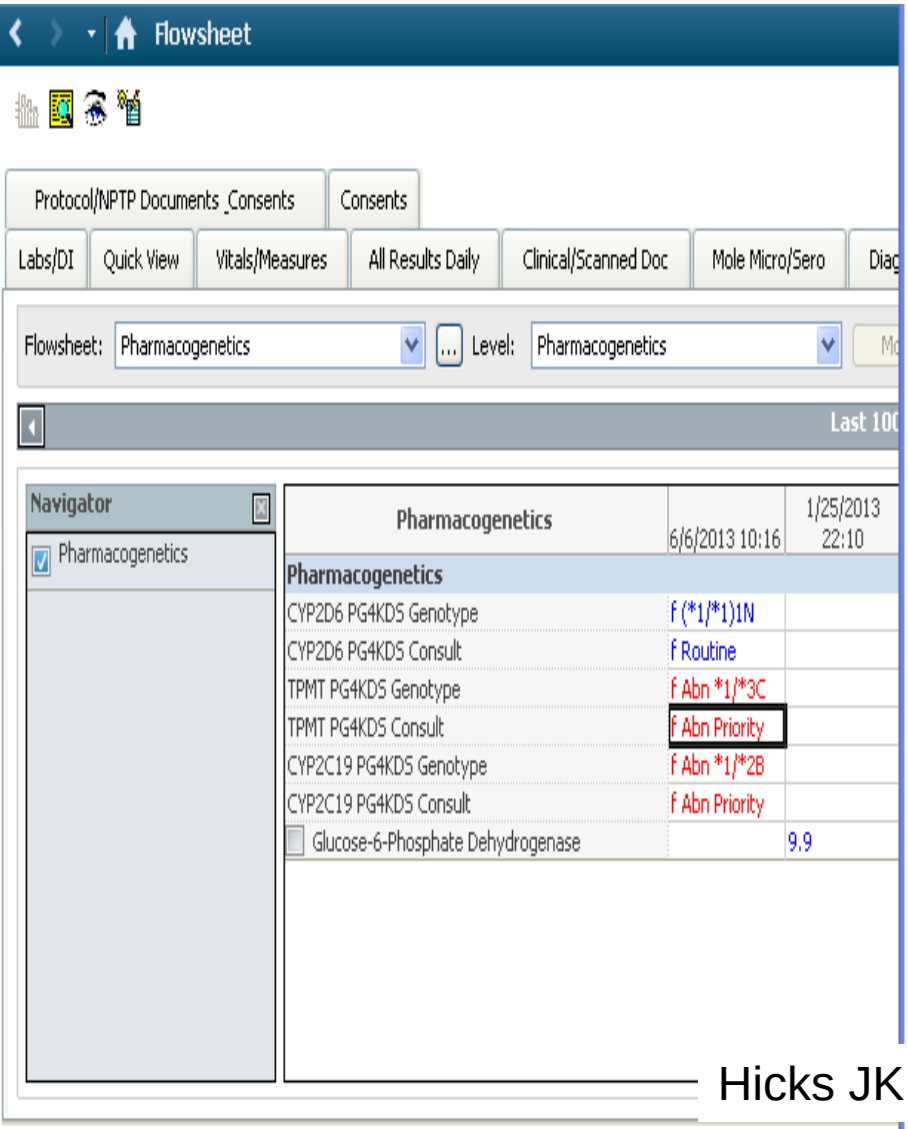
> 111 *CYP2D6* diplotypes have translated into 9 phenotype groups—a few of which are actionable*

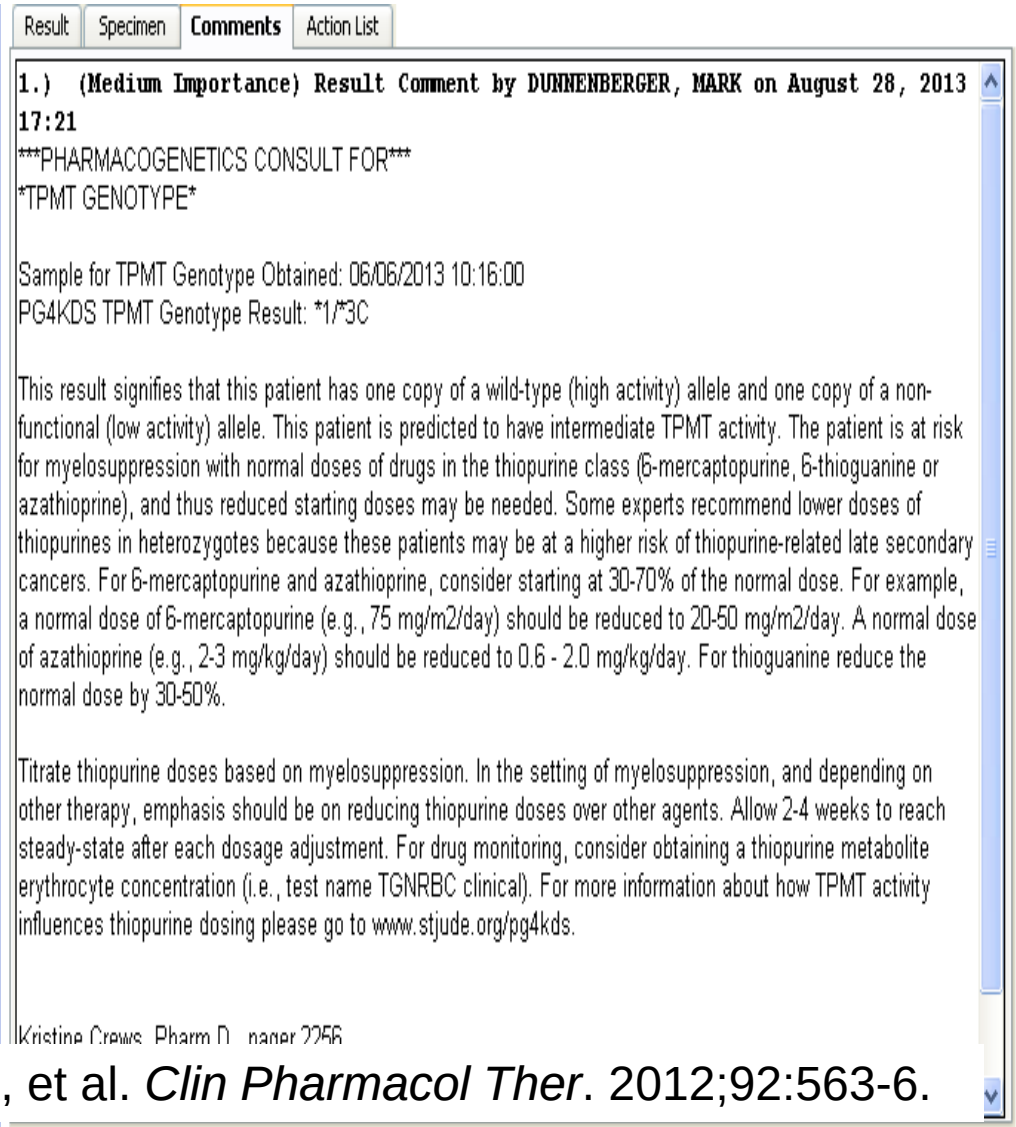


Pharmacogenetics tab added to EHR; all clinically eligible genotypes are entered, along with a gene-specific consult and letter to patient



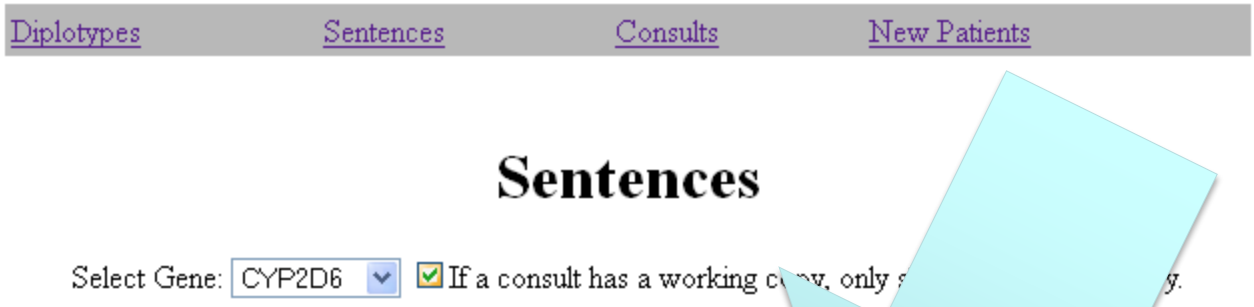
Result and Consult Display: default interpretation is built from ordered, standardized sentences in Consult Builder





Hicks JK, et al. *Clin Pharmacol Ther*. 2012;92:563-6.

Consult Builder



Status	Key Phrase	All
Approved	*1/*5 Diplotype	Diplotype Interpretation
Approved	*10/*5 Diplotype	Diplotype Interpretation
Approved	*16/*5 Diplotype	Diplotype Interpretation
Approved	*17/*5 Diplotype	Diplotype Interpretation
Approved	*2/*5 Diplotype	Diplotype Interpretation
Approved	*29/*5 Diplotype	Diplotype Interpretation
Approved	*3/*5 Diplotype	Diplotype Interpretation
Approved	*36/*5 Diplotype	Diplotype Interpretation
	*4/*5	

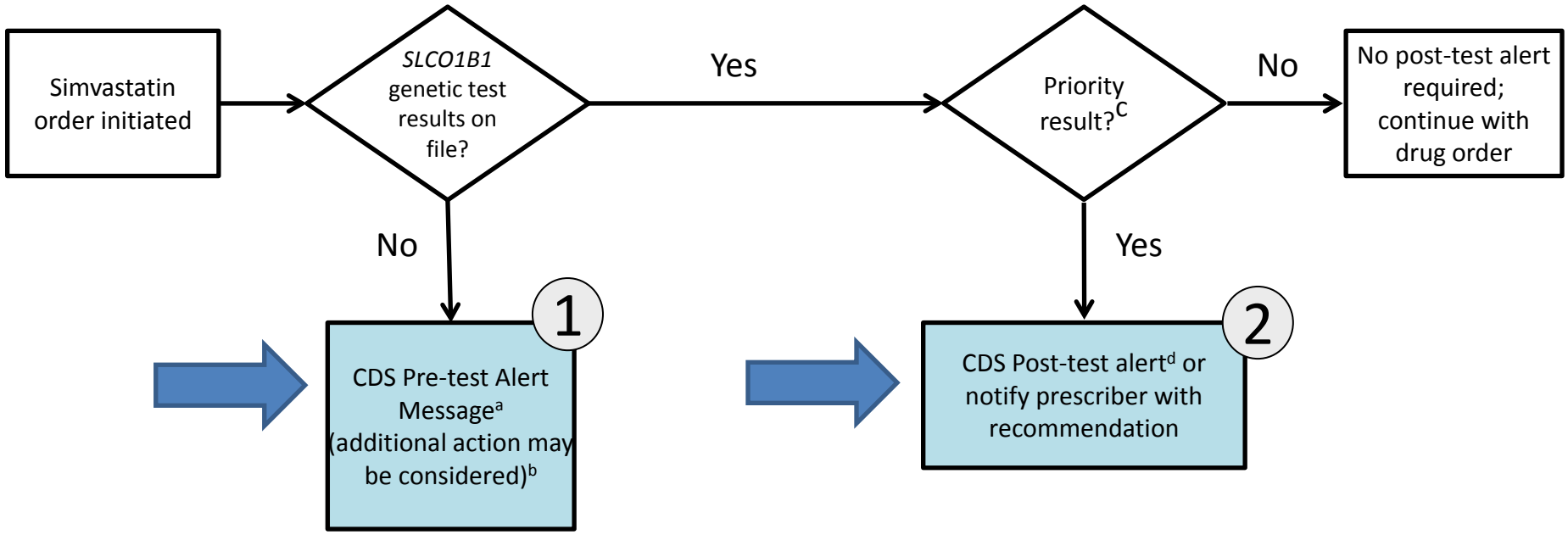
The CYP2D6 genotype result of *1/*1 with a copy number
one copy of a wild-type (*1, normal function) allele and one
The CYP2D6 genotype result of *10/*10 with a copy number of 1 is equivalent to *10/*5. A re
has one copy of a reduced function (*10) allele and one deleted (*5) allele.
The CYP2D6 genotype result of *16/*16 with a copy number of 1 is equivalent to *16/*5. A re
has one copy of a non-functional (*16) allele and one deleted (*5) allele.
The C
has on
The C
one co
The C
has on
The C
one co
The CYP2D6 genotype result of *36/*36 with a copy number of 1 is equivalent to *36/*5. A re
one copy of a non-functional (*36) allele and one deleted (*5) allele.
The CYP2D6 genotype result of *4/*4 with a copy number of 1 is equivalent to *4/*5. A result

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

CPIC Translation Tables: diplotype to phenotype to actionability

Genotype Test Result for *SLCO1B1*	Coded Genotype/Phenotype Summary[a]	EHR Priority Result Notation[b]
*1a/*1a	None	Normal/Routine/Low Risk
*1a/*1b	None	Normal/Routine/Low Risk
*1a/*2	SLCO1B1 Intermediate Function	Abnormal/Priority/High Risk
*1a/*3	SLCO1B1 Intermediate Function	Abnormal/Priority/High Risk
*1a/*4	Indeterminate	None
*1a/*5	SLCO1B1- Intermediate Function	Abnormal/Priority/High Risk
*1a/*6	SLCO1B1 Intermediate Function	Abnormal/Priority/High Risk
*1a/*7	Indeterminate	None
*1a/*8	Indeterminate	None
*1a/*9	SLCO1B1 Intermediate Function	Abnormal/Priority/High Risk
*1a/*10	SLCO1B1 Intermediate Function	Abnormal/Priority/High Risk
*1a/*11	Indeterminate	None
*1a/*12	Indeterminate	None
*1a/*13	Indeterminate	None
*1a/*14	SLCO1B1 Increased Function	None
*1a/*15	SLCO1B1 Intermediate Function	Abnormal/Priority/High Risk
*1a/*16	Indeterminate	None
*1a/*17	SLCO1B1 Intermediate Function	Abnormal/Priority/High Risk
*1a/*18	Indeterminate	None
*1a/*19	Indeterminate	None

SLCO1B1 Genotype and Simvastatin: Point of Care Clinical Decision Support



Note: Circled numerals refer to ***Supplementary Table 12***

[a,d] See **Supplementary Table S12** for diplotype/phenotype specific pre- and post-test alert example.
[b]Additional actions may include ordering a pharmacogenetic test, preventing the clinician from ordering the medication or allowing the clinician to cancel out of the alert.
[c]Priority result defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.

Clinical Pharmacology & Therapeutics (2014); 96 4, 423–428

Supplemental Table S12. Example Implementation of this Guideline: Point of Care Clinical Decision Support

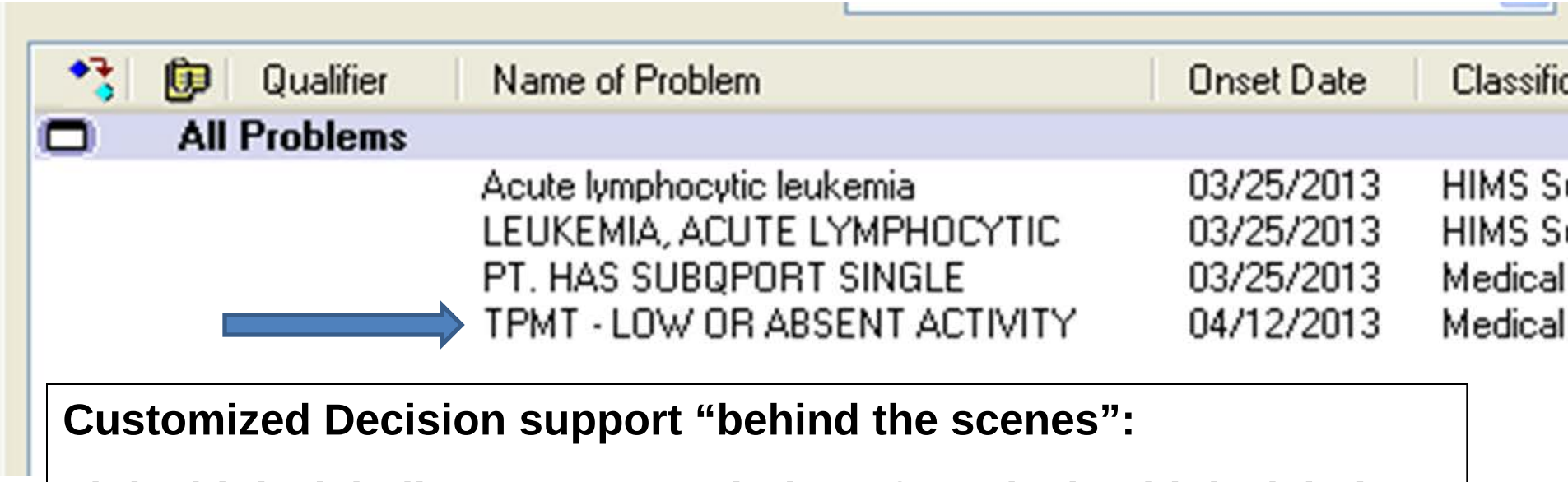
Flow Chart Reference Point (See Supplemental Figure S3)	CDS Context, Relative to Genetic Testing	Trigger Condition	CDS Alert Text[a]
1	Pre-Test	No *SLCO1B1* result on file	*SLCO1B1* diplotype may be important for simvastatin side effects. An *SLCO1B1* genotype does not appear to have been ordered for this patient. Use of an alternative statin or dose may be recommended. Please consult a clinical pharmacist[b] for more information.
2	Post-Test	SLCO1B1 - Intermediate Function	Based on the genotype result, this patient is predicted to have intermediate SLCO1B1 function and may be at increased risk for developing simvastatin-associated myopathy. Consider starting with a lower dose of simvastatin (20 mg/day for adults) or choosing an alternate statin agent. Monitor creatine kinase levels routinely. Please consult a clinical pharmacist[b] for more information.
2	Post-Test	SLCO1B1 – Low Function	Based on the genotype result, this patient is predicted to have low SLCO1B1 function and may be at high risk for developing simvastatin-associated myopathy. Consider starting with a lower dose of simvastatin (20 mg/day for adults) or choosing an alternate statin agent. Monitor creatine kinase levels routinely. Please consult a clinical pharmacist[b] for more information.

[a]The specific wording of the alert text may differ among sites.

[b]Pharmacist, pharmacologist, or a clinician with pharmacogenetic expertise/training.

Clinical Pharmacology & Therapeutics (2014); 96 4, 423–428

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



Customized Decision support "behind the scenes":

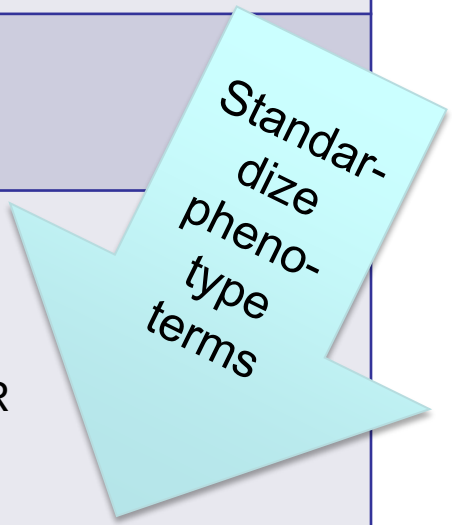
Links high-risk diplotypes to ordering of applicable high-risk drug

Each high-risk result triggers med reconciliation

Allows for manual entries into problem list

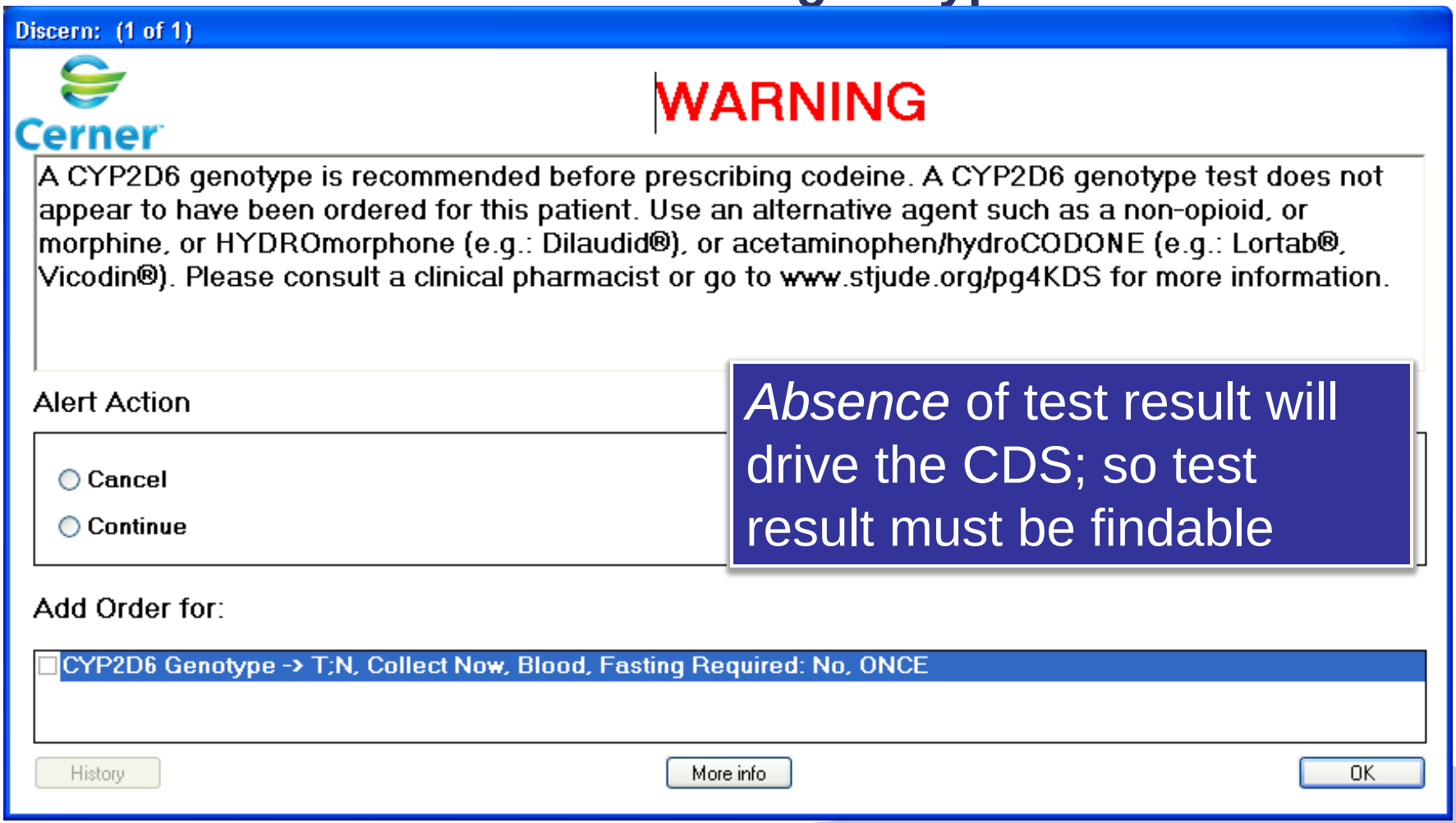
Selected Problem List Entries for Actionable Phenotypes

Gene	Problem List Entry
TPMT	TPMT - INTERMEDIATE ACTIVITY TPMT - LOW OR ABSENT ACTIVITY TPMT - POSSIBLE INTERMEDIATE ACTIVITY
CYP2D6	CYP2D6 - POSSIBLE ULTRA-RAPID METABOLIZER CYP2D6 - ULTRA-RAPID METABOLIZER CYP2D6 - INTERMEDIATE METABOLIZER CYP2D6 - POSSIBLE INTERMEDIATE METABOLIZER CYP2D6 - POOR METABOLIZER CYP2D6 - POSSIBLE POOR METABOLIZER
SLCO1B1	SLCO1B1 - POSSIBLE INTERMEDIATE FUNCTION SLCO1B1 - INTERMEDIATE FUNCTION SLCO1B1 - POSSIBLE LOW FUNCTION SLCO1B1 - LOW FUNCTION
CYP2C19	CYP2C19 - ULTRA-RAPID METABOLIZER CYP2C19 - INTERMEDIATE METABOLIZER CYP2C19 - POOR METABOLIZER CYP2C19 - POSSIBLE POOR METABOLIZER



Hoffman JM, et al. Am J Med Genet C Semin Med Genet. 2014

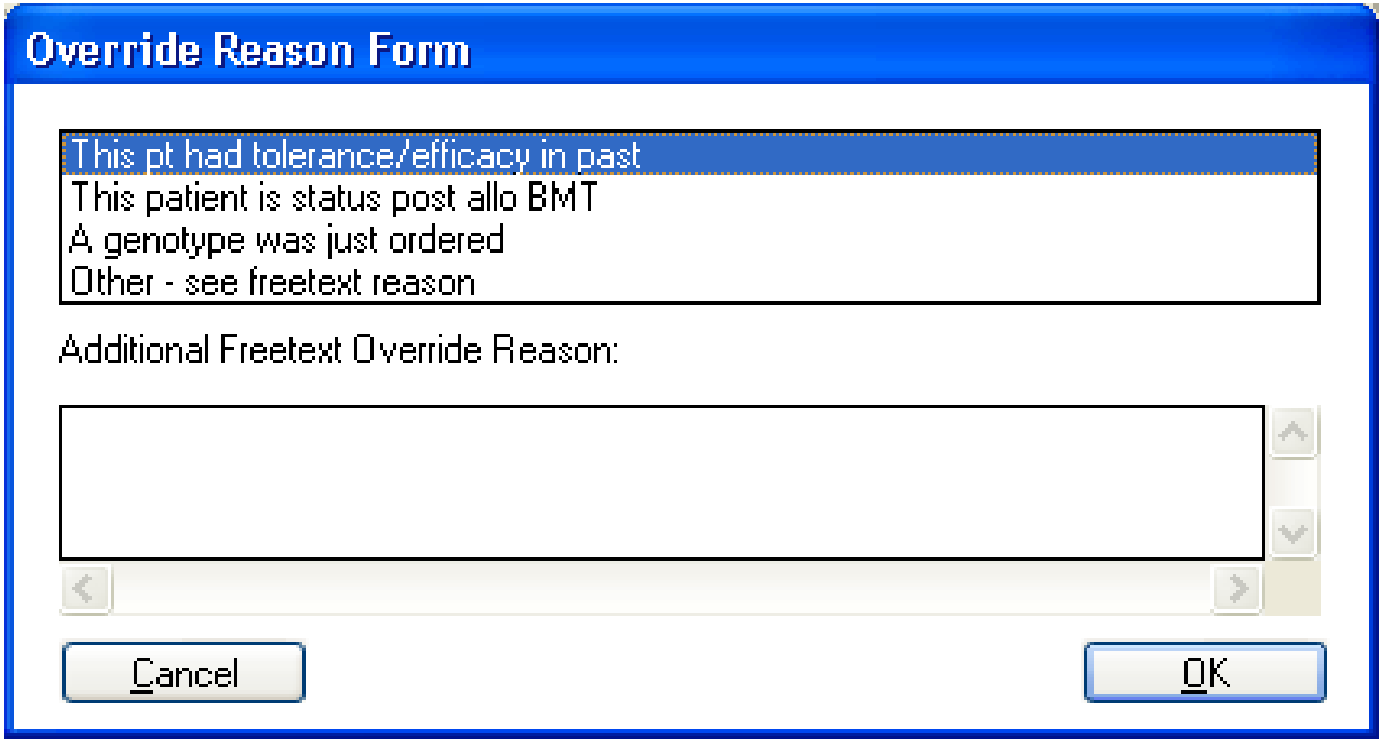
Pre-test alerts contains prescribing recommendations if a patient has not been genotyped



Absence of test result will drive the CDS; so test result must be findable

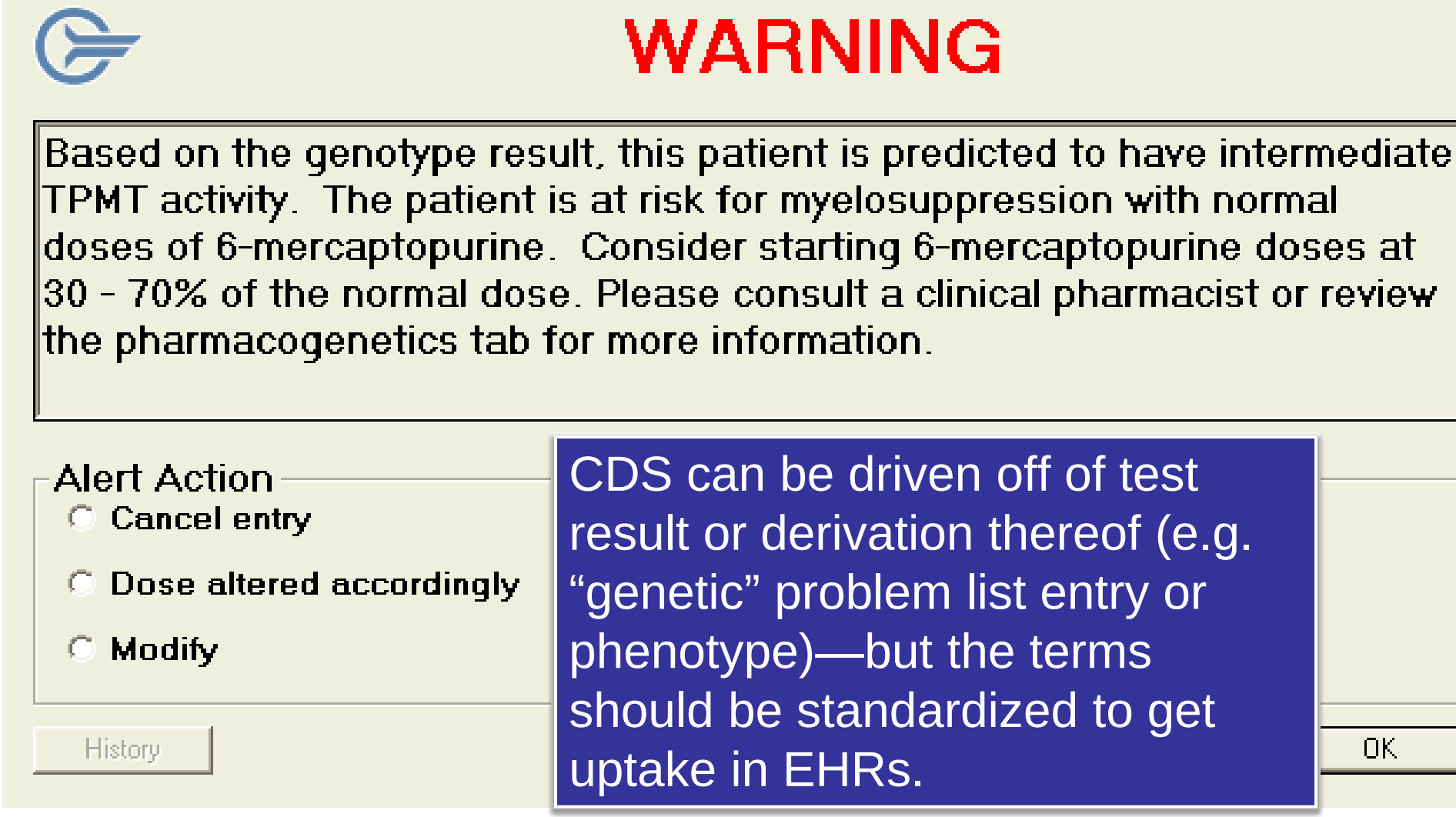
Bell GC, et al. J Am Med Inform Assoc. 2014;21:e93-9

Override alert options for pre-test alerts



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

Post-test alerts contain prescribing recommendations based on the patient's genotype test result



CDS can be driven off of test result or derivation thereof (e.g. "genetic" problem list entry or phenotype)—but the terms should be standardized to get uptake in EHRs.

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BROWSE HISTORY

Action Collaboratives

DIGITizE: Displaying and Integrating Genetic Information Through the EHR

Sandy Aronson, M.A. (Co-Chair)
Executive Director of IT
Partners HealthCare Personalized Medicine

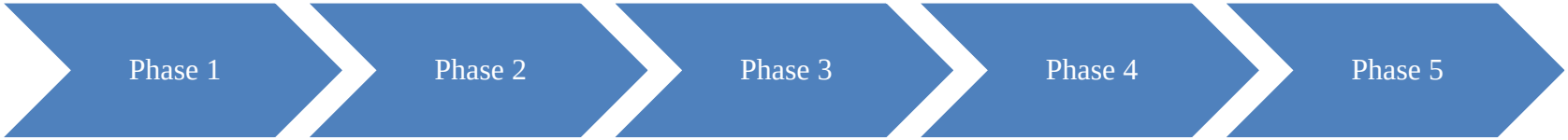
John David Nolen, M.D., Ph.D., M.S.P.H. (Co-Chair)
Senior Director and General Manager
for Laboratory Medicine
Cerner Corporation

EHRs do not currently have the ability to handle genomic information.

There is a lack of standards for the data, interoperability, scalability, privacy, security, and storage.

A coordinated effort of key stakeholders is needed to set these standards in order to improve patient care so that genomic information is successfully integrated into the EHR.

CPIC Phenotype Term Standardization Project: Allele function and Phenotype



- **Development**
  - Created a list of options for terms (literature review and survey to genetic testing labs)
- **Prioritization**
  - Survey 1: Experts specified their level of agreement or disagreement on a symmetric agree-disagree scale (1-4) for each set of gene terms. Experts can also list additional terms.
- **Refinement:**
  - Survey 2: For each gene, retained terms in which 70% of the experts agreed or strongly agreed in Survey 1.
  - Related terms were grouped together into value sets and experts specified their level of acceptance to sets of terms for each gene/gene group (acceptable/not acceptable).
- **Consensus**
  - Survey 3-5: For each gene/gene group, retained top terms selected by experts.
  - Repeat process until 70% consensus achieved.
- **Validation**
  - After 70% consensus reached, terms were circulated to the experts again for final review and feedback (as part of survey 5).

Group memberships for Delphi process surveys for pgen terms

- CPIC
- ClinVar
- PGRN
- CDC Pgx nomenclature WG
- GA4GH's Clinical WG
- ClinGen PG and data modeling WG
- IGNITE
- eMERGE
- IUPHAR
- ACMG Laboratory Standards and Guidelines Committee
- CAP Pharmacogenetics WG
- HL7 Clinical Genomics WG
- IOM's Roundtable on Translating Genomic-Based Research for Health
- AMIA genomics and translational bioinformatics WG
- European Medicines Agency
- G2MC Pharmacogenomics WG

Final Terms-Allele function

Term/Gene Category	Final Term*	Functional Definition	Example diplotypes/alleles
Allele Functional Status-all genes	Increased Function	Function greater than normal function	*CYP2C19*17*
	Normal Function	Fully functional/wild-type	*CYP2C19*1*
	Decreased Function	Function less than normal function	*CYP2C19*9*
	No Function	Non-functional	*CYP2C19*2*
	Unknown Function	No literature describing function or the allele is novel	*CYP2C19*29*
	Uncertain Function	Literature supporting function is conflicting or weak	*CYP2C19*12*

Final Terms-Phenotype

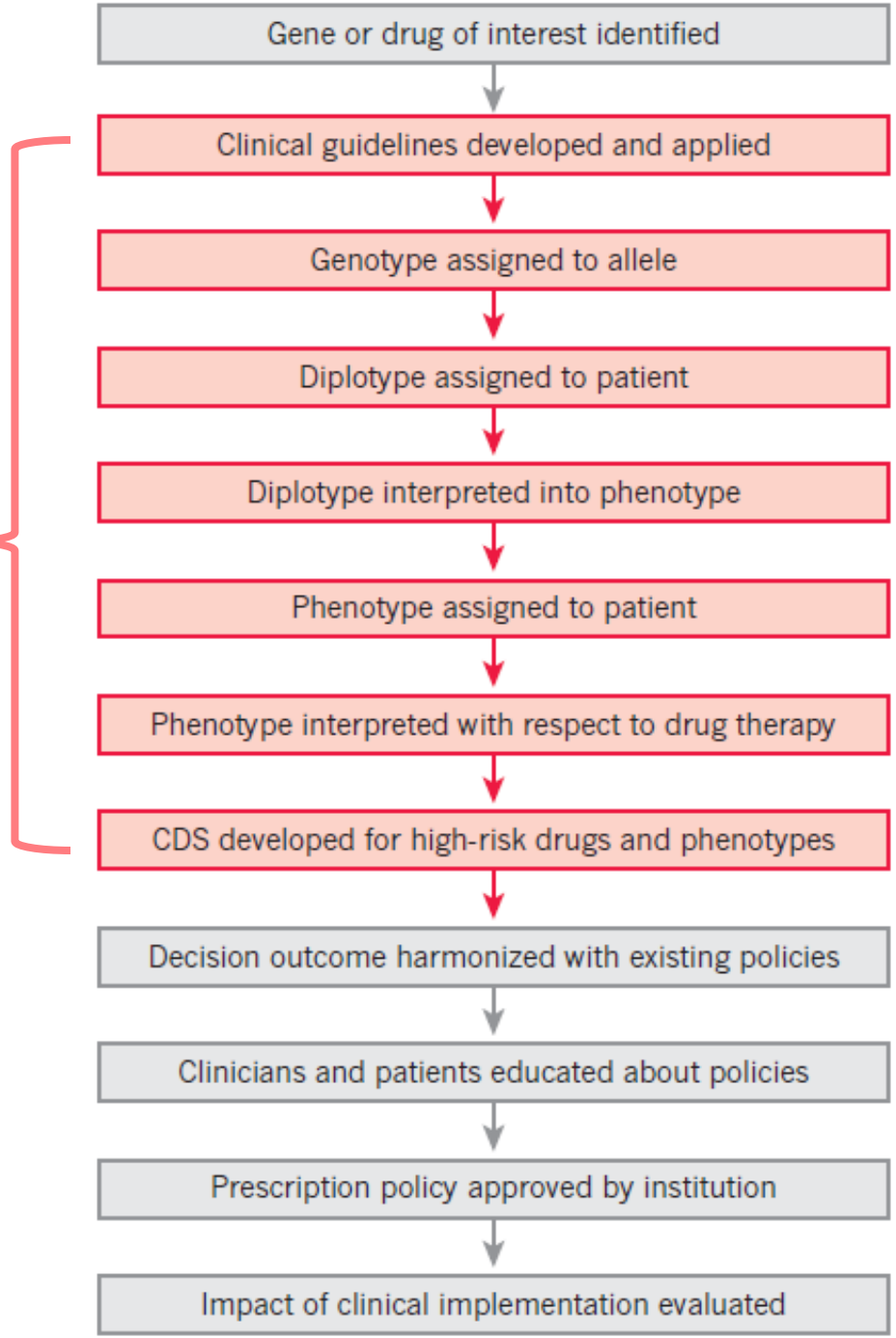
Term/Gene Category	Final Term*	Functional Definition	Example diplotypes/alleles	Term/Gene Category
Phenotype-Drug Metabolizing Enzymes (CYP2C19, CYP2D6, CYP3A5, CYP2C9, TPMT, DPYD, UGT1A1)	Ultra-rapid Metabolizer	Increased enzyme activity compared to rapid metabolizers.	Two increased function alleles, or more than 2 normal function alleles	*CYP2C19*17/*17* *CYP2D6*1/*1XN*
	Rapid Metabolizer	Increased enzyme activity compared to normal metabolizers but less than ultra-rapid metabolizers.	Combinations of normal function and increased function alleles	*CYP2C19*1/*17*
	Normal Metabolizer	Fully functional enzyme activity	Combinations of normal function and decreased function alleles	*CYP2C19*1/*1*
	Intermediate Metabolizer	Decreased enzyme activity (activity between normal and poor metabolizer)	Combinations of normal function, decreased function, and/or no function alleles	*CYP2C19*1/*2*
	Poor Metabolizer	Little to no enzyme activity	Combination of no function alleles and/or decreased function alleles	*CYP2C19*2/*2*
Phenotype-Transporters (SLCO1B1)	Increased Function	Increased transporter function compared to normal function.	One or more increased function alleles	*SLCO1B1*1/*14*
	Normal Function	Fully functional transporter function	Combinations of normal function and/or decreased function alleles	*SLCO1B1*1/*1*
	Decreased Function	Decreased transporter function (function between normal and poor function)	Combinations of normal function, decreased function, and/or no function alleles	*SLCO1B1*1/*5*
	Poor Function	Little to no transporter function	Combination of no function alleles and/or decreased function alleles	*SLCO1B1*5/*5*
Phenotype-High risk genotype status (HLA-B)	Positive	Detection of high-risk allele	Homozygous or heterozygous for high-risk allele	*HLA-B*15:02*
	Negative	High risk-allele not detected	No copies of high-risk allele	

Next Steps for Standardized Terms

- Use final terms in CPIC Guidelines and in our practice
- Dissemination
  - Posted on cpicpgx.org
  - DIGITiZE implementation guide
  - LOINC terms submitted
  - Manuscript submitted
- Several groups have endorsed (e.g. AMP)
- Encourage adoption by EHR vendors and clinical labs

Genetic testing is just one step

CPIC
Clinical Pharmacogenetics Implementation Consortium



Relling & Evans, *Nature*, 2015

But…. there remains significant reluctance to use pharmacogenetic testing in the clinic…

Clinical Chemistry 61:2
319–321 (2015)

Perspective

Clinical Perspective on the Clinical Pharmacogenetics Implementation Consortium Updated 2014 Guidelines for CYP2D6 and Codeine

Wayne T. Nicholson* and Christine M. Formea

"many healthcare providers follow a WHO ladder "type" approach for the treatment of pain". Because second step of the WHO ladder includes opioids "commonly used for moderate pain (e.g., tramadol, codeine, hydrocodone, and possibly oxycodone)" that overlap with medicines to avoid (codeine and tramadol) or use with caution (oxycodone and hydrocodone), genetic testing is questioned because "the use of an unfamiliar [alternative] drug …is likely to carry a greater risk."

Devil's advocate: *CYP2D6* and codeine

- Consequence of providing genetic status could be:
  - Never use codeine—too hard to look up genetics, so overall population pain relief is worse (either everyone uses morphine—or everyone uses NSAIDs)
  - Use a less effective drug (like NSAID) for all with high risk genotypes (too much hassle to use narcotics)
  - Ignore genetics ---"pt tolerated it well in the past"
- If we tolerate illogical prescribing practices that aren't evidence-based, genetics won't help

Reasons cited to NOT use genetics to guide prescribing

- Use of alternatives may create more adverse effects if not prescribed appropriately (e.g. stop using codeine and misuse other narcotics or use NSAIDs)
- To avoid testing, just stop using the drug (e.g. CBZ/phenytoin [PMID: 25355835]; codeine in children)
- Clinicians may not understand genetic test results (hets vs homozygous variants) and make wrong decisions (TPMT and thiopurines)
- “patient tolerates it fine---why change?”
- Health care dollars better spent elsewhere
- Lack of randomized prospective clinical trials comparing genetically based vs conventional prescribing

Discussion Paper

Implementation of Pharmacogenomics: Evidence Needs

Mary V. Relling and David L. Veenstra*

February 26, 2015

**The authors are participants in the activities of the IOM Roundtable on Translating Genomic-Based Research for Health.*

Prospective clinical trials for all testing decisions would be problematic

- “Prescribing decisions are routinely made on the basis of imperfect evidence and on extrapolations between solid evidence of mechanisms underlying interpatient variability in drug response and unstudied clinical scenarios.”
- E.g. dosing based on liver or renal dysfunction, avoidance of drug interactions, almost all prescribing in pediatrics

CPIC level A guideline genes

- *TPMT*
  - MP, TG, azathioprine
- *CYP2D6*
  - Codeine, tramadol, hydrocodone, oxycodone, TCAs*
- *CYP2C19*
  - TCAs*, clopidogrel, voriconazole*
- *VKORC1*
  - warfarin
- *CYP2C9*
  - Warfarin, phenytoin*
- *HLA-B*
  - Allopurinol, CBZ, abacavir, phenytoin
- *CFTR*
  - ivacaftor
- *DPYD*
  - 5FU, capecitabine, tegafur
- *G6PD*
  - rasburicase
- *UGT1A1*
  - Irinotecan, atazanavir
- *SLCO1B1*
  - simvastatin
- *IFNL3 (IL28B)*
  - interferon
- *CYP3A5*
  - Tacrolimus*

Mechanism is PK for 8/13

https://www.pharmgkb.org/page/cpicGeneDrugPairs

For pharmacogene/drug pairs with a pharmacokinetic basis

- If PK is related to drug effect, data relating genetics to PK can be used to extrapolate genetics to drug effect
- Completely analogous to using creatinine clearance to adjust acyclovir doses, bilirubin to adjust vincristine doses, and weight/BSA to adjust doses for children compared to adults
  - Requiring a randomized clinical trial comparing standard to reduced doses of acyclovir in patients with creatinine clearance of 25 ml/min/1.73m^2 would be unethical and a waste of precious resources

Relling & Veenstra, IOM Discussion Paper 2015

PK extrapolations for dosing decisions are ubiquitous

renal

Adults and Adolescents (12 years of age and older): 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days.

Pediatrics (3 months to 12 years of age): 20 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days.

Neonatal Herpes Simplex Virus Infections (Birth to 3 months): 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days. In neonatal herpes simplex infections, doses of 15 mg/kg or 20 mg/kg (infused at a constant rate over 1 hour every 8 hours) have been used; the safety and efficacy of these doses are not known.

Varicella Zoster Infections: Zoster in Immunocompromised Patients:

Adults and Adolescents (12 years of age and older): 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days.

Pediatrics (Under 12 years of age): 20 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days.

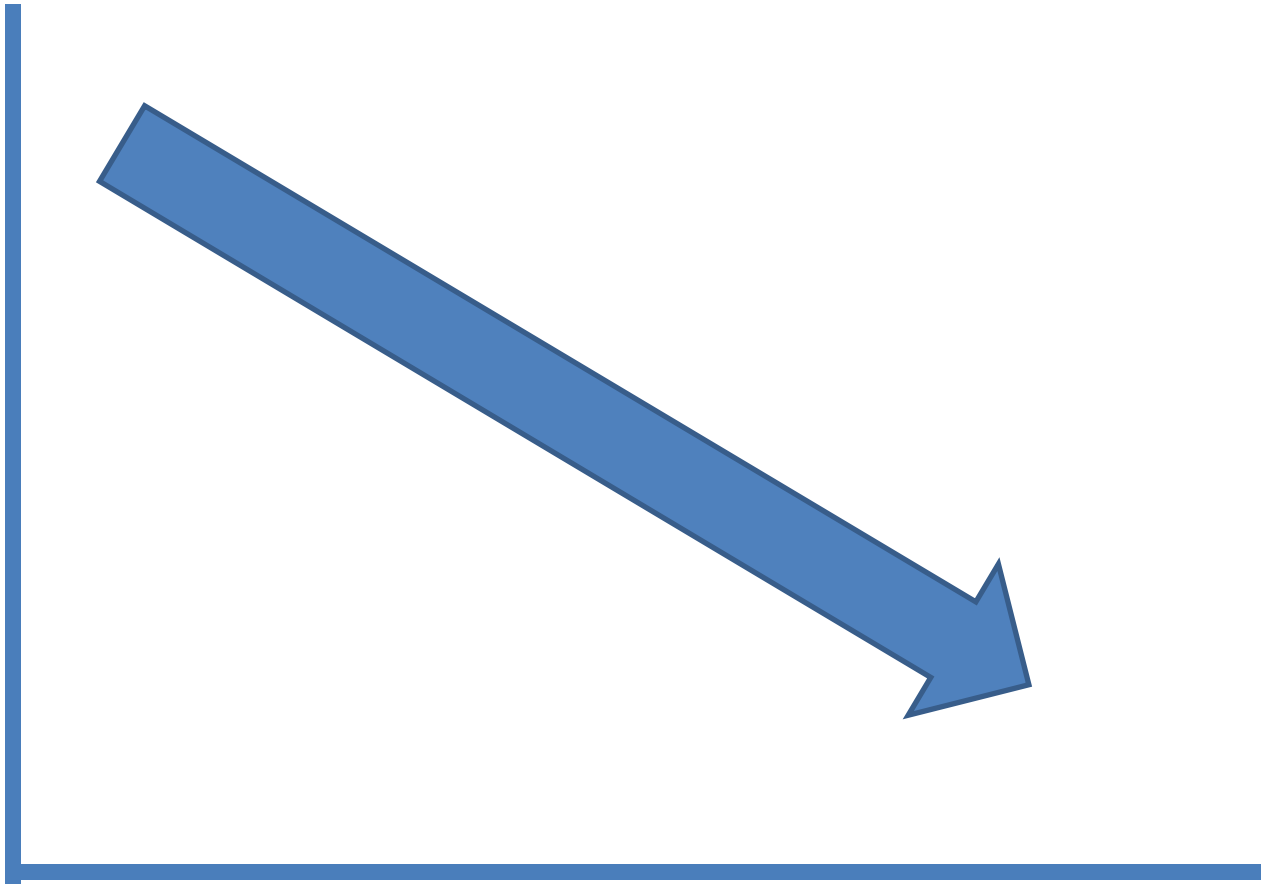
Obese Patients: Obese patients should be dosed at the recommended adult dose using Ideal Body Weight.

Patients with Acute or Chronic Renal Impairment: Refer to DOSAGE AND ADMINISTRATION section for recommended doses, and adjust the dosing interval as indicated in Table 5.

Table 5. Dosage Adjustments for Patients with Renal Impairment

Creatinine Clearance ($mL/min/1.73\ m^2$)	Percent of Recommended Dose	Dosing Interval (hours)
>50	100%	8
25 - 50	100%	12
10 - 25	100%	24
0 - 10	50%	24

The stronger the evidence that the gene variants affect drug PK, the lower the need for clinical trial data



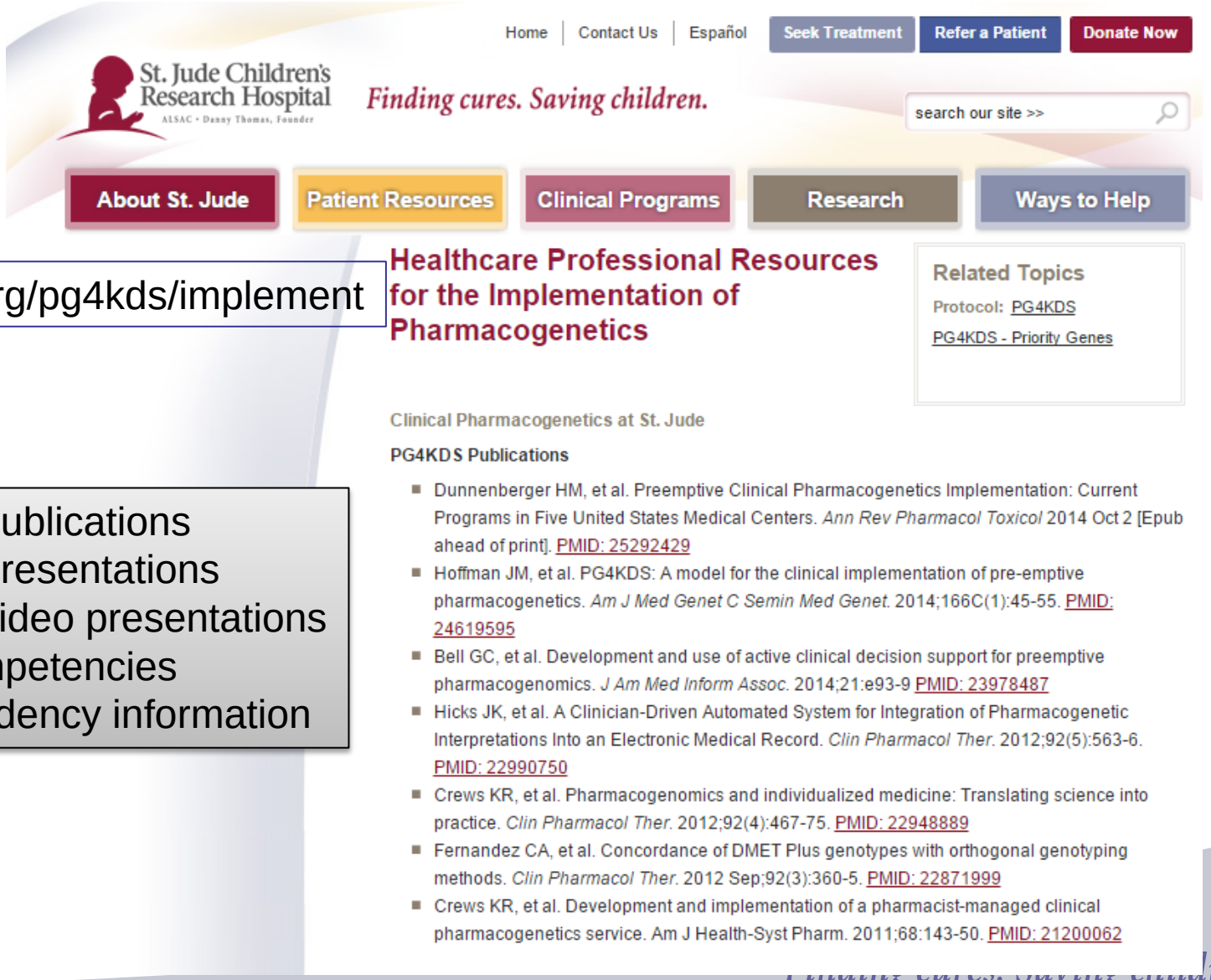
Challenges to implementing pharmacogenetics in the clinic

- Generating sufficient genotype/phenotype and clinical evidence
- Tolerating illogical prescribing practices
- Overcoming hype: “pharmacogenomic testing needs to be viewed as a tool to improve drug therapy that is incremental and affordable, rather than revolutionary and cost- saving.” (Veenstra *CPT* Feb 2016)

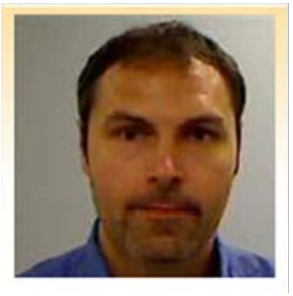
Resources for Implementers

www.stjude.org/pg4kds/implement

- PG4KDS publications
- PG4KDS presentations
- PG4KDS video presentations
- PGEN competencies
- PGEN residency information



5th Year of first ASHP accredited Pharmacogenetics Residency



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http://www.stjude.org/pg4kds/implement

https://cpicpgx.org/

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