Pharmacogenomics: Providing Personalized Medicine

April 28, 2020

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1

Learning Objectives

At the end of this educational activity, participants should be able to:

- Explain the basic science of liver enzymes and their genetic variations.
- Name the various liver enzymes most frequently tested in relation to psychiatric drugs.
- Describe the clinical indications for using pharmacogenomics.
- Discuss resources for interpreting pharmacogenomic test results.
- List the limitations of current pharmacogenomics tests.

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2

Pharmacogenetics is Defined

"The role of genetics in drug responses."

F. Vogel, 1959

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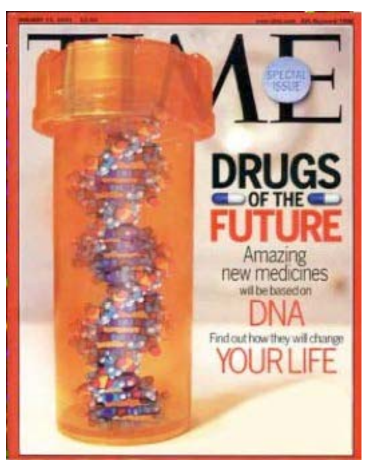
3

January 15, 2001



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4

Genotype <-> Phenotype associations

Relate genetic information (genotype):

1.ATCGCCGGATACCTAGAGAC…
2.ATCGCCGGAGACCTAGAGAC…

to observable traits (phenotypes), e.g.

1. Responds well to cholesterol medication
2. Develops hepatotoxicity

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5

Genome Variation

- About 10 million single nucleotide polymorphisms (SNPs) identified in human population
  (~4 million present in any individual)
- Many small insertions/deletions in genes
- Many "copy number variants" with multiple copies of genes
- Almost anything else you can think of occurs…

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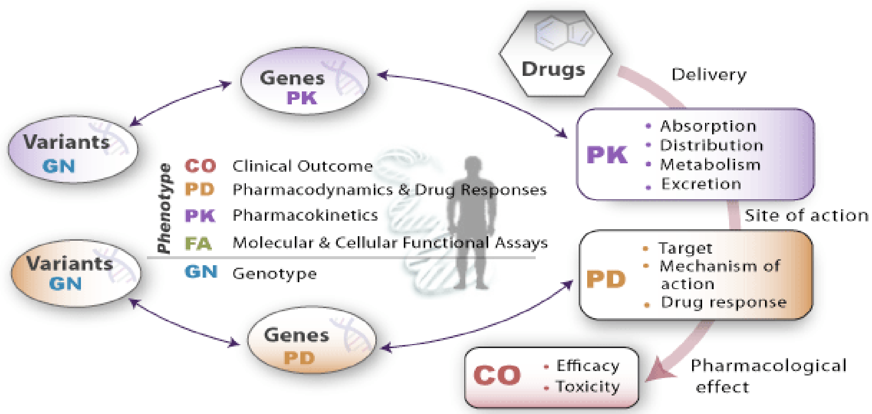
6



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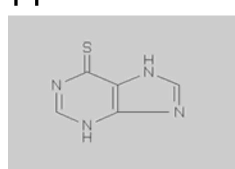
7

Purine analogs

- 6-mercaptopurine, 6-thioguanine, azathioprine
- Used to treat lymphoblastic leukemia, autoimmune disease, inflammatory bowel disease, after transplant
- Interferes with nucleic acid synthesis
- Therapeutic index limited by myelosuppression



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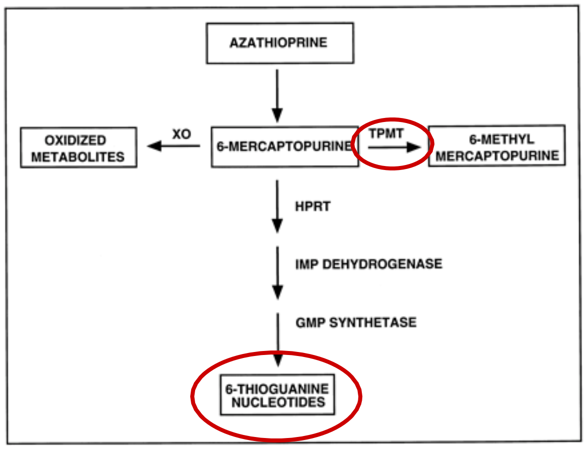
8

Metabolism of 6-MP

Weinshilboum (Mayo Clinic) 2001



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9

Levels of TPMT can drastically affect levels of thioguanines

- More TPMT = less thioguanines
- Associated with risk of severe marrow toxicity
- Shows considerable variability in population

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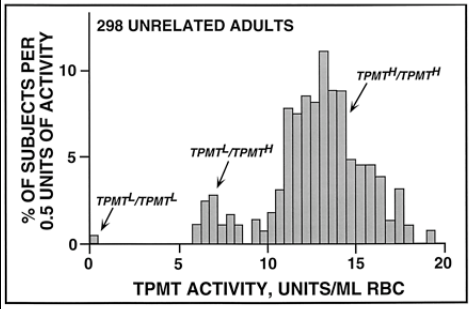
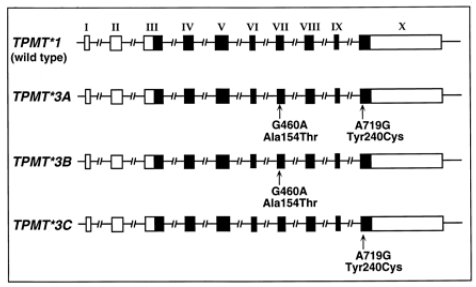
10

Variation in TPMT Activity

Weinshilboum (Mayo Clinic) 2001





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11

6-MP and TPMT Story Summary

- Observation of clinical variability (toxicity)
- Observation of cellular variability (TPMT activity, TGN concentrations)
- Observation of genetic variability (genome variations in TPMT gene)

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12

The logic of pharmacogenetics

1. Identify variation in drug response
2. Associate it with genetic variation
3. Evaluate clinical significance
4. Develop screening tests
5. Individualize drug therapy

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13

What is the clinical promise?

- Focused treatment by pre-identifying genetic backgrounds likely to respond
- Reduce adverse events by predicting who is at risk
- A way to save drugs in the pipeline that are very effective only in subpopulations
- Better understanding of drug interactions

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14

Defining P-etics vs. P-omics

- Pharmacogenetics = study of individual gene-drug interactions, usually the gene that has the dominant effect on a drug response. (SIMPLE relationship)
- Pharmacogenomics = study of the full set of PK/PD genes, often using high-throughput data (sequencing, expression, proteomics) (COMPLEX interactions)

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15

Example: Codeine & CYP2D6

- Codeine is a commonly used opioid
  – must be metabolized into morphine for activity
- CYP2D6 is the protein that performs this metabolism
- 7% of caucasians have a variant version of CYP2D6 with no activity -> codeine does not work

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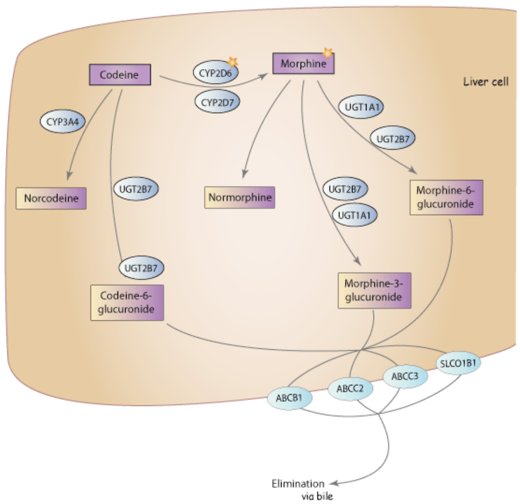
16

Candidate Genes Involved in Metabolism of Codeine and Morphine



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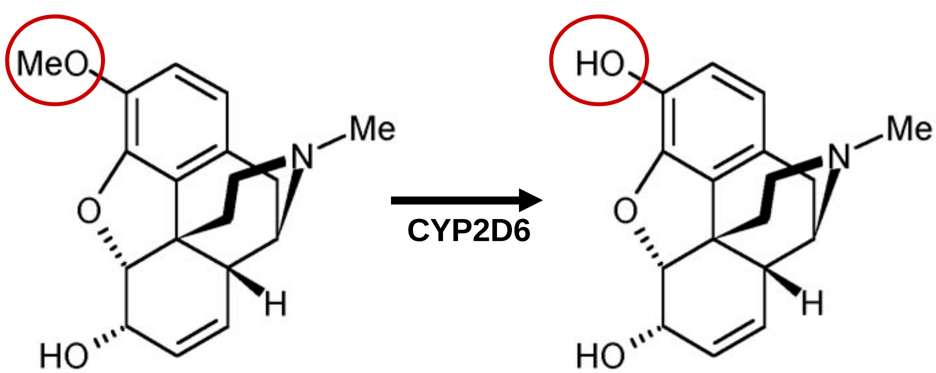
17

The O-dealkylation of Codeine by CYP2D6



codeine **morphine**

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18

Cytochrome P450 2D6

- Absent in 7% of Caucasians
- Hyperactive in up to 30% of East Africans
- Catalyzes the primary metabolism of
  - propafenone
  - Codeine
  - β-blockers
  - tricyclic antidepressants
- Inhibited by
  - **fluoxteine**
  - **haloperidol**
  - **paroxetine**
  - **quinidine**

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19

CYP2D6 Alleles

- >100 alleles reported
- Many alleles function not known
- ~50 alleles have no activity
- ~10 alleles have decreased activity
- The *2 variant can have 1, 2, 3, 4, 5 or 13 copies resulting in increased activity

http://www.cypalleles.ki.se/cyp2d6.htm

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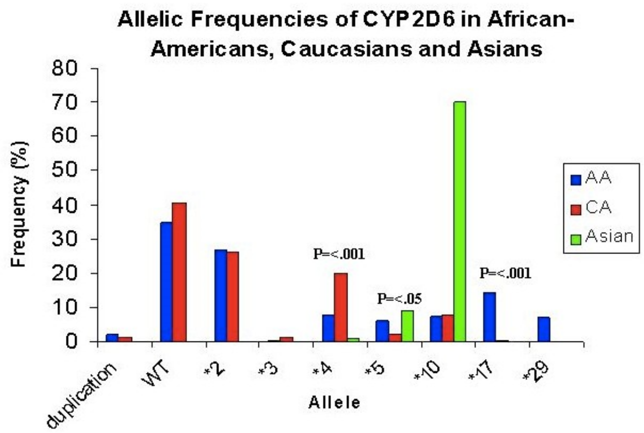
20

Allelic Frequencies of CYP2D6



Wan Y et al. Pharmacogenetics 2001, 11:489-499.
Gaedigk A et al. Clin Pharmacol Ther. 2002 Jul;72(1):76-89.

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21

CYP2D6 and Simvastatin

- Simvastatin = HMG CoA reductase, used to decrease LDL, increase HDL cholesterol.
- Dose of simvastatin required to get cholesterol-lowering effect is related to 2D6 mutations and duplications.
  Clin Pharmacol Ther. 2001 Dec;70(6):546-51.
- Another report demonstrates that "statins" are metabolized differently.
  Biopharm Drug Dispos. 2000 Dec;21(9):353-64.

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22

Copy number polymorphisms = CNPs

- Increasing evidence for variation in the number of copies of a gene in humans
- Won't necessarily be picked up with normal genotyping technology (e.g. sequencing)
- Associated with cancers, genetic diseases, and now with drug response variation
- Methods for quantifying transcript level, to detect CNPs are coming down in costs

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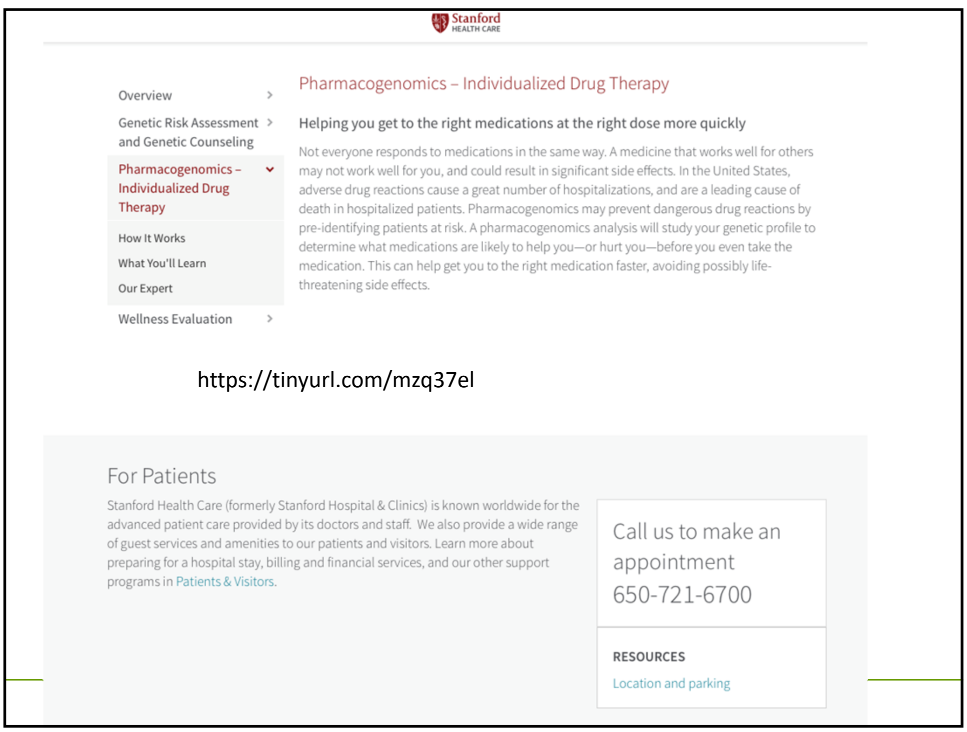
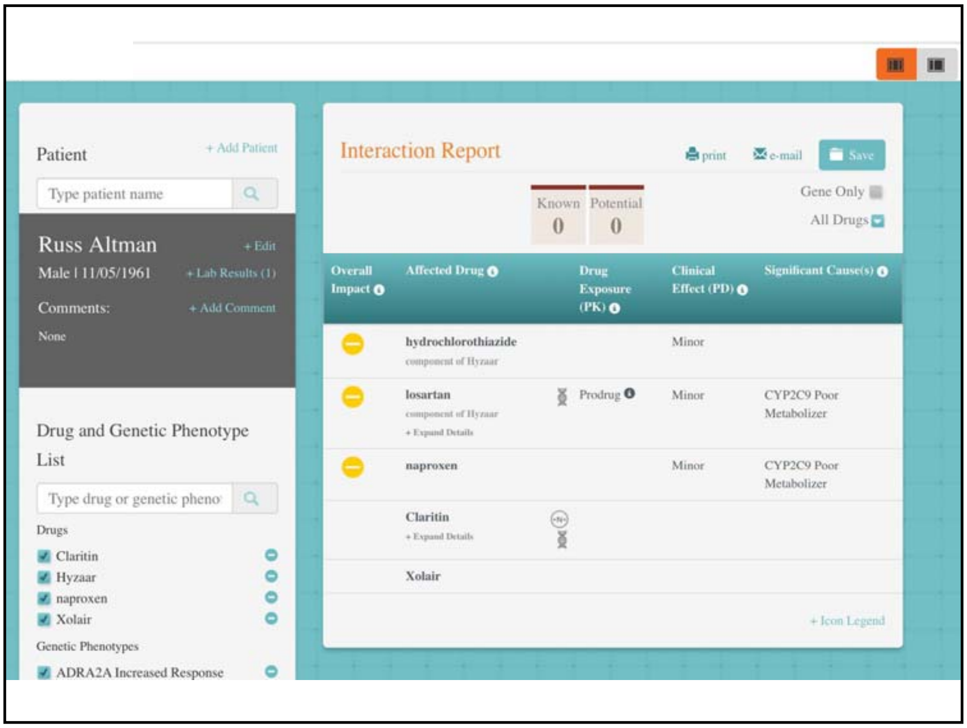
23



24


Patient
+ Add Patient
Type patient name
Russ Altman
+ Edit
Male | 11/05/1961
+ Lab Results (1)
Comments:
+ Add Comment
None
Drug and Genetic Phenotype List
Type drug or genetic pheno
Drugs
Claritin
Hyzaar
naproxen
Xolair
Genetic Phenotypes
ADRA2A Increased Response
Interaction Report
print
e-mail
Save
Known 0
Potential 0
Gene Only
All Drugs
Overall Impact
Affected Drug
Drug Exposure (PK)
Clinical Effect (PD)
Significant Cause(s)
hydrochlorothiazide
component of Hyzaar
Minor
losartan
component of Hyzaar
+ Expand Details
Prodrug
Minor
CYP2C9 Poor Metabolizer
naproxen
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CYP2C9 Poor Metabolizer
Claritin
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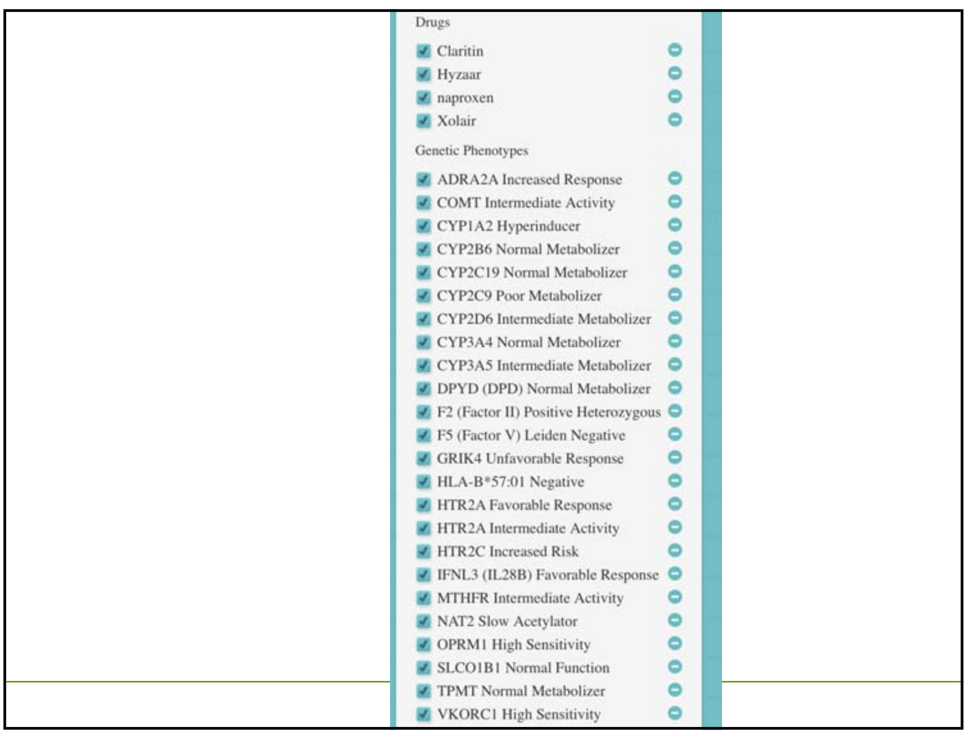
Xolair
+ Icon Legend

25


Drugs
Claritin
Hyzaar
naproxen
Xolair
Genetic Phenotypes
ADRA2A Increased Response
COMT Intermediate Activity
CYP1A2 Hyperinducer
CYP2B6 Normal Metabolizer
CYP2C19 Normal Metabolizer
CYP2C9 Poor Metabolizer
CYP2D6 Intermediate Metabolizer
CYP3A4 Normal Metabolizer
CYP3A5 Intermediate Metabolizer
DPYD (DPD) Normal Metabolizer
F2 (Factor II) Positive Heterozygous
F5 (Factor V) Leiden Negative
GRIK4 Unfavorable Response
HLA-B*57:01 Negative
HTR2A Favorable Response
HTR2A Intermediate Activity
HTR2C Increased Risk
IFNL3 (IL28B) Favorable Response
MTHFR Intermediate Activity
NAT2 Slow Acetylator
OPRM1 High Sensitivity
SLCO1B1 Normal Function
TPMT Normal Metabolizer
VKORC1 High Sensitivity

26

Pharmacogenetic Laboratory Test Report

Patient:	**Date of Birth:**	**Collected:**
Account:	**Lab #:**	**Received:**
Referrer:	**Sample:**	**Reported:**

RESULTS

Test:	Phenotype:	Genotype:
CYP2D6	Intermediate Metabolizer	*1/*4
CYP2C19	Normal Metabolizer	*1/*1
CYP2C9	Poor Metabolizer	*2/*2
CYP3A4	Normal Metabolizer	*1/*1
CYP3A5	Intermediate Metabolizer	*1/*3
VKORC1	High Sensitivity	c.-1639G>A AA
HLA-B*57:01	Negative	*57:01-rs2395029T>G TT
SLCO1B1	Normal Function	*1/*14
TPMT	Normal Metabolizer	*1/*1
DPYD (DPD)	Normal Metabolizer	*1/*1
IFNL3 (IL28B)	Favorable Response	rs12979860C>T CC
NAT2	Slow Acetylator	*5B/*5C
F2 (Factor II)	Positive Heterozygous	c.*97G>A GA
F5 (Factor V) Leiden	Negative	c.1601G>A GG
MTHFR	Intermediate Activity	c.665C>T CT / c.1286A>C AA

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27

CYP2B6	Normal Metabolizer	*1/*1
OPRM1	High Sensitivity	c.118A>G AA
HTR2A	Intermediate Activity	c.-998G>A GA
HTR2A	Favorable Response	c.614-2211T>C TC
HTR2C	Increased Risk	c.-759C>T CC
GRIK4	Unfavorable Response	c.83-10039T>C TT
CYP1A2	Hyperinducer	*1A/*1F
COMT	Intermediate Activity	c.472G>A GA
ADRA2A	Increased Response	c.-1252G>C GG

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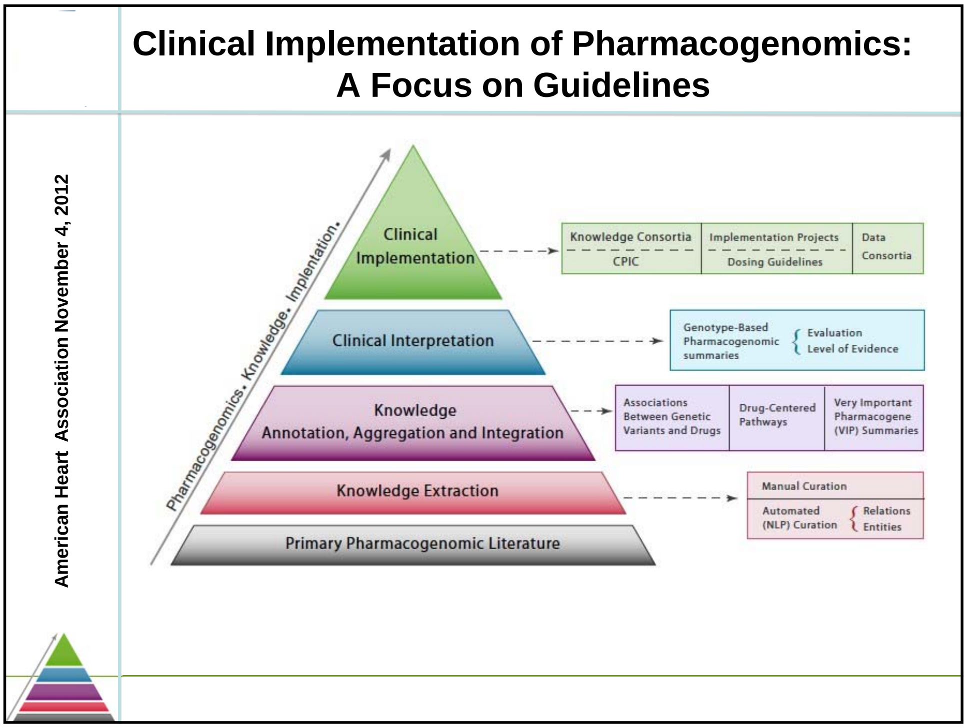
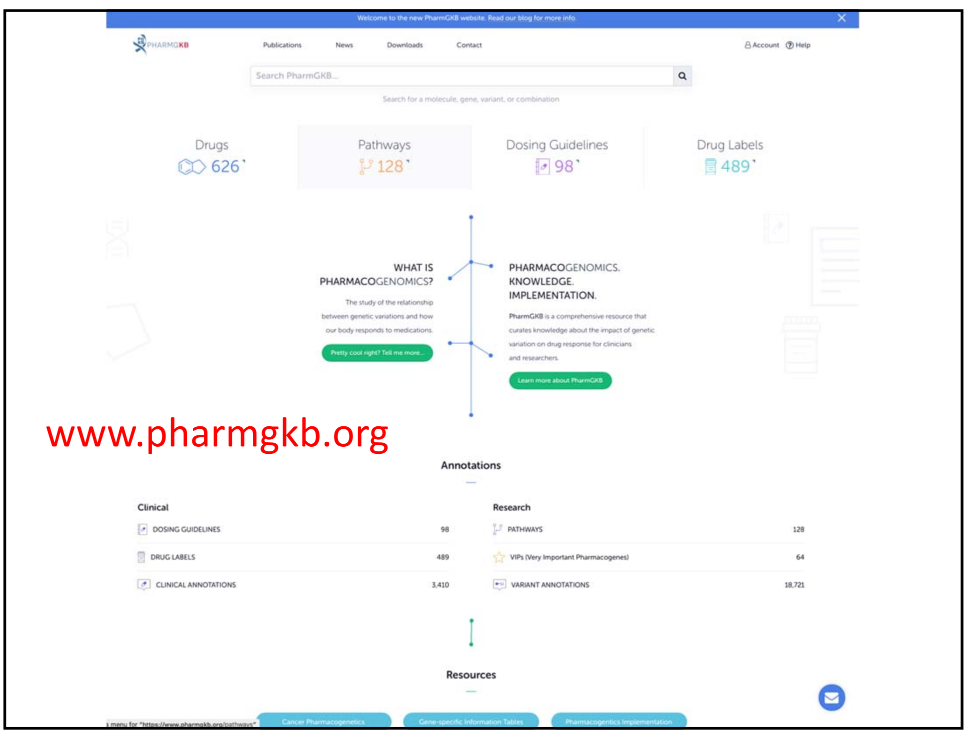
28


Clinical Implementation of Pharmacogenomics:
A Focus on Guidelines
American Heart Association November 4, 2012
Pharmacogenomics. Knowledge. Implementation.
Clinical Implementation
Knowledge Consortia
CPIC
Implementation Projects
Dosing Guidelines
Data Consortia
Clinical Interpretation
Genotype-Based Pharmacogenomic summaries
Evaluation
Level of Evidence
Knowledge
Annotation, Aggregation and Integration
Associations Between Genetic Variants and Drugs
Drug-Centered Pathways
Very Important Pharmacogene (VIP) Summaries
Knowledge Extraction
Manual Curation
Automated (NLP) Curation
Relations
Entities
Primary Pharmacogenomic Literature

29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News
Downloads
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Account
Help
Drugs
626
Pathways
128
Dosing Guidelines
98
Drug Labels
489
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Annotations
Clinical
DOSING GUIDELINES
98
DRUG LABELS
489
CLINICAL ANNOTATIONS
3,410
Research
PATHWAYS
128
VIPs (Very Important Pharmacogenes)
64
VARIANT ANNOTATIONS
18,721
Resources

30

CPIC: clinical pharmacogenetics implementation consortium

- CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy.
- 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.

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31

32

Key Points about a CPIC guideline

- Based on assumption that the test results are in hand and NOT to discuss the merits of doing the test
- Standardized formats
- Grading of evidence and of recommendations
- Peer reviewed
- Freely available
- Updated
- Authorship with COI policy
- Closely follow IOM practices

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33

CPIC guideline genes and drugs, highlights

- *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
- *SLCO1B1*
  - simvastatin
- *IFNL3 (IL28B)*
  - interferon
- *CYP3A5*
  - tacrolimus

http://cpicpgx.org/

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34

Guidelines

CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy, rather than WHETHER tests should be ordered. A key assumption underlying the CPIC guidelines is that clinical high-throughput and pre-emptive (pre-prescription) genotyping will become more widespread, and that clinicians will be faced with having patients' genotypes available even if they have not explicitly ordered a test with a specific drug in mind. CPIC's guidelines, processes and projects have been endorsed by several professional societies – read more.

Each CPIC guideline adheres to a standard format, and includes a standard system for grading levels of evidence linking genotypes to phenotypes, how to assign phenotypes to clinical genotypes, prescribing recommendations based on genotype/phenotype, and a standard system for assigning strength to each prescribing recommendation. The SOP for guideline creation has been published in Current Drug Metabolism: Incorporation of Pharmacogenomics into Routine Clinical Practice: The Pharmacogenetics Implementation Consortium (CPIC) Guideline Development Process. The CPIC authorship guidelines were updated in June 2014.

View CPIC's process for prioritizing CPIC guidelines

Search:

DRUGS	GENES	GUIDELINES
abacavir	HLA-B	*guideline*
allopurinol	HLA-B	*guideline*
amitriptyline	CYP2C19 CYP2D6	*guideline*
atazanavir	UGT1A1	*guideline*
azathioprine	TPMT	*guideline*
capecitabine	DPYD	*guideline*
carbamazepine	HLA-B	*guideline*
citalopram escitalopram	CYP2C19	*guideline*

35

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]

***Clin Pharmacol Ther.* 2013 Feb;93(2):153-8**

Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing: 2013 Update

MV Relling[1], EE Gardner[2], WJ Sandborn[3], K Schmiegelow[4,5], C-H Pui[6], SW Yee[7], CM Stein[8], M Carrillo[9], WE Evans[1], JK Hicks[1], M Schwab[10,11] and TE Klein[9]

***Clin Pharmacol Ther.* 2013 Apr;93(4):324-5.**

Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants

JK Hicks[1], JJ Swen[2], CF Thorn[3], K Sangkuhl[3], ED Kharasch[4], VL Ellingrod[5,6], TC Skaar[7], DJ Müller[8], A Gaedigk[9] and JC Stingl[10]

***Clin Pharmacol Ther.* 2013 May;93(5):402-8.**

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 Pharmacol Ther.* 2013 Sep;94(3):317-23**

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]

***Clin Pharmacol Ther.* 2013 Sep;94(3):324-8.**

Clinical Pharmacogenetics Implementation Consortium Guidelines for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing

KE Caudle[1], CF Thorn[2], TE Klein[2], JJ Swen[3], HL McLeod[4], RB Diasio[5,6] and M Schwab[7,8]

***Clin Pharmacol Ther.* 2013 Aug 29. Epub**

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *IFNL3* (*IL28B*) Genotype and PEG Interferon-α–Based Regimens

AJ Muir[1], L Gong[2], SG Johnson[3,4], MTM Lee[5,6,7], MS Williams[8], TE Klein[2], KE Caudle[9] and DR Nelson[10]

***Clin Pharmacol Ther.* 2014 Feb;95(2):141-6.**

36

Linking genotype to phenotype

Table 1 Assignment of likely thiopurine methyltransferase phenotypes based on genotypes

Likely phenotype	Genotypes	Examples of diplotypes
Homozygous wild-type or normal, high activity (constitutes ~86–97%[a] of patients)	An individual carrying two or more functional (*1) alleles	*1/*1
Heterozygote or intermediate activity (~3–14%[a] of patients)	An individual carrying one functional allele (*1) plus one nonfunctional allele (*2, *3A, *3B, *3C, or *4)	*1/*2, *1/*3A, *1/*3B, *1/*3C, *1/*4
Homozygous variant, mutant, low, or deficient activity (~1 in 178 to 1 in 3,736 patients[a])	An individual carrying two nonfunctional alleles (*2, *3A, *3B, *3C, or *4)	*3A/*3A, *2/*3A, *3C/*3A, *3C/*4, *3C/*2, *3A/*4

Supplemental Table S2. Association between allelic variants[1] and TPMT enzyme activity (49-59)

Functional Status	Alleles
Functional / normal activity/ wild-type[2]	*1, *1S
Non-functional, variant, or mutant / no activity	*2, *3A, *3B, *3C, *4
Probable Reduced-function / decreased activity (most of these alleles are very rare	*5, *6, *8, *9, *10, *11, *12, *13, *16, *17, *18

Clin Pharmacol Ther. 2011 Mar;89(3):387-91.

37

Table2 Recommended dosing of thiopurines by thiopurine methyltransferase phenotype

	MP			Azathioprine		TG		
Phenotype	Implications for MP and azathioprine pharmacologic measures	Dosing recommendations forMP	Classification of recommen-dations•	Dosing recommendations for azathioprine	Classification of recommen-dations•	Implications for pharmacologic measures afterTG	Dosing recommendations forTG	Classification ofrecommen-dations•
Homozygous wild-type or normal, high activity	Lower concentrations ofTGN metabolites, higher methylTIMP, this is the "normal" pattern	Start with normal starting dose (e.g., 75 mg/m2/d or 1.5 mg/kg/d) and adjust doses of MP (and of any other myelosuppressive therapy) without any special emphasis on MP compared to other agents. Allow 2 weeks to reach steady state after each dose adjustment.[4,25,29]	Strong	Start with normal starting dose (e.g., 2-3 mg /kg/ d) and adjust doses of azathiopr ine basedon disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment. [4,27,29]	Strong	Lower concentrations ofTGN metabolites, butnote that TGN afterTG are 5- 10x higher than TGNafterMP or azathioprine	Start with normal starting dose. Adjust doses ofTG and of other myelosuppressive therapy without any special emphasis on TG. Allow 2 weeks to reach steady state after each dose adjustment.[4,16]	Strong
Heterozygote or intermediate activity	Moderate to high concentrations ofTGN metabolites; low concentrations of methyl TIMP	Start with reduced doses (start at 30- 70% of full dose: e.g., at 50 mg/m2/d or0.75 mg/kg/d) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 2-4 weeks to reach steady state after each dose adjustment. In those who require a dosage reduction based on myelosuppression, the median dose may be - 40% lower (44 mg/m2) than that tolerated in wild-type patients (75 mg / m2J,612In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing MP over other agents.[41,3,1s,21,23,2s,291,3,32]	Strong	If disease treatment normally starts at the" full dose", consider starting at 30- 70% of target dose (e.g., 1- 1.5 mg/kg/d), and titrate based on tolerance. Allow 2-4 weeks to reach steady state after each dose adjustment. [4,27,29,31]	Strong	Moderate to high concentrations ofTGN metabolites; but note that TGN afterTG are 5- 10x higher than TGNafterMP or azathioprine	Start with reduced doses (reduce by 30- 50%) and adjust doses ofTG based on degree of myelosuppression and disease-specific guidelines. Allow 2- 4 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing TG over other agents. [4,16]	Moderate
Homozygous variant, mutant, low, or deficient activity	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease; nomethylTIMP metabolites	For malignancy, start with drastically reduced doses (reduce daily dose by 10-fold and reduce frequency to thrice weekly instead of daily, e.g., 10 mg / m2/ dgiven just 3 days/week) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 4-6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing MP over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.[4,24,29,31]	Strong	Consider alternative agents. If using azathioprine start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of azathioprine based on degree of myelosuppression and disease-specific guidelines. Allow 4- 6 week storeach steady state after each dose adjustment. Azathioprine is the likely cause of myelosuppression.[27·29. 31·33]	Strong	Extremely high concentrations ofTGN metabolites; fatal toxicity possible without dose decrease	Start with drastically reduced doses[16] (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses ofTG based on degree of myelosuppression and disease-specific guidelines. Allow 4-6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing TG over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy. [4]	Strong

38

Supplemental Table S5. Evidence linking genotype with phenotype

Type of experimental model (in vitro, in vivo preclinical, or clinical)	Major findings	References	Level of evidence*
In vitro	MP's catabolism to methylmercaptopurine absent in human erythrocytes, lymphocytes, liver, and kidneys from *TPMT* homozygous deficient individuals	(28, 113-115)	High
In vitro	TG's catabolism to methylthioguanine	(116)	High
In vitro	Mechanisms of functional inactivation for *TPMT* *2, *3A, *3B, *3C, *4 demonstrated by expression of specific variant alleles	(31, 117, 118)	High
In vitro	Heterologous expression of *TPMT* catabolizes mercaptopurine to methylmercaptopurine, thioguanine to methylthioguanine, and TIMP to methylTIMP	(119, 120)	High
preclinical	*TPMT* knock-out mice have more morbidity and mortality from thioguanine and mercaptopurine than wild type mice; heterozygotes were at intermediate risk.	(121)	High
clinical	*TPMT* wild-type patients with ALL have higher risk of hematologic relapse than those with at least one variant *TPMT* allele, particularly in regimens that are primarily antimetabolite-based; wild-type patients with IBD have higher risk of treatment failure	(122-124)	High

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information

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39

https://www.uhcprovider.com/content/dam/provider/docs/public/policies/comm-medical-drug/pharmacogenetic-testing.pdf

UnitedHealthcare®

UnitedHealthcare® Commercial
Medical Policy

PHARMACOGENETIC TESTING

Policy Number: 2019T0587E **Effective Date**: October 1, 2019

Instructions for Use

Table of Contents **Page**

Related Commercial Policies

- Cardiovascular Disease Risk Tests
- Chemosensitivity and Chemoresistance Assays in Cancer

Community Plan Policy

- Pharmacogenetic Testing

Medicare Advantage Coverage Summaries

- Genetic Testing
- Laboratory Tests and Services

COVERAGE RATIONALE

The use of pharmacogenetic Multi-Gene Panels to guide therapy decisions is proven and medically necessary for antidepressants and antipsychotics medication when ALL of the following criteria are met:

- The individual has a diagnosis of major depressive disorder or anxiety; **and**
- The individual has failed at least one prior medication to treat their condition; **and**
- The Multi-Gene Panel has no more than 15 relevant genes (refer to Table 1)

The use of pharmacogenetic Multi-Gene Panels for genetic polymorphisms for any other indication, including but not limited to pain management, cardiovascular drugs, anthracyclines, or polypharmacy, is unproven and not medically necessary for evaluating drug-metabolizer status due to insufficient evidence of efficacy.

40

Table 1. Antidepressant, Antipsychotic Drugs and Associated Genes

Drug	Gene(s)	Select Associated References
Sertraline	*CYP2C19, CYP2D6, COMT, TXNRD2*	CPIC Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015)
Citalopram	*CYP2C19, SLC6A4, GRIK4, HTR2A, FKBP5, COMT, TXNRD2*	• CPIC Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015) • Polymorphisms in *GRIK4*, *HTR2A*, and *FKBP5* Show Interactive Effects in Predicting Remission to Antidepressant Treatment (Horstmann et al., 2010)
Escitalopram	*CYP2C19, SLC6A4, COMT, TXNRD2*	• CPIC Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015) • Interaction between serotonin transporter gene variants and life events predicts response to antidepressants in the GENDEP project (Keers et al., 2011)
Fluoxetine	*FKBP5, COMT, TXNRD2*	Polymorphisms in *GRIK4*, *HTR2A*, and *FKBP5* Show Interactive Effects in Predicting Remission to Antidepressant Treatment (Horstmann et al., 2010)
Paroxetine	*CYP2D6, HTR1A, FKBP5, COMT, TXNRD2*	• CPIC Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015) • Polymorphisms in *GRIK4*, *HTR2A*, and *FKBP5* Show Interactive Effects in Predicting Remission to Antidepressant Treatment (Horstmann, et al., 2010) • SSRI response and HTR1A (Yevtushenko et al., 2010)
Fluvoxamine	*CYP2D6, COMT, TXNRD2*	CPIC Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015)
Venlafaxine	*CYP2D6, FKBP5*	Polymorphisms in *GRIK4, HTR2A*, and *FKBP5* Show Interactive Effects in Predicting Remission to Antidepressant Treatment (Horstmann et al., 2010)
Amitriptyline	*CYP2C19, 2D6*	CPIC Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants (Hicks et al., 2017)
Nortriptyline	*CYP2D6*	CPIC Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants (Hicks et al., 2017)
Clomipramine	*CYP2C19, 2D6*	CPIC Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015)
Doxepin	*CYP2C19, 2D6*	CPIC Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of

41

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Medical Coverage Policy

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Next Review Date...................................... **1/15/2020**
Coverage Policy Number................................ **0500**

Pharmacogenetic Testing

Table of Contents

Related Coverage Resources

Genetics
Genetic Testing Collateral: Genetic Tests and Biomarkers File
Genetic Testing Collateral: Not Covered Single CPT® & HCPCS Code Tests
Cystic Fibrosis Transmembrance Conductance Regulator (CFTR) Modulators
Lomatipide Mesylate, Mipomersen Sodium
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42


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Search
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Home / News & Events / FDA Newsroom / Press Announcements / FDA issues warning letter to genomics lab for illegally marketing genetic test that claims to predict patients' responses to specific medications
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FDA issues warning letter to genomics lab for illegally marketing genetic test that claims to predict patients' responses to specific medications
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For Immediate Release: April 04, 2019
Today, the U.S. Food and Drug Administration issued a warning letter to Inova Genomics Laboratory (Inova) of Falls Church, Virginia, for illegally marketing certain genetic tests that have not been reviewed by the FDA for safety and effectiveness. The tests claim to predict patients' responses to specific medications based on genetic variants. Selecting or changing drug treatment in response to the test results could lead to potentially serious health consequences for patients. The FDA is unaware of any data establishing that Inova's tests can help patients or health care providers make appropriate treatment decisions for the listed drugs. The action today reflects the agency's commitment to monitor the pharmacogenetic test landscape and take action when appropriate to address a significant public health risk.
"Consumers are increasingly embracing genetic testing to better understand their individual risk for developing diseases. With this rise in popularity and availability, we're also seeing significant activity in the field of pharmacogenetics, which is the process of understanding what, if any, role genetics plays in a patient's reaction to particular drugs. Without appropriate evaluation to determine whether these tests work, patients are being put at risk—potentially impacting treatment decisions by providing false promise that they will respond well to a certain medicine or keeping them from using therapies that may
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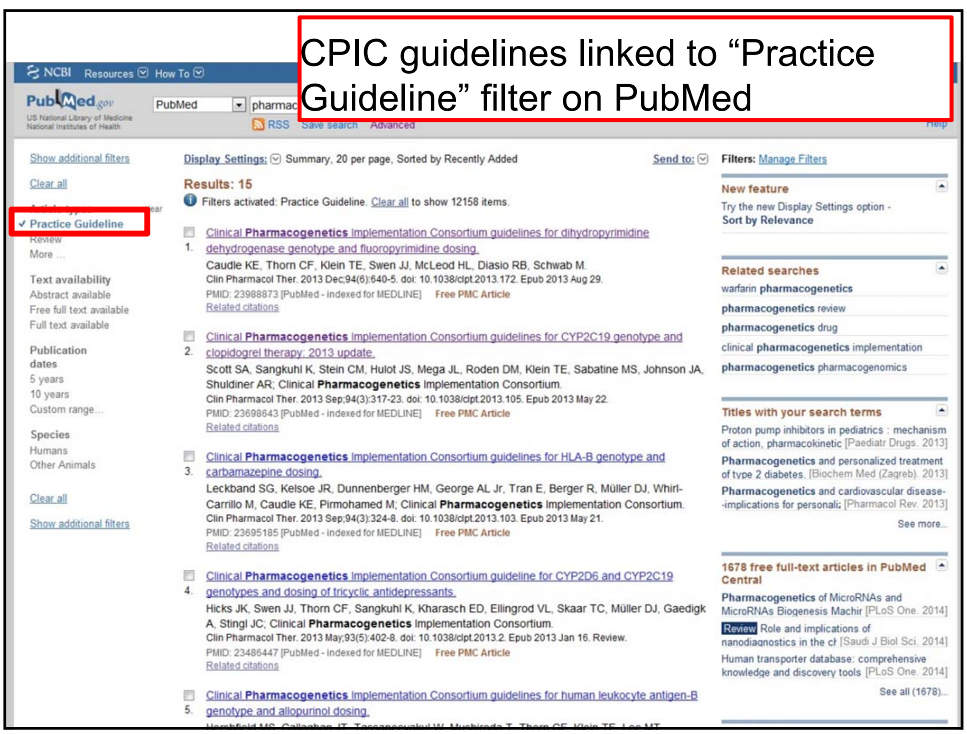
43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Species
Humans
Other Animals
Clear all
Show additional filters
Display Settings: Summary, 20 per page, Sorted by Recently Added
Send to:
Results: 15
Filters activated: Practice Guideline. Clear all to show 12158 items.
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44

Conclusions

1. Pharmacogenomics combines molecular understanding of drug response and human genetic variation to optimize drug use.
2. Currently rolling out in clinical use, mostly based on genotyping → sequencing coming
3. Need good information systems to support clinical use by clinicians (physicians and pharmacists)

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45

Thank you!

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46