WASHINGTON STATE UNIVERSITY

Clinical Implementation of Pharmacogenomics

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Conflict of Interest Disclosure

- Nothing to disclose

Learning Objectives

Identify barriers, challenges, and solutions for implementation of pharmacogenomics services in institutional settings

Discuss the necessary phases of implementation of pharmacogenomics services in institutional settings

Recommend pharmacogenomic testing when appropriate and integrate test results with other clinical variables to optimize medication therapy

Educate health care professionals and patients about the cost, cost-effectiveness, and reimbursement issues relevant to pharmacogenomic tests and services

Describe FDA approved examples of direct-to-consumer pharmacogenomics testing

Identify barriers, challenges, and solutions for implementation of PGx services in institutional settings

Barriers/challenges for implementation of PGx services in institutional settings

- Attaining provider buy-in and acceptance of PGx testing
- Establishing genotyping and result interpretation
- Laboratory and workflow challenges
- Providing clinical decision support (CDS) to inform appropriate therapy
- Reimbursement for genetic testing

Arwood MJ et al. *Clin Transl Sci.* 2016; 9:233–245

Attaining provider buy-in and acceptance of PGx testing

Barriers

- **Lack** of physician **support** or acceptance
- **Evidence** of **successful** implementation of gene-drug pairs relating to clinical utility
- **Data collection plan**

Solutions

- Identify "**physician champion**" (will help bring awareness to other physicians and build rapport)
- Provide institution-specific **evidence** of PGx service **benefits** (key performance indicators and outcomes may lead to acceptance from clinicians)
- Provide **clinician education**
- Create easily accessible clinical decision support **tools** to provide **convenience** and **ease of use**

Arwood MJ et al. *Clin Transl Sci.* 2016; 9:233–245

Establishing genotyping and result interpretation

Barriers

- **Complexity of highly polymorphic enzyme loci**
  - CYP2D6 and available platforms for interrogation of allelic variants

Solutions

- Find an accurate and reliable **platform**
- Keep the **patient population** of the institution in mind when choosing specific gene(s) and a genotyping platform

Arwood MJ et al. *Clin Transl Sci.* 2016; 9:233–245

Laboratory and workflow challenges

Barriers

- Physical **sample** challenges:
  - Quality
  - Timing
  - Type
- **Availability** of phlebotomy or outpatient **services**
- **Uninformed** healthcare team members
  - Specific test tube assignment unknown
  - Sample destination unknown

Solutions

- Use **buccal** swabbing instead of **whole blood** if phlebotomy services are not available
- **Batch** samples together and implement **earlier** lab cutoff times
  - This will allow for faster genotyping turnaround time

Arwood MJ et al. *Clin Transl Sci.* 2016; 9:233–245

Providing clinical decision support (CDS) to inform appropriate therapy

Barriers

- Lack of **efficiency** & **infrastructure**
- **Customization** to workflow
- EHR **alert** fatigue
- **Missing** information

Solutions

- Minimize alerts to **PRN** basis (i.e., only when a test result is ready within the EHR, as opposed to with every new medication order)
- Have **IT support** for help and revisions to system
- Utilize **pilot testing** to ensure smooth workflow

Arwood MJ et al. *Clin Transl Sci.* 2016; 9:233–245

Reimbursement for Pharmacogenomic Testing

Barriers

- Administrative issues
- Third party payers may have different **reimbursement rates**
- Most insurers do not deem PGx testing **necessary** to cover most patients

Solutions

- Obtain **supporting evidence** of the benefits of PGx testing in improving patient outcomes (i.e., **demonstrating clinical utility** through research)

Arwood MJ et al. *Clin Transl Sci.* 2016; 9:233–245

Drivers to PGx Reimbursement

Analytic Validity:
Ability of the test to accurately and reliably measure gene of interest

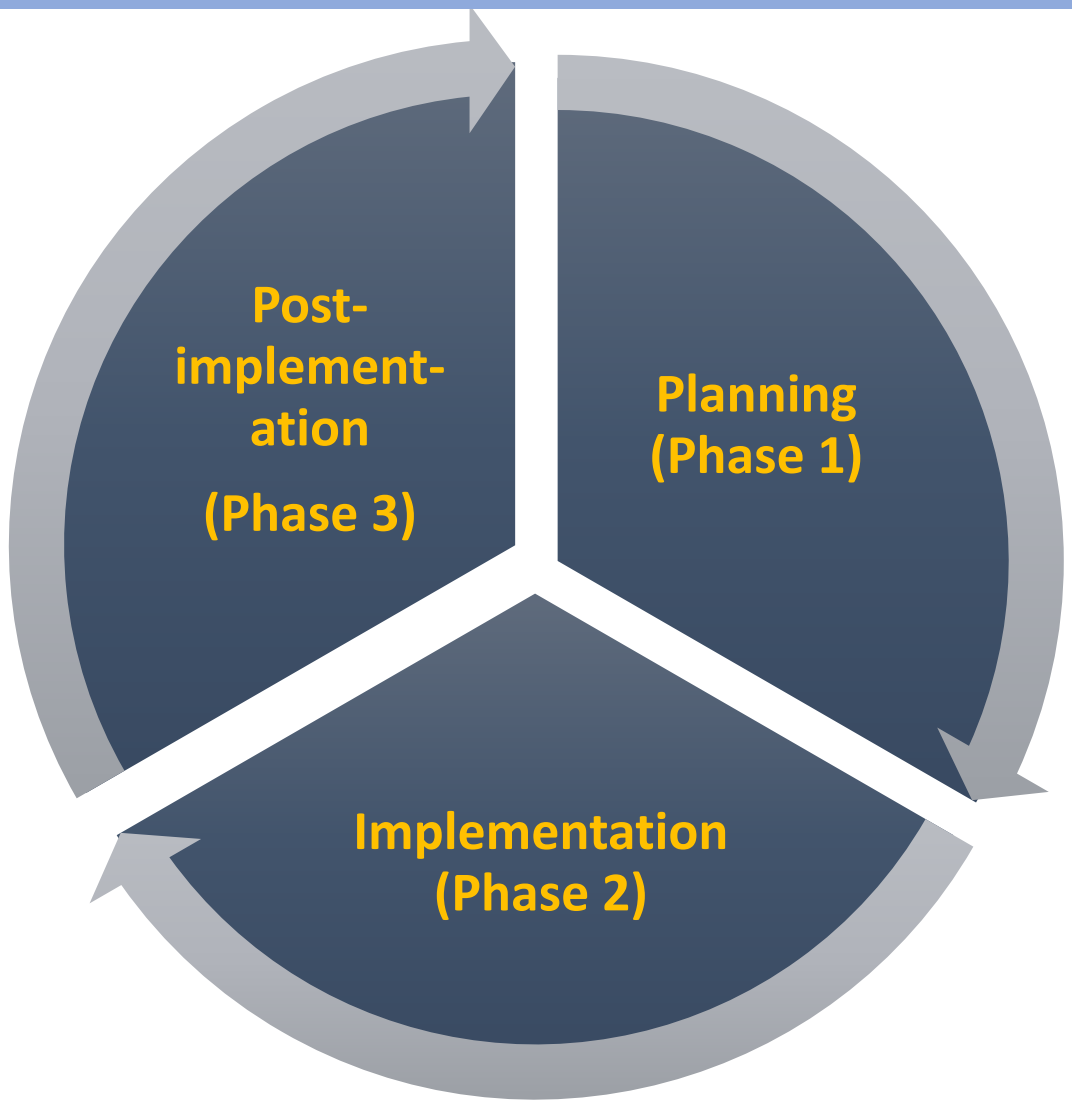
Clinical Validity:
Ability of test to accurately and reliably detect or predict the presence or absence of a phenotype or clinical disease

Clinical Utility:
Likelihood the test will lead to an improved outcome

Zimmern RL & Kroese M. *Journal of Public Health*. 2009; 29(3): 246-250.

Discuss the necessary phases of implementation of pharmacogenomics services in institutional settings

What are the necessary phases of implementation of pharmacogenomics services in institutional settings?



Phase 1: Planning

- **Determine the motivation**
  - Why do you want to start a program?
- **Support with data**
  - Medication vs. patient vs. provider related
- **Evaluate resource needs**
  - Expertise
  - Testing capabilities
  - Infrastructure (return of results to EHR or CDS)
  - Funding sources (institutional, grants, 3rd-party reimbursement)
- **Determine program type**
  - Clinical vs. research

What are the demographics of the clinical population?

Table 1. Selection of P450 allelic variation across populations, highlighting variability within and among populations.

Allelic variant	Function	Africa	African American	Caucasian	East Asia	Americas	Middle East	South Central Asia	Oceania
CYP2C9									
**2*	Decreased	0–9%	1–4%	8–16%	0–1%	0.3–14%	5–27%	2–26%	0–3%
**3*	None	0–3%	0.5–2%	4–11%	1–5%	0–6%	2–19%	6–13%	1–4%
**5*	Decreased	0–3%	0.7–2.5%	0%	0%	0–2%	0–0.1%	0%	n/a
**6*	None	0–2%	0–1.3%	0%	0%	0–1%	0%	0%	n/a
**8*	Decreased	2–8%	3–12%	0–1%	0%	0–2%	0–1%	0–1%	n/a
**11*	Decreased	1–5%	1–2%	0–1%	0–0.2%	0–1%	0%	0–1%	n/a
CYP2C19									
**2*	None	4–22%	12–25%	8–27%	6–49%	2–31%	6–24%	9–51%	20–78%
**3*	None	0–7%	0–1%	0–6.8%	0–21%	0–4%	0–20%	0–6%	2–33%
**4*	None	0%	0%	0–1%	0–0.5%	0–0.2%	n/a	0%	0%
**17*	Increased	10–18%	18–22%	11–33%	0–6.2%	1–25%	22–26%	12–18%	3–6%
CYP2D6									
**4*	None	1–7%	4–8%	8–33%	0–4%	0.2–43%	4–13%	3–18%	0–8%
**5*	Gene deletion	1–17%	3–9%	0–9%	0–10%	0–5%	1–4%	0–16%	1–8%
**10*	Decreased	3–19%	3–8%	0.4–15%	9–64%	0–12%	1–9%	4–55%	0–6%
**17*	Decreased	9–34%	14–26%	0–2.2%	0–0.2%	0–18%	0–3%	0–1%	0–0.2%
**29*	Decreased	4–20%	5–8%	0–0.3%	0%	0–11%	0–2%	0–0.2%	0%

Allele frequencies for *CYP2C9*, *CYP2C19* and *CYP2D6* are from tables compiled for the Clinical Pharmacology Implementation Consortium (CPIC) and available through PharmGKB. Frequencies are rounded and might slightly deviate from those posted as new literature is added.
n/a, no frequencies are available.

Rashmi R. Shah and Andrea Gaedigk. *Ther Adv Drug Saf*. 2018; 9(1) 45–62

Will the selected PGx testing panel cover the allelic variants of interest of the clinical population?

Table 4 List of genetic tests cleared by the Center for Devices and Radiological Health, FDA.[42,43]

Gene	Trade name	Manufacturer	Allele variants detection	DNA source	Approximate turnaround time
CYP2D6	xTAG CYP2D6 Kit v3	Luminex Molecular Diagnostics	**1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *29, *35, *41,* and duplication	Whole blood	8–12 h
	Roche AmpliChip CYP450 microarray	Roche Molecular Systems	**1, *2, *3, *4, *5, *6, *7, *8, *9,*10, *11, *15, *17, *19, *20, *29, *35, *36, *40, *41, *1XN* (duplication), **2XN, *4XN, *10XN, *17XN, *35XN, *41XN*	Whole blood	6 h
CYP2C19	Spartan RX CYP2C19 Test System	Spartan Bioscience	**1,*2, *3, *17*	Buccal swab	1 h
	Verigene CYP2C19 Nucleic Acid Test	Nanosphere	**1, *2, *3, *17*	Whole blood	2.5 h
	INFINITI CYP2C19 Assay	AutoGenomics	**1, *2, *3, *17*	Whole blood	8 h[44]
	Roche AmpliChip CYP450 microarray	Roche Molecular Systems, Inc.	**1, *2, *3, *17*	Whole blood	6 h
CYP2C9 and *VKORC1*	eSensor warfarin sensitivity test and XT-8 instrument	GenMark Diagnostics/ Osmetech Molecular Diagnostics	**2, *3, [*4, *5, *6, *11, *14, *15, *16],*[a] and *VKORC1* -1639 G>A	Saliva Whole blood	3.5 h
	eQ-PCR LC warfarin genotyping kit	TrimGen Corporation	**2, *3,* and *VKORC1* -1639 G>A	Buccal swab Whole blood	1.5 h 2 h
	Gentris Rapid Genotyping Assay - CYP2C9 & VKORC1	ParagonDx, LLC	**2, *3,* and *VKORC1* 1173 C>T	Saliva	1.5 h[42]
	INFINITI 2C9 & VKORC1 Multiplex Assay for Warfarin	AutoGenomics	**2, *3,* and *VKORC1* -1639 G>A	Whole blood	10.5 h[42]
	Verigene Warfarin Metabolism Nucleic Acid Test and Verigene System	Nanosphere	**2, *3,* and *VKORC1* -1639 G>A	Whole blood	1.5 h[45]

FDA, Food and Drug Administration.
[a]These variants are part of an extended panel, which is not FDA-cleared.

Arwood MJ et al. *Clin Transl Sci.* 2016; 9:233–245

Phase 2: Implementation

Establish PGx Oversight committee

Review evidence

Develop PGx protocols

Develop support tools

Design workflow

Launch implementation

What expertise is needed on the PGx Oversight Committee?

- Pharmacists
- Physicians
- Lab expertise
- Informatics
- Genetic Counselors
- Health system administration support and leadership

Phase 2: Implementation/Review Evidence

- Responsibility of a member(s) on PGx oversight committee
- Collection of institutional data to assist with planning phase
- Retrieving evidence supporting drug-gene pair associations (CPIC, FDA labeling, and other practice guidelines)
- *When **considering alternative therapies** need to account for the following factors*
  - Availability/accessibility
  - Associated contraindications and precautions
  - Associated clinically relevant drug-drug interactions

Level Definitions for CPIC Gene-Drug Pairs Updated

CPIC LEVEL	CLINICAL CONTEXT	LEVEL OF EVIDENCE	STRENGTH OF RECOMMENDATION
A	Genetic information should be used to change prescribing of affected drug.	Preponderance of evidence is high or moderate in favor of changing prescribing	At least one moderate or strong action (change in prescribing) recommended.
A/B	Preliminary review indicates it is likely that the definitive CPIC level will be either A or B.	Full evidence review needed to assess level of evidence, but prescribing actionability is likely	Full review by expert guideline group to assign strength of recommendation
B	Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing.	Preponderance of evidence is weak with little conflicting data	At least one optional action (change in prescribing) is recommended.
B/C	Preliminary review indicates it is likely that the definitive CPIC level will be either B or C.	Prescribing actionability based on genetics is not clear without further evidence review	Full review by expert guideline group to assess strength of recommendation
C	There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics makes no convincing difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical or (c) few published studies or mostly weak evidence and clinical actions are unclear. Most important for genes that are subject of other CPIC guidelines or genes that are commonly included in clinical or DTC tests.	Evidence levels can vary	No prescribing actions are recommended.
C/D	Preliminary review indicates it is likely that the definitive CPIC level will be either C or D.	Evidence levels can vary	No prescribing actions are recommended
D	There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. If the genes are not widely tested for clinically, evaluations are not needed.	Evidence levels can vary	No prescribing actions are recommended.

Examples of CPIC Actionable Drug Gene Pairs

Gene	Drug	Guideline	CPIC Level	CPIC Level Status	PharmGKB Level of Evidence	PGx on FDA Label	CPIC Publications (PMID)
HLA-B	abacavir	https://cpicpgx.org/gui	A	Final	1A	Testing required	24561393;22378157
HLA-B	allopurinol	https://cpicpgx.org/gui	A	Final	1A	Testing recommended	23232549;26094938
MT-RNR1	amikacin	https://cpicpgx.org/gui	A	Final	3		34032273
CYP2C19	amitriptyline	https://cpicpgx.org/gui	A	Final	1A		23486447;27997040
CYP2D6	amitriptyline	https://cpicpgx.org/gui	A	Final	1A	Actionable PGx	23486447;27997040
UGT1A1	atazanavir	https://cpicpgx.org/gui	A	Final	1A		26417955
CYP2D6	atomoxetine	https://cpicpgx.org/gui	A	Final	1A	Actionable PGx	30801677
SLCO1B1	atorvastatin	https://cpicpgx.org/gui	A	Final			35152405
NUDT15	azathioprine	https://cpicpgx.org/gui	A	Final	1A	Testing recommended	21270794;23422873;30447069
TPMT	azathioprine	https://cpicpgx.org/gui	A	Final	1A	Testing recommended	21270794;23422873;30447069
DPYD	capecitabine	https://cpicpgx.org/gui	A	Final	1A	Actionable PGx	23988873;29152729
HLA-A	carbamazepine	https://cpicpgx.org/gui	A	Final	1A	Actionable PGx	23695185;29392710
HLA-B	carbamazepine	https://cpicpgx.org/gui	A	Final	1A	Testing required	23695185;29392710
CYP2C9	celecoxib	https://cpicpgx.org/gui	A	Final	1A	Actionable PGx	32189324
CYP2C19	citalopram	https://cpicpgx.org/gui	A	Final	1A	Actionable PGx	25974703
CYP2C19	clopidogrel	https://cpicpgx.org/gui	A	Final	1A	Actionable PGx	21716271;23698643;35034351
CYP2D6	codeine	https://cpicpgx.org/gui	A	Final	1A	Actionable PGx	22205192;24458010;33387367
CACNA1S	desflurane	https://cpicpgx.org/gui	A	Final	1A	Actionable PGx	30499100
RYR1	desflurane	https://cpicpgx.org/gui	A	Final	1A	Actionable PGx	30499100
CYP2B6	efavirenz	https://cpicpgx.org/gui	A	Final	1A	Actionable PGx	31006110
CACNA1S	enflurane	https://cpicpgx.org/gui	A	Final	1A	Actionable PGx	30499100
RYR1	enflurane	https://cpicpgx.org/gui	A	Final	1A	Actionable PGx	30499100
CYP2C19	escitalopram	https://cpicpgx.org/gui	A	Final	1A	Actionable PGx	25974703
DPYD	fluorouracil	https://cpicpgx.org/gui	A	Final	1A	Actionable PGx	23988873;29152729
CYP2C9	flurbiprofen	https://cpicpgx.org/gui	A	Final	1A	Actionable PGx	32189324
CYP2C9	fluvastatin	https://cpicpgx.org/gui	A	Final			35152405
SLCO1B1	fluvastatin	https://cpicpgx.org/gui	A	Final			35152405
CYP2C9	fosphenytoin	https://cpicpgx.org/gui	A	Final		Actionable PGx	25099164;32779747
HLA-B	fosphenytoin	https://cpicpgx.org/gui	A	Final		Actionable PGx	25099164;32779747
MT-RNR1	gentamicin	https://cpicpgx.org/gui	A	Final	1A		34032273
CACNA1S	halothane	https://cpicpgx.org/gui	A	Final	1A		30499100
RYR1	halothane	https://cpicpgx.org/gui	A	Final	1A		30499100
CYP2C9	ibuprofen	https://cpicpgx.org/gui	A	Final	1A		32189324

https://cpicpgx.org/genes-drugs/ Accessed April 12, 2022

Examples of Drug-Gene Pairs Among Various Disease States which have CPIC Guidelines

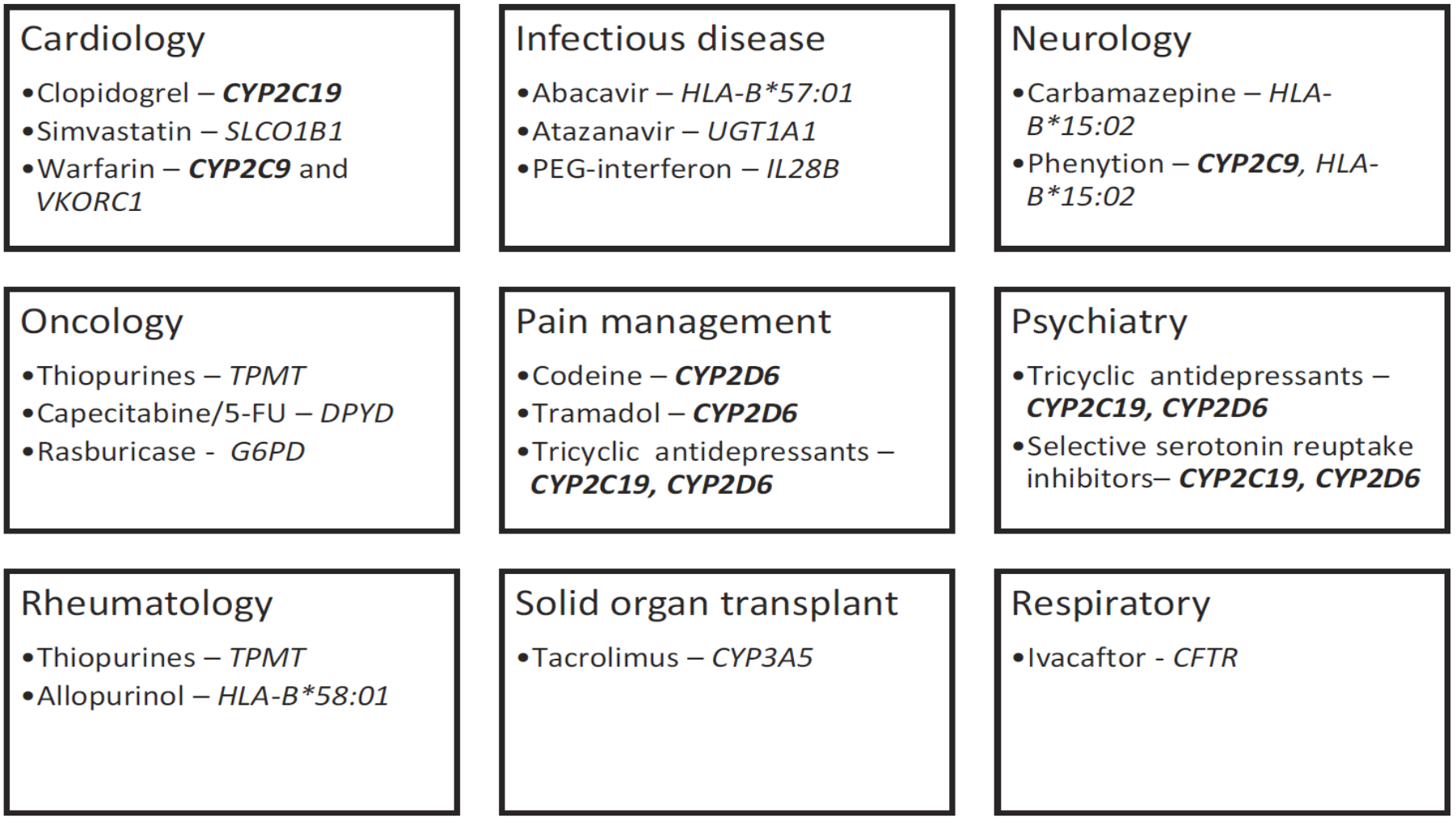


Figure 1. Current drug-gene pairs with Clinical Pharmacogenetics Implementation Consortium guidelines grouped by disease state. The genes in bold (*CYP2C19*, *CYP2C9*, *CYP2D6*) are the backbone genes for a general pharmacogenomics implementation initiative.

Vo TT et al. *Pharmacotherapy* 2017; 37:1014-1022

"Pre-emptive PGx testing may result in the initial highest yield for a health system"

Table 2 **Critical pharmacogenomic drug frequencies**

	Primary Medicare insurance	Outpatient substance abuse	Arthritis	Family medicine outpatient	Chronic kidney disease	Diabetes	Cardiology outpatient	Inpatient any diagnosis	Psychiatry inpatient	Psychiatry outpatient	Total
Ondansetron	174	63	174	236	80	71	59	5284	6501	3501	16 143
Metoprolol	863	129	483	385	463	354	630	2197	2205	4677	12 386
Escitalopram	163	45	101	48	30	41	57	243	549	4758	6035
Simvastatin	381	47	321	154	150	138	184	702	669	2890	5636
Citalopram	114	47	152	84	87	63	33	268	488	3912	5248
Venlafaxine	115	17	106	60	20	45	22	207	399	3530	4521
Clopidogrel	384	67	138	144	221	160	359	825	821	1275	4394
Tramadol	198	30	251	127	105	91	79	637	746	2041	4305
Allopurinol	8	14	260	37	177	55	93	955	851	796	3246
Paroxetine	63	27	72	59	14	27	16	130	253	1724	2385
Amitriptyline	69	36	90	185	60	80	32	120	200	1377	2249
Risperidone	25	11	21	21	5	10	5	131	359	1129	1717
Codeine	48	4	57	49	9	23	7	391	310	584	1482
Celecoxib	54	3	84	27	9	20	22	83	103	541	946
Atomoxetine	1	13	0	6	1	1	0	1	18	810	851
Nortriptyline	40	9	44	38	17	31	7	57	82	466	791
Haloperidol	4	7	2	6	9	2	4	199	403	103	739
Oxcarbazepine	10	4	11	18	0	5	3	14	69	486	620

Heise CW et al. *Pharmacogenetics and Genomics* 2020, 30:91–95

Phase 2: Implementation

Developing PGx protocols

- With evidence in hand, determine type of program (clinical vs. research)
- Determine drug-gene pair(s) for implementation
- Determine testing workflow
  - Preemptive vs. reactive PGx testing
  - Individual gene vs. panel-based testing
  - Funding to support program (grant vs. reimbursement)
  - In-house vs. reference lab for performance of actual PGx testing (how will results be reported/returned? EHR?)
  - Role of clinical decision report (CDS) to guide providers at the point of care

Phase 2: Implementation

Develop Support Tools

- *Clinical decision support (CDS)*
  - Collaboration with informatics expert to enable delivery of CDS to providers in real time
- *Provider support*
  - Education is critical
  - Written materials to support drug-gene specific recommendations
  - Materials can also be included in automated CDS
  - Referral helpline with questions
- *Patient support*
  - How will results be returned to patients?
  - Education on meaning of results
  - Consultation service/PGx clinic/patient satisfaction surveys

Pharmacogenomic Clinical Decision Support: A Review, How-to Guide, and Future Vision

Dyson T. Wake[1], D. Max Smith[2,3], Sadaf Kazi[3,4] and Henry M. Dunnenberger[1,*]

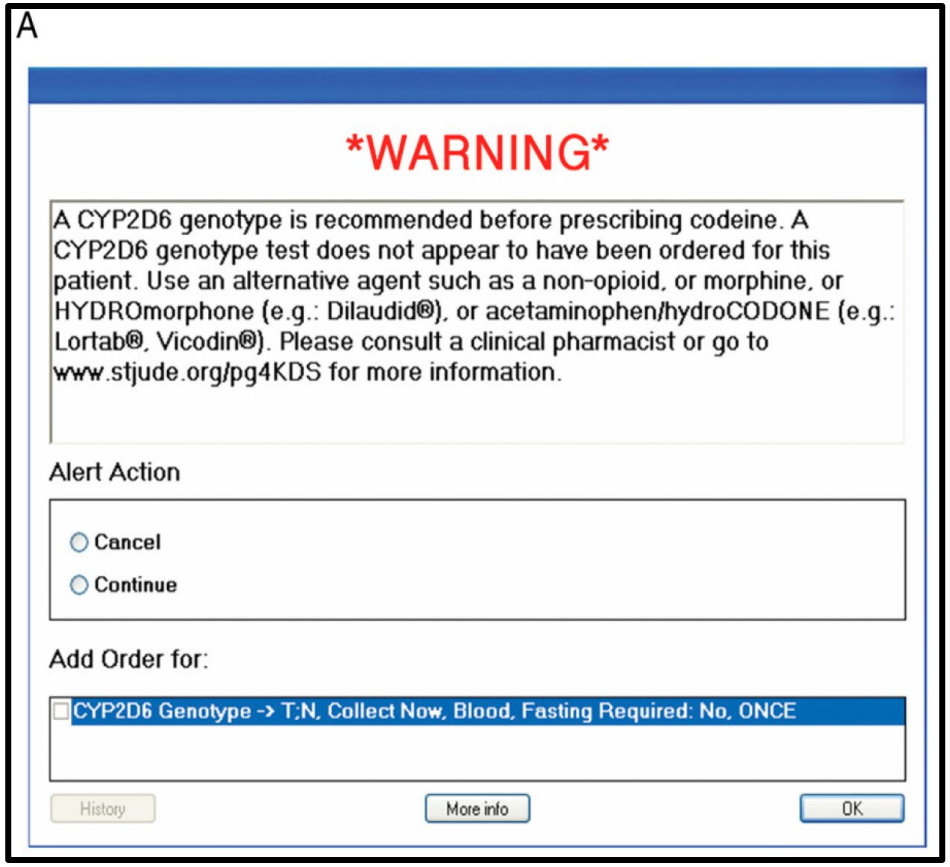
Clinical decision support (CDS) is an essential part of any pharmacogenomics (PGx) implementation. Increasingly, institutions have implemented CDS tools in the clinical setting to bring PGx data into patient care, and several have published their experiences with these implementations. However, barriers remain that limit the ability of some programs to create CDS tools to fit their PGx needs. Therefore, the purpose of this review is to summarize the types, functions, and limitations of PGx CDS currently in practice. Then, we provide an approachable step-by-step how-to guide with a case example to help implementers bring PGx to the front lines of care regardless of their setting. Particular focus is paid to the five "rights" of CDS as a core around designing PGx CDS tools. Finally, we conclude with a discussion of opportunities and areas of growth for PGx CDS.

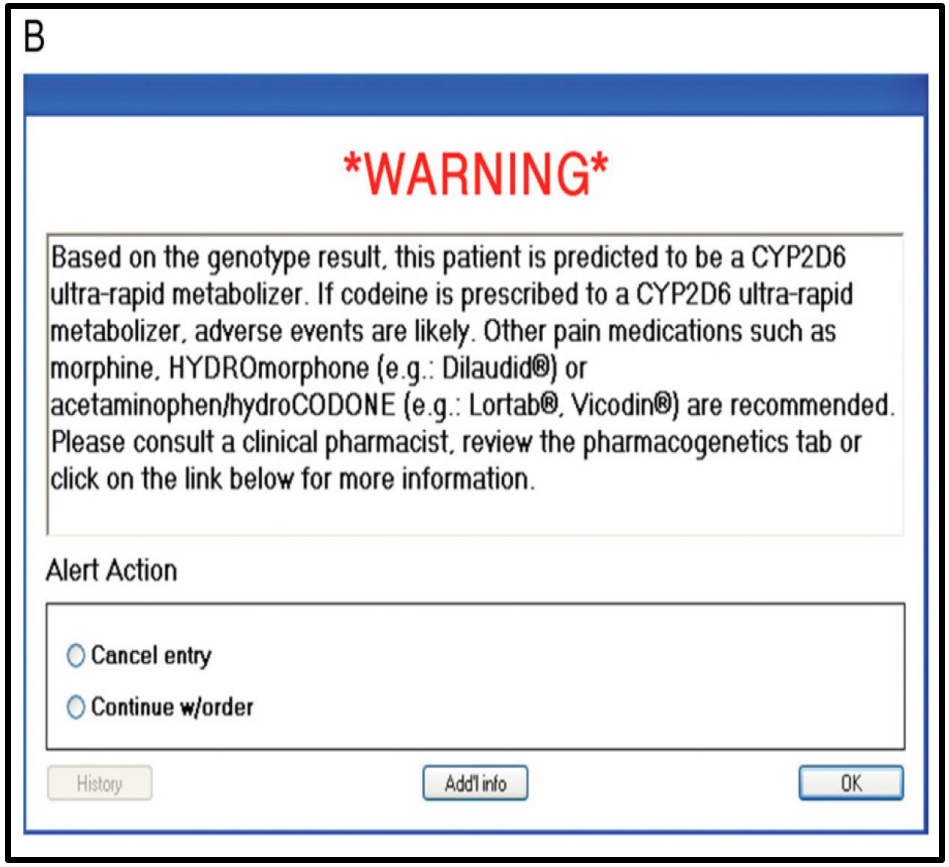
Wake DT et al. *Clin Pharmacol Ther* 2021 Aug 8. doi: 10.1002/cpt.2387.

Example of Clinical Decision Support (CDS) in an Electronic Health Record (EHR)

Pretest Alert

Posttest Alert





Gammal RS et al. *Pediatrics* 2016;138(1). pii: e20153479. doi: 10.1542/peds.2015-3479.

POOR METABOLIZER

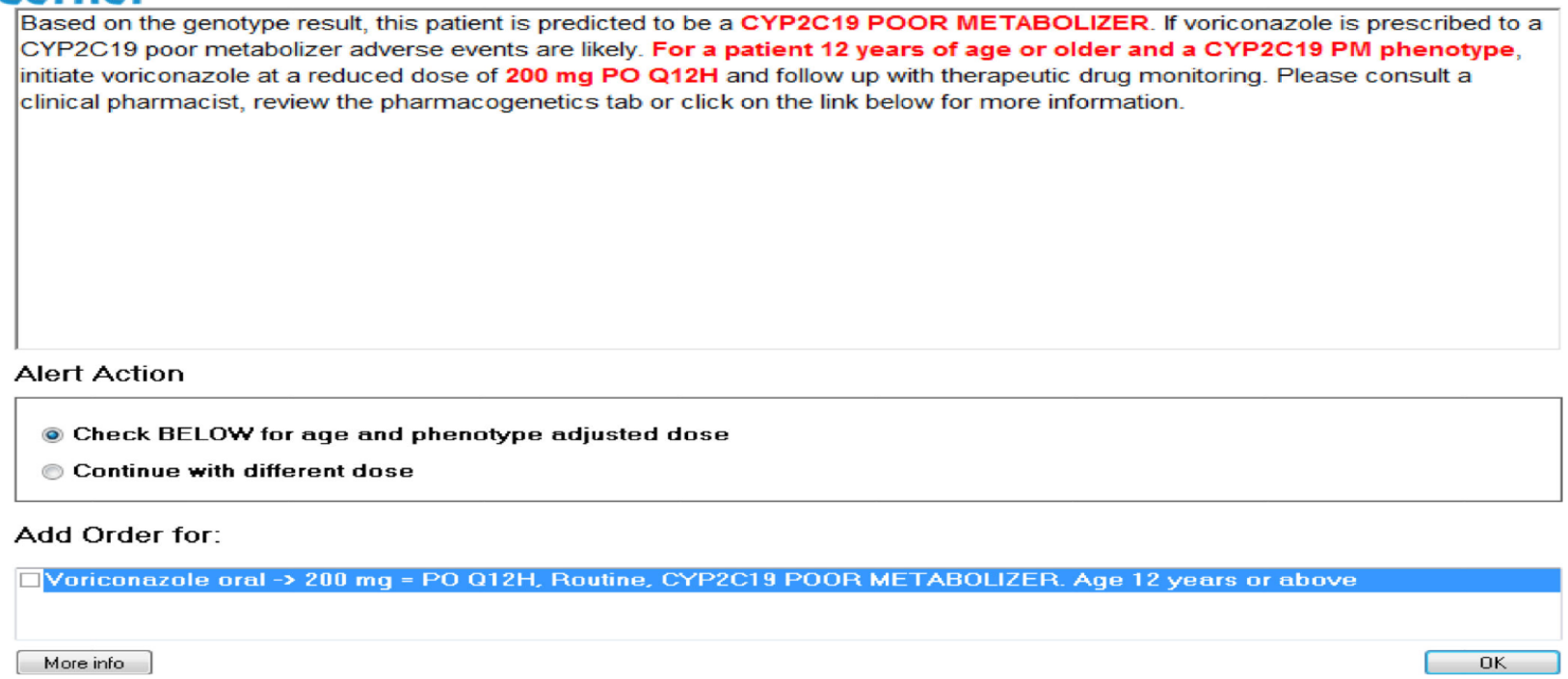
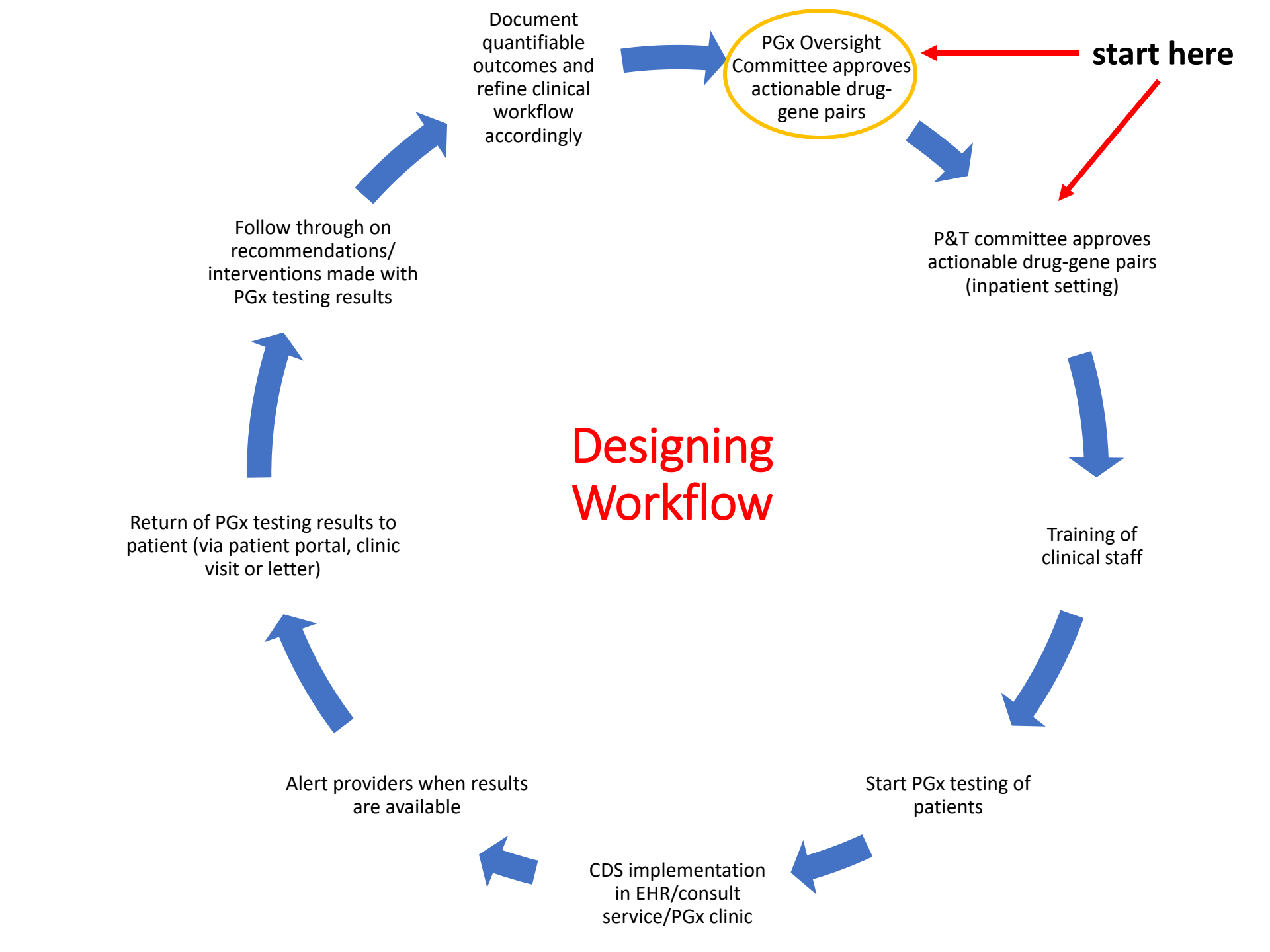


Figure 3.
Example of a pharmacogenomic clinical decision support alert that takes into account non genetic risk factors. In this case, the recommendation displayed to clinicians is age, route and *CYP2C19* phenotype specific. Used with Permission of Cerner.

Five Key Concepts to Integrating Pharmacogenomics into the EHR

1	Document pharmacogenomics results in patient centric and time independent manner
2	Provide a clinical interpretation based on expected phenotype
3	Represent genetic results and interpretation as discrete data
4	Provide drug-specific pharmacotherapy recommendations
5	Deploy CDS so pharmacogenomic information is reliably used at the point of care

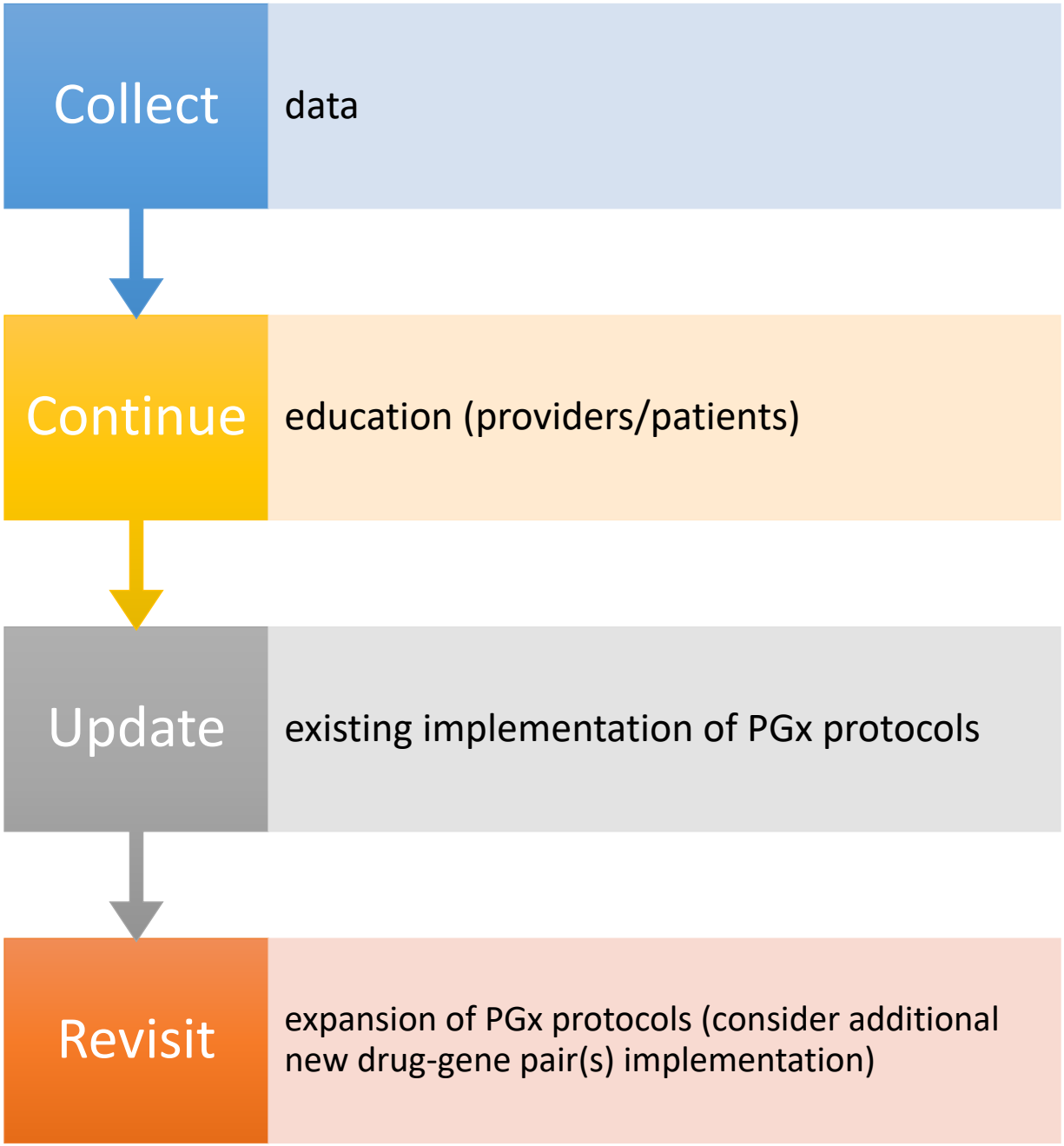
Hicks JK et al. *Am J Health Syst Pharm*. 2016; 73(23): 1967–1976


Designing Workflow
PGx Oversight Committee approves actionable drug-gene pairs
start here
P&T committee approves actionable drug-gene pairs (inpatient setting)
Training of clinical staff
Start PGx testing of patients
CDS implementation in EHR/consult service/PGx clinic
Alert providers when results are available
Return of PGx testing results to patient (via patient portal, clinic visit or letter)
Follow through on recommendations/ interventions made with PGx testing results
Document quantifiable outcomes and refine clinical workflow accordingly

Ready, Set, Launch Implementation

- Discuss and receive feedback on workflow from all members of the PGx Oversight Committee
- Pilot workflow on small number of patients
- Refine workflow as needed
- Set official launch date and spread awareness to all members of institution – not just those involved in the PGx program

Phase 3: Post-Implementation



Post-Implementation Phase/Collecting Data

Automated or manual data collection

Data Metrics of Interest

- ✓Frequency of actionable variants or drug-gene interactions in patient population
- ✓Frequency of changes in treatment due to PGx recommendations (i.e. dose modifications/use of alternative medications)
- ✓Safety/efficacy outcomes before and after implementation of PGx program
- ✓Reimbursement coverage from third party payers
- ✓Cost effectiveness of PGx program implementation

Phase 3: Post-Implementation

Important Measures of Success

- ✓PGx testing of patient population
- ✓CDS implementation of drug-gene pairs
- ✓Provider acceptability of PGx recommendations
- ✓Improved treatment outcomes (reduced toxicity and increased efficacy of medication use)
- ✓Patient satisfaction

Continue education, update and expand existing PGx protocols as necessary

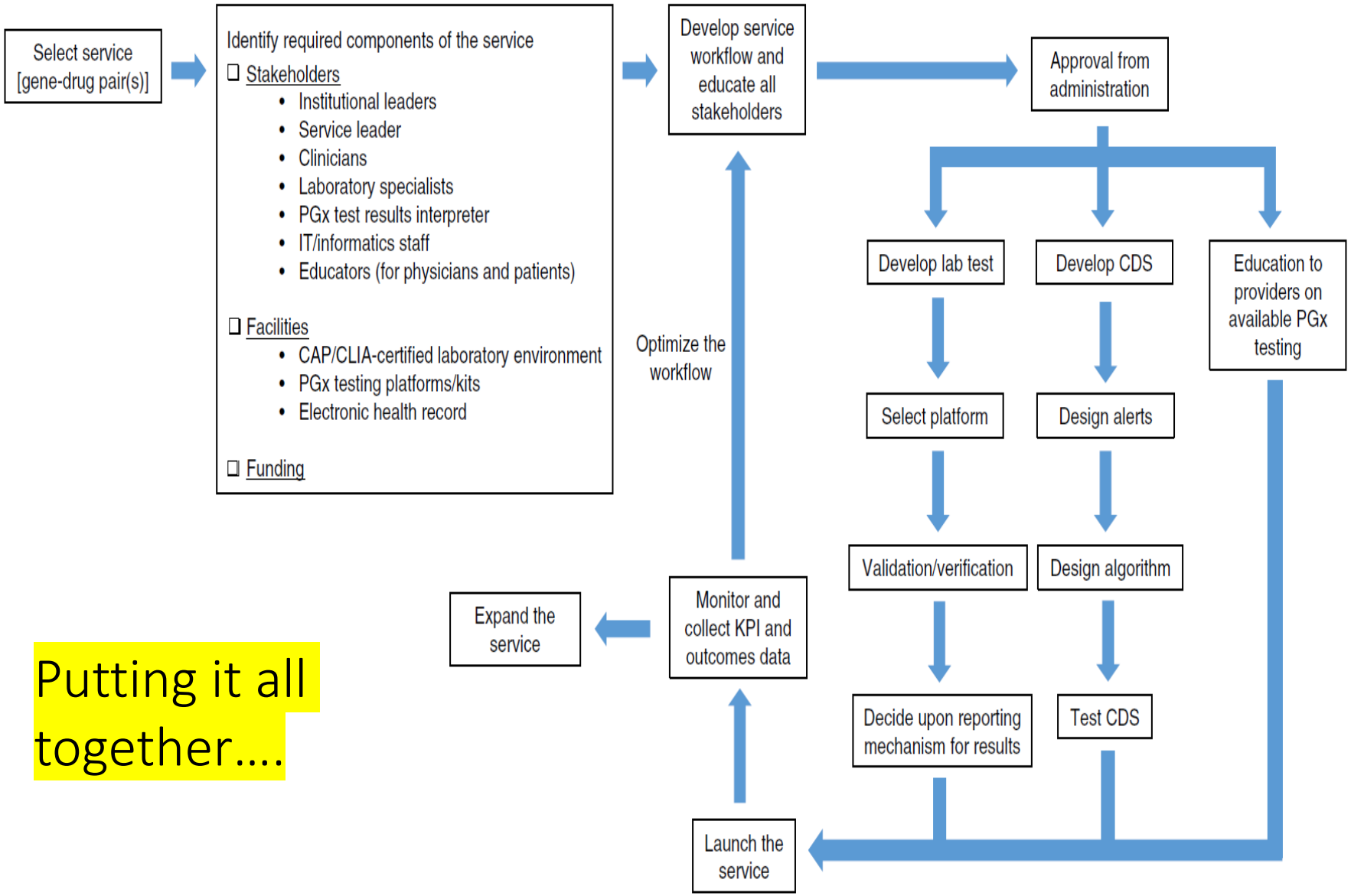
CME/CE, revise educational tools from provider feedback

Remind/educate patients on use of PGx testing results as necessary for management of disease states

PGx Oversight Committee should stay current with evolving new literature making changes to existing protocols where necessary

Assess institutional workflow regularly and refine as necessary

Expand existing PGx protocols with new drug-gene pair implementation



Putting it all together….

Figure 1 Reactive Pharmacogenomics Service Implementation Process. CAP, College of American Pathologists; CDS, Clinical decision support; CLIA, Clinical Laboratory Improvement Amendments; KPI, Key performance indicator; IT, Information Technology; PGx, Pharmacogenomics.

Arwood MJ et al. *Clin Transl Sci.* 2016; 9:233–245

Recommend pharmacogenomic testing when appropriate and integrate test results with other clinical variables to optimize medication therapy

NIH National Library of Medicine
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GTR: GENETIC TESTING REGISTRY

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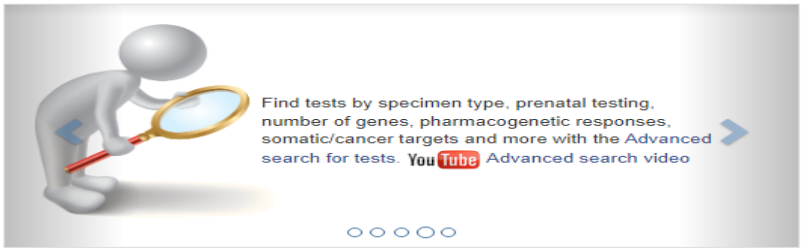
Search all 78110 tests, 22107 conditions, 18739 genes, and 515 labs

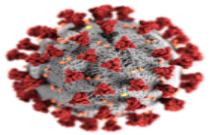
YouTube GTR Tutorials

IMPORTANT NOTE: NIH does not independently verify information submitted to the GTR; it relies on submitters to provide information that is accurate and not misleading. NIH makes no endorsements of tests or laboratories listed in the GTR. GTR is not a substitute for medical advice. ***Patients and consumers*** with specific questions about a genetic test should contact a health care provider or a genetics professional.



Microbe tests in GTR

GTR now has tests for microbes like for SARS-CoV-2 to diagnose COVID-19. Scope includes pathogen-specific genetic tests; panels to identify pathogens; tests that assess viral load; serologic tests for detection of antibodies and antigens to determine prior exposure.



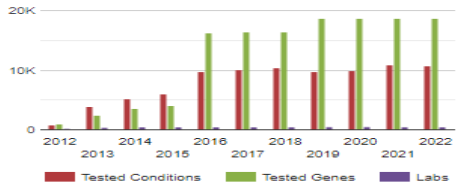
Find COVID-19 tests | Find all microbe tests

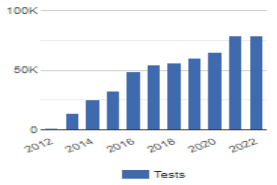
About GTR®

The Genetic Testing Registry (GTR®) provides a central location for voluntary submission of genetic test information by providers. The scope includes the test's purpose, methodology, validity, evidence of the test's usefulness, and laboratory contacts and credentials. The overarching goal of the GTR is to advance the public health and research into the genetic basis of health and disease

- How to use GTR
- Frequently asked questions
- GTR News
- GTR Information at NIH Office of the Director
- GTR in the community
- Contact us and provide feedback

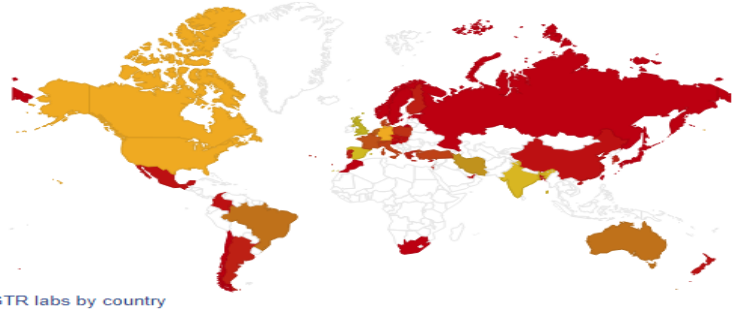
GTR Data





FTP: Download GTR data and documents

Worldwide Lab Participation in GTR



GTR labs by country

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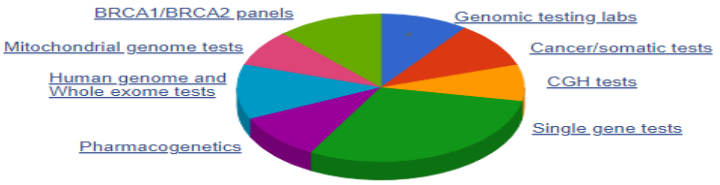
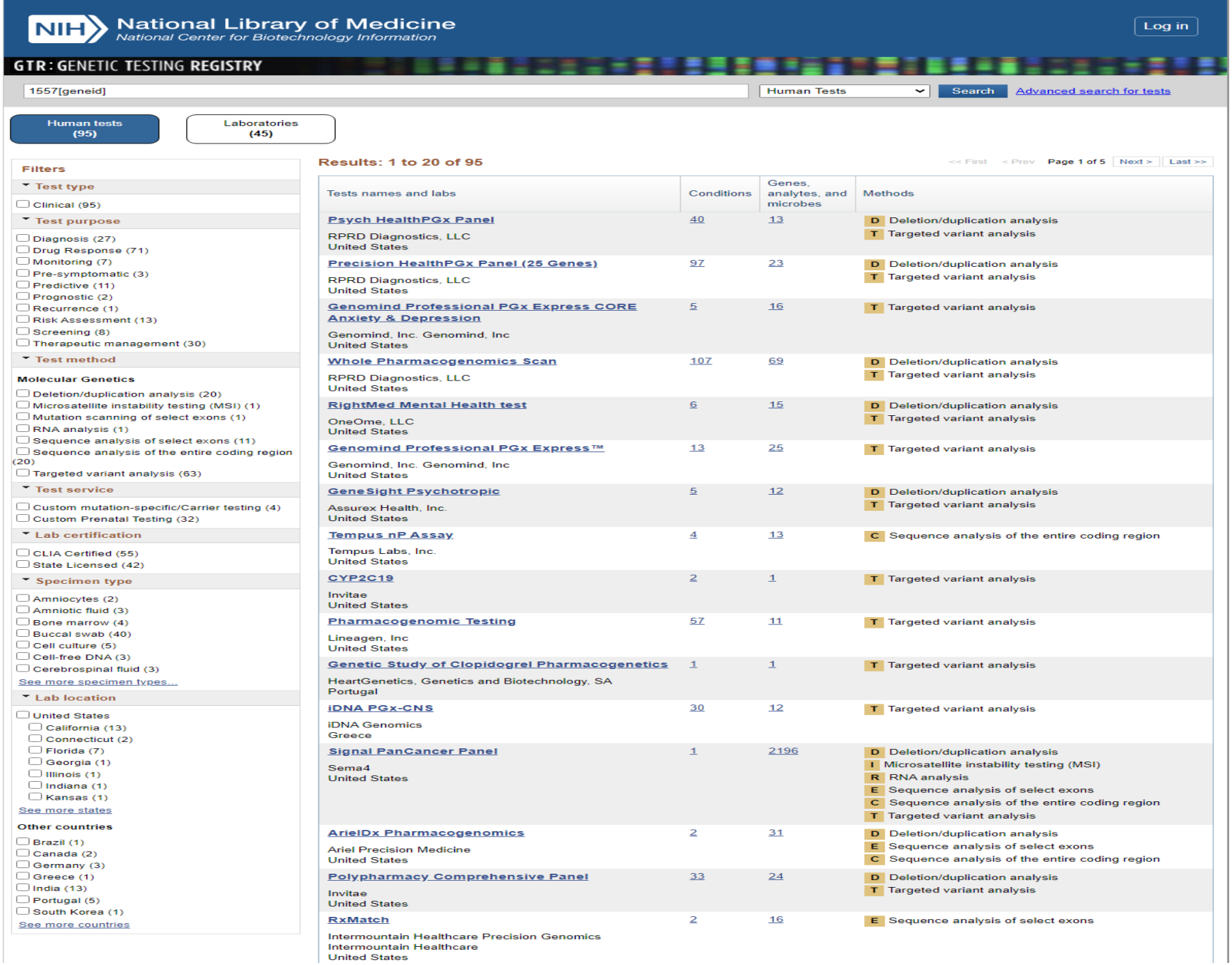


All GTR data

Locate a Genetics Professional

- ABGC Directory
- ABMGG Directory
- NSGC Directory
- NCI Cancer Genetics Services Directory
- ACMG Genetics Clinics Database

https://www.ncbi.nlm.nih.gov/gtr/ Accessed April 13, 2022



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National Library of Medicine
National Center for Biotechnology Information

GTR: GENETIC TESTING REGISTRY

1557[geneid] | Human Tests | Search

GTR Home > Tests > RxMatch

RxMatch

Clinical test for CYP2C19-related poor drug metabolism
Offered by Intermountain Healthcare Precision Genomics

GTR Test ID : GTR000591842.1
Last updated: 2022-02-01
Test version history

Overview | How To Order | Indication | Methodology | Performance Characteristics | Interpretation | Laboratory Contact

Test name

RxMatch

Purpose of the test

This is a clinical test intended for : Drug Response, Monitoring, Therapeutic management

Condition

Click Indication tab for more information.

CYP2C19-related poor drug metabolism
Warfarin response

How to order

Patients give a very simple cheek (buccal) swab. Once the Intermountain Precision Genomics laboratory receives the sample, the patient's DNA is extracted and checked for quality and quantity.

Specimen source

Buccal swab

Methodology

Molecular Genetics	
E Sequence analysis of select exons	Next-Generation (NGS)/Massively parallel sequencing (MPS)

Summary of what is tested

16 genes and variants. Click Methodology tab for more information.

Genes

Gene: ADRA2A (10q25.2)
Gene: ANKK1 (11q23.2)
Gene: COMT (22q11.21)
Gene: CYP2C19 (10q23.33)
Gene: CYP2C9 (10q23.33)
Gene: CYP2D6 (22q13.2)
Gene: CYP3A4 (7q22.1)
Gene: CYP3A5 (7q22.1)
Gene: CYP4F2 (19p13.12)
Gene: F2 (11p11.2)
Gene: F5 (1q24.2)
Gene: HLA-B (6p21.33)
Gene: MTHFR (1p36.22)
Gene: OPRM1 (6q25.2)
Gene: SLCO1B1 (12p12.1)
Gene: VKORC1 (16p11.2)

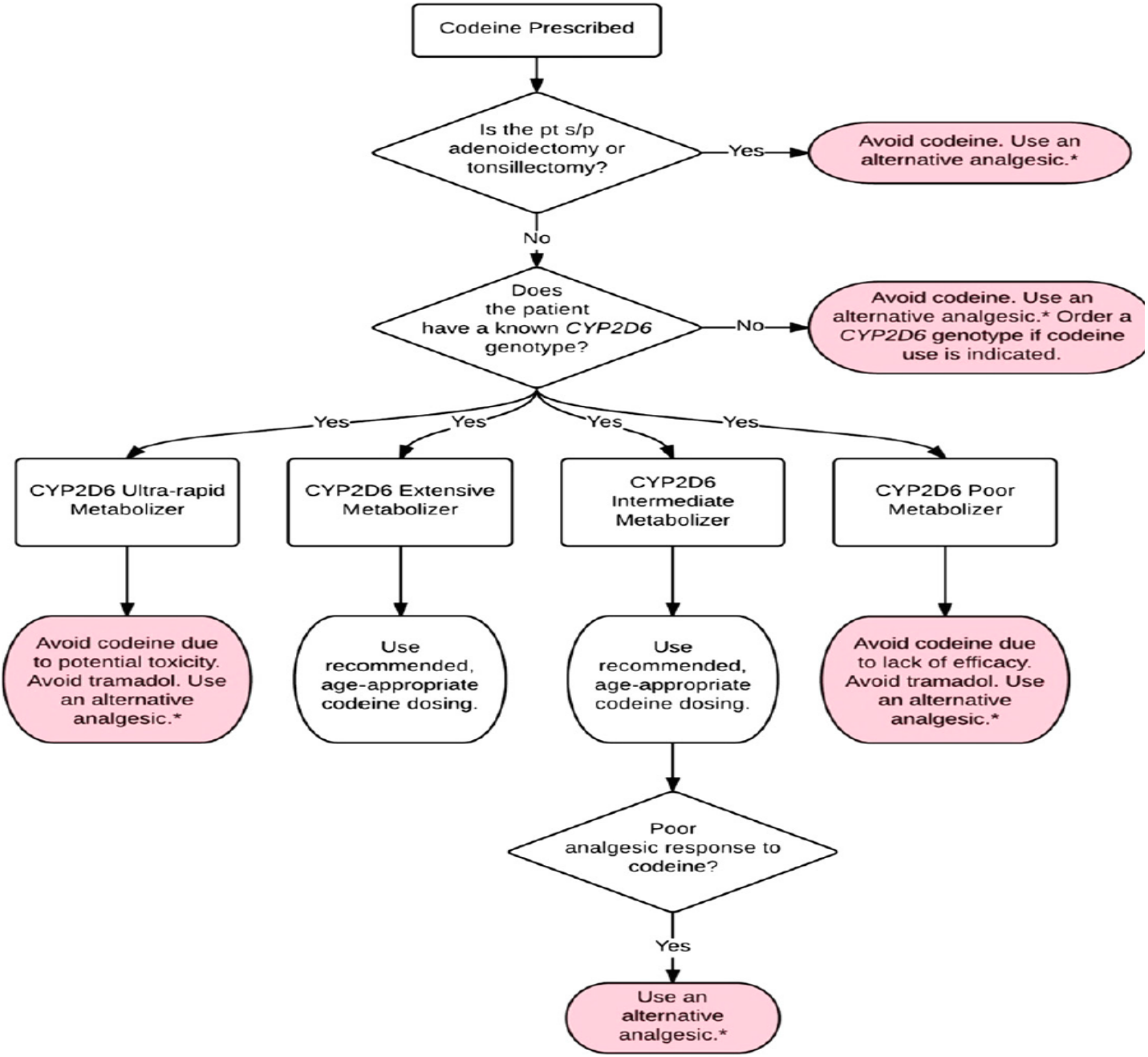
https://www.ncbi.nlm.nih.gov/gtr/ Accessed April 13, 2022

Examples of Five US Programs Implementing Preemptive PGx testing

Summary of the genotyping platform used by 5 U.S. institutions to implement array-based preemptive pharmacogenetic testing

Institution	Genotyping platform	Number of genes assayed
Mayo Clinic (43)	PGRN-Seq	84
Mount Sinai Medical Center (42)	PGRN-Seq	84
St. Jude Children's Research Hospital (65)	Affymetrix DMET Plus array	230
University of Florida and Shands Hospital (35)	Life Technologies Quant Studio Open Array	120
Vanderbilt University Medical Center (69)	VeraCode ADME Core Panel	34

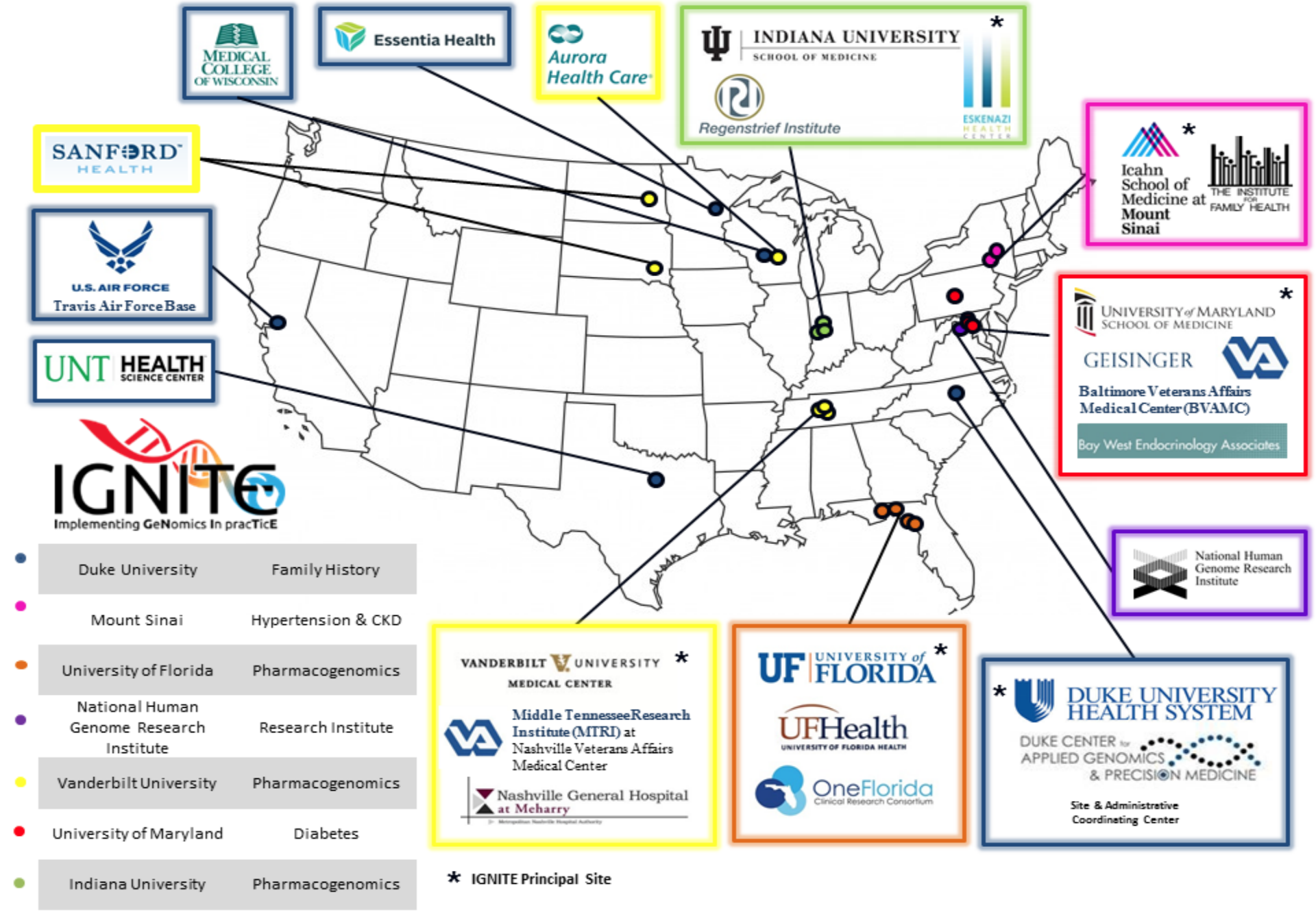
Dunnenberger HM et al. *Annu Rev Pharmacol Toxicol. 2015;55:89–106*



PGx-based <u>codeine prescribing strategy</u> used across all services at

St. Jude Children's Research Hospital

Gammal RS et al. *Pediatrics* 2016;138(1). pii: e20153479. doi: 10.1542/peds.2015-3479. www.stjude.org/pg4kds



Duke University	Family History
Mount Sinai	Hypertension & CKD
University of Florida	Pharmacogenomics
National Human Genome Research Institute	Research Institute
Vanderbilt University	Pharmacogenomics
University of Maryland	Diabetes
Indiana University	Pharmacogenomics

* IGNITE Principal Site

https://ignite-genomics.org. Accessed March 24, 2021

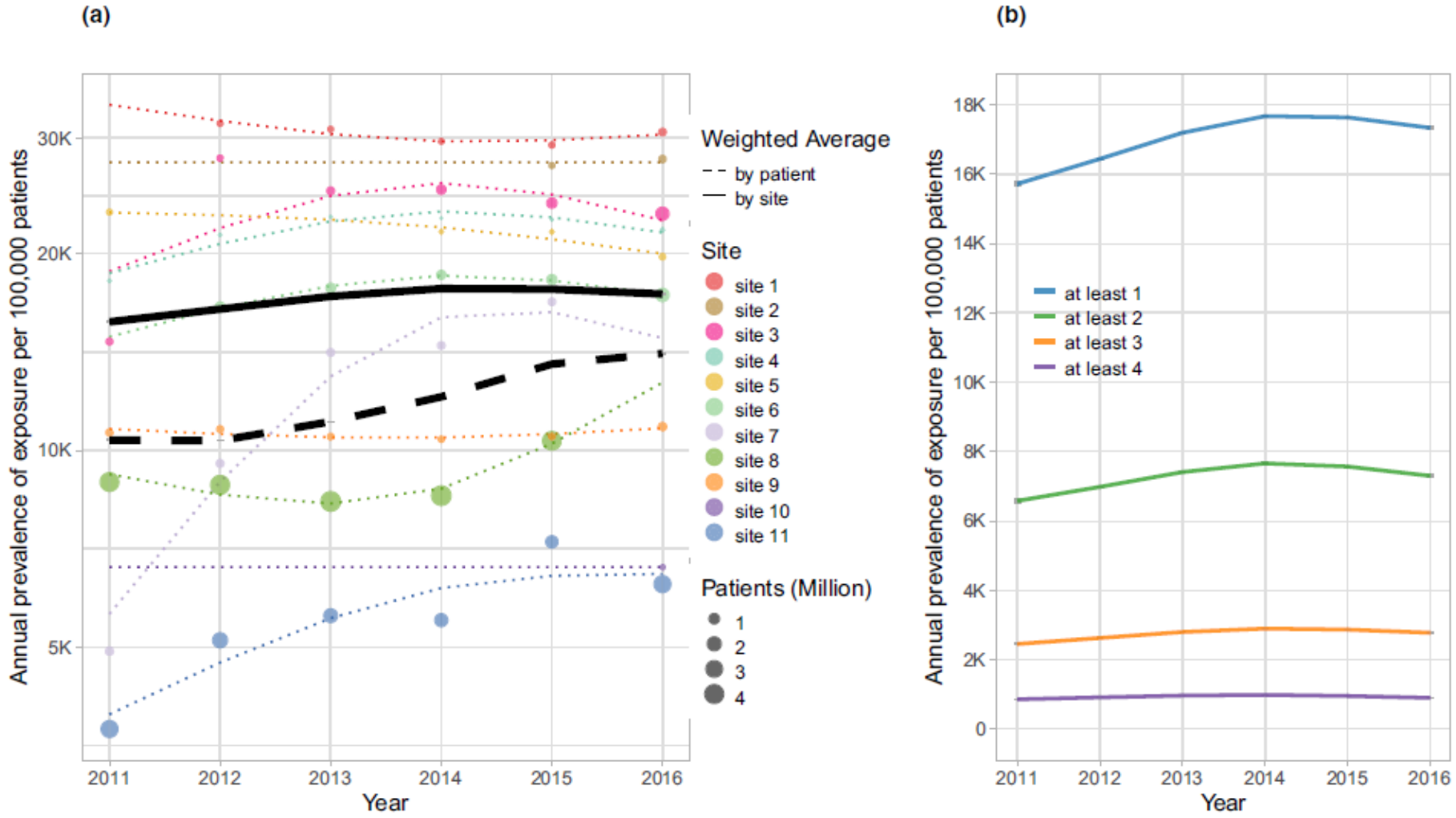
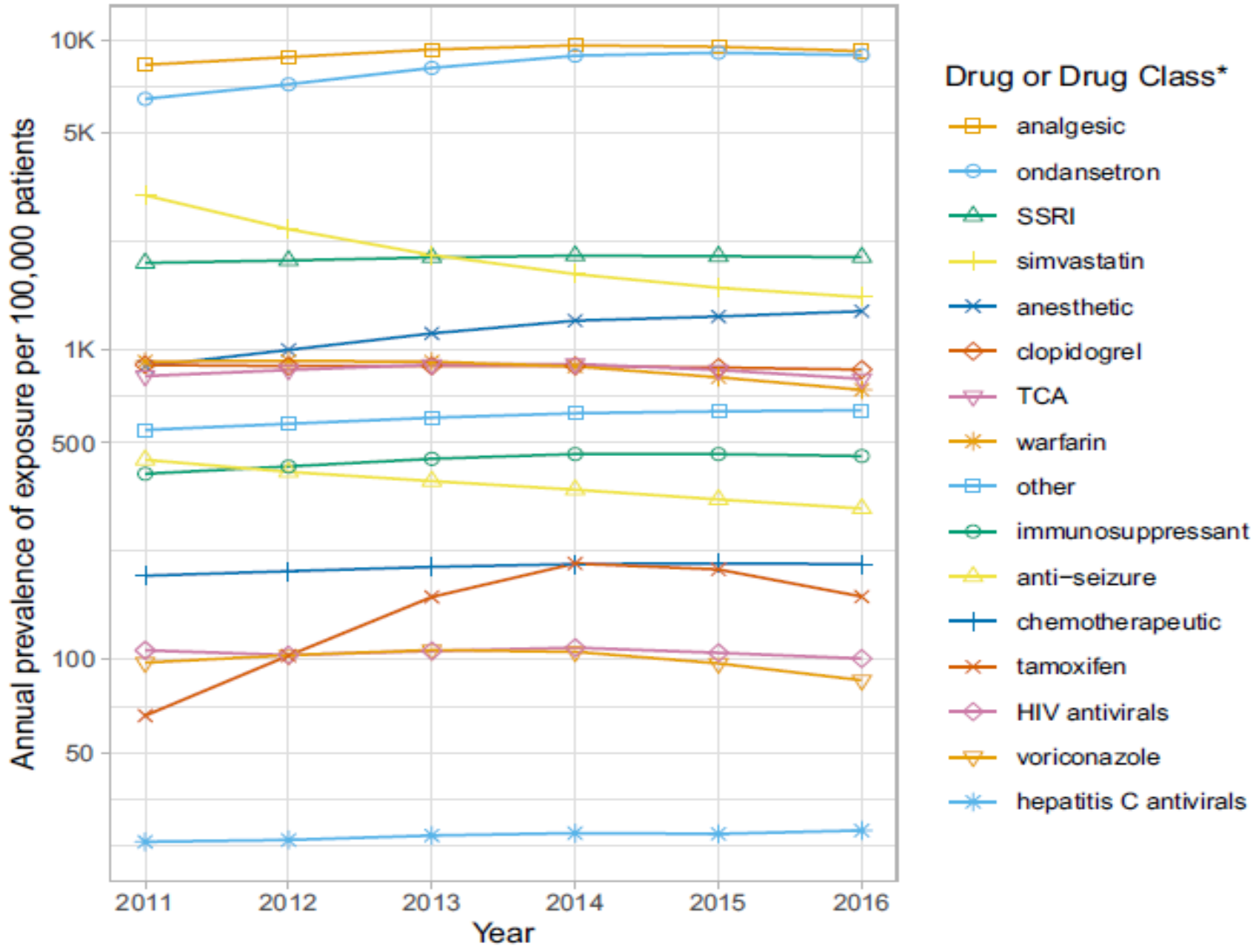
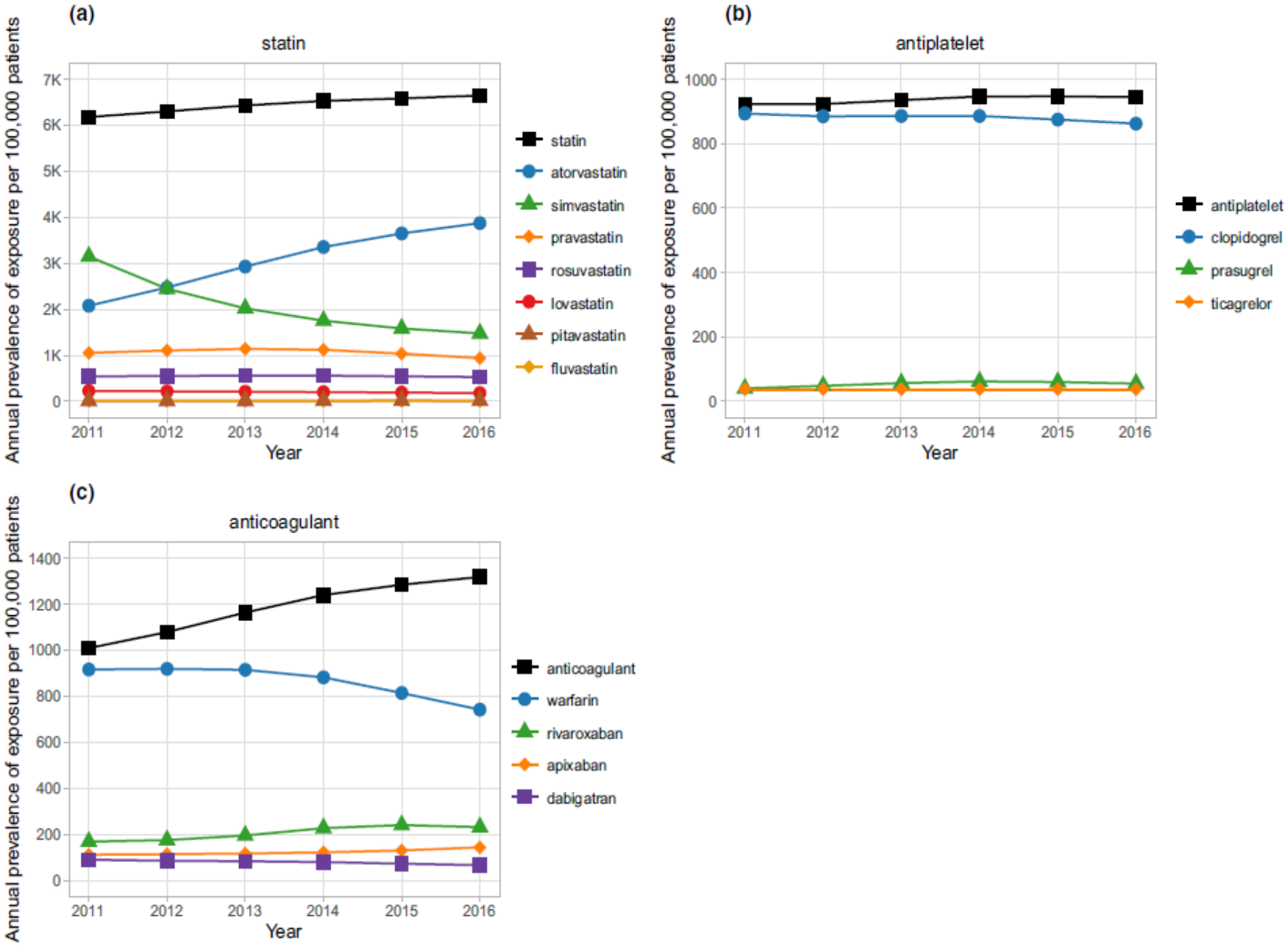


Figure 1 Annual prevalence of exposure to at least one CPIC level A drug by site and to one or more CPIC level A medications. (**a**) Exposure (log scale) to at least one CPIC level A drug for each site from 2011–2016. Each colored circle represents the exposure for the corresponding site. Circles are absent for years where data are not available. The size of the circle is proportional to the number of patients eligible for drug prescribing during the calendar year. The dotted colored lines are the prevalence of exposure estimated from the model fit. The mean prevalence of exposure for the entire cohort weighted by site is represented by the solid black line and weighted by encounters is represented by the dotted black line. The 95% confidence bands for the two means are represented by gray shading but may be too narrow to be observed. (**b**) Mean site-weighted prevalence stratified by at least 1, 2, 3, or 4 CPIC level A drugs from 2011–2016 plotted on a linear scale. Note that confidence intervals are represented by gray shading but may be too narrow to be observed. CPIC, Clinical Pharmacogenetics Implementation Consortium.

Hicks JK et al. *Clin Pharmacol Ther*. 2021; 110(1):179-188



Hicks JK et al. *Clin Pharmacol Ther*. 2021; 110(1):179-188



Hicks JK et al. *Clin Pharmacol Ther*. 2021; 110(1):179-188

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IGNITE Toolbox

The IGNITE Toolbox is an open resource of peer-reviewed genomic medicine implementation tools for clinicians, researchers, educators and patients. The artifacts in the toolbox have been created, collected and vetted by the IGNITE Network researchers and affiliates and include documents and links to websites. For clinicians, the tools provide background information, benefits of adopting genomic medicine in patient care, and key challenges and stakeholders to consider for your implementation. For researchers, the research and data collection tools provide sample consent forms, surveys, data dictionaries, and other resources to help conduct implementation science research in genomic medicine.

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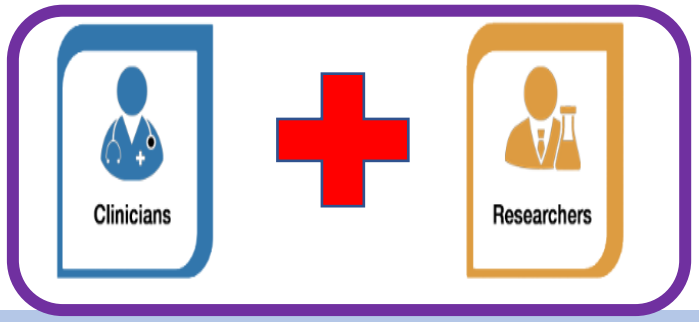

https://dcricollab.dcri.duke.edu/sites/NIHKR/Pages/IGNITEToolbox.aspx Accessed April 15, 2022

Educate health care professionals and patients about the cost, cost-effectiveness, and reimbursement issues relevant to pharmacogenomic tests and services

Potential Costs of a Pharmacogenomics Program

Testing supplies

Expert in pharmacogenomics (pharmacist)

Technology

Local Coverage Determination (LCD): MolDX: Pharmacogenomics Testing (L38337)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
Noridian Healthcare Solutions, LLC	A and B MAC	02101 - MAC A	J - F	Alaska
Noridian Healthcare Solutions, LLC	A and B MAC	02102 - MAC B	J - F	Alaska
Noridian Healthcare Solutions, LLC	A and B MAC	02201 - MAC A	J - F	Idaho
Noridian Healthcare Solutions, LLC	A and B MAC	02202 - MAC B	J - F	Idaho
Noridian Healthcare Solutions, LLC	A and B MAC	02301 - MAC A	J - F	Oregon
Noridian Healthcare Solutions, LLC	A and B MAC	02302 - MAC B	J - F	Oregon
Noridian Healthcare Solutions, LLC	A and B MAC	02401 - MAC A	J - F	Washington
Noridian Healthcare Solutions, LLC	A and B MAC	02402 - MAC B	J - F	Washington

LCD - MolDX: Pharmacogenomics Testing (L38337) (cms.gov) Accessed April 13, 2022.

CMS Reimbursement of PGx Testing

Clinical Indications

PGx tests are indicated when medications are being considered for use (or already being administered) that are medically necessary, appropriate, and approved for use in the patient's condition and are known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable as defined by the FDA (PGx information required for safe drug administration) or Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines (category A and B).

The selection of the medications in question must be derived from clinical factors/necessity rather than from a PGx test. Once the putative therapeutic agents are selected, and those agents are known to have gene-drug interactions as identified above, then a PGx test may be considered reasonable and necessary when the result of that test is necessary for the physician's decision-making process regarding safely administering or dosing the drug.

PGx testing is **not** considered reasonable and necessary merely on the basis of a patient having a particular diagnosis. Unless the record reflects that the treating clinician has already considered non-genetic factors to make a preliminary drug selection, PGx testing is not considered reasonable and necessary.

This LCD does not address (provides neither coverage nor non-coverage criteria) PGx testing for anticoagulation dosing, which is addressed by the National Coverage Determination (NCD) 90.1.

https://www.cms.gov/medicare-coverage-database. Accessed April 13, 2022.

Article - Billing and Coding: MolDX: Pharmacogenomics Testing (A57385)

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Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATES
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Noridian Healthcare Solutions, LLC	A and B MAC	02201 - MAC A	J - F	Idaho
Noridian Healthcare Solutions, LLC	A and B MAC	02202 - MAC B	J - F	Idaho
Noridian Healthcare Solutions, LLC	A and B MAC	02301 - MAC A	J - F	Oregon
Noridian Healthcare Solutions, LLC	A and B MAC	02302 - MAC B	J - F	Oregon
Noridian Healthcare Solutions, LLC	A and B MAC	02401 - MAC A	J - F	Washington
Noridian Healthcare Solutions, LLC	A and B MAC	02402 - MAC B	J - F	Washington

https://www.cms.gov/medicare-coverage-database. Accessed April 13, 2022.

The landscape of pharmacogenetic testing in a US managed care population

Heather D. Anderson, PhD[1], Kristy R. Crooks, PhD[2], David P. Kao, MD[3] and Christina L. Aquilante, PharmD[4]

Purpose: Little is known about how many insured patients receive pharmacogenetic testing. We describe trends of single-gene pharmacogenetic testing in a US managed care population, and demographic and clinical characteristics of patients who received a test.

Methods: We leveraged a random sample of nearly 11 million patients from a data set of paid medical and pharmacy claims to identify patients with at least one claim indicating receipt of at least one of these single-gene pharmacogenetic tests: *CYP2C19*, *CYP2D6*, *CYP2C9*, *VKORC1*, *UGT1A1*, and *HLA* class 1 typing.

Results: From 1 January 2013 to 30 September 2017, 5712 patients received at least one pharmacogenetic test (55% female; mean age = 43 years). The median number of tests per patient was 3 (mean = 2.7, max = 12); 54% were processed through Managed Medicare/Medicaid, while 45% were processed through commercial insurance. The total number of pharmacogenetic tests received more than doubled from 2013 ($n = 1955$) to 2015 ($n = 4192$), then decreased slightly in 2016 ($n = 3946$). The most common test was *CYP2C19* ($n = 4719$), and "long-term (current) use of other medications" was the most common diagnosis.

Conclusion: Pharmacogenetic testing through patients' insurance was low, but more than doubled from 2013 to 2016. This study highlights the need to better understand utilization patterns and insurance coverage for pharmacogenetic tests.

Genetics in Medicine (2020) 22:1247–1253; https://doi.org/10.1038/s41436-020-0788-3

Keywords: pharmacogenetic; pharmacogenomic; testing; insurance; managed care

Table 1 Description of single-gene pharmacogenetic tests.

CPT code	Single-gene pharmacogenetic test	Examples of clinically actionable medications[a]
81225	*CYP2C19* (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)	Clopidogrel, voriconazole, selective serotonin reuptake inhibitors (i.e., citalopram, escitalopram), tertiary amine tricyclic antidepressants (e.g., amitriptyline)
81226	*CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)	Secondary and tertiary amine tricyclic antidepressants (e.g., amitriptyline, nortriptyline), selective serotonin reuptake inhibitors (e.g., paroxetine, fluvoxamine); opioids (e.g., codeine, oxycodone, tramadol), atomoxetine, ondansetron, pitolisant, tamoxifen
81227	*CYP2C9* (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g.,*2, *3, *5, *6)	Phenytoin, siponimid, warfarin
81355	*VKORC1* (vitamin K epoxide reductase complex, subunit 1) (e.g., warfarin metabolism), gene analysis, common variant(s) (e.g., −1639G>A, c.173+1000C>T)	Warfarin
81381	*HLA* class I typing, high resolution (i.e., alleles or allele groups); 1 allele or allele group (e.g., B*57:01P), each	Abacavir, allopurinol, carbamazepine, oxcarbazepine, phenytoin
81350	*UGT1A1* (UDP glucuronosyltransferase 1 family, polypeptide A1) (e.g., irinotecan metabolism), gene analysis, common variants (e.g., *28, *36, *37)	Atazanavir, irinotecan

CPT Current Procedural Terminology.
[a]Clinically actionable, as defined by Clinical Pharmacogenetics Implementation Consortium (CPIC) Level A designation.

Anderson HD et al. *Genetics in Medicine* (2020) 22:1247–1253

Table 2 Most common diagnoses reported for each single-gene pharmacogenetic test of interest[a].

Diagnosis reported on pharmacogenetic test claim	*CYP2C19* (*N* = 4719) *N* (%)	*CYP2D6* (*N* = 3775) *N* (%)	*CYP2C9* (*N* = 3289) *N* (%)	*HLA* class 1 (*N* = 1821) *N* (%)	*VKORC1* (*N* = 1587) *N* (%)	*UGT1A1* (*N* = 191) *N* (%)
Long-term (current) use of medications	*966 (20.5%)*	*883 (23.4%)*	*705 (21.4%)*	110 (6.0%)	*534 (33.7%)*	*48 (25.1%)*
Depression	*976 (20.1%)*	*940 (24.9%)*	*826 (25.1%)*	*507 (27.8%)*	165 (10.4%)	25 (13.1%)
Anxiety	622 (13.2%)	*592 (15.7%)*	*523 (15.9%)*	299 (16.4%)	117 (7.4%)	*32 (16.8%)*
Lipid disorders	*664 (14.1%)*	221 (5.8%)	228 (6.9%)	73 (4.0%)	204 (12.8%)	15 (7.8%)
Hypertension	563 (11.9%)	310 (8.2%)	310 (9.4%)	43 (2.4%)	*293 (18.5%)*	29 (15.2%)
Pain/low back pain	436 (9.2%)	440 (11.7%)	389 (11.8%)	41 (2.2%)	*238 (15.0%)*	*58 (30.4%)*
ADHD	515 (10.9%)	519 (13.8%)	460 (14.0%)	*301 (16.5%)*	53 (3.3%)	25 (13.1%)
HIV	0	0	0	*544 (29.9%)*	0	0

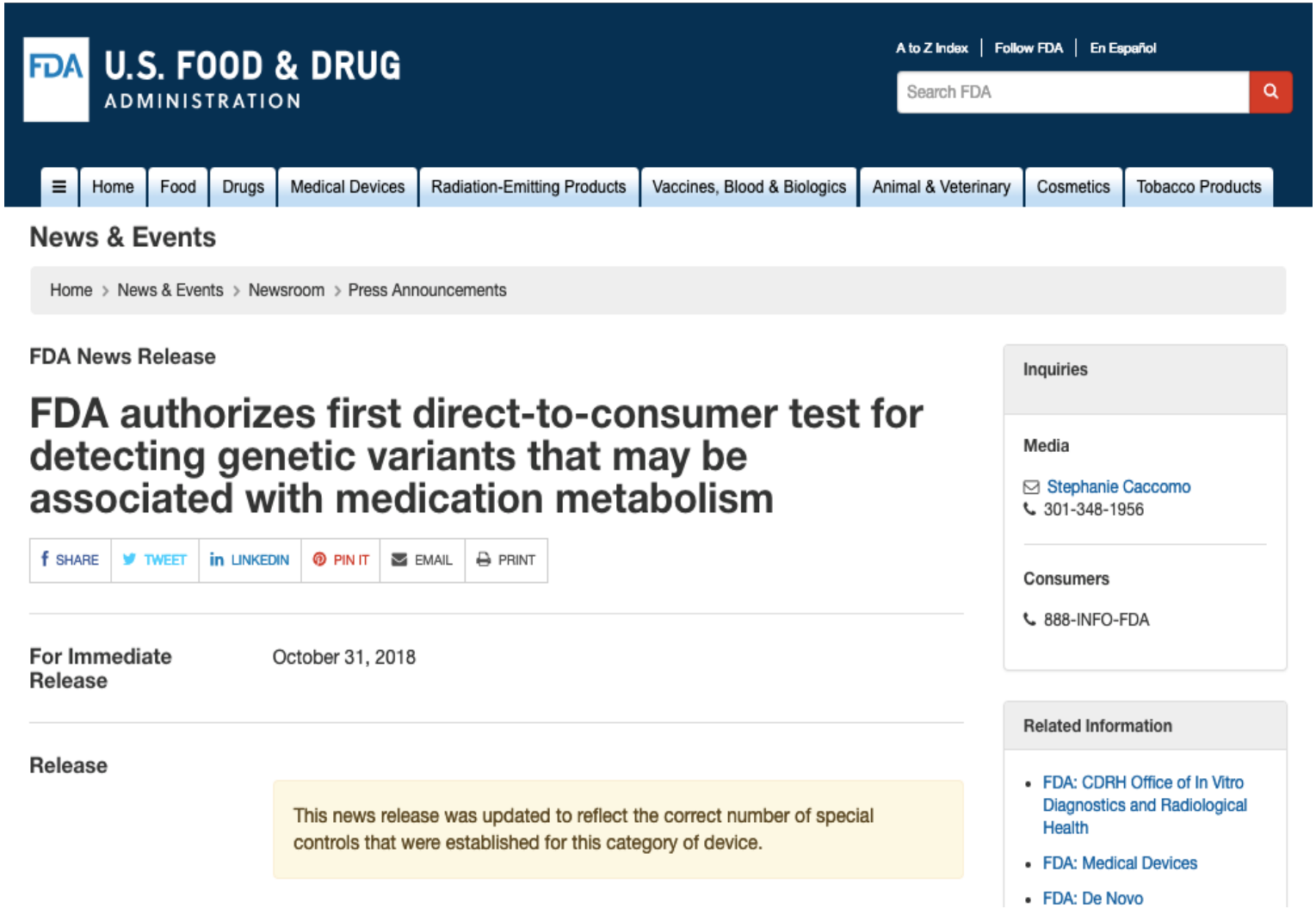
ADHD attention deficit–hyperactivity disorder.

[a]Top three diagnoses for each test are indicated in italics.

Anderson HD et al. *Genetics in Medicine* (2020) 22:1247–1253

Describe FDA approved examples of direct-to-consumer (DTC) pharmacogenomics testing

FDA Approved 23andMe Personal Genome Service Pharmacogenetic Reports DTC Test



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FDA News Release

FDA authorizes first direct-to-consumer test for detecting genetic variants that may be associated with medication metabolism

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

For Immediate Release October 31, 2018

Release

This news release was updated to reflect the correct number of special controls that were established for this category of device.

Inquiries

Media

Stephanie Caccomo
301-348-1956

Consumers

888-INFO-FDA

Related Information

- FDA: CDRH Office of In Vitro Diagnostics and Radiological Health
- FDA: Medical Devices
- FDA: De Novo

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624753.htm Accessed March 10th, 2022.

FDA Approved 23andMe Personal Genome Service Pharmacogenetic Reports DTC Test

"The FDA has permitted marketing of **23andMe Personal Genome Service Pharmacogenetic Reports test** as a direct-to-consumer test for providing information about genetic variants that may be associated with a patient's ability to metabolize some medications to help inform discussions with a health care provider. The FDA is authorizing the test to **detect 33 variants for multiple genes**."

"This test is a step forward in making information about genetic variants available directly to consumers and better inform their discussions with their health care providers"

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624753.htm. Accessed March 10th, 2022.

FDA Approved 23andMe Personal Genome Service Pharmacogenetic Reports DTC Test

"This test should be used appropriately because it does not determine whether a medication is appropriate for a patient, does not provide medical advice and does not diagnose any health conditions. Consumers should not use this test to make treatment decisions on their own. Any medical decisions should be made only after discussing the results with a licensed health care provider and results have been confirmed using clinical pharmacogenetic testing."

"The 23andMe Personal Genome Service Pharmacogenetic Reports test is not intended to provide information on a patient's ability to respond to any specific medication. The test does not describe an association between the detected variants and any specific drug nor whether a person will or will not respond to a particular drug. Furthermore, health care providers should not use the test to make any treatment decisions. **Results from this test should be CONFIRMED with independent pharmacogenetic testing before making any medical decisions**."

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624753.htm Accessed March 10th, 2022.

False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care

Stephany Tandy-Connor, MS, Jenna Guiltinan, MS, Kate Krempely, MS, Holly LaDuca, MS, Patrick Reineke, BS, Stephanie Gutierrez, BS, Phillip Gray, PhD and Brigette Tippin Davis, PhD, FACMG

Purpose: There is increasing demand from the public for direct-to-consumer (DTC) genetic tests, and the US Food and Drug Administration limits the type of health-related claims DTC tests can market. Some DTC companies provide raw genotyping data to customers if requested, and these raw data may include variants occurring in genes recommended by the American College of Medical Genetics and Genomics to be reported as incidental/secondary findings. The purpose of this study was to review the outcome of requests for clinical confirmation of DTC results that were received by our laboratory and to analyze variant classification concordance.

Methods: We identified 49 patient samples received for further testing that had previously identified genetic variants reported in DTC raw data. For each case identified, information pertaining to the outcome of clinical confirmation testing as well as classification of the DTC variant was collected and analyzed.

Results: Our analyses indicated that 40% of variants in a variety of genes reported in DTC raw data were false positives. In addition, some variants designated with the "increased risk" classification in DTC raw data or by a third-party interpretation service were classified as benign at Ambry Genetics as well as several other clinical laboratories, and are noted to be common variants in publicly available population frequency databases.

Conclusion: Our results demonstrate the importance of confirming DTC raw data variants in a clinical laboratory that is well versed in both complex variant detection and classification.

Genet Med advance online publication 22 March 2018

Key Words: classification discrepancy; clinical confirmation direct-to-consumer; false positive; raw data

Tandy-Connor et al. *Genet Med* 2018; 20(12):1515-1521.

FDA grants 23andMe clearance to offer interpretive drug information for two medications

August 18, 2020 By 23andMe under News & Announcements

This week, the U.S. Food and Drug Administration (FDA) granted 23andMe a 510(k) clearance for a pharmacogenetics report on two medications, clopidogrel, prescribed for certain heart conditions, and citalopram, which is prescribed for depression.

The decision this week modifies the labeling of the previously authorized CYP2C19 Drug Metabolism report which was granted FDA authorization in 2018. The new 510(k) clearance for the pharmacogenetics report for CYP2C19 modifies the labeling to remove the need for confirmatory testing and allows 23andMe to report interpretive drug information for two medications.

"This impactful pharmacogenetics information can now be delivered without the need for confirmatory testing, a testament to the clinical validity of 23andMe results," said Kathy Hibbs, 23andMe Chief Legal, and Regulatory Officer. "23andMe remains the only company with direct-to-consumer pharmacogenetic reports cleared by the FDA. Now that we have pioneered a regulatory path, we believe all companies marketing pharmacogenetic reports should go through the FDA review process to ensure the safety and effectiveness of their tests."

https://blog.23andme.com/news/pharmacogenetics-report/ Accessed April 14, 2022

23andMe Pharmacogenetics Reports

Drug Metabolism Enzyme/Drug Transporter	Reported Allelic Variants
CYP2C19*	***2** (c.681G>A), ***3** (c.636G>A), and ***17** (c.-806C>T).
DPYD	***2A** (c.1905+1G>A) and **D949V** (c.2846A>T).
SLC01B1	**c.521T>C** (found in the ***5, *15, and *17** haplotypes)

**The *3/*17 genotype result should be confirmed by an independent genetic test prescribed by your own healthcare provider before taking any medical action. For all other genotypes that result in a predicted metabolizer profile, confirmation is not required.*

https://www.23andme.com/test-info/pharmacogenetics/ Accessed April 14, 2022

Right Drug Dose Now (Right) Act

Requires the Department of Health and Human Services (DHHS) to consider new information on the **role of drug-drug-gene interactions causing ADEs and PGx testing to prevent them** under the 2014 National Action Plan for Adverse Drug Event Prevention

Requires National Human Genome Research Institute to **develop two education campaigns for the general public and providers** to improve knowledge of ADEs and clinically appropriate use of PGx testing

Requires DHHS to update certification data for health information technology to **incorporate drug-gene and drug-drug-gene interactions into alerting systems** when medications are prescribed and ordered

Authorizes $7,000,000 to be appropriated to the National Institutes of Health for FY2022 to FY2025 to **support PGx implementation research** and distribution of genomic resources to the research community

What are YOU going to do to INFLUENCE coverage of PGx testing?

- ✓ Stay up to date with the field (educate yourself and others)
- ✓ Engage in PGx clinical research related to treatment outcomes and cost-effectiveness
- ✓ Become a member of professional organizations that promote PGx education and research (CPIC, PGRN)
- ✓ Advocate for and support grassroot movements focused on moving the PGx field forward
- ✓Educate the next generation of healthcare professionals

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