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Outcomes Assessment Across Multiple Sites in the eMERGE-PGx Project

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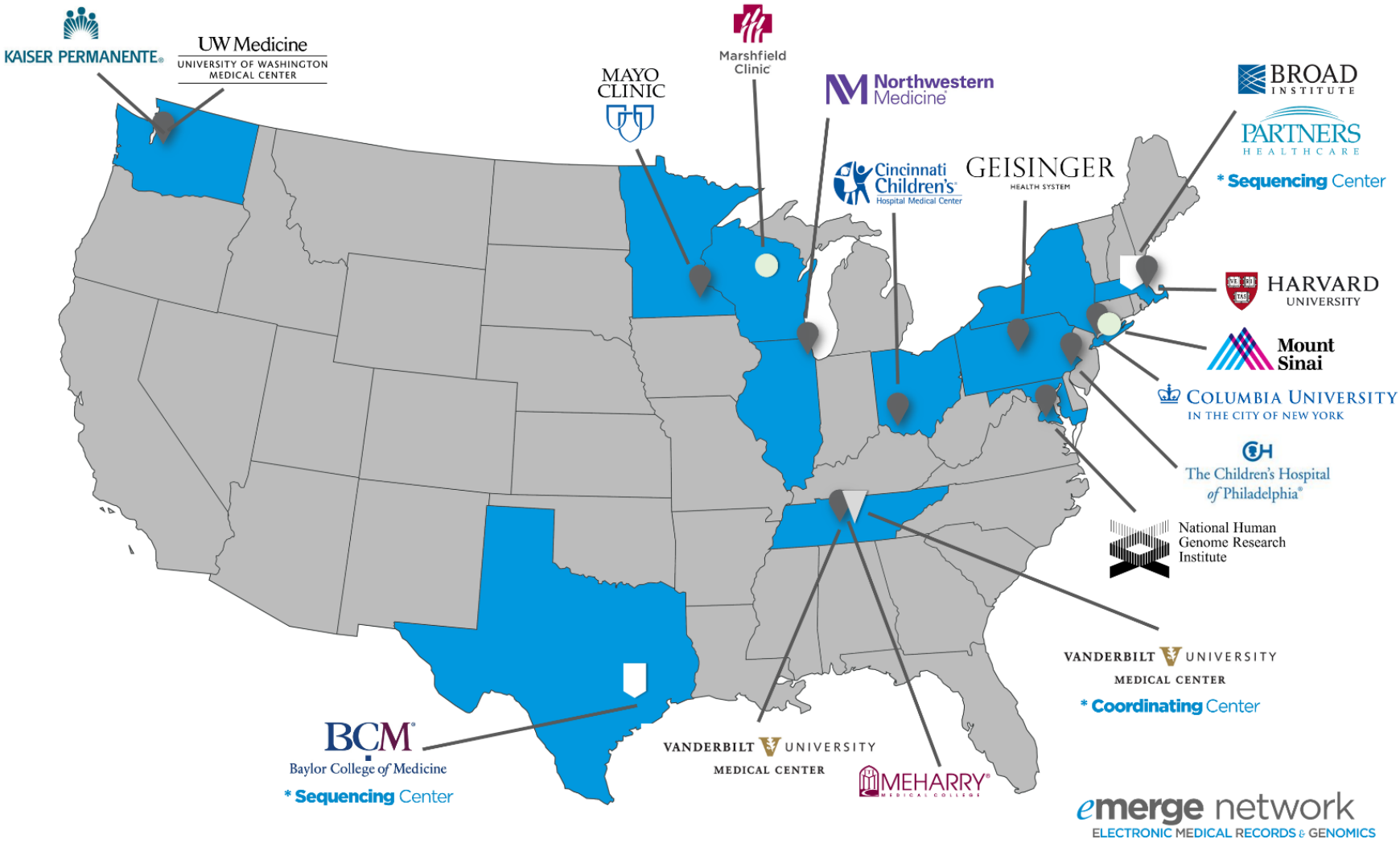
eMERGE PGx *Outcomes*

Laura J. Rasmussen-Torvik

on behalf of the eMERGE-PGx workgroup

Agenda

- Describe eMERGE-PGx
- Detail outcomes published to date in eMERGE PGx
  - Highlight areas where eMERGE-PGx has encountered challenges
- Future directions for eMERGE-PGx outcomes and other outcomes projects to promote implementation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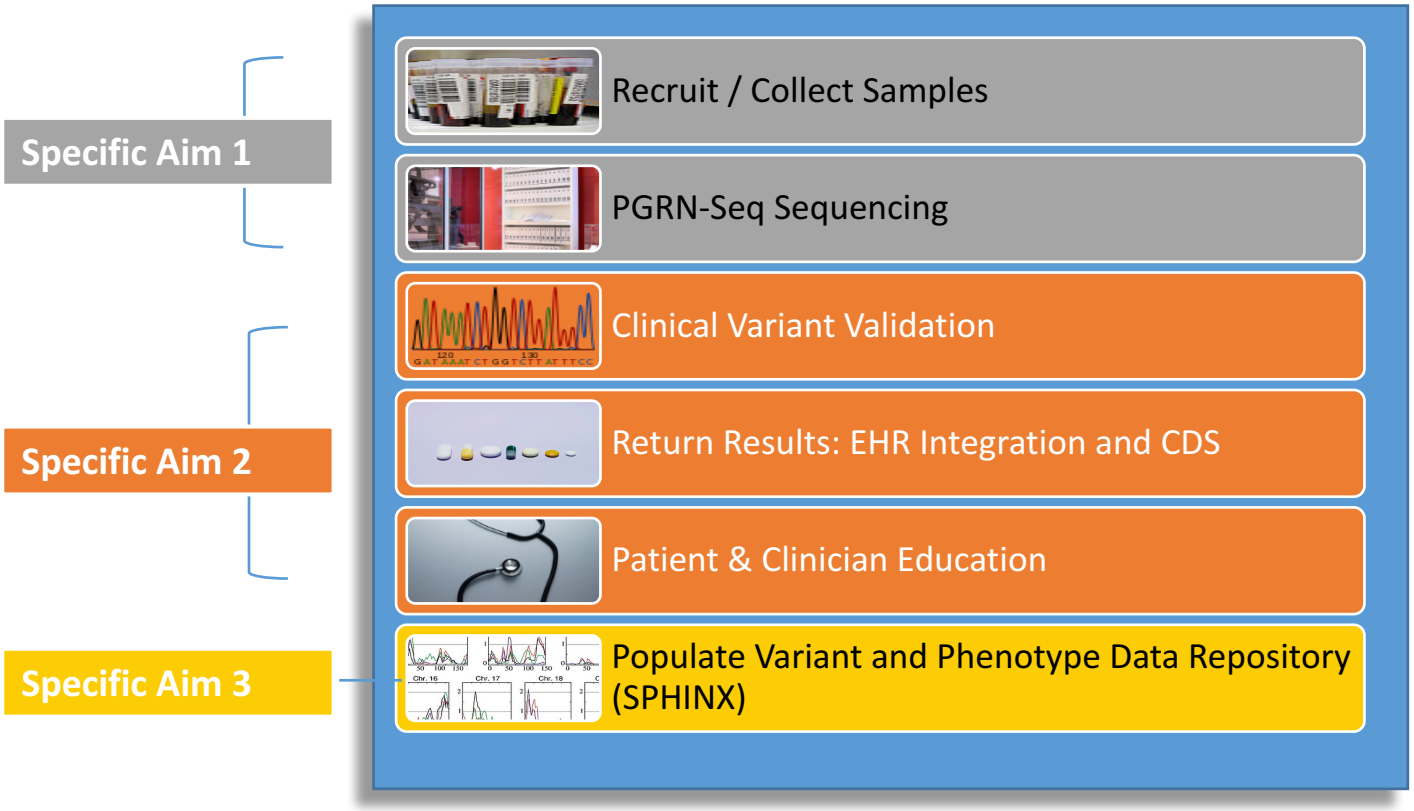
emerge network
ELECTRONIC MEDICAL RECORDS & GENOMICS

eMERGE PGx - Overview by Aim



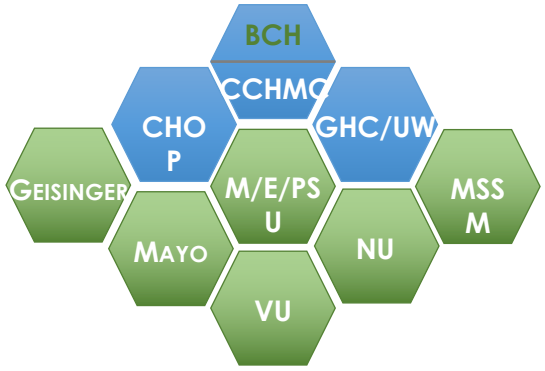
PGRNseq: a targeted capture sequencing panel for pharmacogenetic research and implementation.
Gordon AS, Fulton RS, Qin X, Mardis ER, Nickerson DA, Scherer S.
Pharmacogenet Genomics. 2016 Jan 5. [Epub ahead of print]

Design and Anticipated Outcomes of the eMERGE-PGx Project: A Multicenter Pilot for Preemptive Pharmacogenomics in Electronic Health Record Systems

LJ Rasmussen-Torvik[1], SC Stallings[2], AS Gordon[3], B Almoguera[4], MA Basford[2], SJ Bielinski[5], A Brautbar[6], MH Brilliant[6], DS Carrell[7], JJ Connolly[4], DR Crosslin[3], KF Doheny[8], CJ Gallego[9], O Gottesman[10], DS Kim[3], KA Leppig[7], R Li[11], S Lin[12], S Manzi[13], AR Mejia[10], JA Pacheco[14], V Pan[14], J Pathak[15], CL Perry[13], JF Peterson[16], CA Prows[17,23], J Ralston[7], LV Rasmussen[1], MD Ritchie[18], S Sadhasivam[19,20], SA Scott[21], M Smith[14], A Vega[22], AA Vinks[20,23], S Volpi[11], WA Wolf[13,24], E Bottinger[10], RL Chisholm[14], CG Chute[25], JL Haines[26], JB Harley[20,27,28], B Keating[4], IA Holm[13,24,29], IJ Kullo[30], GP Jarvik[9], EB Larson[7], T Manolio[11], CA McCarty[31], DA Nickerson[3], SE Scherer[32], MS Williams[33], DM Roden[34,35] and JC Denny[16,35]

Clin Pharmacol Ther. 2014 Oct;96(4):482-9. doi: 10.1038/clpt.2014.137.

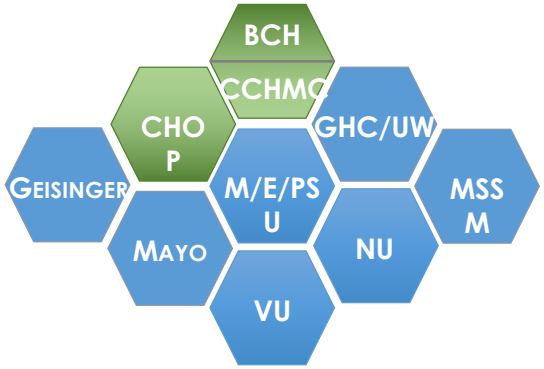
Comparing site implementation details



Drug-Genome pairs study

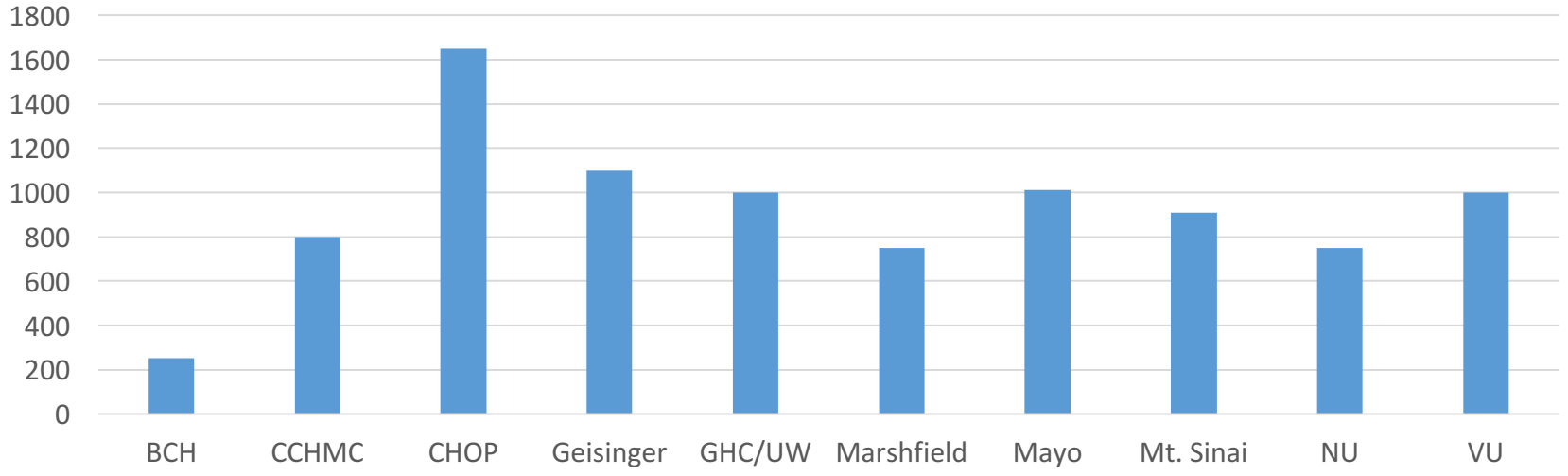
CYP2C19-Clopidogrel
VKORC1/CYP2C9-Warfarin*
SLCO1B1-Simvastatin

* BCH DGI only VKORC1/CYP2C9-Warfarin
* Geisinger and M/E/PSU also have CYP4F2-Warfarin

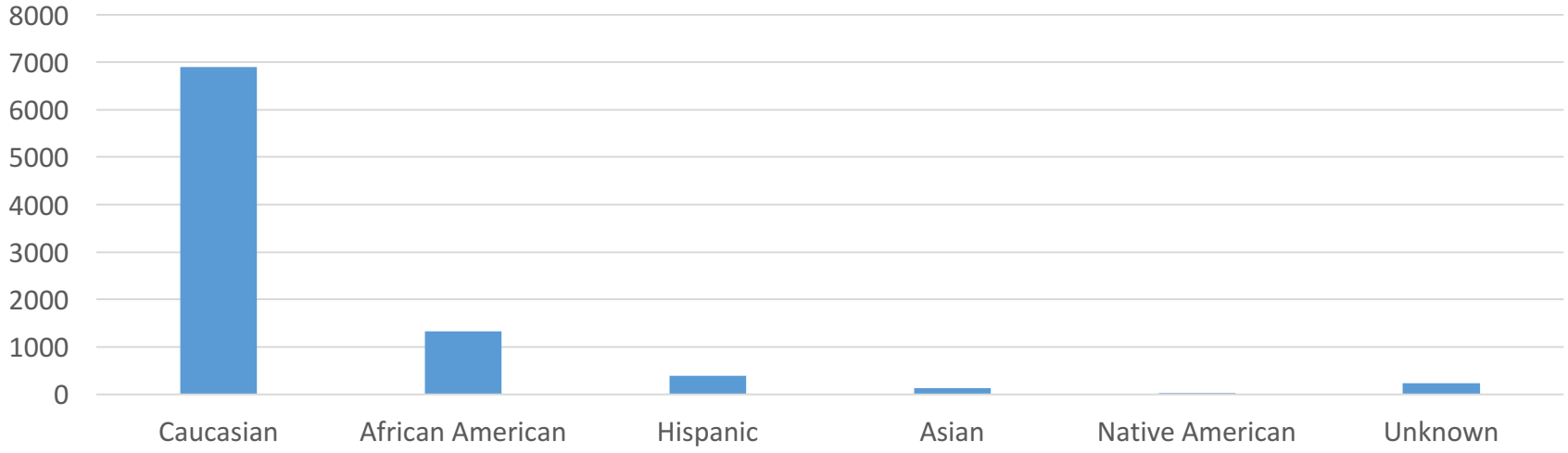


Pediatric Sites

eMERGE-PGx sample size by site



eMERGE-PGx sample size by race / ethnicity



Proposed Outcomes

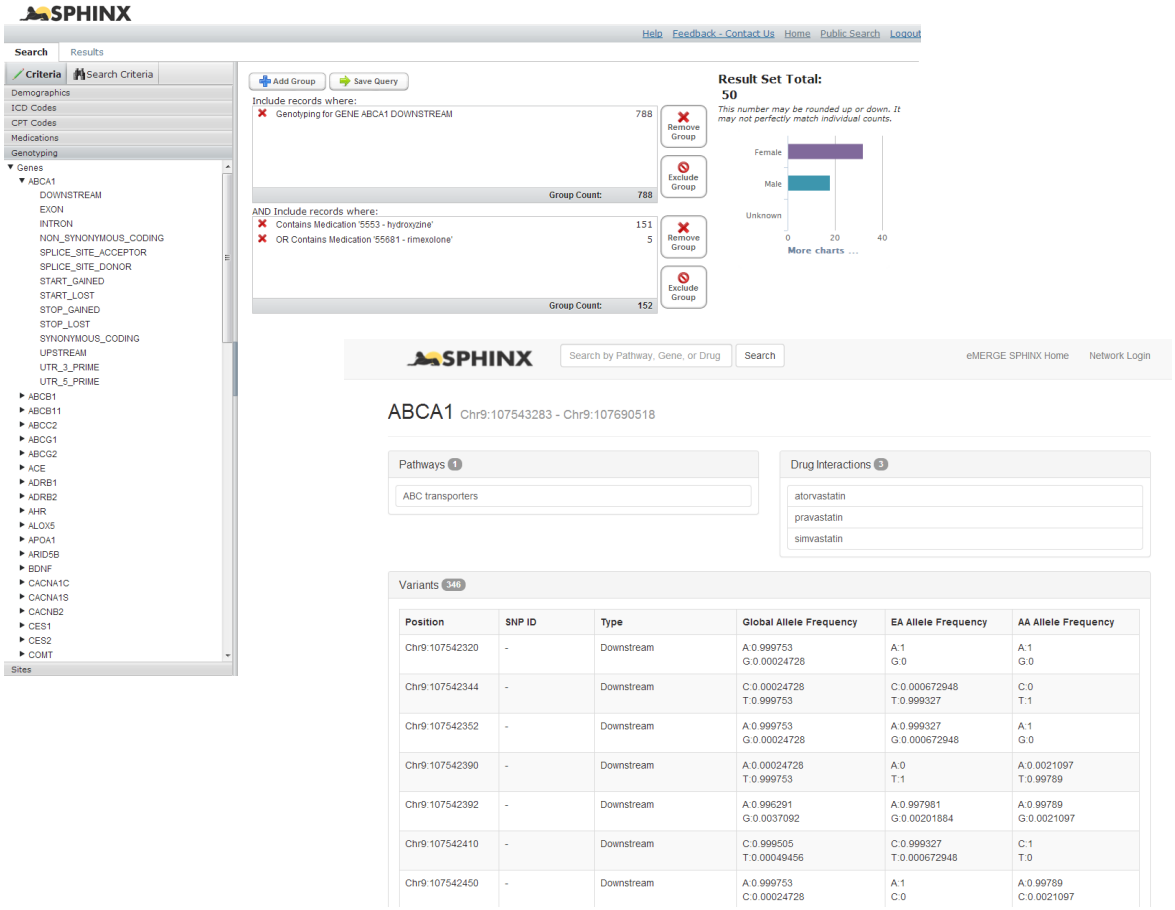
- Sequence 9000+ on pharmacogenes and document variation

  Genetic Variation among 82 Pharmacogenes: the PGRN-Seq data from the eMERGE Network. Bush WS, Crosslin DR, Obeng AO, Wallace J, Almoguera B, et al. Clin Pharmacol Ther. 2016 Jul;100(1):31-3. PubMed PMID: 27037844.

  - In progress: 2nd variation paper, HLA, CYP2D6

- Create a searchable variant repository

SPHINX: *Sequence, Phenotype, and pHarmacogenomics Integration*



SPHINX is a web-based tool for exploring drug response implications of genetic variation across the eMERGE PGx project cohort.

SPHINX will contains data on nearly 9000 subjects from participating electronic medical record (EMR) systems. PGRN-Seq sequencing identifies common variants, some with known clinical implications, and also variants of unknown significance.

SPHINX has a public-facing gene variant repository and a private search tool that provides exploratory data figures from queries of variant summary data plus some phenotype data.

https://www.emergesphinx.org/

SPHINX
A resource of the *e*MERGE Network

emerge network

Proposed Outcomes—Process and Clinical

- eMERGE-PGx sites are collaborating to report descriptive metadata and define quantitative and qualitative outcomes across seven domains: recruitment, sequencing,
  - Genotype validation – in press at JMP
  - Provider education—in press at Pharmacogenomics
  - Patient education– being revised after rejection
  - EHR integration-- Practical considerations in genomic decision support: The eMERGE experience. Herr TM, Bielinski SJ, Bottinger E, Brautbar A, Brilliant M. J Pathol Inform. 2015 Sep 28;6:50. doi: 10.4103/2153-3539.165999. eCollection 2015. PMID: 26605115 PMCID: PMC4629307
  - Actionable rare variation: 1 in press (6 ACMG genes) and Association of Arrhythmia-Related Genetic Variants With Phenotypes Documented in Electronic Medical Records. Van Driest SL, Wells QS, Stallings S, Bush WS, Gordon A, et al. JAMA. 2016 Jan 5;315(1):47-57. doi: 10.1001/jama.2015.17701. PMID: 26746457 PMCID: PMC4758131

What is missing ?

- Cost

- Assessments post-implementation
  - Baseline assumption: outcomes would be largely individual level and assessed through the EHR

  - Planned PGx phenotypes
    - MACE after clopiodogrel
    - Malignant Hyperthermia
    - Methlphenidate Response
    - MACE on statin

eMERGE PGx

was implemented in a highly heterogeneous way. How do we account for this and capitalize on this for future research?

For those that implemented PGx CDS…

1. How did you do it?

2. How well did it work?

Credit: Tim Herr, NU PhD Student, AMIA presentation

How did you do it?

Assessment process:

Informal Interviews

- Representatives from eMERGE-PGx workgroup
- Identified dimensions and facts of interest

Formal Questionnaire

- Multiple-choice questionnaire
- One representative per site, via e-mail
- DGI Details, Alert Characteristics, and Organizational Characteristics

Analysis

- Aggregate and identify trends

Credit: Tim Herr, NU PhD Student, AMIA presentation

How well did it work?

Results:

		Alert Response				Clinical Response		
Drug	Total Alerts	Accept	Override	Ignore	Unknown	Followed	Not Followed	No Action
Codeine	114	102	0	10	2	69	18	27
Clopidogrel	65	14	46	5	0	10	40	15
Simvastatin	24	22	1	1	0	11	13	0
Warfarin	91	45	28	18	0	34	55	2
Total	**294**	**183** *(62%)*	**75** *(26%)*	**34** *(12%)*	**2** *(0.8%)*	**124** *(42%)*	**126** *(43%)*	**44** *(17%)*

Credit: Tim Herr, NU PhD Student, AMIA presentation

Conclusions of CDS analysis

- Despite these areas of agreement, there is significant variation in how PGx CDS alerts are designed throughout the eMERGE Network.
  - Combined, these differences create a significant barrier to analyzing aggregate physician response via alert log data alone.

- Instead, we found that the eMERGE Network has created a series of natural experiments with a variety of alert design and DGI choices.
  - Single-site studies can compare physician response across DGIs on similar technical infrastructure. Multi-site studies could focus on closely targeted analyses of specific DGIs where design choices allow meaningful comparisons.

Credit: Tim Herr, NU PhD Student

Distinguishing clinical research from implementation research

Study feature \ Study type	Clinical research	Implementation research
Aim: evaluate a / an …	clinical intervention	implementation strategy
Typical intervention	drug, procedure, therapy	organizational practice change, training
Typical outcomes	symptoms, health outcomes, patient behavior	adoption, adherence, fidelity, level of implementation
Typical unit of analysis, randomization	Patient, community member	clinic, team, facility, school

Implementation research outcomes

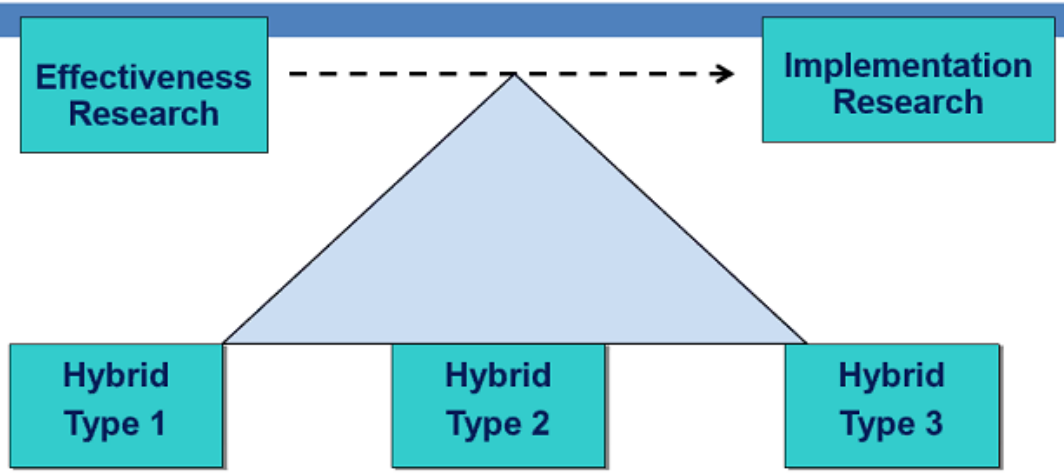
- Adoption
- Adherence
- Fidelity
- Level of implementation
- Sustainability

CONCLUSIONS*:

- Implementation outcomes instrumentation is underdeveloped with respect to both the sheer number of available instruments and the psychometric quality of existing instruments. Until psychometric strength is established, the field will struggle to identify which implementation strategies work best, for which organizations, and under what conditions.

*Lewis CC, Fischer S, Weiner BJ, Stanick C, Kim M, Martinez RG. Outcomes for implementation science: an enhanced systematic review of instruments using evidence-based rating criteria. Implement Sci. 2015 Nov 4;10:155. doi: 10.1186/s13012-015-0342-x.

Types of Hybrids



Hybrid Type 1: test clinical/prevention intervention, observe/gather information on implementation

Hybrid Type 2: test clinical/prevention intervention, test/study implementation strategy

Hybrid Type 3: test implementation strategies, observe/ gather information on clinical/prevention outcomes

From Curran, G. et al. (2012); Medical Care, 50(3), 217-226

Table 1. Sites with PGx Implementation and Education Prior to 2012 eMERGE PGx Initiative

Site	Gene/Drug Pairs	PGx Service Type (# years)	CDS Support	Adopters / Regular Users
Children's Hospital of Philadelphia (CHOP)	Genotyping only CYP2C9 CYP2c19 VKORC1-1639G>A	GC model (1 year)	Results summary letter sent to PCP; PGx specific letter given to patients to share with providers outside EHR	Genetics, Neurology - offered as part of WES
Cincinnati Children's Hospital Medical Center	CYP2D6 / codeine CYP2D6 / SSRIs, tricyclic antidepressants CYP2C19 / SSRIs, tricyclic antidepressants CYP2C9 / warfarin VKORC1 / warfarin TPMT / thiopurines	Prescriber point of care (8 years)	Passive alerts in electronic ordering system; Result reports with therapeutic recommendations including dose adjustment or drug selection alternatives	Psychiatry integrated into standing inpatient orders by 2005; infrequent use by other prescribers
Group Health	Genotype only HLA-B*15:02	Prescriber point of care (8 years)	Popup alert whenever carbamazepine prescribed regardless of HLA status	Neurology, psychiatry and sometimes primary care
Mayo Clinic	CYP2D6 / select SSRIs	Prescriber point of care (8 years)	None	Psychiatry physicians and nurses
Vanderbilt University	CYP2C19 / clopidogrel SLCO1B1 / simvastatin CYP2C9 / warfarin VKORC1 / warfarin TPMT / thiopurines CYP3A5 / tacrolimus	Preemptive and reactive genotyping ordered by provider	Active and passive alerts in electronic ordering; pharmacy support for specific use cases	Physicians and other providers who prescribe

Lessons learned

- Plan to capture outcomes (including institutional-level outcomes) in advance
- Decide: Are we focused on clinical effectiveness? Implementation? Both?
- Validated implementation outcomes are needed
- PGx researchers need to learn how to share implementation challenges

Acknowledgements

- Members of the PGx working group (and other eMERGE working groups)

- Current co-chair: Cindy Prows

- Former co-chairs: Dan Roden, Josh Denny

Questions?

- eMERGE-PGx continues……

PGx Gene	Number of variants that have CPIC guideline (known function and dosing recommendation)	How many variants in column B are on the eMERGE "SNP list"	Total Number of SNPs Associated with Gene on SNP_List	Number of additional variants on CPIC with partial knowledge	Comments
CYP3A5	3	1	1	0	Consider NOT reporting as 2 major variants are not on panel (limitation for African Americans and Latinos) - AA could come across as *1/*1 (*3 is WT) but be *6 or *7
CYP2C9	2	2	2	15 (some known function, no dosing)	Report only for Warfarin (as for phenytoin would need HLAB)
CYP2C19	8	8	8	6 ('decreased' function & weaker dosing +2 with no function but very rare added in 2015)	
TPMT	4	4	4	0	
SLCO1B1	3	1	1	9 ("possible" function & weaker dosing)	The variant present on eMERGE pnl (rs4149056) tags all * alleles (*5, 15, 17). All are associated with decreased function, so same recommendation
IFNL3/IFNL4	1	1	1	0	
VKORC1	1	1	1	0	report with CYP2C9 for warfarin
DPYD	3	3	6	7 (with some known function but no dosing change)	

Suggest to not report CYP3A5

SAMPLE PGx REPORT

Laboratory for Molecular Medicine
Partners Healthcare Personalized Medicine
65 Landsdowne Street, Cambridge, MA 02139
Phone: 617.768.8500 Fax: 617.768.8513
Director:
CLIA#: 22D1005307

Geneticist Approval

Referring Physician: _____

Test performed eMERGE III Sequencing panel

PHARMACOGENOMICS REPORT

Important disclaimers:

This test does not report all pharmacogenomic variants that might alter protein function. Therefore, a normal result does not exclude the possibility that a patient has an increased, intermediate or poor metabolizer phenotype. This risk may vary among ethnic groups. This assay cannot determine if multiple variants are present on the same copy or different copies of the gene, leading to an inability to definitively assign a diplotype and phenotype. This test does not detect copy number variants (CNV). Extrinsic factors (e.g. diet, smoking status, co-administered medications) and intrinsic factors (e.g. gender, age, weight, renal or hepatic function) may affect drug response. In addition, certain ethnic populations may have an increased prevalence of rare genetic variants not reported by this assay that could affect drug response. These factors need to be taken into consideration when interpreting genetic test results. The CPIC Guidelines and PharmGKB website should be consulted for interpretation of all results presented here. These guidelines and frequent updates are found at https://cpicpgx.org/ and https://www.pharmgkb.org/. Please consult a clinical pharmacologist for additional information.

Additional notes are included (column B). For a key please see Appendix B

Results:

INDEX	Diplotype Notes	ACCESSION	LAST NAME (PATIENT ID)	FIRST NAME (STUDY ID)	DATE RECEIVED	DATE REPORTED	TPMT NM_000367.2		CYP2C9 NM_000771.3 VKORC1 NM_024006.5		IFNL3 NM_172139.2		DPYD NM_000110.3		SLCO1B1 NM_006446.4		CYP2C19 NM_000769.1	
							Diplotype	Phenotype	Diplotype	Phenotype	Diplotype	Phenotype	Diplotype	Phenotype	Diplotype	Phenotype	Diplotype	Phenotype
1	1, 6, 8, 9	PM09-00655-A	38432489	16-90081	12/31/16	03/01/17	*1,*1	nl met	CYP2C9*1/*1; VKORC1 Hap A/Hap A	int met	*1,*1	int met	*1,*1	nl met	*1,*1	nl met	*1,*1	nl met

PLANNED SUPPLEMENTAL INFORMATION

TPMT c.238	TPMT c.460	TPMT c.719	TPMT c.626-1	Diplotype
WT (G/G)	WT (G/G)	WT (A/A)	WT (G/G)	TPMT *1/*1
WT (G/G)	WT (G/G)	WT (A/A)	MUT (A/A)	TPMT *4/*4
WT (G/G)	WT (G/G)	WT (A/A)	HET (G/A)	TPMT *1/*4
WT (G/G)	WT (G/G)	MUT (G/G)	WT (G/G)	TPMT *3C/*3C
WT (G/G)	WT (G/G)	HET (A/G)	WT (G/G)	TPMT *1/*3C
WT (G/G)	MUT (A/A)	WT (A/A)	WT (G/G)	TPMT *3B/*3B
WT (G/G)	MUT (A/A)	MUT (G/G)	WT (G/G)	TPMT *3A/*3A
WT (G/G)	HET (G/A)	WT (A/A)	WT (G/G)	TPMT *1/*3B
WT (G/G)	HET (G/A)	HET (A/G)	WT (G/G)	TPMT *1/*3A
WT (G/G)	HET (G/A)	HET (A/G)	HET (G/A)	TPMT *3A/*4
HET (G/C)	WT (G/G)	WT (A/A)	WT (G/G)	TPMT *1/*2
HET (G/C)	WT (G/G)	WT (A/A)	HET (G/A)	TPMT *2/*4
HET (G/C)	WT (G/G)	HET (A/G)	WT (G/G)	TPMT *2/*3C
HET (G/C)	HET (G/A)	WT (A/A)	WT (G/G)	TPMT *2/*3B
HET (G/C)	HET (G/A)	HET (A/G)	WT (G/G)	TPMT *2/*3A
MUT (C/C)	WT (G/G)	WT (A/A)	WT (G/G)	TPMT *2/*2

Diplotype Test Result for *TPMT*	Coded Genotype/Phenotype Summary[b]	EHR Priority Result Notation[c]	Drug	LMM Interpretation and Background	CPIC Consultation (Interpretation) Text Provided with Test Result[d]
*1/*1	TPMT Extensive metabolizer	Normal/Routine/Low Risk	Azathioprine (immunosuppressant)	TPMT, *1/*1, Extensive metabolizer. Thiopurines: Standard dosage. Thiopurine methyltransferase (TPMT) metabolizes thiopurine prodrugs (azathioprine, 6-mercaptopurine, and thioguanine) into their active thioguanine nucleotide (TGN) metabolites. TPMT alleles *3A, *3B, and *3C, lead to reduced protein expression and/or function and carriers may be at risk of life-threatening myelosuppression when treated with standard doses of thiopurines. Adapted from Relling 2011.	Lower concentrations of TGN (thioguanine nucleotide) metabolites, higher methylTIMP (secondary metabolite of mercaptopurine), this is the "normal" pattern. Start with normal starting dose (e.g., 2–3 mg/kg/d) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment
			Mercaptopurine (immunosuppressant)		Lower concentrations of TGN (thioguanine nucleotide) metabolites, higher methylTIMP (secondary metabolite of mercaptopurine), this is the "normal" pattern. Start with normal starting dose (e.g., 75 mg/m^2/d or 1.5 mg/kg/d) and adjust doses of mercaptopurine (and of any other myelosuppressive therapy) without any special emphasis on mercaptopurine compared to other agents. Allow 2 weeks to reach steady state after each dose adjustment
			Thioguanine (immunosuppressant)		Lower concentrations of TGN (thioguanine nucleotide) metabolites, but note that TGN after thioguanine are 5-10x higher than TGN after mercaptopurine or azathioprine. Start with normal starting dose. Adjust doses of thioguanine and of other myelosuppressive therapy without any special emphasis on TG. Allow 2 weeks to reach steady state after each dose adjustment

Phenotype	EHR Priority Result Notation	Drugs with CPIC Guidelines	Dosage Summary*	References - see Appendix D	Gene Background
TPMT					
TPMT Normal metabolizer	Normal/Routine/Low Risk	Azathioprine, Mercaptopurine, Thioguanine (thiopurines, immunosuppressant)	Standard dosage	Relling_2011, Relling_2013	Thiopurine methyltransferase (TPMT) metabolizes thiopurine prodrugs (azathioprine, 6-mercaptopurine, and thioguanine) into their active thioguanine nucleotide (TGN) metabolites. "Individuals who inherit two nonfunctional TPMT alleles are at 100% risk for life-threatening myelosuppression, due to high TGNs, if they receive chronic therapy with conventional doses of MP (or azathioprine). Despite having higher TGNs than wild-type homozygotes, only ~30–60% of patients who are heterozygous for TPMT are unable to tolerate full doses of MP or azathioprine" (Relling_2011).
TPMT Intermediate metabolizer	Abnormal/Priority/High Risk		Decrease dosage		
TPMT Poor metabolizer	Abnormal/Priority/High Risk		Greatly decrease dosage		
CYP2C9 & VKORC1 - these are interpreted together for warfarin dosing.					
CYP2C9 Normal metabolizer & Normal VKORC1 expression	All should consult sources listed at right (col D).	Warfarin (anticoagulant)	Use the algorithms available on http://www.warfarindosing.org and Figures 2 & 3 of Johnson_2017	Johnson_2011, Johnson_2017	Common genetic variants in the cytochrome P450-2C9 (CYP2C9) and vitamin K-epoxide reductase complex 1 (VKORC1) enzymes have an effect on warfarin metabolism. Carriers of the CYP2C9*2, CYP2C9*3, and VKORC1 -1639A alleles are at increased risk of bleeding and may require lower doses of warfarin. (Johnson_2011) The algorithms available on http://www.warfarindosing.org should be used to determine warfarin dosing. The 2016 guideline update (Johnson_2017) includes additional alleles in CYP2C9, CYP4F2, and the CYP2C cluster that are NOT included in this test panel. The update also has important ancestry-specific dosing recommendations, and must be carefully reviewed.
CYP2C9 Normal metabolizer & Intermediate VKORC1 expression					
CYP2C9 Normal metabolizer & Low VKORC1 expression					
CYP2C9 Intermediate metabolizer & Normal VKORC1 expression					
CYP2C9 Intermediate metabolizer & Intermediate VKORC1 expression					
CYP2C9 Intermediate metabolizer & Low VKORC1 expression					
CYP2C9 Poor metabolizer & Normal VKORC1 expression					
CYP2C9 Poor metabolizer & Intermediate VKORC1 expression					
CYP2C9 Poor metabolizer & Low VKORC1 expression					
CYP2C9 Normal metabolizer	Normal/Routine/ Low Risk	Phenytoin/fosphenytoin (anticonvulsant)	Standard dosage	Caudle_2014	The CPIC guidelines for phenytoin include the genes CYP2C9 and HLA-B. (This test does not include HLA-B; the HLA-B*15:02 allele has been associated with an increased risk of SJS/TEN.) However, Supplemental Table 13b of Caudle_2014 provides some recommendations based on CYP2C9 diplotype in the absence of HLA-B testing.
CYP2C9 Intermediate metabolizer	Abnormal/Priority/ High Risk		Decrease dosage		
CYP2C9 Poor metabolizer	Abnormal/Priority/ High Risk				

Themes in implementation science

- Understanding the “voltage” gap
- Successful approaches to program dissemination
- Tension between local context and fidelity