EMR and Genomics at Mayo Clinic From Discovery to Practice

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Genomics and health information technology systems: Exploring the issues

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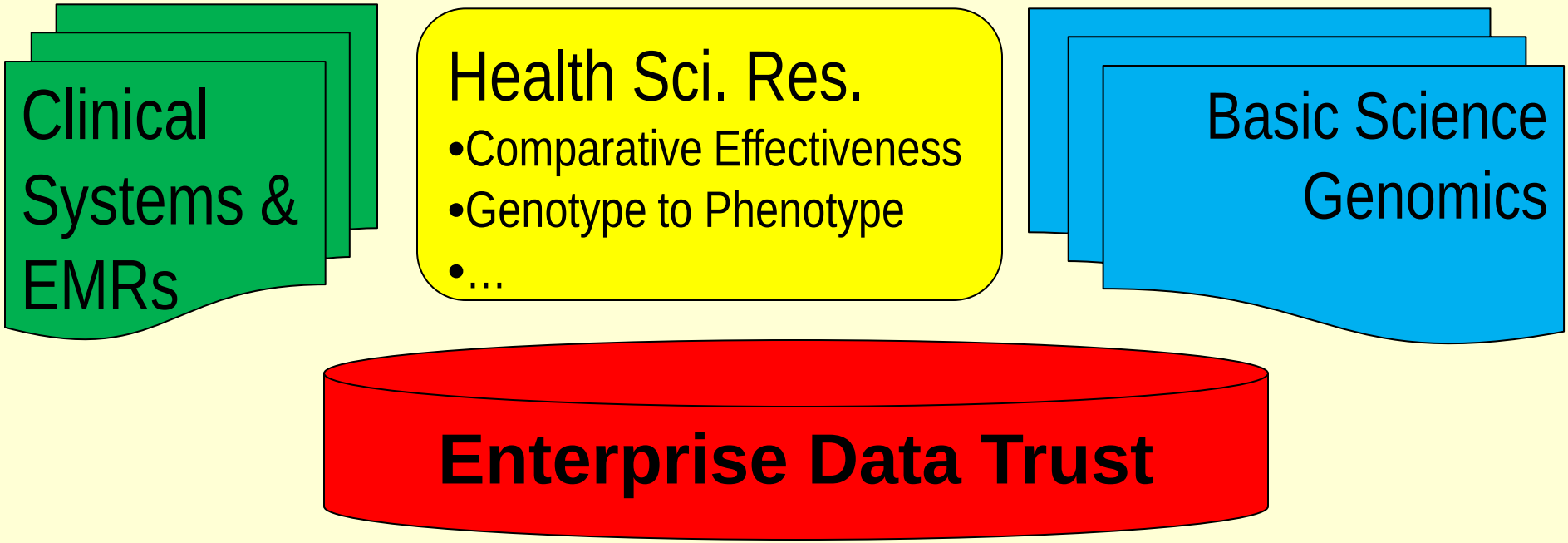
Outline

- Discovery and validation of genomic associations in clinical settings
- Translation of findings into practice
- Foreshadowing of routine clinical use

Enterprise Data Trust
Standards-based Clinical Data Repository



Enterprise Data Governance Program

1. Enterprise Data *Modeling* Activity
2. Enterprise *Metadata* Activity
3. Enterprise *Vocabulary* Environment)

Standards

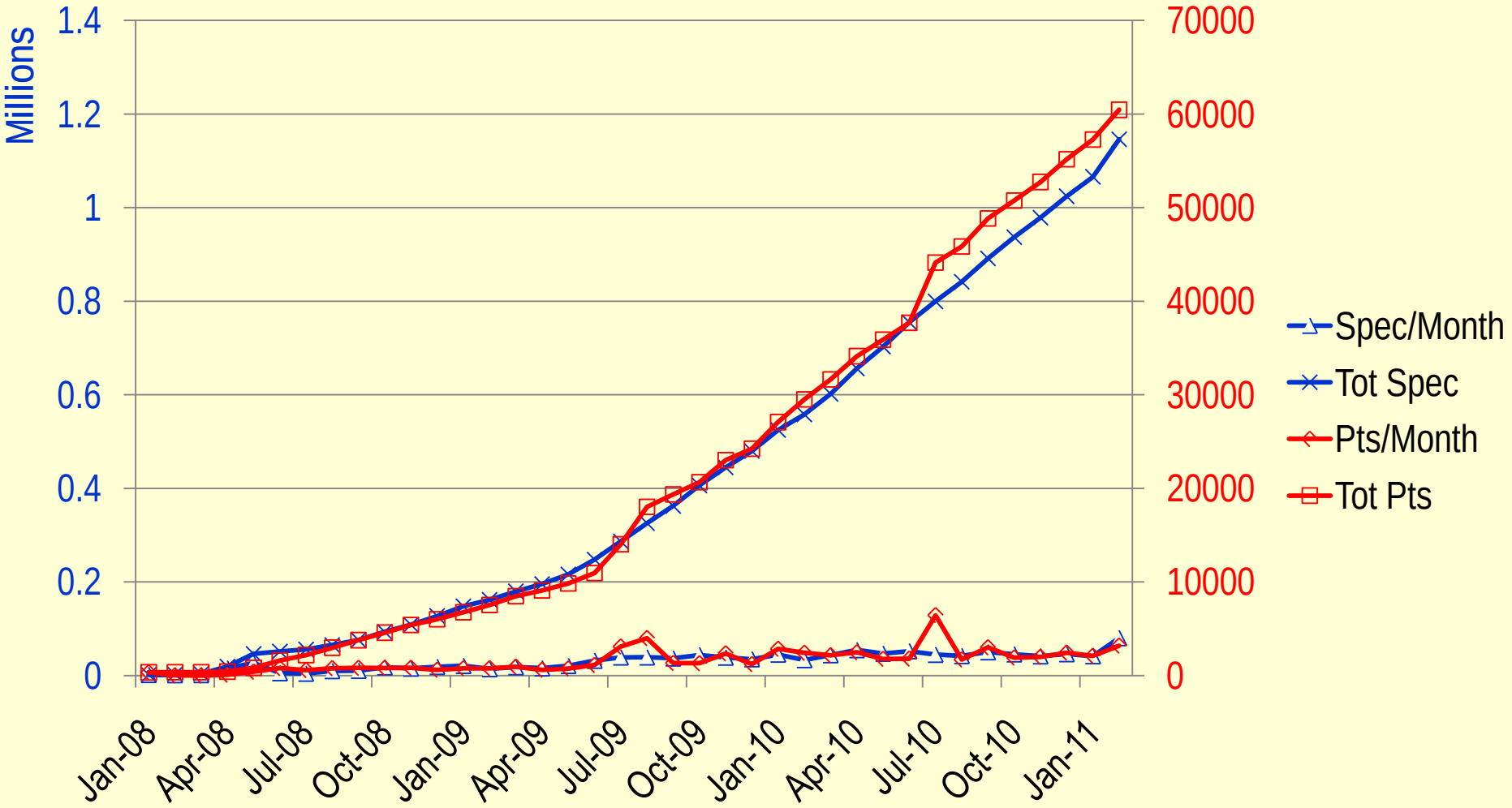
eMERGE@Mayo
electronic MEdical Records and GEnomics

- NHGRI funded GWAS and EMR study
- Emphasis on high-throughput phenotyping
  - Disease and control cohort definitions
  - EMR data sources
  - Portable algorithms (14)
  - Demonstrated Positive Predicative Value across five-member eMERGE consortium

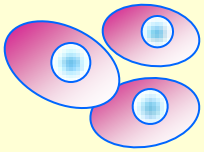
SHARP: Area 4: Secondary Use of EHR Data
A $15M National Consortium

Themes			Projects	Players
Data Normalization	Phenotype Recognition	Data Quality and Evaluation Frameworks	Clinical Data Normalization	IBM, Mayo, Utah, Agilex
			Natural Language Processing (NLP)	Harvard, Group Health, IBM, Utah ,Mayo, MIT, SUNY, i2b2, Pittsburgh, Colorado
			High-Throughput Phenotyping	CDISC, Centerphase, Mayo, Utah
			UIMA and Scaling Capacity	IBM, Mayo
			Data Quality	Mayo, Utah
			Evaluation Framework	Agilex, MN HIE, Mayo, Utah

Biospecimens and Unique Patients
RLIMS (Research Lab Inform Mngmt Sys)



BORA: Biologically Oriented Repository Arch. Integration of Genomics and Clinical Phenotype



RLIMS - Core Labs

BioBank

multiple clinical data source & NLP

Data Manager

genomics raw data

BORA

genomics data integration

EDT

DDQB - ANALYTICS

Mayo Genome Consortia (MayoGC)

- A shared infrastructure for genotyped cohorts
  - "Pointers" to Biobank and patient identifiers
  - Well-defined eligibility criteria (consenting, QC, etc.)
- Drawn from research studies across Mayo Clinic
  - Enables study of novel EMR phenotypes
- Projects to date:
  - eMERGE Hypothyroidism Replication
  - GWAS liver enzymes, colon polyps, prostate volume, and Barrett's esophagus

Mayo Genome Consortia (MayoGC): A Genotype-Phenotype Resource for Genome Wide Association Studies with an Application to the Analysis of Circulating Bilirubin: Bielinski, Chai, Pathak, Talwalkar, Limburg, Gullerud, Sicotte, Klee, Ross, Kocher, Kullo, Heit, Petersen, de Andrade, Chute (Accepted for publication at Mayo Clinic Proceedings)

Study Name (NIH Grant Number)	Principal Investigator	Sample Size	Genotyping Plateform
Phase I (Completed)			
Electronic Medical Record Phenotypes and Community Engaged Genomic Associations (eMERGE) (NHGRI- UO1 HG004599-01)	Dr. Christopher Chute Dr. Iftikhar Kullo	3197 (Cases and controls)	Illumina Human 660W Quad-V1
Mayo Clinic Genome-wide Association Study of Venous Thromboembolism (NHGRI HG04735)	Dr. John Heit	2497 (Cases and controls)	Illumina Human 660W Quad-V1
Mayo Cl			
Molecula			0
Haplotyp R0			
A1ATD			
BT SPOR CA			
A genom mu			
Triple N			
Collabor Breast Cancer		(Controls only)	(iCOGs 204K SNPs)
Collaborative Oncological Gene-Environment Study (COGS) – Prostate Cancer	Dr. Stephen Thibodeau	500 (Controls only)	Illumina custom iSelect (iCOGs 204K SNPs)
Collaborative Oncological Gene-Environment Study (COGS) - Ovarian Cancer	Dr. Ellen Goode	500 (Controls only)	Illumina custom iSelect (iCOGs 204K SNPs)
Genomics of Primary Biliary Cirrhosis DK 80670	Dr. Konstantinos Lazaridis	1300 (Cases and Contols)	Illumina Immunochip (~200K SNPs)
PROGRESS (PSC Resource Of Genetic Risk, Environment and Synergy Studies) DK 84960	Dr. Konstantinos Lazaridis	1200 (Cases Only)	To be decided

MayoGC

n = 11,922 GWA data

n = 2,800 iSelect data

Total Sample Size = 14,722

Pharmacogenomics Research Network Stimulus for Translation at Mayo

- Builds on work of Weinshilboum - TPMT
- Two clinical translational projects
- GWA study of the efficacy of *aromatase inhibitors*
  - NCIC-NCI MA.27 breast cancer adjuvant clinical trial
- GWA study of *SSRI* therapy of depression
  - SNRI therapy of patients who fail to respond

CYP2D6 SNPs
Psychiatry SNP Screening CHIP

CYP2D6		5'UTR	Exon 1	Exon 2		Exon 3			Intron 3	Exon 4	Exon 5		Exon 6				Exon 9
Allele	Enzyme Activity	-1584	100	883	1023	1661	1707	1758	1846	1973	2539	2549	2613	2850	2935	2988	4180
*1	Normal	C	C	G	C	G	T	G	G	G	A	A	A	C	A	G	G
*2A	Increased	G	C	G	C	C	T	G	G	G	A	A	A	T	A	G	C
*2B	Decreased	G	C	G	C	C	T	G	G	G	A	A	A	T	A	G	C
*2D	Decreased	G	C	G	C	C	T	G	G	G	A	A	A	T	A	G	C
*3	None	C	C	G	C	G	T	G	G	G	A	DELETION of A in Exon 5 at 2549 Frame Shift to Left					
*4	None	C	T	G	C	C	T	G	A	G	A	A	A	C	A	G	C
*6	None	C	C	G	C	G	DELETION of T in Exon 3 at 1707 Frame Shift Left										
*7	None	C	C	G	C	G	T	G	G	G	A	A	A	C	C	G	G
*8	None	C	C	G	C	C	T	T	G	G	A	A	A	T	A	G	C
*9	Decreased	C	C	G	C	G	T	G	G	G	A	A	Del AAG	C	A	G	G
*10	Decreased	C	T	G	C	C	T	G	G	G	A	A	A	C	A	G	C
*11	None	C	C	C	C	C	T	G	G	G	A	A	A	T	A	G	C
*12	None	C	C	G	C	C	T	G	G	G	A	A	A	T	A	G	C
*15	None	C	C	INSERTION of T in Exon 1 at 138 Frame Shift to Right													
*17	Decreased	C	C	G	T	C	T	G	G	G	A	A	A	T	A	G	C
*41	Decreased	G	C	G	C	C	T	G	G	G	A	A	A	T	A	A	C

Routine Psychiatry Practice - Screen Result

Patient Genotype

Gene	Genotype	Predicted Phenotype
CYP2D6	*4/*41	Poor Metabolizer
CYP2C19	*1/*2	Intermediate Metabolizer
CYP1A2	See Table Below	Extensive Metabolizer
SLC6A4	L/L	High Activity
HTR2A	T/C	Intermediate Activity

CYP1A2 Genotype

-3860G>A - G/G	-2467T>delT - T/T	-739T>G - T/T	-729C>T - C/C	-163C>A - C/A
125C>G - C/C	558C>A - C/C	2385G>A - G/G	2473G>A - G/G	2499A>T - A/A
3497G>A - G/G	3533G>A - G/G	50590C>T - C/C	5166G>A - G/G	5347C>T - T/C

Patient M

Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH CAUTION AND WITH MORE FREQUENT MONITORING
desvenlafaxine (Pristiq®)	citalopram (Celexa®)	amitriptyline (Elavil®)
fluvoxamine (Luvox®)	duloxetine (Cymbalta®)	bupropion (Wellbutrin®)
selegiline (Emsam®)	escitalopram (Lexapro®)	clomipramine (Anafranil®)
sertraline (Zoloft®)	mirtazapine (Remeron®)	desipramine (Norpramin®)
	trazodone (Desyrel®)	fluoxetine (Prozac®)
		imipramine (Tofranil®)
		nortriptyline (Pamelor®)
		paroxetine (Paxil®)
		venlafaxine (Effexor®)

Antipsychotics

USE AS DIRECTED	USE WITH CAUTION	USE WITH CAUTION AND WITH MORE FREQUENT MONITORING
quetiapine (Seroquel®)	clozapine (Clozaril®)	aripiprazole (Abilify®)
ziprasidone (Geodon®)	olanzapine (Zyprexa®)	haloperidol (Haldol®)
	risperidone (Risperdal®)	perphenazine (Trilafon®)

Catalog of CLIA SNP Clinical Tests

1. APOB for familial hypercholesterolemia
2. BTK for X-linked agammaglobulinemia caused by mutations of the Bruton's tyrosine kinase gene
3. CXCR4 genotyping- determines whether a CCR5 antagonist may be an appropriate drug for a patient with HIV
4. CYP1A2-drug metabolism for drugs metabolized by this CYP enzyme (i.e. olanzapine)
5. CYP2C19-partial gene sequence based analysis for drugs metabolized by this CYP enzyme (several anti-seizure drugs, clopidogrel)
6. CYP2C9 – VKORC1 for warfarin response and resistance
7. CYP2D6-Luminex for drugs metabolized by this CYP enzyme
8. ENG and ACVRL1 sequencing-associated with hereditary hemorrhagic telangiectasia
9. FBN1 sequencing-Marfan Syndrome
10. HLA-B1502 for Identifying individuals of Asian ancestry who are at risk of developing Stevens-Johnson syndrome and toxic epidermal necrolysis when administered carbamazepine, phenytoin, or fosphenytoin therapy
11. HLA-B5701 for predicting likelihood of hypersensitivity reactions to abacavir in HIV-infected patients, based on the presence of the human leukocyte antigen (HLA)-B*5701 allele
12. LDLR for familial hypercholesterolemia.
13. PTP22 point mutation (1858C>T)-risk of erosive rheumatoid arthritis
14. TACI for common variable immunodeficiency.
15. TGFBR for diagnosis of Marfan syndrome.
16. TREC for determining immune reconstitution after BMT.
17. UGT1A1 for irinotecan sensitivity and diagnosis of Gilbert Syndrome and Crigler Najjar.

Summary

- Mayo has extensive discovery and evaluation efforts for genomic testing and practice
- Numerous experimental programs are being introduced into practice – e.g. warfarin
- Psychiatry has fully implemented genomic testing into standard workflow
- Pharmacogenomics is by far the major mode of genomic implementation at present