Implementation of Pharmacogenetics at Cincinnati Children's Hospital Medical Center

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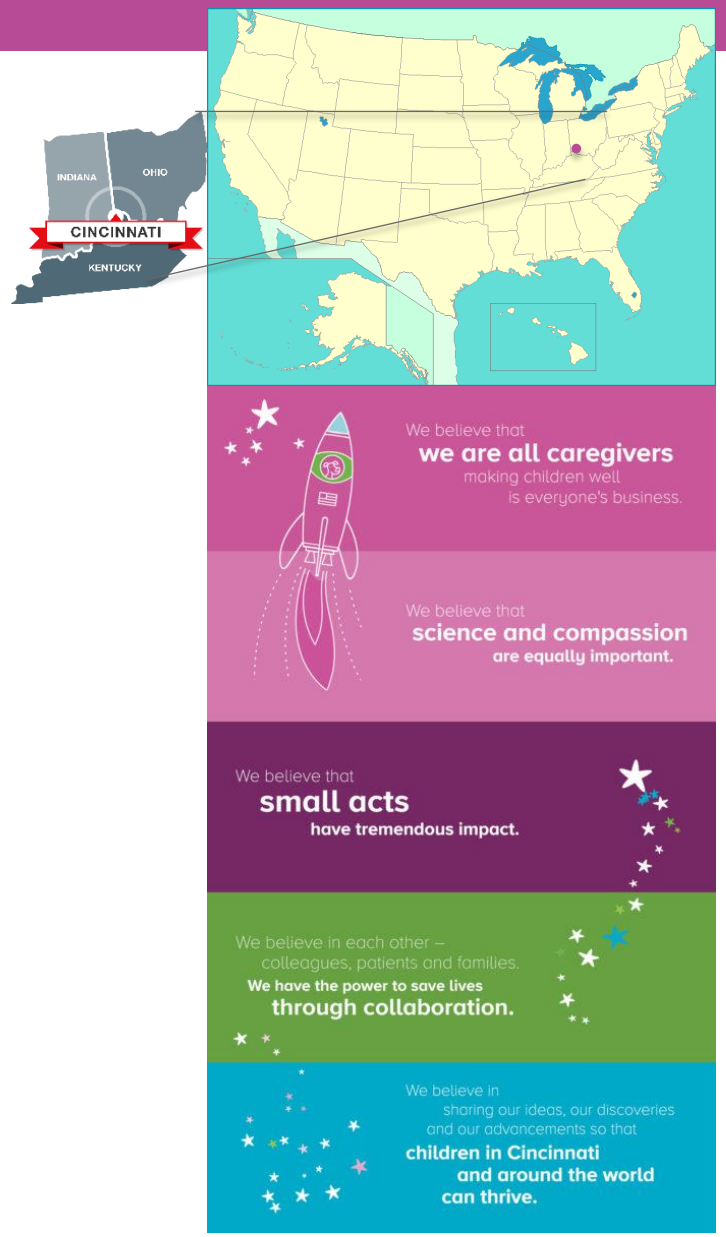
Cincinnati Children's Hospital Medical Center

- Only children's hospital in the Cincinnati metropolitan area (population 2.1 million)
- 628-bed non-profit organization
- Operations totaling $2.1 billion annually, ~15,000 employees, 6 million square feet of facilities and eleven off-site neighborhood facilities
- In 2014, CCHMC had almost 1.2 million patient encounters, including 99,839 Emergency Department visits, 31,851 surgical procedures and 30,848 admissions
- Focused on providing care for the population in our tristate, patients have come from 68 countries and all 50 states



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Case report

- 5 year old adopted child diagnosed with encephalopathy secondary to fetal alcohol syndrome, ADHD, Tourette's
- Treated with clonidine for tics, added fluoxetine at age 6 for OCD
- 5 mg/day fluoxetine increased to 30 mg/day, produced vomiting and diarrhea, 4 day hospitalization for dehydration
- Fluoxetine dose increased to 40 mg/day, more vomiting and another hospitalization
- Methylphenidate 60 mg/day added at age 8 for ADHD
- Fluoxetine dose increased to 80 mg/day, patient had seizure, dose was increased to 100 mg/day, more vomiting, dizziness
- Fatal seizure followed
- Autopsy revealed blood concentration of 21 ug/mL fluoxetine (5-6 ug/mL is fatal), medical examiner recommended death be listed as homicide
- Legal investigation of parents, consultation with clinical pharmacologist
- DNA analysis revealed the patient was a CYP2D6 poor metabolizer

J Child Adolesc Psychopharmacol. 2000 Spring;10(1):27-34.

How do we implement PGx?

- Idea in 2001 to reduce medication-related adverse events with genetic testing
- Genetic Pharmacology Service began in 2004 with Drs. Wenstrup, Glauser, Vinks, Zhang, & APRN Cindy Prows
- Single gene-drug pairs were replaced by panels of drugs that could be prescribed and the genes that influence their metabolism
- Psychiatry Panel launched in 2005 and was updated in 2013

How do we implement PGx?

- Psychiatry Panel, Opioid Panel, single genes
- Genetic testing orderable for *CYP2D6, CYP2C9, CYP2C19, TPMT, VKORC1*
- Performed in Molecular Genetics Lab
- Reported to Results Report tab
- Report (pdf) contains genotype, phenotype & dosing recommendations as percentage of normal dose
- When a provider enters an order for a medication with CDS, they see alert

Sign in to MyChart Directions Language International Enter Search Term

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Genetic Pharmacology Service

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GPSConsult@cchmc.org

Personalized Medicine Through Pharmacogenetics

Scientific evidence indicates that pharmacogenetics – the study of drug interactions with an individual's genetic makeup – may improve patient safety.

GPS Genetic Pharmacology Service

Pharmacogenetic testing for some medications adds genetic information to the usual considerations of patient age, weight, disease process, use of other medications, health behaviors and environment.

The additional information gained from pharmacogenetics can help physicians and nurse practitioners choose and dose medication that best meets the needs of the individual patient.

Benefits of Pharmacogenetics

Pharmacogenetics uses molecular testing to analyze certain genes. A pharmacogenetic test can predict how a patient will metabolize a drug, allowing the clinician to adjust dosages for individual patients to get maximum efficacy from a drug with minimum side effects.

Tests Offered

We offer genetic pharmacogenetic tests for drugs metabolized by major **cytochrome (CYP)** P450 drug metabolizing enzymes (CYP2D6, CYP2C9, CYP2C19) and TPMT.

Tests offered

Test Requisition Form

Download the test requisition form for the Genetic Pharmacology Service in the Molecular Genetics Laboratory at Cincinnati Children's.

Molecular Genetics Lab

The GPS works with the Molecular Genetics Lab to provide state-of-the-art testing with comprehensive interpretation of test results by experts.

Read More

www.cincinnatichildrens.org/gps

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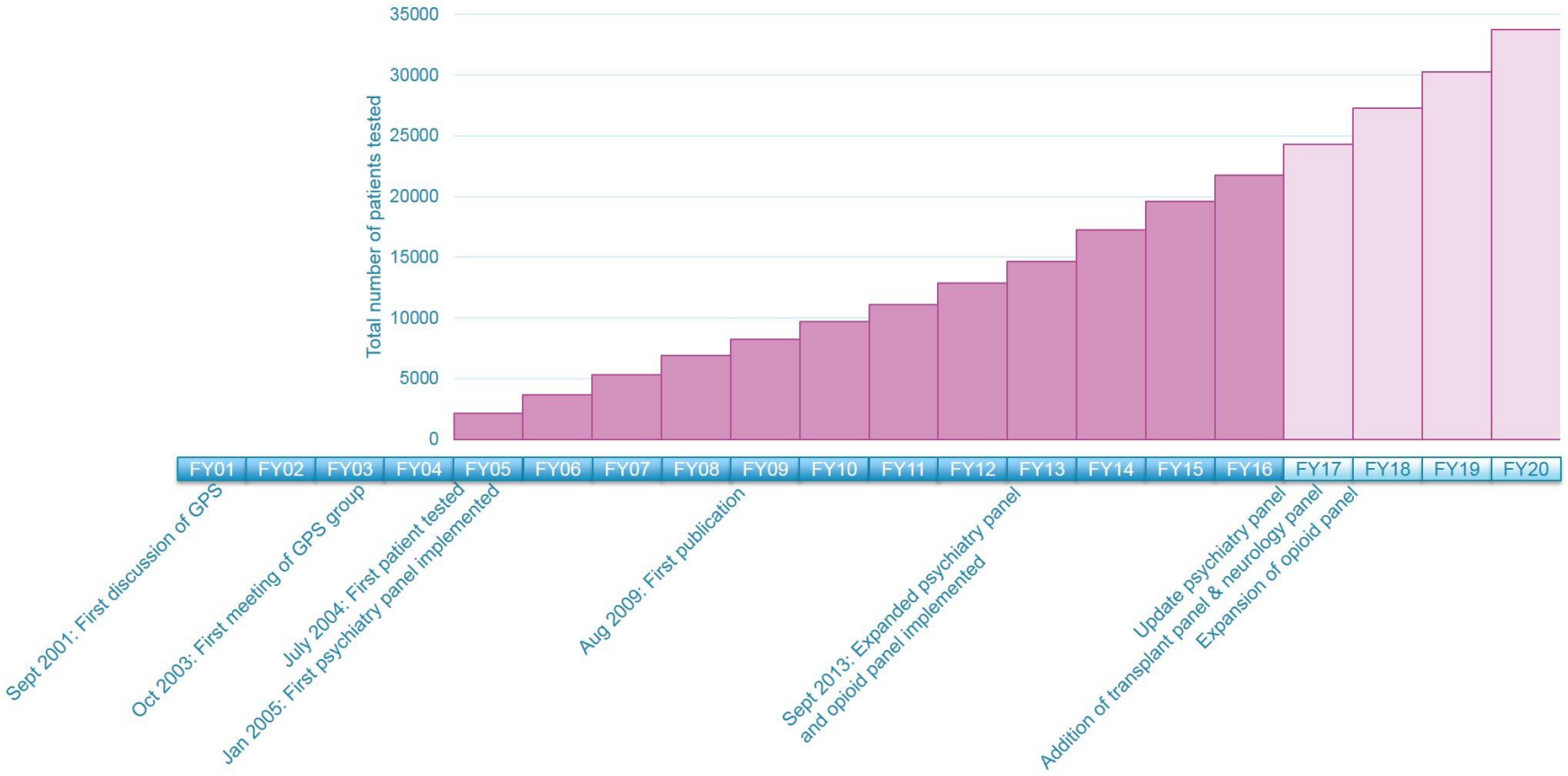
GPS tests offered

- Buccal swabs or blood samples can be tested
- TaqMan® Low Density Array or TaqMan® individual probes used for all tests and long PCR is used for full gene deletion and duplication of *CYP2D6*
- Expanded Psychiatry Panel: *CYP2D6* & *CYP2C19* genotypes, metabolizer status and dosing recommendations for 19 drugs
- Opioid panel: *CYP2D6* genotype, metabolizer status and dosing recommendations for 4 drugs
- Thiopurines (6-MP, 6-TG, Azathioprine) and *TPMT*
- Warfarin and *CYP2C9* & *VKORC1*
- 2 day turn around time

Alleles tested

- 21 *CYP2D6* alleles*:* *2A, *3, *4, *5, *6, *7, *8, *9, *10, *11, *14, *15, *17, *18, *19, *20, *40, *41, *42, *44 and duplication
- 8 *CYP2C19* alleles: *2, *3, *4, *5, *6, *7, *8, *17
- 93-98% of *CYP2D6* and *CYP2C19* genotypes that are associated with null, deficient, or ultra-rapid enzyme activity
- *TPMT* alleles: *2, *3A, *3C (G238C, G460A and A719G)
- *CYP2C9* alleles:*2 and *3
- *VKORC1* alleles:-1639G/A, rs9923231
- *1 genotypes are inferred from the absence of the above alleles

>20,000 GPS tests performed



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Division of Child and Adolescent Psychiatry

- The DCAP at CCHMC provides a continuum of services including outpatient clinics, partial hospitalization, acute inpatient and residential care
- All programs support family-centered care, in which treatment plans focus on the needs of both the patient and families
- 92 inpatient beds across two campuses as well as outpatient clinics at 3 CCHMC satellites
- In fiscal year 2014, the DCAP had 32,670 outpatient encounters and 23,065 inpatient encounters
- These patients come not only from the Cincinnati area, but also Northern Kentucky, Southeastern Indiana and the Dayton area
- Division Director, Michael Sorter, supports use of Psychiatry Panel and has incorporated it into routine care for inpatients

Result Report: Psychiatry Panel

Gene Analyzed: CYP2C19

Genotype - Allele 1: *2
Allele 2: *2

Predicted Phenotype – Poor Metabolizer

Gene Analyzed: CYP2D6

Genotype - Allele 1: *4
Allele 2: *10
Duplication: No

Predicted Phenotype – Intermediate Metabolizer

25%-50%	50%-75%	50%-100%	75%-100%
Doxepin (Silenor®)	**amitriptyline** (Elavil®)	**desipramine** (Norpramin®)	**aripiprazole** (Abilify®)
	clomipramine (Anafranil®)	**nortriptyline** (Pamelor®)	**fluoxetine** (Prozac®)
	imipramine (Tofranil®)	**perphenazine** (Trilafon®)	**fluvoxamine** (Luvox®)
	trimipramine (Surmontil®)	**venlafaxine** (Effexor®)	**haloperidol** (Haldol®)
			maprotiline (Diprilept®)
			olanzapine (Zyprexa®)
			paroxetine (Paxil®)
			risperidone (Risperdal®)
			thioridazine (Mellaril®)
DECREASE under standard dose. **SLOWER** titration may be indicated.	**DECREASE** under standard dose. **SLOWER** titration may be indicated.	***Slight*** **DECREASE** under standard dose. Standard titration indicated.	***Slight*** **DECREASE** under standard dose. Standard titration indicated.

2D6 IM & 2C19 PM

MONOTHERAPY DOSING RECOMMENDATIONS BASED ON FDA-APPROVED PRESCRIBING INFORMATION

atomoxetine (Strattera®) (refs) <70 kg= start: 0.5 mg/kg/day, target: 1.2 mg/kg/day
>70 kg= start: 40 mg/day, target: 80 mg/day

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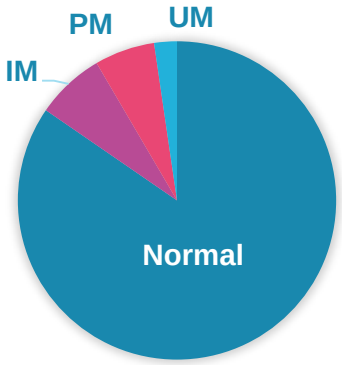
Population frequencies

Translated according to CPIC guidelines

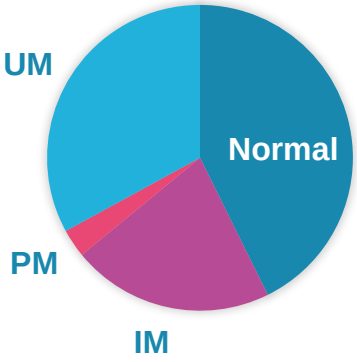
CYP2D6`	N	%
Normal	4255	84.6%
Intermediate	351	7.0%
Poor	308	6.1%
Ultra-rapid	116	2.3%

CYP2D6



CYP2C19`	N	%
Normal	2147	42.7%
Intermediate	1075	21.4%
Poor	151	3.0%
Ultra-rapid	1657	32.9%

CYP2C19



CYP2D6 metabolizer	CYP2C19 metabolizer	%	N
CYP2D6 NM	CYP2C19 NM	35.8%	1803
CYP2D6 NM	CYP2C19 IM	18.4%	925
CYP2D6 NM	CYP2C19 PM	2.4%	121
CYP2D6 NM	CYP2C19 UM	28.0%	1406
CYP2D6 IM	CYP2C19 NM	3.0%	151
CYP2D6 IM	CYP2C19 IM	1.5%	75
CYP2D6 IM	CYP2C19 PM	0.4%	19
CYP2D6 IM	CYP2C19 UM	2.1%	106
CYP2D6 PM	CYP2C19 NM	2.8%	140
CYP2D6 PM	CYP2C19 IM	1.1%	55
CYP2D6 PM	CYP2C19 PM	0.2%	8
CYP2D6 PM	CYP2C19 UM	2.1%	105
CYP2D6 UM	CYP2C19 NM	1.1%	53
CYP2D6 UM	CYP2C19 IM	0.4%	20
CYP2D6 UM	CYP2C19 PM	0.1%	3
CYP2D6 UM	CYP2C19 UM	0.8%	40
		100.0%	5030

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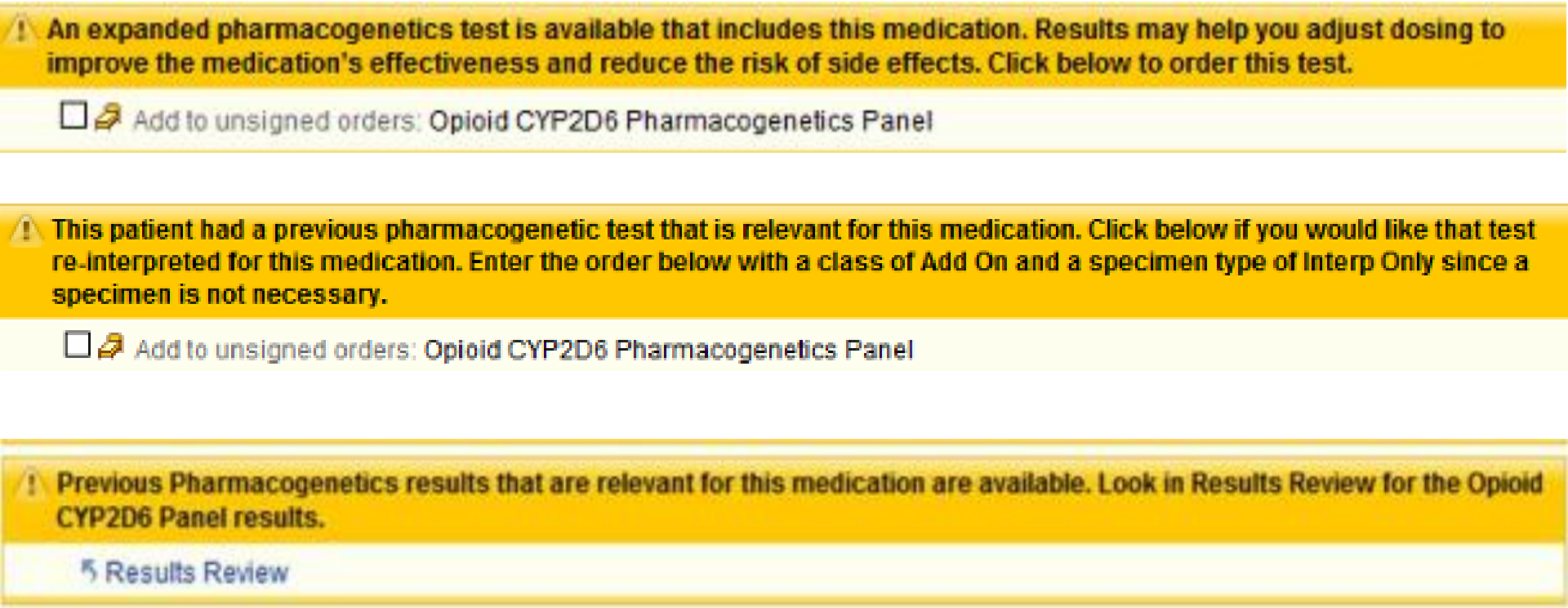
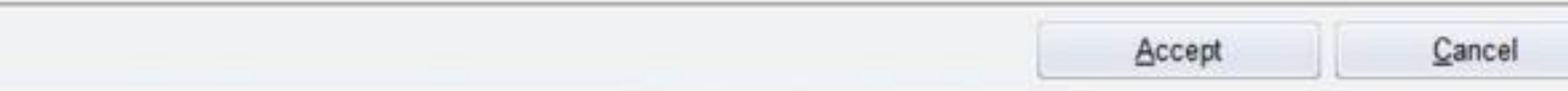
CCHMC PGx implementation

Codeine is being ordered





Result Report: Opioid CYP2D6 PGx Panel

Gene Analyzed: *CYP2D6*

Allele 1: *9

Allele 2: *5

Duplication: No

8% of patients have actionable genotypes for *CYP2D6*
Can be ordered prior to surgery, regularly done now for pectus excavatum

Predicted Phenotype – Intermediate Metabolizer

Drug	Therapeutic Recommendations
Codeine	100% standard starting dose
Hydrocodone	100% standard starting dose
Oxycodone	100% standard starting dose
Tramadol	100% standard starting dose

Alert always fires to look at results, not just actionable results

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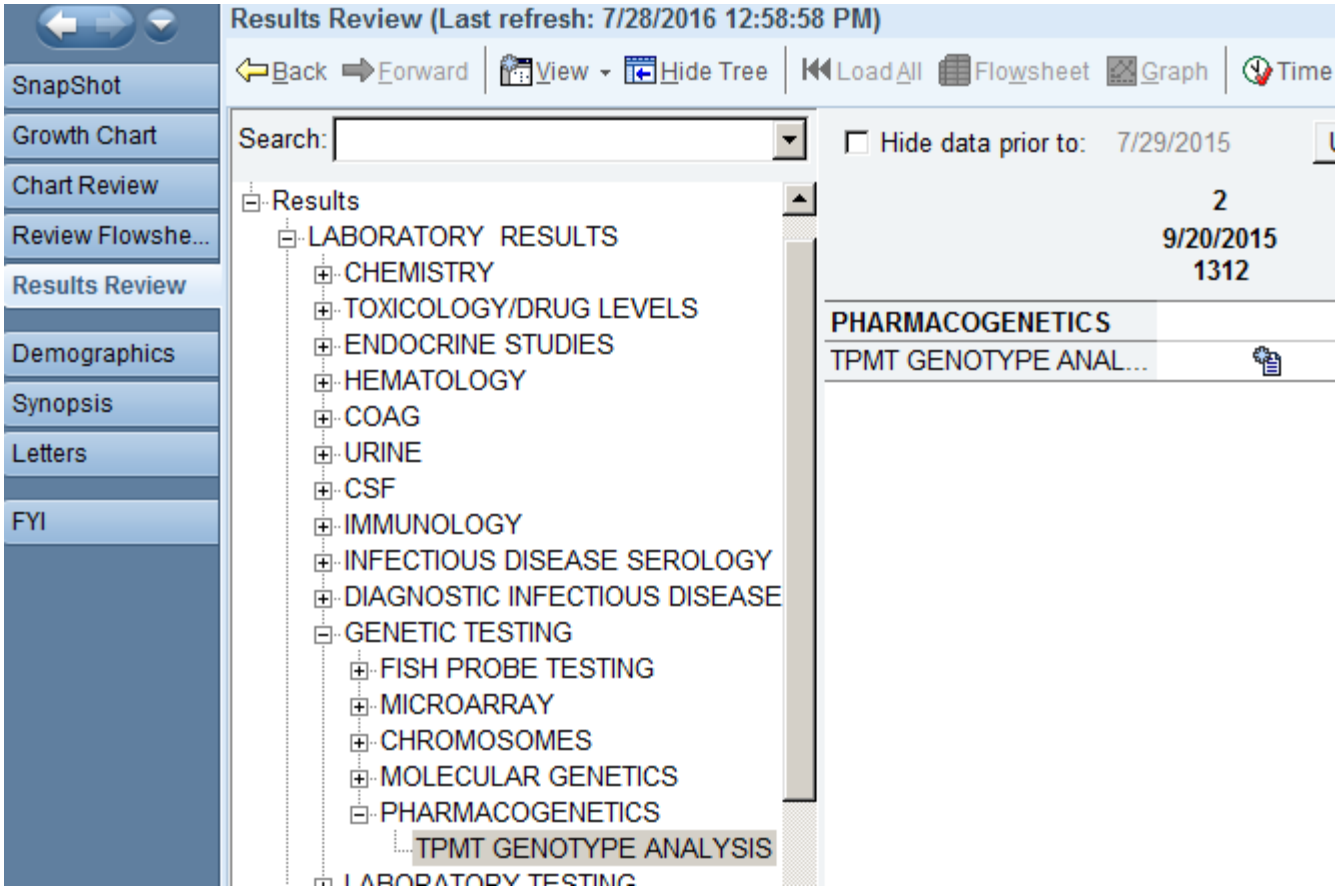
Incorporation in EMR

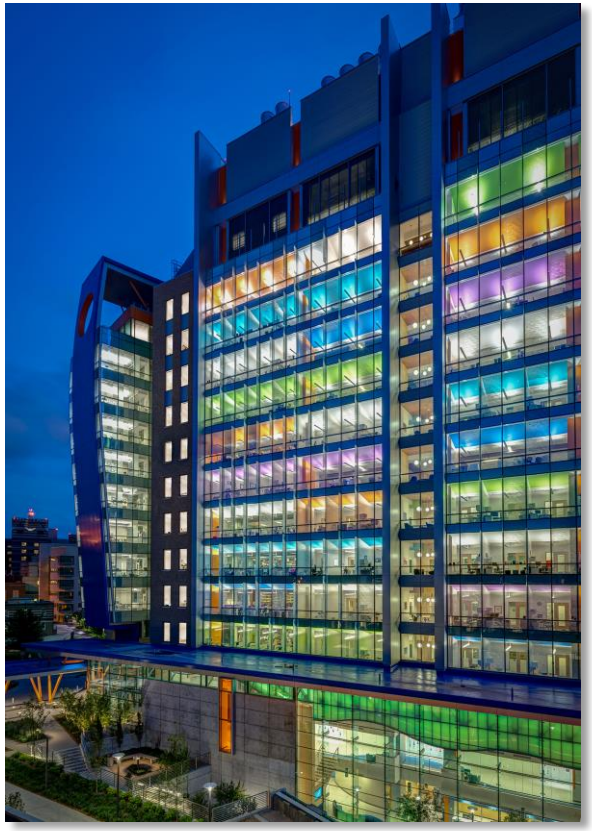
- Results Review tab in Epic



Where do we go from here?

- Improve decision support
  - Work with IS to alert only when actionable results are in report
  - Put results in problem list instead of PDF so CDS can be driven off them
- Implement additional gene-drug pairs
- Add information for patient/family to understand what their results mean
- Learn from the patients already tested
- Education for clinicians
- Expand consult service

PGx Guided Medicine is a *Team Sport*



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Genetic Pharmacology Service

Anesthesiology

Psychiatry

Pharmacy RiPS

Clinical Pharmacology

Division of Human Genetics

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