Implementation of Precision Medicine through Pharmacogenetics at a Large Healthcare System

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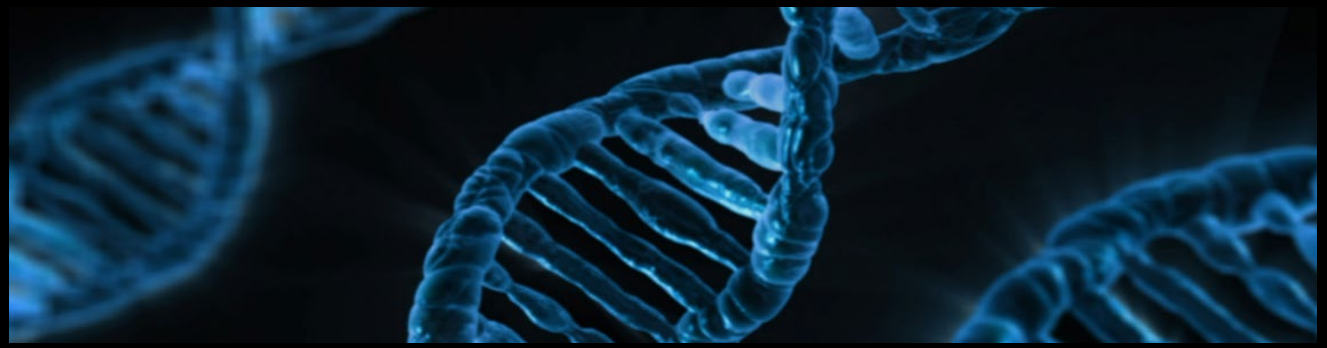
Banner – University Medical Center Phoenix



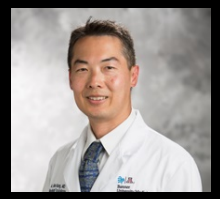
COLLEGE OF MEDICINE PHOENIX
Department of Medicine
Clinical Data Analytics & Decision Support

Banner Health®

Precision Medicine at BUMCP

BUMCP

Department of Medical Toxicology

- Section of Precision and Genomic Medicine
  - 
  - A. Min Kang, M.D.
- Section of Addiction Medicine
  - 
  - Michelle Ruha, M.D.

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Department of Medicine

- Division of Medical Toxicology and Precision Medicine
  - 
  - Steven Curry, M.D.
- Division of Clinical Data Analytics and Decision Support
  - 
  - Steven Curry, M.D.
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  - Raymond Woosley, M.D., Ph.D.

Division of Clinical Data Analytics and Decision Support

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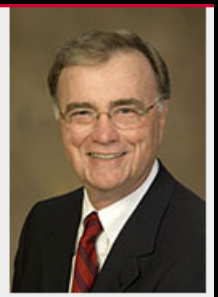

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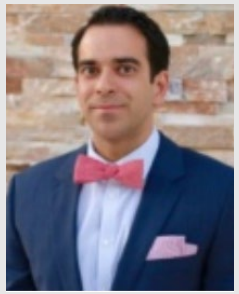

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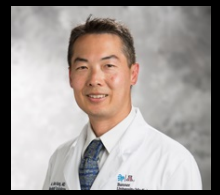
Department
of
Medical Toxicology

Section of
Precision and
Genomic Medicine



A. Min Kang, M.D.

Precision Medicine
Consultation Service
effective Nov 2017

Pharmacogenetics

1. Develop PGx panel

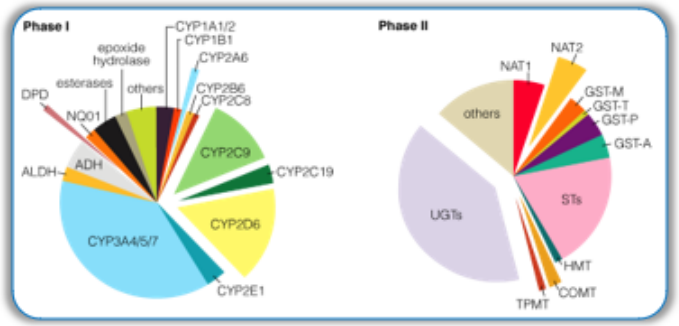
Gene	Genotype	Phenotype
CYP1A2	*1F/*1V	Normal Metabolizer- Possible Inducibility
CYP2B6	*1/*1	Normal Metabolizer
CYP2C19	*1/*1	Normal Metabolizer
CYP2C9	*1/*3	Intermediate Metabolizer
CYP2D6	*4/*5	Poor Metabolizer
CYP3A4	*1/*1	Normal Metabolizer
CYP3A5	*3/*3	Poor Metabolizer
DPYD	*1/*1	Normal Metabolizer
SLCO1B1	521T>C T/T	Normal Function
UGT2B15	*1/*1	Normal Metabolizer
VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity

Banner PGx profile tests for polymorphisms involving:

Cytochromes:	CYP1A2; CYPB6; CYP2C9; CYP2C19; CYP2D6 (including gene duplication); CYP3A4; CYP3A5
Glucuronidation:	UGT2B15
Transporters:	SLCO1B1
Other:	DPYD; VKORC1

Pharmacogenetic Consultations

Department of Medical Toxicology
Section of Precision and Genomic Medicine
602-839-3940



98% of patients have at least one genetic variant that affects clinical response to pharmaceuticals, explaining:

- **Adverse & toxic effects with standard therapeutic dosing.**
- **Lack of response with standard therapeutic dosing.**

Commonly implicated drugs include:

- analgesics
- anticoagulants
- anticonvulsants
- antipsychotics
- antiplatelet agents
- cardiac drugs
- antidepressants
- proton pump inhibitors

The Department of Medical Toxicology is now offering inpatient pharmacogenetic consultations at BUMCP.
Call:
602-839-3940

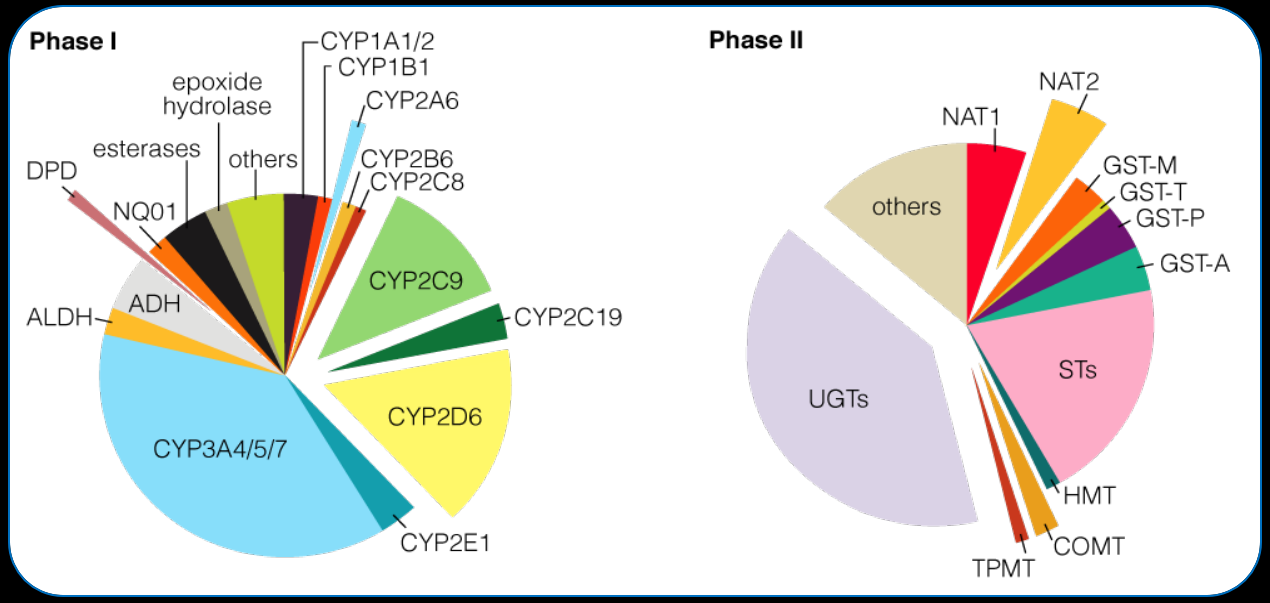
To order a pharmacogenetic profile in Cerner for common genetic polymorphisms,* order "Esoteric Testing" and type in the following test name: "Banner PGx Profile".

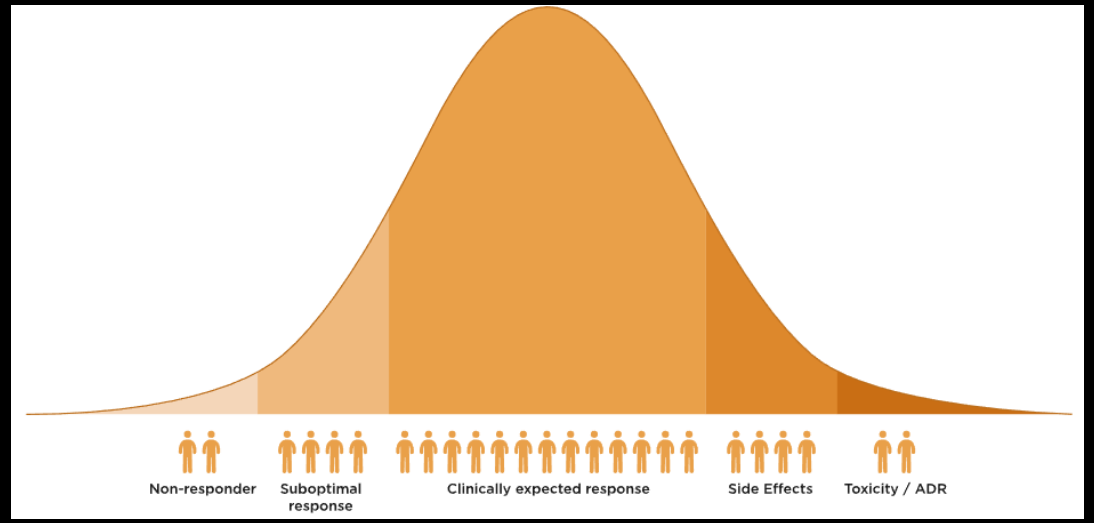
Banner PGx profile tests for polymorphisms involving:

Cytochromes:	CYP1A2; CYPB6; CYP2C9; CYP2C19; CYP2D6 (including gene duplication); CYP3A4; CYP3A5
Glucuronidation:	UGT2B15
Transporters:	SLCO1B1
Other:	DPYD; VKORC1

* Additional or different testing for genetic variants might be recommended by consultants.

2. Consultation Service





98% of us carry at least 1 high-risk phenotype for genetic variations pertaining to drugs or drug responses

3. Free Testing!

CPIC®
Clinical Pharmacogenetics Implementation Consortium

# (N=359)	GENE (UNIQUE = 127)	DRUG (UNIQUE = 226)	GUIDELINE	CPIC LEVEL	PHARMGKB LEVEL OF EVIDENCE	PGX ON FDA LABEL	CPIC PUBLICATIONS (PMID)
1	HLA-B	abacavir	Guideline	A	1A	Testing required	• 24561393 • 22378157
2	HLA-B	allopurinol	Guideline	A	1A		• 23232549 • 26094938
3	CYP2C19	amitriptyline	Guideline	A	1A		• 23486447 • 27997040
4	CYP2D6	amitriptyline	Guideline	A	1A	Actionable PGx	• 23486447 • 27997040
5	UGT1A1	atazanavir	Guideline	A	1A		• 26417955
6	CYP2D6	atomoxetine	Guideline	A	1A	Actionable PGx	• 30801677
7	NUDT15	azathioprine	Guideline	A	1A		• 21270794 • 23422873 • 30447069

Ambulatory View
Acute View
Results Review
PMP Gateway (AZ and NV
Orders
Documentation
New Results
Visit Summary
Activities and Interventions
Advance Directives
Allergies
Clinical Media
Clinical Notes
Clinical Research
Diagnoses and Problems
Form Browser
Growth Chart
Health Maintenance
Histories
Immunization Forecast
Interactive View and I & O
MAR
MAR Summary
Medication List
mPages
Outside Records
Patient Information
Patient Schedule
Referrals

Vitals | Labs/POCT | Microbiology | Imaging | Diagnostics | Assessments | Ambulatory | Delivery Record

Flowsheet: Lab/POCT ... Level: Lab/POCT (Table / Group / List)

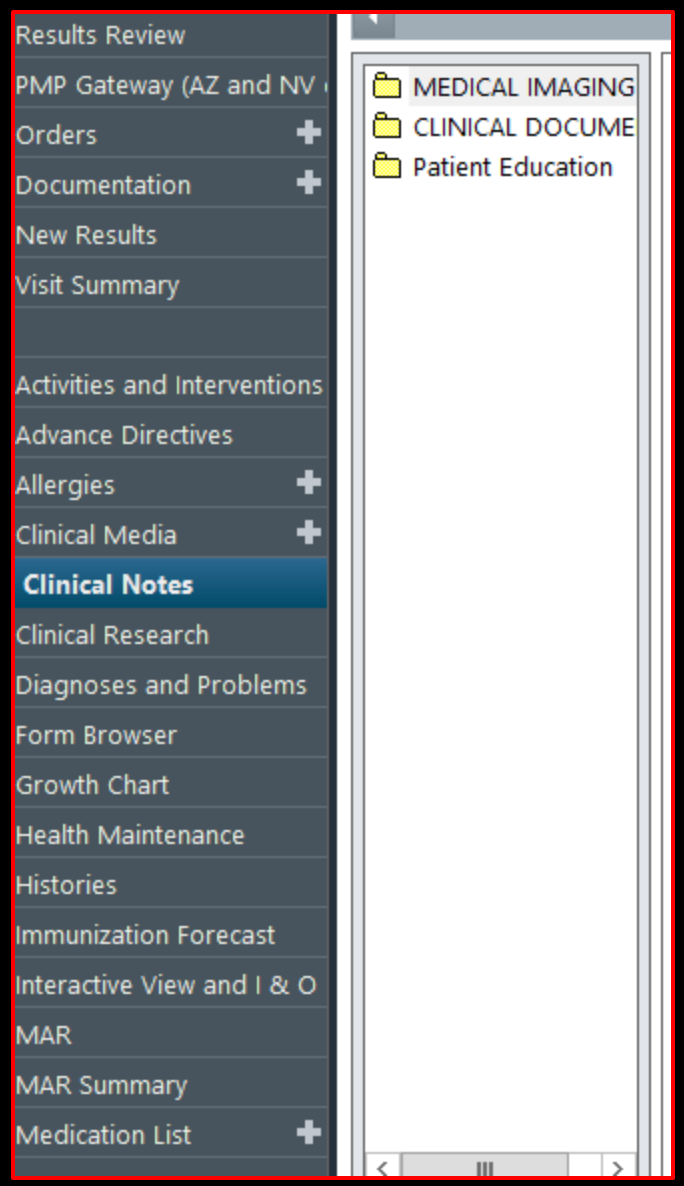
Last 999 Results in th

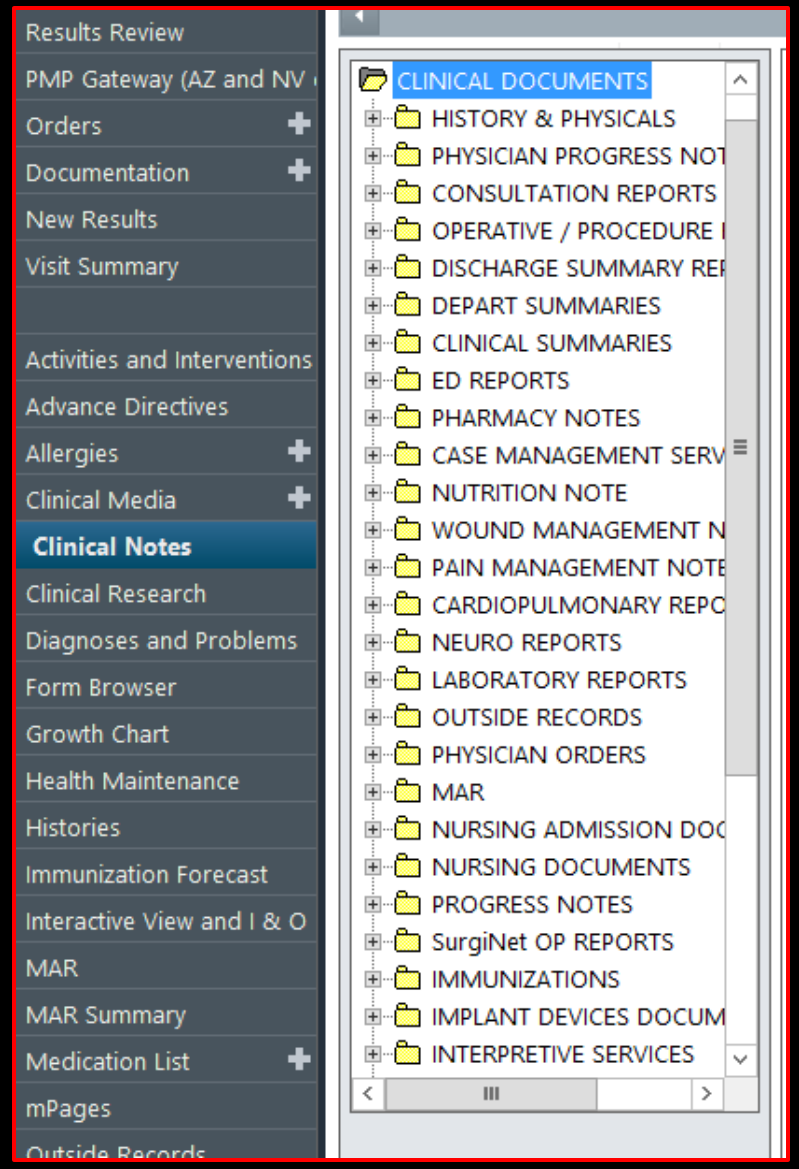
Navigator

- CBC
- WBC Differential
- Absolute Cell Counts (#)
- Percentages (%)
- Slide Review Findings
- GENERAL COAGULATION
- CHEM GENER
- ENDOCRINOLOGY
- PROT-IMMUNO-TUMOR
- URINE DRUGS
- URINALYSIS

Showing results from (12/22/2015 - 01/13/2020) Show more results

Lab/POCT	01/13/2020 6:19 MST	01/12/2020 14:44 MST	01/12/2020 14: MST
HGB	12.2 g/dL	13.1 g/dL	
HCT	36.3 %	38.9 %	
MCV	97 fL	97 fL	
MCH	32.7 pg	32.6 pg	
MCHC	33.6 g/dL	33.7 g/dL	
RDW-CV	13.0 %	12.8 %	
RDW-SD	46.5 fL	45.8 fL	
Nucleated RBCs, Automated	0 %	0 %	
Platelet	131 K/MM3	151 K/MM3	
Immature Platelet Fraction (IPF)			
MPV	13.1 fL H	13.0 fL H	
WBC Differential			
Differential Method	Automated	Automated	
Absolute Cell Counts (#)			
Neutrophils #	2.2 K/uL	3.9 K/uL	
Lymphocytes #	1.7 K/uL	1.4 K/uL	
Monocytes #	0.8 K/uL	0.9 K/uL	
Eosinophils #	0.2 K/uL	0.1 K/uL	
Basophils #	0.0 K/uL	0.0 K/uL	
Immature Granulocytes #	0.0 K/uL *	0.0 K/uL *	
Percentages (%)			
Neutrophils %	43 % *	61 % *	
Lymphocytes %	35 % *	23 % *	
Monocytes %	16 % *	14 % *	
Eosinophils %	5 % *	2 % *	


Results Review
PMP Gateway (AZ and NV
Orders
Documentation
New Results
Visit Summary
Activities and Interventions
Advance Directives
Allergies
Clinical Media
Clinical Notes
Clinical Research
Diagnoses and Problems
Form Browser
Growth Chart
Health Maintenance
Histories
Immunization Forecast
Interactive View and I & O
MAR
MAR Summary
Medication List
MEDICAL IMAGING
CLINICAL DOCUME
Patient Education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CONSULTATION REPORTS
OPERATIVE / PROCEDURE
DISCHARGE SUMMARY REP
DEPART SUMMARIES
CLINICAL SUMMARIES
ED REPORTS
PHARMACY NOTES
CASE MANAGEMENT SERV
NUTRITION NOTE
WOUND MANAGEMENT N
PAIN MANAGEMENT NOTE
CARDIOPULMONARY REPO
NEURO REPORTS
LABORATORY REPORTS
OUTSIDE RECORDS
PHYSICIAN ORDERS
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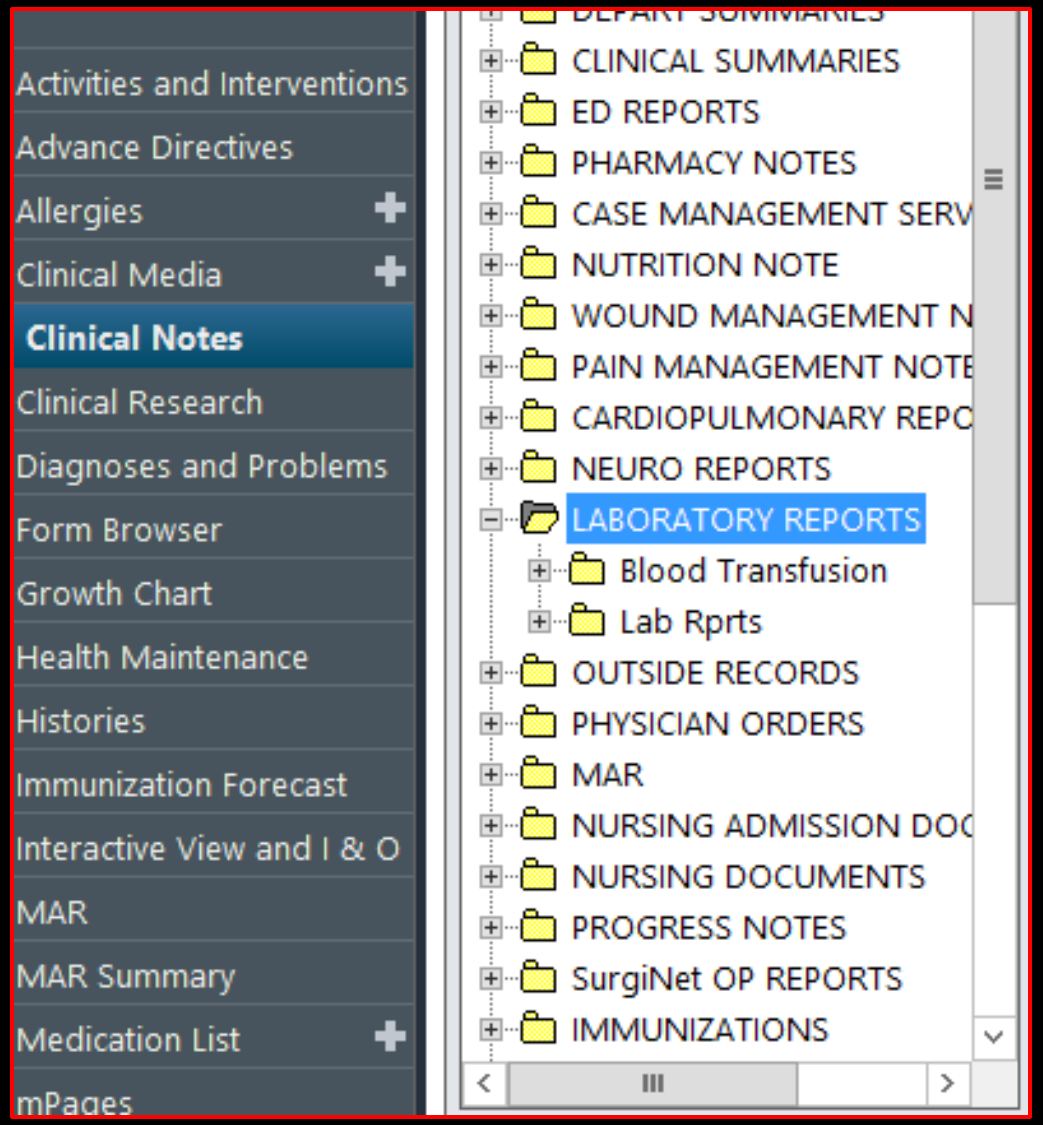
NURSING ADMISSION DOC
NURSING DOCUMENTS
PROGRESS NOTES
SurgiNet OP REPORTS
IMMUNIZATIONS
IMPLANT DEVICES DOCUM
INTERPRETIVE SERVICES


Activities and Interventions
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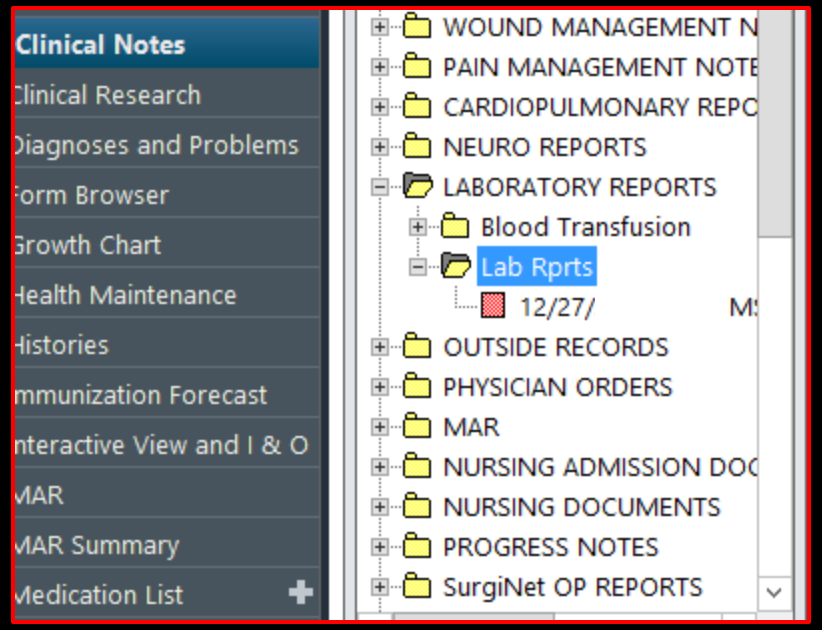


Patient
Patient Name:
Date of Birth:
Gender:

Ordered By
Ordering Physician: Curry, Steven
Physician ID:
Client: Vantari Test Provider

Specimen
Collected Date:
Received Date:
Reported Date:
Specimen Type: Blood
Accession #: 18010300219
Test(s) Requested: CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, DPYD, SLCO1B1, UGT2B15, VKORC1
Requisition #:
Indication for testing: None provided.

Test Details

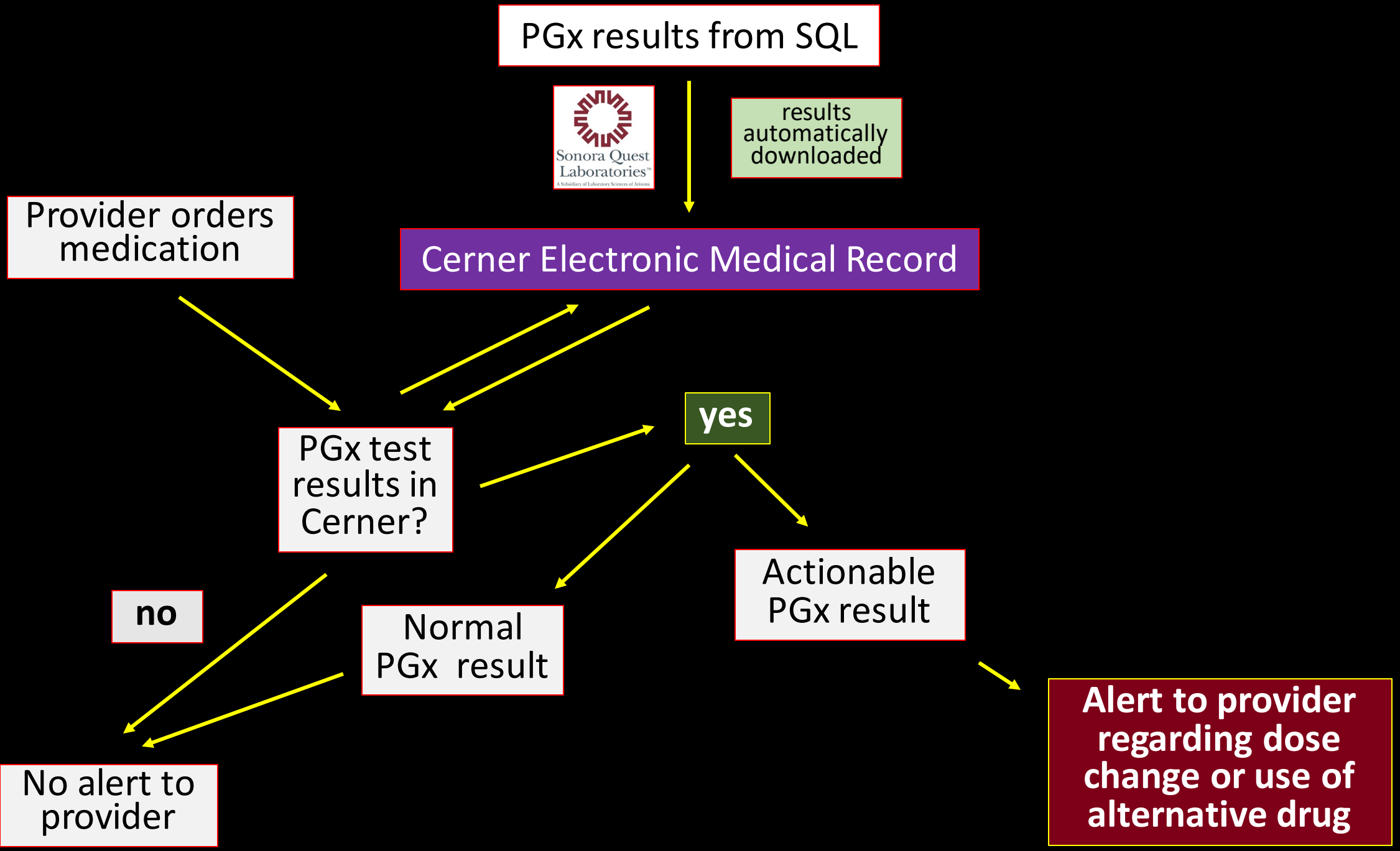
Gene	Genotype	Phenotype
CYP1A2	*1A/*1V	Normal Metabolizer- Possible Inducibility
CYP2B6	*1/*1	Normal Metabolizer
CYP2C19	*1/*1	Normal Metabolizer
CYP2C9	*1/*1	Normal Metabolizer
CYP2D6	*2/*5	Normal Metabolizer
CYP3A4	*1/*1	Normal Metabolizer
CYP3A5	*3/*3	Poor Metabolizer
DPYD	*1/*1	Normal Metabolizer
SLCO1B1	521T>C T/T	Normal Function
UGT2B15	*1/*2	Intermediate Metabolizer
VKORC1	-1639G>A A/A	High Warfarin Sensitivity

Report Comment: None provided.

Overall Plan of Action

Banner Health®

- Expand test profile
- Establish Lab and Reporting Company
- Create PGx Result Fields in EMR
- Develop Interface between Lab and EMR
- Choose Source for Recom-mended Drug-Gene Guidelines
- Develop Clinical Decision Support Rules for Drug-Gene Pairs
- Manual entry of old PGx test results in EMR
- Test Decision Support Tool in Background
- Implement Decision Support Tool in all Banner Inpatients and Outpatients


PGx results from SQL
Sonora Quest Laboratories
A Subsidiary of Laboratory Sciences of Arizona
results automatically downloaded
Provider orders medication
Cerner Electronic Medical Record
PGx test results in Cerner?
yes
no
Normal PGx result
Actionable PGx result
No alert to provider
Alert to provider regarding dose change or use of alternative drug

SQL developed PGx Panel

Sonora Quest Laboratories™
A Subsidiary of Laboratory Sciences of Arizona

- 22 Genes
- >120 genetic mutations/variations

Translational™ software

Reporting by TSI

	SQL	Vantari
ABCB1	3	-
CYP1A2	10	8
CYP2B6	10	3
CYP2C	1	-
CYP2C9	16	5
CYP2C19	15	10
CYP2D6	29	16
CYP2D6 deletions/CNV	Yes	Yes
CYP2D6 Hybrids	Yes	No
CYP2D6 distal enhancer (WBP2NL)	Yes	No
CYP3A4	6	6
CYP3A5	7	8
CYP4F2	1	-
DPYD	5	2
IFNL3	1	-
NAT2	5	-
NUDT15	2	-
RARG	1	-
SLC28A3	1	-
SLCO1B1	4	4
TPMT	5	-
UGT1A1	3	-
UGT1A6	1	-
UGT2B15	1	1
VKORC1	2	1

Comprehensive Pharmacogenetic Report

Test Details

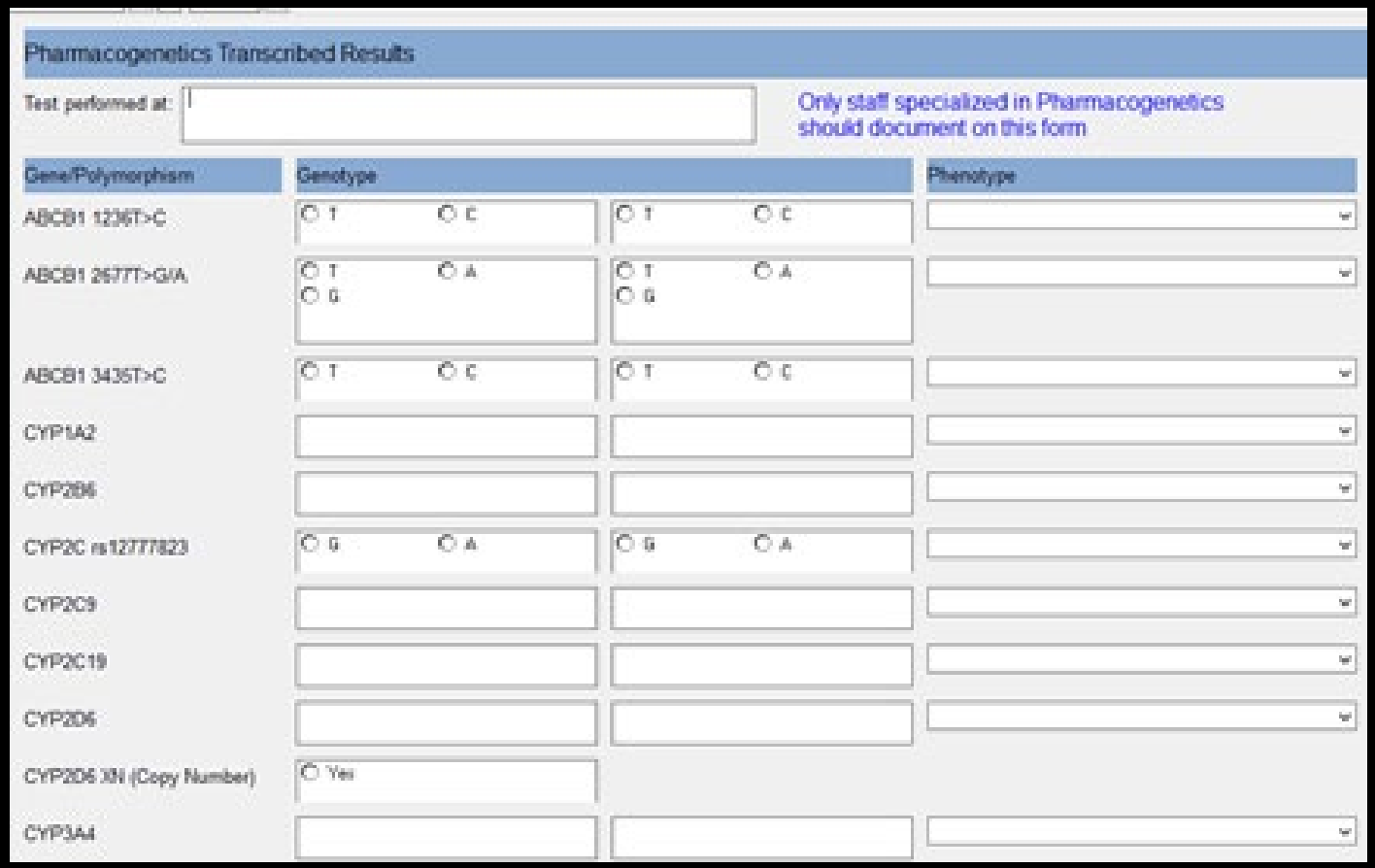
Gene	Genotype	Phenotype	Clinical Consequences
ABCB1	1236T>C T/C	Heterozygous- Variant Allele Present	Consistent with decreased transporter expression.
ABCB1	2677G>T G/T	Heterozygous- Variant Allele Present	Consistent with decreased transporter expression.
ABCB1	3435C>T C/T	Heterozygous- Variant Allele Present	Consistent with decreased transporter expression.
CYP1A2	*1A/*1A	Normal Metabolizer- Possible Inducibility	Consistent with a typical CYP1A2 activity in absence of inducing substances. Rapid metabolism may occur in presence of inducers such as barbiturates, cruciferous vegetables, carbamazepine, rifampin and smoking.
CYP2B6	*1/*1	Normal Metabolizer	Consistent with a typical CYP2B6 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
CYP2C	g.96405502G>A G/A	High Sensitivity	
CYP2C19	*2/*17	Intermediate Metabolizer	Consistent with a moderate deficiency in CYP2C19 activity. Potential risk for side effects or loss of efficacy with drug substrates.
CYP2C9	*1/*1	Normal Metabolizer	Consistent with a typical CYP2C9 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
CYP2D6	*1/*2	Normal Metabolizer	Consistent with a typical CYP2D6 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
CYP3A4	*1/*1	Normal Metabolizer	Consistent with a typical CYP3A4 activity. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
CYP3A5	*3/*3	Poor Metabolizer	Consistent with a poor CYP3A5 activity. This phenotype is the most common in the general population. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
CYP4F2	1347G>A G/G	Homozygous for the G allele (rs2108622)	
DPYD	Activity Score: 2	Normal Metabolizer	Consistent with a typical DPD activity and a typical risk of side effects with conventional doses of fluoropyridines.
IFNL3	rs12979860 C/T	Heterozygous for rs12979860 T allele	Unfavorable Response to Peginterferon alfa-2a and alfa-2b and Ribavirin Based Regimen for Hepatitic C Genotype 1
NAT2	c.191G>A G/G	Homozygous for rs1801279 G allele	
NAT2	c.341T>C T/C	Heterozygous for rs1801280 C allele	
NAT2	c.364G>A G/G	Homozygous for rs4986996 G allele	
NAT2	c.590G>A G/A	Heterozygous for rs1799930 A allele	
NAT2	c.857G>A G/G	Homozygous for rs1799931 G allele	
NUDT15	*1/*1	Normal Metabolizer	Consistent with a typical NUDT15 activity and a typical risk of side effects with conventional doses of thiopurines.
RARG	rs2229774 C/C	Normal Function	Normal receptor function and normal repression of topoisomerase-II beta (TOP2B) expression
SLC28A3	rs7853758 C/C	Normal Function	Normal SLC28A3 influx transporter function
SLCO1B1	521T>C T/T	Normal Function	Consistent with a typical SLCO1B1 transporter function. The patient's risk for statin-induced myopathy is not increased.
TPMT	*1/*3A	Intermediate Metabolizer	Consistent with a moderate deficiency in TPMT activity. Increased risk for serious side effects with conventional doses of thiopurines.
UGT1A1	*1/*80	Intermediate Metabolizer	Consistent with a moderately decreased UGT1A1 glucuronidation function (intermediate activity). Potential risk for side effects with drug substrates.
UGT1A6	rs17863783 G/G	Normal Metabolizer	Consistent with typical UGT1A6 glucuronidation metabolism.
UGT2B15	*2/*2	Poor Metabolizer	Consistent with a decreased UGT2B15 glucuronidation function. Potential risk for side effects with drug substrates.
VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity	VKORC1 is the site of action of warfarin. The patient may require a decrease in warfarin dosage.
VKORC1	c.3730G>A G/A	Heterozygous for rs7294 T allele	
WBP2NL	c.63-2604G>A A/G	Heterozygous for rs5758550 G allele	

Alleles Tested: ABCB1 3435C>T, 1236T>C, 2677G>T; **CYP1A2** *1C, *1D, *1E, *1F, *1J, *1K, *1L, *1V, *1W, *7; **CYP2B6** *4, *5, *6, *7, *8, *9, *11, *13, *16, *18; **CYP2C** g.96405502G>A; **CYP2C19** *2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *16, *17, *24, *25, *35; **CYP2C9** *2, *3, *4, *5, *6, *7, *8, *9, *11, *12, *13, *15, *16, *25, *31, *36; **CYP2D6** *2, *3, *4, *4M, *6, *7, *8, *9, *10, *11, *12, *14A, *14B, *15, *17, *18, *19, *29, *31, *33, *35, *38, *41, *42, *44, *51, *56A, *56B, *59, *62, *5 (gene deletion), XN (gene duplication); **CYP3A4** *1B, *2, *3, *12, *17, *22; **CYP3A5** *1D, *2, *3, *3C, *6, *7, *8, *9; **CYP4F2** 1347G>A; **DPYD** 1905+1G>A, 1679T>G, 2846A>T, 557A>G, c.1129-5923C>G; **IFNL3** rs12979860; **NAT2** 590G>A, 191G>A, 341T>C, 857G>A, 364G>A, c.590G>A, c.191G>A, c.341T>C, c.857G>A, c.364G>A; **NUDT15** *2, *3, *5; **RARG** rs2229774; **SLC28A3** rs7853758; **SLCO1B1** 521T>C; **TPMT** *2, *3A, *3B, *3C, *4; **UGT1A1** *6, *27, *80; **UGT1A6** rs17863783; **UGT2B15** *2; **VKORC1** 3730G>A, -1639G>A, c.3730G>A; **WBP2NL** 63-2604G>A, c.63-2604G>A

Sonora Quest Laboratories™

Translational software

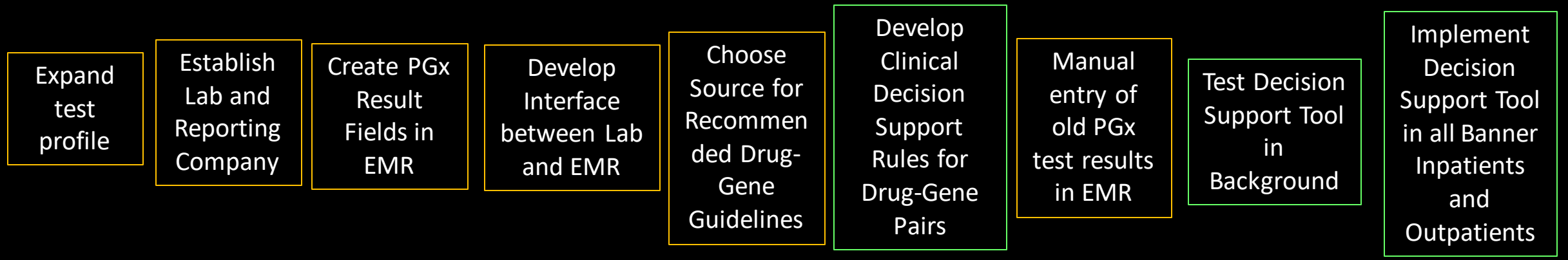
22 genes; > 120 alleles

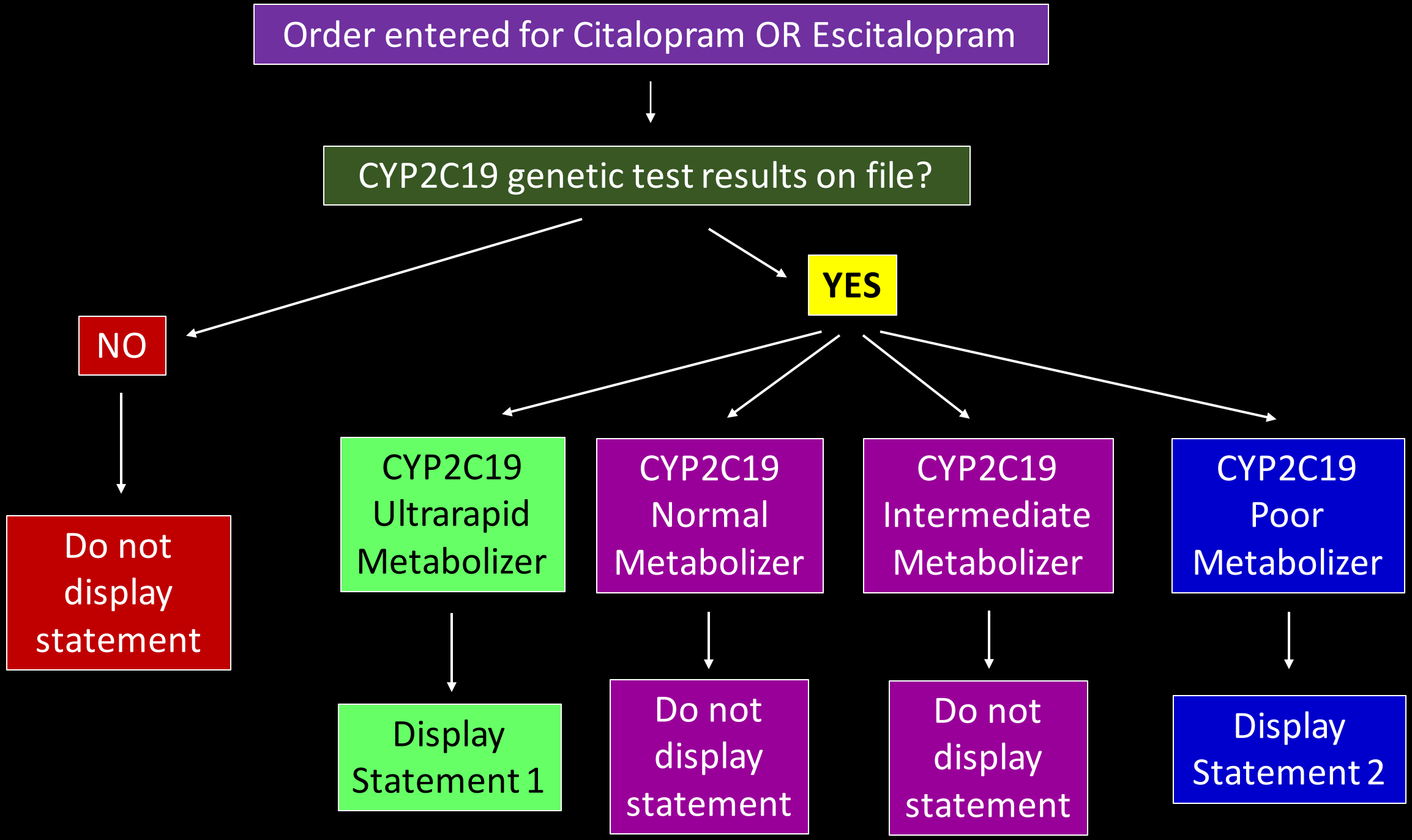


Autodownload interface completion April 2020

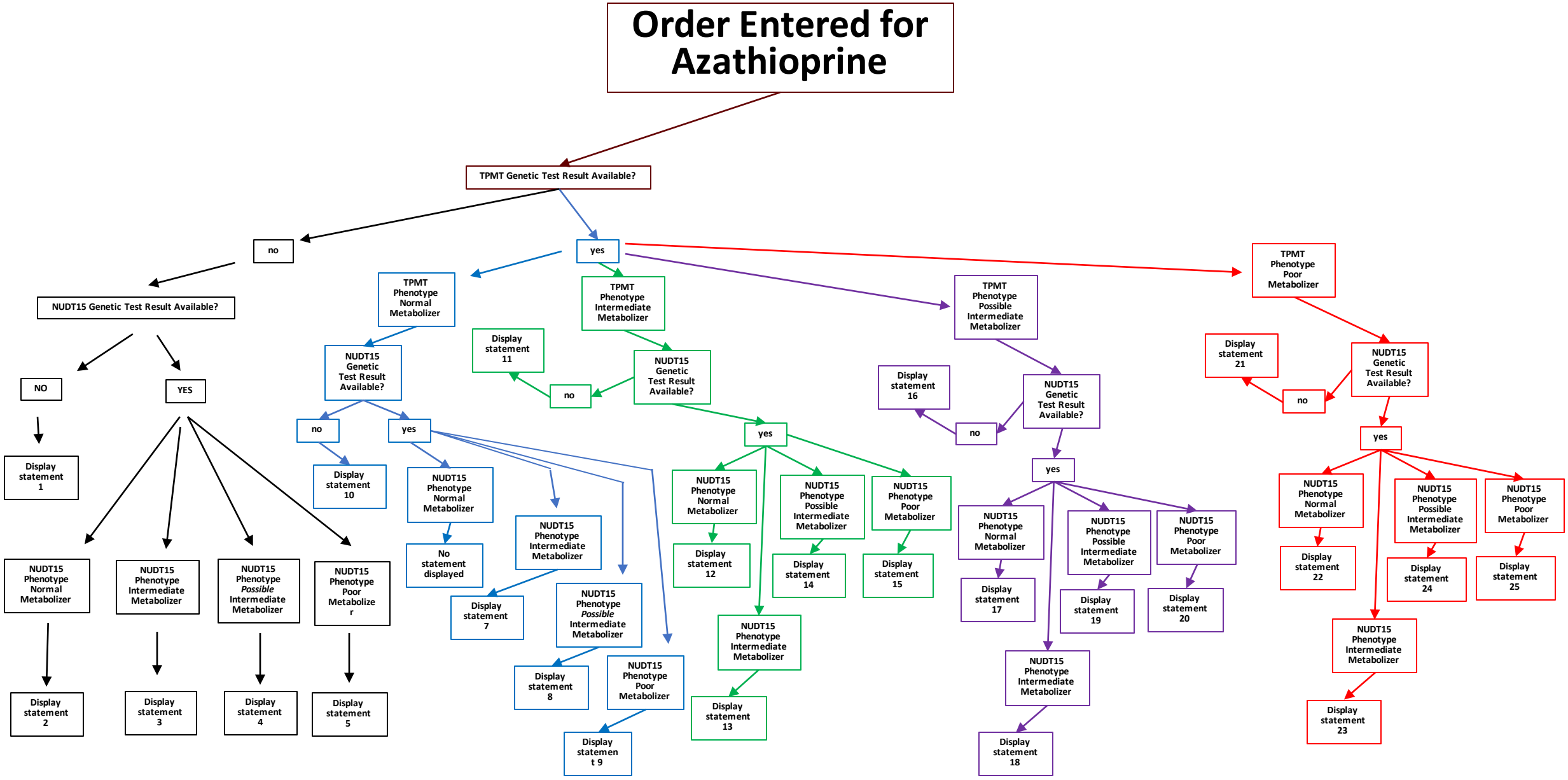
Manual Entry of Previous PGx Test Results

Pharmacogenetics Transcribed Result Form			Pharmacogenetics Transcribed Result Form (c
Pharmacogenetics Transcribed Results			
Test Performed at			Vantari Genetics (c)
CYP1A2 Genotype 1			*1F (c)
CYP1A2 Genotype 2			*1F (c)
CYP1A2 Phenotype			Normal metabolizer - higher inducibility (c)
CYP2B6 Genotype 1			*1 (c)
CYP2B6 Genotype 2			*1 (c)
CYP2B6 Phenotype			Normal metabolizer (c)
CYP2C9 Genotype 1			*1 (c)
CYP2C9 Genotype 2			*1 (c)
CYP2C9 Phenotype			Normal metabolizer (c)
CYP2C19 Genotype 1			*1 (c)
CYP2C19 Genotype 2			*17 (c)
CYP2C19 Phenotype			Rapid metabolizer (c)
CYP2D6 Genotype 1			*1 (c)
CYP2D6 Genotype 2			*4 (c)
CYP2D6 Phenotype			Ultrarapid or normal metabolizer (c)


Expand test profile
Establish Lab and Reporting Company
Create PGx Result Fields in EMR
Develop Interface between Lab and EMR
Choose Source for Recommended Drug-Gene Guidelines
Develop Clinical Decision Support Rules for Drug-Gene Pairs
Manual entry of old PGx test results in EMR
Test Decision Support Tool in Background
Implement Decision Support Tool in all Banner Inpatients and Outpatients

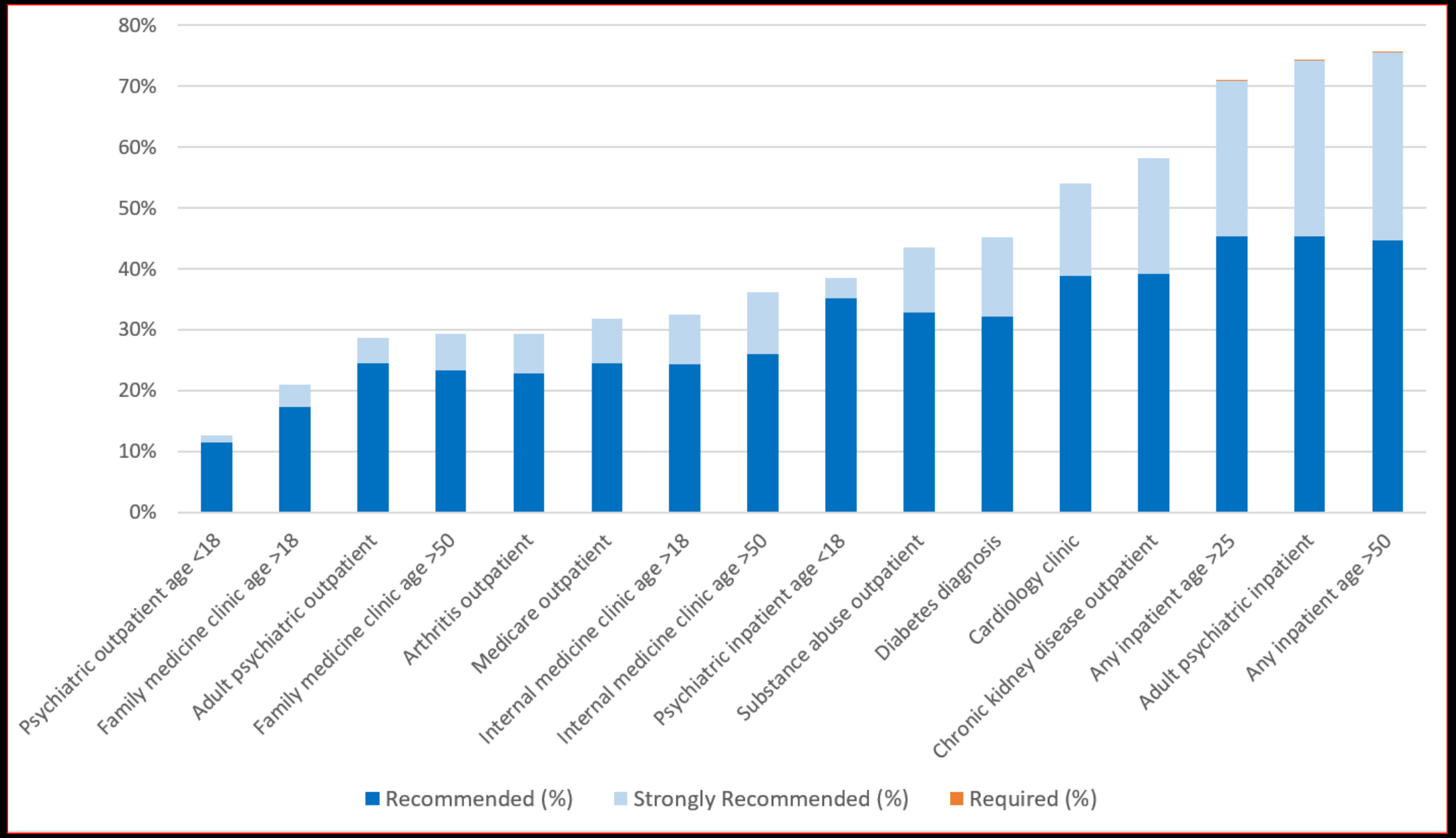

Order entered for Citalopram OR Escitalopram
CYP2C19 genetic test results on file?
NO
YES
Do not display statement
CYP2C19 Ultrarapid Metabolizer
CYP2C19 Normal Metabolizer
CYP2C19 Intermediate Metabolizer
CYP2C19 Poor Metabolizer
Display Statement 1
Do not display statement
Do not display statement
Display Statement 2

Order Entered for Azathioprine

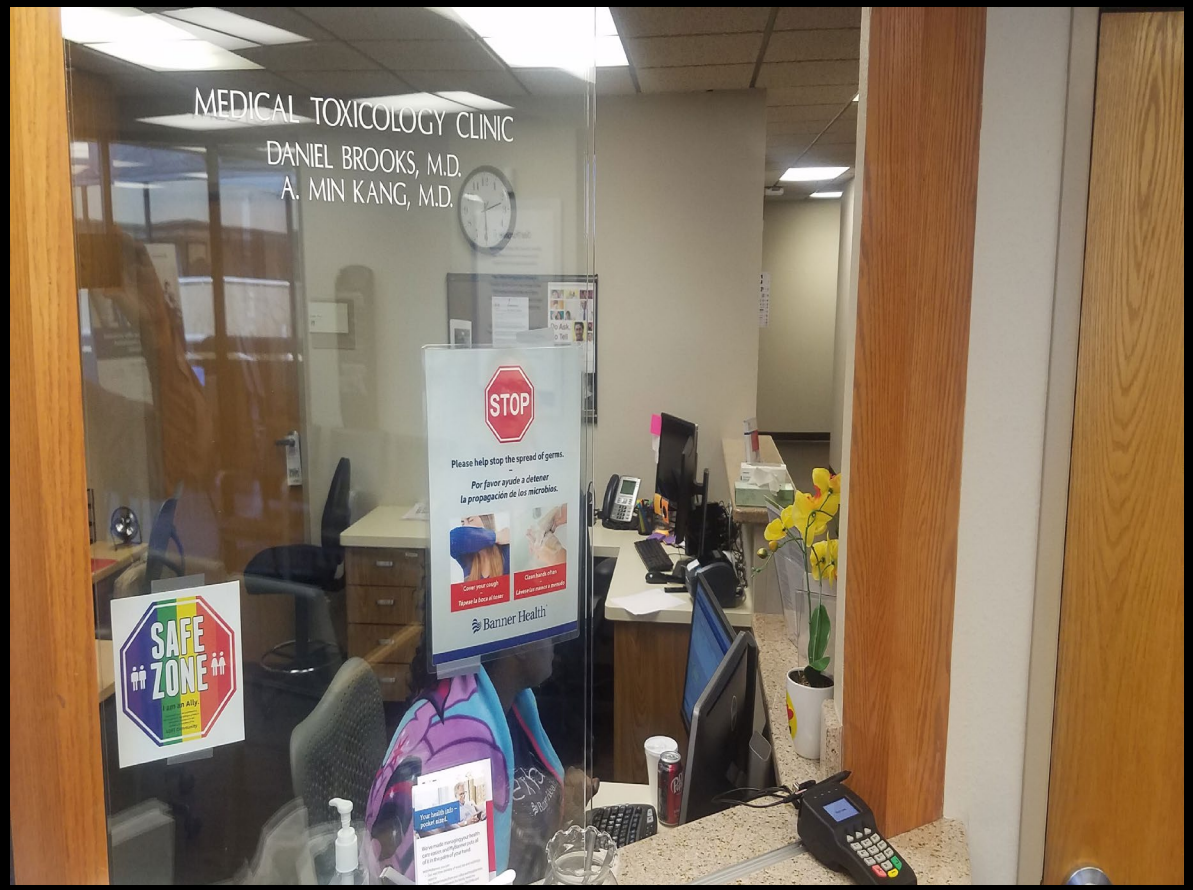


Which Patients Most Likely To Benefit From PGx Testing?

- Toxicology
- Transplant
- DM/Obesity
- Warfarin
- RCT Psych

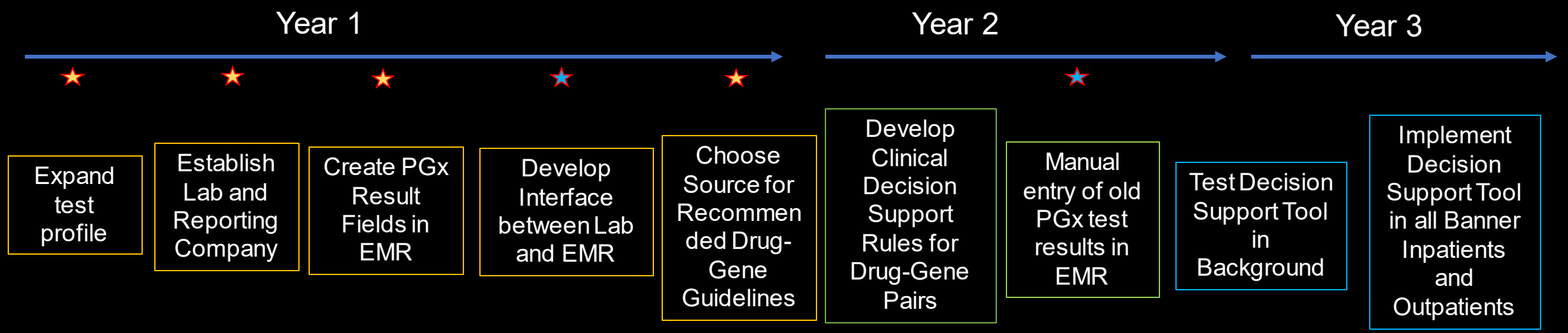


Expansion of PGx Activities



- PGx clinic
- Now partnering with VA Medical Center
- Discussions with other UA partners

PGx July 2019 - 2021 Activities



- Preemptive Test Populations
- Develop Outpatient PGx clinic
- Expand/Share with other UA partners
- Research