The Who, What, Where, When and Why of Pharmacogenomics and Clinical Implications

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Objectives

Review basics of pharmacogenomics

Discuss evidence-based resources

Identify appropriate patient population for testing

Determine how to enter order for pharmacogenomic saliva sample

Interpret/analyze pharmacogenomic report

Evaluate clinical implications of pharmacogenomics

The Era of Precision Medicine: What is PGx?

- **Pharmacogenomics (PGx):** using genetic information to guide drug dosing and selection
  - Goals: Maximize efficacy and reduced adverse events

- **Another tool for treatment success**
  - *Minimize trial and error process* in medication management and selection
  - Patient specific factors: ancestry, smoking status, caffeine
  - Concurrent medications
  - All factors MUST be taken into consideration
  - Does NOT provide all answers of which medications will work

AHRQ, publication 01-0020, 9/24/2013;www.uptodate.com

Major Categories of Pharmacogenomics

- **Effect on drug pharmacokinetics and pharmacodynamics**
  - Multiple copies of the gene (duplications xN)
  - Increased/decreased enzyme activity
  - Non-functional enzymes
  - Receptor and transporter polymorphisms
- **Effects on idiosyncratic reactions and likelihood of a hypersensitivity reaction to a certain drug**
  - i.e. HLA hypersensitivity for neuroleptic agents
- **Effects on disease pathogenesis or severity and response to specific therapies**
  - i.e. chemotherapy agents, targeted gene therapies

CYP isoenzymes: 58 different human CYP genes with growing pharmacogenomic implications

- **CYP2D6 (25-30% CYP mediated metabolism)**
  - TCAS, SSRIS, Antipsychotics, beta-blockers, tamoxifen
- **CYP2C19 (10% CYP mediated metabolism)**
  - TCAs, SSRIs, clopidogrel
- **CYP 3A4 (50% CYP mediated metabolism)**
  - Antipsychotics, statins, opioids, benzos

- **CYP2B6**
  - Bupropion, methadone
- **CYP2C9**
  - Warfarin, NSAIDs,
- **Drug therapy targets and transporters**
  - ie HTR2A Receptors, MTHFR, ADRA2A, COMT

Resources

- PharmGKB (https://www.pharmgkb.org/)
  - Dosing Guidelines
  - FDA and other Drug Labels
  - Clinically Actionable Drug-Gene Associations
  - Genotype-Phenotype Relationships
  - Publishes Guidelines, summaries, and drug-centered pathway

- CPIC (https://cpicpgx.org/)
  - Peer-reviewed, evidenced-based guidelines
  - Posted to PharmGKB
  - Supplemental information and updates

- Indiana University SOM: Flockhart table
  - https://drug-interactions.medicine.iu.edu/MainTable.aspx
  - Table of which drugs are substrates of, inhibit, and induce which CYP enzymes
  - Searchable
- FDA Product Labeling
  - https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm

Recommendations for medication changes

1. **Levels of Evidence PharmGKB**
    1. Actionable PGx
    2. Informative PGx
    3. Product Labelling

2. **Levels of Evidence CPIC**
    - **High**: Evidence includes consistent results from well-designed, well-conducted studies.
    - **Moderate**: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence.
    - **Weak**: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.
    - **Strength of Recommendations** : Strong , Moderate, Optional, No rec

FDA labeling information for pharmacogenomics

- May include outline of risk for adverse events, genotype specific dosing, drug exposure and clinical response variability, mechanism of action of the drug, polymorphic drug target and disposition genes, trial design features

Amitriptyline	Amoxapine	Amphetamine	Aripiprazole	Atomoxetine	Brexipiprazole	Cariprazine
Citalopram	Clomipramine	Clozapine	Desipramine	Desvenlafaxine	Doxepin	Duloxetine
Escitalopram	Fluoxetine	Fluvoxamine	Iloperidone	Imipramine	Modafinil	Nefazodone
Nortriptyline	Paliperidone	Paroxetine	Perphenazine	Pimozide	Pitolisant	Protiptyline
Risperidone	Thioridazine	Trimipramine	Venlafaxine	Vortioxetine		

Guidelines for behavioral health practice

SSRIs

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors

JK Hicks[1], JR Bishop[2], K Sangkuhl[3], DJ Müller[4], Y Ji[5], SG Leckband[6], JS Leeder[7], RL Graham[8], DL Chiulli[9], A LLerena[10], TC Skaar[11], SA Scott[12], JC Stingl[13], TE Klein[3], KE Caudle[14] and A Gaedigk[7]

Tricyclic antidepressants

Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update

JK Hicks[1], K Sangkuhl[2], JJ Swen[3], VL Ellingrod[4], DJ Müller[5], K Shimoda[6], JR Bishop[7], ED Kharasch[8], TC Skaar[9], A Gaedigk[10], HM Dunnenberger[11], TE Klein[2], KE Caudle[12] and JC Stingl[13]

Atomoxetine

Clinical Pharmacogenetics Implementation Consortium Guideline for Cytochrome P450 (*CYP*)*2D6* Genotype and Atomoxetine Therapy

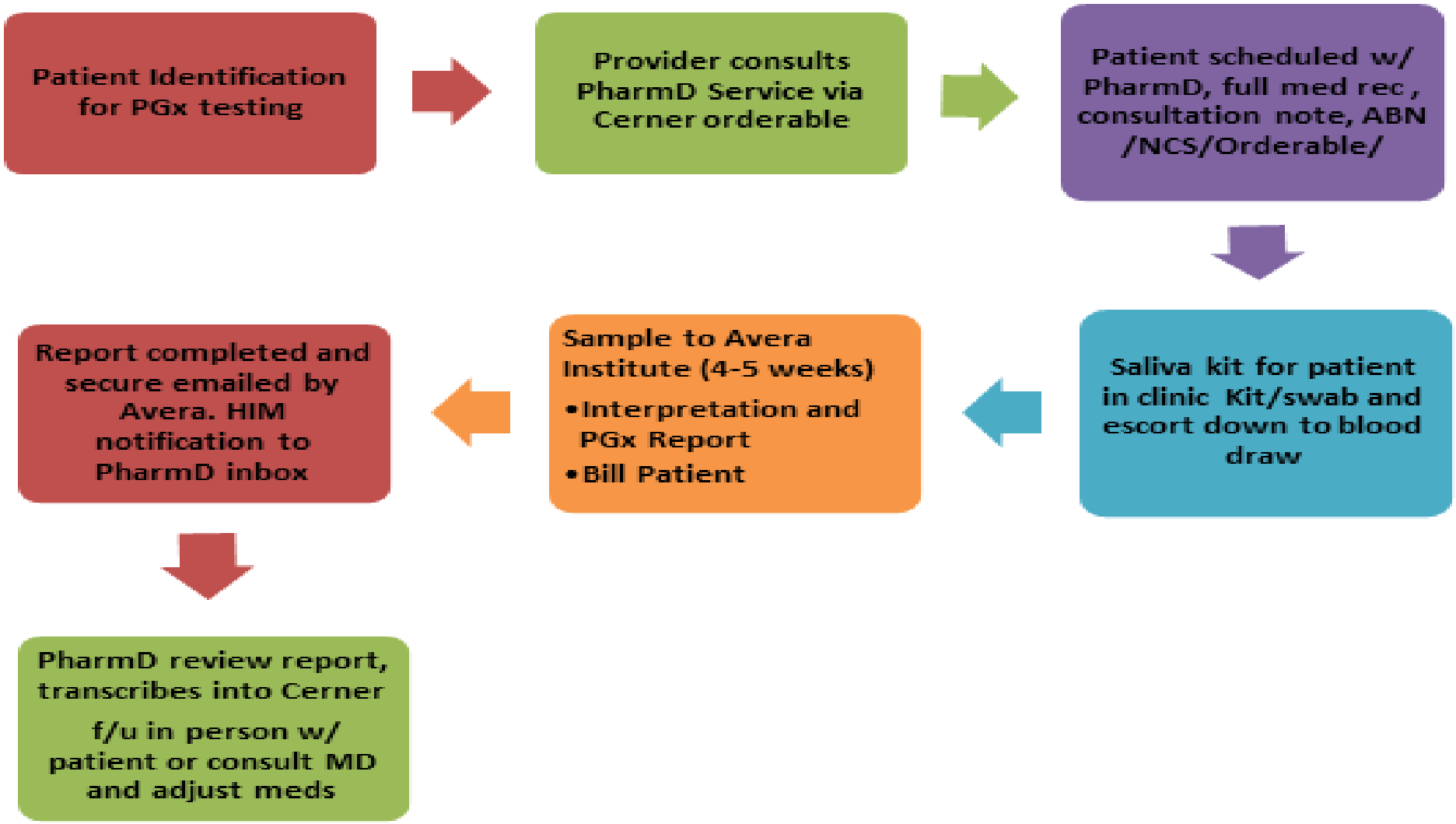
Jacob T. Brown[1], Jeffrey R. Bishop[2], Katrin Sangkuhl[3], Erika L. Nurmi[4], Daniel J. Mueller[5,6], Jean C. Dinh[7], Andrea Gaedigk[7,8], Teri E. Klein[3], Kelly E. Caudle[9], James T. McCracken[4], Jose de Leon[10] and

Real-world integration of pharmacogenomics

Who – identifying appropriate patients

- Diagnosis – uncontrolled:
  - Anxiety
  - Depression
  - ADHD
- Previously failed medication trials and adverse drug reactions
- On a drug that has pharmacogenomic data available
- Realistic expectations
- Several barriers and evidence gaps for indication of PGx testing

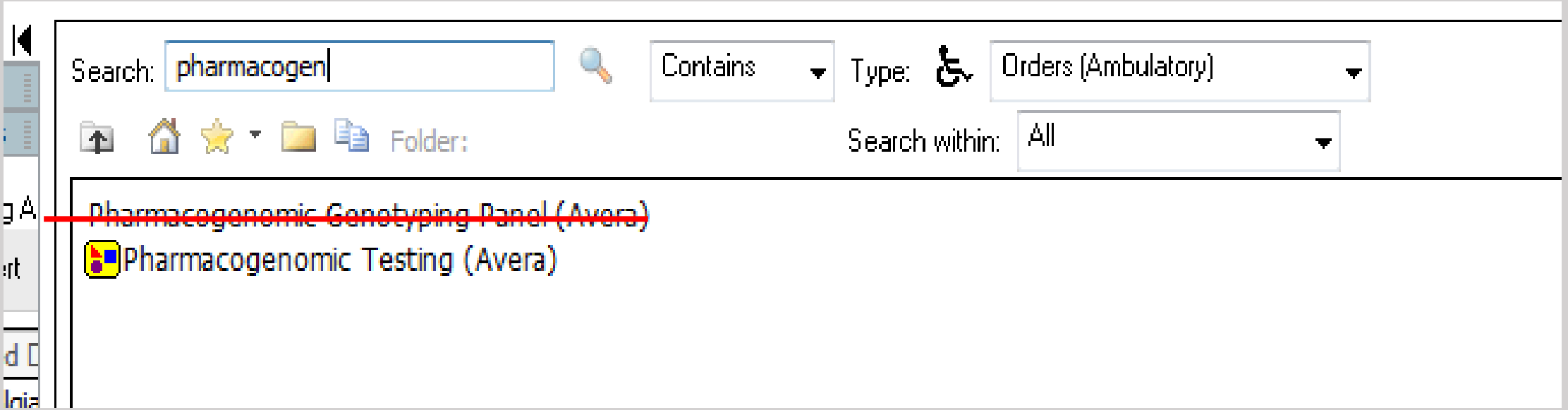
Workflow Design for Pharmacogenomic Ordering



Pharmacogenomics Orderable

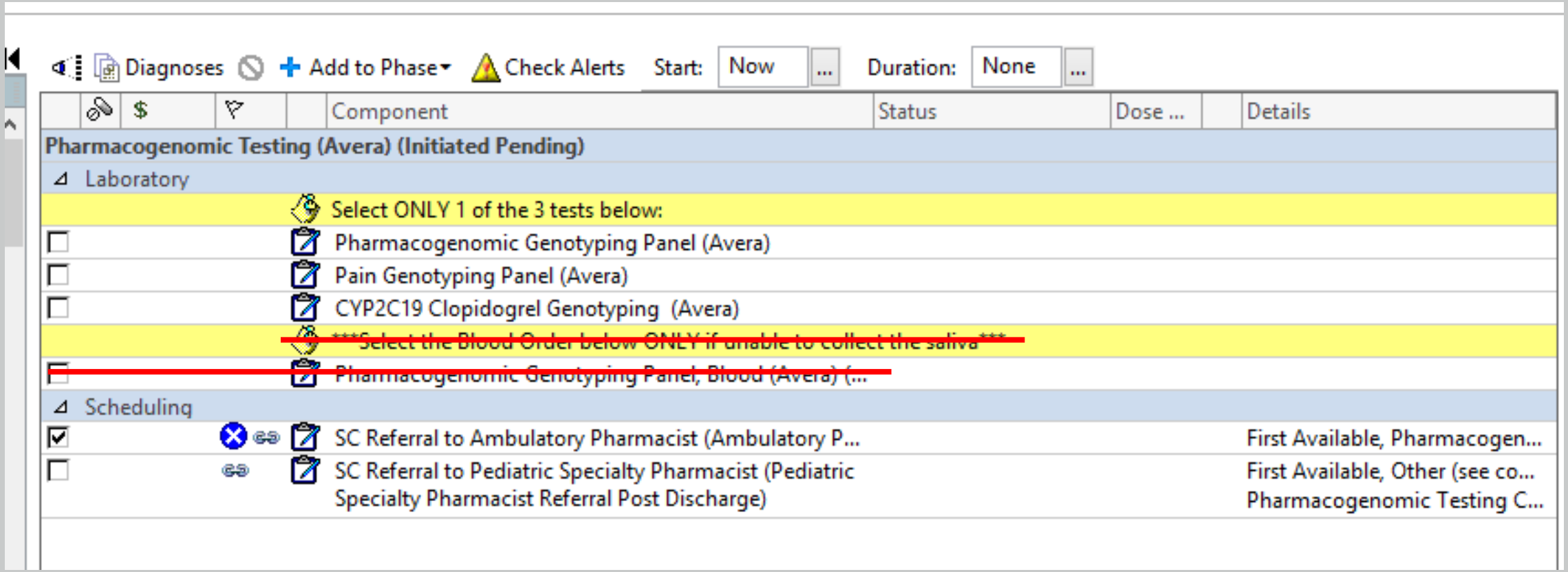
Orders→ Orders Ambulatory (Can also be ordered inpatient)

CHOOSE THE POWERPLAN ORDERABLE

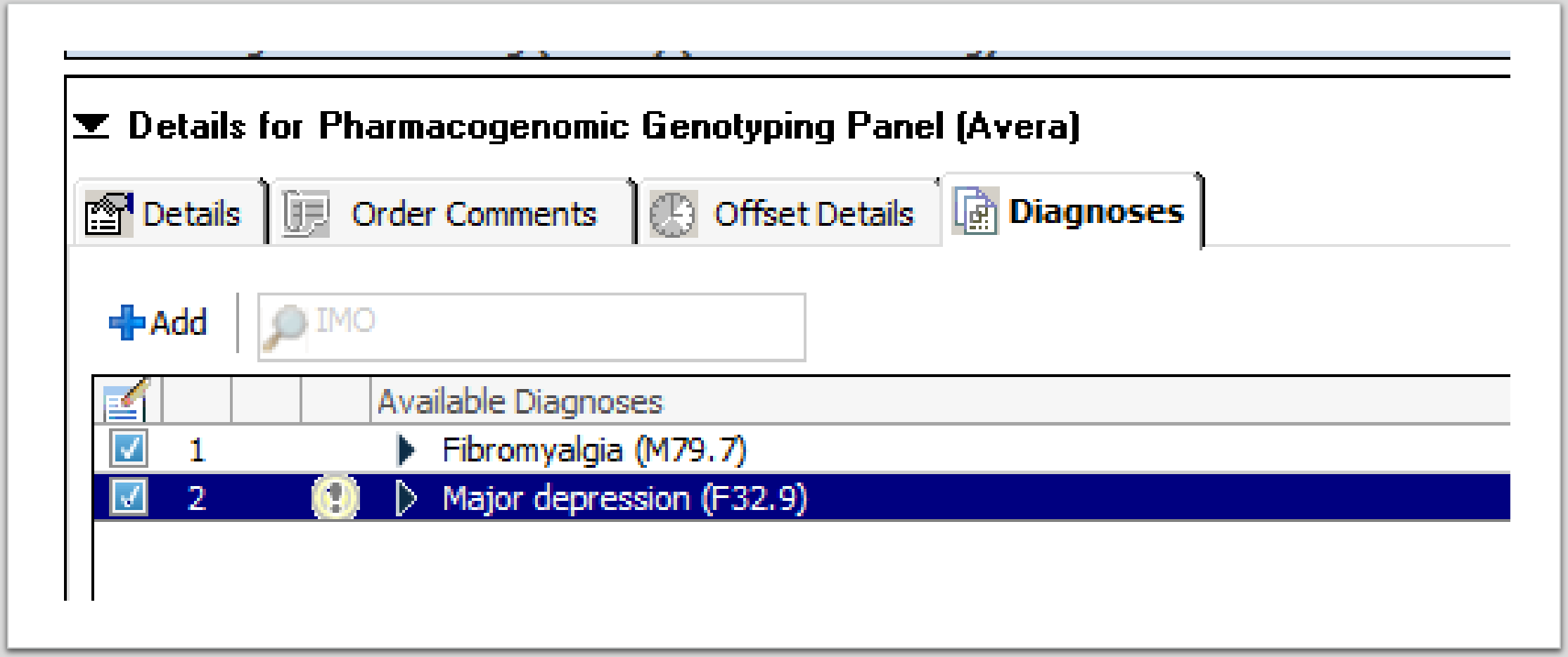


Powerplan Selections

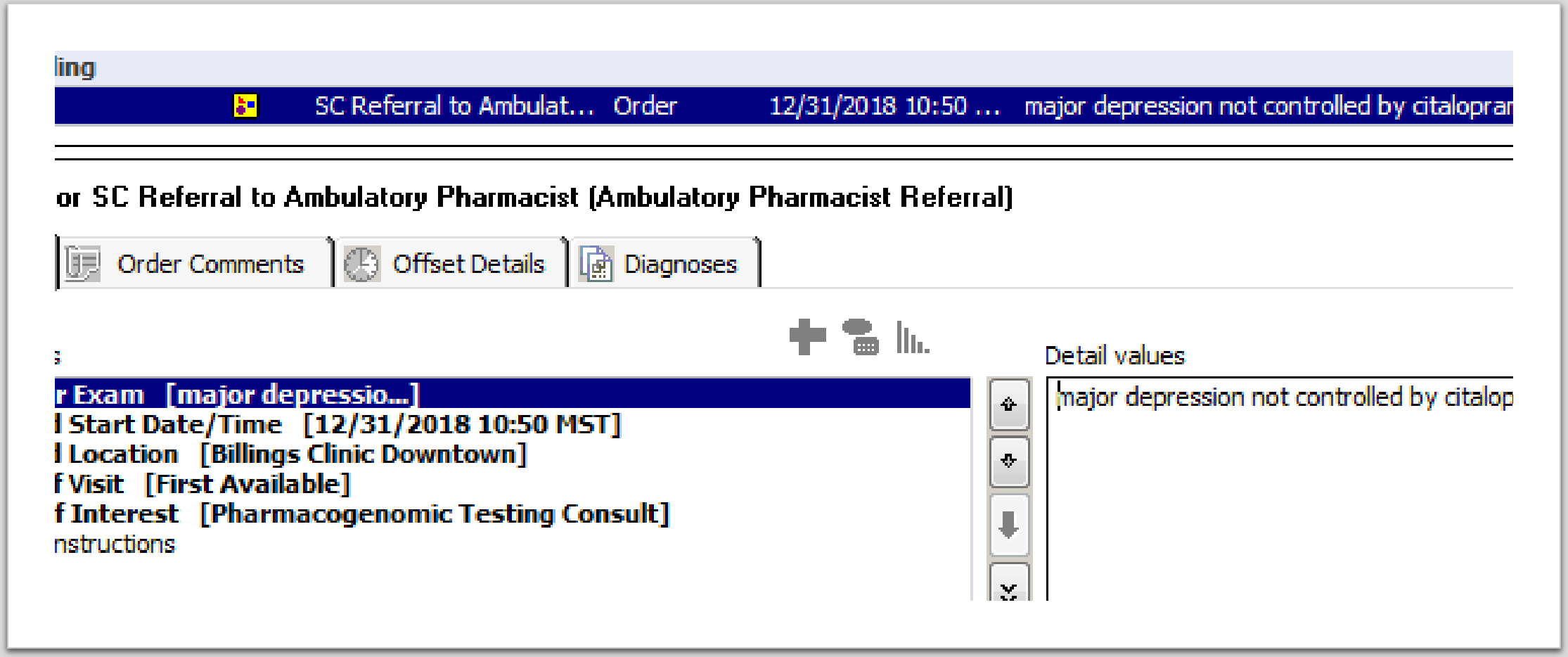
- Please select “Pharmacogenomic Genotyping Panel (Avera)
- Auto populates to SC Referral Amb Pharmacist
  - Can select Peds Pharmacist if < 15 years old or it is forwarded to my queue



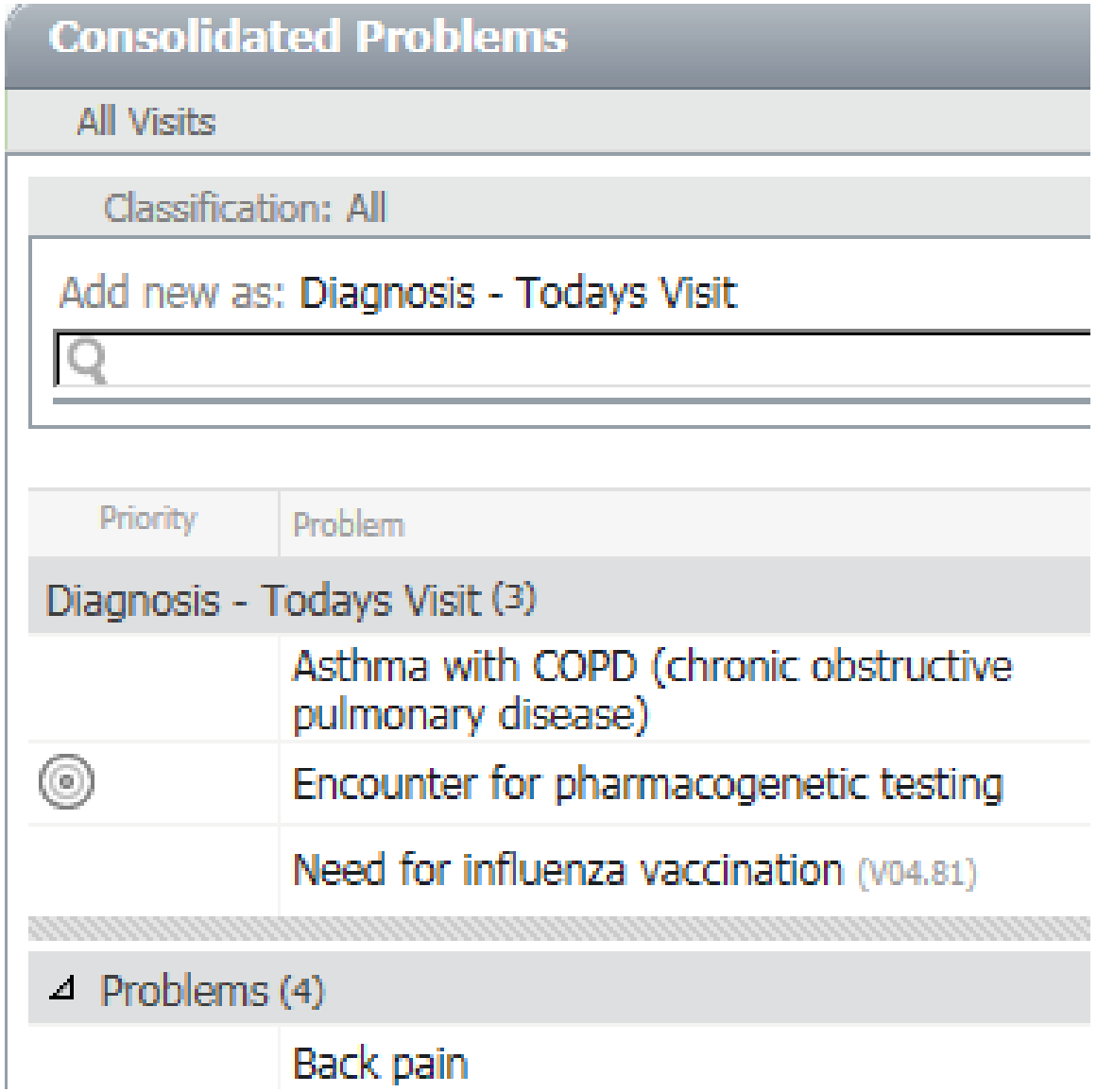
Orderable→ Modify→ Link Diagnoses



SC Referral to Ambulatory or Pediatric Pharmacist (Results review)

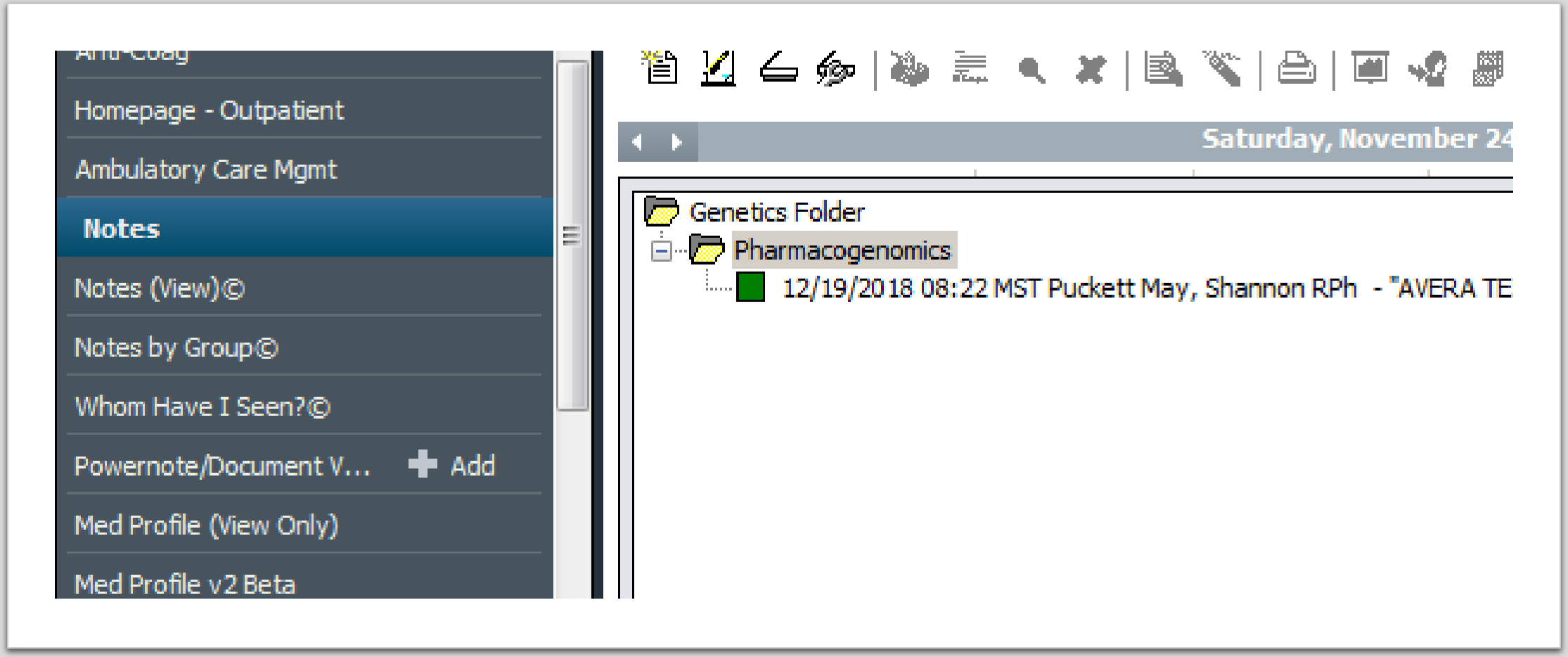


How to utilize pharmacogenomic findings



How to know if a patient has had PGx testing

Where to find results in Cerner



How to evaluate results

- Are there clinically significant drug-drug interactions?
- Are there clinically significant drug-gene interactions?
  - Is the patient at risk for adverse events?
  - Is the patient at risk for failure of treatment or higher dose needed?
  - Is there a guideline?
    - What is level of evidence for recommendation?
  - Does the patient feel medication is currently working?
  - Is dose optimized?
- Is there specific product labeling in the package insert?
- Is the patient's therapy optimized
  - Ie with comorbidities
- Does the patient need additional therapy if so, which is the best option

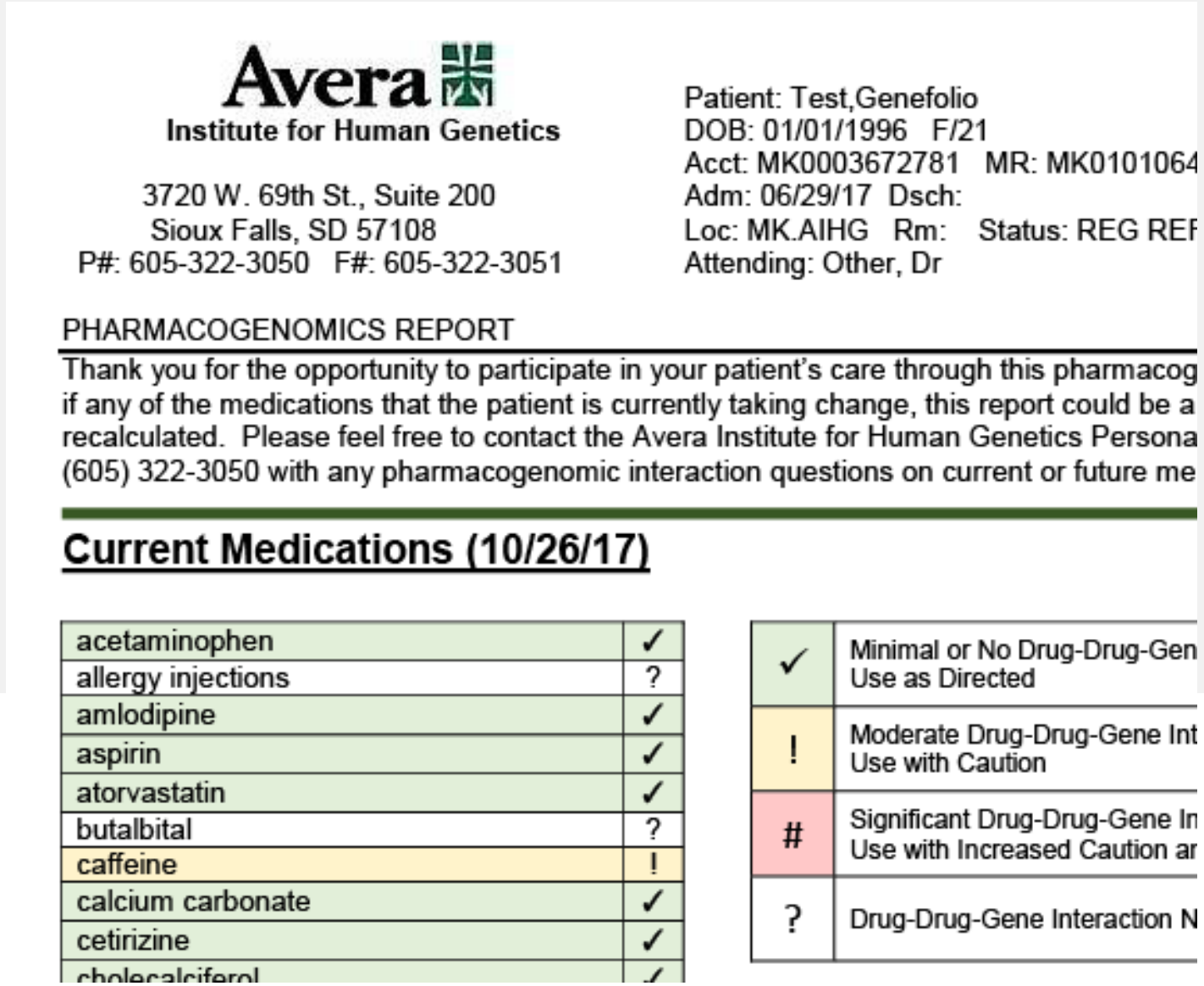
Evaluating the report

Green: (no significant drug-drug-gene interactions)

Yellow: (moderate drug-drug-gene interactions)

Red: (significant drug-drug-gene interactions)

Superscripted with Avera consultation recommendations, no LOE or SOR



Avera
Institute for Human Genetics

3720 W. 69th St., Suite 200
Sioux Falls, SD 57108
P#: 605-322-3050 F#: 605-322-3051

Patient: Test,Genefolio
DOB: 01/01/1996 F/21
Acct: MK0003672781 MR: MK0101064
Adm: 06/29/17 Dsch:
Loc: MK.AIHG Rm: Status: REG REF
Attending: Other, Dr

PHARMACOGENOMICS REPORT

Thank you for the opportunity to participate in your patient's care through this pharmacog
if any of the medications that the patient is currently taking change, this report could be a
recalculated. Please feel free to contact the Avera Institute for Human Genetics Persona
(605) 322-3050 with any pharmacogenomic interaction questions on current or future me

Current Medications (10/26/17)

acetaminophen	✓
allergy injections	?
amlodipine	✓
aspirin	✓
atorvastatin	✓
butalbital	?
caffeine	!
calcium carbonate	✓
cetirizine	✓
cholecalciferol	✓

✓	Minimal or No Drug-Drug-Gen Use as Directed
!	Moderate Drug-Drug-Gene Int Use with Caution
#	Significant Drug-Drug-Gene In Use with Increased Caution ar
?	Drug-Drug-Gene Interaction N

Sample report

Sample report

Patient: Test,Genefolio
Acct: MK0003672781

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1. The patient is taking butalbital-acetaminophen-caffeine (Fioricet) one tablet every 4-6 hours as needed for migraine. Caffeine is in the 'moderate drug-drug-gene interaction' column due to the patient's reduced CYP1A2 function. Caffeine serum concentration may be increased at standard dosing, therefore increasing the potential for adverse reactions. Utilize the lowest effective dose and be alert for adverse reactions (i.e. agitation, palpitation, insomnia).

2. The patient is taking clopidogrel 75mg daily. Clopidogrel is in the 'significant drug-drug-gene interaction' column due to the patient's decreased CYP2C19 function. Per the Clinical Pharmacogenetics Implementation Consortium (CPIC), it would be recommended to use an alternative antiplatelet therapy (e.g. prasugrel, ticagrelor) if there is no contraindication in patients with acute coronary syndromes who undergo percutaneous coronary intervention. The combination of genetic results and potential inhibition/induction from any current medications imply that the patient would be at risk for significantly reduced platelet inhibition, increased residual platelet aggregation, and be at an increased risk for adverse cardiovascular events with clopidogrel use.

3. The patient is taking cyclobenzaprine 10mg three times daily as needed. Cyclobenzaprine is in the 'moderate drug-drug-gene interaction' column due to the patient's reduced CYP1A2 function. Cyclobenzaprine serum concentration may be increased at standard dosing, therefore increasing the potential for adverse reactions. Utilize the lowest effective dose and be alert for adverse reactions (i.e. drowsiness, xerostomia).

Sample report

Psychotropic Medications

Selective Serotonin Reuptake Inhibitors (SSRIs)

Minimal or No Drug-Drug-Gene Interaction	Moderate Drug-Drug-Gene Interaction	Significant Drug-Drug-Gene Interaction
vilazodone31	fluvoxamine28	citalopram25

Meditech report ID number: 1119-1080 Facility: MCK/MR

Signed

Tricyclic Antidepressants (TCAs)

Use as Directed	Moderate Drug-Drug-Gene Interaction	Significant Drug-Drug-Gene Interaction

Benzodiazepines

Use as Directed	Moderate Drug-Drug-Gene Interaction	Significant Drug-Drug-Gene Interaction
alprazolam45		

Monoamine Oxidase Inhibitors (MAOIs)

Use as Directed	Moderate Drug-Drug-Gene Interaction	Significant Drug-Drug-Gene Interaction

Second Generation Antipsychotics (SGAs)

Use as Directed	Moderate Drug-Drug-Gene Interaction	Significant Drug-Drug-Gene Interaction
aripiprazole52	cariprazine54	

Sample report

Genomic Laboratory Results

Genetic Marker	Result	Enzyme Function
CYP1A2	*1F/*1F	Normal Function but Highly Inducible + five weak inhibitors, + no inducers
CYP2B6	*1/*1	Normal Function + one weak inhibitor, + no inducers
CYP2C9	*1/*1	Normal Function + six weak inhibitors, + no inducers
CYP2C19	*1/*2	Intermediate (Reduced) Function + one weak inhibitor, + one weak/moderate inducer
CYP2D6	*1/*6 with 2 copies	Intermediate (Reduced) Function + one weak inhibitor, + no inducers
CYP3A4	*1/*1	Normal Function + two weak inhibitors, + no inducers
CYP3A5	*3/*3	Poor Function + no inhibitors, + no inducers
SLCO1B1	*1A/*1A	Normal Function + one uncategorized inhibitor, + no inducers
VKORC1	A/G	Intermediate Sensitivity to Warfarin
COMT	Val/Met	Intermediate Enzyme Activity + no inhibitors, + no inducers
OPRM1	A/A	Normal Response
SERT	La/La	Normal Serotonin Transporter Levels
ADRA2A	C/C	Reduced Response
MTHFR	C/C	Normal Enzyme Function
HTR2A rs6311	C/T	N/A
HTR2A rs6313	A/G	N/A
HTR2A rs6314	A/G	N/A
HTR2A rs1805055	G/G	N/A
HTR2A rs7997012	G/G	N/A

Medications

	CYP1A2	CYP2B6	CYP2C9	CYP2C19	CYP2D6	CYP3A4	CYP3A5	SLCO1B1
	Substrate (minor)		Substrate (minor)		Substrate (minor)	Substrate (minor)		
[redacted]								
	Inhibitor (weak)		Inhibitor (weak)			Substrate (major), Inhibitor (weak)		
			Substrate (minor)	Inducer (weak/moderate)				
						Substrate (major), Inhibitor (weak)		Substrate

Sample report

Enzyme Function Analysis

CYP1A2:	The patient has two normal function but highly inducible alleles (*1F) for CYP1A2. She is taking five weak inhibitors (amlodipine, caffeine, estradiol (topical), ondansetron, propranolol) of CYP1A2 and no inducers of the enzyme. Overall enzyme function would be estimated to be slightly reduced. Non-pharmacologic inducers of the enzyme include smoking, grilled meats, and cruciferous vegetables. The patient is not a smoker but please note that if she eats large quantities of the mentioned foods that her CYP1A2 function could be significantly increased.
CYP2B6:	The patient has two normal function alleles (*1) for CYP2B6. She is taking one weak inhibitor (clopidogrel) of CYP2B6 and no inducers of the enzyme. Overall enzyme function would be estimated to be very slightly reduced.
CYP2C9:	The patient has two normal function alleles (*1) for CYP2C9. She is taking six weak inhibitors (amlodipine, cholecalciferol, clopidogrel, ondansetron, valproic acid, valsartan) of CYP2C9 and no inducers of the enzyme. Overall enzyme function would be estimated to be slightly to moderately reduced.
CYP2C19:	The patient has one normal function allele (*1) and one nonfunctional allele (*2) for CYP2C19. She is taking one weak inhibitor (cholecalciferol) of CYP2C19 and one weak/moderate inducer (aspirin) of the enzyme. Overall enzyme function would be estimated to be moderately reduced.
CYP2D6:	The patient has one normal function allele (*1) and one nonfunctional allele (*6) for CYP2D6. She is taking one weak inhibitor (diphenhydramine (systemic)) of CYP2D6 and no inducers of the enzyme. Overall enzyme function would be estimated to be moderately reduced.
CYP3A4:	The patient has two normal function alleles (*1) for CYP3A4. She is taking two weak inhibitors (amlodipine, atorvastatin) of CYP3A4 and no inducers of the enzyme. Overall enzyme function would be estimated to be slightly reduced.
CYP3A5:	The patient has two nonfunctional alleles (*3) for CYP3A5. She is taking no inhibitors of CYP3A5 and no inducers of the enzyme. Overall enzyme function would be estimated to be negligible.
SLCO1B1:	The patient has two normal function alleles (*1A) for SLCO1B1. She is taking one uncategorized inhibitor (clopidogrel) of SLCO1B1 and no inducers of the transporter. Overall transporter function would be estimated to be very slightly reduced.
VKORC1:	The patient is heterozygous (A/G) for the -1639G>A polymorphism in the VKORC1 gene. This result suggests that she will exhibit intermediate sensitivity to warfarin.
COMT:	The patient is heterozygous (Val/Met) for the Val158Met polymorphism in the COMT gene. The Val allele

Sample report

Very limited evidence for efficacy/utility

	is associated with a higher pain threshold and the Met allele is associated with a lower pain threshold. This result suggests that she will have an average pain threshold and will likely require average doses of pain medications. She will also be more likely to have a typical response to certain stimulant medications.
OPRM1:	The patient is homozygous for the A allele for the 118A>G polymorphism in the OPRM1 gene. This result suggests that she would be expected to have normal analgesia with standard opioid doses.
SERT:	The patient is homozygous for the long (L) allele for SERT, the serotonin transporter gene. The long (L) allele has been associated with quicker responses, better responses, and fewer adverse effects with SSRI therapy.
ADRA2A:	The patient is homozygous for the C allele for the -1291G>C polymorphism in the ADRA2A gene. This result suggests that she could have a reduced response to certain ADHD medications.
MTHFR:	The patient is homozygous for the C allele for the 677C>T polymorphism in the MTHFR gene. This result suggests that she will likely have normal folic acid conversion, normal serum folate levels, and normal homocysteine levels.
HTR2A:	The patient is heterozygous reference/variant for HTR2A rs6311, rs6313, and rs6314 and homozygous for the reference allele for HTR2A rs1805055 and rs7997012. The result for HTR2A rs6311 indicates that she may experience an increase in certain adverse effects with escitalopram use, the result for HTR2A rs6314 suggests that she may respond better to clozapine therapy, and the HTR2A rs7997012 result implies that the patient may be less likely to respond to citalopram.

Limitations

Challenges of PGx Testing

- Limitations in the design of published pharmacogenetic studies (GWAS)
  - lack of RCT showing benefit of genotype-assisted dosing vs conventional dosing
- Regulatory and ethical concerns
- Limitations in changes of clinical outcomes
- Lack of cost effectiveness, insurance coverage?
- Limitations in available pharmacogenomic tests and lack of guidelines for test implementation
  - Pre-emptive vs Reactive testing
- A lack of education on the risks and benefits of pharmacogenomic testing, both for patients and providers
- Potential for delay in therapy while awaiting results of genotyping

FDA Statement and Warning

- **Lack of Evidence and Literature to Support**
  - Consult FDA Labelling and evidence-based references
- **Recommendations for Patients**
  - Avoid discontinuing medications
  - Consult a healthcare professional familiar with PGx
- **Recommendations for Providers**
  - Consider lack of evidence for DNA PGx polymorphisms and relationship to medication effects prior to testing
  - Direct to consumer tested patients provide education
  - Understand levels of evidence vs informative PGx

Questions