Center for Personalized Medicine
Pharmacogenomics
1000 Central Avenue Suite 620
Evanston, IL 60201
847.570.GENE

1/12/2017

Dear,

This letter is regarding your recent pharmacogenomic testing. Enclosed is a report containing your test results. To help you interpret the report please visit www.northshore.org/medcluerx-results where you will find an example report explained in detail. If, after reviewing the report, you determine that you need additional information or clarification please contact the ordering clinician or schedule an office visit to our specialty clinic with the pharmacogenomics team. During this visit you will have an opportunity to have your questions and concerns addressed. To schedule an appointment, please call 847.570.GENE (4363).

Sincerely,

Mark Dunnenberger
Program Director – Pharmacogenomics
NorthShore University HealthSystem

Enclosures (1)

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Evanston, IL 60201
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Pharmacogenomics Results -- *Summary Report*

Patient Name: First Last
Date of Birth: XX/XX/XXXX
Date of Reporting: 01/12/2017

What is this report and how should it be used in my care?

This report contains the clinical interpretation of your pharmacogenomics testing. A pharmacogenomics test was performed to investigate variations in genes associated with drug metabolizing enzymes, drug targets, and transporter proteins. The results of this test should be used as a supplement to the clinical decision making process and should not replace or override appropriate clinical judgment. Based on the results of your test and available literature, some medications may be categorized as either "Use with Caution" or "Avoid Use". The "Use with Caution" list contains medications to which you are more likely to respond sub-optimally than the average patient. In light of this, your provider may choose another available treatment option or may consider a dose adjustment. "Avoid Use" indicates that you have a significant increase in the incidence of side effects or treatment failure with these drugs. Since their usage may result in serious negative outcomes, the use of these medications should be reserved for cases of clinical necessity. However, there may be clinical situations where the use of drugs on either list are justified and necessary. Therefore, no changes to medication(s) should be made without first discussing them with the ordering clinician.

High Risk Medications

Drugs to avoid:

Drug name	Common uses
Codeine[1,a]	Pain Management
Tramadol[1,a]	Pain Management
Risperidone[2,a]	Psychiatry; Antipsychotic
Thioridazine[2,a]	Psychiatry; Antipsychotic
Venlafaxine[2,a]	Psychiatry; Depression
Tamoxifen[1,a]	Chemotherapy

[a]CYP2D6
[1]Increased risk of therapeutic failure
[2]Increased risk of adverse events

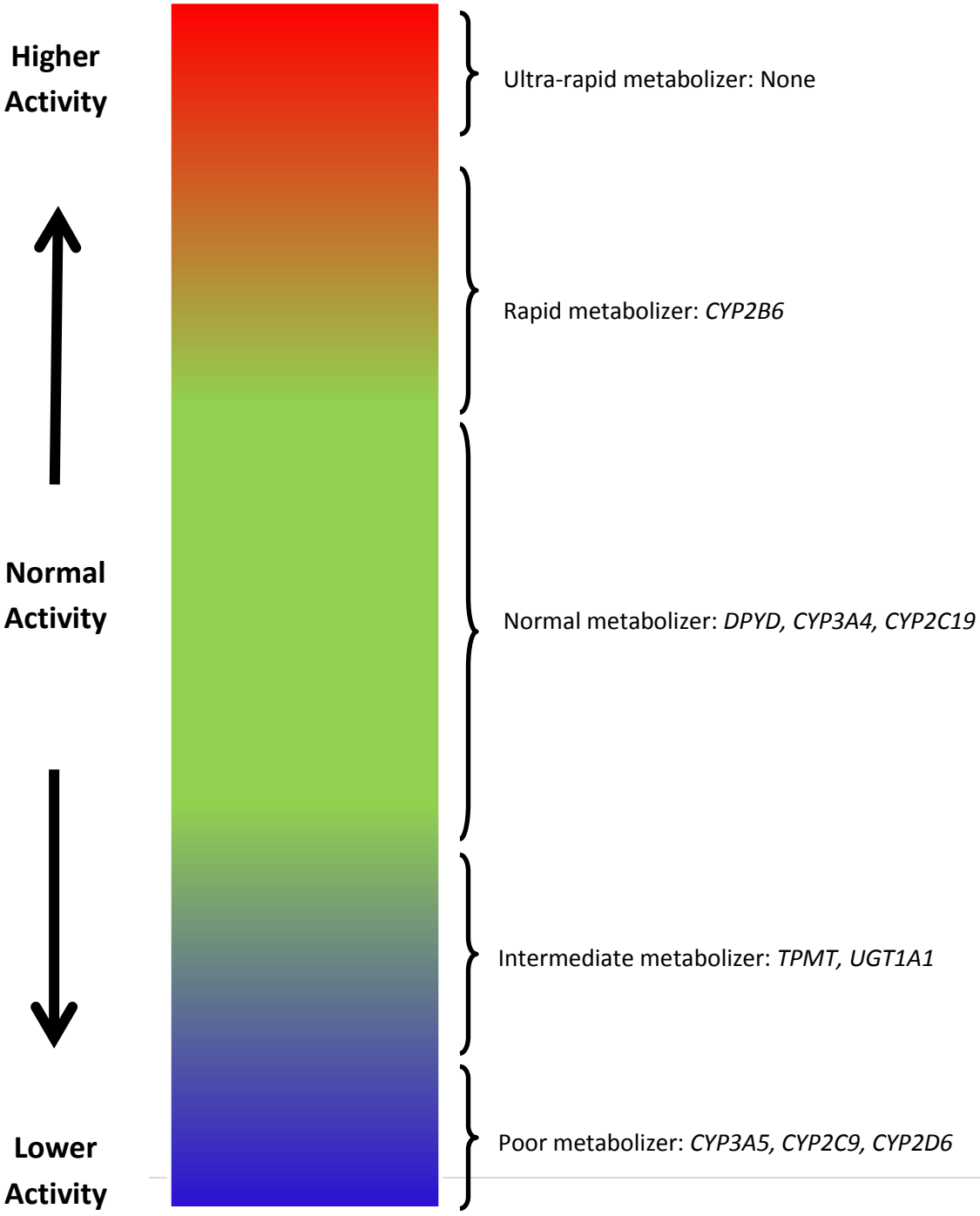
Drugs to use with caution or may need dose adjustments:

Drug name	Common uses
Oxycodone[1,a]	Pain Management
Hydrocodone[1,a]	Pain Management
Vortioxetine[3,a,b]	Psychiatry; Depression
Fluoxetine[3,b]	Psychiatry; Depression
Aripiprazole[2,a]	Psychiatry; Depression
Fluvoxamine[3,a,b]	Psychiatry; Depression
Paroxetine[3,a,b]	Psychiatry; Depression
Citalopram[3,b]	Psychiatry; Depression
Escitalopram[3,b]	Psychiatry; Depression
Sertraline[3,b]	Psychiatry; Depression
Haloperidol[2,a]	Psychiatry; Antipsychotic
Amitriptyline[2,a]	Psychiatry; Anxiety, Depression, Pain Management
Clomipramine[2,a]	Psychiatry; Anxiety, Depression, Pain Management
Trimipramine[2,a]	Psychiatry; Anxiety, Depression, Pain Management
Desipramine[2,a]	Psychiatry; Anxiety, Depression, Pain Management
Nortriptyline[2,a]	Psychiatry; Anxiety, Depression, Pain Management
Doxepin[2,a]	Psychiatry; Anxiety, Depression, Pain Management
Imipramine[2,a]	Psychiatry; Anxiety, Depression, Pain Management
Flecainide[2,a]	Cardiology; Antiarrhythmic
Propafenone[2,a]	Cardiology; Antiarrhythmic
Metoprolol[2,a]	Cardiology; High Blood Pressure
Phenytoin[2,c]	Neurology; Epilepsy
Warfarin[2,c,d]	Cardiology; Blood Thinner

[a]CYP2D6
[b]SLC6A4
[c]CYP2C9
[d]VKORC1
[1]Increased risk of therapeutic failure
[2]Increased risk of adverse events
[3]Increased risk of adverse events and therapeutic failure

Metabolizer Status

What is metabolizer status? For some drug metabolizing enzymes, patients can be grouped into phenotype categories based on predicted enzyme activity level. The following chart is a depiction of the enzyme activity scale and which category your specific enzymes belong. Drug-drug interactions and other clinical factors could change your enzyme activity and should be considered when making clinical therapeutic decisions.



Genotype Results

Gene: CYP2D6	Genotype: *4/*4	Phenotype: Poor Metabolizer
Interpretive comment: Based on the genotype result this patient is predicted to be a poor metabolizer of CYP2D6 substrates. This patient may be at risk for poor therapeutic response to medications that are activated by CYP2D6 and at risk for increased adverse effects from medications that are inactivated by CYP2D6.		

Gene: CYP2C9	Genotype: *1/*2	Phenotype: Intermediate Metabolizer
Interpretive comment: Based on the genotype result this patient is predicted to be an intermediate metabolizer of CYP2C9 substrates. This patient may be at an increased risk for toxicity from select medications that inhibit or are inactivated by CYP2C9.		

Gene: VKORC1	Genotype: rs9923231:C/T	Phenotype: Intermediate Warfarin Sensitivity
Interpretive comment: This individual is heterozygous for the A allele and G allele of the c.-1639G>A polymorphism for Vitamin K Epoxide Reductase Complex. This patient's CYP2C9 and VKORC1 genotypes are consistent with a starting maintenance warfarin dose of 3-4mg. Other clinical factors should be evaluated when determining a maintenance warfarin dose (e.g. age, gender, weight, and drug interactions). Consider using warfarindosing.org to aid in therapeutic decisions.		

Gene: SLC6A4	Genotype: S/S	Phenotype: Poor Responder
Interpretive comment: This patient has two copies of the Short S (S) allele of the serotonin transporter gene and may have an increased risk for drug-induced side effects or may be less likely to achieve remission of depression with selective serotonin reuptake inhibitors (SSRIs) compared to non-SSRIs.		

Gene: CYP2B6	Genotype: *1/*2	Phenotype: Normal Metabolizer
Interpretive comment: Based on the genotype result this patient is predicted to be a normal metabolizer of CYP2B6 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by CYP2B6.		

Gene: CYP2C19	Genotype: *1/*1	Phenotype: Normal Metabolizer
Interpretive comment: Based on the genotype result this patient is predicted to be a normal metabolizer of CYP2C19 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by CYP2C19.		

Gene: CYP3A4	Genotype: *1/*1	Phenotype: Normal Metabolizer
Interpretive comment: Based on the genotype result this patient is predicted to be a normal metabolizer of CYP3A4 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by CYP3A4.		

Gene: CYP3A5	Genotype: *3A/*3A	Phenotype: Poor Metabolizer
Interpretive comment: Based on the genotype result this patient is predicted to be a poor metabolizer of CYP3A5 substrates. This is consistent with the majority (60-80%) of the population. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by CYP3A5.		

Gene: DPYD	Genotype: *1/*1	Phenotype: Normal Metabolizer
Interpretive comment: Based on the genotype result this patient is predicted to be a normal metabolizer of DPYD substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by DPYD.		

Gene: TPMT	Genotype: *1/*1	Phenotype: Normal Metabolizer
Interpretive comment: Based on the genotype result this patient is predicted to be a normal metabolizer of TPMT substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by TPMT.		

Gene: UGT1A1	Genotype: *1/*1	Phenotype: Normal Metabolizer
Interpretive comment: Based on the genotype result this patient is predicted to be a normal metabolizer of UGT1A1 substrates. There is no reason to selectively adjust the dose of most medications that inhibit or are inactivated by UGT1A1.		

Gene: SLCO1B1	Genotype: *1/*1B	Phenotype: Normal Function
Interpretive comment: Based on the genotype result, this patient is predicted to have normal SLCO1B1 function. There is no reason to adjust the dose of most medications that are affected by SLCO1B1 (including simvastatin) on the basis of SLCO1B1 genetic status.		

Gene: COMT	Genotype: rs4680: A/G	Phenotype: Intermediate Activity
Interpretive comment: This individual is heterozygous for the A and G alleles of the c.472G>A polymorphism for COMT. This is consistent with intermediate COMT enzymatic activity. COMT is an enzyme that degrades dopamine and norepinephrine, primarily in the prefrontal cortex. The G allele has higher enzymatic activity resulting in higher dopamine degradation as compared to those carrying the A allele. The GA genotype results in intermediate COMT activity and dopamine levels, and patients with this genotype are more likely to respond to psychotropic medications than those with the GG genotype.		

Gene: F2	Genotype: rs1799963: G/G	Phenotype: Normal Thrombosis Risk
Interpretive comment: This patient's genotype revealed that the patient does not possess the c.*97G>A 3 prime UTR variant (formerly known as G20210A), which is consistent with no increase in genetic risk for thromboembolic events in patients taking oral contraceptives.		

Gene: F5	Genotype: rs6025: C/C	Phenotype: Normal Thrombosis Risk
Interpretive comment: This patient's genotype revealed that the patient does not possess the c.1601G>A variant, (formerly known as Leiden, G1691A or R506Q) which is consistent with no increase in genetic risk for thromboembolic events in patients taking oral contraceptives.		

Gene: HTR2A	Genotype: rs6311: C/T	Phenotype: Normal Sensitivity
Interpretive comment: This individual is heterozygous for the G allele and A allele of the c.-1437G>A polymorphism for the Serotonin Receptor Type 2A. This genotype is not predictive of adverse drug reactions with selective serotonin reuptake inhibitors.		

Gene: HTR2A	Genotype: rs6313: A/G	Phenotype: Normal Sensitivity
Interpretive comment: This individual is heterozygous for the T and C alleles of the c.102C>T polymorphism for the Serotonin Receptor Type 2A. This genotype is not predictive of adverse drug reactions with selective serotonin reuptake inhibitors.		

Gene: HTR2A	Genotype: rs6314: G/G	Phenotype: Normal Responder
Interpretive comment: This individual is homozygous for the C allele of the c.1354C>T polymorphism for the Serotonin Receptor Type 2A. This genotype is not predictive of an increase in therapeutic failure with selective serotonin reuptake inhibitors.		

Gene: HTR2A	Genotype: rs9316233: C/C	Phenotype: Normal Responder
Interpretive comment: This individual is homozygous for the C allele of the n.*2921C>G polymorphism for the Serotonin Receptor Type 2A. This genotype is not predictive of an increase in therapeutic failure with selective serotonin reuptake inhibitors.		

Gene: MTHFR	Genotype: rs1801131:G/T; rs1801133:G/A	Phenotype: Uncertain Significance
Interpretive comment: This patient has one copy of the C allele of c.665C>T, formerly referred to as 677C>T or "thermolabile" variant and one copy of the C allele of c.1286A>C, formerly referred to as 1298A>C. MTHFR polymorphisms are only one of many factors contributing to the overall clinical picture, the utility of MTHFR status testing is currently limited in terms of risk prediction.		

Gene: OPRM1	Genotype: rs1799971: A/A	Phenotype: Normal Opioid Responder
Interpretive comment: This individual is homozygous for the A allele of the c.397A>G polymorphism for the opioid receptor mu 1 and is consistent with the need for average doses of opioids to achieve the desired therapeutic effect at opioid initiation. The AA genotype is found in approximately 60% of Caucasians, 80% of African Americans, and 30% of Asians.		

Gene: TYMS	Genotype: rs2853539: A/A	Phenotype: Poor Responder
Interpretive comment: This individual is homozygous for the T allele of the c.-1582 T>C polymorphism for thymidylate synthase. Patients with the TT genotype and rheumatoid arthritis who are treated with methotrexate may be less likely to have improvement in disease activity compare to the average patient. The data for this relationship is of moderate quality.		

These results should always be interpreted in context with the clinical picture and all co-administered medications. The results should not be used as the sole means of treatment decision making and should be regarded as adjunctive to the overall patient management strategy. These genotyping results do not eliminate the necessity to account for non-genetic factors that can influence dose modifications for or responses to medications that are metabolized by these enzyme systems. Drug-drug and drug-gene interactions that lead to enzymatic inhibition or induction may lead to altered metabolism. This assay was designed utilizing a variety of laboratory methods. These include: PCR amplification with allele-specific hybridization, restriction fragment length polymorphism analysis, fragment analysis by capillary electrophoresis, and quantitative real-time PCR. This test was developed and its performance characteristics determined by the Molecular Diagnostics Laboratory, NorthShore University HealthSystem. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. When possible the results are reported as diplotypes using star allele nomenclature, otherwise the rsID and the nucleotide at that position in the positive DNA orientation of the genomic DNA is reported. This may differ from the orientation used in other representations of this variant which use the forward strand of the cDNA. The genotyping results have been reviewed and approved by the Clinical Laboratory Director. The star allele translation was determined by an internally developed translation table and reviewed by a committee of subject matter experts. The alleles interrogated in the assays are:

CYP2B6	*2, *5, *6,*7,*16,*22,*28, *34
CYP2C9	*2, *3, *4, *5, *7, *8, *9, *10, *11, *13, *16, *27
CYP2C19	*2A, *2B, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *13, *17
CYP3A4	*2, *3, *12, *13, *15, *17, *22
CYP2D6	*2, *2A, *3, *4, *5, *6, *7, *8, *10, *11, *12, *14, *17, *20, *29, *35, *35A, *41, *91, duplication
CYP3A5	*2, *3A, *3B, *3C, *3K, *6, *7, *8, *9
DPYD	*2, *9A, *9B, *10, *13, rs67376798
SLCO1B1	*5, *15, *17,*21
TPMT	*2, *3A, *3B, *3C, *4
UGT1A1	*6, *28, *36, *37
SLC6A4	LA, LG, S
COMT	rs4680
F2	rs1799963

F5	rs6025
HTR2A	rs6313, rs6311, rs6314, rs9316233
MTHFR	rs1801131, rs1801133
OPRM1	rs1799971
TYMS	rs2853539
VKORC1	rs9923231

For additional questions or information please call the Pharmacogenomics Clinic at 847.570.GENE.

Thank you

Henry Dunnenberger, Pharm.D.