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PGX Antidepressant (*CYP2C19* and *CYP2D6*) Genotyping

For detection of CYP2D6 and *CYP2C19 variants affecting antidepressant metabolism*

Clinical Background

- *CYP2D6* is an isoenzyme of the *CYP450* superfamily that metabolizes and eliminates common prescription drugs, including amitriptyline, atomoxetine, codeine, nortriptyline, doxepin, paroxetine, clozapine, olanzapine, risperidone, and carvediol.
- *CYP2D6* is responsible for the metabolism and elimination of approximately 25% of clinically used drugs.
- *CYP2C19* is an isoenzyme of the *CYP450* superfamily that metabolizes and eliminates common prescription drugs, including anti-convulsants, anti-depressants, proton pump inhibitors, and antithrombotics (clopidogrel/Plavix®), as well as anti-malaria and anti-ulcer drugs.
- Metabolizer phenotypes can be predicted by the genotype
- The clinical impact of the genotype is influenced by whether a drug is activated or inactivated, involvement of other metabolic pathways, and other non-genetic factors (e.g., other medications).
- The following medications are impacted by *CYP2D6* and/or *CYP2C19:*

TCAs

amitriptyline (Elavil and Endep are discontinued brands in the US)
Clomipramine (Anafranil)
desipramine (Norpramin)
doxepin (Sinequan and Adapin are discontinued brands in the US)
imipramine (Tofranil)
nortriptyline (Pamelor; Aventyl is a discontinued brand in the US)
trimipramine (Surmontil)

SNRIs

Venlafaxine (Effexor)
Desvenlafaxine (Pristiq, Khedezla)

SSRIs
citalopram (Celexa)
escitalopram (Lexapro)
fluvoxamine (Luvox)
paroxetine (Paxil, Paxil CR, Pexeva)
sertraline (Zoloft)
vortioxetine (Trintellix, formerly known as Brintellix)

Epidemiology

- *CYP2D6* and *CYP2C19* variant frequency is ethnicity dependent.
- The poor metabolizer phenotype (caused by two non-functional *CYP2D6* alleles) is present in approximately 10% Caucasians; sensitivity is unknown in other ethnicities.
- The poor metabolizer phenotype (caused by two non-functional *CYP2C19* alleles) is present in 4% of Caucasians, 5% of African Americans, and up to 25% of Asians.

Genetics

- The *CYP2D6* gene has nine exons and is located on chromosome 22q13.1
- The *CYP2C19* gene has nine exons and is located on chromosome 10q23.33.
- Inheritance is autosomal recessive.
- Penetrance is drug-dependent.

Indications for Ordering

- Pre-therapeutic testing to identify individuals who should avoid, or may require unconventional doses, of medications metabolized by *CYP2D6* and/or *CYP2C19*.

Interpretation

- If no variants are detected, this suggests *1 allele and normal enzymatic activity.
- If one decreased functional or non-functional variant is detected, intermediate-to-normal enzymatic activity is predicted.
- If two non-functional variants are present on opposite allele, this predicts low enzymatic activity and a poor metabolizer phenotype.
- If more than two functional copies are present, this predicts high enzymatic activity and an ultra-rapid metabolizer phenotype.
- Genotype results should be interpreted in context of the individual clinical situation. Consultation with a clinical pharmacy professional is recommended.

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Methodology

- Realtime Polymerase chain reaction (PCR) and microarray and copy number analysis

Variants in *CYP2D6* and *CYP2C19* Assay

Allele	variant	dbSNP	Predicted enzyme activity
*1	Assumed when no variant detected		normal
CYP2D6*2	2851C>T, 4181G>C	rs16947 rs1135840	Normal function
CYP2D6*3	2550delA	rs35742686	No function
CYP2D6*4	1847G>A, 100C>T	rs3892097 rs1065852	No function
CYP2D6*5	CYP2D6 deleted		No function
CYP2D6*6	1707delT	rs5030655	No function
CYP2D6*7	2936A>C	rs5030867	No function
CYP2D6*8	1759G>T	rs5030865	No function
CYP2D6*9	2615delAAG	rs5030656	Decreased function
CYP2D6*10	100C>T, 4181G>C	rs1065852 rs1135840	Decreased function
CYP2D6*17	1022C>T, 2851C>T	rs28371706 rs16947	Decreased function
CYP2D6*29	1660G>A 2851C>T, 3184G>A, 4181G>C	rs61736512 rs16947 rs59421388 rs1135840	Decreased function

CYP2D6*41	2989G>A 2851C>T, 4181G>C	rs28371725 rs16947 rs1135840	Decreased function
CYP2D6*1XN	Duplication		Increased function
CYP2D6*2XN	Duplication		Increased function
CYP2D6*4XN	Duplication		No function
CYP2D6*6XN	Duplication		No function
CYP2D6*9XN	Duplication		Normal function
CYP2D6*17XN	Duplication		Normal function
CYP2D6*29XN	Duplication		Normal function
CYP2D6*41XN	Duplication		Normal function
CYP2C19*1	Assumed when no variant detected		Normal function
CYP2C19*2	c.681G>A	rs4244285	No function
CYP2C19*3	c.636G>A	rs4986893	No function
CYP2C19*4	c.1A>G	rs28399504	No function
CYP2C19*6	c.395G>A	rs72552267	No function
CYP2C19*8	c.358T>C	rs41291556	No function
CYP2C19*17 (also *4 haplotype [*4B])	c.-806C>T	rs12248560	Increased function