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Focus Pharmacogenomics and Precision Medicine

- by Allen Lefkovitz

Precision medicine (previously referred to as "personalized medicine") is defined by the National Institutes of Health (NIH) as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." The NIH likewise defines pharmacogenomics (PG) as "the study of how genes affect a person's response to particular drugs." Described as a combination of pharmacology and genetics, the goal of PG is to help develop "effective, safe medications and doses that are tailored to variations in a person's genes."

Even though genetic testing is not widespread in long-term care, some clinicians have obtained pharmacogenetic testing in an attempt to guide their disease state management and to provide more patient-centered care. The information obtained through testing can be complex and often requires detailed interpretation by a trained professional for the best outcomes. While avoiding ineffective therapies or selecting lower risk therapies is appealing, confusion about the application and limitation of PG may sometimes result in data being misinterpreted or over-interpreted, which could potentially result in unnecessary costs and changes in therapy.

On November 1, 2018, the U.S. Food and Drug Administration (FDA) issued a warning to consumers and health care professionals regarding genetic tests that claim to predict an individual's response to specific medications. Various genetic tests have been available from certain laboratories for many years, but in April 2017 the FDA also began approving direct-to-consumer tests that provide information on an individual's genetic predisposition toward certain medical conditions (e.g., Alzheimer's disease, Parkinson's disease, Celiac disease).

Within their recent warning, the FDA stated that based upon test results, some health care providers and some direct-to-consumer tests have made **inappropriate** claims about:

- how an individual will respond to medications used to treat certain conditions (e.g., depression, heart conditions, acid reflux)
- medications that may be less effective or have increased side effects
- suggested changes in therapy

The FDA recommends that healthcare professionals review the FDA-approved drug label and/or the FDA-approved genetic test information to see if genetic information should be used to determine treatment decisions, as FDA-approval of a test does not imply specific treatment guidance. However, the FDA also reminded everyone that there are "a limited number of cases for which at least some evidence does exist to support a correlation between a genetic variant and drug levels within the body".

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The FDA maintains a table of drugs that have labeling that include pharmacogenomics biomarkers at www.fda.gov/Drugs/ScienceResearch/ucm572698.htm. Although it is becoming more common (especially with medications used to treat various cancers), currently, just over 200 medications have any evidence-based guidance included in their FDA-approved labeling. When PG-related guidance is accepted by the FDA, this information may be included in one or more sections of the FDA-approved labeling (available at: https://dailymed.nlm.nih.gov/), including but not limited to the following sections:

Boxed Warning	Warnings	Precautions	Indications and Usage	Use in Specific Populations

Because it may be challenging to locate this information, the FDA also maintains an even more comprehensive guidance table of drugs (currently spanning 111 pages) available at: www.fda.gov/downloads/Drugs/ScienceResearch/UCM578588.pdf.

While some PG-related language in FDA-approved labeling may conclude that no special considerations are needed, other FDA-approved language may include specific guidance about:

- genetic markers that need to be identified for use of a drug (e.g., being Philadelphia chromosome positive or HER-2 negative for various chemotherapy regimens)
- use being contraindicated [e.g., quinine sulfate in someone who has Glucose-6-phosphate dehydrogenase (G6PD) deficiency]
- combinations of drugs that result in a greater risk of a drug-interaction (e.g., metoprolol with a CYP2D6 inhibitor such as paroxetine in someone who is a CYP2D6 poor metabolizer may triple the drug concentration of metoprolol)
- increasing or decreasing a dose (e.g., dosage reductions needed for select antipsychotics including aripiprazole, brexpiprazole, and clozapine)
- a lower maximum dose (e.g., a maximum dose of citalopram 20 mg for someone who is a CYP2C19 poor metabolizer)
- an increased risk of serious side effects (e.g., Stevens-Johnson syndrome with carbamazepine)
- reduced effectiveness (e.g., clopidogrel in someone who is a CYP2C19 poor metabolizer, dextromethorphan/quinidine in someone who is a CYP2D6 poor metabolizer)

CYP = cytochrome P450 enzyme system involved with the metabolism of many drugs; more commonly discussed families of P450 genes include 2C19, 2D6, and 3A4.
HER-2 = human epidermal growth factor receptor 2, which may play a role in the development of breast cancer

In addition to the FDA, the international Clinical Pharmacogenetics Implementation Consortium (CPIC) provides genetic-related clinical practice guidelines for various drugs including:

- Allopurinol
- Carbamazepine
- Clopidogrel
- Ondansetron
- Paroxetine
- Phenytoin
- Sertraline
- Simvastatin
- Tricyclic Antidepressants (e.g., amitriptyline, nortriptyline)
- Warfarin

Additional information on the warning from the FDA is available at: www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm624725.htm.

Please refer to the following resources for additional information related to the topic of PG and precision medicine:

- Genetics Home Reference: https://ghr.nlm.nih.gov/
- The Clinical Pharmacogenetics Implementation Consortium (CPIC): https://cpicpgx.org/
- Cleared or Approved Companion Diagnostic Devices (FDA): www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm
- Direct-to-Consumer Testing (FDA): www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm624726.htm

While PG research continues to increase, the value of widespread pharmacogenetic testing remains unproven in the long-term care population.

NEW Generic Medications

- by Allen Lefkovitz

Generic Name	Brand Name	Date Generic Available
Vardenafil 2.5 mg, 5 mg, 10 mg, and 20 mg Tablet	Levitra® Tablet	11/2/18
Estradiol 0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, and 0.1 mg Transdermal System	Minivelle® Transdermal	11/1/18
Clobazam 10 mg and 20 mg Tablet	Onfi® Tablet	10/26/18
Clobazam 2.5 mg/mL Oral Suspension	Onfi® Oral Suspension	10/26/18
Testosterone 20.25 mg/1.25 g Topical Gel	AndroGel® Gel	10/12/18

NEW Drug

Xofluza™ Tablets

- by Dave Pregizer

Brand Name (Generic Name)	**Xofluza [zoh-FLEW-zuh] (baloxavir marboxil) [ba-LOX-A-veer mar-BOX-el]**
How Supplied	20 mg and 40 mg tablets
Therapeutic Class	Antiviral - Polymerase acidic (PA) endonuclease inhibitor
Approved Indication	Treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. Clinical trials for approval did not include those 65 years and older. Xofluza is NOT approved for prophylaxis.
Usual Dosing	One dose orally within 48 hours of onset of symptoms, with or without food. Dosing is weight-based: 40 kg to < 80 kg = a single dose of 40 mg; ≥ 80 kg = a single dose of 80 mg.
Select Drug Interactions	Polyvalent cation-containing products (e.g., calcium, iron, magnesium) may decrease absorption of baloxavir thereby reducing efficacy. May inhibit viral replication of live attenuated influenza vaccines decreasing the effectiveness of vaccination.
Most Common Side Effects	Diarrhea, bronchitis, nasopharyngitis, headache, and nausea
Miscellaneous	Avoid co-administration with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, zinc).
Website	https://www.xofluza.com/

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