Personalized Medicine and Psychiatry: Dream or Reality?

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This article explores the current state of knowledge regarding personalized medicine in psychiatry and discusses how the tools might be used to help psychiatrists understand the components of their patients’ unique endophenotypic profiles.

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Article Goal
The goal of this activity is to present information on personalized medicine and how it may be used to guide the decision making process in psychiatry.

Learning Objectives
At the end of this article, readers should be able to:
1. Identify the factors that make up a patient’s physiological psychiatric profile.
2. Recognize the role of genetics, environment, and epigenetics in personal medicine.
3. Describe how clinical phenotype can be used to more clearly identify a diagnosis.

Target Audience
This continuing medical education activity is intended for psychiatrists, psychologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals who seek to improve their care for patients with mental health disorders.

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Dr Nemeroff is a consultant for Xhale, Takeda, SK Pharma, Lundbeck, Shire, Roche, Eli Lilly, and Allergan; has received grant/support from the National Institutes of Health, Agency for Healthcare Research and Quality; is a stock shareholder of CeNeRx BioPharma, PharmaNeuro Boost, Reevax Pharma, Xhale, and NovaDel Pharma; is or has been on the Board of Directors of American Foundation for Suicide Prevention (AFSP), Mt Cook Pharma (2010), NovaDel Pharma (2011), Skyland Trail, Gratitude America, and Anxiety and Depression Association of America (ADAA); sat on the Scientific Advisory Board for AFSP, CeNeRx BioPharma, National Alliance for Research on...
Schizophrenia and Depression, Xhale, PharmaNeuroBoost, ADAA, Skyland Trail, and AstraZeneca Pharmaceuticals (2009); holds a patent for method and devices for transdermal delivery of lithium (US 6,375,990B1) and for a method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2); and has equity or other financial interests in AstraZeneca Pharmaceuticals, PharmaNeuroBoost, CeNeRx BioPharma, NovaDel Pharma, Reevax Pharma, American Psychiatric Publishing, and Xhale.

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Dream or reality: to be fair, personalized medicine in psychiatry in its current state is best described as a dream not yet realized. We’re closer than ever before, although to say there are many examples of personalized medicine in psychiatry would be an overstatement. However, we are at an exciting time, when a paradigm shift is occurring: we can begin to factor in data beyond the constellation of symptoms described or exhibited by our patient, and make better educated decisions for his or her clinical care. In fact, the reservoir from which we draw our patient information is growing exponentially—from the traditional self-report to genetics, neuroimaging, and environmental exposures. In the challenging field of psychiatry, we are not yet at the same level of understanding as in, notably, oncology, where there are highly personalized treatments based on molecular diagnostic testing.

This article explores the current state of knowledge regarding personalized medicine in psychiatry and discusses how the tools might be used to help psychiatrists understand the components of their patients’ unique endophenotypic profiles. How psychiatrists can leverage neuroimaging and genetics to personalize their patients’ care is also discussed.

Personalized medicine and what it means for psychiatry
Personalized medicine centers on the principle that by integrating data from a person’s genetic makeup, epigenetic modifications, clinical symptoms, biomarker changes, and environmental exposures, we can achieve greater accuracy in diagnosis, prediction of disease susceptibility, and ultimately, therapy targeted to the individual.

Personalized medicine is certainly not a new concept, although it has been considerably more visible since the completion of the Human Genome Project and associated efforts. Personalization of medicine is best exemplified in oncology, which, for example, has had successes with the selective use of genetic testing of breast cancer susceptibility genes (BRCA 1, BRCA 2) to guide the clinical decision-making process.1

Few examples of personalized medicine exist in psychiatry, because of a host of factors, such as complicated inheritance patterns, reliance on subjective self-report, and clinical heterogeneity of disease. However, the potential for personalized medicine to revolutionize psychiatry is quite pronounced. As an example, consider MDD: more than 10% of the population older than 12 years report taking antidepressants, and remission rates achieved with current antidepressants are unacceptably low, while the morbidity and mortality of poor treatment or no treatment are exceedingly high.2-4 Even a small improvement in the odds of remission would likely have a large public health benefit, improve patient outcomes, reduce suicide rates, and increase treatment compliance and patient and physician satisfaction.

Interpreting a patient’s physiological psychiatric profile
An initial challenge in personalized medicine in psychiatry is identifying useful information. One way of conceptualizing the patient for whom individualized care is needed is to acknowledge that each person has a unique phenotypic profile capable of informing clinical decisions. Some proposed categories include genetics, epigenetics, environment, biomarkers, and clinical phenotype. Each
category has the propensity to help zero in on the ideal care for the patient, although the greatest benefits will surely be achieved when factoring in components from multiple categories.  

**Genetics**  
One expectation of personalized medicine is that susceptibility or protective factors mediated by genetic change can be determined. Other expectations are that genetic data can guide drug development and that treatment outcome can be predicted. It is important to note that even in the era of genome-wide association studies, the majority of these replicable genetic findings do not pinpoint the common genes that underlie disease; instead, our understanding centers around rare genetic variants that account for relatively small percentages of heritability. Nonetheless, certain influential findings deepen our understanding of major psychiatric illnesses and have introduced possibilities for predicting susceptibilities and targeting therapy via pharmacogenomics.

For example, ethnic differences in the alcohol dehydrogenase (ADH) and the mitochondrial aldehyde dehydrogenase (ALDH2) enzymes may underlie susceptibility to alcohol dependence. The ADH enzyme is encoded by a polygene family that includes ADH1B. The typical ADH1B isoform is found in approximately 95% of whites, while the atypical ADH1B isoform is found in 90% of Pacific Rim Asian ethnic groups, and it demonstrates much more rapid alcohol metabolism than the typical isoform. A similar relationship exists for ALDH2: ALDH2 has predominantly 2 major isozymes, one that is common in many ethnic groups (ALDH2*1), and the other (ALDH2*2) that is catalytically inactive and more prevalent in Pacific Rim Asians. Both isozymes that are more common in Asians, atypical ADH1B and ALDH2*2, have been associated with acute alcohol sensitivity and with protection against alcoholism. The ALDH2*1 isozyme, on the other hand, is more common in non-Asian populations and has a demonstrated association with alcoholism.  

**Environmental exposures and epigenetics**  
Some environmental exposures have been associated with psychiatric disease; for example, there is an 8-fold increase in the risk of schizophrenia in children whose mothers were diabetic during pregnancy. Environmental exposures likely underlie the perplexing finding that monozygotic twins are concordant for schizophrenia in only 45% of cases despite having identical DNA. Stress, especially early life trauma (child abuse and neglect), represents another environmental exposure linked to many psychiatric illnesses, most notably, mood disorders.

Epigenetics refers to gene regulation changes caused by mechanisms that do not involve nucleotide sequence modification. In many instances, epigenetic modifications have been demonstrated to occur after stress exposure.

**CASE VIGNETTE**

Jeremy is a 65-year-old man with chronic depression who, after years of being lost to follow-up, comes to the office for an initial psychiatric evaluation. A dozen trials with various antidepressants have failed. He reveals that his father died when he was 11 years old, and his mother remarried 2 years later. Jeremy suffered extensive physical abuse at the hands of his stepfather. He eventually dropped out of school and moved out at age 16.

Jeremy and his psychiatrist decided to change the treatment approach to a cognitively based analysis system of psychotherapy, consisting of elements from both interpersonal therapy and cognitive-behavioral therapy. Within 6 months, Jeremy’s depressive symptoms were in remission. There is evidence of differential responses to antidepressant therapy and psychotherapy, which is contingent on the presence or absence of early life trauma. Patients who had experienced early life trauma responded significantly better to psychotherapy than to pharmacotherapy, while patients without early life trauma responded better to pharmacotherapy. An especially pronounced positive psychotherapy response rate was seen for patients who had experienced parental loss at a young age. Incorporating this environmental exposure into Jeremy’s therapeutic plan helped achieve remission when previous interventions had failed.

**Biomarkers and clinical phenotype**  
Biomarkers are characteristics that reflect biological function or dysfunction, response to a therapeutic measure, or indication of the natural progression of disease. Clinical phenotypes or endophenotypes are similar to biomarkers, but they do not require clinical manifestation of the disorder. These become most relevant when considering a patient who may not neatly fit into a diagnostic category. Grouping patients on the basis of heritable, consistent, clinical characteristics without regard to their strict nosological clinical diagnosis has the potential to broaden our clinical definition for certain illnesses and in some ways may be more likely to reflect a shared biological underpinning.

Electroencephalography is one modality that provides a reliable biomarker for characterizing
epilepsy, and it has also been proposed to generate reliable biomarkers of psychiatric pathology. In fact, electroencephalographic (EEG) measures provided the foundation for the first FDA-approved medical device based on brain function to assess ADHD. Similarly, EEGs of patients with schizophrenia show consistent, replicable diminished amplitude of the P300 component of event-related potentials. Moreover, Mathalon and colleagues suggest that the characteristic reduction in event-related potentials amplitude can be used to differentiate schizophrenia from schizoaffective disorder.

One of the most rapidly developing subset of biomarkers leverages neuroimaging to develop quantitative biological phenotypes capable of characterizing or differentiating between psychiatric illnesses (Table). Some researchers are moving beyond merely characterizing psychiatric disease using neuroimaging, to monitoring the progression of treatment of such disease.

If we build in another layer of complexity by adding genetics to the equation, the burgeoning field of neuroimaging genetics is launched. This field harnesses genetics, psychiatry, and neuroscience to relate genetic variation to brain structure, function, and connectivity. The field is in a position to conduct experiments relating genetic profiles to outcomes of measurable, repeatable tests of brain structure and function. One example demonstrates the association between smaller hippocampal volumes and polymorphisms in the 5-HTT and BDNF genes.

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Technique</th>
<th>Pros</th>
<th>Cons</th>
<th>Primary use</th>
<th>Examples of psychiatric use</th>
</tr>
</thead>
<tbody>
<tr>
<td>General radiography</td>
<td>Passes electromagnetic radiation (x-ray) through body, which either is absorbed by dense objects (e.g., bone) or passes through to a detector on the other side of the body, creating an image</td>
<td>Rapid, inexpensive, noninvasive</td>
<td>Limited use in psychiatry, minor radiation exposure</td>
<td>Diagnostic</td>
<td>Limited; gross abnormality or organic lesion detection, largely replaced by CT</td>
</tr>
<tr>
<td>CT</td>
<td>Passes x-rays through the body while the x-ray detector on the other side of the body creates an image</td>
<td>Rapid, noninvasive</td>
<td>Radiation exposure</td>
<td>Diagnostic, morphology</td>
<td>Evaluate for organic cause of illness, characteristic disrupted morphology in disease states</td>
</tr>
<tr>
<td>MRI</td>
<td>Uses magnetic field and radio waves to create images of variable aligned and imaged hydrogen ions in the tissue</td>
<td>Noninvasive, precise, no radiation</td>
<td>Expensive, cannot use in some patients with metal biomedical implants or claustrophobia</td>
<td>Diagnostic, neuroanatomical activity</td>
<td>Evaluate location and strength of neurological activation in response to a task or treatment</td>
</tr>
<tr>
<td>fMRI</td>
<td>Tracks blood flow and oxygen levels, which approximate neuronal activity; often superimposed on structural MRI slices for orientation; can be linked in time with EEG</td>
<td>Noninvasive; no radiation, injections, or oral agents required</td>
<td>Blood flow/oxygen levels dependent on neurotransmitter response; results in temporal delay between stimulus and output</td>
<td>Diagnostic, neuronal connectivity</td>
<td>Characterize white matter tract disorganization in disease states</td>
</tr>
<tr>
<td>DTI</td>
<td>Tracks water movement along neural pathways as proxy for neuronal activity; simultaneously captures density of neuronal tracts along which the water is moving</td>
<td>Noninvasive; no radiation, injections, or oral agents required</td>
<td>Interpretation can be complex, especially in heterogeneous fiber distributions</td>
<td>Diagnostic, neuronal tract connectivity</td>
<td>Characterize white matter tract disorganization in disease states</td>
</tr>
<tr>
<td>PET/PECT</td>
<td>Uses radiolabeled agents to image selective regions of the brain or functional activity</td>
<td>Molecular changes visible in real time</td>
<td>Radioactive substance, motion, minor radiation exposure</td>
<td>Diagnostic areas of biochemical activation</td>
<td>Evaluate specific neurotransmitter receptor binding density before and after therapy</td>
</tr>
<tr>
<td>fMRI/ERP</td>
<td>Measures electrical brain wave activity in outer layer of brain in real time; can be used in combination with fMRI/ERP</td>
<td>Noninvasive, portable</td>
<td>Limited by spectral resolution</td>
<td>Diagnostic, regional metabolic, functional activity</td>
<td>Evaluate neural metabolism and nucleotide synthesis</td>
</tr>
<tr>
<td>EEG</td>
<td>Measures electrical brain wave activity in outer layer of brain in real time; can be used in combination with fMRI/ERP</td>
<td>Noninvasive, portable</td>
<td>Limited by spectral resolution</td>
<td>Diagnostic, regional metabolic, functional activity</td>
<td>Evaluate neural metabolism and nucleotide synthesis</td>
</tr>
<tr>
<td>MEG</td>
<td>Measures magnetic fields created by brain waves</td>
<td>Noninvasive</td>
<td>Limited by spectral resolution</td>
<td>Diagnostic, regional metabolic, functional activity</td>
<td>Evaluate neural metabolism and nucleotide synthesis</td>
</tr>
</tbody>
</table>

**Table: Neuroimaging techniques in psychiatry**

**The future of personalized medicine in psychiatry**

Psychiatry has long been plagued by unacceptably low response rates to available treatments—both psychotherapeutic and pharmacological interventions—because trial and error often drive the decision-making process. Having tools that aid the psychiatrist in identifying which patients are likely to respond to a particular treatment will surely improve patient outcomes and satisfaction. Although personalized medicine in psychiatry has progressed rapidly in the past decade, most of the findings are not ready for clinical application. Personalized medicine encourages clinicians to use all of the data at their disposal to provide the most effective care. Continued progress can be expected concomitant with our increasing comprehension and applicability of data and with studies that replicate and validate original findings.

**What to do when a patient asks about personalized medicine**
You may have a patient who asks, for example, “I heard that there is a new test for figuring out if a person has ADHD. Do you think I should take it?”

Keep in mind that such diagnostic tools are an adjunct to—and not a replacement for—sound clinical judgment. Ask yourself the following questions: Is this test appropriate for the patient? Is this likely to change the clinical management of the patient? If the answer to either of these questions is no, then there is no need to do the test—you would be doing a disservice to your patient. However, you could use these types of patient inquiries to fuel continuous learning during your practice. Also, you might encourage appropriate patients to enroll in clinical trials that are validating useful methods for personalization of psychiatric health care.18

Disclosures:

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