Psychiatric Pharmacogenomics: How to Integrate into Clinical Practice

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Pharmacogenomic testing can be integrated into modern mental health practices to help select psychotropic drugs for individuals who have failed first-line evidence-based treatments. This can be done by the process of “equipoise”—namely, balancing the weight of all available evidence. That evidence now includes not only diagnosis-specific treatment guidelines and “personalized” patient information, such as an individual’s specific symptom profile, past response to medications, side effects, family history, and patient preference, but also “precision medicine,” which incorporates the ever-expanding base of pharmacogenomic evidence for how an individual’s own biomarkers alter the odds for that individual’s treatment response or treatment intolerance.

Introduction

Psychiatric pharmacogenomics and biomarkers are on the cutting edge between research and clinical practice, where the action can be quite turbulent and even controversial.1–13 Payors who do not want to reimburse useful if expensive tests are accused of being greedy or Luddites; laboratories are accused of profiting from tests that do not alter clinical practice or patient outcomes; clinicians are accused of over-interpreting test results. So, what is the truth? Should we just stick with the classical model of mental health practice (Table I)? Maybe the truth is actually a bit of all the above. Here we will take a quick inventory of the state of the art of “precision medicine” for mental health practices.

Genomics to Diagnose?

Currently, it is not at all clear what role genomics and biomarkers have in the diagnosis of mental illnesses, or in risk for mental illnesses.4,11,13 Application of new tests for clinical diagnoses of mental illnesses is proving problematic, not least because diagnosis in mental health is undergoing a paradigm shift from categorical...
since genes do not code for psychiatric disorders, nor for any drug response to psychiatric disorders.

Prescribers do.

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Genes code for proteins and epigenetic factors, many of which regulate the efficiency of information processing in brain circuits, which can be visualized with neuroimaging techniques.

Psychiatric research is attempting to link treatment response to neuronal circuits upstream and to numerous regulatory genes downstream.

Pharmacogenomic testing adds to the balance of the evidence of what to do, and the data behind each test is ever-evolving although the genetic test results themselves will never change.

Genomics for Initial Drug Selection?

Much of the effort in the development of biomarkers has been dedicated to finding tests that would tell us what drug to prescribe or what drug not to prescribe, in order to find a drug with efficacy but not side effects for an individual patient. So, where are we in the process of integrating such “precision medicine” into drug selection in mental health practices? One thing is already clear from pharmacogenomics in psychiatry: Tests do not select drugs. Prescribers do.

That is, it is highly unlikely that any single test will ever dictate what drug to prescribe or not to prescribe in most cases. There is no known single gene for any major psychiatric disorder nor for any drug response to a psychiatric disorder, nor is one ever likely to be found, since genes do not code for psychiatric disorders, nor for psychiatric symptoms, nor for drug responses to psychiatric symptoms (Table 2). Instead, genes code for proteins and epigenetic factors that regulate the efficiency of information processing in brain circuits, and that can be increasingly visualized with neuroimaging techniques.

Rather than looking for a single gene that regulates drug response, psychiatric research is instead currently attempting to link treatment response to a portfolio of genes that regulate brain circuits that are the substrates of various psychiatric symptoms (Table 2). Such a portfolio of biomarkers will hopefully show which drugs will be somewhat more likely to work or to cause a side effect in a given patient. Right now, however, it is not clear that the available genomic tests add substantial value proportionate to their cost for selection of first-line treatments of mental disorders. For selection of a first-line therapy, current treatment guidelines alone may be most cost effective. If there is a place for current pharmacogenomic testing, it may be in the selection of drugs for patients who are treatment-resistant or treatment-intolerant to trials of evidence-based therapies (Tables 3 and 4), particularly when these test results are augmented with therapeutic drug-level monitoring combined with classical approaches to selecting treatments (Table 1).
who has failed to tolerate or respond adequately to numerous evidence-based treatments. Because large, randomized, controlled trials or all these approaches have failed, A dozen or two well-studied single nucleotide polymorphisms (SNPs) associated with drug response, Some highly replicated, others not, Each individual SNP has effects that are only weak/small in determining overall treatment response, Most are neurobiologically plausible, Danger of “over-interpretation” by patients or eager/unsophisticated clinicians, Orients the advanced prescriber for treatment-resistant cases toward recent data organized along a neurobiological perspective, Useful in developing rational hypotheses for novel treatments or combinations in individual patients who are resistant to multiple agents, Gives hope to patients, enhances optimism and motivation of prescribing clinicians, and provides a scientific basis (if weak and evolving) to selection of agents in the absence of controlled trials.

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Table 3. Pharmacogenomic testing in modern psychiatric practice

- A strategy to use when there is no evidence from large, randomized, controlled trials or all these approaches have failed
- A dozen or two well-studied single nucleotide polymorphisms (SNPs) associated with drug response
- Some highly replicated, others not
- Each individual SNP has effects that are only weak/small in determining overall treatment response
- Most are neurobiologically plausible
- Danger of “over-interpretation” by patients or eager/unsophisticated clinicians
- Orients the advanced prescriber for treatment-resistant cases toward recent data organized along a neurobiological perspective
- Useful in developing rational hypotheses for novel treatments or combinations in individual patients who are resistant to multiple agents
- Gives hope to patients, enhances optimism and motivation of prescribing clinicians, and provides a scientific basis (if weak and evolving) to selection of agents in the absence of controlled trials

Table 4. Proposal for a modern model of psychiatric practice for treatment resistance

- Exhaust evidence-based solutions.
- Think.
- Take another history, including from a new informant.
- Reconsider the diagnosis.
- Eg, TRD may be bipolar, mixed features, pseudobulbar affect, dementia, etc.
- Collect new data, including therapeutic drug levels and available pharmacogenomic markers.
- Use this new information to rebalance the evidence (equipoise) and come up with a genetically informed, neurobiologically empowered, data-oriented, novel, and rational treatment or combination.

It’s the Strategy, Not the Test Result

So far, therefore, there have been some surprises from pharmacogenomic testing as it enters mental health practice (Table 3). First, as mentioned above, we now know that no single test will tell us what to prescribe or what not to prescribe for a given patient. It is clear that each test result only “biases” us a small amount for or against a given drug choice, and that information must be balanced (ie, with equipoise) with other personal information from that unique patient. Second, perhaps the most important outcome from pharmacogenomic testing is not necessarily the specific test result, but how this testing leads to drug selection that improves outcomes and reduces costs. That is, interpreting pharmacogenomic test results orients the advanced prescriber’s thinking along a neurobiological perspective in order to select treatments that are biologically plausible, rather than just utilizing intuition, habit, or trial and error. This appears to have the potential to improve drug selection. Third, we now know that how one utilizes pharmacogenomic test results is not that different from how one utilizes any other personalized clinical information from a given patient. That is, each bit of information from a specific patient, whether
clinical or pharmacogenomic testing, contributes at best a very small amount to the variance explaining why someone responds or fails to respond, or tolerates or fails to tolerate a given drug or drug class. Having more information from pharmacogenomic test results provides additional individualized data for a given patient to help weigh the many factors in favor or against prescribing any given drug.

Some skeptics conclude from all of this that no biomarker or genomic test is valuable enough to be part of the standard of psychiatric care, nor useful enough to be reimbursed. Integrating new technologies into clinical practice has always been a messy affair as we learn whether clinical outcomes are better when the test results are utilized than when they are not. Early adopters strive to discover the best utility of new information, while nay-sayers and especially payors remain doubtful. Some practitioners may be more comfortable at the present time using the time-honored classical approach (Table 1). On the other hand, early initiators of new technology who study the literature and learn how to properly interpret evolving test results may prefer a more cutting-edge, if controversial, approach (Table 4). That approach is not to take a classical trial-and-error approach to selecting treatments, but instead to put the results of pharmacogenomic testing into the decision-making formula by pursuing a genetically informed, neurobiologically empowered, data-oriented, novel, and rational approach to selecting a treatment or combination that is already showing signs of yielding better symptomatic outcomes, better dosing, and reduced cost of treatment (Table 4). 18–24

References: