Clinical Insights Into Pharmacogenetics and Schizophrenia, Part 1

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Introduction

Dr. Kane: Schizophrenia is a heterogeneous disorder in terms of course and treatment response. The field of pharmacogenetics, which seeks to reveal how genetic factors affect patients' response to drugs, holds promise to help clinicians develop a better understanding of antipsychotic therapy,[1] such as which patients might respond better or worse to specific agents or treatment in general or which patients might be at particular risk for serious adverse effects.

Implementing Pharmacogenetic Tests in Clinical Practice

Dr. Kane: What do practicing psychiatrists need to know about using genetic tests?

Dr. Malhotra: Practicing psychiatrists need more education regarding both the benefits and potential pitfalls of genetic testing.

Dr. Perlis: Individuals practicing psychiatry are not accustomed to having useful tests available, except for tests that measure drug levels or screen for potential adverse effects. Psychiatrists must learn that the usefulness of genetic tests depends on some simple concepts and can be evaluated just like any other diagnostic tool.

Dr. Malhotra: Genetic tests, however, do vary from other types of tests in that the results are somewhat ambiguous. For instance, clinicians can easily determine if a patient's cholesterol is within the normal range. In contrast, the results of genetic tests cannot be interpreted as normal or abnormal. Rather, these tests reveal how a risk-benefit ratio might shift one way or the other.

Dr. Kane: In other words, the power of these tests to predict a particular outcome has yet to be established, which may be challenging for clinicians attempting to use the tests to inform treatment decisions or recommendations.

Dr. Perlis: Furthermore, we do not want to overstate what these tests are measuring. Clinicians will need to be educated about when these genetic tests will actually be useful. Pharmacogenetic tests are primarily useful for estimating risk and may not yet be fully validated or well calibrated, so clinicians must think about when these tests are going to be useful and how the tests might change their way of thinking. It is crucial to realize that these tests typically will not yield "yes/no" answers but rather estimates of potential risk or benefit.

Dr. Kane: Also, the utility of genetic tests may be influenced by what is at stake. A clinician might settle for less sensitivity and specificity if the test is used to predict a serious adverse effect rather than to predict an outcome of less concern.

Dr. Perlis: One way to consider the importance and usefulness of genetic tests is similar to the concept of *number needed to treat*, which is used in drug testing studies to determine how many patients need to be treated with the drug to avoid a single incidence

of a certain outcome or side effect. Pharmacogenetic testing can be viewed in a similar way, where *number needed to test* is the number of people who need to be tested to achieve a particular end, such as preventing a dangerous adverse effect or achieving an additional remission. The testing may have wide variations in predictive properties, so having an idea of the range of accuracy will make the data more meaningful when used in routine clinical practice.

Dr. Malhotra: The number needed to test will differ in terms of testing for adverse events versus testing for efficacy. For instance, an important reason for pharmacogenetic testing might be so that a clinician could accurately and reliably predict an adverse event such as clozapine-induced agranulocytosis. Efficacy prediction, on the other hand, may be a much more difficult goal because predicting a 10% or a 20% better chance of response to a particular drug is much more ambiguous than predicting either the presence or absence of agranulocytosis.

Dr. Kane: Do you see a risk that these tests might be overused before their predictive power is fully established?

Dr. Perlis: That is a concern. As soon as a test that provides information on outcomes becomes available, clinicians will want to use it. Because we have so few useful diagnostic tools in psychiatry, we might feel pressure to use these tests before we fully understand how well they work.

Costs of Pharmacogenetic Testing

Dr. Kane: The cost-effectiveness of pharmacogenetic testing is debatable. If these tests could identify a more effective treatment that would result in significant reduction of costs, such as reduced service utilization or hospitalization, the test would clearly be cost-effective. However, if such clear cost reductions do not exist, the utility of these tests will need to be validated on a number of different levels.

Dr. Malhotra: I agree. Data are needed showing that the commercially available pharmacogenetic tests are cost-effective. We do not yet have prospective evidence showing that the pharmacogenetic tests currently available have an influence on distinct outcome measures such as treatment costs, relapse rates, and hospitalization rates over a period of time.

Dr. Perlis: Studies assessing these types of cost measures are just starting to be conducted outside of psychiatry. For instance, a clinical trial[2] employing genotyping examined warfarin metabolism and found that patients with a certain genetic variation needed 32% to 67% lower doses of warfarin than those in the control group. By tailoring the dose to the patient, the hope is a test like this can avoid many of the negative consequences of warfarin use, including the potential for bleeding complications.

Dr. Kane: In terms of cost-effectiveness, knowing how common a particular risk factor is in the population would inform the number needed to test.

Dr. Perlis: That is correct. A useful analogy is testing for human immunodeficiency virus (HIV). Testing everyone in the general population for HIV would not be cost-effective, and the risk of false-positives would be particularly high. On the other hand, testing at-risk populations has been more practical because the number needed to test is fairly low. Similarly, we might be more interested in testing for agranulocytosis in certain high-risk groups.

Dr. Kane: For example, people with neutropenia.

Dr. Malhotra: I would argue, though, that all people being considered for treatment with clozapine should be tested for risk of agranulocytosis, because the number of people considered for clozapine therapy is already limited.

Dr. Perlis: My colleagues and I[3] previously attempted to do a cost-effectiveness analysis of clozapine pharmacogenetic testing. Admittedly, we used a rather primitive model, but we found that it was much more cost-effective to put everyone on clozapine treatment regardless of the test results.

Dr. Malhotra: But in that study,[3] the outcome being measured was efficacy. A great deal of the decision to use genetic testing will depend on what the dependent measure is and what its impact would be on the ultimate outcome.

Dr. Perlis: One would assume that if a patient is being treated with clozapine and is known to be at a low risk for agranulocytosis, monitoring white blood cell counts would still be necessary. Although costs would definitely improve, clinicians are likely to still need to monitor laboratory results regularly unless an incredibly sensitive test or a test with exceptional negative predictive value was available. Nevertheless, clozapine may be cost-effective simply because patients need a highly effective treatment to avoid expensive negative outcomes. The money saved when patients are not monitored may still not make the genetic testing cost-effective.

Dr. Malhotra: I agree, but the actual cost of the test will also influence its cost-effectiveness.

Dr. Kane: Who should pay for pharmacogenetic tests and under what circumstances? Also will what clinicians think is appropriate be in agreement with what the payers think is justified?

Dr. Malhotra: Studies are needed showing that these tests have an effect on cost or other concrete outcome measures. If evidence demonstrates positive benefits from using the tests versus not using them, payers could see the justification in paying for the tests.

Dr. Kane: The timeframe between the genetic testing and the putative outcome may present a challenge. At present, most people in the United States change health plans frequently. Insurance companies may not be as interested in funding a genetic test that indicates a side effect may develop in

2 years as they would be if the test reveals a risk for a side effect that may develop in a couple of weeks.

Dr. Malhotra: The risk for long-term side effects may not be an issue in patients with schizophrenia, with the exception of tardive dyskinesia, because most side effects experienced tend to be acute. For instance, agranulocytosis occurs relatively early in treatment. Weight gain may also occur early in treatment, although it may not have a direct effect on costs until related adverse events begin to occur.

Dr. Perlis: Although the ability to predict agranulocytosis would unquestionably be useful, the ability to predict weight gain may not be as valuable. Why would testing for the potential of weight gain be more useful than trying a medication for 1 or 2 weeks to see if weight gain occurs? Is it that useful or cost-effective to save 2 or 3 weeks to determine if a patient is gaining weight?

Dr. Malhotra: Two weeks may not be long enough to observe weight gain; it may take up to 8 weeks. Additionally, if a patient responds well to a drug, the patient may be committed to long-term treatment with the drug despite the weight gain and, therefore, be reluctant to switch. If a test were able to reveal that the patient is at risk to gain weight, and if an alternative drug were available that did not have the potential for causing weight gain, the clinician could start the patient on treatment with the alternative drug and avoid the need to switch.

Dr. Perlis: Why not give the patient the weight-neutral agent from the start?

Dr. Malhotra: Because the drug associated with weight gain may be more efficacious.

Dr. Perlis: I think this discussion reinforces the fact that the usefulness of pharmacogenetic tests is going to be highly dependent on both the specifics of the drugs and the specifics of the tests. One drug may be a better fit for some patients, while a different drug may be better for others. A similar situation exists for antidepressants. For example, individuals who are poor metabolizers of the cytochrome P450 2D6 enzyme (CYP2D6) have been found to poorly tolerate some antidepressants, namely tricyclics and venlafaxine.[4] Some have argued that because most antidepressants have roughly equivalent efficacy, clinicians should prescribe everyone an antidepressant that is not dependent upon CYP2D6 rather than attempting to individualize treatment for variant genotypes.[4] This is a reasonable strategy if all the drugs have equivalent efficacy, but this is not necessarily the case in schizophrenia.

Table 1. Cross-Tabulation of Responder–Nonresponder Subjects According to Genotypes ($\chi^2 = 9.87$, df = 2, p = .007)[a]

SERTPR Genotype	Nonresponder, N = 163 (%)	Responder, N = 385 (%)
L/L	39 (21.4)	143 (78.6)
L/S	83 (32.7)	171 (67.3)
S/S	41 (36.6)	71 (63.4)

[a]Adapted with permission from Serretti et al.[5]
Abbreviations: *L* = long variant, *S* = short variant, SERTPR = serotonin transporter-gene–linked polymorphic region.

Table 2. Reduction of Mean HAM-D Score According to 5-HTTLPR Genotype (ANOVA: F = 3.6, df = 545, p = .027)[a]

5-HTTLPR Genotype	Percentage of Reduction of HAM-D (mean ± SD)
L/L	0.72 ± 0.30
L/S	0.65 ± 0.36
S/S	0.61 ± 0.35
All	0.67 ± 0.34

[a]Reprinted with permission from Serretti et al.[5]
Abbreviations: 5-HTTLPR = serotonin transporter gene polymorphism, ANOVA = analysis of variance, HAM-D = Hamilton Rating Scale for Depression, *L* = long variant, *S* = short variant.

Dr. Kane: A certain degree of trial and error is clearly involved when prescribing antipsychotics. Few patients remain on treatment with their original medication, and many patients switch treatment, which indicates that initial treatment selections are frequently ineffective. Clearly, a tool that informs the early decision-making process would be extremely helpful and probably cost-effective. Identification of patients who are likely to respond to a particular drug rather than having to wait 2 weeks to determine response, could have great implications for the patients' treatment satisfaction, adherence, and service utilization.

Dr. Perlis: Another limitation of current genetic tests is that although these tests may be able to reveal which patients with certain genetic variations will show less response to a particular drug, the tests do not indicate to which drugs these patients *are* likely to respond. In other words, a test that says "do not use clozapine" is less useful than one that says "use risperidone."

Dr. Malhotra: Unfortunately, most of the pharmacogenetic studies to date have not been able to clearly differentiate within drug classes. For instance, a meta-analysis by Serretti and colleagues[5] found that an individual's genotype was associated with better or worse response to all selective serotonin reuptake inhibitors (SSRIs)(Tables 1 and 2). This has also been the case with antipsychotics. Dr. Kane and I were involved in a study[6] that found that dopamine D_2 receptor gene polymorphisms predicted time to response to olanzapine or risperidone in patients with first-episode schizophrenia, but we did not determine which group of patients should be treated with olanzapine as opposed to risperidone or vice versa.

Dr. Perlis: Clearly, just detecting an association is a crucial first step, but just as clearly, this will rarely be enough to take to the clinic. We will need to know something about specificity of effect. Otherwise, we are not actually going to be able to influence treatment outcomes.

Dr. Malhotra: Exactly. However, this will not be an easy task in schizophrenia or depression because many of

the drugs are designed to bind and act at the same receptors. Identifying drug-specific associations between genetic variations and response will be challenging because many drugs have been developed to essentially be the same as other drugs. We may be more successful at identifying the likelihood that genetic factors will predict drug-specific responses if we consider drugs with different mechanisms of action.

Dr. Perlis: This strategy may also be helpful for determining side effect risk because some of the side effects that are of greatest concern are off-target effects of these drugs. Therefore, if the atypical antipsychotics as a class have a relatively common mechanism of action for therapeutic effect but perhaps have different mechanisms of action for inducing side effects, we may be able to determine which drug is more or less likely to cause a particular side effect.

Using Pharmacogenetics to Improve Adherence

Dr. Kane: Predicting therapeutic response may positively affect adherence because patients who experience positive outcomes may be more likely to continue treatment. In what other ways might genetic testing be used to improve adherence over time?

Dr. Malhotra: Genetic testing could be extremely useful for improving adherence by being able to predict side effects. Currently, if a patient experiences a side effect early in treatment, we will switch the medication. If we could avoid that side effect altogether, the patient may be more likely to adhere to the initial drug.

Dr. Kane: I agree, because certainly the side effects that people experience during the acute phase may have a considerable impact on long-term adherence.

Dr. Perlis: Another advantage of genetic testing would be that, in the cases where side effects can be anticipated, the drug may still be used, but a preventative measure can be implemented or patients can be educated about it beforehand to give them a sense of what to expect. These measures may still lead to better adherence and improved outcomes.

Dr. Malhotra: Genetic tests may also have the potential to suggest dosing parameters. Thus, instead of only having the option to switch a drug after experiencing problems, clinicians may be able to use the same drug but perhaps start it at a different dose than would usually have been initiated without genetic testing to either minimize the expected side effect or achieve greater efficacy.

Dr. Perlis: In addition, these tests may provide an opportunity early in the course of treatment to influence how patients feel about their medication. Patients tend to decide fairly quickly whether they like or dislike a medication. If patients are aware of what to expect and know that clinicians are going to ally with them to address it, adherence will certainly improve.

Dr. Malhotra: Therefore, pharmacogenetics may be able to improve overall treatment outcomes and strengthen the therapeutic alliance. If patients experience a response without unanticipated side effects, they are certainly going to have a better relationship with and more confidence in their physician.

Using Pharmacogenetics to Assess Response

Dr. Kane: How might genetic testing impact the ways in which physicians measure and document response? In other words, will pharmacogenetic data be useful if clinicians are using global, subjective outcome measures? Do we need to advocate the use of more quantitative assessments of outcome to really make use of these predictive tools?

Dr. Malhotra: Quantitative assessments to measure response would certainly be beneficial. Some outcomes are too subtle to be detected by a global, subjective approach. More precise measurements are needed for clinicians and patients to see the benefits of these tests.

Dr. Perlis: Another important issue to consider is that different polymorphisms may have differential effects depending on the specific drugs or outcomes under consideration. For instance, studies[7–11] of olanzapine response have found evidence that genetic variations differentially influence positive and negative symptom response. Thus, symptoms may need to be considered individually and quantified separately. Furthermore, schizophrenia is a heterogeneous disorder. Global measures do not fully capture the diversity of presentations of the illness, which is another important reason to quantify symptoms, particularly because genetic variations may influence one set of symptoms but not others. To use pharmacogenetic tests effectively, ways to break down and quantify symptoms in the clinical setting are needed.

Issues of Confidentiality

Dr. Kane: Some patients may have concerns about confidentiality and the ways in which genetic test results may be used. Will patients be resistant to genetic testing?

Dr. Malhotra: My colleagues and I try to collect DNA samples from most of our patients, and approximately 90% to 95% are willing to participate in this research procedure, which has really no outcome or benefit for the individual patient at this point. Issues may arise once the results of these tests actually carry treatment implications, but in my experience, patients, including those who are acutely ill and have psychotic disorders, have accepted pharmacogenetic testing.

Dr. Perlis: My experience has been the same. Around 90% or more of patients will consent to participate if the test is part of a research protocol. A common concern, however, is

how insurance companies may use the results of genetic tests. For instance, a test may establish that an individual is resistant to standard treatments for chronic illnesses like schizophrenia. The insurance company may be willing to pay for the test, but these results could potentially be used to influence coverage once the information is in the medical record. Legislation has been proposed that would protect patients from this.

Dr. Kane: Unfortunately, that legislation has not yet been passed.

Genes Associated With Illness Risk and Treatment Response

Dr. Kane: In either schizophrenia or affective disorders, have any genes been identified that are associated with both illness risk and treatment response?

Dr. Perlis: Regarding affective disorders, the serotonin (5-HT) transporter promoter polymorphism has been associated with depression liability, at least in terms of gene-environment interactions.[12] In other words, this polymorphism increases vulnerability to depression as the number of stressful life events increases. Also, the *S/S* genotype of this polymorphism has been associated with less responsiveness to antidepressants compared with the *L/L* and *L/S* genotypes, although the precise definition of *response* seems to vary from study to study. For example, some studies[13,14] found that when compared to other genotypes, this polymorphism causes people to respond more slowly to antidepressants, whereas other studies[15,16] have found that this polymorphism causes people to respond less well.

These findings are problematic, however, because the largest cohort study[17] to date, which was basically equivalent to or greater in size than all the other studies put together,[13–16] reported no evidence of a relationship between 5-HT neurotransporter polymorphisms and the efficacy of SSRIs. Until recently, I would have said the 5-HT transporter polymorphism was definitely involved in illness risk and treatment response. Although an association clearly exists, the relationship is not yet fully understood. Some studies[18–20] have shown evidence of an association between these polymorphisms and side effect burden. In bipolar disorder, convincing data concerning risk genes have not been established, and currently there are no particularly useful predictors of response.

Dr. Malhotra: In schizophrenia, potential candidates for risk genes have been identified, but none of these genes have been shown to definitely influence drug response. The one potential exception would be catechol-*O*-methyltransferase (*COMT*) gene. The *Val158Met* polymorphism in the *COMT* gene has been shown to increase risk for schizophrenia in some studies,[21] while other studies and meta-analyses[22–24] have not shown the same association. A limited number of studies[25–27] have indicated that certain *COMT* genotypes might be associated with specific types of responses to antipsychotic drug treatment—particularly cognitive responses—but the current database is small and certainly needs more work.

Current Prospects for the Application of Pharmacogenetic Tests

Dr. Kane: Pharmacogenetic testing clearly has the potential to become an invaluable clinical tool. Are tests ready for widespread application now or in the near future? The PGxPredict:CLOZAPINE test to detect the risk for clozapine-induced agranulocytosis is available, but are other tests available?

Dr. Malhotra: The U.S. Food and Drug Administration has approved the AmpliChip CYP450 test, but aside from these 2 tests, I am unaware of any other imminent pharmacogenetic testing options for schizophrenia. Although the AmpliChip test is commercially available, data illustrating the effects of testing on patient outcomes are still relatively scarce. However, some studies[28–30] of risperidone treatment for schizophrenia have demonstrated that metabolic status as assessed by the CYP450 genotype did contribute to response rates and adverse effects of treatment. Although these clinical trials were not rigorous, the results are interesting and warrant further investigation.

Dr. Perlis: Recently, a federal agency released a review[31] of the evidence for using the AmpliChip in antidepressant prescribing, and this agency did not find conclusive evidence that testing was valuable for antidepressant treatment. The review also reported that, although CYP450 status does affect drug metabolism, a number of additional factors such as age, medications, diet, smoking, and alcohol consumption can influence metabolic status, and these factors change over time. Contrary to the misconception that pharmacogenetic testing can reveal an individual's metabolic status for life, tests such as the AmpliChip do not have that capability.

Dr. Malhotra: We must remember however, that the federal agency review examined antidepressant treatment. The results may be different for antipsychotics.

Dr. Perlis: Absolutely, which further emphasizes that pharmacogenetic tests may be useful in some situations and not in others. Therefore, these tests will need to be used selectively. Regarding antipsychotic prescribing, for example, a patient's CYP450 status may be useful if another CYP450 substrate is being used or if the patient has other risk factors for being a poor drug metabolizer. On the other hand, this information may be less useful for a patient who is treatment-naive, otherwise healthy, and not taking any other medications.

Table 3. Variations of CYP2D6 and CYP2C19 Phenotypes According to Ethnicity (Approximate Frequencies, %)[a]

Phenotypes	Caucasians	East Asians	African Americans	North Africa and Middle East	Mexican Americans[b]
CYP2D6 PM	5–10	1	1–2	2	3
CYP2D6 UM	1–10[c]	0–2	2	10–29	1
CYP2D6 Other	80–94	> 90	96–97	69–88	96
CYP2C19[d] PM	2–4	10–25	1–5	2	4
PM for both[e]	0.1–0.4	0.1–0.25	0.01–0.1	0.04	0.12

[a]Reprinted with permission from de Leon et al.[4]
[b]Not homogeneous; they have a mix of European and Asian genes.
[c]This is based on patients having at least 3 active alleles, which means they have at least 1 normal allele and 1 duplicated allele that is also active. Current genotyping methods are suspected of underdiagnosing CYP2D6 UMs.
[d]The rest of people are CYP2C19 EMs.
[e]These are independent probabilities of being both a CYP2D6 PM and a CYP2C19 PM. To calculate, a multiplication is needed (eg, for Mexican Americans, $0.03 \times 0.04 = 0.0012$, or 0.12%, or 1.2 per 1000, or 12 per 10,000).
Abbreviations: CYP = cytochrome P450, EM = extraordinary metabolizer, PM = poor metabolizer, UM = ultrarapid metabolizer.

The Impact of Ethnicity on Pharmacogenetic Tests

Dr. Kane: What role does ethnicity play in the process of validating pharmacogenetic tests? Will these tests need to be independently validated in a variety of subpopulations?

Dr. Perlis: Ethnicity definitely is relevant to pharmacogenetics, but its role is not yet fully understood. For example, McMahon and colleagues[32] examined the genetic basis for interindividual antidepressant response. They found that the 5-HT_{2A} receptor gene occurred 6 times more frequently in white subjects than in black subjects, and those with the A allele were more likely to respond to treatment. Thus, genetic variations associated with ethnicity were found to affect antidepressant response.[32] Since allele frequencies vary so greatly across ethnic groups[4] (Table 3), tests that are informative for many ethnic groups are desirable.

Dr. Malhotra: I agree to a certain extent; however, when testing for the functional variant within the gene that influences the designated response parameter, even though the allele frequency differs in populations, once an individual has an allele, the effect of having that allele may still be the same or similar. Thus, even though individuals may be less likely to carry the allele within their ethnic population, if they actually have the functional variant that mediates the response, the test should still work regardless of ethnicity. This is an empirical question, however, and if other genes or other factors are interacting with the test that differ from ethnic group to ethnic group, the tests may not be valid in some ethnic groups.

Dr. Perlis: Even if patients have that particular variant, a risk still exists that the informative power of the test would differ from ethnic group to ethnic group. In other words, if a genetic variant is much more common in a particular group, testing may be worthwhile, but if it is exceedingly rare in another, testing may not be necessary.

Dr. Malhotra: I agree, but I hope that the tests that are developed are at the level of the functional variant so that they would provide valid results in all ethnic groups.

Future Directions in Pharmacogenetics

Dr. Kane: Have any new developments been made in the field of genetics that will influence the future of pharmacogenetic testing?

Dr. Malhotra: An immediate goal of using pharmacogenetic tests is to be able to predict the outcome of treatment. However, a long-term goal of pharmacogenetics is to develop a better class of drugs to treat disorders such as schizophrenia, and the ultimate goal of pharmacogenetics is to understand the molecular basis of response parameters and side effects. We want to use genetic information to achieve greater long-term impact on the treatment of these disorders by developing better drugs rather than simply predicting how a patient will respond to a currently available treatment.

Dr. Kane: Or even prevent these disorders, ultimately.

Dr. Malhotra: Correct.

Dr. Perlis: As we move from small-scale candidate gene studies implicating particular genes because we know the drug acts within that system to studies examining the whole genome, we may encounter truly novel findings. For instance, we may be able to discover that drugs act on different systems or that different systems are involved in schizophrenia. These types of findings may then allow for the development of drugs with novel targets. The aforementioned studies[13–17] examined genes related to 5-HT simply because the treatments in question are known to affect 5-HT. This type of study will not really point us to an entirely new class of drugs in the way that findings from whole genome studies might.

Dr. Malhotra: I agree. Whole genome sequencing could eliminate the need for specific genetic tests. If, over the next 5 to 10 years, the cost of whole genome sequencing becomes manageable, it will definitely have ramifications for pharmacogenetic testing. Admittedly, numerous ethical, social, and financial issues would first need to be considered, but whole genome sequencing could completely change how clinicians practice medicine.

Dr. Perlis: To date, at least 3 companies intend to do direct-to-consumer genome scans, and in at least 1 case the estimated cost is under $1000. Eventually, everyone may have scans of their entire genome in their medical record, and as discoveries are made, clinicians may become better at using patients' genetic information. In other words,

someone could be tested once, and over the years that test becomes more and more informative. Furthermore, since inexpensive pharmacogenetic tests of individual genes probably will not become available soon, scans of the whole genome may be much more cost-effective.

Dr. Malhotra: Currently, my colleagues and I often find that conducting a whole genome association study is cheaper than genotyping 4 or 5 individual genes.

I believe that the use of genome scans may enter the clinical domain in the near future, but I do have concerns about direct-to-consumer testing. One main challenge will be how individuals will handle these kinds of data without any type of supervision or counseling on how to interpret the results. Many companies already have promotional literature stating that different genes indicate different outcomes such as drug response or cognitive status, thus creating unrealistic expectations among consumers. Some of these companies are already encouraging consumers to send in cheek swabs. Although the role of the federal government in genetic testing is unclear, efforts are being made at the federal level to regulate these companies.

Dr. Kane: Many whole genome association studies are failing to replicate previous findings. How should the average practitioner interpret these discrepancies?

Dr. Malhotra: Deciding that genome replication studies have failed may be premature. These are new and comprehensive approaches, and the phenotypes being dissected are extremely complex. The tools that we have may not be sufficient to accomplish this task. Perhaps the focus should be on other factors that have not received as much attention, such as the clinical phenotypes being examined. Additionally, large, multicenter studies may introduce clinical and environmental heterogeneity that overwhelms the subtle effects of genetic variation, so perhaps more homogeneous, rigorous, clinically-defined samples may provide better power to detect effects.

Dr. Perlis: The whole genome approach has had success with other complex genetic diseases, and I believe it will also work in psychiatry, but we just do not have adequate sample sizes yet. As studies are conducted, clinicians may find many relevant genes, each with a relatively small effect but requiring recalculations. These findings will lead to nonreplication at first because the replication samples generally need to be larger than the original sample that was used to detect the effect. Thus, study samples that go from 400 to 1000 to 10,000 should start to get into the range in which the effects of genetic variations are detectable.

The Role of Practicing Clinicians

Dr. Kane: Will academic centers and networks primarily be responsible for advancing knowledge about pharmacogenetic testing, or can the average clinician participate in the further evolution of this field?

Dr. Malhotra: As I see it, research enterprises will need to be primarily responsible for the long-term validation of these tests. However, practicing clinicians who use these tests will be able to contribute valuable data about outcomes and costs possibly by developing more effective quantitative assessments or by providing data by tracking patient outcomes. Of course, because most genetic work requires large sample sizes, information from practicing clinicians would need to be standardized to be used collectively. Thus, challenges exist, but practicing clinicians will have opportunities to contribute to the progress of pharmacogenetics.

Dr. Perlis: If you want to know how well a test is going to perform in the real world, you have to study it in the real world. Difficulties arose in moving from drug efficacy studies to drug effectiveness studies in schizophrenia and bipolar disorder, and real-world applicability will be an even bigger issue with pharmacogenetic tests. Thus, I foresee opportunities for clinicians to participate in some way, perhaps in large networks that are trying to understand how to use and interpret these tests. This type of practical information cannot be obtained from the typical, multicenter, 300-patient clinical trial.

Conclusion

Dr. Kane: In conclusion, pharmacogenetics holds promise for improving treatment outcomes in a number of disorders, particularly schizophrenia. Although antipsychotic medications are effective for treating schizophrenia, the way in which patients will respond to or experience adverse events from these agents is highly variable. By utilizing pharmacogenetic tests, clinicians may be able to use genetic information to predict which patients will respond best to different types of treatments and thereby employ pharmacotherapies that will increase treatment adherence and help patients achieve optimal outcomes. Pharmacogenetics, therefore, may revolutionize the way clinicians practice medicine.

Drug names: clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa), risperidone (Risperdal), venlafaxine (Effexor and others), warfarin (Coumadin, Jantoven, and others).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

REFERENCES

1. Kawanishi Y, Tachikawa H, Suzuki T. Pharmacogenomics and schizophrenia. Eur J Pharmacol 2000;410:227–241
2. Moridani M, Fu L, Selby R, et al. Frequency of CYP2C9 polymorphisms affecting warfarin metabolism in a large anticoagulant clinic cohort. Clin Biochem 2006;39:606–612
3. Perlis RH, Ganz DA, Avorn J, et al. Pharmacogenetic testing in the clinical management of schizophrenia: a decision-analytic model. J Clin Psychopharmacol 2005;25:427–434

4. de Leon J, Armstrong SC, Cozza KL. Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19. Psychosomatics 2006;47:75–85
5. Serretti A, Cusin C, Rausch JL, et al. Pooling pharmacogenetic studies on the serotonin transporter: a mega-analysis. Psychiatry Res 2006;145:61–65
6. Lencz T, Robinson DG, Xu K, et al. DRD2 promoter region variation as a predictor of sustained response to antipsychotic medication in first-episode schizophrenia patients. Am J Psychiatry 2006; 163:529–531
7. Ellingrod VL, Perry PJ, Lund BC, et al. 5HT2A and 5HT2C receptor polymorphisms and predicting clinical response to olanzapine in schizophrenia. J Clin Psychopharmacol 2002;22:622–624
8. Houston JP, Adams DH, Kirkwood SC, et al. Neuroreceptor gene polymorphisms and olanzapine depressive symptom response in schizophrenia. J Clin Psychopharmacol 2007;27:520–523
9. Bozina N, Kuzman MR, Medved V, et al. Associations between MDR1 gene polymorphisms and schizophrenia and therapeutic response to olanzapine in female schizophrenic patients. J Psychiatr Res 2008;42:89–97
10. Lin YC, Ellingrod VL, Bishop JR, et al. The relationship between P-glycoprotein (PGP) polymorphisms and response to olanzapine treatment in schizophrenia. Ther Drug Monit 2006;28:668–672
11. Mancama D, Mata I, Kerwin RW, et al. Choline acetyltransferase variants and their influence in schizophrenia and olanzapine response. Am J Med Genet B Neuropsychiatr Genet 2007;144:849–853
12. Smith GS, Lotrich FE, Malhotra AK, et al. Effects of serotonin transporter promoter polymorphisms on serotonin function. Neuropsychopharmacology 2004;29: 2226–2234
13. Serretti A, Mandelli L, Lorenzi C, et al. Serotonin transporter gene influences the time course of improvement of "core" depressive and somatic anxiety symptoms during treatment with SSRIs for recurrent mood disorders. Psychiatry Res 2007;149: 185–193
14. Pollock BG, Ferrell RE, Mulsant BH, et al. Allelic variation in the serotonin transporter promoter affects onset of paroxetine treatment response in late-life depression. Neuropsychopharmacology 2000;23:587–590
15. Arias B, Catalán R, Gastó C, et al. 5-HTTLPR polymorphism of the serotonin transporter gene predicts non-remission in major depression patients treated with citalopram in a 12-weeks follow up study. J Clin Psychopharmacol 2003;23:563–567
16. Smeraldi E, Zanardi R, Benedetti F, et al. Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. Mol Psychiatry 1998;3:508–511
17. Kraft JB, Peters EJ, Slager SL, et al. Analysis of association between the serotonin transporter and antidepressant response in a large clinical sample. Biol Psychiatry 2007;61:734–742
18. Hu XZ, Rush AJ, Charney D, et al. Association between a functional serotonin transporter promoter polymorphism and citalopram treatment in adult outpatients with major depression. Arch Gen Psychiatry 2007;64:783–792
19. Murphy GMJ, Kremer C, Rodrigues HE, et al. Pharmacogenetics of antidepressant medication intolerance. Am J Psychiatry 2003;160:1830–1835
20. Popp J, Leucht S, Heres S, et al. Serotonin transporter polymorphisms and side effects in antidepressant therapy: a pilot study. Pharmacogenomics 2006;7:159–166
21. Egan MF, Goldberg TE, Kolachana BS, et al. Effect of COMT $Val^{108/158}$ Met genotype on frontal lobe function and risk for schizophrenia. PNAS 2001;98: 6917–6922
22. Fan JB, Zhang CS, Gu NF, et al. Catechol-O-methyltransferase gene Val/Met functional polymorphism and risk of schizophrenia: a large-scale association study plus meta-analysis. Biol Psychiatry 2005;57:139–144
23. Munafò MR, Bowes L, Clark TG, et al. Lack of association of the COMT (Val158/108Met) gene and schizophrenia: a meta-analysis of case-control studies. Mol Psychiatry 2005;10:765–770
24. Williams HJ, Glaser B, Williams NM, et al. No association between schizophrenia and polymorphisms in COMT in two large samples. Am J Psychiatry 2005;162: 1736–1738
25. Weickert TW, Goldberg TE, Mishara A, et al. Catechol-O-methyltransferase val108/158met genotype predicts working memory response to antipsychotic medications. Biol Psychiatry 2004;56:677–682
26. Bertolino A, Caforio G, Blasi G, et al. Interaction of COMT (Val(108/158)Met) genotype and olanzapine treatment on prefrontal cortical function in patients with schizophrenia. Am J Psychiatry 2004;161: 1798–1805
27. Illi A, Mattila KM, Kampman O, et al. Catechol-O-methyltransferase and monoamine oxidase A genotypes and drug response to conventional neuroleptics in schizophrenia. J Clin Psychopharmacol 2003;23:429–434
28. Bork JA, Rogers T, Wedlund PJ, et al. A pilot study of risperidone metabolism: the role of cytochromes P450 2D6 and 3A. J Clin Psychiatry 1999;60:469–476
29. Llerena A, Berecz R, Dorado P, et al. QTc interval, CYP2D6 and CYP2C9 genotypes and risperidone plasma concentrations. J Psychopharmacol 2004;18:189–193
30. de Leon J, Susce MT, Pan RM, et al. The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation. J Clin Psychiatry 2005;66:15–27
31. Matchar DB, Thakur ME, Grossman I, et al. Testing for cytochrome P450 polymorphisms in adults with non-psychotic depression treated with selective serotonin reuptake inhibitors (SSRIs). Evid Rep Technol Assess (Full Rep) 2007;146:1–77
32. McMahon FJ, Buervenich S, Charney D, et al. Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. Am J Hum Genet 2006;78:804–814

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