Sometimes in our field of psychiatry it seems like we pick drugs like we throw darts at a dart board, combining drugs without a real prediction of what the interactions will be. How would you respond to this?

My view is more positive, based on experience with pharmacogenomic testing over the past 8 years. In the recently released *The Language of Life: DNA and the Revolution in Personalized Medicine,* by Francis Collins, MD, PhD, who is the new Director of the National Institutes of Health, he is extremely optimistic about how the testing of the genes that influence drug response will revolutionize not only psychiatry, but every branch of medicine.

An overriding principle is to follow the traditional dictum of “First do no harm.” Clinicians who treat psychiatric patients know that medications can be life saving, but they also know that all psychotropic medications can have serious side effects. We now have a tool in pharmacogenomic testing that can minimize the adverse effects of psychotropic medications and, increasingly, our patients are going to demand that we use this new tool.

A first priority is to determine whether or not a patient can tolerate a particular medication or if the patient is at increased risk for an adverse effect. We have made more progress in predicting adverse effects because the early work in pharmacogenomics focused on enzymes involved in metabolizing drugs, ie, the cytochrome P450 (CYP) system. Patients with defects in the genes that code for these enzymes may have severe problems when prescribed drugs that are the substrates of these enzymes. In the worst case, patients who were poor metabolizers have had fatal toxic reactions as a consequence of their inadequate metabolic capacity.

The patients who are at most increased risk are children or geriatric patients who may have difficulty informing their clinicians about adverse events so that they can decrease the dose and abort a bad outcome.

CYP enzymes are produced by the liver. Is that where many of these tests are focused or are there other metabolic systems that also can be identified?

It is helpful to think about three different categories of genes. The first category is metabolic genes. Some of these genes code for liver enzymes. At the Mayo Clinic, we genotype four different genes that code for CYP enzymes. The tests indicate whether a patient has an...
adequate amount of each particular enzyme within their system. The second category includes genes such as catechol-O-methyltransferase (COMT). COMT is involved with the catabolism of monoamines. Testing for COMT gives us some idea about the likelihood of an individual having a therapeutic response to some psychotropic medications. The third category is receptor and transporter genes. Progress in testing for variations in these genes is increasingly exciting. We are not as far along in understanding all of the clinical implications of variability in these genes, but for the serotonin transporter gene and for some of the serotonin receptor genes, we do know that there are associations with medication response. At the Mayo Clinic, we genotype the serotonin transporter gene (SLC6A4) as well as the serotonin (5-HT2A and 5-HT2C) receptor genes.

Are certain classes of drugs more often implicated in creating problems with respect to interactions or tolerability?

That is an important question because it really focuses on the importance of understanding the pharmacology of each drug. Psychotropic drugs in each class are sometimes considered to be equivalent. This leads to the dart board mentality that you described. However, two very widely used selective serotonin reuptake inhibitors (SSRIs), paroxetine and citalopram, have very different mechanisms of metabolism. Paroxetine is particularly interesting, because of all of the SSRIs, it has the most exclusive pattern of metabolism. For the average person with adequate CYP 2D6 enzymes, almost the entire metabolism of paroxetine is through the 2D6 pathway. Approximately 10% of our patients who are of European ancestry do not have adequate levels of the CYP 2D6 enzyme, because they have a genetic defect in one or both of their 2D6 genes. Consequently, they are unable to tolerate standard doses of paroxetine. In contrast, patients with an inadequate CYP 2D6 enzyme, but who have adequate CYP 2C19 enzymes, would have no trouble metabolizing citalopram. The adequacy of both the 2D6 and 2C19 enzymes provides useful information for some patients about that initial selection of an SSRI.

You referred to patients of European ancestry. Would Asian patients react to drugs differently?

This is a critical concept that has been increasingly well-studied over the past decade. All of the CYP genes show variability that is specific to ancestral origin. The contrasts are often most dramatic between Asian and European populations. In the case of one of the most commonly genotyped genes, CYP 2C19, the incidence of inadequate metabolism is more than twice as great in Japanese populations when compared to Norwegian populations.

What is the most effective way to educate clinicians about all of these different gene variations?

That has been a very important issue for me personally because we have had to do an enormous amount of professional education related to this complicated topic of genomic variability. In 2000, the Mayo Clinic received a large gift from one of our patients to help us work with all our colleagues, both in psychiatry as well as other medical disciplines, to get our physician workforce up to speed in individualized molecular medicine.

Clinicians learn by “doing” much more effectively than by listening. In 2003, we started testing for variability in the CYP 2D6 gene. We have conducted thousands of tests over the intervening years, in psychiatry as well as in oncology. As an example, today no woman at the Mayo Clinic will be prescribed tamoxifen without determining the adequacy of her 2D6 enzyme activity. This is a basic expectation. Collins specifically notes in his new book that women with breast cancer need to know their genotype prior to taking tamoxifen. If the patient has inadequate enzyme capacity, she will not have an adequate tamoxifen response and should receive a different treatment.

We have been working on different ways to educate psychiatrists. Every summer we give a 5-day course devoted to updating psychiatric clinicians on what they need to know about genetics in order to be able to comfortably use this new pharmacogenomic technology. For the last 8 years, we have had more than 100 people every summer subscribe to this course. On the first day of the course, we focus on genomic vocabulary and concepts that psychiatrists need to know. By the end of the first day, if a lecturer begins to talk about “an exonic SNP,” the attendees will actually understand that she is referring to a single nucleotide polymorphism that is located in the coding region of a gene. Many Grand Rounds speakers expect their audiences to know genomic jargon from the first minute of a presentation. We know that this is just not realistic for many clinicians. A very big issue is to make these technological breakthroughs accessible to clinicians. I learned from giving our course that there was no written material that I could easily provide our students to help them with this information in a clinician-friendly way. Consequently, I wrote Psychiatric Pharmacogenomics to address this gap. The book is written so that it can be understood by someone who knows very little about genetics. Understanding high school biology provides enough of a foundation to get started. Within the book, there are twenty clinical vignettes that are designed to give clinicians insights into how pharmacogenomic testing can help them to manage particular patients.

At the Mayo Clinic, do you conduct comprehensive genotyping to identify genetic variations that influence patients’ metabolism of medications?

If you had asked me that question even 5 years ago, I would have said that you would have to send a blood sample to one of the major reference laboratories, such as Mayo Medical Laboratories, to have your patient’s drug metabolizing enzyme genes accurately genotyped. This is no longer true.

The problem with many laboratory reports currently is that after a reference laboratory sends back the genotyping results, clinicians often do not know what the results mean unless they have done some homework. Most clinicians have needed to refer to a Website or textbook in order to help them to interpret the results of genotyping.
Recently, Mayo Clinic has partnered with a new biotech company called AssureRx. In the spirit of full disclosure, AssureRx has licensed intellectual property from Mayo Clinic, so Mayo Clinic benefits from the work that this company does. This new company is dedicated to making genotyping somewhat more affordable and insuring that clinicians get the results very quickly. However, of greatest importance, their laboratory provides decision-making guidance regarding the clinical implications of a patient’s atypical genotype.

It has been interesting to see this process unfold. I have been a consultant to AssureRx and I have encouraged them to think about a couple of key issues. The most important issue is to make sure that their report can be quickly understood by a practicing psychiatrist. A report may indicate that a patient has a normal genotype and should convey the message that the clinician can proceed as usual. Alternatively, if the report identifies atypical genotypes, it should clearly highlight any problems the patient may have. It is also now easier to collect samples. Clinicians are often reluctant to send patients many miles to get a blood draw. Today, these tests can be conducted using a cheek swab in the clinician’s office. A clinician can simply rub the swab on the inside of the cheek of the patient and put the swab in a FedEx envelope. The genotyping results are available for review within 48 hours on a secure Website.

The cost of pharmacogenomic testing is highly variable. Many labs charge between $250–$300 per genotype and clinicians can order specific genotypes in an a la carte fashion. Larger panels of multiple genes, like the AssureRx package, currently cost between $1,000–$1,500 for an entire set of genotypes and include an interpretation.

Some patients seem unable to tolerate anything. It might actually be cost effective to rule out some kind of a genetic basis for why that is. On the other hand, if there is nothing abnormal, the clinician has to focus more on whether or not the patient is somatizing related to taking the medication. Either way, testing can be very helpful.

Testing is not the whole answer, but it can provide clues. There is a lot of individual variation in how people take medications, as well as how they respond to medicine. We have had some fascinating stories over the years. There were two sisters seen in my department who were given a number of clinical diagnoses over many years, including an accusation that they were histrionic. Both of them would respond badly to even the smallest doses of medications and they often reacted in the same way. There were plenty of psychological explanations put forward to explain their behavior. We tested them both in 2003 and discovered that both of them had no enzyme activity for either 2D6 or 2C19. It was immediately clear that they were exquisitely sensitive to all of the SSRIs, except fluvoxamine, which happens to be an SSRI that is metabolized by a different enzyme. When the sisters received this information, they made a personal commitment to get back to the doctors who had looked after them and who had often accused them of “not being on board” with the treatments that they had prescribed. It was a very empowering experience for them. Parenthetically, they both had a good response to fluvoxamine.

When patients take multiple medications, some medications undergo several steps of metabolism. Other medications can inhibit some of those steps.

That is absolutely true. If there is a drug-drug interaction with one of the medications being an inhibitor, the clinician may unknowingly prescribe a dose which results in the parent drug accumulating. Sometimes a patient may need a very high dose, but it is important to realize that their actual serum level is influenced by their innate metabolic capacity and possible inhibition of the enzyme.

There are many different formulations of stimulants used to treat attention-deficit/hyperactivity disorder (ADHD) that have various release patterns. Has there been any work that might identify whether the metabolic pathway makes a difference in which drug is chosen for a given child?

There is a lot of research in this area, but we still do not have available genetic testing to help with answering that question. There is a recent article by McGough and colleagues reporting evidence from the UCLA group that is related to this question. Researchers have focused on candidate genes that include specific dopamine receptors as well as the COMT gene. All of these genes have variants associated with differential response to stimulants. It is particularly complicated because of the issue that we talked about earlier, which is that individuals of Asian ancestry tend to have different genetic variants than individuals of European ancestry. The studies conducted in the United States and Europe tend to have different results than the studies conducted in Korea and Japan. I predict that in 5 years there will be products available to guide the selection of stimulants and alternative treatment choices, such as atomoxetine, when treating ADHD.

Depending on the long and short arm of the serotonin transporter gene, there have been conflicting reports about who is more susceptible to stress-induced illness. Is that research being validated or is it being looked at now with more skepticism?

It is certainly being looked at aggressively. Frye at the Mayo Clinic is focusing on the question of antidepressant-induced mania. Previous literature tends to support the view that the short variant is more likely to be associated with induced mania. However, there is not absolute consistency in the research studies.

There are at least two reasons for these inconsistencies. The first is the ancestral difference. Again, with the serotonin transporter gene
there are big differences between Asians and Europeans. Another consideration is that we are beginning to understand variations within genes in a more comprehensive manner. The early studies that looked at the long versus the short alleles did not consider any other variability in the serotonin transporter gene. Approximatively five years ago, it became clear that additional genetic variations work in conjunction with these long and short variants to regulate the amount of the transporter protein produced. Nowadays, you really have to look at three regulators of this gene. As this research moves forward, we will have more power in our ability to identify vulnerable patients and be able to make better predictions of how this gene will function for an individual patient.

Obessive-compulsive disorder (OCD) appears to be a spectrum disorder with different symptom clusters. Has anyone actually identified genetic differences in subtypes of OCD?

There are clearly different subtypes. I hope that the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,7 will begin to address this problem. The hoarding disorder is particularly different and hopefully will be split off as an independent category.

Considering the rest of the OCD spectrum, researchers at Harvard, including Pauls,8 are studying the genetic variability of these subtypes. Their findings have not yet been translated to clinical guidance, but there are clear differences between these groups. The goal will be to use genetic testing to classify these patients more accurately so that particular treatments can be developed.

The one place today that we certainly use pharmacogenomic testing with OCD patients is related to the choice of an SSRI. When administering paroxetine, fluoxetine, or fluvoxamine for a patient with OCD, clinicians want to have as good an idea about how their patient will metabolize these drugs. Kirchheiner wrote an article9 that makes very specific dose recommendations based on genotypes. When a patient is a poor metabolizer, it suggests which of the antidepressants need adjusting and how much the adjustment needs to be for each of the SSRIs. This paper was designed to clearly communicate what we know and I have found it to be very helpful.

Is there a computer program that sends reports when they pick up a red flag about adverse drug reactions?

The product developed by AssureRx provides alerts related to possible adverse reactions that can guide clinical decision making. A computerized algorithm has been developed to adjust for the implications of the variability of a set of informative genes. Even experts in the field have to carefully sort through the implications of multiple gene variants, but this is not feasible in the clinical practice. The beauty of programming a computer to sort through the complex implications of these variants is that it can accomplish this task in nanoseconds.

The AssureRx computer program sorts through the genetic implications for 18 antidepressants, including the tricyclics, SSRIs, and serotonin norepinephrine reuptake inhibitors. It also considers the implications of genetic variations for six atypical and two typical antipsychotic medications.

Is there anything you would like to add?

It is important to think about not just what testing is available today, but also what our future testing capacity will be. There is extraordinary news on the horizon. The price of sequencing the entire genome of a patient is expected to cost <$1,000 within 5 years. According to Collins,2 when testing reaches this price point, every patient will have access to his or her genomic sequence. DNA will not have to be sent to the laboratory to identify variation in one gene after the other. Instead, pediatricians will know the entire genome of each of their patients. The challenge will no longer be DNA analysis, but rather analyses of the clinical implications of the sequence variations. This technology will revolutionize pediatrics as well as psychiatry because the question, “Which genotype should I order?” will no longer be relevant. Instead, clinicians will “ask” their computer support system to tell them what is unique about each of their patients. This advance in technology will remove a huge step in the translation of the implications of genetic variations.

REFERENCES