# Clinical and Ethical Considerations in Pharmacogenetic Testing: Views of Physicians in 3 "Early Adopting" Departments of Psychiatry

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***Objective:*** Pharmacogenetic testing for polymorphisms affecting drug response and metabolism is now clinically available, and its use in psychiatry is expected to become more widespread. Currently, few clinical and ethical standards exist for the use of these new tests. As a step toward building consensus about testing, we assessed the attitudes and practices of psychiatrists at 3 academic departments of psychiatry where pharmacogenetic testing is clinically available. We hypothesized that testing would be used primarily in treatment-resistant illness and that clinicians would believe such tests carried little risk.

***Method:*** Residents and faculty at 3 departments of psychiatry considered to be "early adopters" of pharmacogenetic testing were invited during the academic year 2006–2007 to complete an Internet-based survey, including questions regarding clinical practices and opinions about testing utility, risks, and necessary safeguards.

***Results:*** The 75 respondents had ordered pharmacogenetic testing a mean of 20.86 times in the previous 12 months. Testing was judged most useful in cases of treatment-resistant depression and medication intolerance. There was a lack of consensus about the risks of testing, particularly the risk of secondary information about disease susceptibility. Respondents endorsed the use of several safeguards, including confidentiality, pretest and posttest counseling, and informed consent, but consensus about other safeguards was lacking. Women and those who had not ordered testing in the prior year were more concerned about risks and need for safeguards than were men and those who had recently ordered testing.

***Conclusions:*** Physicians at early adopting departments of psychiatry endorsed the clinical utility of pharmacogenetic testing and the use of some patient safeguards, but showed a lack of consensus about other safeguards and risks.

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The long-awaited genomic era in medicine has brought with it new hope for improving the treatment of individuals who suffer the burden of mental illness. Since the late 1990s, research has greatly expanded our understanding of how genetic factors influence the pharmacokinetic and pharmacodynamic properties of major classes of psychotropic drugs, including antidepressant and antipsychotic medications. For example, it is now clear that the cytochrome P-450 2D6, 2C19, and 2C9 enzyme systems are involved in the metabolism of most of the antidepressant medications used today. An estimated 7% of Caucasians are poor metabolizers of CYP 2D6, while 2% of Asians and 2%–4% of African Americans are poor metabolizers.[1] Poor metabolizers may experience more adverse effects from antidepressant treatment, whereas ultrarapid metabolizers might have no clinical response to antidepressants given at the usual dosages.

In addition, genetic variants that affect the pharmacodynamics of psychotropic medications have also been identified. For example, the serotonin transporter gene *(5-HTT)* contains promotor polymorphisms that are thought to contribute to adverse effects and delay response to antidepressants that act on the serotonin system, such as selective serotonin reuptake inhibitors (SSRIs). In a randomized, double-blind study of 246 geriatric patients with depression, those with a shortened form of the *5-HTT* gene experienced less antidepressant response to paroxetine (an SSRI) than to mirtazapine (a non-SSRI) and more side effects with paroxetine than mirtazapine.[2] Thus, patients with a short *5-HTT* allele may not achieve optimal response or minimal side effects when treated with an SSRI. A recent meta-analysis of 15 studies and 1,435 patients reported a significant association between serotonin gene transporter polymorphisms and clinical response to SSRIs in patients with depression.[3] Another meta-analysis showed that the same polymorphisms as well as variants in the serotonin 2A receptor gene (*HTR2A*) significantly modulated the risk of antidepressant side effects.[4]

In theory, such research may have important applications to the clinical care of people with mental illness—providing psychiatrists with rational bases for selecting appropriate medications and dosages to avoid adverse effects and nonresponse.[5,6] A recent survey of a small, random sample of US psychiatrists (n = 48) suggests that clinicians would welcome these applications: 82% of those surveyed believed that pharmacogenetic testing to predict serious adverse effects would be somewhat or extremely useful in the clinical

setting, and 73% believed that testing to determine optimum dosages would be extremely or somewhat useful.[7]

As data are being gathered about the clinical benefits of pharmacogenetic testing, understanding has also grown about its potential risks. Because of the biologic phenomenon of genetic pleiotropy (ie, a single gene may have multiple biologic effects), pharmacogenetic testing may inadvertently yield secondary information about susceptibility to disease (including diseases other than the condition being treated).[8–11] For example, *5-HTT* has been associated in some samples not only with response to SSRIs but also with suicidal behavior, borderline personality traits, autism, and many other conditions.[12–15] Similarly, a variant in the guanine nucleotide binding protein β polypeptide 3 (*GNB3*) has been linked with antidepressant response and risk of diabetes and hypertension.[9,16–18] Genetic variants in the dopamine receptor 2 (*DRD2*) have been associated with response to bupropion and susceptibility to alcoholism.[9,19,20] Variants in the gene for the CYP450 2D6 enzyme has been associated in some samples with specific personality types.[21]

It is thus possible that a test undertaken purely to drive decision-making about SSRI treatment may provide genotype data that in the future can be interpreted to demonstrate that the individual is at elevated risk of a disease or condition. This information may be unwanted and distressing and could conceivably result in harms such as social stigmatization or discrimination,[9–11] although a new federal law promises to bar some forms of insurance and employment discrimination based on genetic testing.[22]

While the evidence base is growing regarding pharmacogenetic testing risks and benefits, it is unclear whether, how, and when pharmacogenetic testing should be introduced into clinical practice. The Centers for Disease Control's (CDC's) Evaluation of Genomic Applications in Practice and Prevention Working Group in 2007 published an evidence-based review of testing for the CYP450 genotype in adults with nonpsychotic depression.[23,24] The review considered 5 studies of the association of genotype with clinical response and 9 studies that related genotype and adverse drug effects. The group found a lack of consistent evidence to support the clinical validity of testing. No studies were found in the literature addressing the clinical utility of testing—that is, the effect on outcomes. Due to the lack of data, the CDC Working Group discouraged the use of CYP450 genotyping for the initiation of SSRI treatment of nonpsychotic depression.[23,24]

As the CDC review makes clear, a considerable body of new knowledge must be created before consensus is reached about the appropriate clinical use of pharmacogenetic testing in psychiatry.[23,25] Data are especially needed regarding actual patient outcomes, including identifying the benefits of testing and any harms that may result. An understanding of how clinical psychiatrists and their patients assess the benefits and harms of testing is crucial in developing this knowledge base. To date, however, there have been no systematic attempts to assess the attitudes or experiences of any stakeholder group regarding the role and the key clinical and ethical issues relevant to pharmacogenetic testing in psychiatry.

This preliminary study was designed to begin to address the evidentiary gap by surveying psychiatrists at 3 US academic medical centers considered to be at the forefront of pharmacogenetic testing. These are settings where at least some psychiatrists have begun to offer clinical testing to psychiatric patients and where at least some patients are seeking care, especially because of the availability of genetic testing. We sought to understand how and why clinicians at these "early adopting" departments of psychiatry used (or chose not to use) the new technology, to learn from their unique experiences, and to gather baseline data in the event that pharmacogenetic testing enters widespread use in psychiatric practice. We hypothesized that pharmacogenetic testing would be used primarily for treatment-resistant illness and that clinicians would believe that testing provided many benefits and few risks.

## METHOD

### Participants

All 204 psychiatry attending physicians and residents at 3 academic medical centers during the 2006–2007 academic year were invited to participate in this voluntary, anonymous survey. The 3 sites were geographically dispersed departments of psychiatry in the United States identified by experts in pharmacogenetic testing to be on the forefront of its clinical use—Mayo Clinic, University of Louisville, and Georgia Medical College. The institutional review boards at Medical College of Wisconsin and Mayo Clinic (ie, the home sites of the investigators) approved this study.

### Survey

The survey was based on a previously developed self-administered written questionnaire to assess psychiatrists' views and practices regarding genetic medicine. The development of the prior questionnaire has been described elsewhere.[7,26] The survey was modified to be Internet-based and to focus specifically upon pharmacogenetic testing. The survey included 67 yes/no, rating scaled, and short-answer questions to assess demographics, practice patterns, and views on pharmacogenetic testing, including clinical usefulness and effect on psychiatry, psychosocial risks, self-assessed competency, ethical issues, and need for specific safeguards. One open-ended question asked participants to express their views on the topic. To ensure content validity, the survey was pretested with clinical psychiatrists and experts in survey design, data analysis, and psychopharmacogenetics.

### Procedure

Psychiatry attending physicians and residents at each site were sent e-mails explaining the purpose and nature of the study and inviting them to participate via an electronic hyperlink. To increase response rates, a follow up e-mail was distributed 1 week after the first invitation. Survey responses



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were gathered electronically and stored anonymously in a central data repository.

### Data Analysis

Categorical response frequencies are reported. Small differences in sample size arise from sporadic missing responses. Cohen *d* is reported as a measure of effect size. Separate repeated-measures multivariate analyses of variance with location, gender, current position (faculty or resident/fellow), amount of pharmacogenetics training, clinical demand for pharmacogenetic testing, and recent ordering of tests (no tests vs 1 or more tests ordered in prior 12 months) were conducted as between-subjects variables, with item as the within-subjects variable. To create the pharmacogenetics training variable, the responses for the item regarding amount of pharmacogenetics training were coded as "none or minimal" vs "moderate or extensive." To create the clinical demand variable, participants' answers to the item regarding the number of patients inquiring about pharmacogenetic testing were used as a median split variable, in which approximately 50% of the values were set equal to 1 (3 or fewer patients inquiring about testing in prior 12 months) and 50% were set equal to 2 (more than 3 patients). Significant differences between groups are reported.

## RESULTS

### Participant characteristics

We received a total of 75 responses, yielding an overall response rate of 37%. There were uneven response rates across the 3 sites: 69% at Mayo Clinic, 26% at Georgia Medical College, and 11% at University of Louisville. These differences are roughly consistent with observed differences in the 3 departments' emphases on pharmacogenetic testing. There were no significant differences among the 3 locations for any survey item or set of items. Respondents were approximately evenly divided between residents and faculty and between men and women (Table 1).

**Table 1. Participant Characteristics**

| Characteristic | Responses | |
|---|---|---|
| | Frequency | % |
| Gender | | |
| Women | 34 | 45 |
| Men | 34 | 45 |
| Position | | |
| PGY1 resident | 5 | 7 |
| PGY2 resident | 9 | 12 |
| PGY3 resident | 7 | 9 |
| PGY4–6 resident or fellow | 11 | 15 |
| Faculty | 35 | 47 |
| | Mean | SD |
| No. of patients seen in a month | 72.86 | 52.9 |
| Years since most recent training in genetics | 6.62 | 6.86 |
| | Responses, % | |
| Amount of training in pharmacogenetics | | |
| None | | 5 |
| Minimal | | 56 |
| Moderate | | 21 |
| Extensive | | 5 |

Abbreviation: PGY = postgraduate year.

**Table 2. Experience With Pharmacogenetic Testing Among Physicians at 3 Early Adopting Departments of Psychiatry**

| Item | Responses (N = 69) | | | |
|---|---|---|---|---|
| | Mean | | SD | |
| No. of requests by psychiatric patients regarding pharmacogenetic testing (per mo) | 11.59 | | 41.47 | |
| No. of times clinical pharmacogenetic tests were ordered for psychiatric patients (per past y) | 20.86 | | 48.5 | |
| No. of patients referred for pharmacogenetic testing or assessment (per past y) | 0.94 | | 2.52 | |
| | Yes | | No | |
| Type of test ordered | n | % | n | % |
| CYP450 | | | | |
| *2D6* | 57 | 76 | 13 | 17 |
| *2C19* | 51 | 68 | 17 | 23 |
| *2C9* | 46 | 61 | 22 | 29 |
| Serotonin transporter (*5-HTT*) | 23 | 31 | 41 | 55 |
| Serotonin receptor (*HTR2A, HTR2C*) | 12 | 16 | 49 | 65 |

### Psychiatrists' Experience With Pharmacogenetic Testing

Participants had ordered pharmacogenetic testing a mean of 20.86 times in the previous 12 months (Table 2). Responses from 11 individuals (14.7%) indicated they had not ordered any pharmacogenetic testing during the prior 12 months (data not shown). Forty-eight individuals (64%) indicated they had ordered testing 1 or more times during that period. (Proportions do not total 100% due to sporadic missing responses.)

### Self-Assessed Competency Regarding Pharmacogenetics

Respondents were asked to rate their level of agreement with 5 statements on a scale of 1 = "strongly disagree" to 4 = "strongly agree" (Table 3). There was significantly more agreement with the statement "I feel that it is a psychiatrist's role to offer pharmacogenetic testing in appropriate clinical circumstances" (mean = 3.10) than the other 4 items concerning the individual's personal competency [$F_{4,260} = 8.37$, $P < .001$, maximum $d = 0.63$].

There were significant multivariate effects for 3 of the between-subjects variables on these items. First, respondents with moderate or extensive pharmacogenetics training (mean = 3.38) more strongly endorsed all 5 items than those with no pharmacogenetics training or minimal training (mean = 2.63) [$F_{1,63} = 49.78$, $P < .001$]. Second, respondents who reported greater clinical demand reported more agreement with all statements except "I feel competent to identify clinical situations in which pharmacogenetic testing is indicated" [$F_{1,65} = 21.24$, $P < .001$].

Finally, respondents who had ordered testing during the prior 12 months had significantly higher overall scores on these items (mean = 2.96) than those who had not ordered testing (mean = 2.36) [$F_{1,56} = 16.33$, $P < .001$].

### Perceptions of the Clinical Usefulness of Pharmacogenetic Testing

Participants were asked to rate on a scale of 1 = "not useful" to 4 = "extremely useful" the value of pharmacogenetic

**Table 3. Self-Assessed Competency in Pharmacogenetic Testing Among Physicians in 3 Early Adopting Departments of Psychiatry**

| Item[a,b,c] | Self-Assessment by Gender (mean score) | | | Self-Assessment, Overall (N = 67) | |
|---|---|---|---|---|---|
| | Men (n = 34) | Women (n = 33) | $d$[d] | Mean | SD |
| It is a psychiatrist's role to offer pharmacogenetic testing in appropriate clinical circumstances | 3.18 | 3.03 | 0.23 | 3.10 | 0.58 |
| I feel competent to… | | | | | |
| Order pharmacogenetic tests | 3.03 | 2.76 | 0.43 | 2.89 | 0.62 |
| Identify clinical situations in which testing is indicated | 2.94 | 2.64 | 0.48 | 2.79 | 0.64 |
| Inform patients of the risks and benefits of testing[e] | 2.97 | 2.58 | 0.62 | 2.77 | 0.69 |
| Make treatment recommendations based on results[e] | 2.91 | 2.52 | 0.63 | 2.71 | 0.69 |

[a]Responses scaled from 1 = "strongly disagree" to 4 = "strongly agree."
[b]Means are from a repeated-measures item × gender multivariate analysis of variance. Item main effect, $P < .01$. Gender main effect, $P < .05$. Pooled SD = 0.65. Differences in item means > 0.16 differ at $P < .05$ by Fisher least significant difference.
[c]Means within single columns differing by 0.22 for gender, 0.25 for overall, are significantly different by Fisher least significant difference at $P < .05$.
[d]Cohen $d$, an effect size that is the standardized mean difference.
[e]Gender means differ at $P < .05$ by analysis main effect for marginal means and Fisher least significant difference for item comparisons.

**Table 4. Perceived Usefulness of Pharmacogenetic Testing in 7 Clinical Situations Among Physicians at 3 Early Adopting Departments of Psychiatry**

| Item[a,b,c] | Perception of Usefulness by Gender (mean score) | | | Perception of Usefulness, Overall (N = 65) | |
|---|---|---|---|---|---|
| | Men (n = 32) | Women (n = 33) | $d$[d] | Mean | SD |
| Medication intolerance | 3.59 | 3.73 | −0.16 | 3.66 | 0.59 |
| Treatment-resistant depression | 3.50 | 3.70 | −0.23 | 3.60 | 0.70 |
| Chronic schizophrenia | 2.91 | 3.06 | −0.18 | 2.98 | 0.86 |
| Delirium or cognitive impairment in a geriatric patient | 2.81 | 2.67 | 0.17 | 2.74 | 0.86 |
| New-onset severe depression and suicidal ideation requiring hospitalization | 2.63 | 2.82 | −0.23 | 2.72 | 0.91 |
| Newly diagnosed psychiatric syndrome | 2.66 | 2.64 | 0.02 | 2.65 | 0.93 |
| New-onset severe psychosis requiring hospitalization | 2.59 | 2.67 | −0.09 | 2.63 | 0.96 |

[a]Responses scaled from 1 = "not useful" to 4 = "extremely useful."
[b]Means are from a repeated-measures item × gender multivariate analysis of variance. Item main effect, $P < .001$. Pooled SD = 0.84. Differences in item means > 0.24 differ at $P < .05$ by Fisher least significant difference.
[c]Means within single columns differing by 0.40 are significantly different by Fisher least significant difference at $P < .05$.
[d]Cohen $d$, an effect size that is the standardized mean difference.

testing in various clinical situations (Table 4). Those surveyed rated testing as significantly more useful for medication intolerance (mean = 3.66) and treatment-resistant depression (mean = 3.60) than for the other items, though testing was considered at least somewhat useful for all the scenarios: $F_{6,378} = 36.22$, $P < .001$, maximum $d = 0.17$. Only 1 respondent believed that testing was *not* useful in cases of medication intolerance. There were no significant between-subjects differences on this group of items.

### Perceptions of the Risks of Pharmacogenetic Testing

Participants were asked to rate their level of agreement with 5 statements about the possible risks of pharmacogenetic testing on a scale of 1 = "strongly disagree" to 4 = "strongly agree." There were significant differences by gender on these items, with women more strongly agreeing that testing carried specific risks ($F_{4,136} = 7.39$, $P < .01$, maximum $d = -1.06$) (Table 5).

### Typical Practices Regarding Pharmacogenetic Testing

Respondents answered "yes" or "no" to 13 questions about what their typical practices are or would be regarding informed consent, confidentiality, and other safeguards for testing. There were significant differences by recent ordering of testing (Table 6) and by gender and position (data not shown). Women were more likely than men to state that they would meet with the patient to answer questions and explain the results (100% vs 88%, $P < .05$). Faculty members were more likely than trainees to say they would test only those over 18 years (56% vs 19%, $P < .01$) and only those with decisional capacity (70% vs 44%, $P < .05$).

### Ethical Aspects of Pharmacogenetic Testing

Participants were asked to rate their level of agreement with 10 statements about ethically relevant aspects of pharmacogenetic testing. Respondents reported significantly less agreement with the statement that psychiatrists should "provide testing to everyone who requests it" than to the other 9 items ($F_{9,576} = 46.58$, $P < .001$, maximum $d = 0.72$) (Table 7).

### Acceptability of Racial Identification as a Proxy for Pharmacogenetic Testing

Using a scale of 1 = "not at all acceptable" to 4 = "completely acceptable," respondents were asked to rate the acceptability of a physician using a person's self-identified



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**Table 5. Perceived Risks of Pharmacogenetic Testing Among Clinicians at 3 Early Adopting Departments of Psychiatry**

| Item[a,b,c] | Perception of Risk by Gender (mean score) | | | Perception of Risk, Overall (N = 36) | | |
|---|---|---|---|---|---|---|
| | Men (n = 19) | Women (n = 17) | $d$[d] | Mean | SD | Don't Know, %[e] |
| Test results could provide secondary information about susceptibility to disease or prognosis | 2.95 | 2.82 | 0.20 | 2.89 | 0.53 | 25 |
| Testing could cause a patient psychological distress[f] | 2.53 | 3.18 | −1.06 | 2.85 | 0.58 | 9 |
| Testing could negatively affect a patient's insurability[f] | 2.47 | 3.00 | −0.86 | 2.74 | 0.61 | 21 |
| Other than the risks of having blood drawn, there are no identifiable risks associated with testing[f] | 2.79 | 2.18 | 1.00 | 2.48 | 0.68 | 8 |
| Testing could negatively affect a patient's employability[f] | 2.21 | 2.71 | −0.81 | 2.46 | 0.66 | 27 |

[a]Responses scaled from 1 = "strongly disagree" to 4 = "strongly agree."
[b]Means are from a repeated-measures item × gender multivariate analysis of variance. Item main effect $P < .05$; view × gender interaction, $P < .01$. Pooled SD = 0.67. Differences in item means > 0.39 differ at $P < .05$ by Fisher least significant difference.
[c]Means within single columns differing by 0.26, 0.29, or 0.39, respectively, are significantly different by Fisher least significant difference at $P < .05$.
[d]Cohen $d$, an effect size that is the standardized mean difference.
[e]Percentage of "don't know" responses.
[f]Gender means differ at $P < .05$ by analysis main effect for marginal means and Fisher least significant difference for item comparisons.

**Table 6. Typical Practices for Pharmacogenetic Testing Among Clinicians at 3 Early Adopting Departments of Psychiatry[a]**

| Item | No. of Pharmacogenetic Tests Ordered (past 12 mo) | | | | Overall | |
|---|---|---|---|---|---|---|
| | None (n = 11) | | 1 or More (n = 48) | | Pearson's $\chi^2$ (df = 1) | $P$ |
| | Frequency | % | Frequency | % | | |
| Practices when ordering testing | | | | | | |
| Tell patients the test is being ordered | 11 | 100 | 47 | 100 | 0.00 | 1.000 |
| Obtain the patients' verbal consent | 10 | 100 | 46 | 98 | 0.22 | .642 |
| Tell patients about the cost of testing | 11 | 100 | 41 | 87 | 1.57 | .211 |
| Test only patients for whom there is an immediate medical benefit | 7 | 64 | 28 | 60 | 0.061 | .804 |
| Test only those with decisional capacity | 6 | 55 | 24 | 53 | 0.005 | .942 |
| Test patients who are unlikely to have an immediate medical benefit but who request testing to gain information that may be useful in the future | 5 | 45 | 27 | 60 | 0.764 | .382 |
| Test only those over 18 | 4 | 36 | 19 | 41 | 0.09 | .0764 |
| Obtain the patients' written consent | 6 | 55 | 8 | 17 | 6.61 | < .05 |
| Practices when receiving test results | | | | | | |
| Meet with patients to answer questions and explain the results | 10 | 91 | 45 | 96 | 0.43 | .514 |
| File results in the patients' medical record | 9 | 82 | 46 | 97 | 4.68 | < .05 |
| Tell patients that results may also pertain to family members | 10 | 91 | 30 | 64 | 3.05 | .081 |
| Communicate results to the patients' primary doctor | 8 | 73 | 34 | 72 | 0.001 | .979 |
| Tell patients that results may provide secondary information | 8 | 73 | 16 | 35 | 5.24 | < .05 |
| Create a separate file for test results kept apart from the official medical record | 2 | 18 | 1 | 2 | 4.56 | < .05 |

[a]Items were phrased as follows: "When ordering pharmacogenetic testing for a patient, which of the following actions are or would be part of your typical practice?" and "When receiving pharmacogenetic test results, which of the following actions are or would be part of your typical practice?" Responses were scaled as "yes/no."

**Table 7. Opinions Regarding Ethically Relevant Aspects of Pharmacogenetic Testing Among Physicians at 3 Early Adopting Departments of Psychiatry**

| Item[a,b,c] | Responses, Mean | | | Overall (N = 66) | |
|---|---|---|---|---|---|
| | Men (n = 33) | Women (n = 33) | $d$[d] | Mean | SD |
| To use pharmacogenetic testing in an ethical manner, psychiatrists should… | | | | | |
| Ensure that test results are confidential | 3.42 | 3.27 | 0.24 | 3.35 | 0.54 |
| Demonstrate competence in interpreting test results | 3.24 | 3.36 | −0.19 | 3.30 | 0.58 |
| Obtain informed consent before testing | 3.24 | 3.33 | −0.14 | 3.29 | 0.63 |
| Provide pretest and posttest counseling | 3.09 | 3.30 | −0.34 | 3.20 | 0.66 |
| Provide testing only if the psychiatrist believes benefits outweigh risks | 3.06 | 3.03 | 0.05 | 3.05 | 0.51 |
| Test only those with decision-making capacity | 2.85 | 2.55 | 0.48 | 2.70 | 0.80 |
| Treat pharmacogenetic tests like genetic tests for susceptibility to disease | 2.42 | 2.55 | −0.19 | 2.49 | 0.56 |
| Test only those age 18 years and older | 2.30 | 2.33 | −0.05 | 2.32 | 0.64 |
| Treat pharmacogenetic tests like routine laboratory tests[e] | 2.52 | 2.06 | 0.72 | 2.29 | 0.70 |
| Provide testing to everyone who requests it | 2.09 | 2.06 | 0.05 | 2.08 | 0.66 |

[a]Scaled from 1 = "strongly disagree" to 4 = "strongly agree."
[b]Means are from a repeated-measures item × gender multivariate analysis of variance. Item main effect, $P < .001$; view × gender interaction, $P < .05$. Pooled SD = 0.63. Differences in item means > 0.21 differ at $P < .05$ by Fisher least significant difference.
[c]Means within single columns differing by 0.24, 0.25, or 0.33, respectively, are significantly different by Fisher least significant difference at $P < .05$.
[d]Cohen $d$, an effect size that is the standardized mean difference.
[e]Gender means differ at $P < .05$ by analysis main effect for marginal means and Fisher least significant difference for item comparisons.

race or ethnicity as part of the basis for selecting medications and doses, given that some genetic variants associated with drug response and metabolism occur in different frequencies in different population groups. Respondents answered that this would be somewhat acceptable (mean = 3.29; SD = 0.73) (data not shown).

### Predictions of Effect of Pharmacogenetic Testing on Psychiatry

Respondents were asked to rate their level of agreement with 6 statements concerning the professional impact of testing, using a scale of 1 = "strongly disagree" to 4 = "strongly agree." Psychiatrists agreed with statements that pharmacogenetic testing would "benefit many psychiatric patients" (mean = 3.03) and "dramatically change the way psychiatry is practiced" (mean = 2.77). They neither agreed nor disagreed that testing would "be too expensive for most patients" (mean = 2.60). Respondents disagreed with statements that testing would "have little effect on how most psychiatrists practice" (mean = 2.04), "expose psychiatric patients to many risks" (mean = 1.93), and "be irrelevant to my own work" (mean = 1.93 [$F_{5,310} = 40.39$, $P < .001$, maximum $d = -0.74$]).

There were significant multivariate effects for gender and clinical demand with this set of items. Women (mean = 2.79) rated significantly more agreement than men (mean = 2.32) with the statement that pharmacogenetic testing would "be too expensive for most patients" ($F_{5,310} = 3.25$, $P < .05$). Respondents with greater clinical demand reported significantly more agreement with the statement that pharmacogenetic testing would "benefit many psychiatric patients" and significantly less agreement with statements that it would "be irrelevant to my own work," "expose psychiatric patients to many risks," and "be too expensive for most patients" ($F_{5,310} = 4.21$, $P < .01$).

### Narrative Comments

Of the 75 participants, 17 (23%) responded to an open-ended question inviting additional comments about pharmacogenetics and psychiatry. Qualitative analysis identified 5 dominant themes in the narrative comments, as well as comments about the survey itself. The 5 themes were as follows:

Optimism about the potential of psycho-pharmacogenetic testing:

> *I think it has great potential to help our patients, but it is done far too little.*

> *I anticipate that a significant portion of our lack of specificity in psychiatry (eg, who will respond to which antidepressant, who will get certain side effects from meds, all the subtypes of depression and ADHD [attention-deficit/hyperactivity disorder], etc, etc) is attributable to genetic differences. I can't wait till we have more available information and the clinical tools to make it useful in our work with patients.*

Dismissal of concerns about risks of testing:

> *Pharmacogenetic testing will no more negatively impact insurance and employment status … than the current diagnosis and treatment….The term "pharmacogenetic" implies no relation to disease susceptibility but drug choice and genetic basis for response or tolerability.*

> *[Pharmacogenetic testing] should be treated as a useful new laboratory test rather than a potential "scarlet letter."*

Identification of barriers to widespread clinical testing:

> *[We] need clear, peer-reviewed published evidence that the test results correlate with side effects or treatment responses in a predictable and measurable manner.*

> *Pharmacogenetic testing is more effective at determining slow metabolizers versus extensive metabolizers. There are clearly individuals that have an amazing capacity to metabolize certain medications and until the tests are perfected to include those patients, widespread use in the field is not likely to happen.*

> *[I] found it most useful to date for antipsychotics and antidepressants. [I am] still struggling for benefit in assessing stimulant metabolism.*

> *[There is] limited training in the more ethical applications.*

> *Insurance and informed consent issues are the biggest barriers currently to pharmacogenetics.*

General skepticism about the current benefits of testing:

> *I think we have a long way to go yet before this is more clinically useful.*

> *I think the whole pharmacogenetics thing is way out of proportion. I don't think it's nearly as important or helpful for future practice as all the hype it has created. Clinical practice will still be the same without it.*

Concerns that testing is being used inappropriately:

> *I have concerns that current testing availability provides information that has very limited current clinical application (eg, serotonin transporter gene). I do not believe that current standard of care supports some of the extensive testing I have seen. Issues of cost and timeliness of [laboratory] results are critical and must be considered in risk/benefit analysis just like other testing.*

> *I don't think that there is enough pretest counseling being done and that often providers overstate the value of this test to the average patient. It is often presented to patients as being "the answer" to why they are not improving rather than being included as only a part of why they may have limited response. I become concerned at times because it seems that providers are almost too quick to order it and that when patients request the test it is ordered without the patient really getting the level of counseling that may be done with other genetic testing.*



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## DISCUSSION

To our knowledge, this work represents the first empirical data regarding the clinical use of pharmacogenetic testing in psychiatry. This preliminary work was designed to capture some of the experiences and attitudes of psychiatry faculty and trainees at departments that are early adopters of pharmacogenetic testing. These individuals, who ordered a mean of 20.9 such tests in the prior year, represent an unusual and important intellectual resource for the creation of clinical and ethical guidelines for this emerging technology. As practitioners with clinical experience in providing testing, they have had an opportunity to observe firsthand the benefits and harms that accrue to their patients and to learn which safeguards may be needed to protect them.

The respondents to this study clearly have clinical experiences and competencies that set them apart from most psychiatrists. More than a quarter of the sample reported that they had moderate or extensive training in pharmacogenetics, a higher percentage than might be expected among general psychiatrists. The clinicians in this study also expressed confidence in their skills related to pharmacogenetic testing. They more strongly endorsed feeling competent than did residents at 55 psychiatry training programs,[27] only 9% of whom said that they felt competent to offer genetic testing and interpret results. Furthermore, only 9% of a probability sample of US psychiatrists reported self-assessed competence regarding genetic testing.[26]

The views and experiences of this unique group of physicians yield several findings with implications for the creation of guidelines for clinical testing. First, and as expected, physicians in early adopting departments of psychiatry generally perceive pharmacogenetic testing in a positive light, though a few voiced serious concerns in narrative comments that testing is being overhyped or overused. While those who reported higher clinical demand for testing tended to be more positive in their assessment of the professional impact of testing than those with less clinical demand, the participants were in agreement about the usefulness of testing in a variety of clinical situations. They viewed pharmacogenetic testing as somewhat useful in several situations, and most useful in cases of medication intolerance and treatment-resistant depression. The CDC's Working Group on the application of genomic medicine has thus far addressed only the use of CYP450 testing for the initiation of treatment of nonpsychotic depression.[23,24] The data reported here indicate that a review of the clinical validity and utility evidence for CYP450 testing for medication intolerance and treatment-resistant depression would be a useful and timely addition to the literature.

The second major finding of this study is the lack of consensus among our participants about the risks of pharmacogenetic testing. There were significant differences in the responses of participants by gender, with women tending to agree more strongly with the statements that pharmacogenetic testing carried particular risks. The effect size of these differences was large (Table 5). This preliminary study was not designed to explore the bases for such between-subjects effects, though one might speculate differences in risk-taking or approaches to new technology are associated with gender. It is interesting to note that gender differences have been demonstrated in surveys of medical trainees regarding ethics, with women more likely to endorse the importance of ethics education or ethical safeguards.[28–30] Future studies that employ qualitative methods will be necessary to understand the meaning of this disparity in the perception of risks.

The third key finding of this study is our participants' general endorsement of specific patient safeguards and ethical requirements for clinical pharmacogenetic testing, including obtaining informed consent, protecting confidentiality, and providing pretest and posttest counseling. It appears that most clinicians viewed pharmacogenetic information as somewhat "exceptional" compared with routine laboratory testing,[31] though not necessarily requiring the level of safeguards used for predictive genetic testing—which typically includes testing only adults and those with decisional capacity.[32]

Our findings regarding safeguards were complex, however, with clear differences among some subgroups of participants on some items. Psychiatry residents and fellows were less concerned with patients' capacity to consent than faculty were, and physicians who had not ordered testing during the prior 12 months were more concerned about safeguards to protect against the harms due to secondary information than were physicians who had ordered testing. The cause of these disparities is not clear. It may be, for example, that some physicians had not ordered testing because they perceive a need for institutional safeguards that do not exist (such as heightened confidentiality protections for test results). This possibility is underscored by the narrative comments, which indicate that some members of early adopting departments believed that testing is premature and exposes patients to unnecessary risks.

The lack of agreement about risks and safeguards may in part be due to the timing of our survey, which was conducted during the 2006–2007 academic year, before recent publications regarding risks of pharmacogenetic testing, in particular the risk of unwanted secondary information.[8–11] Follow-up study is needed to assess early adopters' current practices regarding these and other safeguards.

Finally, our respondents rated as somewhat acceptable the use of self-identified race or ethnicity as a partial basis for selecting medications and doses, given that the frequency of some pharmacogenetic variants varies among ancestral populations. The use of self-identified ethnicity as a proxy for genetic ancestry is not without precedence in clinical medicine. For example, the US Food and Drug Administration in 2007 recommended screening Asian patients for the HLA-B*1502 genetic marker before initiating carbamazepine treatment, to reduce the incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis.[33] The recommendation has been criticized on scientific grounds, however, because of the high potential for a mismatch between self-

identified ethnicity (or "physician-identified" ethnicity) and genetic ancestry, and on ethical grounds because of the potential for unfair access to treatment or costs of care based upon social groupings.[34] The current study suggests that psychiatrists may have little objection to such practice, but additional study is clearly required to better understand how and why psychiatrists would tailor treatment or pharmacogenetic screening to patients of various subgroups and what the implications of this might be for patients' access to care.

This novel, preliminary study has several limitations. First, this work does not claim to be generalizable to all psychiatrists, because physicians in early adopting departments of psychiatry are a unique population whose views are relevant in their own right. In addition, we make no claim of generalizability to all psychiatrists, even at the 3 departments, because response rates for 2 of the 3 sites were low. It should be noted that the overall response rate for this study is equivalent to other published Internet-based surveys,[35] and that the response rate was unusually high (69%) for the department with the greatest national presence in pharmacogenetic testing. Furthermore, there were no significant location-specific differences in the responses to individual items or sets of items. The lack of differences indicates that achieving more responses from the 2 sites with low rates might not have substantially altered the results of the survey, suggesting that our study, though small, may have generalizable findings.

The overall response rate does raise the possibility that self-selection may bias our results—that is, those who chose to respond to the survey invitation may differ in important ways from those who did not. If this is a factor, we would expect that it resulted in more extreme attitudes (positive *and* negative) toward testing. Nevertheless, it is unlikely that selection bias alone could account for the study's major findings—the uniformity of opinion about the clinical usefulness of testing and lack of consensus regarding the risks and appropriate safeguards.

Finally, this study relied upon self-report data rather than objective measures of psychiatrists' practices. It is possible that some answers were biased by errors in recall or by the tendency to choose socially desirable responses. The latter bias would most likely skew data toward greater endorsement of the use of specific practice safeguards.

## CONCLUSIONS

Pharmacogenetic testing appears to hold great promise for providing "individualized medicine" to psychiatric patients, who have long suffered disparities in access to state-of-the-art care. This study is among the first such surveys regarding pharmacogenetic testing in any field, and it is unknown whether other specialties have been more or less aggressive in embracing the new technology. Compared with some other specialties, psychiatry has a much smaller empirical evidence base, and psychiatrists historically have had no choice but to practice with less guidance from the scientific literature. This should not translate into a lack of caution about the introduction of pharmacogenetic testing into everyday practice in advance of clear evidence of its risks and benefits. In our efforts as a profession to bring potentially valuable technological innovations to the care of our patients, it will be crucial to also bring companion safeguards.

Before the widespread introduction of testing, several challenges must be met. First, in the words of one of our participants, we need "clear, peer-reviewed published evidence that the test results correlate with side effects or treatment responses in a predictable and measurable manner." Second, we need greater understanding of the potential harms associated with testing, which can be extrapolated from data about other types of testing and assessed prospectively in psychiatric populations. Third, we need leaders in the field to create and frequently update consensus statements and clinical practice guidelines, setting forth "best practices" for pharmacogenetic testing and safeguards. Finally, but no less important, we will need to develop pharmacogenetics curricula to help teach current and future psychiatrists to provide testing in a manner that meets the high clinical and ethical standards that our patients deserve.

***Drug names:*** bupropion (Aplenzin, Wellbutrin, and others), carbamazepine (Carbatrol, Equetro, and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others).

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