

Translational Psychiatry: Bringing Pharmacogenomic Testing into Clinical Practice

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ABSTRACT

Significant inter-individual variability exists in antidepressant response, therapeutic dosage, and adverse effect profile. Prolonged times to response or remission represent a period of suffering associated with increased risk for morbidity and mortality. Improving care in depression treatment using a more biologically informed selection of psychopharmacologic agents through genotyping has become a reality in psychiatric practice. Routine genotyping has now become available for gene variations that code for proteins involved in neurotransmission and for drug-metabolizing enzymes involved with the disposition of many pharmacologic agents including antidepressants. Clinical validation and reliability of genotyping, access to testing, uniformity and clarity in test interpretation, and clinician and patient education are critical to this process of innovation diffusion. This article focuses on the introduction of pharmacogenetic testing to the daily practice of psychiatry. Challenges inherent in innovation diffusion in general and in the application of pharmacogenetic testing in particular are addressed. Study data involving the introduction and integration of pharmacogenomic testing into two different types of community psychiatric practice are presented. The article concludes with a discussion of the ethical issues raised in this process and its impact on the physician-patient relationship.

FOCUS POINTS

- On average, there exists a 10-year gap between medically relevant bio-technological advances and appropriate application, or translation, of those technologies into routine medical practice.
- Pharmacogenetic testing represents a major advance for translational psychiatry and its goal of advancing personalized medicine.
- Barriers to change are multifaceted and complex; enhancing the knowledge base of physicians will facilitate the process of clinical acceptance.
- Psychopharmacogenetic testing that leads to a comprehensible report which provides clinical guidance is a new tool that is now available for implementation in the clinical practice of psychiatry.

INTRODUCTION

It has been over 60 years since antidepressants were introduced into clinical practice, and these medications have become among the most widely prescribed pharmacologic agents used in medicine today. Despite the number of agents available and recent advances in drug design, significant individual variability exists in drug response, therapeutic dosage, and adverse effect profile. Only 35% to 45% of depressed patients have a complete remission of their illness when initially treated with these medications.¹ Variation in drug response is complex and is dependent upon numerous factors. These include other pharmaceutical use, age, gender, renal and hepatic function, medical comorbidity, nutritional status, substance use, and genetic

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factors.² The selection of an appropriate agent is usually achieved through an informed trial and error process which considers these factors. The time to maximum therapeutic response can extend to 12 weeks. This delayed time to response contributes to the potential for substantial morbidity and mortality associated with depressive illness. The use of pharmacogenomic testing provides a new tool to improve time to response and remission, as well as decrease the likelihood of potential side effects.

Recent developments in pharmacogenomic testing allows for the more efficient and effective treatment of mood disorders that have proven difficult to manage in the clinical setting. Within the past 7 years, routine genotyping has become available to detect genetic variations that code for proteins that influence serotonergic and noradrenergic function, as well as drug-metabolizing enzymes that play a role in the disposition of many psychotropics, including antidepressants.³ Genotyping for the cytochrome P450 (CYP) 2D6, 2C19, and 1A2 drug-metabolizing enzymes, and genotyping of the serotonin transporter gene and the 5-HT_{2A} and 5-HT_{2C} receptors, is now available clinically, and the rationale for testing has been explicitly defined.⁴ Pharmacogenomic testing can be used to predict potential side effects, receptor sensitivity, and possible drug interactions. In its current iteration it cannot clearly predict response or remission in association with the use of a particular agent, and may not necessarily predict all side effects that a particular patient may experience.

The reliability of the genotyping, access to testing, and the usefulness of the interpretation of test results are critical to the process of innovation diffusion, which involves acceptance, adoption, and appropriate utilization of genomic testing in the clinical setting. It has been estimated that it is typical for a decade to pass between the discovery of applicable technology and its routine application in the clinical setting. This traditional delay in adoption represents a challenge for the implementation of powerful new technologies.

The use of genetic testing to improve the efficacy of psychotropics is a clear example of translational psychiatry. Given the promise of pharmacogenomic testing, it is prudent to analyze the barriers that may affect its adoption.⁵

Issues related to the introduction of pharmacogenetic testing in clinical practice are likely to result from the extension of testing at academic medical centers to surrounding community medical centers. After a discussion of concepts that are integral to translational medicine, the challenges inherent in implementation science will be discussed. This will be illustrated by a description of a pilot project that was designed to specifically address this process. This study examined the introduction of pharmacogenomic testing into two different community practice settings and documented the lessons learned from this experience.

TRANSLATIONAL PSYCHIATRY, PERSONALIZED MEDICINE, AND IMPLEMENTATION SCIENCE

Recent advances in biotechnology, bioinformatics, and studying “real world” patients have improved our understanding of the biological underpinnings of depression as well as the treatment of depression. The sequencing of the human genome was a landmark event which was achieved shortly after the beginning of the new millennium. This was followed by technological advances in gene sequencing and functional genomics, proteomics, metabolomics, and epigenetics. The evolution of functional neuroimaging technology has provided even greater degrees of precision in the definition of biological vulnerabilities. Other advances include the documentation of brain neuroplasticity, an expanding armamentarium of psychopharmacologic agents with ever more specific disease targets, and a greater emphasis on the critical analysis of the extant research regarding treatment efficacy using evidence-based methodology. Additionally, the introduction of more creative research paradigms that involve “real world” patients, who are often not included in traditional research paradigms, adds to the applicability of many current studies.

Coupled with social forces of politics, economics, and cultural expectations, these multiple advances offer the promise of an “upstream shift” in the practice of medicine from primarily a reactive response to a more proactive approach to prevention in combination with informed treatment. Bidirectional communication and effective transmission of technology between researchers and clinicians which this implies is a process that has come to be known as translational medicine.⁶ Such a process applied to psychiatric patients is appropriately labeled translational psychiatry.

The use of genotypic information to stratify disease and select a therapy that is particularly suited to an individual patient is now described as personalized medicine.⁷ It is the ultimate goal of personalized medicine to identify individuals who are at-risk for a pathophysiologic process and to prevent the onset of symptoms of that process. As this knowledge base is still not well developed, the current goals include retardation, arrest, or even reversal of pathologic processes. Implementation research is the study of methods used to promote the incorporation of evidence-based research findings into routine practice in order to improve the quality and effectiveness of health services and care.⁸ The challenge in the implementation of evidence-based innovative technologies is to apply the right technology to the right person in the right way to effect clinical goals which are mutually defined by the physician and patient.

BARRIERS TO EFFECTIVE IMPLEMENTATION

Advancing pharmacogenetic medicine in clinical settings is an iterative process with many challenges. Barriers exist at the interface between research and practice that impede bidirectional discovery and communication. Foremost among these barriers are communication barriers that exist between researchers and clinicians. These communication barriers are influenced by pragmatic, economic, ideologic, informational, and training parameters.⁹ McGovern and colleagues¹⁰ has emphasized the importance of interdisciplinary communication between clinicians, administrators, regulatory agencies, and researchers. To this list, the input of patients should be added.

Bridging this divide calls for innovative and flexible thinking. It ultimately requires clinicians and researchers to participate in a dialogue. This innovation-to-organizational fit is influenced by the forces outlined by McGovern and colleagues.¹⁰ Mittman has likened the impact of these dynamic forces upon treatment as pliable bands representing semantics, advocacy, intellectual, regulatory, economic, ideologic, tradition, training, and social forces, which attach to and suspend a concrete block representing current treatment protocols (Willinbring M, personal communication, December, 2007). Ultimately, a transformation in treatment by novel scientific innovation requires a dynamically poised system.

Prochaska and DiClemente¹¹ outlined how clinicians and patients are participating in the process of change. There exists a need for clinician scholars to bridge these gaps with their research colleagues. Similarly, basic scientists need to be rewarded for clinical communications initiatives. Clinicians who are often preoccupied with day to day clinical demands need to be provided with high quality, but concise scientific data in order to effect change. Finally, the use of evidence-based guidelines, identification of appropriate metrics of outcome, and delineation of performance gaps with feedback loops can powerfully improve treatment delivery.

PSYCHOPHARMACOGENETIC TESTING: IMPLEMENTATION ISSUES

While psychopharmacogenetic testing is becoming more commonplace in academic and tertiary medical care centers, its use in clinical practice is not yet routine. As with other new technologies, ethical issues are important to consider.⁵ A recent article utilizing a clinical example from oncology demonstrates differences in patient outcome based upon access to testing. It also identifies disparities in our health-care systems which negatively impacts access to testing.¹²

There is no simple pathway that leads from a novel technology to a change in the belief systems of clinicians

providing care. This too is an iterative process that has an evolutionary pattern of its own. Important issues such as quantification of validity, establishment of regulatory policy, and insuring reimbursement must be resolved in order to provide these services.¹³⁻²¹

Key issues are provided in the Table. Responses to these challenges are underway. Research funded by the Pharmacogenetics Research Network of the National Institute of General Medical Sciences continues to define pharmacogenetic practices for specific disease treatment. Improved communications and cooperation between stakeholders at various levels with the support of public policy are leading to improved validation of research findings, the development of quality cost-effectiveness measures, the evolution of clinical guidelines for the application of testing in clinical practice, and the creation of appropriate incentives for use in clinical practice.

One objective of this article is to focus on innovation diffusion at the level of clinical practice. Specifically, the authors discuss the introduction of psychopharmacogenetic testing into two community practices. This discussion focuses on

TABLE KEY IMPLEMENTATION ISSUES

1. Standardization, validation, and reliability of testing in patients of diverse ancestry to be able to more accurately interpret testing results.
2. Clinical validation studies that define cost-effectiveness.
3. Development of safeguards to ensure the confidentiality of testing results within the electronic medical record.
4. Consistent regulatory management of genotyping technologies.
5. Development of clinical guidelines based on best-evidence which take into account epigenetic variability.
6. Enhancement of the availability of testing (ie, a bedside genotyping collection system).
7. Rapid availability of testing results.
8. Informative interpretation of testing results for both clinicians and patients.
9. Availability of testing with established insurance reimbursement guidelines.
10. Communication of the availability of this technology and how to access the technology.
11. Appropriate physician education regarding the biologic rationale for psychopharmacogenomic testing.
12. Appreciation of changes in technology and development.
13. Logistic issues related to the pragmatic support of testing.
14. Issues related to having sufficient time to spend with patients to introduce a new technology.
15. Patient anxiety related to genomic testing.
16. The impact of healthcare disparities that limit access to testing.

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those issues which most directly face the community clinician. A report²² issued by the Consortium on Pharmacogenetics in the United Kingdom stated that:

“Perhaps the greatest single factor affecting the penetration of pharmacogenomics into clinical practice and the pace at which it will occur will be the knowledge and acceptance of physicians. Studies indicated that many physicians lack basic knowledge of genetics and also frequently fail to take into account available information about drugs.”²²

It is clear from empirical studies that effective behavioral change in established medical practices will require an enhancing of the knowledge base of physicians.²³ However, more will be required than introducing new information. Making behavioral change in any clinical setting requires at least three cognitive steps. First, there must be a willingness to acknowledge that a problem or situation exists which can be improved. Second, there must be an awareness of the means to make the improvement. Third, one must believe that the individual or system can effect this change. Addressing these issues will require educational efforts targeted at physicians and patients. It will require the incorporation of guidelines for testing and interpretation as well as appropriate research incentives for testing. Addressing the time pressures facing primary practitioners will require a simplification of the means of transmission of this information. One option would be involvement of a focused liaison team from an academic institution which could present on-site information and evaluate outcomes of the introduction of testing. This team could also monitor related quality outcomes including patient satisfaction and quality of life.

IMPLEMENTATION OF PSYCHOPHARMACOGENOMIC TESTING IN CLINICAL PSYCHIATRIC PRACTICE: A PILOT PROJECT

A study designed to introduce pharmacogenomic testing into two clinical psychiatric practices has been initiated and is currently in progress with ongoing data collection. This testing utilizes a panel that includes five genes: three cytochrome P450 drug-metabolizing genes, as well as the serotonin transporter and serotonin receptors 2A genes. Results of the panel are summarized in a format designed to provide clinicians with useful clinical information. In the consent process what testing can and cannot provide at the present time is reviewed with patients and physician alike. It is important to note that such testing cannot clearly predict response or remission, and may not fully predict an individual's psychotropic or other medication side-effect profile. Rather, it does provide information that may guide

a physician's choice of psychotropic agent that is likely to be tolerated by the patient and that would minimize the potential of adverse drug interaction and extended trial-and-error clinical attempts to find “the right drug.”

The two clinical practices chosen for this pilot study are structurally quite different. They serve patients from two different psychosocial and ethnic backgrounds. One practice primarily provides psychopharmacologic intervention. The second practice integrates medication management with psychotherapy in an ethnically diverse population. Continuity with practitioners is a core value in each program. At both institutions, testing is offered as an initial study arm examining “practice as usual.” Testing is conducted at the end of an 8-week period of standard treatment. The second phase introduces testing at the time of study entry and includes rapid feedback to both physicians and patients within 48 hours of specimen collection. Data points are then monitored to measure the potential impact of testing on practice, with attention given to the frequency of side effects experienced, need to change medications, usefulness of the interpretive report, time to response and remission, and impact on the utilization of resources both within the practice and associated settings such as the hospital emergency room or hospital. Perceptions of physicians and patients are measured. Variables include medication changes, number of visits to emergency rooms, and days in the hospital. Physician and patient satisfaction is also being documented.

A high level of physician satisfaction with the interpretive report is critical for the incorporation of this technology into clinical practice. A copy of this report is shown in the Figure. The report also includes specific genotyping results, an interpretation of these results, and practically categorized information on drug-drug interactions including drugs known to increase and decrease specific enzyme activity. The clinical usefulness of the report in patient education, guidance of medication choice, development of potential side effects and risk/benefit assessments, improvement in the rapport with patients, and confidence in medication choice by both physician and patient will be analyzed. Patient satisfaction evaluation includes assessing the quality of the explanation of the interpretive report, the ease of understanding of report findings, and the perception of benefit from this report in treatment. Overall satisfaction ratings for the report and the clinical visit are also being assessed.

A key to the overall success of clinical implementation is that medical directors at each practice are stakeholders in the process. These clinical leaders must be well-educated in the scientific rationale and supportive of the clinical objective of offering more personalized care for individual patients. The first practice consists primarily of psychiatrists offering brief counseling in conjunction with pharmacotherapy. In this group there is general acceptance among the

physicians of the potential benefit of testing. This may be offset by limitations in training, time pressures, competing priorities, and difficulties inherent in making the cognitive changes necessary to incorporate a new concept into their practices. In this setting, patients themselves appear to be a more positive force for change as they expressed interest in testing as a means of dealing with the chronic frustration in the management of their depressive symptoms. However, it is critical to keep patients grounded in what the testing can and cannot offer. Both patients and physicians informally report finding the ease of the reporting process quite helpful in promoting elements of the healing relationship.

There has been some anxiety on the part of non-physician practitioners which have raised concerns about biological reductionism and the implications of genomic technology on their future practice opportunities. Educational research designed to define the role of these clinicians should be a high priority. The relationships between therapists and patients should be investigated in future study in a manner which would challenge Cartesian dualism. Pelletier and Dorval²⁴ summarized some of these challenges in an article on the impact of translational psychiatry in the field of psychology.

TRANSLATIONAL PSYCHIATRY AND THE PHYSICIAN-PATIENT RELATIONSHIP

Ultimately, one of the most critical factors in the introduction of a new technology that may have an impact on the practice of medicine is the effect that the technology has on the physician-patient relationship. Traditionally, this relationship has accepted a Cartesian reductionism that views the body as a machine and the physician as a technician whose job it is to repair that machine. However, in recent years this way of thinking has given way to the more complex notion that the doctor-patient relationship is in its essence one of healing. In the philosophical model of medicine advanced by Pellegrino and Thomasma,²⁵ the “center of medicine” is a relationship that has the central purpose of healing. Technical competence, including incorporation of appropriate new technologies, is not denied in this model because “the act of medical profession is inauthentic and a lie unless it fulfills the expectation of technical competence...however...Competence must itself be shaped by the end of a medical act, a right and good healing action for the patient.”

Scott and colleagues²⁶ have built upon this foundation to describe the Healing Relationship Model. In this model, healing is defined as “being cured when possible, reducing suffering when cure is not possible, and finding meaning beyond the illness experience.” Critical to this relationship are mutual respect (valuing), a recognition of the inherent asymmetry of the relationship (appreciating power), and continuity (abiding). On the part of the patient three relational factors are critical. They include trust (a willingness to be vulnerable), hope (that some future beyond the present suffering is possible), and a sense of being known. (Parenthetically, the word “patient” is etymologically traced to the Latin verb *patior*, to suffer.) On the clinician’s side of this relational equation are four essential clinical competencies: self-confidence, emotional self-management, mindfulness, and clinical knowledge. Of particular import to the discussion of pharmacogenetic testing is what this latter competency implies: the store of knowledge of empirical medicine, and the ability to synthesize and tailor that knowledge for the benefit of a particular individual. These factors influence the bidirectional accuracy and flow of information between physician and patient, helping to ensure a cooperative spirit with mutually agreed upon treatment goals and components. Examples of this cooperation include receptivity to medication use and compliance. Other discussions of the physician-patient relationship have centered on the four pillars of ethical reasoning, which include beneficence, autonomy, non-maleficence, and justice. One could argue the forces of translational medicine have the potential to enrich the physician-patient relationship and move clinical practice beyond reactivity to a hybrid of reactivity and proactivity.

FIGURE ASSURERX REPORT

Drug Report (Antidepressants)

Use as Directed	Use with Caution	Use with Caution and with More Frequent Monitoring
Celexa® (citalopram) Lexapro® (escitalopram) Luvox® (fluvoxamine) Zoloft® (sertraline)	Cymbalta® (duloxetine) Remeron® (mirtazapine) Desyre® (trazodone)	Elavil® (amitriptyline) Wellbutrin® (bupropion) Anafranil® (clomipramine) Norpramin® (desipramine) Prozac® (fluoxetine) Tofranil® (imipramine) Pamelor® (nortriptyline) Paxil® (paroxetine) Effexor® (venlafaxine)

Drug Report (Antipsychotics)

Use as Directed	Use with Caution	Use with Caution and with More Frequent Monitoring
Seroquel® (quetiapine) Geodon® (ziprasidone)	Clozaril® (clozapine) Zyprexa® (olanzapine) Risperdal® (risperidone)	Abilify® (aripiprazole) Haldol® (haloperidol) Trilafon® (risperidperphenazineone)

Genotyping interpretive report of a healthy middle-aged patient with a history of difficult-to-treat major depressive disorder, without substantive Axis I or Axis II comorbidity. Genotyping reveals two copies of the gene producing inactive enzymatic forms of cytochrome P450 2D6 and a phenotypic form of the 5-HT_{2A} receptor that is associated with decreased response to those antidepressants that bind to that receptor site. In this case, drugs listed in the “Use with Caution” category may need to be used in lower doses than usual as elevated serum levels may be expected with standard dosing in the presence of the aforementioned genotypic profile. Agents listed in the “Use with Caution with More Frequent Monitoring” category may be associated with an increased risk of side effects with this genotyping profile. Parenthetically, the use of other non-psychiatric medications such as tamoxifen may be adversely affected by the enzymatic activity associated with this profile.

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CONCLUSION

It is imprudent to allow a 10-year gap between research discovery and practice implementation. Pharmacogenetic testing represents a major advance for translational psychiatry and its goal of advancing personalized medicine. There is a need to proceed judiciously and focus on barriers to change that need to be addressed. The authors summarized challenges to a timelier implementation of personalized medicine with particular reference to psychopharmacogenetic testing. Enhancing the knowledge base of physicians will facilitate the process of clinical acceptance. The authors discussed efforts to address translational challenges. Their initial impressions offer a snapshot of key practical issues which occur in a "real world" setting. Psychopharmacogenetic testing that leads to a comprehensible report which provides clinical guidance is a new tool that is now available for implementation in the clinical practice of psychiatry. **PP**

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