

Ethical and public policy challenges for pharmacogenomics

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It is timely to consider the ethical and social questions raised by progress in pharmacogenomics, based on the current importance of pharmacogenomics for avoidance of predictable side effects of drugs, and for correct choice of medications in certain cancers. It has been proposed that the entire population be genotyped for drug-metabolizing enzyme polymorphisms, as a measure that would prevent many untoward and dangerous drug reactions. Pharmacologic treatment targeting based on genomics of disease can be expected to increase greatly in the coming years. Policy and ethical issues exist on consent for large scale genomic/pharmacogenomic data collection, public vs corporate ownership of genomic research results, testing efficacy and safety of drugs used for rare genomic indications, and accessibility of treatments based on costly research that is applicable to relatively few patients. In major psychiatric disorders and intellectual deficiency, rare and de novo deletion or duplication of chromosomal segments (copy number variation), in the aggregate, are common causes of increased risk. This implies that the policy problems of pharmacogenomics will be particularly important for the psychiatric disorders.

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Introduction

Untoward reactions to medications are a major cause of medical morbidity and mortality, and genetic tests for susceptibility to these reactions have entered into pharmaceutical regulations in many countries. The potential for other applications of pharmacogenomics, such as development of personalized medicine based on the patient's genetic susceptibility to disease, has so far been realized only for a few drugs, but a large number of such applications may be expected in the future. In this paper we endeavor to anticipate the research that will lead to these pharmacogenomics innovations, and the ethical and public policy challenges that may emerge in the development of this knowledge and in its application to public health.

Current state of the art

Decades ago, it was discovered that normal variants in metabolizing enzymes can lead to serious reactions to medications (drug-gene interactions; DGIs) in patients

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who metabolize medications much more slowly than average. DGIs can also cause lack of efficacy in patients who are rapid metabolizers. At this time, the most efficient way to determine susceptibility to these DGIs is by measuring the single-nucleotide polymorphisms (SNPs) that are associated with specific variants of the drug-metabolizing enzyme.¹ Drug prescribing regulations in the United States, for example, include multiple cautions on drug-drug interactions (DDIs) as well as on DGIs.² Genetic variants within the cytochrome P450 enzyme system (ie, CYP genes) have been a major focus of DGI research. In psychiatry, this has resulted in US Food and Drug Administration (FDA) recommendations that individuals with CYP2D genotypes associated with slow drug metabolism take reduced doses of the antipsychotics aripiprazole and pimozide. The metabolism of tricyclic antidepressants has also been found to be affected by CYP variants, in the CYP2D and CYP2C19 genes.³ It has been proposed⁴ that genotyping for drug-metabolizing enzyme variants be done as a routine medical test early in life on a population-wide basis, to prevent a wide range of adverse reactions. Virtually all of these tests are single SNPs or human leukocyte antigen (HLA) types; complex interactions between genes, and epigenomic data, are not yet ready for inclusion in tests.

For most common diseases, pharmacodynamics, pharmacokinetics, and disease-related genetic association indications for clinically meaningful medication efficacy or for risk of adverse effects have not yet been found. The reason may lie in the current state of the genetics of common diseases. For most common diseases, most patients do not have any genetic association with a large effect on risk. Schizophrenia is typical. As of their July 2014 paper,⁵ the Psychiatric Genomics Consortium had identified 108 single SNP associations with schizophrenia, based on tens of thousands of patients and controls; no single association had an effect on risk that would increase disease risk by an appreciable amount (no common SNP increases disease risk to an individual to 1.5% from the population disease risk of 1%). Furthermore, in the aggregate, a large number of SNPs (tens of thousands) contribute substantially to risk,⁶⁻⁸ but it has not yet been possible to parse these SNPs into coherent modifiers of disease biology (see below).⁶

The current state of SNP association with psychiatric disorders is that our knowledge of statistical genetic association with disease has advanced, but the development of pharmacogenomic molecular targets from this knowledge has been elusive.

New types of genetic analysis may provide a basis for pharmacological development based on genetic disease associations

Common SNPs associated with disease frequently have known functional effects.⁹ The direction of effects of a risk allele on function such as gene expression can be the basis for predicting pharmacologic response.¹⁰ Rare variants of genes whose common SNPs are associated with a disease may also give important clues toward treatment. In our own work,¹¹ we found that a patient with Timothy syndrome, caused by a very rare mutation of *CACNA1C* and with which only a handful of patients survive past childhood, developed bipolar disorder. *CACNA1C* is the gene for Ca(v)1.2, a subunit protein of L-type calcium-channels expressed in brain, most strongly so in the cerebellum. A common polymorphism of *CACNA1C* has long been the most strongly associated SNP with bipolar disorder.¹² Separately, we found that the two common alleles of the risk SNP produce differential expression of *CACNA1C* in brain: patients with the risk allele have lower expression of *CACNA1C*. Currently, calcium channel blocking drugs (CCBs) are in wide use for cardiac arrhythmias and hypertension, and have previously been reported to have positive therapeutic effects in a proportion of patients with mania and depression, although the overall evidence for therapeutic effect is ambiguous.¹³ Based on all of these findings, we predicted that CCBs would differentially benefit patients with higher expression of *CACNA1C*, that is, with the non-risk allele. This prediction was based on functional genomics of a common SNP, as well as the effect of a rare mutation that profoundly altered the gene in which that SNP is present; it is not based on the strength of a statistical association of the SNP on risk of disease. Similar reasoning was offered at the XXIth World Congress of Psychiatric Genetics,¹⁴ by Ruderfer on multiple disruptive mutations within calcium channel genes in bipolar disorder, and by Nurnberger on synuclein in Parkinson's disease. This perspective has broad implications as a strategy for choosing therapeutic molecular targets.

Pathways and networks

The multigenic nature of the major psychiatric disorders has been reinforced by findings of polygenic inheritance (ie, non-Mendelian inheritance) in schizo-

phrenia, and by the finding that a given configuration of genetic markers cross multiple diagnostic boundaries.⁷ A similar finding was found for large (>100 kilobases) de novo copy number variants (CNVs), where presence of *any* de novo CNV mutation in the genome is associated with greatly increased risk for schizophrenia, bipolar disorder, and autism.¹⁵ Presumably some de novo CNV mutations are harmless, but the implication is that there are a very large number of locations in the genome where any CNV can result in disease. These findings carry two important implications: first, that there are multiple interactions among many genes (ie, epistasis) producing risk for psychiatric disorders, many of them nonspecific for diagnosis. Second, that disruption of any of the large numbers of illness-related genes by a CNV, which covers very large stretches of the genome and not a single nucleotide position, may have a large effect on illness.

The above observations and implications will need pathway and network approaches that parse the genetic associations with illness into groups of gene functions that are similar or related (pathways),^{16,17} or have quantifiable functional interactions (networks).

In a molecular network, nodes represent molecules and edges represent relationships between the nodes; for example, the nodes may represent proteins and the edges protein-protein interactions. Network-based approaches stem from systems biology, a holistic approach to studying biological systems, in which disease-associated molecular changes are studied in their larger biological context, rather than in isolation. There is accumulating evidence that alterations in network structure are associated with neuropsychiatric disorders (for review, see ref 18) and psychotropic drug response.^{19,20} Molecular network approaches have a number of strengths. They can account for nonlinear interactions between molecules, such as feedback loops and oscillations, as well as detect and model phenomena such as epistasis (when one gene masks the effect of another gene) and pleiotropy (when one gene affects multiple traits). From a therapeutic point of view, nonlinearities of molecular network structure may explain why so many highly specific, single target compounds have failed in later phases of clinical trials,²¹ and why developing such compounds in the absence of network analysis of their molecular targets may have been futile from the start.²² Network structure may also underlie the effectiveness of multimodal therapeutics,²³ which

use a combination of compounds with different pharmacological actions.

These molecular network approaches are still being developed; they have produced intriguing results, but have not yet led to any major breakthrough in neuropsychiatric disease studies. Network structure is highly context-dependent, meaning that networks vary through time and across tissues, cell types, brain layers, etc.^{24,25} Many existing networks and network building tools do not take this spatiotemporal specificity into account.

Horvath and colleagues developed a mathematical algorithm for creating networks, which they called Weighted Gene Co-expression Network Analysis (WGCNA).²⁶ This method identifies groups of genes (modules) whose expressions are highly correlated. These modules can then be compared between cases and controls, among different tissues, species, or other phenotypes or clinical traits.²⁷⁻²⁹ This method was first applied to psychiatric disorders by Torkamani et al.³⁰ Chen et al³¹ used WGCNA to identify two co-expression modules in human brain that differentiated schizophrenia patients from controls. These modules were reproducibly found in other brain collections, the schizophrenia-control difference was also replicated, and one of the modules was also found to distinguish bipolar patients from controls. The most strongly associated module had *NOTCH2*, a member of the Notch gene family, with the highest intramodular connectivity. This module is enriched with neuron development and neuron differentiation genes. The second module had metallothienin (MT) genes most prominently, with *MTIX* as the hub gene. Expression changes in these MT genes in schizophrenia and bipolar had been previously reported,^{32,33} but, so far, no positive SNP associations of disease with these genes were found. The hub genes and their modules thus offer rationally developed new targets for pharmaceutical development, and the genotypes of patients within these modules may offer opportunity to target treatment.

In summary, many genes or gene products may be suitable targets for the pharmacological treatment of individuals with particular genetic dispositions. The ethical and public policy challenges these findings may present for research and public health progress through pharmacogenomics are worth discussing passionately now, when no practical application yet exists.

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Ethical and public policy issues

Open consent vs informed consent

Very-large-scale patient studies will be needed to detect and replicate drug responses and side effects beyond associations with drug-metabolizing enzymes. Participants in drug trials that collect blood but did not specify genetic tests, and patients who provide blood specimens to a hospital laboratory often have not consented to further research and testing on the specimens they provided (see review in ref 34). In the case of laboratory specimens (and autopsy specimens) consent is not considered required by current ethical standards in the United States, although serious issues would arise if an individual's identity were to be disclosed from the data. For prediction of therapeutic response and adverse events, it would obviously be very valuable to mine medical records and do genetic testing on leftover laboratory specimens on a very large scale. At present, data mining of hospital diagnostic and demographic records, where the individuals are made anonymous (ie, deidentified) is commonly done in research. Accessing medical test results is an informatics problem but not an ethical one. When consent is required, under current standards it cannot be a broad-based consent to any future research, and this is another barrier. It is impractical to recontact individuals for every additional study.

For an individual for whom a significant number of genetic polymorphisms were assayed, the data itself could lead to unwanted identification, such as the well-known instances where it is possible to determine if an individual's genetic data was included in a genetic database on a particular disease, even if there were no personal identifiers in the disease database. Conflicting demands result, then, between medical research advances and the rights of an individual to privacy.

The solution should lie in some combination of modifying the rules on consent to research to allow open-ended consent, continuing the policy of allowing research on existing laboratory and pathological specimens collected for medical testing, and establishing more vigorous deterrent penalties for violations of privacy. The United States Genetic Information Nondiscrimination Act of 2008 (Pub.L. 110–233, 122 Stat. 881), which prohibits the discrimination against individuals based on genetic information in matters involving health insurance and employment, might serve as a le-

gal precedent and template for penalties on illegitimate use of an individual's genetic information.

Public vs corporate ownership of genetic information

Biological patents that concern artificially modified genes are accepted around the world, but there are differences between jurisdictions on patenting a discovery of the function of a naturally occurring genetic variant. In Australia, the Federal Court in 2013 affirmed the Myriad corporation patent on the *BRCA1* variant as a test for breast cancer (*Cancer Voices Australia v. Myriad Genetics Inc.* [2013] FCA 65), but the United States Supreme Court, ruling on the same test in 2013, found that naturally occurring DNA sequences are ineligible for patent protection (*Association for Molecular Pathology v Myriad Genetics, U.S. Supreme Court, No. 12-398*). A utilitarian approach to ethics would weigh the benefits and costs on each side of such a decision. The benefit of no eligibility for a patent is that testing based on existing knowledge becomes cheaper, and the cost is that research into new information of this type becomes less economically worthwhile. The ultimate outcome of these issues is not predictable, but the unintended cost of inhibiting development of personalized medicine, under the US ruling, may be considerable.

Duty to warn of drug-gene interactions

As discussed by Wertz,³ in a suit against a vaccine maker, the plaintiffs argued that about 30% of the population has a genotype that elevates their risk for developing Lyme disease after taking the company's vaccine, and that the company failed to warn of the need for genetic screening. Such cases may lead to a legal requirement for manufacturers of a drug/treatment to provide direct disclosure to the patient on genetic risks associated with a treatment, as contrasted with information given to the health care providers to use in interpreting risk to their patients.

Testing personalized treatment for patients with rare genetic variants

All of the approaches to treatment development discussed so far are built on quantitative approaches to genetics and genomics, usually quantitative associations based on large samples and thus applicable to

large numbers of patients. However, a considerable proportion of individuals with psychiatric disorders, schizophrenia, bipolar, and autism spectrum disorder, have rare variants as their major risk component.³⁵ This statement refers to de novo CNVs as discussed above, which can be a rare variant or a very rare private mutation (ie, one that exists only within one person or one kindred), but in the aggregate the deleterious mutations are common. Development of treatments that address these individual variants can be based on bioinformatic methods and by functional study of new cellular and animal models.

The ethical challenges of these treatments include their costs, as well as the inadequacy of current procedures of pharmaceutical regulation to deal with questions for which there are no statistical samples of individuals to guide the regulators. For new drugs, the standard sequence of testing in humans is (in the United States): Phase 0: Pharmacodynamics and pharmacokinetics; Phase 1: Screening for safety in a small sample of human volunteers; Phase 2: Establishing the efficacy of the drug, usually against a placebo, in a limited sample of patients in a research setting; Phase 3: Final confirmation of safety and efficacy in a large sample; and Phase 4: Sentry studies after approval for medical use during sales to large numbers of patients.

This sequence is appropriate for common and even some fairly uncommon diseases, but is obviously not appropriate for diseases associated with rare genetic variants. There may not be enough patients in the world to establish efficacy with statistical methods. Safety studies in normal volunteers or other patients with similar diseases may not provide information on risks directly related to a particular patient's genetic makeup. Yet, in the aggregate, rare and very rare diseases are common. Therefore, new general methods for testing personalized drugs are needed for this type of medicine to advance.

One approach would be studies of the patient's rare variant, or of his or her entire genome, in suitable models. Neuron-like pluripotent stem cells can be developed from an adult patient's skin fibroblasts,³⁶ where physiological effects of particular drugs can be studied, including some adverse effects and effects of drug combinations. Transgenic animal models, particularly mammalian ones, may offer another approach. In mice there are large numbers of genetic backgrounds into which the transgenes may eventually be placed and their pharmacologic responses studied. Bioinformatic prediction

of mutation effects or of drug response is generally not effective enough for clinical use at this time, but one may anticipate that the field will develop and that in silico prediction of drug response (ie, prediction using computer modeling) may become possible in the future. Nonetheless, it appears at this time that very innovative treatment of disease associated with rare variants will be associated with risks that cannot be prevented by the usual process of drug development.

Accessibility of results: pharmacogenomics and clinical treatment

The benefits of assaying individuals' drug metabolizing enzyme phenotypes to predict adverse drug reactions makes this area of pharmacogenomics uncontroversial. First, specific side effects related to genotype can be identified, and thus risk is reduced. Second, specific indications for use of a treatment can be identified from genetic testing. As a result, more drugs could theoretically be approved by regulatory agencies, with requirements or recommendations for genetic testing of individuals receiving the drug. Wertz has proposed routine testing for drug metabolizing enzymes as a public health preventive measure.⁴ The patient's consent can be readily obtained (if required; see above discussion).

The public enthusiasm for personalized medicine began in 1998, when trastuzumab was approved for treatment of breast cancer in cases where the tumor is overexpressing the HER2 protein. Currently, the FDA lists a considerable number of treatments for which pharmacogenomic biomarkers are recommended.² However, a 2013 review by Tutton,³⁷ which analyzed the Pharmacogenomics Knowledgebase (PharmGKB) and FDA recommendations, found that:

Approximately 12% of drugs licensed in the period 1998–2012 had PGx (Pharmacogenomic) biomarker information included in their labels at the time of their approval. Of that number, labels direct clinicians to utilize PGx testing prior to prescribing treatments in only 14 cases. This clearly falls short of expectations many had in the 1990s about the transformative impact of PGx. In most cases, the inclusion of this information currently has limited or no direct clinical utility.

FDA approval of genetic test *indications* on the label has been considered a frustrating process by many investigators, and has occurred in many cases after the period of patent protection had expired.³⁷

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The cost of custom drug development for rare variants is another barrier to accessibility of genomic technologies in pharmaceuticals development. Wertz³ quotes a spokesperson for Bristol-Myers-Squibb who stated that “individualized treatment doesn’t play to our core interests.” As Wertz continues, “health policy-makers may have to draw some lines, while making sure that people whose genetic constitutions require more expensive drugs receive them.” This raises the inevitable specters of health-care rationing, and of who will bear the costs of development of rare treatments for rare disease. This issue is similar to the orphan drugs development issue, where in the US there is some governmental support and regulatory easement for certain types of drug development.

General genetic testing issues as applied to pharmacogenomics

There are multiple ethical issues in genetic testing for disease markers that may well carry over into pharmacogenomics-based treatment. We have reviewed these issues elsewhere,³⁵ and will only touch upon them here. Genetic testing of children is an ethical issue when direct benefit to the child may not result before the child can consent to testing, such as in *BRCA1* variant testing of a child for breast cancer susceptibility. When choice of treatment would be guided by testing, this is no longer an issue; the parent or guardian can reasonably give consent for testing a child who is under age, because of the potential benefit to the child who is tested.

Within families, conflicts over testing for high-risk genomic markers can arise, because of concern over implications of test results for persons who have not been tested, and because of stigma within families and within society.³⁵ In the major psychiatric disorders, the high-risk variants known today are rare and *de novo* CNVs and some single nucleotide variant (SNV) mutations. Since these variants may be transmitted within fami-

lies, the issues arise of whether a relative has a right to genetic test results, and whether a relative can impede genetic testing, and these have not been fully resolved. Again, however, when the test would have potential benefit for treatment of the person tested, or for a relative who is at risk, one would expect these issues to become moot.

In the discussion above, we anticipated that the use of stem cells and transgenic animal models may become more extensive for efficacy and toxicity analyses when a disease is rare and there is no statistical basis for conducting large-scale human studies. Apart from ethical controversies over experimental methods, we would also anticipate ethical and social policy controversy over the amount of risk a patient might reasonably undertake, or be advised to undertake, for a drug that cannot be tested for toxicity as extensively as drugs for common diseases.

Lastly, there have been issues raised over protecting genetic information in a medical record, or from disclosure to insurance companies or employers. These are not issues specific for clinical pharmacogenomics, and we do not discuss them here, but they will become pertinent as this type of diagnosis and treatment matures.

Conclusion

To summarize, there is a vast potential for pharmacogenomics applications to treatment of psychiatric disorders, but it has only recently become clear that this can be realized. The ethical and public policy issues do not appear to be insurmountable, or uniquely different from other issues of medical testing, such as infectious diseases where other family members or associates may be at risk. The technological problems of developing effective and safe treatments for rare variants appear formidable, as do the expense of developing treatments for large numbers of rare and unique genetic predispositions. □

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Desafíos para la ética y las políticas públicas de la farmacogenómica

Es oportuno tener en cuenta las preguntas éticas y sociales que surgen del progreso en la farmacogenómica, dada la importancia actual de ésta para evitar los efectos secundarios predecibles de los fármacos y para la elección correcta de medicamentos en ciertos tipos de cáncer. Se ha propuesto que se le realice el genotipo para el polimorfismo de las enzimas metabolizadoras de fármacos a toda la población, como una medida que podría prevenir muchas reacciones adversas y peligrosas a fármacos. Se puede esperar que el tratamiento farmacológico focalizado basado en la genómica de la enfermedad aumente de manera importante en los próximos años. Existen aspectos políticos y éticos en el consentimiento de la obtención a gran escala de datos genómicos/farmacogenómicos, en la propiedad pública versus privada de los resultados de la investigación genómica, en las pruebas de eficacia y seguridad de fármacos utilizados en indicaciones genómicas raras, y en la accesibilidad a tratamientos basados en costosa investigación que sea aplicable a relativamente pocos pacientes. La delección rara y de novo o la duplicación de segmentos cromosómicos (variación en el número de copias) son en general causas comunes de aumento del riesgo de los principales trastornos psiquiátricos y del déficit intelectual. Esto implica que los problemas políticos de la farmacogenómica serán especialmente importantes para los trastornos psiquiátricos.

Enjeux éthiques et de politique publique de la pharmacogénomique

Les progrès de la pharmacogénomique pour éviter les effets indésirables prévisibles des médicaments et pour choisir correctement les traitements dans certains cancers, ont soulevé des questions éthiques et sociales qu'il est temps d'examiner. Le génotypage de la population entière pour les polymorphismes enzymatiques métabolisant les médicaments a été proposé afin de prévenir des effets indésirables nocifs et dangereux. Le ciblage des traitements pharmacologiques fondé sur la génomique va vraisemblablement augmenter considérablement durant les années à venir. Des questions éthiques et politiques se posent au sujet de l'autorisation du recueil de grande envergure des données génomiques et pharmacogénomiques, de la propriété publique vs privée des données de recherche génomique, des essais d'efficacité et de sécurité d'emploi des médicaments utilisés pour des indications génomiques rares, et de l'accessibilité des traitements basés sur une recherche coûteuse bénéficiant à relativement peu de patients. Dans les troubles psychiatriques majeurs et la déficience intellectuelle, la délétion rare et de novo de segments chromosomiques ou leur duplication (variation du nombre de copies), sont dans l'ensemble des causes courantes d'augmentation du risque. Ceci signifie que les questions de politiques publiques par rapport à la pharmacogénomique seront particulièrement importantes avec les troubles psychiatriques.

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