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Misleading Guidance From Pharmacogenomic Testing

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Which of the following outcomes was observed in this report of a patient with treatment-resistant schizophrenia who had pharmacogenetic testing?

A. The testing provided information on specific doses which were tolerated by the patient
B. Genetic testing recommendations identified the most efficacious choice for the patient
C. Rapid improvement on clozapine contradicted the recommendations from the testing
D. The patient continued to be treatment unresponsive as confirmed by the testing

"Mr. A" is a 25-year-old man with schizophrenia who was admitted to the university hospital on an involuntary basis. The patient was brought to the hospital by police because of bizarre behavior at his residential care facility, which included opening all the windows and cabinets in the common areas and leaving a gas stove on and unattended. At the time of admission, Mr. A was distressed by command auditory hallucinations. On the inpatient unit, he tried to stab himself with a pen, and he stated that he was responding to "20,000 voices."

Mr. A was born full-term and met normal developmental milestones. His psychotic symptoms began at age 16, manifesting initially as disorganized speech and behavior and later as auditory hallucinations and bizarre delusions. Mr. A's mother had been diagnosed with and treated for schizophrenia, albeit at a later age; her treatment history is unknown.

Mr. A's medication treatment began at age 16, and significant improvement was seen with olanzapine at 40 mg/day. However, 3 years later, Mr. A had a severe exacerbation of psychosis, and his family noted that his psychotic symptoms were more pronounced than in the past. Subsequently, Mr. A was hospitalized multiple times, during which repeated episodes of agitation and aggression required seclusion and restraints. He failed to respond to numerous psychiatric medications, including lithium, valproic acid, citalopram, haloperidol, haloperidol decanoate, olanzapine, ziprasidone, paliperidone, and long-acting injectable paliperidone, as well as combinations of these.

Because of Mr. A's deteriorating mental state, his outpatient psychiatrist ordered pharmacogenetic testing, via a mail-order saliva test, in hopes of better understanding his treatment resistance. The pharmacogenetics laboratory advertising indicated that its reports were designed to help clinicians make more effective prescribing decisions that are "personalized" for each patient and would allow clinicians to prescribe "the right drug at the right dose" rather than operating through trial and error. On his current admission, both his family and his case worker provided the pharmacogenetics results to the team and insisted that the team utilize the information outlined in the report to guide Mr. A's medication management.

continued

Pharmacogenetics

In order to better understand the management of cases such as Mr. A's involving pharmacogenetic testing issues in psychiatry, it is important to have some understanding of the role of such test profiles in clinical cases. Medical genetics is defined as the study of how genes are identified and used for medical applications, including identification of disease or predilection for disease, and for tailoring treatment through targeted drug therapy. Pharmacogenomics, more specifically, is the study of how a person's genome affects his or her response to certain medications. It must be mentioned that medications can be influenced by a multitude of other factors, including age, sex, ethnicity, liver and kidney function, concomitant medications, and so on (2). Pharmacogenetics seeks to identify specific genetic polymorphisms in or near the coding region of genes that encode protein structures with which a drug interacts (3). The identified genetic polymorphisms are then assessed for the putative role in the observed individual variability in the clinical profile of the drug, most notably the drug's pattern of response and/or side effects (4).

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The team considered his documented history of antipsychotic resistance and concluded that a trial of clozapine would be the next appropriate step. Unfortunately, Mr. A's family and outpatient provider vehemently disagreed with this recommendation, as it strayed from the recommendations delineated in the pharmacogenetics report. Mr. A's pharmacogenetic test profile identified him as a heterozygous carrier for a single-nucleotide polymorphism in the DRD2 gene. Further evaluation of the test profile revealed that the specific variation in the DRD2 genetic locus predicted "a poor response" to olanzapine, risperidone, and clozapine. Several other genetic loci, including UGT2B15, CYP2C19, CYP2D6, HLA-B15.02, HTR2C, and MTHFR, were also characterized in the genetic profile.

Nonetheless, Mr. A's case was discussed with the university medical director, and a consensus was made to try clozapine, to which the patient consented. Mr. A subsequently had a rapid improvement on 400 mg/day of clozapine in divided doses. The family confirmed his progress, and he was subsequently discharged to a residential care facility, where he gradually returned to his previous level of autonomous functioning. He tolerated the clozapine quite well overall, but he developed a mild neutropenia, which was successfully managed using lithium (1).

Increased accessibility, low cost, and ease of use for genetic testing (through a saliva sample), which itself promises to identify how an individual's genetic makeup can contribute to inherited differences in drug metabolism (pharmacokinetics) and drug action (pharmacodynamics), have created an environment in which misinterpretation can easily occur in the rapidly growing field of pharmacogenetics. Knowledge of the relationship between candidate gene variation and response to various drugs indeed has potential. If performed and used validly, these genetic tests may lead to personalized pharmacotherapy in which drugs with the greatest likelihood of benefit and least likelihood of harm are selected for individual patients (3). Research has grown and uncovered numerous polymorphisms across multiple genes. Older studies concentrated on genetic markers involved in the metabolism of antipsychotic medications through hepatic cytochrome P450 enzymes (5). More recently, commercial pharmacogenetic tests have included several of these genetic variants in antipsychotic-related genetic testing panels. The clinical validity and utility of these antipsychotic panels remain unclear (5). Laboratory reports with varying degrees of interpretation and therapeutic recommendations, as in the case of Mr. A, highlight the need for standardization. While several consortium groups are working on guidelines for the application of pharmacogenomic information in clinical practice, large blinded pharmacogenetic clinical trials with head-to-head drug comparisons will ultimately be needed to validate the strategy of selecting and dosing drugs based on genetic testing.

The recommendation against clozapine therapy for Mr. A had significant implications. Clozapine is an underutilized agent, and it is the only antipsychotic to show significant response when multiple other antipsychotics have failed (6); approximately 50% of patients who do not respond to other antipsychotics benefit from clozapine (2). A 2013 review of 124 pharmacogenetics studies attempting to identify key gene mechanisms predicting clozapine response and side effects had mixed and controversial results (2). Despite decades of research, no biological or clinical predictors of response to antipsychotic medication or development of side effects has been identified. The available data and sample sizes are not large enough to detect viable associations.

The genetic profile obtained for Mr. A characterized several genetic loci that the pharmacogenetics lab claimed *could* influence his treatment response, including DRD2, UGT2B15, CYP2C19, CYP2D6, HLA-B15.02, HTR2C, and MTHFR. This alone is not congruent with the information that is available when amassing the research that is currently available for clozapine and pharmacogenetics.

From a candidate gene perspective, DRD2 studies may predict response because dopamine D_2 receptor occupancy by antipsychotic agents has been demonstrated to occur with all antipsychotic agents (7). In the genetic testing profile, Mr. A was identified as being heterozygous for DRD2, which translates into having one normal DRD2 allele and one allele with a single-nucleotide polymorphism in the promotor region of DRD2 that has been reported to increase expression in in vivo assays and have decreased affinity for D_2 ligands (7). As a result, olanzapine, risperidone, and clozapine were declared to be medications to which Mr. A would respond poorly. When questioned on these claims, the company that performed Mr. A's pharmacogenetic testing provided two research articles that proved to have little application to his presentation. The first article (8) addressed the role of genetic polymorphisms in susceptibility to developing schizophrenia, with no mention of treatment. The second article (9) was a small study that found a relationship between DRD2 genetic variation and treatment response in first-episode schizophrenia patients. No further validating study was provided by the company or found in a literature search.

Companies specializing in the sale of genetic test results for profit have proliferated in the past several years. Consumers and clinicians may not be aware of the full implications associated with genetic testing results. We next discuss how clinicians might respond to similar clinical decision making scenarios.

Clinical Decision Making With Pharmacogenomic Test Results

Psychiatrists will likely encounter pharmacogenomic tests in clinical practice in a wide variety of settings and diagnoses.

Established treatment guidelines have not yet incorporated the use of such testing, and thus the results may be misleading or even harmful to patients. In this case, evidence from the literature suggests that Mr. A may be a poor responder in first-episode schizophrenia because of his genetics. However, Mr. A had been struggling with schizophrenia for years, and evidence-based practice guidelines were neglected in favor of genetic testing.

Numerous experts, ethicists, publications, and legislative bodies have weighed in on the topic of genetic information. As seen in the case of Mr. A, when that information has become available, more questions than answers may arise. A valid argument can be made that the family and outpatient provider wanted him to have the best possible treatment outcome, and that more information and knowledge of Mr. A's genetic background would be helpful. However, given the lack of robust, controlled data regarding pharmacogenomics in clinical practice, the case illustrates how inadequate the information may be and how it may even have the potential for harm.

By contrast, genetic testing for breast cancer markers, such as human epidermal growth factor 2 (HER2), provides specific information leading to treatment that can be lifesaving (10). Such information is currently not applicable in mental disorders, which have a wide array of putative environmental and genetic etiologies. Given the lack of pharmacogenetics data in clinically driven models of research, we argue that it is unethical to claim that certain medications should not be used as treatment for a mental illness based solely on the current state of pharmacogenetic testing.

Numerous studies identify a core set of interventions, including medications and psychosocial interventions, that are effective in the treatment of severe mental illness to help patients attain superior symptom management, functional status, and quality of life (11). These well-documented interventions constitute the foundation of the treatment guidelines that practitioners are familiar with. Research indicates that these guidelines should not be modified extensively in considering local and individual circumstances, as adherence to a specific evidence-based practice is necessary to produce desirable outcomes (12–14). Pharmacogenetic testing does not have sufficient valid data to alter such treatment algorithms.

The use of pharmacogenetic profiles should be carefully considered before being ordered and may raise unintended harms. Difficult treatment cases are a commonly encountered problem in psychiatry, and therefore it is critically important for psychiatrists to understand the importance of adherence to evidence-based interventions to guide care toward ethical treatment.

C. Rapid improvement on clozapine contradicted the recommendations from the testing

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