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Ethical and Policy Considerations in the Application of Pharmacogenomic Testing for Tardive Dyskinesia: Case Study of the Dopamine D3 Receptor

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Abstract

Tardive dyskinesia (TD) is a serious adverse effect often associated with the first generation antipsychotic medications used in the management of mental health disorders such as schizophrenia. Pharmacogenomics is the study of human genomic variation in relation to individual and population variability in medication response and side effects. Neuropsychiatry is one of the clinical domains in which pharmacogenomic approaches have been extensively studied. In the late 1990s, the Glycine9 (Gly9) allele of the Serine-9-Glycine (Ser9Gly) polymorphism in dopamine D3 receptor gene (*DRD3*) was found to be associated with both a liability to, and worsened severity of, TD in schizophrenic patients treated with typical antipsychotics. This initial discovery has been subsequently replicated and testing for the Ser9Gly polymorphism has now become commercially available. The question that currently presents itself is whether its use should be encouraged for patients who may be prescribed a typical or atypical antipsychotic medication. However, the translation of this new technology to clinical practice presents multiple social, ethical and policy challenges. Though pharmacogenomic testing holds much promise in this scenario, many important questions remain to be answered before its widespread use can be medically and ethically justified. This article highlights the key advances in our understanding of the role of human genetic variation in the D3 receptor in relation to TD. Then, issues of uncertainty, consent, confidentiality, and access are considered with respect to the use of *DRD3* polymorphism testing in risk stratification for susceptibility to tardive dyskinesia. We propose three recommendations that may help bring this technology into the clinic: 1) prospective pharmacogenomic studies of *DRD3* polymorphism and TD risk should be conducted; 2) the design of such studies should be influenced by scientists, ethicists and policy makers to protect potentially vulnerable patients; and 3) appropriate knowledge transfer to front-line health care workers must take place.

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Keywords

DRD3; ethics; pharmacogenomics; prospective policy; tardive dyskinesia

1. INTRODUCTION

Tardive dyskinesia (TD) is an iatrogenic movement disorder characterized by disabling and disfiguring involuntary movements that result from dysfunction of the brain's extrapyramidal motor system. TD occurs predominantly in patients with psychosis, a thought disorder in which delusions and hallucinations disrupt patients' sense of reality. Schizophrenia is the most prevalent psychotic disorder. Antipsychotic drugs are the mainstay of treatment for the psychoses, in that they reduce the psychotic disturbance and improve quality of life. However, long-term exposure to antipsychotic drugs may induce tardive dyskinesia in many patients [1, 2]. In addition to contributing to the further stigmatization of this already marginalized population, TD impairs function and may contribute to mortality in psychiatric patients [3]. Therefore, reducing the incidence of TD remains a priority.

The rise of pharmacogenomic technology presents an important opportunity to better manage the risk of tardive dyskinesia. Pharmacogenomics is the study of human genomic variation in relation to individual and population variability in medication response and side effects. Much of the research in this growing field has been directed towards understanding how different individuals respond to neurologically and psychiatrically active medications. The clinical use of pharmacogenomic technology has remained relatively limited due to our still developing understanding of its applicability, as well as to significant associated costs. However, a growing body of evidence suggests that a particular polymorphism in the dopamine D3 receptor gene (*DRD3*) increases the chance that a patient will develop tardive dyskinesia. Identified in the 1990s, the Serine-9-Glycine polymorphism in *DRD3* has been implicated in several studies to increase the risk of tardive dyskinesia in patients exposed to first generation antipsychotics (Table 1).

Testing for this genetic polymorphism could be useful in selecting patients in whom to avoid these 'typical' antipsychotics. However, the potential application of this genetic tool to clinical practice presents several ethical challenges. Issues of uncertainty, consent, confidentiality and access will be considered here, with reference to the clinical consequences that may arise in developed and developing nations. Though pharmacogenomic technology holds much promise, many important questions must be answered before its widespread use can be medically and ethically justified. This article aims to highlight the key advances in our understanding of the role of human genetic variation in the D3 receptor in relation to TD, to consider the ethical and policy implications of these developments, and to propose several recommendations that may help to accelerate the translation of pharmacogenomic technology into the clinic.

2. TARDIVE DYSKINESIA AND *DRD3* POLYMORPHISM: 'TYPICAL' AND 'ATYPICAL' ANTIPSYCHOTICS

Shortly after the introduction of the first generation of antipsychotic medications in the 1950s, physicians identified patients afflicted with orofacial dyskinesias, or abnormal involuntary movements of the lips, jaw, tongue and, less often, the glottis. Dance-like, writhing movements of the truncal and appendicular muscles could also occur [4–6]. The term 'tardive dyskinesia' was coined by Faurbye *et al* [7] in 1964 in recognition of the delayed onset of these symptoms following long-term exposure to antipsychotic medications. The cumulative incidence of TD has been shown to be 5% after one year, 27% after 5 years, 43% after 10 years, and 52% after 15 years of typical antipsychotic exposure [8].

Exposure to the so-called 'typical' antipsychotics (eg., chlorpromazine, haloperidol and fluphenazine) is thought to be the main risk factor for tardive dyskinesia. The best corrected estimate of prevalence is about 15% in patients on these drugs [1, 2]. 'Typical' antipsychotics act predominantly *via* blockade of dopamine D2 receptors in the mesocorticolimbic system of the brain [9], a network involved in the regulation and expression of emotion as well as in the ability to plan and organize both goal-directed and reward-driven behaviours. The emergence of tardive dyskinesia is, in part, thought to relate to upregulation of dopamine D2-like receptors outside of the mesocorticolimbic system, particularly in the extrapyramidal or nigrostriatal system (basal ganglia and its connections).

In the 1980s and 1990s, a second generation of antipsychotic medications emerged, led by the prototypical drug, clozapine. These drugs (eg., olanzapine, risperidone, quetiapine and ziprasidone) are referred to as 'atypical' in that they have a decreased propensity to produce abnormal movements such as TD [10]. However, the 'atypicals' are not without tardive dyskinesia: large randomized trials suggest an overall rate of 2.1%, with 0.8% in adults younger than 50 years and 5.3% among those older than 50 years of age [11]. Moreover, they are significantly more expensive than typical agents, and carry their own profile of side effects, most notably an increased tendency to weight gain, metabolic abnormalities and subsequent atherosclerotic risk.

In the late 1990s, the Glycine9 (Gly9) allele of the Serine-9-Glycine (Ser9Gly) polymorphism in *DRD3* was found to be associated with both a liability to, and worsened severity of, TD in schizophrenic patients treated with typical antipsychotics [12, 13]. One of the earliest studies was performed by our research group, and our findings have subsequently been replicated [12, 13]. Testing for the Ser9Gly polymorphism has now become commercially available, and the question that presents itself is whether its use should be promoted for patients who may be prescribed a typical or atypical antipsychotic medication.

2.1. Medical and Ethical Analysis of the Status Quo

In the absence of pharmacogenomic testing for the *DRD3* polymorphism, antipsychotic medications are prescribed to patients on a trial and error basis. In North America, patients

are initiated on treatment with doses recommended by the manufacturer and then these doses are titrated upwards to maximize efficacy while minimizing side effects. If patients have a poor response to a particular drug despite reaching the recommended maintenance dose, or if they prove intolerant of the drug due to adverse drug reactions, patients will be switched to another antipsychotic, often from a different class. Several different medications may be tried before the 'right' one is identified; occasionally, that 'right drug' is never found. As a consequence, patients may be exposed to the adverse effects of trialed medications with no guarantee of beneficial therapy. It is under these circumstances that many patients develop tardive dyskinesia. Therefore, the implication of not applying available pharmacogenomic testing to the clinic is to perpetuate a status quo in which potentially avoidable harms are encountered over extended periods of time in an already marginalized population. This large risk-to-benefit ratio produces a suboptimal state with regards to medical and ethical outcomes.

Following large-scale clinical trials of the atypical antipsychotics in the 1990s, they are increasingly used as first-line agents in the management of psychosis in wealthy nations. However, atypical agents increase the risk of metabolic syndrome. Also known as Syndrome X, this clinical entity is characterized by increased abdominal or visceral adiposity, atherogenic dyslipidemia (decreased high density lipoprotein [HDL], elevated low density lipoprotein [LDL] and elevated fasting triglycerides), hypertension, and impaired fasting glucose or overt diabetes mellitus [14, 15]. Results from the recent CATIE trial of 1460 patients confirmed that the atypical agents produced significant elevations in weight and an increased risk of the metabolic syndrome when compared to typical antipsychotic drugs [16]. This increased risk of metabolic syndrome may translate into increased mortality from atherosclerosis (stroke, ischemic heart disease and peripheral vascular disease). Patients with schizophrenia have a lifespan that is approximately 20% shorter than that of age-matched controls, with much of this effect attributed to metabolic syndrome [16, 17].

The advent of pharmacogenomic testing for the Ser9Gly polymorphism heralds a new paradigm of clinical practice in which a directed approach to antipsychotic prescription replaces this flawed status quo. In patients known to harbor the high-risk allele, typical antipsychotics could be prescribed at low doses or avoided entirely. Long-acting injected (depot) formulations would likely be contraindicated in this population. Atypical agents would be used at the lowest possible doses to control symptoms. At risk patients could be more closely monitored for the development of early signs of tardive dyskinesia.

These measures would likely reduce the incidence and severity of TD while maximizing the beneficial effect of antipsychotic medications. Testing for the *DRD3* polymorphism could therefore improve the current system of practice with the potential of a 'personalized' pharmacotherapy for psychotic disorders. This technology could reduce both direct and indirect health care costs and improve quality of life for patients and their families. However, the introduction of this new technology would import new ethical challenges in matters of uncertainty, consent, confidentiality and access.

In 2003, The Nuffield Council on Bioethics compiled a report that reviewed the ethical challenges posed by the application of pharmacogenomic technology to the provision of

health care and the conduct of clinical research [18]. Although a comprehensive discussion is beyond the scope of this paper, the key issues addressed by the Nuffield Council included the maintenance of anonymity and the protection of privacy in pharmacogenomic trials, the consideration of equity and cost-effectiveness in the allocation of pharmacogenomic treatments, the validation of pharmacogenomic testing in different populations, the recognition of the potential for prejudice arising from racial stereotyping, the need for proper training of health care professionals about consent issues and in the interpretation and communication of test results, and the importance of safeguarding pharmacogenomic information from insurance agencies for the purposes of establishing individualized premiums. When applying these themes to the matter at hand, concerns about uncertainty, consent, confidentiality and access emerge as relevant to *DRD3* pharmacogenomic testing in TD. Though similar challenges arise with many other forms of genetic testing, we will focus on those circumstances specific to the testing for the *DRD3* allele.

2.2. Uncertainty

Uncertainty is an epistemological problem that complicates nearly every medical decision; it becomes an ethical problem when information that is not certain is assumed to be true, and when decisions are made based on this false assumption. As Edmund Pellegrino writes, “perhaps the most dangerous and unethical use of evidence is not deliberate lying but gratuitous assertion—saying what we do not know to be true but think, feel, or want to be true [19].” A recent survey explored psychiatrists’ opinions of pharmacogenomic testing and identified the need for “clear, peer-reviewed published evidence that the test results correlate with side effects or treatment responses in a predictable and measurable manner [20].” Several areas of uncertainty challenge the current viability of pharmacogenomic testing in the context of TD, and are likely to persist into the near future: the pathophysiology of TD remains incompletely understood; the association between Ser9Gly and the development of TD is one of percentages and risks rather than guarantees; and the sensitivity, specificity and predictive value of Ser9Gly genetic testing have not yet been established. No clinical test will ever be devoid of uncertainty or false results, but the acceptable threshold for uncertainty in pharmacogenomic testing remains to be established.

How much of the disease process of tardive dyskinesia is due to antipsychotic medications [21–23]? Spontaneous dyskinesias have been described in antipsychotic-naïve patients suffering from schizophrenia with a frequency of up to 5% [1, 2]. Risk factors other than antipsychotic exposure may play a significant role in the development of TD. Epidemiologic studies have identified advanced age (in fact the strongest demographic risk factor), the presence of organic brain disease, and a family history of tardive dyskinesia as potential contributors [8, 22]. Higher doses of, and prolonged exposure to, antipsychotics are the strongest environmental risk factors for TD [8, 22] though no consistent pharmacokinetic relationship has been identified between antipsychotic dose, plasma drug level, and the risk of TD [24].

What is the relationship between race and TD? Several studies have suggested African ancestry to be an important risk factor for the development of TD [25–33]. Though African Americans with schizophrenia are more likely to receive higher doses of typical

antipsychotic drugs given as depot formulations [27], the risk of TD seems to be higher in those of African ancestry regardless of antipsychotic dosing [34]. Even among our original studies of the Gly9 polymorphism, we noted that African Americans had a higher frequency of the Gly9 allele than Caucasians, and African Americans with the Gly9 allele had more severe TD than Caucasians with the same polymorphism [12].

How strong is the association between the Ser9Gly polymorphism and the risk of developing TD, and how reliable is the genetic test itself? Our original study demonstrated that the Ser9Gly *DRD3* polymorphism accounted for approximately 30% of the variance in the severity of TD after controlling for age, sex and ethnicity [12]. In a combined analysis of 780 patients using stepwise logistic regression, Lerer *et al.* [35] demonstrated that TD was significantly associated with the presence of the *DRD3* Gly9 allele and also with the *DRD3* Gly9/Gly9 genotype. Lerer's group also confirmed that the presence of the Gly9 allele was significantly associated with more severe TD [35]. In their meta-analysis, the Mantel-Haenszel pooled odds ratio for the *DRD3* Gly9 allele carrier status increasing susceptibility to TD was 1.33 [35]. More recent meta-analyses yielded less significant findings with Ser9Gly [36, 37], but they did not include all published studies. Positive findings are still being reported [38], as described in Table 1. The definitive test to address many of these concerns would be a prospective study establishing the incidence of TD in patients with and without the Gly allele taking typical and atypical antipsychotics; no such study has yet been completed.

2.3. Consent

Another challenge to the general application of pharmacogenomic testing is the matter of consent. The importance of informed consent is a reflection of the centrality of respect for patient autonomy in contemporary medical ethics [39]. In the matter of pharmacogenomic testing, a patient's ability to provide informed consent is limited by the issues of uncertainty discussed above; moreover, the future applications of genetic information remain a source of controversy within the field. Karen Peterson-Iyer questions how we can ensure informed consent when "scientists and clinicians themselves may not be aware of all the potential uses of the genetic information gathered." She argues that the patient must be conceptualized as "a concrete historical person, with interests that will stretch forward in time and be intertwined with the interests of others —who may themselves benefit from the information embedded in that patient's DNA [40]." In their 2003 report, the Nuffield Council on Bioethics distinguished between 'narrow' and 'broad' consent; namely, that the specificity of consent procedures may vary to include as yet unseen applications of genetic information collected for a particular purpose. With broader consent come less stringent controls on the use of samples and the greater potential for scientific discovery; these benefits are balanced by an individual's limited ability to restrict access to his or her genome [41].

In the context of achieving consent from schizophrenic patients, an added layer of complexity arises. Patients with schizophrenia are very frequently incapable of providing consent for health matters. Though definitions of 'capacity' vary, the term generally refers to patients' abilities to understand the nature of what is being asked of them and to appreciate the consequences of their health decisions. A recent study suggests that as many as 44% of

psychiatric patients admitted to hospital were deemed incapable with regards to decisions in matters of health [42]. Who then would consent to pharmacogenomic testing on behalf of incapable patients with schizophrenia? In many jurisdictions, the law sets out a specific hierarchy of potential substitute decision makers for incapable patients. In the province of Ontario, spouses, then parents and children represent the first levels in that algorithm, unless a specific decision-maker has been identified *a priori.* Substitute decision makers are asked to make the decision that the patient would have made, were he or she able to do so. Family members are often most likely to know patients' wishes, but in the matter of genetic testing their participation may be biased by a desire to gain insights about their own genetics or to avoid such knowledge. State-appointed guardians are required to consent on behalf of patients who do not have a designated substitute decision-maker, but they too may be biased by a desire to minimize costs to publicly-funded systems by identifying those patients in whom the older, cheaper typical antipsychotics could be used. Multiple examples exist to demonstrate instances in which government-subsidized health providers have attempted to limit short-term costs in the domain of psychiatric care, often at the expense of long-term costs and eventual patient outcomes [43]. There is a potential for conflicting medical, ethical and financial interests in the determination of substitute consent for pharmacogenomic testing in the psychiatric population.

Though pharmacogenomic testing for the *DRD3* polymorphism could lead to more rational pharmacotherapy and therefore potentially improved health outcomes for patients taking antipsychotic medications, such analyses would not be morally justified unless the complications described above, and others to be described below, are controlled for in the construction of the relevant tests. Challenges to consent, and to surrogate consent, are not new nor are they limited to the application of *DRD3* testing. Resolving these conflicts is not within the scope of our discussion, but it is essential that physicians and policy-makers working in the field of pharmacogenomics be aware of these issues.

2.4. Confidentiality

The challenge of obtaining consent is intimately related to problems of patient privacy and confidentiality. When DNA samples are collected from patients for the purposes of pharmacogenomic studies, who should have access to that information, and what should happen to the samples afterwards? The potential to use genetic information that was collected for one purpose towards other ends has led to the promotion of banking samples and data. For example, the new technology of genome-wide association studies (GWAS) requires comparing genetic information from a large number of individuals to identify single nucleotide and copy number variations that might explain similar clinical characteristics, and would certainly benefit from access to DNA samples obtained for other purposes. The scientific and ethical elements of biobanking have been extensively discussed elsewhere [44]. However, it is important to note that consenting to pharmacogenomic testing is not the same as consenting to biobanking, and access to patients' genetic information by pharmaceutical companies or researchers does not need to come with consent to pharmacogenomic testing.

The ethicist and psychiatrist Tony Hope explains that our notions of confidentiality have traditionally been built on the 'personal account' model, in which health information belongs to that patient alone [45]. However, the rise of genetic testing "challenges the individualistic nature of many of the moral assumptions made in discussions of medical ethics" and suggests that a 'joint account' model may be more applicable: genetic information may be considered to belong to all 'account holders,' unless there are good reasons to withhold that information [45]. 'Account holders' are to be distinguished from 'stake holders,' which are all those participants who may benefit from access to that genetic information. Family members with a shared genetic heritage would certainly be considered stake holders; so too may agents of the government that funds the services provided to the patient in question; so too may the test provider, who seeks to refine current or develop future genetic tests. However, a stake holder is not necessarily an account holder as well.

In their discussion of the handling of pharmacogenomic data, Joly *et al.* [46] propose the notion of differing 'confidentiality levels,' which may vary between studies or even within a given study. The highest level of confidentiality is the anonymization of samples; double-coded and coded samples represent decreasing levels of protection. Because the purpose of pharmacogenomic testing for the *DRD3* allele is to rationalize pharmacotherapy for a given individual, anonymization would be impractical. However, given the marginalized and vulnerable population most likely to take part in testing for *DRD3*, a double-coded system would guarantee the security of genetic information with its release allowed only under certain prespecified circumstances, ie., for the determination of therapy for that patient [46].

2.5. Access

One potential application of pharmacogenomics is to provide guidance to physicians in developing nations. The World Heath Organization publishes an Essential Medicines List (EML) whose purpose is to help developing nations focus their health care expenditures on medicines most likely to be of benefit to their population [23, 47, 48]. Recent editions of this list include three typical antipsychotic drugs: chlorpromazine, haloperidol, and fluphenazine [23]. Though beneficial and inexpensive, these medications carry a high risk of TD. As Özdemir *et al* [23] have proposed, pharmacogenomic strategies could generate an "Essential Biomarkers" Library which could be produced alongside the Essential Medicines List. This combined approach could help to reduce the adverse effects and maximize the response to medications in countries where resources are most limited. The atypical agent risperidone has recently come off patent and may be added to the EML in the near future; in that event, pharmacogenomic testing could help to choose between different classes of antipsychotics on the EML. However, patients in developing nations may be deemed 'genetic lost causes' if their testing shows them to be at high risk of developing TD regardless of the drug used [48, 49]. Further stigmatization and ostracization could occur. Moreover, the cost of administering pharmacogenomic testing to one patient may deprive another of access to lifesaving intervention.

Unfortunately, disparities in access to health care resources do not simply exist along norm-south or east-west axes; they are present in every major city of the developed world, and often parallel racial and ethnic lines. Concerns exist that the application of

pharmacogenomic testing to clinical practice would further enhance existing inequalities, in that access to genetic tests (and the resultant information and theoretically improved care) would likely be limited to those of the highest socioeconomic status. In the United States, where race correlates strongly with health outcomes as well as with metabolic syndrome, with the incidence of schizophrenia and with the risk of TD, the situation becomes even more complicated [50]. Peterson-Iyer explains that “One of the most controversial of the issues raised by pharmacogenetics is whether and how to integrate the category of race into drug development and marketing. The background for such a question is an insidious history of race-based differences in health status in the United States [40].” We can imagine a patient with schizophrenia (perhaps poor, perhaps African American) who is denied access to pharmacogenomic testing and as a consequence develops TD from long term typical antipsychotic use. However, we can also imagine a patient who undergoes pharmacogenomic testing, is found to be at increased risk of TD, but who cannot afford an atypical medication. Several Health Movement Organizations do not include atypical agents in their formularies because of the increased costs [51, 52]. Or we could imagine a patient who is prescribed an atypical agent due to his/her genetic testing but dies of a premature heart attack or stroke. Which of these outcomes is preferable? Is any better than the status quo?

The ethical issue of using race as a proxy for pharmacogenomic information to guide treatment is contentious and has been extensively discussed elsewhere [18, 53, 54]. It is our view that although the frequency of the Gly9 allele may indeed be higher in African Americans than in Caucasians, many patients of both backgrounds will not have the risk allele. Therefore, we strongly support the premise that race should not be used as a proxy for determining whether someone is at risk of developing TD on antipsychotic therapy; rather, the pharmacogenomic result should be included as one factor among many to aid in rational clinical decision-making.

3. RECOMMENDATIONS AND FUTURE DIRECTIONS

The translation of pharmacogenomic technologies from a research methodology to a clinically-relevant tool will require addressing these issues of uncertainty, consent, confidentiality and access. Khoury *et at.* [55] have recently proposed that the adaptation of novel scientific tools to the clinical environment requires the completion of four phases, enumerated T1-T4. In T1, epidemiological observations identify a so-called ‘candidate application’ for a new technology: the discovery of the role of the *DRD3* polymorphism in TD would be such a scenario. In T2, the clinical utility of this new technology is assessed through epidemiological studies. In T3, challenges to the widespread implementation of the new technology are identified. In T4, the impact of this new technology on population health outcomes is documented. This article reflects an attempt to predict T3 concerns and to correct for them prior to the implementation of T2 epidemiological studies. We propose three steps which will help to overcome the epistemological and ethical challenges posed by the application of testing for the Ser9Gly polymorphism.

First, it will be necessary to conduct prospective, longitudinal observational studies of patients exposed to both typical and atypical antipsychotics to determine the relative risk of

developing TD based on the *DRD3* Ser9Gly polymorphism. These studies should control for dose-response relationships and also for drug-drug interactions. We recommend the use of a predictive statistical model that can incorporate testing for other genetic variants recently implicated in TD [56] and that can accommodate genetic factors that may be discovered in future. International collaborations may be required to achieve the necessary sample sizes in a reasonable time frame. Parameters such as sensitivity, specificity, and positive and negative predictive values should be calculated. Ideally, such studies would then be replicated in independent samples. We will need to deepen our understanding of the pharmacogenomics of other adverse effects associated with antipsychotic use, most importantly the metabolic syndrome [57, 58] in the context of atypical antipsychotic exposure.

Second, scientists, ethicists and policy-makers will need to be involved in the design of these studies and in the development of guidelines in order to ensure the proper protection of patients' rights to informed consent, confidentiality and access. This will likely require consensus building between governments, physicians, patient advocates and industry to establish how patients will be enrolled if they are unable to consent, and to determine in advance how acquired genetic information will be used.

One potential solution would be to establish a collaborative non-profit organization to determine capacity, obtain consent, collect and analyze the genetic samples. Only those data relevant to the study of *DRD3* polymorphisms would be released to investigators, thereby creating a firewall between the acquisition of data and its content. Similar consortia could be established for each pharmacogenomic study, with specific consent and confidentiality policies established *a priori* given the particulars of the effect being studied and the patient population involved. With a healthy, wealthy and informed population, potentially looser safeguards may be acceptable. Given the vulnerability of the *DRD3* population to be tested, narrow consent (ie., providing access to samples only for the direct purpose of *DRD3* testing) and double-coded confidentiality (ie., releasing information only for clinical decision-making related to that patient) would likely be warranted. Though this construction would limit the potential scientific benefit of samples collected for *DRD3* testing, it protects those members of our society who are least likely to be able to advocate for themselves. In their 2010 statement on personalized medicine, the Nuffield Council on Bioethics highlights the need to safeguard privacy, to reduce harms, and to share responsibility for the protection of the most vulnerable among us [59]. As it is beyond the scope of pharmacogenomic studies to resolve the gross inequalities present in the provision of health care across the world, we see such measures as the most reasonable means at our disposal of addressing issues of access as well as consent and confidentiality.

Ultimately, clinicians, patients and their caregivers will make the decisions about antipsychotic treatment, perhaps informed by pharmacogenomic testing. Therefore, our third recommendation is to ensure proper knowledge transfer from the scientists, ethicists, and policy-makers involved in studying *DRD3* polymorphisms to front-line clinicians. The strengths and weaknesses of pharmacogenomic testing will need to be appreciated; as Nikolas Rose argues, pharmacogenomics will likely provide probabilistic information and not guarantees [60]. Moreover, any pharmacogenomic testing for TD will need to be simple, quick and inexpensive form it to be relevant in clinics, emergency departments, and on

hospital wards. Kathryn Montgomery writes that medicine is a science of individuals; this is true from genetic and clinical perspectives [61]. As such we believe that a 'genetically-informed' approach to clinical decision-making will rationalize the management of patients with schizophrenia.

CONCLUSIONS AND OUTLOOK

Though pharmacogenomic testing for the Ser9Gly polymorphism in the *DRD3* gene holds great promise as a risk stratification tool for tardive dyskinesia and represents a means to guide therapeutic choices, many important questions remain unanswered. The implication of these questions of medical uncertainty, consent, confidentiality and access is to cast doubt on the immediate benefits of pharmacogenomic testing in this clinical situation. In reference to pharmacogenomics, Khoury and Bradley explain that "the premature introduction of technologies into healthcare settings could potentially overwhelm the health system financially, legally and ethically [62]". A stringent, proactive approach that recognizes the medical and ethical consequences of Ser9Gly testing alongside its potential contributions to patient care will be required. We anticipate that our suggestions will help to facilitate the transition of pharmacogenomic testing for TD from an exciting research methodology to a clinical tool that improves outcomes for a marginalized patient population. Skepticism must go hand in hand with optimism in the adoption of any medical advance, and pharmacogenomic testing for TD is no exception

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ABBREVIATIONS

AIMS	Abnormal Involuntary Movement Scale
DRD3	Dopamine D3 receptor gene
EML	Essential Medicines List
Ser9Gly	Serine-9-Glycine polymorphism
TD	Tardive dyskinesia

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Table 1

Selection of *DRD3* Ser9Gly Polymorphism Association Studies with TD

Rating Scales	>1 Rating	Sample Size	Ethnicity or Nationality	Main Findings	Ref
AIMS	Yes	100	Caucasian	Association with TD and the Gly-allele (p=0.03) and with the Gly/Gly genotype (p=0.01)	[13]
AIMS	No	112	85: Caucasian; 25: African American	Higher AIMS total scores associated with Gly/Gly genotype compared to Ser/Gly and Ser/Ser genotype (p=0.0005)	[12]
AIMS	No	116	Ashkenazi and non-Ashkenazi	TD associated with Ser/Gly genotypes (p=0.0008); total AIMS scores with genotypes carrying Gly alleles (p=0.02)	[63]
AIMS	No	71	European Caucasian	Tendency for an association between homozygosity for the Gly-variant and TD (p=0.20)	[64]
AIMS	No	115	Taiwan Chinese	Higher AIMS scores with Ser/Gly genotypes compared to Ser/Ser and Gly-Gly genotypes (p=0.01)	[65]
AIMS	?	113	Korean	Gly/Gly genotype significantly associated with TD (p=0.02), but no allelic association in AIMS analysis	[66]
AIMS	Yes	317	Chinese	Non-significant; but Ser/Ser genotype associated with TD in logistic regression analysis (p=0.01)	[67]
AIMS	Yes	101	Chinese	Higher TD observed in ser-gly heterozygotes (p=0.08)	[68]
AIMS	No	516	American mix	Presence of at least one Gly-allele associated with limb TD in white women (OR 2.2, 95% CI 1.0–4.9); severe TD (n = 49) associated with Gly-alleles	[69]
AIMS	?	102	Greek	Gly genotypes (Gly/Gly or Gly/Ser vs. Ser/ser) associated with AIMS scores (p=0.001)	[70]
AIMS	No	146	Russian	Non-significant; but Gly-variant significantly associated with TD in log-normal regression (p=0.02)	[38]
Meta-Analysis					
Various	?	780	African-American, Ashkenazi, Caucasian, Chinese, German, Japanese	Gly-allele carrier status increased susceptibility to TD (OR = 1.33)	[35]
Various	?	695	Ashkenazi, Caucasian, Chinese, German, Japanese, Korean	The Gly allele increased the risk relative to the Ser allele (OR=1.17)	[36]
AIMS (12 of 13 studies)	?	2026	European, Asian, Mixed (US)	No or little effect of the DRD3 Ser9Gly polymorphism and occurrence of TD	[37]