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Review

IMPLICATIONS OF THE USE OF GENETIC TESTS IN PSYCHIATRY, WITH A FOCUS ON MAJOR DEPRESSIVE DISORDER: A REVIEW

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Advances in technology have enabled research to link many genetic markers to specific disease risk. This has led to the commercialization of genetic tests across a wide range of medical disorders. Public interest in one's own future health and an increasing desire for autonomy over one's health care have facilitated a large and growing market for such genetic tests to be sold direct to the consumer (DTC). Amidst a plethora of tests for a broad range of medical conditions, DTC genetic tests currently include a number of tests related to risk for various psychiatric illnesses including major depressive disorder (MDD), bipolar disorder, schizophrenia, and obsessive-compulsive disorder and also for prediction of individual response to psychotropic medication. Although a large number of studies show that there is strong public interest in genetic susceptibility testing for psychiatric disorders, little is known about the impact on individuals of receiving the results of genetic tests. Moreover, the low predictive power and uncertain clinical validity and utility of DTC genetic tests for psychiatric disorders have led to both controversy and difficulties of interpretation of results. This review summarizes the rationale for using genetic risk tests in psychiatry, as an intervention for protective cognitive and behavioral change, and to predict medication response, with a focus on MDD. Since genetic risk information has the potential to influence major life-changing health decisions, there is an imperative to ensure that there is an appropriate evidence base to support the use of such genetic tests. Depression and Anxiety 30:267–275, 2013.

Key words: *major depressive disorder; direct-to-consumer genetic testing; psychiatric genetics; gene–environment*

INTRODUCTION

Genome-wide association studies (GWAS) and other genetic studies have led to reports of the association of many genetic markers, in particular single-nucleotide polymorphisms (SNPs) and genetic variants associated with many common complex traits and diseases. Some of these findings have been incorporated in commercialized genetic tests marketed directly to

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TABLE 1. Selected genetic testing definitions

Diagnostic genetic test	A genetic test for individuals who are already symptomatic in order to confirm or establish a genetic diagnosis.
Predictive genetic testing	
Pre-symptomatic genetic test	A genetic test for an asymptomatic person for a condition that will manifest later in life.
Susceptibility genetic test	A genetic test for susceptibility to common complex disorders that may manifest later in life.
Pharmacogenetic test	A genetic test that determines the influence of genetic variations in response to medication

the public (this has been termed direct-to-consumer or DTC marketing). To date, over 1,000 genetic markers have been identified as being associated with over 200 different traits and diseases (www.genome.gov/gwastudies).[1–4]

The rapid advances in technology used in human genetics research have led to the commercialization of genetic tests, including "whole genome scans," marketed directly to the public. These products can be purchased for between US$ 400 and US$ 2,000 via company websites,[5] and provide risk estimates for a large number of medical conditions or drug responses (e.g., www.navigenics.com, www.23andme.com). For definitions of types of genetic testing see Table 1.

The development of next-generation sequencers now enable the DNA sequencing of the complete genome, known as personal genome sequencing. Unlike genetic tests for variants, which analyze less than 0.1% of the genome,[6] personal genome sequencing sequences all 46 chromosomes. It currently sequences each base in the genome an average of 40 times to a greater than 99% accuracy,[7] and detects small insertions, deletions, and larger rearrangements known as structural variants.[7] In 2009, the cost to institutions of personal genome sequencing with 30-fold base-pair coverage had dropped from US$ 48,000 (e.g., www.completegenomics.com) to US$ 5,000 with 40-fold base-pair coverage (e.g., www.illumina.com).[8]

By 2010, various genome centers had sequenced more than 2,000 individual genomes.[9] Commentators suggest that a target price of less than US$ 1,000 by 2014 will bring personal genome sequencing to the consumer market.[9]

The marketing of personal genome sequencing and genetic susceptibility testing for common complex disorders, such as psychiatric disorders and for response to psychotropic medications to the public is potentially problematic because the predictive power of genetic variants is low, clinical validity and utility of such tests is uncertain,[10] and such interventions are not currently linked to associated treatment.[11] Genetic tests are at present substantially less useful in terms of determining risk for an individual to develop a psychiatric disorder than a detailed three-generation psychiatric family history. The application of genomic information to individual health care may be presently unclear but the amassing of databases of complete genome sequences could lead to a comprehensive understanding of the molecular basis of disease in the future. This article will explore the phenomenon of DTC genetic testing generally across mental health, and specifically as applied to major depressive disorder (MDD).

GENETIC SUSCEPTIBILITY FINDINGS FOR PSYCHIATRIC DISORDERS

GWAS have identified a growing number of genetic variants associated with psychiatric disorders including schizophrenia, bipolar disorder, MDD, autism, and attention deficit hyperactivity disorder.[1]

Recent meta-analysis of three GWAS datasets of European ancestry have identified variants in several genes that suggest a role in the etiology of MDD with the strongest evidence for variants in the metabotropic glutamate receptor gene (*GRM7*) and a V-type proton ATPase subunit B, brain isoform (*ATP6V1B2*).[12] Another recent GWAS found evidence of an association of a susceptibility locus in the homer protein homolog 1 gene (*HOMER 1*).[13] A previous GWAS conducted on two European datasets followed by meta-analysis found no variants that achieved genome-wide significance.[14]

Recently, two psychiatric GWAS consortia have reported on the hitherto largest studies in schizophrenia and bipolar disorder, identifying (for both conditions) novel susceptibility loci,[3,4] while confirming a number of other regions previously associated with these conditions. GWAS add to the increasing evidence that multiple common variants are likely to be responsible for a high proportion of the heritable risk for psychiatric disorders, though each individual variant only contributes a small proportion of the genetic variance for these conditions.[10]

Much of the genetic variance is yet to be explained. For conditions such as schizophrenia and autism, some of this "missing heritability" appears to be the result of rare structural variants (copy number variants or CNVs).[1,15]

The genetic contribution to MDD is likely to be heterogeneous and is likely to involve multiple genes each of small effect. It is likely that many more common variants conferring a risk of psychiatric disease will be identified in the coming years, but is not known whether this would lead to increasing accuracy of individual risk estimates. Further replication of novel loci associated with MDD is required using larger datasets.

GENETIC PREDICTION OF ANTIDEPRESSANT RESPONSE

Recently, several GWAS for response to antidepressants have been published.[16–18] One of these

identified a significant contribution of multiple genetic variants combined with clinical features in the prediction of patient response to antidepressant pharmacotherapy.[18] However, markers investigated in these multifocal analyses failed to reach significance following correction for multiple testing and replication has not been achieved.

GENE–ENVIRONMENT (G × E) INTERACTIONS

Some environmental exposures may have varying effects between individuals depending on the presence or absence of certain genetic variations. This is referred to as gene–environment (G × E) interaction. Understanding how genotype interacts with environmental triggers in the development of psychiatric disorders provides an opportunity to improve accuracy of risk assessment and selectively target genetically vulnerable individuals for preventive interventions. However, to date, relatively few examples of G × E interactions have been reported.

A G × E interaction was reported by Caspi et al. in 2003,[19] whereby risk for MDD was related to an interaction between a functional variation in the promoter region (*5-HTTLPR*) of the serotonin transporter gene (*SCL6A4*) and exposure to multiple stressful life events.

This G × E interaction provides an excellent opportunity to examine the G × E association in the psychiatric setting. This association has been replicated in nonclinical populations in adults,[20–23] adolescents,[24] and children,[25,26] with some failures to replicate.[27–29]

In terms of basic physiological mechanisms, several studies[19–22,24,25] have suggested that *5-HTTLPR* may play a role in mediating response to stress per se, with *s/s* genotype carrying individuals demonstrating hyperreactivity to stressors and/or deficient problem-solving coping.[30] Three meta-analyses of this literature have been recently reported, with both negative[31,32] and positive findings.[33] Discrepancies in these findings have been attributed to methodological heterogeneity such as measures of specific stressors based on operational criteria (e.g., childhood maltreatment and medical illness) versus measures of self-reported stressful life events).[34,43]

To address possible confounding by methodological inconsistencies of earlier meta-analyses, Karg et al.[33] stratified included studies by the type of stressor studied. These stressor groups were "childhood maltreatment," "specific medical condition," and "stressful life events." The authors found a positive and significant association between the *s* allele and increased stress sensitivity in the "childhood maltreatment" and the "specific medical condition" groups of studies, but only a marginal association in the "stressful life events" group of studies. This suggests that the *5-HTTLPR* "*s*" allele could have clinical validity as a predictor of stress sensitivity among people who have experienced a particular type of stressor.

In summary, although future replication might produce effect sizes that may be too small to be clinically useful, current findings suggest evidence to support a strong but complex *5-HTT* stress-sensitivity interaction despite the negative results of the smaller earlier meta-analyses.

DTC GENETIC TESTS FOR PSYCHIATRIC DISORDERS

Despite the growing evidence that known SNPs contribute only a small proportion of the genetic variance for these conditions, and that each individual variant only increases risk by a small amount,[10] genetic tests are currently marketed DTC for risk to MDD, bipolar disorder, schizophrenia, and other psychiatric disorders.[35] Additionally, genetic tests that claim to predict individual response to psychiatric medications including mood stabilizers, antipsychotics, antidepressants, and benzodiazepines are also available.[35] Such tests are shown in Table 2.

Some companies, including the high-profile 23andMe (www.23andme.com), Navigenics (www.navigenics.com), and more recently, Lumigenix (www.lumigenix.com), market "whole genome scans" for about US$ 300 to US$ 475. These products are not whole genome sequencing, but typically analyze around 700,000 loci for a suite of genetic variants associated with range of medical conditions and medication responses. Many of the genetic tests currently available online for susceptibility to psychiatric disorders and medication response can be ordered without the involvement of a physician. Companies usually state in their marketing literature that such tests are intended for educational and not medical purposes. Currently, not all of the companies marketing genetic tests related to psychiatric disorders include genetic counseling as part of the purchase price.[35] The recent UK Human Genetic Commission's (UK HGC) Common Framework of Principles for DTC genetic testing services includes an initiative for the establishment of a code of conduct for commercial genetic testing companies that may increase the number of companies offering genetic counseling as part of their services.[36]

One of the earliest DTC genetic tests for MDD was a "depression risk genetic test" marketed online by a US-based biotech company, Neuromark (http://www.neuromark.com), in 2006. The test was based on the published association between a functional polymorphism in the promoter region (*5-HTTLPR*) of the serotonin transporter gene (*SCL6A4*) and the risk of MDD in response to stressful life events.[19] Another biotech company, Psynomics, based in San Diego, California (psynomics.com), began marketing two DTC "bipolar tests," the following year. These purported to identify both increased risk for bipolar disorder, and identify individual patient response to psychotropic medication for bipolar disorder. These tests were based on several studies of SNPs in the *GRK3* (G-protein receptor kinase 3) gene. At that time two other companies also planned to

TABLE 2. Psychiatric risk tests and pharmacogenetic tests offered by DTC companies as at January 2011

DTC company	Psychiatric disorder	Allele, region, or SNP tested	Pharmacogenetic tests	Allele, region, or SNP tested
23andMe[c]	Bipolar disorder	rs4948418/10q21	Antidepressant response (medication not specified)	Not specified
	Schizophrenia	Not specified		
Map My Gene[d]	Depression	Not specified		
	Schizophrenia	Not specified		
Gene Planet[d]	Bipolar disorder	Not specified	Antidepressant response (medication not specified)	ABCB1 rs2032583
	Depression	Not specified		
Lumigenix[d]	Bipolar disorder	Not specified	Not specified	Not specified
	Schizophrenia	Not specified	Not specified	Not specified
Genelex[a,d]			SSRIs: fluoxetine, sertraline, paroxetine, citalopram	CYP2D6, 5HTT
			SNRIs: venlafaxine	Not specified
			Tricyclics: amitriptyline	CYP1A2, CYP2C9
			Antipsychotics: haloperidol, olanzapine	CYP1A2, CYP2D6
			Benzodiazepines: diazepam	CYP1A2, CYP2C19
Navigenics[a,b]			Carbamazepine hypersensitivity	HLA-B*1502
Pathway Genomics[a,b]			Carbamazepine hypersensitivity	Not specified
Genomas[a]			Response to 80 widely used psychotropic drugs including aripiprazole, atomoxetine, citalopram, duloxetine, escitalopram, fluoxetine, and sertraline	34 variants in genes CYP2D6, CYP2C9 and CYP2C19 (20, 6, and 8 alleles, respectively
AssureRx[a]			Most common antidepressants and antipsychotics	Polymorphic genes of the CYP450 family

DTC, direct to the consumer; SNP, single-nucleotide polymorphism, SSRIs, Selected Serotonin Reuptake Inhibitors, SNRIs, Selected Norepinephrine Reuptake Inhibitors.

Source: www.23andme.com, www.mapmygene.com, www.geneplanet.com, www.lumigenix.com, www.healthanddna.com, www.navigenics.com, www.pathway.com, www.genomas.com, www.assureRx.com (accessed November 29, 2011); Society and Genetics and Public Policy Center, Johns Hopkins University (updated August 2011).[46]

[a]DTC genetic tests ordered through a physician.

[b]Genetic counseling provided by a board-certified genetic counselor and included in cost.

[c]Genetic counseling provided at an additional cost.

[d]Genetic counseling availability not stated.

launch genetic tests for the risk of psychosis and prediction of response to antipsychotics. These products drew controversy because evidence for the associations was weak.[37] By 2010 all of these products had either been withdrawn from, or never reached, the market.

The first study to critically evaluate the scientific evidence for commercially marketed tests for a range of health conditions, including depression and schizophrenia, was published in 2008.[38] The authors found that less than half of the 56 genes examined had statistically significant associations with disease risk, and 24 of those had not been subject to meta-analysis. Of the associations that were statistically significant, the odds ratios were modest. That study concluded that there was insufficient scientific support for commercial genomic profiling being useful in measuring genetic risk for common complex disorders.

That study highlighted that one of the major problems of DTC genetic testing is that marketing claims frequently do not match the scientific evidence. Some companies tend to overstate the predictive power of such tests and fail to communicate the potential limitations of genetic information.[38] Communicating the results of "whole-genome scans" is especially challenging because the product includes multiple test results for many different medical conditions.

COMMUNITY INTEREST IN GENETIC TESTING FOR PSYCHIATRIC DISORDERS

Previous studies have reported a high level of interest (in the range of 83–97%) in genetic testing for susceptibility to bipolar disorder,[39–41] schizophrenia,[42,43] or psychiatric disorders in general.[44–46]

Wilde et al. reported data from the first large national survey on public attitudes toward genetic testing for a depression marker.[47] Using the well-publicized, although scientifically debated example of the serotonin transporter *5-HTTLPR* marker as a hypothetical genetic test for MDD risk,[16,28–30] the study found that interest in such a genetic test was significantly higher if the test was available from a doctor (63%), while significantly fewer participants (49%) were willing to have such a test directly from an online genetic testing company.[47] The most frequently endorsed perceived benefits of genetic testing were that it would encourage patients to seek

psychological help early and minimize stress factors. The main concerns about genetic testing were worries about potential discrimination from insurers or employers and loss of privacy of personal genetic data.

IMPACT OF DISCLOSURE OF A PSYCHIATRIC GENOTYPE

There is a dearth of research on the impact of DTC genetic test result disclosure for risk of common complex disorders, irrespective of whether these are psychiatric or otherwise.

Only one study[48] has investigated impact of actual genotype disclosure for a reported psychiatric marker. Using a sample in which a G × E interaction involving *5-HTTLPR* had been previously demonstrated, Wilhelm et al.[48] found no marked distress associated with the receipt of test results in any of the genotype groups [*s/s* ("high risk"), *l/l* (low risk), and *s/l* (average risk)], although the higher risk *s/s* group showed higher test-related distress than the other two groups. The study[48] also found that participants were positive about receiving such genetic test results for depression risk, irrespective of genotype.

The largest study to investigate consumer response to genotype disclosure in general was a collaboration between the high-profile biotechnology company Navigenics and its business partners, Scripps Translational Science Institute and affiliates, which recruited 2,037 Scripps employees into a study of DTC testing.[5]

This Scripps study evaluated emotional and behavioral response to receiving genetic test results that claimed to predict response to 12 medications and risk status for 28 common complex medical disorders, which included Type 2 diabetes, Alzheimer disease, myocardial infarction, obesity, rheumatoid arthritis, multiple sclerosis, and some forms of cancers. These genetic tests are included in Navigenics "Health Compass" package, which study participants purchased for US$ 300 (full price US$ 2,500). Navigenics does not include genetic tests related to psychiatric disorders among its products; however, the study may inform research into disclosure of psychiatric markers to consumers.

The researchers found no adverse psychosocial effects of risk disclosure and no measurable changes in diet or exercise behavior or elective use of screening tests. The Scripps study was criticized for using only generic measures of anxiety and not measuring anxiety directly related to genetic test result disclosure.[49] Insufficient data exist to determine whether test-related distress is a significant concern.

INTERPRETATION OF DTC GENETIC RISK INFORMATION

A US Government Accountability Office (GAO) investigation in 2006 found selected DTC companies made medically unproven disease predictions for nutrigenomic (the effects of foods and food constituents on gene expression) genetic tests.[50] The latest GAO investigative report in 2010, which evaluated the results of genetic tests offered by four DTC companies for a range of gene–disease associations, also cited a lack of standardization of results among DTC genetic testing companies testing identical DNA samples, as well as deceptive marketing practices and erroneous medical advice.[51] To the author's knowledge, there have been no authoritative investigations into the consistency of interpretation of DTC genetic tests for psychiatric variants.

The principal concern is the risk of consumers making life-changing health decisions based on spurious, unreplicated, or limited risk information. DTC genetic testing services could undermine public confidence in future substantive evidence-based clinical psychiatric genetic services by prematurely marketing genetic tests that have uncertain clinical validity and utility. Initiatives for the establishment of a code of conduct for DTC genetic testing, such as the UK HGC's Common Framework of Principles,[36] are likely to influence the development of this field.

FAMILY HISTORY AS A PROXY FOR GENETIC RISK ESTIMATES

In the absence of genetic testing, predictive validity of family history has been assessed for utility in predictive and preventive interventions for asymptomatic or symptomatic individuals (probands) who have multiple family members with common chronic disorders, such as diabetes, cardiovascular disease, and cancer syndromes.[52] Increasing evidence that family history is as a major risk factor for most psychiatric disorders[53–55] has led to the promotion of family history as a potential predictive tool in the prevention of mood disorders.[56]

GENETIC RISK INFORMATION AND BEHAVIORAL CHANGE

Few studies have examined anticipated health behaviors as a consequence of genetic testing for common complex disorders, including psychiatric disorders. How individuals respond to genetic risk is especially complex when the penetrance and predictive power of the particular genotype are low or uncertain. Furthermore, since the results of such genetic tests involve probabilities rather than absolute risk values, effective communication of uncertain risk to lay audiences is challenging. Large variation in the way people understand risk information complicates how genetic test result recipients might respond to such information.[57]

Although "low-risk" results might provide relief or reassurance, as shown in a randomized control trial of disclosure of a marker for Alzheimer disease,[58] there is also the possibility that "high-risk" genetic test results may not be sufficient to change health-related behavior.[59–61]

Since G × E factors underlie the etiology of depression,[19,62] environmental factors need to be considered in any risk prediction intervention.

Most studies have focused on behavioral change following predictive genetic testing for Mendelian disorders such as hereditary breast, ovarian, and/or colorectal cancer.[63,64]

The ability to extrapolate from such studies to predict health behavior outcomes from genetic susceptibility testing for psychiatric (or other common complex disorders) is limited, as gene mutations for familial cancers are highly penetrant and specific well-known guidelines for screening, surveillance, and surgery have been developed. Also, data on actual uptake of testing suggest that uptake has been much lower than suggested by attitudinal surveys, particularly for disorders with no or limited preventive potential. A case in point is predictive genetic testing for Huntington disease, a serious adult onset genetic disorder with no curative treatment. A review showed that among people at risk of Huntington disease, 40–79% expressed intention to have the test, whereas only about 10–20% of people requested testing.[65]

In the large national survey on public attitudes toward genetic testing for a depression marker by Wilde et al.,[66] researchers also assessed community preparedness to ameliorate risk for depression through cognitive and behavioral interventions following genetic testing. Endorsement of a G × E model for MDD-predicted intent to engage in protective health behaviors.[66] The most frequently rated health behaviors that participants indicated an intent to engage in in response to a hypothetical increased genetic risk for MDD risk were helping one's own children learn how to be more resilient to stress (92.2%), modifying potential life stressors (82.6%), and starting therapies or courses to learn better coping strategies (79.7%). Endorsement of "family environment" and "abuse" as causal attributions to MDD were significantly and positively associated with the intention to take up such behaviors.[66] These findings suggest that such individuals may view risk for MDD as modifiable and could be effectively targeted for preventive interventions.[66] The study[66] did not suggest that provision of genetic risk information directly promotes protective health behaviors, rather it showed that individuals may be receptive to undertaking protective health behaviors as part of a genetic risk assessment for MDD. The findings should be interpreted with caution given the contention that intended behavior may not translate into actual uptake of behaviors.

Further, the perception of having a higher than the average population risk for MDD was significantly and positively associated with willingness to start therapies and modify stress, but having a personal history of mental illness was not a predictor of willingness to engage in protective health behaviors.[66] These latter findings support the value of targeting preventive interventions at groups with a perceived elevated risk of future depressive episodes, who are more likely to be interested in preventive behavioral strategies.[66]

Few quality randomized control trials (RCTs) are available to assess the broader impact of molecular disease risk estimates—clinical or hypothetical—on behavioral change. Indicative of this was a recent Cochrane review of 17 "poor quality" studies that found little evidence that communicating DNA-based disease risk estimates had an effect on smoking and physical activity although there was a possible small effect on self-reported diet and on intentions to change behavior.[67]

In general, these studies show that the perceived cause of a health problem may influence what intervention is preferred and selected. That is, individuals may seek biological-based interventions when a health risk is perceived as genetic in origin and "less preventable," or behavioral-based interventions when risk is perceived as environmental in origin and "more controllable."[68,69] By contrast, the study of Wilde et al.[66] suggested that genetic risk information about MDD is unlikely to discourage individuals from considering reducing risk through behavioral change, nor inducing a sense of genetic fatalism as shown by previous authors.[68,69] Rather, the findings show that motivation to modify risk of a hypothetical genetic predisposition appears to be driven by perceptions that environmental factors contribute to overall risk of MDD and that these could be controlled by adopting preventive behaviors. The findings may differ from previous studies[68,69] because endorsement of both genetic and environmental causes of disease or endorsement of G × E interactions as a causal mechanism has not been previously evaluated in such research.

Little support was found for the contention that a hypothetical increased genetic risk for MDD would lead to the decision to not have children in the event of receiving an unfavorable genetic test result.[66] The minority of participants (10.5%) who said that an increased risk of MDD would deter them from having children were older and had no postschool education. Previous studies have reported reluctance to have children in the event of having an increased genetic risk of MDD,[44] bipolar disorder,[41,70] or schizophrenia[42,44] among individuals unselected for family history[42,44] and individuals with a strong family history of bipolar disorder.[42,70] Furthermore, overestimation of risk among unaffected relatives of individuals with psychosis favored plans to have no or fewer children.[42] Given the low predictive power of psychiatric gene markers, the provision of genetic tests to assist reproductive decision making may be unethical. Since genetic risk information has the potential to influence reproductive decisions, further research is required to assess the influence of actual genetic risk status on reproductive decisions among individuals with a family history of MDD.

These findings require investigation in a prospective study to evaluate how the impact of actual risk estimates may differ from the hypothetical scenario posited in this survey.[66] RCTs of risk-reduction behaviors among

targeted healthy adults following provision of risk estimates for a psychiatric disorder are required to inform the planning and monitoring of health promotion and risk-reduction strategies associated with genetic testing.

GENETIC RISK INFORMATION IN PSYCHIATRIC PRACTICE AND PRIMARY PREVENTION

Given the uncertainty of individual genetic risk estimates for psychiatric disorders and medication response, the marketing of current DTC genetic tests would appear premature. The UK HGC's Common Framework of Principles for DTC genetic testing services 2010,[36] found little rationale for the commercial provision of DTC genetic tests based on lack of broad validation of such tests and limited therapeutic benefit.

The UK HGC does not believe an outright ban of DTC genetic testing is enforceable or warranted since some clinically validated genetic tests marketed DTC within commercial test "packages," such as those offered by Navigenics and 23andMe, are already available through mainstream health care services.

Instead, the Principles advocate that DTC test providers should be urged to provide clear information to consumers about the limitations of genetic tests for disease predispositions that have not been broadly replicated or for which there are only limited preventive or therapeutic intervention. This should accompany the provision of pre- and posttest genetic counseling or referral to appropriate accredited genetic counseling services.

Pre- and posttest genetic counseling will not however adequately address the impact of pharmacogenetic tests obtained DTC, which could result in consumers self-medicating or changing their prescribed medication regimen without consultation with their prescribing physician. The Principles highlight this concern by urging providers of such tests to provide follow up care to consumers obtaining pharmacogenetic tests.

The UK HGC Principles call for guidelines for evaluating genetic susceptibility tests on an individual basis based on validation and limitations of such tests before they are made commercially available. To develop a validated genetic test for MDD, a risk algorithm should be powered by replicated data from very large pooled GWAS and meta-analyses that identify rare alleles with large effect sizes, as well as G × G effects. Such a genetic test should achieve high sensitivity and specificity for optimal prediction of risk and/or treatment response. Given the validated contribution of nongenetic factors to risk to the disorder, it is clear that a clinically valid risk assessment for MDD in primary prevention initiatives should also incorporate evidence-based measures for family history, environmental (including family environment), personality, and lifestyle risk factors. Such preventive initiatives should be able to identify individuals most at risk and prescribe recommended changes to modifiable environmental risk factors as a step toward reducing depression morbidity.

Risk management strategies may be either evidence-based (e.g., cognitive behavioral therapy, regular exercise) or represent potential risk-reducing strategies that correspond to universally recognized standards for healthy living (e.g., avoiding illicit drugs and excessive consumption of alcohol, or getting adequate sleep).

Those charged with designing molecular-based preventive mental health interventions for psychiatric disorders should consider potential communication issues between clinician and patient since individual interpretation of the predictive power of genetic variants associated with depression may be variable. This may especially be the case for patient and public understanding of risk probabilities.[71]

Furthermore, given the relatively low frequency of recurrence of psychiatric disorders among close family members compared to Mendelian pedigrees, recurrence risks should be kept in perspective when informing individuals with affected relatives of their probability of developing MDD and when designing preventive mental health interventions.

Anticipated obstacles to the efficacy of such interventions include the possibility that fatalistic interpretation of a predisposition to MDD may lead to unhealthy behaviors or preventive inaction. It is important that empirical studies using educational interventions are developed to replace current assumptions, speculation, and conjecture about anticipated behavioral response to genetic risks. The first component of such an agenda relates to the need to develop and rigorously evaluate innovative training interventions for health professions working in clinical genetics and psychiatry with evidence-rated information on managing patients with a familial risk for psychiatric disorders and the provision of advice on evidence-based and recommended preventive strategies.

CONCLUSIONS

Benefits from genetic susceptibility tests, should they become available, can only be realized if MDD or some of its consequences can be prevented or ameliorated, for example, by allowing those at higher risk to make better and more informed life choices that result in improved clinical outcomes.

Health professionals will need to be knowledgeable about the genetic contribution to psychiatric disorders, recurrence risk estimation, decision making about options for dealing with recurrence risks, and how genetic risk information might be used to help patients make reproductive decisions or engage in preventive health behaviors.[72]

It will be necessary to determine the clinical utility of identifying people at increased risk for MDD on the basis of family history and/or genetic risk variants; the effectiveness of educational interventions about genetic and environmental risk for mood disorders, targeting

high-risk groups; the effectiveness of training programs about psychiatric genetics targeting psychiatrists, geneticists, and genetic counselors; identify and target the population groups that are most likely to gain optimum benefit from genetic-based preventive interventions in psychiatry; how target groups should be approached; how molecular-based preventive interventions in psychiatry should be disseminated; how this could be done most effectively and efficiently and finally, the optimal timing of such strategies. Since most adults with recurrent MDD experience their initial depressive episodes as teenagers, adolescence is an optimum life stage to introduce a preventive intervention for people at high risk for affective disorders based on genetic risk, family history, and other known risk factors.

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