MEMORANDUM

FROM: Samantha Lane, Biomedical Humanities major, Campbell University
TO: Dr. Michaux R. Kilpatrick, North Carolina Medical Board President-Elect
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SUBJECT: FEASIBILITY OF USING PHARMACOGENOMICS AS STANDARD PRACTICE IN PSYCHIATRIC HEALTHCARE

Introduction

Mental illness has increased significantly over the past few decades, leading to the development of medication for its treatment. “In addition to counseling and other forms of behavioral treatment, treatment commonly involves one or more psychotropic medications that are aimed at alleviating symptoms of the disorder” (BCBS) According to the American Medical Association’s 2022 report on psychopharmacology, the current practice of prescribing psychiatric medication involves assessing the patient, creating a diagnosis, and prescribing a commonly used medication that treats the diagnosis. Prescribers are taught to “share what will be tried first, the likelihood of it working, and what the next steps may be if the first treatment is not working. It can be helpful to share that not all psychotropic medications work to the same degree for everyone, and therefore, the plan may require some adjustments” (AMA). This method raises concerns because some psychiatric medications can increase mental illness symptoms if they do not correspond with the neurotransmitter receptors that are unique to each patient. “In addition, non-responders are disproportionately burdened by adverse effects compared to patients who achieve remission, with almost 90% of those experiencing serious adverse effects unable to achieve remission” (NIH). Pharmacogenomics, the field that studies how a person’s genes will cause them to respond to medications, has been optimized throughout the past decade. Simple genetic tests can now predict patient responses for medications in several fields, including

psychiatry. This can be done by testing a number of genes, but CYP2C19 and CYP2D6 genes, a part of the cytochrome P450 system, are most significant in predicting negative side effects, sensitivities, and ineffective medications. These genes are responsible for coding enzymes that metabolize the medication (Frontiers, AFP). In order to test these genes, a probe binds to the sequence of nucleotides that make up the relevant gene and amplifies the gene to be analyzed. Depending on which probe binds, the genetic variant can be determined. Studies over several decades have compared patients that have had success with the same medications and have been able to identify matching DNA sequences between these individuals, which correlates to receptor and neurotransmitter structure. Each medication is optimized for a particular receptor structure, so having this genetic basis allows for elimination of medications that are unlikely to help. Given this clear benefit, genetic testing for psychiatric medication should be implemented into the standard practice of prescription.

Overview of Alternatives

The current trial-and-error method is outdated, unethical, and ineffective. One article notes that "it has been reported that only 30% of patients use psychopharmacological treatment with perceived clinical success" (SBU rapport Swedish Research Council, 2004; Walker et al., 2004). This is a shockingly low percentage of patients and is likely a result of patients using medications that do not match their chemical receptors, which are primarily acted on by psychiatric medications. Classifications of psychiatric medications include antidepressants, anti-anxiety medications, stimulants, antipsychotics, and mood stabilizers. Within each classification, there are various medications that target different receptors, neurotransmitters, or chemical compositions in the brain. The structural components of each of these can vary between individuals, as a result of their genetic composition. Now that genetic testing and genome

mapping technology has developed to be able to identify best medications for each patient, there is no reason that the standard practice should continue to be trial-and-error. Patients subjected to the trial-and-error method are at a greater risk for suicide, increased psychiatric symptoms, dizziness, dry mouth, headache, nausea, weight gain, decreased sexual desire, and other side effects (Frontiers). "A systematic review showed that non-responders to one or more treatments have a 15% likelihood of suicide ideation compared to 6% of patients with treatment-responsive depression and 1% in the general population" (Mrazek et al., 2014). Pharmacogenomics minimizes the trial-and-error process by eliminating ineffective or damaging medications and suggesting compatible ones for each patient's genome.

There are multiple pathways for implementing pharmacogenetics. First, the healthcare system could focus on increasing accessibility without changing any policies. Ideally, genetic testing would be available through primary care facilities and psychiatric care facilities, and would be covered by insurance, at least in part. The healthcare system would benefit from making genetic testing more accessible and affordable, even if getting insurance coverage is not feasible. Pharmacogenomics is not as cost-effective as trial-and-error, but the benefit of its implementation is centered around patient care, rather than finances. Another alternative is to change healthcare policy, which would require insurance companies to change their coverage. Several major insurance companies consider pharmacogenomics for mental health to be "investigative" or "experimental". If patients were required to have genetic testing, insurance companies would be required to provide coverage. However, requiring patients to complete another task before receiving care makes getting prescriptions more difficult, instead of more accessible. Upon the first office visit, patients should be able to receive treatment as quickly as possible, especially given the nature of psychiatric disorders. One proposed solution to this

concern is to offer an initial medication, tailored to the patient assessment, diagnosis, and family history. If this medication is unsuccessful, pharmacogenomics may become a requirement, but the patient is given an opportunity to receive treatment before having to jump through additional hoops.

Criteria

Any evaluation of medical practices must consider several factors, including cost, insurance coverage, urban and rural accessibility, and ethics. These criteria outline the considerations that the medical board must make before implementing a new standard care practice into psychiatric healthcare. Insurance companies are typically hesitant to accommodate more expensive treatment options, which means that there must be additional motivation to cover pharmacogenomics. The cheapest option is not necessarily the most ethical, and that is precisely the case here. Therefore, adding pharmacogenomics to psychiatric healthcare policy is necessary for feasibly implementing it in patient care. "Medication management guided by pharmacogenetics has been shown to increase therapeutic efficacy and improve symptoms in patients diagnosed with depression, but limited data are available on the cost savings of pharmacogenetic-guided interventions outside of psychiatric clinical specialties" (NIH).

There are three major companies that conduct genetic testing for psychiatric medications: GeneSight ®, Genomind ©, and ClarityX ©. GeneSight uses a pay scale to determine self-pay cost, which is based on household income. With Medicare or Medicaid, GeneSight testing is fully covered. Major corporate or commercial insurance companies that cover this testing will typically have a co-pay of $330 or less, but coverage can vary on a case-by-case basis. Some private insurance companies have not begun covering pharmacogenomics for mental health, such as Blue Cross Blue Shield (BCBS). GeneSight requires ordering and review by an affiliated

healthcare provider, which limits patient access. Patients can have the test shipped to their home, but they must contact a GeneSight provider to order their test, and again to receive the results (GeneSight). The American Family Physician, however, mentions that GeneSight may go beyond what is necessary, since it looks at twelve enzymes instead of two significant ones (AFP). Genomind, another privately-owned genetic testing corporation, costs a flat rate of $2,000 for uninsured or self-paying patients, but is covered fully by Medicare, and is covered up to $1,601 by some private insurance companies. Though it can be more expensive, Genomind can be accessed by any healthcare professional, and is not exclusive to Genomind-affiliated providers. This gives it additional accessibility for patients because they do not have to seek out a new provider (Genomind). Another major testing company, ClarityX, does not take any form of insurance, but is a flat rate of either $400 or $500 depending on the number of genes tested by the selected panel. This company sends the test and results directly to the patient, without going through a provider. The patient can then share their results with their provider, so they can review them together as they make a care plan.

The other alternative is to continue the trial-and-error method. To gather a broad understanding, the most prescribed generic psychiatric medications were assessed for cost-effectiveness. For thirty tablets, Sertraline (Zoloft) 50mg costs up to $55 without insurance, and $0 to $1 with insurance. Alprazolam (Xanax) 1mg costs up to $12 without insurance, and $0 to $5 with insurance. Escitalopram (Lexapro) 10mg costs up to $38 without insurance, and $0 to $1 with insurance. Bupropion (Wellbutrin) 150mg costs up to $12 without insurance, and $0 to $2 with insurance. Amphetamine-Dextroamphetamine (Adderall) 30mg costs up to $253 without insurance, and up to $27 with insurance. Patient access is mostly related to proximity to pharmacies, so rural areas may have less access.

Method	Self-pay cost	Cost with insurance coverage	Accessibility	Ethical considerations
Genetic testing prior to prescription	**GeneSight ®:** Self-pay cost varies by household income. **Genomind ©:** Self-pay is $2,000. **ClarityX ©:** $400-$500 based on selected test.	**GeneSight ®:** Full cost covered by Medicare and Medicaid; typically less than $330 out-of-pocket with some commercial insurance. **Genomind ©:** Approx. $1,601 covered by some commercial insurance companies, full cost is covered by Medicare. **ClarityX ©:** n/a	**GeneSight ®:** 50 GeneSight affiliated providers found within 100mi of Raleigh; test can be shipped to patient's house or done in-office. Results are reviewed by affiliated clinician. **Genomind ©:** Works with unaffiliated clinicians or can match patients with Genomind clinicians; tests are shipped to patient and results are sent to clinician for review. **ClarityX ©:** Shipped directly to patient; results are sent through patient portal and can be shared with clinician.	Genetic testing through any company gives providers a genetic basis for prescribing psychiatric medication, reducing the "guessing game". This subsequently reduces patient side effects, medication resistance, and untreated psychiatric illnesses.
Trial-and-error prescription, using most prescribed psychiatric prescriptions in 2018 (GoodRx)	**Sertraline** (Zoloft) 50mg: $55 for 30 tablets **Alprazolam** (Xanax) 1mg: $12 for 30 tablets **Escitalopram** (Lexapro) 10mg: up to $38 for 30 tablets **Bupropion** (Wellbutrin) 150mg: $12 for 30 tablets **Amphetamine-Dextroamphetamine** (Adderall) 30mg: $253 for 30 tablets	**Sertraline** (Zoloft) 50mg: $0-$1 for 30 tablets **Alprazolam** (Xanax) 1mg: $0-$5 for 30 tablets **Escitalopram** (Lexapro) 10mg: $0-$1 for 30 tablets **Bupropion** (Wellbutrin) 150mg: $0-$2 for 30 tablets **Amphetamine-Dextroamphetamine** (Adderall) 30mg: $1-$27 for 30 tablets	All are available at most major pharmacies and are prescribed by psychiatric healthcare providers. Proximity to the nearest healthcare facility and/or pharmacy would determine accessibility, so more rural areas may have decreased access.	The first prescription may work well for some patients, but many will require adjustments and multiple changes before finding the optimized medication and dose. This can increase psychiatric symptoms and give unwanted side effects.

Figure 1, above, outlines the criteria of healthcare methods that must be considered.

Methods

Research for this feasibility report began with a literature review, which highlighted the preexisting research that already discussed psychopharmacology, pharmacogenomics, genetic testing insurance coverage, psychiatric medication outcomes, and patient and provider interest in pharmacogenomics. The American Medical Association's "How-to Guide for Psychopharmacology" gives providers an overview of the expectations and best practices for assessing, diagnosing, and treating mental illness (AMA). Though this information guide was published in 2022, it fully endorses the trial-and-error method, with no reference to pharmacogenomics. However, the AMA does refer to the Behavioral Health Integration Services (BHI), which is an initiative to integrate behavioral and mental healthcare into primary care (BHI). This implies the AMA's desire to integrate mental health with primary care, which has become an increasingly prevalent issue in the past decade. The desire for more holistic care, as reflected in this guidebook, is inconsistent with the commitment to outdated prescription methods. Frontiers in Pharmacology discusses this exact concern in their editorial, "From Trial and Error to Individualized Pharmacogenomics-Based Pharmacotherapy in Psychiatry." Authors R. van Westrhenen and M. Ingelman-Sundberg emphasize specific genetic variations in genes CYP2C19 and CYP2D6 that are known to cause increased side effects when taking psychiatric medications, or when switching between medications. "Indeed, a higher frequency of subjects with an ultrarapid (UM) CYP2D6 phenotype has been observed in patients committing suicide indicating non-optimal dosing of antidepressants in these patients" (Frontiers).

I gathered data directly from genetic testing companies, insurance companies, and pharmacies for original research. First, I spoke to customer service representatives on the phone at GeneSight ®, Genomind ©, and ClarityX © about self-pay costs, commercial insurance

coverage, and federal insurance coverage. Each conversation provided additional information about pricing and insurance coverage, and the results are listed in Figure 1. Much of this information can be found on the websites associated with each company. Next, I read corporate medical policies from several major insurance companies, such as Blue Cross Blue Shield, United Healthcare, and Aetna, regarding pharmacogenomics for psychiatric medication. Each company periodically publishes these reports as technology improves. I also reviewed the prices of psychiatric medication from pharmaceutical companies and pharmacies listed online by GoodRx and WebMDRx. These websites give both the generic and brand-name costs, but I included only the generic costs in my data, in order to represent the alternatives most clearly and accurately. Cost-effectiveness of pharmacogenomics was also considered in the original research. As seen in Figure 1, adding genetic testing to a patient's care plan is significantly more expensive than prescribing medication alone. Blue Cross Blue Shield of North Carolina considers pharmacogenomics to be "investigational in all situations," and is therefore not covered in any plans (BCBS). Similarly, Aetna "considers genotyping for other cytochrome P450 polymorphisms (diagnostic tests to identify specific genetic variations that may be linked to reduced/enhanced effect or severe side effects of drugs metabolized by the cytochrome P450 system including opioid analgesics, warfarin, tamoxifen, proton pump inhibitors, antipsychotic medications, and selective serotonin reuptake inhibitors) experimental and investigational" (Aetna). However, United Healthcare considers that "genetic information for CYP2C19 and CYP2D6 would likely be most beneficial for individuals who have experienced an inadequate response or adverse reaction to a previous antidepressant or antipsychotic trial" (United).

Another significant consideration is the ethics of patient care. This brings about a more subjective concern but is still relevant to the discussion. Given that we have the ability to test for

predispositions, is psychiatric healthcare obligated to provide access to this? Many insurance companies that do not cover testing for mental health are willing to cover testing for cancer markers or other genetic diseases. This is partially due to the cost difference in cancer treatment versus mental healthcare, but it is also related to the difference in mortality rates. Preventative screenings for cancer and other life-threatening genetic disorders can protect individuals from years of treatment, or even an untimely death. For example, the BRCA-2 gene is associated with breast and ovarian cancer. Women with a mutation in the BRCA-2 gene have approximately an 80% chance of developing breast or ovarian cancer during their lifetime. Because of this startling statistic, many women choose to have mastectomies or hysterectomies before they develop cancer. However, psychiatric pharmacogenomics does not work this way. This testing involves identifying enzymes that metabolize various medications, assessing their structure based on genetic predispositions, and comparing them with optimal receptors for each type of psychiatric medication. There is no true preventative method for mental illness, nor is there a one-size-fits-all option for psychiatric medicine. Every person's CYP2C19 and CYP2D6 genes produce the associated metabolic enzymes in a similar, but unique, way.

> "The translation of the genetic variations in these genes to firm recommendations to be used in the clinics represents is an important but also difficult task based on i) the need for concordance in opinions between different organizations and regulatory units regarding the importance of different pharmacogenomic biomarkers and ii) the problem of application of such advice in clinical practice due to the complexity of a real-life patient setting and unwillingness of the physicians to comply with such advice" (Roberts, 2018).

Evaluation

United Healthcare's coverage policy suggests a notable alternative, where patients try psychiatric medication after their initial diagnosis, prior to any genetic testing. If the patient responds well, the cost of pharmacogenomics was avoided, and the patient outcome is still positive. If the patient responds poorly, the care plan can shift to include genetic testing before continuing to try additional medications. This saves time and money for both patients and insurance companies and allows patients to receive immediate treatment upon their initial visit. The downfall to this suggestion is that psychiatric medications can be dangerous for individuals with certain genetic variations, and prescribing these with no genetic basis can lead to preventable suicides and negative side effects. This is especially likely when trying the first medication because that is when symptoms and side effects are likely to first appear. However, this is also a downfall of the trial-and-error method, but this alternative resolves several of the safety concerns of the current method. The other proposed amendment to the current practice is to require or recommend pharmacogenomics to any patient seeking psychiatric medications. This eliminates most of the risk of severe negative side effects and increased mental illness. However, it makes psychiatric medication more difficult to access, because genetic testing adds another obstacle to getting a prescription. Further research should be done about the number of patients that will suffer from negative side effects and increased illness versus patients that will not be treated if medication becomes less accessible due to pharmacogenomics.

Limitations

Because of the scope of this project, there were time constraints on gathering and analyzing data. Further research should be conducted on additional genetic testing companies and commercial insurance companies. Studies on patient and provider interest in accommodating

pharmacogenomics may also improve the understanding of the relevance of this issue. If very few providers and/or patients are interested in genetic testing, then this issue may be a lower priority. However, because of its clear clinical benefit, I would expect a large percentage of patients and providers to consider genetic testing. Further study may also be needed on the genes that should be evaluated in testing. The CYP2C19 and CYP2D6 genes are certainly significant determinants of patient outcomes, but there may be additional genetic factors that should be considered. Finally, a deeper knowledge of healthcare policy processes may benefit the research focuses throughout this project.

Conclusions

As previously stated, the current practice of psychiatric prescription is no longer most beneficial within patient care. Its cost-effectiveness is its most positive attribute, but it falls short when considering the ethics. At some point, patient care must prevail over cost, though finances are still an important consideration.

> "In general, a more cost-effective approach might be to have for each patient a DNA passport for medication, covering most polymorphic genes involved in commonly prescribes drugs, and for which dosing recommendations are available. This would increase the benefit of pharmacogenetic tests, also beyond psychiatry, and would avoid that each separate clinical field would have to worry about cost effectiveness" (NIH).

Because of the increased cost associated with pharmacogenomics, it may be most beneficial to perform genetic testing after a patient has responded negatively to one type of psychiatric medication, instead of testing before any prescriptions have been administered. Insurance companies may also benefit from the flexibility of this plan, which eliminates unnecessary genetic testing for individuals who respond well to their first medication. However, it is unlikely

that insurance companies will begin to cover testing that is not a part of the policy for its related issue. Therefore, either many of the genetic testing sites will need to reduce their out-of-pocket cost for self-pay, or public healthcare policy will need to change so that insurance companies are required to cover psychiatric pharmacogenomics. This should be viewed as a priority in mental healthcare, due to the ethics of trial-and-error versus those of pharmacogenomics.

Recommendations

In response to the data gathered from genetic testing resources and insurance companies, I recommend an adjustment to the current healthcare policy within the North Carolina Board of Medicine in favor of adding pharmacogenomics to the psychiatric treatment guide for providers in the upcoming term. I believe the most mutual benefit between patients, providers, and insurance companies is the proposal of giving patients an immediate first prescription, prior to any genetic testing, and then proceeding with pharmacogenomics if more trial-and-error is needed. This gives patients immediate access to care and allows providers to continue some parts of their normal procedure for prescription. This also prevents insurance companies from having to pay for unnecessary testing when patients may benefit from the first medication they take. “Despite the challenges described, there is an increase in uptake for clinical care, making harmonization and clinical guidelines important to bring this field further in facilitating effective and safe treatment of patients” (NIH).

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