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**THE MOVEMENT TOWARDS PERSONALIZED MEDICINE:
PHARMACOGENOMICS FOR DIAGNOSIS AND TREATMENT IN MOOD
DISORDERS**

**A thesis submitted to
Regis College
Honors Program
in partial fulfillment of the requirements
for Graduation with Honors**

by

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May 2019

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1. Pathologically Unique: Pushing Towards Personalized and Holistic Treatment of Bipolar Disorder

Bipolar disorder is a debilitating and chronic mood disorder characterized by the recurrence of depressive and manic or hypomanic episodes. These ‘mood swings’, as they tend to be defined in popular media, are not just periods of erratic behavior and impulsiveness. For the person living with bipolar disorders, these constant fluctuations in mood affect their ability to function in an everyday setting. Work performance, relationships with friends and family, financial stability - all of these factors can be negatively impacted by bipolar disorder. Bipolar disorder requires a huge utilization of resources and frequent hospitalizations, which are particularly necessary in managing manic episodes (Squassina, Manchia, and Del Zompo, 2010). Financially, bipolar disorder has an annual cost of approximately \$45 billion per year in the United States; \$7 billion of that direct cost comes from expenditures for inpatient and outpatient care (Squassina et al., 2010). With a prevalence rate of 0.8-1.2%, and increased risk of early death, disability, and suicide, bipolar disorder produces substantial socioeconomic and psychosocial burden worldwide (Pisanu, Heilbronner, and Squassina, 2018).

Currently, there is no cure for bipolar disorder, only treatment to ameliorate the symptoms. However, even the treatments currently used are not conclusively effective, and they each present with their own array of side effects. For a fair amount of people living with bipolar disorder, treatments are not effective at all. This begs the question: if these drug interventions are ineffective and dangerous, why are they still in use? Nonetheless, bipolar disorder is considered a fairly manageable disorder. Assuming patients receive an accurate diagnosis, the vast majority of people can achieve substantial stabilization of their mood and related symptoms with the proper treatment (Oedegaard et al., 2016). This ideal, however, relies on the patient receiving an accurate diagnosis. The

unfortunate truth is, for many people living with bipolar disorder, there are multiple visits to various specialists and several second opinions before even a semi-accurate diagnosis can be achieved. This process alone can have a negative impact on the patient's well-being. Furthermore, bipolar disorder not only manifests itself physically, it impacts mental, emotional, and social well-being as well. Due to its high morbidity, disability, and premature mortality, bipolar disorder is a major health problem with severe socioeconomic implications (Squassina et al., 2010). Bipolar disorder negatively affects a person's relationships, both personal and professional, and comes with higher financial costs. The severity of these costs, both economic and emotional, highlight the full extent of strife that those living with bipolar disorder experience.

Too often the health care industry relies on broad scientific background in order to diagnose a patient. While this foundational knowledge is key, doctors and health care professionals would do well to apply their knowledge to each individual patient. Extensive and detailed information should be collected before a patient receives treatment, such as the patient's symptoms or their family history. By establishing this level of detail, doctors will have greater understanding of the patient's needs, and provide them with better treatment. A movement towards personalized medicine needs to be pursued, especially in the field of mental health. Treating the patient rather than their symptoms can yield more accurate diagnoses, efficient treatment, and improved quality of life.

1.1 Bipolar Disorder: The Structural and Biochemical Basis

Bipolar disorder can be considered a spectrum disorder, with pathology and symptoms presenting uniquely across patients. For clinical purposes, however, there are clearly defined classifications. Bipolar disorder is broken down into type I and type II. Those living with type I suffer from recurrent manic episodes, often accompanied by an inflated sense of self-esteem, increased talkativeness, racing thoughts, and increased goal-directed activity (Bear, Connors, and

Paradiso, 2016). . Manic periods can last for months, and onset is not easily predicted. Conversely, patients with type II present with depression-like symptoms. Patients suffer from hypomania, a milder form of mania that is not associated with marked impairments in judgements or performance, but with greater episodes of major depression (Bear et al., 2016). Type I occurs in about 1% of the population, equally across men and women, and type II occurs in about 0.6% of the population (Bear et al., 2016), which appears to be more common in women.

The deterioration of several brain regions and structures have been implicated in the development of bipolar disorder. Bipolar disorder is characterized by neurotrophic alterations resulting in impaired signaling and neuroplasticity with a significant overall reduction in cortical volume (Squassina et al., 2010). This decreased volume can be found throughout the cortex, though there are a few key regions consistent with bipolar disorder behavior. For example, frontal lobe abnormalities are often seen with bipolar disorder and are consistent with observed deficits in executive functioning (Abe et al., 2015). Specific brain volumetric alterations such as enlargement of the ventricles, reduced grey matter in the orbital and medial prefrontal cortex, and reduced volume in the frontal lobe and hippocampus could correspond to reduced neuronal size and density (Squassina et al., 2010). These brain regions are associated with proper executive cognitive functioning, suggesting that cortical reduction to this area contributes to the impulsive, erratic behavior characteristic of manic episodes.

What remains unclear is whether damage to the brain produces the bipolar behavior, or if the physical decline is due to the progression of the disorder. Reduced grey matter may be the cause of bipolar disorder - or, it might be a byproduct. The extent of cognitive functioning impairment is correlated with the number of manic episodes a patient experiences (Abe et al., 2015). Patients can show significant cortical volume decrease in frontal regions after just one manic episode. This finding helps to illustrate how rapidly damaging manic episodes can be, challenging the notion that

damaged structure precedes altered behavior. Furthermore, no significant change in cortical volume has been seen in patients who did not experience a manic episode. Patients did present with a decrease in cortical surface area. However, the effects of this decrease may be mitigated by an increase in cortical thickness, resulting in an overall unaltered cortical volume. Cortical deterioration may be exacerbated by recurrent manic episodes, and the combination produces the overall behavior characteristic of bipolar disorder. This relationship between anatomy and physiology requires further exploration.

As of yet, no neurotransmitter system has been concretely tied to the etiology and pathology of bipolar disorder. The interaction of several neurotransmitter systems might contribute to susceptibility to the disease (Shi et al., 2008). Much of the research into neurotransmission comes from looking into possible genetic variants in each neurotransmitter system, highlighting the potential insights genetic testing could provide. Dopaminergic dysfunction could contribute to the etiology of mood disorders; but evidence of stress-induced GABAergic functional changes exists as well (Shi et al., 2008). A variant of the tryptophan hydroxylase 1 gene, which catalyzes the rate limiting step of serotonin synthesis, may be connected as well (Pisanu et al., 2018). In recent years, data has pointed to a glutamatergic explanation of bipolar disorder. Glutamate functions in excitotoxicity, a process where over-stimulation of neurons due to increased intracellular calcium levels leads to cellular death. This excitotoxicity could lead to an increase in the synthesis of reactive species, promoting inflammation and causing the tissue damage characteristic of bipolar disorder (Data-Franco et al., 2017). The glutamatergic hypothesis is promising, though more research should be performed. Some currently propose that an imbalance between the main excitatory neurotransmitter, glutamate, and the main inhibitory neurotransmitter, GABA, could be at play in the physiology of the disorder (Data-Franco et al., 2017). The imbalance between these two neurotransmitters could contribute to the alternating manic-depressive periods of bipolar disorder.

Raised levels of glutamate have been found in the frontal cortex of bipolar patients (Data-Franco et al., 2017). Abnormal expression of several subunits for NMDA, AMPA, kainate, and metabotropic glutamate receptors have also been discovered in regions relevant to bipolar disorder, such as the hippocampus and the frontal cortex (Data-Franco et al., 2017). Exploring the role of glutamate synthesis and neurotransmission may be of great importance in determining bipolar disorder etiology and pathology. Future research would do well to explore all the possible genetic variants related to glutamatergic synthesis, and neurotransmission in order to conclusively address the underpinnings of bipolar disorder.

The inositol 1,4,5-triphosphate / calcium (InsP_3 / Ca^{2+}) signaling pathway is responsible for generating Ca^{2+} signals throughout the body. It is well known that Ca^{2+} signaling plays a role in countless processes such as metabolism, cell proliferation, smooth muscle contraction, and memory formation in neurons. In the InsP_3 / Ca^{2+} pathway, phospholipase C receptors are activated and InsP_3 and diacylglycerol are produced. These products act as intracellular signals that trigger calcium release and activate protein kinase C. Inositol monophosphatase (IMPase) and inositol polyphosphatase (IPPase) then enzymatically dephosphorylate the inositol products into free inositol, which can be recycled to the membrane. Bipolar disorder may arise as a result of an overactive inositol signaling pathway (Berridge, 2016). Data has shown that key components of this pathway are present in the occipital cortex of patients with bipolar disorder. Furthermore, stimulating inositol 1,4,5-triphosphate or ryanodine Ca^{2+} receptors creates a depressive state in mice; when this pathway is inhibited, an antidepressant like effect is observed (Galeotti, Bartalini, and Ghelardini, 2006). Research exists regarding the factors that may affect the activity of this pathway. Pharmacological research has also been conducted to see how this pathway might be biochemically manipulated. The InsP_3 / Ca^{2+} signaling pathway may represent the most solid hypothesis that exists regarding bipolar disorder, and it should continue to be explored.

1.2 The Missing Genetic Link

In recent years, research has searched for genetic variants implicated in bipolar disorder. Assessing the role of genetic polymorphisms in bipolar disorder is informative because it opens doors regarding personalized treatment, and may hint at possible preventative measures. Twin and adoption studies are characterized by high heritability, suggesting genes exert a high-magnitude effect on the development of bipolar disorder (Squassina et al., 2010). Genetic variation could affect how well patients respond to treatment and drug intervention. Common genetic variation accounts for up to 42% of variance in antidepressant response (Perez et al., 2017). The theory of genetic mosaicism may explain why bipolar disorder symptoms appear on a spectrum. One person's symptoms will not be identical to another, so logically, their treatment plans should not be identical either. Introduction of personalized medical approaches would account for patient variables, such as genetic history, and provide patients with more holistic and effective care.

Neurological disorders arise and progress due to interactions between genetics, environmental factors, and patient histories. No single factor operates in isolation. Understanding the interconnectedness is crucial, but understanding each factor completely is foundational. Therefore, the current aim of this investigation is to explore the effect of genetics on the development and treatment of bipolar disorder. Genetic variance is undoubtedly at play in bipolar disorder, but specific loci, mechanisms, and effects have yet to be concretely determined. Genetic testing will be essential in providing answers, and may lead to improved treatment plans for patients.

Pharmacogenomics is a novel approach to genetic testing that analyzes how genetic variants modulate patient response to drug intervention. Testing considers both pharmacokinetics and pharmacodynamics. Pharmacokinetics encompasses drug metabolism and transport, specifically focusing on how hepatic biotransformation impacts the drug concentration to drug

effect relationship (Lombard and Doraiswamy, 2013). Pharmacodynamics studies the drug's effect on receptors, transporters, enzymes, and second messengers. Effects are examined in both the brain and in non-specific tissues, allowing clinicians to determine their efficacy for producing the desired treatment effect (Lombard and Doraiswamy, 2013). Pharmacogenomics could provide a method of reducing heterogeneity of diagnoses and treatment, and by extent, highlight the biological underpinnings of bipolar disorder. The integration of pharmacogenomic techniques and practice with individual treatment represents a powerful instrument for the development of personalized therapies (Squassina et al., 2010). Implementation of genetic testing across mental health could move current knowledge ahead of where it currently stands. Genetic approaches to mental illness diagnoses and treatment could identify clinically significant predictors of efficacy and possible side effects caused by psychiatric medications (Dubovsky and Dubovsky, 2015). Theoretically, by establishing a genetic profile for any given patient, clinicians could use a more targeted treatment approach right away, and avoid the barrage of side effects that is inherent to trial-and-error treatment. Mental healthcare needs a shift in perspective. Clinicians are not just tackling a disorder by battling the symptoms - they are treating a patient, whose needs should extend beyond their immediate condition. Starting a movement towards personalized medicine, by way of pharmacogenomic testing, could provide patients with the more holistic and efficient treatment that is right for them, and perhaps lead to profound scientific discovery in the process.

2. Band-Aid Solutions: Inefficacy and Inefficiency in Bipolar Disorder Treatment

2.1 . Current Treatments

While medicine and pharmaceutical interventions have come a long way, treatment for bipolar disorder has yet to be perfected. Advances in pharmacological treatment exist. However, patient response and remission rates for current antidepressants remain nonoptimal, emphasizing the need for improved utilization of current therapeutic tools (Perez et al., 2017). In current practice, lithium remains the standard against which other medications are compared (Oedegaard et al., 2016). Modern research continues to investigate if antipsychotics or anticonvulsants have use as bipolar disorder treatments. These agents include valproic acid (VPA), lamotrigine (LTG), and carbamazepine (CBZ). Some research exists regarding the brain regions these medications may interact with, but specific mechanisms have not been discovered. Despite lithium's popularity amongst clinicians, it is not well understood biochemically. In fact, many patients do not respond well to the inherent side effects. Pharmaceutical sciences have vital contributions to creating the medicines that we use today. Most remain useful and effective, but how they work remains a mystery. Furthermore, if there are still people who are unresponsive to current medical interventions, then more research and work needs to be done.

Lithium is the most heavily prescribed treatment for patients with bipolar disorder. Lithium can reduce the frequency of manic episode recurrence by at least 30% (Squassina et al., 2010); however, 30-40% of patients fail to respond to lithium treatment, or cannot endure sustained treatment due to intolerable side effects such as weight gain, acne, thyroid suppression, and gastrointestinal-related issues. Because success with lithium seems to vary from patient to patient, it is likely that

good lithium responders constitute a clinically and genetically distinct group (Oedegaard et al., 2016). In fact, several studies in recent years have worked to demonstrate the existence of lithium-mediated gene expression changes. One such study documented changes in the expression of various genes in response to lithium treatment, including those involved in signal transduction pathways (Oedegaard et al., 2016). A link seems to exist between certain genes and lithium response, yet there is still inconsistent treatment success across patients. Further genetic testing could be beneficial in developing a method to predict individual response to lithium treatment. Not only would this genetic information be of great benefit to clinicians in making prescriptions, but it may also accelerate the patient's recovery and reduce their financial costs (Oedegaard et al., 2016). Genetic testing could provide better foresight, and shine light on the best treatment needed to fit the patient's needs.

Alternatives to lithium including different classes of antipsychotics and anticonvulsants, have been explored in recent years. Much of the focus concerns valproic acid (VPA), lamotrigine (LTG), and carbamazepine (CBZ). Among anticonvulsants, VPA, LTG, and CBZ have strong evidence-based support for use in clinical states of bipolar disorder, and data has also supported their roles as potential long-term treatments to prevent relapse (Squassina et al., 2010). VPA yields the most effective treatment in mania, at least for a particular subgroup of bipolar disorder. Good responders to VPA are characterized by: the presence of pure, mixed, or dysphoric mania; early age of onset; rapid cycling; concurrent substance abuse; and a lack of response or intolerance to lithium (Oedegaard et al., 2016). LTG is effective for patients with earlier onset of symptoms, nonepisodic course of the illness, comorbidity with panic disorders, fewer hospitalizations, fewer prior medications, and especially is effective in males (Oedegaard et al., 2016). Less seems to be known regarding CBZ's applications, but successful treatment seems to be predicted by more clinical features, such as mood-incongruent psychosis, lack of response, or intolerance to lithium (Oedegaard

et al., 2016). These medications all find success with a very specific subgroup of bipolar disorder, and are often used for patients whose initial treatment with lithium was ineffective. The need for these alternate drug options reinforces lithium's lack of universality. Furthermore, it emphasizes the likeliness of a patient variable. Lithium, VPA, LTG, and CBZ all have viable treatment applications, but are only effective for a particular subset of patients with bipolar disorder. If more was known about the patient's history, genetic background, and specific symptoms, clinicians would not have to follow down the list of possible drug interventions. They would know which drug to administer right away, and the patient could have a more personalized, more effective treatment.

2.2 *Genetic Influences*

Though not the only etiological factor, genetic variation across patients is nonetheless a vital source of variability that should be thoroughly examined. Genetic polymorphisms affect both drug targets and drug metabolism, and therefore are important sources of individual variability in treatment and adverse effects (Dubovsky and Dubovsky, 2015). There are efforts to define the mechanism of medications in the context of these genetic polymorphisms, though their overall connection to bipolar disorder remains unclear. As it stands there is no single gene firmly connected to bipolar disorder. Research has proposed several regions that warrant further study. MicroRNA have links to current pharmacological treatment of bipolar disorder. MicroRNAs are short, noncoding post-translational regulators of gene expression that have been linked to circadian clock machinery, a biological mechanism associated with bipolar disorder as well as major depression (Dubovsky and Dubovsky, 2015). MicroRNAs could be a target site for antipsychotic medications (Perez et al., 2017), and may be affected by lithium use. Sadly, the usefulness of microRNAs as biomarkers for bipolar disorder is limited by their associations with several disorders. It is hard to elucidate the true mechanism of microRNAs in bipolar disorder. Another protein of significant interest is GSK-3 β .

GSK-3 β is a highly conserved protein involved in the regulation of apoptosis, circadian rhythms, and a wide range of neuronal functions and pathways associated with tissue development (Squassina et al., 2010). It is affected by administration of both lithium and valproate. MicroRNAs and GSK-3 β both seem to regulate similar functions, and they are both affected by current bipolar disorder treatments. Understanding how these genes function and how they can vary will be essential to understanding the true genetic variables of bipolar disorder.

The inositol pathway is currently being investigated as a target for drug intervention. Research has shown that lithium directly inhibits both enzymes of the inositol pathway (Oedegaard et al., 2016; Squassina et al., 2010; Pisanu et al., 2018). The inositol depletion hypothesis is based on the observation that Li⁺ acts by inhibiting the inositol monophosphatase (IMPase) that hydrolyzes inositol monophosphate to form free inositol, which could inhibit the inositol pathway signaling (Berridge, 2016; Oedegaard et al., 2016). VPA is also suggested to impact this pathway, though by a different action than lithium (Squassina et al., 2010). Lithium can be considered a homeostatic drug: it has no effect on the InsP₃ / Ca²⁺ pathway when it is operating normally, but its therapeutic action becomes increasingly effective to match the degree of hyperactivity exhibited by the pathway (Berridge, 2016). The belief is that the effect of Lithium alters to match the severity of bipolar disorder. However, given that lithium does not work for every patient, there must be an exception to this logic. Perhaps there are genetic markers that reveal information about the activity of the InsP₃ / Ca²⁺ pathway. Genetic testing could reveal genetic polymorphisms that predispose a person to abnormal InsP₃ / Ca²⁺ activity, which may in turn be suggestive of bipolar disorder risk. There is consensus that good predictors of viable lithium response include lower inositol monophosphatase mRNA expression (Squassina et al., 2010). Genetic testing could help to elucidate the true connection between inositol signaling and bipolar disorder etiology. This may be the most promising research route discovered in recent years, and no doubt requires further investigation.

2.3 The Risk of Adverse Drug Effects

The fact of the matter is that most pharmaceutical treatments do not selectively interact with the target of interest, but bind to several different regions. This promiscuity could set off downstream, and sometimes adverse, reactions. Because of this, use of a single isolated treatment, or monotherapy, is not always effective (Oedegaard et al., 2016). In an attempt to combat this nonspecific binding, some physicians may choose to employ a combination of treatments. However, by increasing the chance of successful binding to the desired target, the risk of adverse chain reactions also increases. Exposing patients with a barrage of drugs likely will not increase the efficacy of the treatment. Knowing which medicine is best for each patient can be discovered with genetic testing, and will ensure the patient receives more holistic and effective care.

Though drug intervention can mitigate the effects of bipolar disorder, patients can still experience symptoms. Sometimes the side effects of medication only cause more issues. A prominent concern is neurocognitive deficits brought on by certain medications. In fact, cognitive slowing is not an uncommon side effect for many of the currently used mood stabilizers (Oedegaard et al., 2016). Though not a desired outcome, it can be difficult for doctors and pharmacologists to tackle one aspect of a disorder without causing some downstream adverse effects. Measures such as genetic testing would enable physicians to determine if there are physical markers for side effects, such as the neurocognitive deficiencies, or even a risk of relapse, and see if they are associated with a specific gene (Oedegaard et al., 2016).

However, the problems bipolar disorder and drug intervention create are not always physical. Besides failure with first- or second-line therapy, disability and economic costs associated with bipolar disorder are linked to high rates of drug-induced adverse effects (Perez et al., 2017). With time adverse effects can impair a patient's emotional, mental, and financial well-being. What does it say about modern medicine if the desire to target a particular symptom is weighed more heavily

than the patient's individual needs? Consciously, people might agree that treatment needs to be more holistic - but is that actually being achieved? The reality is that bipolar disorder is a major cause of hospitalizations and healthcare expenditures (Squassina et al., 2010). In some cases, bipolar disorder can even lead to suicide (Oedegaard et al., 2016; Pisanu et al., 2018). These are not easy things to think about. It can be easier to focus on the 'science' of the disorder, rather than the more personal aspects. But from these facts alone, it can be presumed that the mental health and emotional well-being of bipolar patients is not being adequately addressed.

The financial toll treatment takes on patients is not given proper attention either. Lithium still remains the drug of choice among clinicians, despite inevitable side effects. Other medications such as VPA, LTG, and CBZ have shown moderate success for different subsets of patients in the clinical setting. However, the cost of treatment with these newer agents is in excess of 10 times higher than that of lithium; for example, it can cost \$60 per month for valproic acid, while it may cost as little as \$1 a month for lithium treatment (Oedegaard et al., 2016). This large difference in price creates a dilemma for patients. Do they use lithium because of its low financial cost, regardless of the side effects they may experience? Or do they take the chance with valproic acid? It may prove to be more effective for them, but it does present a big economic gamble. If only patients had a way of knowing which drug would be the most effective for their needs.

Adverse drug effects are often the result of complex factors that are several steps removed from simple biochemical pathways, such as metabolism. At this level the drug's efficacy, or lack thereof, is more likely determined by the patient's genetics than the drug's design. There is a strong relationship between economic burden and genetic variation as it related to treatment for schizophrenia (Herbild, Andersen, Werge, Rasmussen, and Jurgens, 2013). Four functionally distinct groups of metabolizers exist, classified by the number of functional copies of each CYP gene they had present. Patients classified as hyper metabolizers or as poor metabolizers incur substantially higher

costs than similar patients with a more moderate metabolizing genotype. Because these groups of people have a more extreme, inconsistent metabolism, it is difficult for physicians for doctors to discern the best treatment route. Too much time gets spent trying to find the proper dosage. This process not only racks up financial costs, but negatively impacts the patient both emotionally and physically. However, there is a solution that could account for this patient variability and transition towards more effective, personalized care.

2.4 The Advent of Pharmacogenomic Testing

Pharmacogenomic testing could be used as a preemptive measure to screen patients and provide precise and personalized treatment (Herbild et al., 2013). In essence, pharmacogenomic testing would create a genetic profile of sorts that would allow physicians to see which genetic polymorphism are present. They could then see which polymorphisms are associated with a disorder and target that specific mutation. This method of testing could be extremely useful in the diagnosis and treatment of poor metabolizers and hyper metabolizers. Identifying these patients and taking their baseline metabolic capacity into account when prescribing medication is suggested to reduce the adverse effects associated with frequent changes in pharmacological treatment (Herbild et al., 2013). Pharmacogenomic testing would not only establish a more accurate and effective treatment option for patients, but it would decrease the time, cost, and energy that is usually devoted to a ‘trial and error’ treatment route.

Some remain unconvinced. If a certain gene is genuinely connected to a drug’s action, irrefutable evidence must show that the relationship is caused by the drug administration and not by the natural pathology of the disorder. For example, can it be proven that a single nucleotide polymorphism (SNP) is associated to lithium response and not to some other biochemical process unrelated to the drug’s administration (Oedegaard et al., 2016)? If the drug is working, why can’t it be left at that? Furthermore, once in the central nervous system, the role of genetic polymorphisms

becomes much harder to assess than examining other biochemical processes, like the role of metabolizing enzymes (Dubovsky and Dubovsky, 2015). Truthfully, it is difficult to separate out the exact factors determining a drug's effectiveness, or lack thereof. Drug response and tolerability profiles depend on the combined effects of different genes as well as environmental and clinical factors (Perez et al., 2017). The significance of these external, uncontrollable variables are not something to be glanced over. Success with a given treatment might occur, but only because certain external or environmental factors were in effect. Genetic testing has potential to lead to greater success rates for drug intervention, but 100% efficacy may not be attained because there are still other factors involved.

This thought should not negate the importance of genetic testing. Some might say it is enough to see the correlation between genetic makeup and effective treatment. If a patient presents with Gene X, then they can be prescribed Drug Y, and the 'why' of it doesn't really need to be explored. At the macroscopic level, however, data on genetic polymorphisms is invaluable. Knowing a relationship exists between a gene and a medication allows researchers to investigate possible mechanisms of action. They can then study pharmacokinetics and pharmacodynamics, investigate drug inhibitors and activators, and possibly elucidate a pathway towards a cure. Genes can be influenced by environmental and clinical factors, and may change as a result. But having foundational knowledge of genetics and what a healthy patient looks like can give a roadmap to the genetic polymorphisms of bipolar disorder. With this degree of direction, clinicians could provide patients with exactly what they need.

In an ideal world, the pathology behind every disorder would be clearly outlined, and a treatment could be easily developed. But the aim of mental disorder research and treatment needs to be refocused. Scientific pursuit can easily get wrapped up gene variants and mechanisms and statistical significant. Too often, the patient gets overlooked. Mental health needs to regain a

personalized element. Doctors are not just battling a disorder; they are treating a person. Genetic testing could help to bridge this gap by having doctors focus on the data pertaining to an individual patient. Research should continue to find the root cause of bipolar disorder. But until a cure is found, patient care should focus on the specific treatment and holistic care of an individual person.

3. Pharmacogenomics in Practice: Addressing Ethical, Administrative, and Legislative Concerns

Pharmacogenomics represents an innovative approach to healthcare and patient prioritized treatment. The innovative utilization of genetic testing has revealed genetic variants that may contribute to psychiatric disorders, and has revolutionized the approaches people can take in disorder diagnosis and management. Genome-wide association studies represent one technology capable of examining many genetic variants in the genome simultaneously, without any sort of preliminary hypothesis (Mistry, Harrison, Smith, Escott-Price, and Zammit, 2018). The degree of data resulting from these kinds of studies is monumental. Not only do genetic tests provide a wealth of information, they can reveal genetic connections to disorder etiology or treatment efficacy that were otherwise unnoticed. From promoting personalized medicine and reducing the risk of adverse drug effects, the potential benefits of pharmacogenomics and genetic testing are far reaching. However, many of these practices are not time-tested, and government and administrative policies lag behind the technological advancements. Pharmacogenomics makes groundbreaking and vital contributions to modern medicine, but its application raises several clinical, economic, and legislative concerns.

These ethical and logistical concerns must be adequately addressed for genetic testing to be effectively implemented in healthcare policies. Not having clear guidelines and policies in place before the technology becomes standard clinical practice may have detrimental economic, ethical, and operational effects, and may also give health care providers, consumers, and service providers free reign in the procurement and use of testing (Bashir an Ungar, 2015). Ambiguity is not beneficial to clinicians or to patients. For pharmacogenomic testing to be beneficial and effective, there must be guidelines, procedures, and even laws in place. Knowing who will be providing and financing services, who should be able to requisition the technology, and how the information will be used

must be clear at both the federal and local level (Bashir an Ungar, 2015). Pharmacogenomic testing can improve mental health diagnosis and treatment. But it must be proven that the costs of implementing genetic testing practices and policies will not outweigh the benefits of the data.

3.1 The Patient Perspective

Often in health care, the clinical voice becomes the loudest. The focus is on tackling symptoms the best clinicians can with the treatments and procedures they have available to use. Patient voices can then be overshadowed, and their wellbeing can be overlooked. Even though clinicians have the scientific expertise and training, patients have a right to be an active part of their health care. Patients deserve ample knowledge about their health care options in order to make informed decisions. As genetic testing advances, patients should have access to information and resources pertaining to pharmacogenomics. Because little information is offered, patients have limited understanding regarding genetic testing. In theory patients welcome the benefits of pharmacogenomic testing for improved diagnosis and care; but, they have concerns about the emotional burden of genetic results, the value of testing, and whether testing could be used to ration care (Bashir an Ungar, 2015). Patients need to be convinced that the ordeal of genetic testing will be beneficial to their overall health, and not bring about any more pain or problems. The patient perspective is too easily overlooked in mental health care, and it is time their concerns were properly addressed.

Privacy is a prominent concern when it comes to personal information. Genetic testing can be invasive, and not knowing who can access results gives patients anxiety. A considerable issue with genetic testing is the practice of genetic discrimination. Genetic discrimination occurs when people are treated differently due to their genetic makeup, with some definitions specifying that discrimination would occur as a direct result of the genetic testing (Bashir an Ungar, 2015). The patient concern is that their genetic background will be unfairly used by insurance providers or employers

to determine coverage or employment. Though perhaps unlikely, this is a concern that required further thought. Many states have passed laws to address these concerns, and there have been attempts to pass federal legislation banning the use of genetic risk information in health insurance underwriting (Garrison et al., 2008). Some have argued that these kinds of laws infringe on the rights of private business, such as insurance companies, because it forces some to assume the risks of others. While the spirit of the law is to protect people, the true logistics implications require further consideration.

Pharmacogenomic testing can be instrumental in giving patients accurate diagnoses and effective treatment. It has the power to reduce financial costs of care, and reduce the patient's risk to adverse side effects. While this information is invaluable, people often fail to consider the emotional stress genetic testing can create. Patients can feel empowered to take a proactive stance in their health care by requesting pharmacogenomic tests; but, they are often ill equipped from a knowledge and emotional standpoint to handle their results (Bashir and Ungar, 2015). Pharmacogenomic testing can establish genetic profiles and reveal regions of interest. If a patient is told they have a genetic risk variant for bipolar disorder, are they given resources on how to go forward? Are clinicians and genetic testing services required to give the patient a referral for treatment? With no sort of system or procedure in place, patients are left to flounder and seek out medical advice for themselves. The wealth of information pharmacogenomic testing can provide is useless if patients and clinicians do not know how to respond to it. Patients deserve to move through the health care system more smoothly. They should have the right to informed clinicians and ample resources so that they can receive effective, compassionate, and holistic care.

3.2 Clinical Concerns

Pharmacogenomic testing is understandably not well-known amongst the general population. But surprisingly, it remains novel in the clinical setting as well. According to a 2008

National Survey, only 10% of physicians nationwide feel that they have adequate understanding of pharmacogenomic tests, even though 98% believe pharmacogenomic testing would benefit their patients (Heale, Khalifa, Stone, Nelson, and Del Fiol, 2017). Theoretical knowledge alone is not enough if clinicians do not even have the training to utilize genetic testing properly. Clinicians often adopt a ‘berry-picking’ information-seeking model, in which they ‘pick’ information from different locations that is relevant to their inquiries. This strategy can hinder both the physician and the patient. The clinician gets an incomplete understanding of a given testing procedure, and will not know when or how to use it properly. The patient misses out on holistic treatment because they are not presented with a thorough list of options. The physician and patient relationship needs to be more balanced, and therefore both parties should have resources to be knowledgeable about the methods and interpretations of pharmacogenomic testing.

What is the best way for clinicians to stay up to date on pharmacogenomic knowledge and practices? Some have suggested that a pharmacogenomic database may prove quite useful. A platform of this kind would allow doctors to seek out genetic testing information in a user-friendly yet comprehensive way. They would have access to a plethora of resources, but navigate it with their particular focus in mind. Additionally, structured search forms could help guide clinicians through the search process by employing a PICO- based search model (Population, Intervention, Comparison, and Outcome) (Heale et al., 2017). With this type of clear cut and efficient system clinicians could focus their investigations specifically to the needs of their patient. More so, in researching for a specific genetic variant or pharmacogenomic test, a database could guide clinicians to alternate routes of investigation - perhaps refining their searches and given both clinician and patient a more holistic understanding of the treatment options. Another approach to assisting clinical searches involves integrating online resources with patient information in an electronic health record (EHR) system. This kind of system could reduce necessary navigation

efforts and decrease the physician's short-term memory overload (Heale et al., 2017). Moreover, it would put the pharmacogenomic information directly in context with the patient's symptoms and history, likely letting clinicians see a treatment path more clearly.

Direct-to-consumer companies are an alternative to traditional health care and genetic testing. They allow individuals to have greater autonomy in their health care. The direct-to-consumer pharmacogenomic testing gives the patient the ability to become more proactive in their health care decisions, an idea that is increasingly popular in current health care systems (Bashir and Ungar, 2015). These companies can provide easily accessible and quick results, and are a good resource to patients in their health care journeys. However, there are certain considerations patients should have when entrusting their genetic information to a private cooperation. Direct-to-consumer testing may be difficult to regulate in terms of quality care, and may create an increased demand for follow up health care resources (Bashir and Ungar, 2015). Because it functions as a private company, their genetic testing practices will likely be unaffected by any state or federal regulations. Patients might not be assured that they are receiving accurate or adequate information, and may not even have a guarantee to their privacy. Furthermore, direct-to-consumer companies may not have an obligation to act on the results of genetic testing. Patients may desire to respond to their results and seek out additional consults, but their demand for appropriate medical treatment may not be financially possible. These hypotheticals do highlight the concern regarding who should be allowed to perform genetic testing, and whether or not restrictions should be imposed (Bashir and Ungar, 2015). This very question is the center of debate for many administrative and legislative measures

3.3 Legislative Logistics

In order for pharmacogenomic testing to be effectively implemented throughout health care, structure, guidelines, and policies need to be in place. Genetic exceptionalism is the view that genetic information is fundamentally different from other kinds of medical information, and as a

result, deserves special protection, regulation, and legislation (Garrison et al., 2008). Genetic history is sensitive and private information, and needs to be considered with gravity.

Four characteristics of genetic testing are frequently cited when arguing for exceptional treatment. Genetic information is (1) predictive of future health, (2) permanent and unchangeable, (3) uniquely identifying, and (4) informative about the health of family and community members (Garrison et al., 2008). Genetic profiles can be used to predict a person's health and their risk for different disorders. But, the same can be said for cholesterol and blood glucose levels. These factors are indicative of disorders such as heart disease and diabetes, and are often considered in medical evaluations. Some would argue that just like insurance providers are allowed to test blood pressure, they should be allowed to request genetic profiles. Being predictive of future health alone is not a good justification for genetic exceptionalism. However, genes are indeed permanent and unchangeable. No one is capable of altering their genetic profile, and where science currently stands, there are no means of stopping genetic polymorphisms before they manifest. But what is there to stop insurance companies from labeling a genetic risk as a preexisting condition? While some diseases are brought on by environment and lifestyles, genetic profiles cannot be altered or avoided. Genetic information is uniquely identifying, creating concern regarding privacy. Similarly, genetic information can be extrapolated to a person's immediate family. Many people do not like the idea of genetic information being traced back to them. Furthermore, while one person may give consent for genetic evaluation, what is to prevent that information from being connected to other parties? These factors lay the foundation of the argument supporting genetic exceptionalism. Whether or not these arguments give justification for genetic exceptionalism in health care administration, legislation, and regulation will be decided through debate and policy creation. But the significance of these factors should not be ignored and do call for careful evaluation.

Actualizing the benefits of pharmacogenomic testing requires dedicated efforts, but it is not without its challenges. All of these concerns, brought forth by both clinicians and patients, can be addressed through adequate policy implementation in places where they currently do not exist, at all appropriate levels of government (Bashir an Ungar, 2015). All levels of mental health care would benefit from a structured system. Clinicians would benefit from guidance and established policy on how to utilize genetic testing with the most effective and efficient methods. Patients would benefit from clear and enforced legislation regarding the use of genetic information. Legislation and policy creation would give structure to pharmacogenomic testing, and allow it to operate at its most effective capacity. However, the matter of private business shines a new light on policy creation. Often, private business, such as private insurance companies, are not regulated by federal and state law. Pharmacogenomic testing in the private sector presents another element to consider.

Just as the clinical perspective should shift towards a patient-oriented model, insurance companies might become more patient oriented as well. Private insurance companies claim they are concerned with providing high quality products, profits, and sustainability (Bashir an Ungar, 2015). They aim to provide their patients with quality service; but, in reality, they function as a business and have their own business model and interests to maintain. For this reason, many people are concerned regarding insurance companies' intentions when evaluating genetic risk. Patients and health care providers support laws prohibiting genetic discrimination, but insurance providers may challenge these laws if they prove to be detrimental to their sustainability (Bashir an Ungar, 2015). Insurance functions by evaluating a person's history and current situations, judging their risk for a multitude of accidents and diseases, and providing corresponding coverage. But genetic risk is not something a person can combat. It can't always be resolved with diet and exercise. Do insurance companies have a right to deny coverage based on conditions the individual has no control over? For private insurers, until genetic discrimination laws are in place, they are free to include a

patient's genetic information in their calculation of risk and coverage level (Bashir an Ungar, 2015). Whether this should be considered legal or not remains to be decided, but it does highlight the necessity of legislative investigation and policy creation.

Obviously, the overall benefit of pharmacogenomic testing is the heart of any legislative initiations. Does the good outweigh the harm? Pharmacogenomic testing is a novel and ground-breaking tool from a scientific and clinical perspective. But do the ethical, regulatory, and legislative concerns contradict its usefulness? Does the cost of creating policy outweigh the good that may come from the practice? While costly adverse events may be averted with pharmacogenomic testing, the costs of policy reform, service coordination, delivery, health technology assessments, and training resources may offset any true cost savings (Bashir an Ungar, 2015). There are several practical and logistical points to address in any conversation regarding pharmacogenomic testing. Pharmacogenomics undoubtedly would excel mental health care. It would decrease the time, energy and money spent trying out diagnoses before the right one is named. It would ensure patients no longer have to play trial-and-error treatment games, and could get the solution designed for their needs sooner. Legislative and policy debates must weigh the good of pharmacogenomic testing with the cost and logistics of policy implementation, and decide if it is ultimately worth the effort.

3.4 The Power of Pharmacogenomic Testing

Pharmacogenomic testing provides undisputed benefit to both scientific research and clinical practice. While public policy may waffle over the cost of policy creation, the benefits of genetic testing cannot be denied. As discussed earlier, there are several studies showing genetic testing leads to reduced treatment costs. Additionally, research has shown a correlation between pharmacogenomic testing and a decrease in adverse drug effects. Pharmacogenomic testing provides invaluable data by revealing genetic variants of interest that deserve further study. This

kind of evidence may even lead towards preventative measures for bipolar disorder - it may even be instrumental in the development of a cure.

As previously stated, there is a strong correlation between pharmacogenomic testing and reducing cost to the patient (Herbild et al., 2013). Treatment costs tend to be considerably higher for people with more extreme, unregulated metabolism. However, pharmacogenomic testing allowed researchers to identify this group of extreme metabolizers and direct their treatment accordingly. From this research, it can be shown that pharmacogenomic testing not only reduces excess cost of care or drug intervention, but also decreases the patient's risk for adverse drug effects. Clearly, genetic testing has financial benefit. What policy makers worry about is whether the cost of savings outweighs the cost of genetic testing itself. However, if procedures were designed to be simple and efficient, then this worry wouldn't need to exist. Though some may doubt the usefulness of genetic testing, easy methods of obtaining relevant DNA samples through blood or saliva would decrease the cost of genotyping, and could make genotyping a routine component of medical care (Dubovsky and Dubovsky, 2015). Cost effective pharmacogenomic practices exist. It just requires efforts on part of policy makers and health care administration to make them a reality.

Considerably the most compelling benefit of pharmacogenomic testing is the reduction of adverse drug effect risk. In Canada roughly 3600 hospital deaths occur annually as a result of adverse drug effects. Furthermore, adverse drug effects were found to prolong hospital stay by an average of 4.6 days and increase hospital costs by \$300 million per year (Bashir an Ungar, 2015). Fortunately, genetic testing can be used to account for adverse drug effects, and possibly reduce the prevalence rate. This fact alone speaks to the significance of pharmacogenomic testing. Patients can be provided with more personalized, holistic medicine and have more effective and efficient treatments. This is the goal of genetic testing. This is what should be driving policy and practice creation.

From a larger perspective, pharmacogenomics also has applications in pharmacology. Genetic variants revealed by genetic testing can be used to create better drug design and delivery methods. Pharmacogenomic testing information could allow for smaller, shorter, faster, and cheaper drug trials with improved success rates (Garrison et al., 2008). Genetic information could be used to identify the different subtypes of a given disorder, which would let drug designers create more targeted medications. Additionally, an understanding of the relationship between a genetic marker and drug efficacy could enable the design of a clinical trial that is enriched with likely responders (Garrison et al., 2008). By knowing which gene a medication might interact with, or knowing which specific symptoms a drug best combats, drug trials will be made more efficient. Genetic research could bring science close to the discovery of a key genetic polymorphism, possibly pointing researchers towards a more directed search for a cure.

Ultimately, the benefits of pharmacogenomic testing cannot be denied. Efforts to create legislation and administrative practices are difficult. There are indeed many ethical and systematic concerns to address. But pharmacogenomics has so many widespread applications. It is proven to be beneficial from both a clinical and patient perspective. Genetic testing is known to decrease the risk of adverse drug effects. It is also proven to reduce cost to both the clinician and the patient. Furthermore, pharmacogenomic testing can provide scientific clarity. It provides the possibility of uncovering key genetic variants related to bipolar disorder, and may even refocus research towards an obtainable cure. Pharmacogenomic is a groundbreaking scientific and clinical technology, and therefore warrants further investigation so that it can be effectively implemented into modern health care practices.

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