

**Addressing Psychiatric Disorders in Genetic Counseling**

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### **Abstract**

Psychiatric genetic counseling (PGC) is a growing specialty. With discoveries of new treatments, improved risk calculations, elucidation of genes associated with psychiatric disorders, and rising public interest in mental health, the occasion for genetic counselors to address psychiatric genetics in sessions will likely become more common. Several papers have addressed the utility and efficacy of PGC. Additionally, studies have shown that experience with mental illness, training for psychiatric genetic counseling, stigma towards individuals with mental illness, and concerns about communicating complex information all affect genetic counselors' attitudes and practices regarding psychiatric genetics. It is important to determine whether and how nonpsychiatric genetic counselors employ it to determine what information would most enhance practices and how best to disseminate that information.

This study looked at how exposure, training, and resources influence genetic counselors' practices and confidence by surveying 108 members of the National Society of Genetic Counselors about their current practices, what factors influence those practices, and what resources or information would benefit patient care. The majority of counselors indicated they have never seen a patient whose primary indication was a psychiatric condition (n=68), referred a patient to a psychiatric genetic counselor (n=88), disclosed secondary findings related to a psychiatric condition (n=83), or ordered genetic testing primarily for a psychiatric disorder (n=87).

These findings indicate that although dedicated clinics are being developed and interest is rising, PGC is not used by the majority of genetic counselors. Nevertheless, recent graduates of genetic counseling programs were more likely to have attended a training program that addressed psychiatric genetics and were more confident in their knowledge of psychiatric genetics, indicating that changes in the field of genetic counseling and individual experience in the field may affect familiarity, confidence, and practice. This study demonstrates that development of training programs, resources, and educational opportunities may increase adoption of psychiatric genetic counseling practices, potentially improving care of patients with mental illnesses. Caring for those with mental illness is an important focus in public health, and development of policies, guidelines, and provider resources can be informed by this study's assessment of factors involved in PGC decisions.

## Table of Contents

Preface.....	xi
<b>1.0 Introduction.....</b>	<b>1</b>
<b>1.1 Specific Aims.....</b>	<b>3</b>
<b>2.0 Literature Review .....</b>	<b>4</b>
<b>2.1 History of Psychiatric Genetics .....</b>	<b>4</b>
<b>2.1.1 Heritability Studies .....</b>	<b>5</b>
<b>2.1.2 Candidate Genes and Loci .....</b>	<b>7</b>
<b>2.1.2.1 Linkage Analyses .....</b>	<b>7</b>
<b>2.1.3 Genome-Wide Association Studies .....</b>	<b>8</b>
<b>2.1.3.1 Gene Expression Studies .....</b>	<b>9</b>
<b>2.1.4 Copy Number Variants .....</b>	<b>10</b>
<b>2.1.5 Epigenetics .....</b>	<b>10</b>
<b>2.1.6 Autism Spectrum Disorders.....</b>	<b>11</b>
<b>2.1.6.1 Genetic Testing for Autism Spectrum Disorders.....</b>	<b>12</b>
<b>2.1.7 Developmental Brain Disorders.....</b>	<b>12</b>
<b>2.1.8 Polygenic Risk Scores .....</b>	<b>14</b>
<b>2.2 Pharmacogenetics.....</b>	<b>16</b>
<b>2.3 Psychiatric Genetic Counseling.....</b>	<b>18</b>
<b>2.3.1 History of Psychiatric Genetic Counseling .....</b>	<b>18</b>
<b>2.3.1.1 Psychiatric Genetic Counseling Clinics .....</b>	<b>20</b>
<b>2.3.2 Outcomes and Practice .....</b>	<b>21</b>

2.3.3 Effects on Management .....	24
2.3.3.1 Management of Nonpsychiatric Multifactorial Conditions .....	24
2.3.3.2 Management of Psychiatric Conditions.....	25
2.4 Provider Attitudes .....	27
2.5 Continuing Education .....	29
2.6 Study Goals .....	33
<b>3.0 Manuscript.....</b>	<b>34</b>
3.1 Background.....	34
3.2 Methods .....	38
3.2.1 Sample .....	38
3.2.2 Survey.....	38
3.2.3 Data Analysis .....	39
3.3 Results.....	40
3.3.1 Demographics .....	40
3.3.2 Practice.....	42
3.3.3 Education and Resources .....	48
3.4 Discussion .....	55
3.4.1 Practice.....	55
3.4.2 Confidence/Education.....	57
3.4.2.1 Resources .....	58
3.4.3 Study Limitations .....	60
3.4.4 Future Directions .....	61
3.5 Conclusion.....	62

<b>4.0 Public Health Significance .....</b>	<b>64</b>
<b>Appendix A: IRB Approval Letter .....</b>	<b>66</b>
<b>Appendix B: Survey .....</b>	<b>67</b>
<b>Bibliography .....</b>	<b>78</b>



## List of Tables

Table 1: States, Territories, and Provinces in each Region .....	41
Table 2: Demographic Distributions of Thesis and PSS Respondents .....	42
Table 3: Percent of Respondents Who Have Performed Psychiatric Genetic Counseling Practices .....	44
Table 4: Percent of Respondents Who Have Ordered Genetic Testing for Certain Psychiatric Conditions .....	45
Table 5: Types of Instruction by Graduation Decade.....	48
Table 6: Percent of Respondents Who Would Find Certain Types of Information Useful .....	50
Table 7: Associations Between Demographic Factors and Psychiatric Genetics Practices .....	52
Table 8: Psychiatric Genetics Practices Given Demographic Category .....	53
Table 9: Association of Demographic Factors with Confidence .....	54
Table 10: Agreement with the statement “I feel confident in my understanding of psychiatric genetics” .....	55

## List of Figures

Figure 1: Frequency of History-Taking Practices (n=99).....	43
Figure 2: Degree of Influence of Various Factors on Testing Decisions (n=95).....	46
Figure 3: Degree of Confidence (n=99).....	47
Figure 4: Preferred Genetics Resources.....	49
Figure 5: Likelihood of Training Program Addressing Psychiatric Genetics by Graduation Decade .....	53

## **Preface**

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## 1.0 Introduction

Psychiatric genetic counseling involves evaluation of patients' psychiatric histories, recognition of patterns or trends of psychiatric disorders or other neurodevelopmental disorders in family histories, assessment of risks, and communication of risks, causes of mental illness, and potential genetic testing or management, as well as discussion of patients' fears, guilt, blame, and other emotions surrounding psychiatric disorders.<sup>1,2</sup> Understanding the complex etiologies of mental illness can reduce stigma and shame, help individuals feel more in control of their mental health, and potentially influence treatments and therapies.<sup>3,4</sup>

Over 46.6 million people over 18 in the United States, or 18.9% of the population, had a mental illness in 2017.<sup>5</sup> This is a significant increase from 18.1% in 2014, 17.8% in 2011, and 17.7% in 2008.<sup>6,7</sup> This increase is reflected in rising disability payments, with average monthly benefits for all disabled beneficiaries with mental disorders increasing from \$6473 in 2010 to \$7228 in 2017.<sup>6,7</sup> The large affected proportion of society and the financial burden of mental healthcare have increased public interest and funding for psychiatric research, allowing for development of new treatments, identification of risk factors, and better understanding of brain development and function.<sup>8</sup> Genetic associations and links between psychiatric conditions, developmental and intellectual disabilities, and physical symptoms contribute to development of medications and treatments, as well as more accurate risk conceptualizations. Early hypotheses of candidate genes based on targets of psychiatric medications were later tested with linkage analysis studies and genome-wide association studies (GWAS), which then led to identification of more loci and genes associated with psychiatric disorders.<sup>9,10,11,12</sup>

Public health campaigns have improved public awareness and acceptance of mental illnesses, which, in combination with revised Diagnostic and Statistical Manual for Mental Disorders (DSM) criteria and other factors, have contributed to higher numbers of referrals to mental health professionals and prescriptions of psychiatric medications.<sup>13</sup> Demand for care of individuals with psychiatric disorders and for genetic counseling services are both growing; therefore it can be expected that psychiatric genetic counseling will be increasingly called for.<sup>7,14,15</sup> As knowledge improves of the mechanisms of psychiatric illness pathophysiology, identification of genes, loci, and epigenetics involved in mental health, clearer determinations of heritability and recurrence risks, and applications of pharmacogenomics, the role of genetic counselors in psychiatry is growing and changing.

Dedicated psychiatric genetic counseling clinics have developed strategies for working with patients and families with histories of mental illness, and studies have revealed positive outcomes of these clinics.<sup>4,6,7,16</sup> Genetic counselors in other specialties also see patients with personal or family histories of psychiatric conditions but have received varying levels of education and training to provide psychiatric genetic counseling.<sup>17</sup> The field of psychiatric genetics has changed greatly from early descriptions of psychiatric disorders in families to recent identification of specific genes increasing risk of mental health issues, and communicating new findings and conceptualizations may be beneficial to genetic counselors' practice and patients' care.

## 1.1 Specific Aims

- **Aim 1** – Establish whether and how genetic counselors are currently incorporating knowledge of psychiatric disorders into their counseling sessions.
- **Aim 2** – Determine what information about psychiatric disorders is most important and most desired by genetic counselors.
- **Aim 3** – Propose methods to disperse this information and increase genetic counselors' knowledge and comfort with discussing psychiatric disorders.

## 2.0 Literature Review

### 2.1 History of Psychiatric Genetics

Psychiatry has been studied for centuries, from early observations by ancient cultures to the creation of the American Psychiatric Association in 1844, and much of these studies have focused on the origins and causes of mental illness.<sup>18</sup> Early anecdotal recognition of psychiatric disorders clustering in families directed later research towards familial explanations of mental illness. The German Research Institute for Psychiatry was founded in 1917 with a “Genealogic-Demographic Department,” approximately 50 years after Gregor Mendel’s work on inheritance.<sup>19</sup> Since then, numerous research programs and clinics have been developed.<sup>20,21</sup> In 1983, a clinical and research team was developed by Russell Schachar to study attention-deficit disorder (ADHD) and genetics.<sup>20</sup> Dr. Schachar also helped develop a joint clinical and research program involving psychiatric genetics at The Hospital for Sick Children in Toronto, Canada.<sup>20</sup> Since 2006, Washington University School of Medicine in St. Louis has had a “First Contact Assessment Service” designed to provide evaluations of individuals with psychiatric conditions to their psychiatrists and other providers.<sup>21</sup> Their Psychiatric Genetics Assessment evaluates those with psychiatric disorders related to genetic conditions.<sup>21,21</sup>

Many universities and researchers are involved in the Psychiatric Genetics Consortium, formed in 2007 to use open-source data to investigate the genetic basis of psychiatric disorders, possible therapeutic targets for psychiatric drugs, improve diagnoses, and other initiatives.<sup>22</sup> The elucidation of “nature” vs. “nurture” has long been a topic of debate, with recent consensus that both play a role.<sup>23,24,25</sup> Determining the specific roles of genetics, environment, experiences, and

other factors in the development of psychiatric disorders has been one of the focal points of recent research, as understanding the pathophysiology and origination of psychiatric conditions may lead to improved treatments and therapies.<sup>19</sup>

### **2.1.1 Heritability Studies**

The heritability of psychiatric disorders has long been studied, and the heritability of schizophrenia was one of the first focuses, followed next by depression, bipolar disorder, autism spectrum disorder (ASD), anxiety disorders, and other psychiatric conditions.<sup>9</sup> As early as 1911, family studies on psychiatric disorders were performed.<sup>26</sup> Family, twin, and adoption studies helped to define characteristics of the heritable phenotypes, estimate heritability, and investigate contributions and interactions of genetic and environmental factors.<sup>27</sup> In 1946, Franz Kallmann performed a landmark twin study including 691 twin families, including monozygotic and dizygotic twins, full siblings, half-siblings, step-siblings, parents, and twins' marriage partners to elucidate the environmental and genetic contributions to development of schizophrenia.<sup>28</sup> Given that the concordance rates Kallmann found were higher than those in other family studies of schizophrenia, his investigations of “the genetic theory of schizophrenia” contributed to growth of the field.<sup>28</sup> Sullivan et al. used 12 twin studies of schizophrenia published between 1941 and 1999 in Europe and the United States to estimate the heritability of schizophrenia at 73-90%.<sup>29</sup> These studies recruited subjects systematically, but typical exclusion data was relaxed to allow for inclusion of older studies performed before blinding of diagnosis and zygosity and systematic data collection and diagnosis were the norm. Nevertheless, comparison of “inferior studies” with “methodologically superior” studies revealed similar estimations of genetic and environmental effects.<sup>29</sup>



Meta-analysis of five family studies and six twin studies on major depressive disorder (MDD) and qualitative analysis of three adoption studies estimated heritability of depression to be approximately 31-42%.<sup>27</sup> These studies, published between 1980 and 1999 and performed primarily in the United States, as well as Europe and Australia, were selected for systematic recruitment, distinction between unipolar major depressive disorder and bipolar depression, blinded diagnoses, and direct collection of diagnostic data.<sup>27</sup> The subjects were recruited from clinical settings, the general population, and screened medical patients.

Johansson et al. used data from the Swedish Twin Register and the National Patient Register of twins born in Sweden between 1940 and 2005 to estimate heritability of bipolar disorder (BPD) at approximately 60%.<sup>30</sup> The authors utilized the liability-threshold model to evaluate additive genetic and environmental effects and accounted for the fact that subjects may still be at risk to develop or be diagnosed with BPD by the end of the study's follow-ups, because due to the uncertainty of whether a depressive episode will eventually develop into bipolar disorder, there can be a lag before individuals are diagnosed with BPD.<sup>30</sup>

Tick et al. reviewed all twin studies of ASD at time of publication and analyzed seven twin studies that met systematic recruitment criterion.<sup>31</sup> Six of these studies were performed in Europe and one in Japan, all published between 1985 and 2015. The authors analyzed concordance between monozygotic and dizygotic twins, calculating the heritability of ASDs to be 64-91%.<sup>31</sup>

The heritability of generalized anxiety disorder was estimated at 32% by Hettema et al. in 2001, who performed a meta-analysis of five family studies and three twin studies of generalized anxiety disorder as well as panic disorder, obsessive-compulsive disorder, and phobias.<sup>32</sup> The authors included studies using adults, systematic ascertainment, direct interviews, and blindness of affected status.<sup>32</sup> The highly heritable nature of these conditions explains why genetic

counselors may see patients who report multiple family members with intellectual, behavioral, and psychiatric disorders.

### **2.1.2 Candidate Genes and Loci**

Another significant area of research in the field of psychiatric genetics has been the identification of candidate genes associated with psychiatric illnesses. Candidate genes were largely hypothesized based on targets of antipsychotics, antidepressants, and other psychiatric drugs, particularly in dopaminergic and serotonergic pathways.<sup>9</sup> Few of these candidate genes, however, have been proven to be significantly associated with psychiatric disorders when studies in large genome-wide association studies.<sup>11,12</sup> Using a genome-wide association study conducted by the Psychiatric Genetic Consortium and the 1000 Genomes Project, Johnson et al. tested 25 candidate genes historically associated with schizophrenia and found they were not significantly associated with schizophrenia any more than non-candidate control genes.<sup>11</sup> This finding supported a similar study conducted in 2012, which compared 732 hypothesis-driven candidate genes for schizophrenia to the International Schizophrenia Consortium's GWAS. No significant enrichment was found for these candidate genes.<sup>12</sup> Border et al. conducted a similar study in 2019, examining 18 highly studied candidate genes hypothesized to be associated with depression, finding no significant associations.<sup>33</sup>

#### **2.1.2.1 Linkage Analyses**

Linkage analysis, linkage disequilibrium mapping, and association analysis were used to find chromosomal locations of variation associated with psychiatric disorders.<sup>9</sup> Early linkage analysis studies were small scale, but eventually were performed on larger samples.<sup>34</sup> The first

such linkage study was performed on an Amish pedigree in 1987, linking bipolar disorder to a region on 11p;<sup>10</sup> however, replication of this and later linkage studies was difficult, due to the small effects of each individual risk variant and the genetic heterogeneity.<sup>9,35</sup> A more recent study by Ng et al. in 2009 used a genome scan meta-analysis including 7413 cases of schizophrenia or related disorders and found evidence for linkage on 2q, supporting the same team's earlier finding of linkage on 2q in 2003.<sup>36</sup>

Psychiatric disorders are complex, genetically heterogeneous, and have variable penetrance and expressivity, making linkage and association analyses less than ideal for identifying associated genes.<sup>9</sup>

### **2.1.3 Genome-Wide Association Studies**

Since the first family study on schizophrenia by Rudin in 1916, researchers have recognized that psychiatric disorders do not follow Mendelian inheritance.<sup>37</sup> The difficulty replicating associations and the conflicting findings in different studies revealed the complex, multifactorial nature of psychiatric conditions.<sup>19</sup> Because complex psychiatric disorders are influenced by combinations of many loci, each with small effects, large sample sizes are needed to find these loci. The development of databases of genetic information, along with collaborative efforts, allow for larger sample sizes, enabling more powerful analyses.<sup>9</sup>

With the completion of the Human Genome Project in 2003 and subsequent technological advances, including easier, faster, and cheaper sequencing methods, researchers could perform genome-wide association studies (GWAS), allowing for the identification of hundreds of common single nucleotide polymorphisms (SNPs) and rare copy number variants (CNVs) involved in a variety of processes and pathways related to pathophysiology of psychiatric disorders.<sup>9</sup>

Pathway analyses implicate disease-associated genes in several types of pathways.<sup>38,39</sup> A meta-analysis by Wray et al. identified 44 variants associated with major depression risk; many of these variants were found in genes involved in regulatory networks, FMRP binding, synapse development and action, neuronal morphogenesis, differentiation, and maturation, calcium channels, immune response, and the retinoid X receptor.<sup>38</sup> Meta-analysis of GWAS of bipolar disorder and schizophrenia identified genes involved in circadian rhythm, immune systems, regulation of gene expression, synaptic plasticity, and neurodevelopment.<sup>39</sup>

### **2.1.3.1 Gene Expression Studies**

The majority of identified psychiatry-related polymorphisms lie in non-coding regions, so gene expression studies are used to elucidate the functionality of these genetic variants.<sup>40</sup> Gene set enrichment analysis (GSEA) is a method used to determine if significant differences in gene expression are present between two different phenotypes, i.e. affected versus unaffected.<sup>41</sup> GSEA has demonstrated the most significant enrichment of genetic variants related to psychiatric disorders in cortical tissues, particularly the prefrontal and anterior cingulate cortex, and that molecular pathways related to synaptic plasticity are highly enriched.<sup>40,42</sup> Other gene expression studies have found neurons are the cell types affected by some of the identified genetic variants, rather than astrocytes, microglia, or oligodendrocytes.<sup>38</sup> Gene expression studies of post-mortem brain tissue have illuminated functional effects of psychiatric disease-related SNPs, including post-transcriptional gene expression regulation, alternative splicing, and transcriptional regulation.<sup>40</sup> Darby et al. found that ribosomal genes were overexpressed in post-mortem brain tissue of individuals with a psychiatric disorder and that genes related to neuronal processing, signaling, endocytosis, and antigen processing were under-expressed.<sup>43</sup>

#### **2.1.4 Copy Number Variants**

Several rare CNVs, some large, have been associated with schizophrenia, bipolar disorder, and other neurodevelopmental disorders.<sup>44</sup> The first CNV associated with schizophrenia was the 22q11.2 microdeletion, causing DiGeorge syndrome; approximately one-third of individuals with the CNV developing schizophrenia or schizoaffective disorder.<sup>45</sup> The 22q11.2 microdeletion was later found to be associated with ADHD, anxiety, and autism spectrum disorder as well.<sup>46</sup> De novo CNVs have been found to be more strongly associated with sporadic schizophrenia than rare, inherited CNVs; in familial cases of schizophrenia, however, the rare inherited CNVs are more strongly associated, as would be expected.<sup>47</sup> These rare CNVs, including 1.q21.1, 15q13.3, and 22q11.2 deletions and 1q21.1, 15q11.2-q13.1, and 16p13.1 duplications, are somewhat less rare in other neurodevelopmental disorders, besides bipolar disorder.<sup>47</sup>

#### **2.1.5 Epigenetics**

Many studies of the effects of epigenetics on psychiatric conditions have been undertaken, illuminating some of the mechanisms by which environment and genetics interact in psychiatric pathophysiology. Tomassi et al. found childhood trauma affected methylation of several genes differently in healthy subjects than in subjects with first-episode psychosis.<sup>48</sup> The authors identified global hypomethylation, as well as differences in expression of specific genes in subjects with childhood trauma and first-episode psychosis versus healthy subjects. Other adverse life events such as parental loss, low socioeconomic status, and prenatal exposure to maternal stress can affect regulation of the stress hormone system, a possible explanation for how these events increase risk of developing psychiatric disorders, especially anxiety and depression.<sup>49</sup>

Furthermore, because the majority of SNPs found to be associated with psychiatric disorders lie in non-coding regions, these regions may be affecting development of disorders through epigenetic means, modifying the effects of life events on gene regulation.<sup>50</sup>

### **2.1.6 Autism Spectrum Disorders**

Individuals with autism spectrum disorders are frequently seen in pediatric genetic clinics, in part due to the difficulty determining the causes of individuals' conditions, hopes for interventions guided by genetic findings, concerns about recurrence, and the genetic conditions that often co-occur with ASDs.<sup>51,52</sup>

Rare CNVs and single nucleotide variants have been implicated in development of ASD, along with more common multifactorial factors and polymorphisms.<sup>53,54</sup> Individuals whose ASD is thought to be caused by rare gene variants and CNVs often have a syndrome that causes other psychical, behavioral, or intellectual symptoms; this is termed "syndromic autism."<sup>54</sup> Typically, these rarer variants have larger effects than the more common variants, which combine with other variants or factors.<sup>53,54</sup> Using SNP arrays and WES, Leblond et al. found more rare CNVs in exons, more homozygosity of rare deleterious variants, and higher inbreeding status in individuals with autism than controls.<sup>53</sup> A GWAS of information from the Psychiatric Genomics Consortium and the Danish iPSYCH project identified multiple loci significantly associated with ASDs.<sup>54</sup> Enrichment analysis by this study also revealed that some of the common variants associated with ASD are in the same genes as rare variants associated with ASD.<sup>54</sup>

### **2.1.6.1 Genetic Testing for Autism Spectrum Disorders**

Genetic counselors often see prenatal or preconception patients who have a previous child with ASD or a family history of ASD. Several national professional organizations recommend Fragile X testing and microarray as front-line evaluations for children with ASD.<sup>55</sup> Increasingly, medical geneticists are ordering whole exome sequencing (WES) for individuals with ASD, as diagnostic yields of WES for individuals with neurodevelopmental disorders and/or ASD are comparable or better than microarrays.<sup>51</sup> The diagnostic yield of microarrays ordered for individuals with either developmental delay, intellectual disability, ASD, or multiple congenital anomalies is 15-20%, whereas whole exome sequencing for individuals with any of these neurodevelopmental disorders is 26-29%.<sup>51</sup> For individuals with ASD specifically, the diagnostic yield of microarrays is 7-14%, and 8-20% if WES is ordered.<sup>51</sup>

With many overlaps found between ASD and other psychiatric disorders, ASD is increasingly recognized as not genetically and etiologically distinct from other disorders – diagnostic criteria and conceptualizations are beginning to evolve.<sup>52,56</sup> The DSM-5 eliminated subdivisions such as Asperger Syndrome in favor of autism spectrum disorder, which reflects the continuum along which individuals with autism may fall.<sup>55</sup> The diagnostic criteria for ASD also includes symptoms such as “neurodevelopmental, mental, or behavioral disorder” when determining severity, acknowledging their common co-occurrence.<sup>55</sup>

### **2.1.7 Developmental Brain Disorders**

A categorization of Developmental Brain Disorders (DBDs) encompasses all developmental, neurological, and psychiatric conditions that have impairments of cognition, motor

development, language, and behavior. This broader categorization reflects the idea that these conditions have varying degrees of dysfunction along a continuum of traits.<sup>52,56</sup>

Finucane et al. recommends study of DBDs using quantitative measurements of these traits, rather than dichotomous clinical diagnostic boundaries.<sup>52,56</sup> ASD and psychiatric or neurodevelopmental disorders co-occur often and share many of the same risk factors and genetic associations, so the distinction between DBDs may impair calculations of recurrence risks, and association studies could be more effective by reducing this separation.<sup>56</sup> Chaste et al. analyzed the Simons Simplex Collection for associations between SNPs and autism spectrum disorders in 2015.<sup>57</sup> The authors found that sub-phenotyping within ASD did not increase the power of significant association signals, showing that distinctions between different phenotypic presentations along a spectrum may not improve discovery of associated genetic variants.<sup>57</sup> In 2016, Gonzalez-Mantilla et al. also found that consideration of brain-related disorders as a group increased discovery of novel candidate genes.<sup>58</sup>

Distinctions between ASD, MDD, schizophrenia, epilepsy, and other DBDs may in fact impair interpretation of pedigree and variant analyses.<sup>56</sup> If an individual has a family history with different psychiatric disorders, a genetic counselor may not recognize that although there may not be multiple individuals with the same diagnoses, there could be a familial or heritable susceptibility to psychiatric disorders in general.<sup>56,57,59,60</sup> Similarly, if studies do not group psychiatric disorders when analyzing relationship between variants and psychiatric conditions, there may not be enough statistical power to identify true associations, whereas combining multiple disorders in the analysis could enable identification of variants that increase risk for multiple types of psychiatric conditions.<sup>58,59</sup>



Recurrence risks are also being redefined as distinctions between DBDs are rethought – if a family has one child with ASD, they have a 10% chance of having another child with ASD and a 38% chance of having another child with any neurodevelopmental or psychiatric disorder.<sup>61</sup> Childhood-onset disorders, such as tics, ADHD, intellectual disability, or oppositional disorders, are most strongly associated with ASD, while schizophrenia, affective disorders, and anxiety disorders are also associated, but to a lesser degree.<sup>61</sup> Findings like this can allow genetic counselors to more accurately provide recurrence risk information and discuss patient pedigrees.

The basis of this new conceptualization of psychiatric and neurodevelopmental disorders lies in the overlaps of genes and pathways implicated in their pathophysiologies, as well as their common co-morbidities.<sup>56</sup> For example, several studies have found shared genetic associations between depression, bipolar disorder, schizophrenia, autism, ADHD, epilepsy, and intellectual disabilities.<sup>40,41,62</sup> Correlations between major depressive disorder and body mass index, sleep quality, and educational attainment (although not IQ) provide new areas to investigate for possible etiologies and interventions.<sup>38</sup> Depression has also been linked to alcoholism historically by clinical presentations of comorbid major depressive disorder and alcohol dependence, and more recently by association of alcohol dependence with MDD polygenic risk scores calculated using the Psychiatric Genomics Consortium’s meta-analysis.<sup>63,64</sup>

### **2.1.8 Polygenic Risk Scores**

As there are many risk factors yet unidentified for psychiatric conditions, risk calculations are complicated. Research is, however, attempting to clarify these risks, with goals of developing polygenic risk scores with more predictive power, as well as polygenic risk scores encompassing non-genetic and genetic factors.<sup>65</sup> Because schizophrenia, bipolar disorder, and ASD have such

high heritabilities (73-90%, 80-85%, and 64-91%, respectively) they may be more suitable for polygenic risk scores than other, less heritable psychiatric disorders, such as major depression and generalized anxiety disorders.<sup>27,29,30,31,32,66</sup> Large sample sizes are necessary for accurate risk prediction, so as more individuals are enrolled in studies and more samples are collected, current risk estimates will become more accurate and clinically relevant.<sup>67</sup> Researchers have calculated polygenic risk scores, but further studies of accuracy, utility, wide applicability, and replicability will be important for decisions about clinical use.<sup>68,69</sup> Musliner et al. used genotype information from the Danish iPSYCH2012 study and the Psychiatric Genomics Consortium to calculate polygenic risk scores for major depression, bipolar disorder, and schizophrenia.<sup>70</sup> They found that an increase of one standard deviation in polygenic risk scores corresponded to a 30% increase in risk for major depression, 5% increase in risk for bipolar disorder, and 12% increase in risk for schizophrenia.<sup>70</sup>

De Jong et al. analyzed polygenic risk scores in a 260-person pedigree with approximately one-third of individuals diagnosed with either major depression or bipolar disorder.<sup>68</sup> Anticipation, ascertainment effects, and assortative mating, with married-in individuals more likely than the general population to have a psychiatric condition, may have contributed to the observed increase of psychiatric disorders over generations.<sup>68</sup> The authors concluded that polygenic risk scores in this study were primarily useful for identifying effects and patterns of the anticipation and assortative mating.<sup>68</sup> The International Society of Psychiatric Genetics has determined that there is not currently clear clinical utility for such polygenic risk scores, as part of their recommendations regarding psychiatric genetics clinical practices.<sup>69</sup>

## 2.2 Pharmacogenetics

Increased knowledge and research in pharmacogenetics is becoming an increasingly important factor in psychiatric genetic counseling, particularly as precision medicine is increasingly strived for in research and clinical practice. The Precision Medicine Initiative and the All of Us Research Program are large scale efforts to gather physical samples and health information from individuals across the nation, with the intent to better tailor research and treatment to individuals and groups.<sup>71,72</sup> The All of Us Research Program is particularly aiming to include individuals from populations and communities that have historically been underrepresented in research.<sup>72</sup> This will enable more accurate studies and treatments for people outside of the most common research populations. The Precision Medicine Initiative aims to use its wide reach to enable studies with large sample sizes to develop treatment, therapies, preventions, and accurate diagnoses to more effectively help individuals based on their specific characteristics, such as genotypes.<sup>71</sup>

CYP2C19 and cytochrome P450 variations for example, have been shown to affect metabolism of several different drugs, including antidepressants and antipsychotics.<sup>73,74</sup> Although there is some understanding of variants' effects on drug metabolism, tests to assess drug suitability based on genotype are not currently routinely used in psychiatry, partly due to the paucity of large studies of testing utility, efficacy, and reliability.<sup>75,76,77,78</sup> Although there are approximately 40 commercially available pharmacogenetic tests, only nine have been subject to published clinical studies, and there is wide variability in the variants and genes assessed by different test kits.<sup>79,80,81</sup> Randomized controlled trials have been performed for five of these kits: GeneSight, CNSDose, Genelex, Neuropharmagen, and NeuroIDgenetix.<sup>81</sup> These trials found borderline significant increased response rates for individuals who underwent pharmacogenetic testing, higher rates of

remission and response, and somewhat lower fewer side effects, although not all of these trials used power analysis to estimate required sample size, blinded prescribers and raters, or provided information about individuals who dropped out of the trials.<sup>81</sup>

Identification by genetic studies of potential targets for new drug therapies is highly anticipated. In 2017, Pan et al. identified metabolic abnormalities in the cerebrospinal fluid of 21 out of 33 patients with treatment-refractory depression, particularly deficiencies in tetrahydrobiopterin, a cofactor required for synthesis of serotonin, and 5-MTHF, a product of folic acid required for formation of amino acid methionine.<sup>82</sup> When synthetic analogues of the patients' deficient biochemicals were supplemented (sapropterin and folinic acid) patients improved significantly. Individuals who had been catatonic or had recurrent suicidal ideations and suicide attempts even after numerous trials of antidepressants, electroconvulsive shock therapy, and other interventions, had reduced depressive symptoms after supplementation, some with full remission.<sup>82</sup> Identification of associated gene variants could allow future development of tests to determine if individual patients could be helped by this method of supplementation.<sup>82</sup> The success of this approach exemplifies the novel methods of psychiatric pharmacotherapy that can arise from new research into the genetic etiologies of psychiatric disorders.

SNPs associated with side effects of antipsychotics, antidepressants, and other medications have also been discovered.<sup>83</sup> Other pharmacogenetic studies involve identifying genetic predictors of treatment response or prognosis.<sup>84,85</sup> Zwicker et al. developed a polygenic risk score calculation for C-reactive protein that was associated with an improved response to escitalopram and worsened response to nortriptyline.<sup>85</sup> This finding also points toward investigation of the effects of inflammation on antidepressant response. Many studies are searching for genes and loci associated with effects of lithium treatment on bipolar disorder, but conclusive findings predicting treatment

response have not been proven.<sup>85</sup> Not all studies are focused on response to medication - Roberts et al. suggested associations between genes and psychological therapy outcomes.<sup>86</sup> As more findings enable prescribers to select the most suitable drug and therapy treatments, psychiatric genetic counseling will likely expand to regularly include pharmacogenetic testing.

## **2.3 Psychiatric Genetic Counseling**

### **2.3.1 History of Psychiatric Genetic Counseling**

Psychiatric genetic counseling grew out of early acknowledgement of heritability of psychiatric disorders, identification of loci and genes associated with psychiatric disorders, and understanding that genetics and treatment interact.<sup>3</sup> As information became available, psychiatric genetics became of interest to genetic counselors and their patients. A survey of the National Society of Genetic Counselors in 1995 revealed that 96% of respondents expected growth of the field of psychiatric genetic counseling.<sup>87</sup> Finn and Smoller predicted in 2006 that identification of risk genes would increase demand for genetic counseling and explored possible roles of genetic counseling in psychiatry.<sup>88</sup> The authors identified potential issues, particularly the uncertainty of risk estimates and questionable utility of testing, and espoused the necessity of genetics education for clinicians.<sup>88</sup> Beliefs about causes of mental illness have been shown to affect adaptation to illness, indicating that education and/or counseling may benefit patients.<sup>89</sup> Phelan et al. used the 1996 General Social Survey and the Genes, Disease, and Stigma study to look at associations between how people perceive the genetic etiologies of depression and schizophrenia and their perceptions of treatment recommendations and effectiveness.<sup>89</sup> The 1996 General Social Survey

presented vignettes describing individuals with schizophrenia or depression to over 600 randomly chosen respondents nationwide. Respondents answered how likely they thought it was that the mental health issues described had a genetic cause, what their treatment recommendations were, and how effective they thought the treatment would be.<sup>89</sup> The Genes, Disease, and Stigma study was conducted similarly, but each vignette included a hospital expert attributing the individuals' mental illness to genetic factors, partly to genetic factors, or not due to genetic factors. Respondents answered what their treatment recommendations were and how effective they thought the treatment would be. The authors determined that perceptions of genetic causes of mental illnesses appeared to encourage individuals to seek more extreme interventions, such as medication or hospitalization, as well as lead to doubtful expectations of intervention effectiveness.<sup>89</sup> This study suggested that knowledge of genetic causes of psychiatric conditions may increase individuals' likelihood of seeking treatment for their mental illnesses.<sup>89</sup> Lyus 2007 surveyed individuals with schizophrenia and their family members about their awareness of genetic counseling and how useful they thought it could be.<sup>90</sup> Lyus found the majority of participants thought genetic counseling would be useful to them, and that none of the individuals with schizophrenia and only 5% of their relatives had received genetic counseling.<sup>90</sup>

The British Columbia Provincial Medical Genetics program (BCPMG) was formed in 1968, and as the sole provider of psychiatric genetic counseling in British Columbia, a study of its referrals for psychiatric genetic counseling due to a primary indication of schizophrenia provided a good indication of psychiatric genetic counseling demand over approximately four decades.<sup>91</sup> Between 1968 and 2007 in British Columbia, there were 288 referrals for psychiatric genetic counseling.<sup>91</sup> These referrals usually involved a relative of an affected individual and were typically for preconception genetic counseling. Referrals peaked between 1988 and 1992, possibly

due to the launch of the Human Genome Project or publicized research linking schizophrenia with a location on chromosome 5. Referrals did not increase over time as expected by the authors, perhaps due to lack of awareness, access, stigma of mental illness, or other healthcare professionals providing genetic counseling.<sup>92</sup>

### **2.3.1.1 Psychiatric Genetic Counseling Clinics**

Austin et al. in 2008 investigated the usefulness of psychiatric genetic counseling for unaffected parents of individuals with psychotic disorders and found that almost all participants found the genetic counseling session useful, and their concerns about recurrence were reduced.<sup>3</sup> Patients and family members were interested in genetic counseling for psychiatric disorders, but few utilized the psychiatric genetic counseling that was available, such as that at the BCPMG.<sup>12,86,87,93</sup> Positive outcomes, high demand, low supply, and assumed lack of awareness of how to access the service, led to the opening of the first clinic specializing in psychiatric genetic counseling in 2012, in British Columbia.<sup>4</sup>

There are currently two specialized psychiatric genetic counseling clinics – one in Canada, and one in the United States – but genetic counselors in other clinics also provide psychiatric genetic counseling.<sup>94</sup> According to the National Society of Genetic Counselors 2019 Professional Status Survey, there are fifteen genetic counselors whose primary specialty is psychiatric genetic counseling, making up 1% of the genetic counselors in the survey.<sup>95</sup> Without widely accepted polygenic risk score calculations and guidelines for genetic testing for psychiatric conditions, genetic counselors focus more strongly on the psychological impacts of understanding the heritability of mental health disorders and discussion of recurrence risks based on family history.<sup>1,59</sup>

### 2.3.2 Outcomes and Practice

Although psychiatric genetic counseling is a recently developed field, studies have been done to assess its utility and efficacy. In 2018, Low et al. used a survey to assess the perceived preparedness of 286 current students and recent graduates of genetic counseling training programs to provide psychiatric genetic counseling.<sup>17</sup> Two respondents expressed that psychiatric genetic counseling or education about psychiatric genetic counseling may not be appropriate without the availability of further genetic testing and concrete recurrence risk information.<sup>17</sup> Some genetic counselors have reported hesitancy, or feelings that the information's complexity and uncertainty could be confusing for patients, particularly without adequate time to work with patients.<sup>17,96</sup> Nevertheless, when Hippman et al. surveyed 37 patients with serious mental illnesses after they received genetic counseling, twice as many patients reported being unconcerned with uncertainty as reported being concerned, and they found the genetic counseling helpful.<sup>96</sup> Despite the limitations of time, concrete risk numbers, and clinical use of genetic testing for psychiatric disorders, genetic counseling can be beneficial.<sup>96</sup>

Genetic counseling also clarified perceptions of risk for patients and family members. Individuals tended to overestimate recurrence risks.<sup>96</sup> In a study of parents of individuals with psychotic disorders who received genetic counseling, almost all found the genetic counseling useful, reported reduced concern for other relatives, had higher perceived control, and had an improved understanding of mental health.<sup>3</sup>

Alleviation of guilt and shame, relief at finding an explanation, and increased comfort and willingness to discuss mental health have been significant psychological benefits of psychiatric genetic counseling, demonstrated in studies of psychiatric genetic counseling clinics.<sup>3,4,16,96,97,98</sup> Patients' empowerment and self-efficacy were also improved, both in psychiatric genetic clinics



and in prenatal counseling.<sup>99</sup> Costain et al. studied 35 subjects with schizophrenia before and after genetic counseling.<sup>4</sup> Genetic counseling improved these subjects' accuracy of recurrence risk estimation, understanding of the etiology of schizophrenia, and reduced stigma and blame.<sup>4</sup> Costain et al. conducted another, similar study, on 78 family members of individuals with schizophrenia.<sup>100</sup> Post-counseling, these family members also had improved knowledge and decreased stigma.<sup>100</sup>

Feelings of family vulnerability and use of coping mechanisms were examined by Peay et al. using interviews with 48 individuals with bipolar disorder, as well as with their parents and siblings.<sup>101</sup> Participants indicated desire and attempts to modify risk for relatives and used monitoring and cognitive distancing to cope with feelings of vulnerability.<sup>101</sup> Parents with bipolar disorder themselves reported monitoring their children and feeling more control after genetic counseling, but no reduction in worrying.<sup>102</sup> Families and affected individuals thought education and psychological support were useful but were uncertain about the benefits of risk assessment.<sup>90,101,105</sup> These findings suggest that focusing on causes of mental illness, risk modification options, reproductive options and decisions, early intervention, and healthy coping mechanisms are some areas in which psychiatric genetic counseling could help families.

There can be drawbacks to discussing psychiatric genetics as well, such as fear, fatalism, over-medicalization, "geneticization," and increased anxiety.<sup>12,103,104</sup> Parents of children with 22q11 deletion syndrome reported that risk of psychotic illness was "their greatest source of anxiety."<sup>105</sup> Most of these parents were not provided information about association with psychiatric disease at time of diagnosis, and rarely after diagnosis.<sup>105</sup> Instead, parents reported gathering much of their information from non-medical sources, especially the internet.<sup>105</sup> The finding that oversimplified ideas about risk were associated with deciding to have fewer children

and positive attitudes toward genetic testing emphasizes the necessity of ensuring patients and their families are fully informed.<sup>106</sup> Furthermore, some patients find that a greater understanding of how psychiatric illnesses develop is helpful in reducing the stigma of mental illness.<sup>2</sup> Other patients may find that genetics' role in mental illness and the classification of "disease" is frightening.<sup>12,106</sup> These studies highlight the need to improve information, resources, and support for families with psychiatric disorders.

Some resources have been created to help genetic counselors learn to provide this information and support, such as Jehannine Austin's continuing education activity for healthcare professionals to increase their understanding of mental illnesses and improve patient experience.<sup>107</sup> In this activity, she introduced genetic counseling and psychiatric genetic counseling, then used her experience from the British Columbia psychiatric genetic counseling clinic to describe how one should ascertain a patient's current understanding and perceptions about their mental health and mental health in general, as insight into the patient's mindset and any misconceptions aid in tailoring the session toward their situation, interest, and knowledge level, as well as correcting misconceptions. She also explains that one should gather tailored personal and family history information to allow for discussion of possible contributing factors to psychiatric disorders, including heritability, as well as strategies for treating, protecting, or dealing with their mental health. Along with discussing recurrence risks and other factual information, she describes counselors' aim to identify and address emotional issues around patients' or family members' psychiatric conditions. Austin also explained that psychiatric genetic counseling can lead to increased empowerment and self-efficacy as well as increased willingness to pursue talk therapy and medications.<sup>107</sup>

### **2.3.3 Effects on Management**

#### **2.3.3.1 Management of Nonpsychiatric Multifactorial Conditions**

As few studies have measured the effects of psychiatric genetic counseling on adherence to or initiating treatment, effects of genetic information about other complex diseases may provide useful information. Vorderstrasse et al. evaluated how personalized counseling about risk assessment for US Air Force retirees and beneficiaries at risk for type 2 diabetes and coronary heart disease along with health coaching affected adherence to health recommendations.<sup>108</sup> Half of the 200 participants' risk counseling involved genetic testing. The study suggests personalized risk assessment may increase adherence, and that using genetic testing to further personalize the assessment may increase adherence even more.<sup>108</sup>

Dar-Nimrod et al. found that individuals who learned about genetic effects on obesity subsequently ate more, suggesting the influence of genetic fatalism.<sup>109</sup> Conversely, patients told they did not have genes increasing their predisposition to obesity considered health actions less important and chose unhealthier foods, suggesting influence of genetic invincibility.<sup>110</sup> Ideas about genetic etiology influenced how much control individuals felt over their weight, and therefore influenced how much they ate.<sup>109,110</sup>

A 2013 study of carriers of genetic risk factors for melanoma revealed that following delivery of results, unaffected carriers adhered better to recommendations for skin examinations, while noncarriers' adherence decreased.<sup>111</sup> Affected carriers' and noncarriers' adherence did not change significantly. In 2015, Aspinwall et al. measured perceived control ratings in individuals with positive family histories of melanoma.<sup>112</sup> The genetic counseling sessions in this study emphasized ways to reduce risk and detect melanoma early and explained residual risk for noncarriers.<sup>112</sup> This focus on risk education and helpful actions may explain why noncarriers and

unaffected carriers reported increased perceived control, in addition to carriers. Approximately 45% of participants reported increased perceived control, while only 16.67% reported decreased perceived control.

Cameron et al. discusses strategies to present information about genetic testing and risk-reducing or -enhancing behaviors to individuals with an increased risk of colon cancer. Different modes were used to provide information regarding low-fat diets' effect on risk given genotype. Recipients of all modes reported higher comprehension and higher belief that low-fat diets reduce risk of colon cancer, as well as lower perceived risk from positive test results.<sup>113</sup>

Although it is not multifactorial, Marteau et al. found in another study that patients with clinically-diagnosed familial hypercholesterolemia and their families did not feel less control following genetic testing and did not change adherence.<sup>114</sup> Individuals with positive genetic testing did have altered perceptions of cholesterol-lowering methods, ascribing more importance to cholesterol-lowering medications and less importance to diet.<sup>114</sup> These studies of nonpsychiatric conditions reveal an important consideration for psychiatric genetic counseling: delivering information about nongenetic etiologies and risk reduction methods along with genetic etiologies and genetic test results may reduce patients' feelings of fatalism or genetic determinism.

### **2.3.3.2 Management of Psychiatric Conditions**

Of course, obesity, melanoma, and colon cancer each have some specific guidelines to reduce risk. The National Comprehensive Cancer Network, for example, has published guidelines for evaluation, surveillance, and management of individuals at increased risk for colon cancer.<sup>115</sup> Although there are not clear-cut guidelines on risk-reduction methods for unaffected or mildly affected individuals regarding psychiatric disorders, there are some recommendations of things that may be done or avoided to adjust risk. Basic self-care such as healthy eating, exercise, and

good sleep habits are suggested, as well as more psychological self-care, such as meditation, self-reflection, healthy social connections, and other methods of coping with stress or struggles.<sup>116,117</sup> Pursuing talk, music, art, bright light, or other therapy can be valuable for individuals at risk for mental illness.<sup>118</sup> Individuals at higher risk for psychosis may wish to avoid certain drugs, illicit or prescription, known to trigger episodes of psychosis, particularly methamphetamines, cannabis, and cocaine.<sup>119</sup>

Awareness of risk for psychiatric illnesses can also prompt individuals or family members to be alert to early signs of disease.<sup>120,121,122,123</sup> Early detection and intervention, as well as familiarity and comfort discussing mental illness, can have significant positive effects on prognosis.<sup>120,121</sup> Lebowitz et al. assessed participants with depressive symptoms' ideas about causes of their mental health symptoms and expected duration of mental health symptoms.<sup>104</sup> The authors found that individuals with depressive symptoms who endorsed biochemical and genetic etiologies of depression reported longer expected symptom duration than those who assigned higher attributions to other etiologies; however, when subsequent education emphasized the pliable nature of genetics' and neurochemistry's effects, participants' pessimism, agency, and hopelessness improved.<sup>104</sup> These attitudes can be very important to patient outcomes. Hippman et al. divided participants with diagnoses of schizophrenia, bipolar disorder, or schizoaffective disorder into three groups: one group received genetic counseling, one group read an educational booklet with the same information the genetic counselor provided, and one group was put on a waitlist.<sup>16</sup> Each group completed a questionnaire prior to receiving genetic counseling or the educational booklet (baseline), immediately after the intervention, and one month after intervention. The waitlist group was assessed with questionnaires for their baseline and pre-intervention measures on the same day. The study demonstrated that both genetic counseling and

an educational booklet increased patient knowledge, but only genetic counseling improved the accuracy of patients' risk perceptions.<sup>16</sup>

Patients with schizophrenia found to have no clinically relevant genetic variant initially overestimated recurrence risk, had high concern about this risk, had incorrect knowledge about schizophrenia, and felt self-blame.<sup>16</sup> Post-counseling assessments showed improvement in all measures. Patients were satisfied and saw the need for this counseling. Family members of individuals with schizophrenia also overestimated recurrence risk, and after counseling had more accurate risk perceptions and lower concern about recurrence, along with increased knowledge and decreased stigma.<sup>16</sup>

## **2.4 Provider Attitudes**

With possibilities of both positive and negative effects on patients, some genetic counselors are hesitant to adopt psychiatric genetic counseling.<sup>17,96</sup> Furthermore, although information about risk and recurrence is increasing, specific risk numbers are difficult to determine.<sup>69,96</sup>

A study focusing on recent graduates and current students found significant associations between perceived preparedness to deliver psychiatric genetic counseling and frequency of psychiatric genetic counseling instruction, active opportunities to practice, and education about referrals and patient resources.<sup>17</sup> Approximately half of the respondents (48.5%) reported feeling “somewhat” or “very” prepared to provide psychiatric genetic counseling. However, many of the recent graduates (37.6%) felt their training programs' education about psychiatric genetics was “inadequate.” Those who reported learning about providing patient resources and referrals were more likely to feel prepared for psychiatric genetic counseling. Of the practicing respondents,

approximately half had provided resources or referrals.<sup>17</sup> From these findings, it is clear that further development and dispersal of patient-oriented resources, and education regarding these resources, would be beneficial to genetic counselors' preparedness. Currently, there are few resources for patients with rare CNVs and SNVs or newly found common variants. The study also examined stigma and stereotype; respondents who had personal experience with mental health issues or exposure via volunteering, family members, friends, or other means presented lower measurements of desire for social distance from individuals with psychiatric disorders.<sup>17</sup>

One issue some genetic counselors identify in psychiatric genetic counseling is that typical genetic counseling systems often involve a single appointment. They worry that without a longer-term relationship or multiple sessions, such a complex, personal, and sensitive subject cannot be addressed with the proper depth or therapeutic techniques.<sup>17</sup>

Other studies have found that attitudes toward and perceptions of mental illness greatly impact how healthcare providers interact with patients in regard to mental health.<sup>124,125,126</sup> Perceived usefulness and perceived complexity also influence decisions to adopt newly developed methodology, more so than knowledge and ease of use, as determined by surveying members of the NSGC Cancer Special Interest Group.<sup>127</sup> This survey identified that more experienced genetic counselors were more likely to intend use of refined cancer risk estimates than more recent graduates.<sup>127</sup> It is possible this is due to differences in confidence of clinical skills and patient interactions. Evaluation of physicians' decisions to refer patients to psychiatric genetic counseling showed that referrals were influenced by ideas about the purpose of psychiatric genetic counseling and patient cues, as well as confidence in knowledge base.<sup>125,128</sup>

## 2.5 Continuing Education

With genetic counseling training programs providing different types of education and practice in the field of psychiatric genetic counseling, and many genetic counselors having graduated from programs prior to this era of psychiatric genetics, continuing education and exposure to current knowledge is very important. Continuing education is required for licensed/certified genetic counselors, but psychiatric genetic counseling may be underrepresented in continuing education opportunities. Nonetheless, this emerging field has attention and interest, and conferences, online courses, and journal articles are increasingly available.<sup>129,130</sup>

The Educational Breakout Session presented by the Psychiatric Special Interest Group of the National Society of Genetic Counselors (NSGC) at the 2006 Annual Education Conference created a two-part Professional Development series to guide genetic counselors in taking family histories and conceptualizing recurrence risks in relation to psychiatric disorders, including case simulations.<sup>59,60</sup> The uncertainty associated with psychiatric disorders' etiology, type, severity, diagnostic criteria, and risk is an important consideration, but does not preclude benefits from genetic counseling. This series recommends discussion of how genetics and environment affect development of psychiatric diseases, along with the way these interact.<sup>59,60</sup>

Ascertaining a client's preexisting understanding of the etiology of psychiatric disorders, ideas about control over management and risk-reduction, risk perceptions, and attitudes about mental illness is necessary to combat misinformation, blame, genetic determinism, and stigma. The NSGC Professional Development series reminds genetic counselors that they routinely deal with these same issues in relation to other genetically related conditions and can utilize these methods and skills throughout genetic counseling, such as contracting, awareness of client



reactions, assessing client decision-making methods, assessing client comprehension, and anticipatory guidance.

This series also emphasizes the importance of self-reflection and self-awareness regarding attitudes, knowledge, and confidence about mental illness, psychiatric disorders, and their genetic etiologies. This will allow genetic counselors to adapt attitudes and practices or seek additional education or information as needed. There are suggestions of how to use risk information to assess and convey individual risk. This series is a valuable tool for genetic counselors who encounter patients with personal or family histories of psychiatric disorders.

Edwards et al. evaluated the outcomes of communication methods used to discuss risk with clients in 28 studies, including studies that used communication models or decision aids.<sup>131</sup> The majority of these studies addressed risks related to cancer genetics. The authors found that the supportive and emotional elements of counseling were more beneficial to clients than the educational elements.<sup>131</sup>

Of course, genetic counselors are not the only medical professionals who will provide information about psychiatric genetics. Education for other healthcare providers is important as well – including psychiatrists, primary care physicians, pediatricians, pharmacists, and specialists. German et al.'s study of pharmacists compared their training and experience to perceived preparedness to provide pharmacotherapy regarding psychiatric disorders.<sup>124</sup> The pharmacists with specialized training and experience in psychiatric pharmacy reported higher preparedness and fewer barriers to providing pharmacotherapy than pharmacists without specialized training or experience. Some of the barriers reported were time, lack of a private consultation area, and reimbursement for services. Pharmacists with specialized training and experience were more likely to provide services to patients with psychiatric disorders.<sup>124</sup> These findings highlight the

importance of education and training for healthcare professionals who will work with individuals with psychiatric disorders. The finding that even pharmacists with training and/or experience in pharmacotherapy did not feel prepared to utilize online resources with up-to-date information about treating psychiatric disorders reiterates the need for more patient and provider resources about psychiatric genetics and associated pharmacogenetics.<sup>124</sup>

Professional organizations, such as the International Society of Psychiatric Genetics, have developed recommendations for training programs and knowledge for their medical professionals to remain up-to-date, relevant, and prepared for the growing field of psychiatric genetics.<sup>132</sup> The National Society of Genetic Counselors has developed psychiatric genetics resources for provider education, such as an online course, “Psychiatric Genetics across Genetic counseling Practice Settings,” as well as patient resources, including a section in “Making Sense of Your Genes: A Guide to Genetic counseling.”<sup>129,133</sup> In this modern era, sources such as webinars, podcasts, blogs, social media, and other Internet-based learning have become significant sources of information for genetic counselors and other medical professionals.<sup>134,135,136</sup> More traditional forms of education are, however, still widely used.

In 2003, Maio et al. found that pharmacists primarily used printed materials for continuing education, followed by lectures and seminars, Internet materials, and less frequently, symposia.<sup>137</sup> De Leo et al. assessed physicians’ consultation of websites for medical information.<sup>138</sup> Physicians reported primarily using targeted websites rather than search engines, particularly secondary data sources such as Up-toDdate, Medscape, or Webmd, research databases with access to medical journals such as Pubmed or Ovid, specialized sites, or medical web portals such as Mercmedicus. The landscape of the internet has changed significantly since 2006, so an update to these assessments would be valuable.

Grierson et al. touts video-based observation in combination with practice, self-assessment, expert feedback, and peer-to-peer feedback for effective improvement in student nurses' learning of clinical skills.<sup>139</sup> Internet-based learning for a variety of healthcare professionals had significant effects on educational outcomes, more so than traditional instruction.<sup>139</sup> Web-based learning encompasses a variety of methods, including written text, multimedia, chat or videoconferencing, patient cases, and self-assessment.<sup>135</sup> Electronic continuing education was effective when it involved other components, but not when involving only text. This supports conclusions that further engagement or hands-on activity are of considerable importance in education.<sup>139</sup> These studies all suggest that more interactive, nontraditional training and educational resources are necessary to improve clinician knowledge and clinical practice. Increasing the effectiveness of continuing education is important for many professions, especially psychiatric genetic counseling.

Studies of the efficacy and utility of continuing education in medical professions have had mixed results. Increased knowledge, skills, attitudes, and patient outcomes have been demonstrated, but these do not always correlate with changes to clinical practice.<sup>140,141</sup> O'Brien et al. found that while interactive workshops led to changes in practice, didactic sessions did not.<sup>141</sup> Forsetlund et al. found educational meetings could improve practice and healthcare outcomes, but were not likely to change complex behaviors.<sup>142</sup>

In Low et al.'s study, active education and practice in providing psychiatric genetic counseling were associated with feeling prepared to engage in psychiatric genetic counseling when surveying current students and recent graduates.<sup>17</sup> Exposure to clinical observations or practice, engagement with individuals with mental illness, and role plays or activities were significant in increasing levels of preparedness and reducing stigma towards mental illness.<sup>17</sup>

## 2.6 Study Goals

As evidenced in the literature, a wealth of new information is available regarding the interaction of genetics and psychiatry. Researchers and clinicians are working to integrate this new information into clinical practice, and psychiatric genetic counseling in particular is a developing field with significant potential to improve health care for patients with mental illness. Although studies have shown the utility of specialized psychiatric genetic counseling, patient and clinicians' interest in psychiatric genetic counseling, and new applications of genetic testing, pharmacogenetics, and risk calculations for psychiatric conditions, this thesis project aims to investigate genetic counselors' current practices and confidence regarding psychiatric genetics, as well as the factors that affect their practice and confidence, in order to determine what resources and information would benefit genetic counselors and their patients with personal or family histories of psychiatric conditions. Ideally, this understanding will direct future research on development of training programs, continuing education, and patient and provider resources.

### 3.0 Manuscript

#### 3.1 Background

The origins of psychiatric disorders have been studied since the inception of the field of psychiatry. From observations of familial clustering to early family and twin studies, the strength of genetic and environmental contributions has been investigated. Family and twin studies have been used to calculate the heritability of psychiatric disorders and autism spectrum disorder, finding that schizophrenia, bipolar disorder, and ASD have large genetic sources (approximately 60-90%), while other conditions like depression and anxiety, are approximately 30-40% heritable.<sup>29,29,30,31</sup>

Findings from family studies, hypothesis-driven candidate gene studies, and linkage analysis studies proved the complex, heterogenous nature of psychiatric disorders.<sup>28,29,30,31,35</sup> These have been followed by newer methods such as genome-wide association studies, pathway analyses, and gene expression analyses, allowing for discovery of genetic variants and epigenetic changes associated with ASD, depression, anxiety, schizophrenia, bipolar disorder, and other psychiatric disorders.<sup>34,38,39,40,41,42,43</sup> Researchers are attempting to clarify risks calculations for psychiatric disorders, aiming to improve risk polygenic risk scores and identify risk factors yet unidentified for psychiatric conditions.<sup>65,66,67,68</sup> Applicability of pharmacogenetic tests to psychiatric conditions is also being investigated, with need for more studies of testing utility, efficacy, and reliability before widespread use.<sup>77,78,77,78,79</sup> Development of new drug therapies based on genetic studies is highly anticipated.<sup>78</sup>

With approximately 19% of the United States population suffering from a mental illness and increased public health attention, research on psychiatric genetics and care of individuals with mental illness are in growing demand.<sup>5,8</sup> The role of genetic counselors in psychiatry is growing and changing, due to knowledge improving on psychiatric illness pathophysiology, genes, loci, and epigenetics involved in mental health, clearer heritability and recurrence risk estimations, and pharmacogenomics. With increasing knowledge and public interest in psychiatric genetics, the field of psychiatric genetic counseling developed. Dedicated psychiatric genetic counseling clinics and genetic counselors in other specialties have begun to work with patients and families with histories of mental illness, and studies have revealed positive outcomes of these clinics.<sup>3,4,97,98</sup>

ASD is being recognized as having overlapping etiologies and occurrences with other neurodevelopmental and psychiatric disorders, and ASD itself is considered a continuum of traits and severity.<sup>52,56</sup> Developmental Brain Disorders (DBDs) has been proposed as a continuous category encompassing all developmental, neurological, and psychiatric conditions that have impairments of cognition, motor development, language, and behavior. This new conceptualization of psychiatric and neurodevelopmental disorders arose from discovery of overlapping genes and pathways implicated in their pathophysiologies, as well as their common co-morbidities.<sup>52,56</sup>

Although uncertainty is still present in discussions of risk for psychiatric disorders, recipients of psychiatric genetic counseling have demonstrated more accurate risk perceptions, reduced concern, improved understanding of mental health, as well as alleviation of guilt and shame, relief at finding an explanation, and increased comfort and willingness to discuss mental health.<sup>3,4,97,98,99</sup> Patients' empowerment and self-efficacy are also improved.<sup>99,100</sup> Studies have

highlighted the need to improve information, resources, and support for families with psychiatric disorders.<sup>3,105</sup>

While the provision of genetic counseling for psychiatric genetics is still relatively new, studies of genetic counseling for nonpsychiatric multifactorial conditions suggest personalized risk assessment for individuals at risk for type 2 diabetes and coronary heart disease may increase adherence to treatment protocols, and that using genetic testing to further personalize the assessment may increase adherence even more.<sup>108</sup> Another study found that patients with familial hypercholesterolemia and their families did not change adherence, but did have altered perceptions of cholesterol-lowering methods.<sup>109</sup> Genetic fatalism and genetic invincibility are concerns, but focus on risk education and helpful actions can increase perceived control.<sup>110</sup>

Although there are not yet guidelines on risk-reduction methods for individuals identified to have increased risk for psychiatric disorders from genetic tests, healthy eating, exercise, good sleep habits, meditation, yoga, self-reflection, healthy social connections, and therapy can be emphasized to maintain mental health.<sup>116,117,118</sup> Awareness of risk for psychiatric illnesses can also aid early detection and intervention, as well as familiarity and comfort discussing mental illness, can have significant positive effects on prognosis.<sup>121,122,123</sup>

With possibilities of both positive and negative effects on patients and uncertainty of risk estimates, some genetic counselors are hesitant to adopt psychiatric genetic counseling.<sup>17</sup> Low et al.'s survey of current and recent genetic counseling students revealed that genetic counseling training programs, access to patient resources, and attitudes toward mental health have been shown to affect preparedness and willingness to provide counseling for psychiatric genetic disorders.<sup>17</sup>

Conferences, online courses, and journal articles are increasingly available to supplement genetic counselors' knowledge of psychiatric genetics, with professional development series, continuing education activities, an online course by NSGC, and patient resources.<sup>59,60,129,133</sup>

The purpose of this study is to investigate genetic counselors' current practices and confidence regarding psychiatric genetics, as well as the factors that affect their practice and confidence. This will help determine what resources and information would benefit genetic counselors and their patients with personal or family histories of psychiatric conditions.



## 3.2 Methods

### 3.2.1 Sample

An anonymous survey was distributed through the National Society of Genetic Counselors (NSGC) email listserv in a weekly email notifying the membership of student research surveys. NSGC has over 4000 members, but the exact number of members on this email listserv is not available.<sup>95</sup> The first email went out on June 19, 2019, with a reminder email sent on July 3, 2019. All current genetic counselors, regardless of current practice area, were invited to participate between June 19, 2019 and July 10, 2019. This study was approved as exempt by the University of Pittsburgh Institutional Review Board (IRB), Study #19050028 (see Appendix A for IRB approval letter)

### 3.2.2 Survey

A survey containing 25 questions was developed with consideration of several studies that also assessed medical professionals' attitudes, perceived preparedness, and decision-making in relation to psychiatric diseases.

Leach et al.'s 2016 survey investigated how physicians decide whether to refer patients for psychiatric genetic counseling, which influenced development on questions about important factors in decision-making.<sup>125</sup> Phokeo et al. questioned pharmacists' attitudes toward and interactions with patients prescribed psychiatric medications, which, along with a study from Durham in 2019 and two unpublished University of Pittsburgh genetic counseling students' theses, informed questions about medical professionals' practices.<sup>126,143</sup> A survey by German et al.

completed in 2018 assessed how prepared pharmacists felt to treat patients with psychiatric disorders, and Low et al.'s 2018 survey investigated relationships between perceived preparedness, attitudes toward mental illness, personal experiences, and training in recent graduates and current students of genetic counseling training programs.<sup>17,124</sup> Both studies were consulted for development of questions about confidence, preparedness, and educational methods.

The electronic survey was constructed with the University of Pittsburgh Qualtrics system and utilized skip logic (see Appendix B for full survey). Demographic information was collected first, including gender, graduation decade, region, and specialty. Subsequent multiple-choice questions assessed participants' practices when interacting with patients who have personal and/or family histories of psychiatric disorders. For example, participants were asked whether they had ever referred a patient for psychiatric genetic counseling. A six-item, 4-point Likert-type scale then asked participants to indicate how much each factor listed influenced their decisions about ordering genetic testing for psychiatric conditions. For example, participants were asked the level of influence of their confidence in their knowledge of psychiatric genetics. A 2-item, 5-point Likert-type scale then evaluated participants' confidence regarding psychiatric genetics. Multiple choice questions followed regarding genetic counseling training programs and educational resources. An optional open-ended question concluded the survey by asking about participants' views on psychiatric genetic counseling's future. The survey was piloted by members of the thesis committee and edited before being distributed. The survey was open for three weeks.

### **3.2.3 Data Analysis**

Microsoft Excel and Stata software were used to complete statistical analyses.<sup>144</sup> All responses were used, including partial responses. Fisher's exact test was used to determine whether

demographic variables were significantly associated with genetic counseling practices, because observed values in some groups were below 5. Statistically significant associations were defined as those with p-values under 0.05. Descriptive analysis and bar graphs were used to indicate response frequencies and percentages.

### **3.3 Results**

#### **3.3.1 Demographics**

The survey was distributed to the NSGC Student Survey listserv program, and it received 108 responses. Because respondents were not required to answer each question, skip logic was used, and some individuals did not complete the full survey, different questions received different numbers of responses. Almost all (90.74%, n=98) respondents were genetic counselors who saw patients, and the other 9.26% (n=10) was in research or laboratory, education, and one responder who is not currently practicing as a genetic counselor. Two of the respondents were counselors whose specialty was psychiatric genetic counseling.

The majority of respondents graduated from a genetic counseling training program in the last ten years, with 82.86% (n=87) graduating between 2010 and 2019. No respondents graduated before 1980, 1.91% (n=2) graduated between 1980 and 1989, 5.71% (n=6) graduated between 1990 and 1999, and 9.52% (n=10) graduated between 2000 and 2009. 94.29% (n=99) were female, 3.81% (n=4) were male, and 1.90% (n=2) answered “Other” or “Prefer not to answer.” Regions II and IV had the largest percentages, 23.81% (n=25) and 37.14% (n=39), respectively. (Regions denoted in Table 1)

**Table 1: States, Territories, and Provinces in each Region**

<b>Region I</b>	CT, MA, ME, NH, RI, VT, Canadian Maritime Provinces
<b>Region II</b>	DC, DE, MD, NJ, NY, PA, VA, WV, Quebec, Puerto Rico, Virgin Islands
<b>Region III</b>	AL, FL, GA, KY, MS, NC, SC, TN
<b>Region IV</b>	AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, SD, WI, Ontario
<b>Region V</b>	AZ, CO, MT, NM, TX, UT, WY, Alberta, Manitoba, Saskatchewan
<b>Region VI</b>	AK, CA, HI, NV, OR, WA, British Columbia

The breakdown of gender, region, graduation year, and specialty were compared to the National Society of Genetic Counselors 2019 Professional Status Survey.<sup>95</sup> (Table 2) Genetic counselors who graduated between 2010 and 2019 were more highly represented in the thesis survey (82.86%) than in the Professional Status Survey (56%), and all other graduation decades were underrepresented in the thesis sample. The gender distribution of thesis survey respondents was almost equivalent to the PSS. Regions I and V were underrepresented, and Region VI was overrepresented in the thesis sample versus the PSS. There was a lower percentage of cancer and preconception genetic counselors than represented in the PSS, and a higher percentage of prenatal and pediatric genetic counselors and those involved in education. Other specialties were similarly represented in both samples.

**Table 2: Demographic Distributions of Thesis and PSS Respondents**

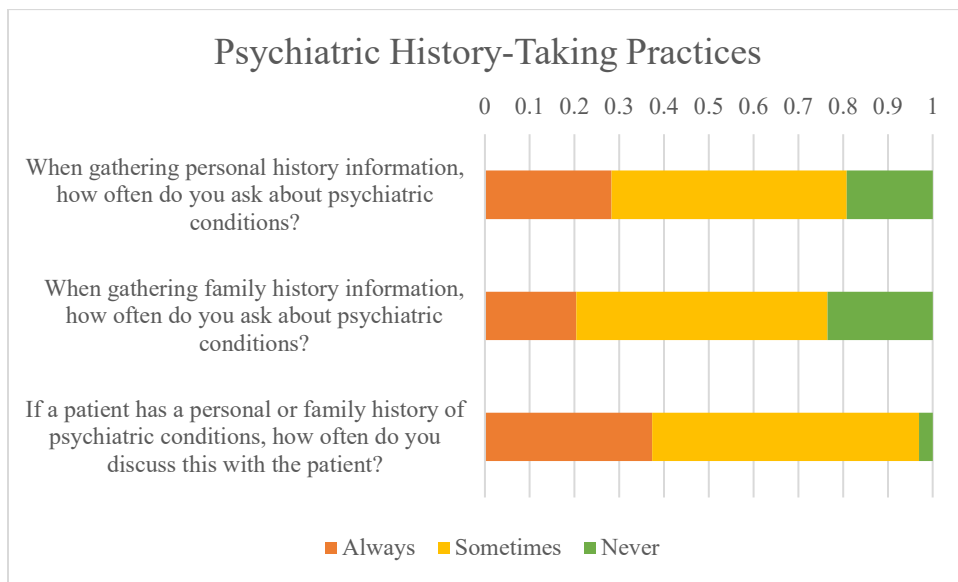
<b>Year of Graduation</b>	<b>Thesis</b>	<b>PSS</b>
<b>1971-1979</b>	0.00%	1.00%
<b>1980-1989</b>	1.91%	4.00%
<b>1990-1999</b>	5.71%	11.00%
<b>2000-2009</b>	9.52%	28.00%
<b>2010-2019</b>	82.86%	56.00%
<b>Gender</b>	<b>Thesis</b>	<b>PSS</b>
<b>Female</b>	94.29%	95.00%
<b>Male</b>	3.81%	5.00%
<b>Region</b>	<b>Thesis</b>	<b>PSS</b>
<b>Region I</b>	2.86%	7.00%
<b>Region II</b>	23.81%	21.00%
<b>Region III</b>	15.24%	12.00%
<b>Region IV</b>	37.14%	28.00%
<b>Region V</b>	4.76%	13.00%
<b>Region VI</b>	16.19%	19.00%
<b>Specialty</b>	<b>Thesis</b>	<b>PSS</b>
<b>Psychiatric</b>	1.90%	1.00%
<b>Cancer</b>	19.05%	30.00%
<b>Prenatal</b>	28.57%	18.00%
<b>Pediatric</b>	20.00%	10.00%
<b>Preconception</b>	0.00%	2.00%
<b>Cardiology</b>	1.90%	3.00%
<b>Specialty</b>	5.71%	5.00%
<b>General</b>	5.71%	5.00%
<b>Laboratory</b>	2.86%	2.00%
<b>Education</b>	3.81%	2.00%

### 3.3.2 Practice

The clinical genetic counselors were then asked about their interactions with patients. 68.69% (n=68) have never seen a patient whose primary indication was a psychiatric condition, and 31.31% (n=31) have. They were then asked how often they discussed or asked about psychiatric conditions during sessions. Figure 1 indicates the percentage of respondents who always, sometimes, or never discuss patients' personal or family histories of psychiatric conditions, ask about family history of psychiatric conditions, and ask about personal history of psychiatric conditions. Counselors report discussing patients' personal or family history of

psychiatric conditions if present more than they report asking about psychiatric conditions in the personal or family history.

The two respondents who are psychiatric genetic counselors always ask about psychiatric conditions when gathering history information, and always discuss if psychiatric history is present. 10% of cancer genetic counselors indicated that they “Never” discuss psychiatric conditions if they are present in a personal or family history, as did 4.76% of pediatric genetic counselors. All other respondents indicate they “Sometimes” or “Always” discuss if psychiatric history is present. Of the nonpsychiatric genetic counselors, adult genetic counselors were most likely to say they “Always” ask about psychiatric conditions when taking personal or family history information (66.67% and 33.33%, respectively), and cancer genetic counselors were least likely (5% and 0%, respectively).



**Figure 1: Frequency of History-Taking Practices (n=99)**

When asked how they presented risk information to patients, 5.27% (n=5) indicated they provide quantitative risk information, such as recurrence risk, 57.90% (n=55) indicated they

provide qualitative risk information, 29.47% (n=28) provide both quantitative and qualitative information, and 7.37% (n=7) provide other risk information; individuals who selected “Other” explained they provide information such as who else in the family should be evaluated by genetics or information about complex inheritance. Another individual wrote that they employ the “jar model” in explaining risk to patients, which is a method of explaining genetic and environmental contributions to multifactorial conditions. The majority of respondents indicated they “Sometimes” ask about or discuss histories of psychiatric conditions, which alongside two respondents who wrote in that they would tailor the type of risk information discussed based on what the patient was interested in hearing, reflects counselors basing questions and discussions off of individual patient indications, interests, and time constraints.

Table 3 describes the percentages of respondents who have referred a patient to a psychiatric genetic counselor, disclosed secondary findings related to a psychiatric condition, and ordered genetic testing specifically for a psychiatric condition. Few respondents have referred a patient to a psychiatric genetic counselor (9.28%, n=9) or ordered genetic testing for a psychiatric condition (11.22%, n=11), and 15.31% (n=15) have disclosed secondary findings related to a psychiatric condition.

**Table 3: Percent of Respondents Who Have Performed Psychiatric Genetic Counseling Practices**

<b>Practice</b>	<b>Yes (%)</b>	<b>Yes (Count)</b>	<b>No (%)</b>	<b>No (Count)</b>
Seen a patient whose primary indication was a psychiatric condition	31.31%	31	68.69%	68
Referred a patient to a psychiatric genetic counselor	9.28%	9	90.72%	88
Disclosed secondary findings related to a psychiatric condition	15.31%	15	84.69%	83
Ordered genetic testing primarily for a psychiatric condition	11.22%	11	88.78%	87

Respondents then selected conditions for which they had ordered genetic testing, as presented in Table 4. Almost half of the respondents (41.90%, n=44) have ordered genetic testing for autism, but other conditions were ordered for less often. Tests for dementia (8.57%, n=9) and ADD/ADHD (6.67%, n=7) were the next most ordered. A few counselors have ordered tests for depression (0.95%, n=1), anxiety (1.91%, n=2), and schizophrenia/schizoaffective disorder (2.86%, n=3), but no one had ordered a test for psychosis, bipolar disorder, personality disorders, alcohol or substance abuse, or eating disorders. Participants who selected “Other” listed behavioral concerns and combinations of psychiatric issues with dysmorphic features or developmental delay.

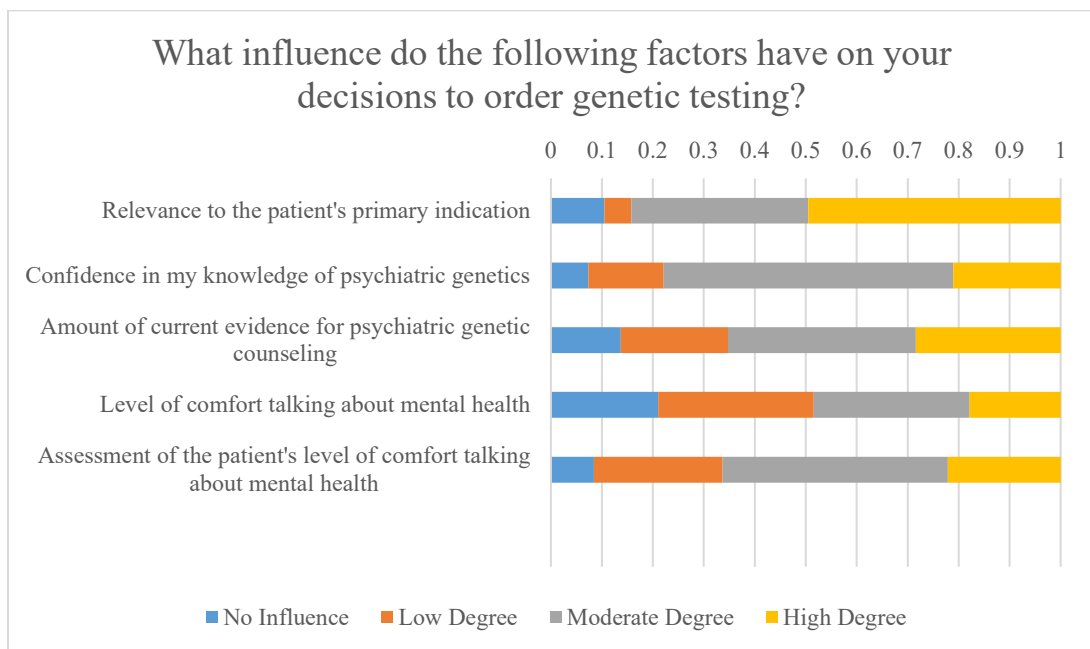
**Table 4: Percent of Respondents Who Have Ordered Genetic Testing for Certain Psychiatric Conditions**

<b>Condition</b>	<b>Percent</b>
Depression	0.95%
Anxiety	1.90%
ADD/ADHD	6.67%
Schizophrenia/schizoaffective	2.86%
Psychosis	0.00%
Bipolar disorder	0.00%
Personality disorder	0.00%
Alcohol/substance abuse	0.00%
Eating disorder	0.00%
Autism spectrum disorder	41.90%
Dementia	8.57%
Other	5.71%

Survey respondents assessed the influence of various factors in their decisions to order genetic testing and indicated their responses on a Likert-type scale that ranged from “No Influence” to “High Degree.” Approximately half of the respondents answered that relevance to the patient’s



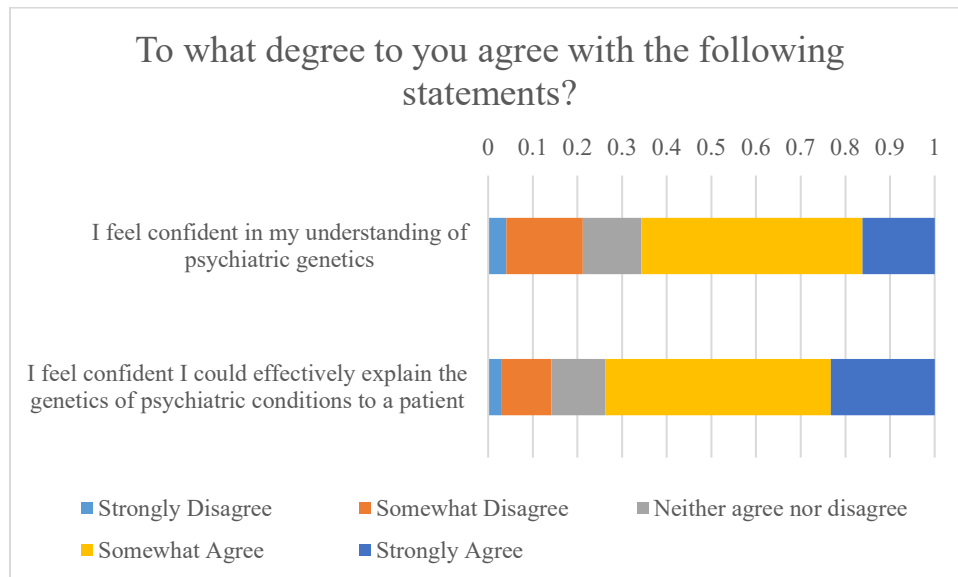
primary indication had a high degree of influence on their decisions to order genetic testing, while fewer respondents assigned a high degree of influence to confidence in their knowledge base, current evidence for psychiatric genetic counseling, or personal and patient levels of comfort with discussing mental health. Other factors respondents described in an open text box when “Other” was selected were the amount of time in the session, relevance to psychosocial issues, strength of the family history of psychiatric disorder, patient’s concerns identified in contracting, the severity of the patient’s psychiatric presentation, type of psychiatric conditions in history, and patient’s interest or targeted questions. Of those who indicated other, four answered that time considerations had an influence. These results are summarized in Figure 2.



**Figure 2: Degree of Influence of Various Factors on Testing Decisions (n=95)**

Respondents were then asked to what degree they agreed with statements that they feel confident in their understanding of psychiatric genetics and confident they could explain psychiatric genetics to a patient. (Figure 3) 65.67% (n=65) responded that they “Somewhat” or “Strongly Agree” with the statement “I feel confident in my understanding of psychiatric

genetics,” and 21.21% (n=21) “Somewhat” or “Strongly Disagreed.” To the statement “I feel confident I could effectively explain psychiatric genetics to a patient, 73.74% (n=73) of respondents answered they “Somewhat” or “Strongly Agreed,” and 14.14% (n=14) “Somewhat” or “Strongly Disagreed.” Figure 3 provides more detail, with responses on a Likert-like scale ranging from answer choices of “Strongly Disagree” to “Strongly Agree.” The large proportion of respondents who agree that they are confident about psychiatric genetics belies the lower proportion who have provided psychiatric genetic counseling services and the 19.19% and 23.47% of respondents “Never” who ask about family or personal histories of psychiatric disorders, respectively. It is also interesting to note that although respondents indicate high confidence, this level of confidence was the second-least likely to have a “High Influence” on ordering genetic testing for psychiatric disorders.



**Figure 3: Degree of Confidence (n=99)**

### 3.3.3 Education and Resources

The majority of respondents, 68.69% (n=68), indicated that their genetic counseling training programs had included information about psychiatric genetic counseling. 23.23% (n=23) said their training program did not include this information, and 8.08% (n=8) did not remember. When asked how this information was provided, 55.77% (n=58) responded that it was presented through classes, 11.54% (n=12) through clinical rotations, 3.84% (n=4) through extra-curricular activities, 19.23% (n=20) through conferences or seminars, and 9.62% (n=10) through other methods, such as simulations of patients, journal articles, NSGC educational tools, and workshops. One individual explained that her thesis focused on an aspect of psychiatric genetic counseling.

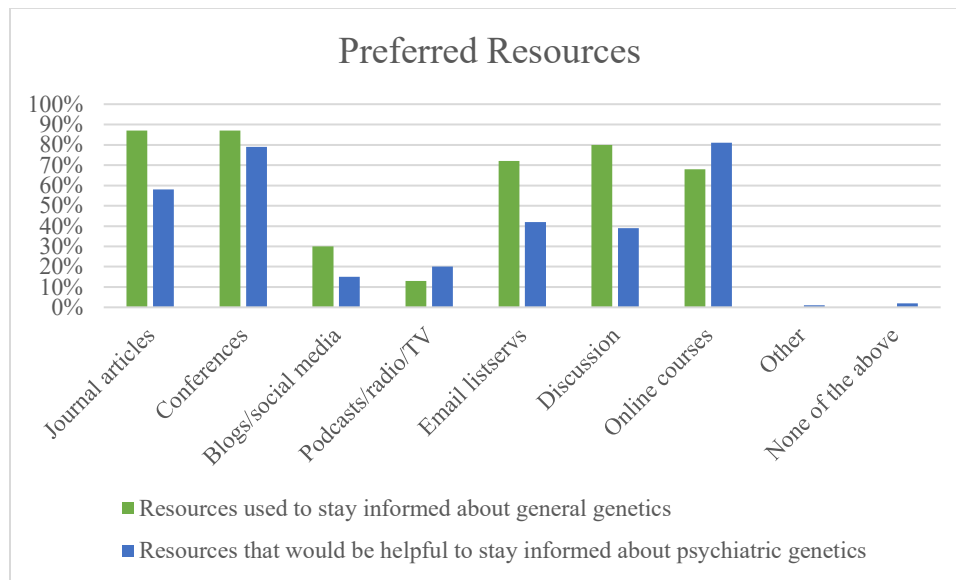
Table 5 illustrates the ways instruction was provided based on graduation decade. Only one respondent who graduated in the 1990s attended a training program that provided information about psychiatric genetics, and that information was provided in classes and clinical rotations. Graduates from 2000-2009 also received all of their information from classes and clinical rotations. Graduates from the last decade, however, were most likely to receive information about psychiatric genetics from classes and conferences or seminars. Information was also provided to them in clinical rotations and through extra-curricular activities.

**Table 5: Types of Instruction by Graduation Decade**

	<b>Classes</b>	<b>Clinical Rotations</b>	<b>Extra-Curricular Activities</b>	<b>Conferences or Seminars</b>
<b>1980-1989</b>	0	0	0	0
<b>1990-1999</b>	1	1	0	0
<b>2000-2009</b>	5	2	0	0
<b>2010-2019</b>	52	9	4	20

Figure 4 compares the resources used to stay informed about general genetics with the resources that would be helpful to stay informed about psychiatric genetics. “Other” resources specified by respondents were books, school notes, and the National Coalition for Health Professional Education in Genetics website.

The most frequently selected resources for general genetics and psychiatric genetics were journal articles, conferences and seminars, and online courses. Email listservs and discussion with colleagues were also frequently chosen as resources for general genetics, but not psychiatric genetics. Blogs, social media, podcasts, radio, and television were rarely chosen, by less than 30% of respondents. The only resources ranked more highly for psychiatric genetics than general genetics were online courses and podcasts, radio, and television.



**Figure 4: Preferred Genetics Resources**

When asked what kind of information about psychiatric genetics would be most useful, the most frequently selected answer was recurrence risks, selected by 90.82% (n=89) of respondents. 33.67% (n=33) and 36.73% (n=36) selected pharmacogenetics and polygenic risk scores, respectively. 22.45% (n=22) said they would case find studies useful, 77.55% (n=76) said

information about associations between psychiatric conditions and other patient indications would be useful, and 44.90% (n=44) said studies of the utility and efficacy of psychiatric genetic counseling would be useful. (Table 6)

**Table 6: Percent of Respondents Who Would Find Certain Types of Information Useful**

<b>Type of Information</b>	<b>Percent</b>
Recurrence risks	90.82%
Pharmacogenetics	33.67%
Polygenic risk scores	36.73%
Case studies	22.45%
Associations between psychiatric conditions and other patient indications (i.e. genetic syndromes, neurodevelopmental disorders)	77.55%
Studies of psychiatric genetic counseling utility and efficacy	44.90%
Other	1.02%

Three respondents (3.03%) have taken the NSGC online course “Psychiatric Genetics across Genetic Counseling Practice Setting.” 39.40% (n=39) indicated they were aware of the course but have not taken it, and 57.58% (n=57) were not aware of the course. 43.43% (n=43) of survey respondents said they have attended a speaking event regarding psychiatric genetics in the past year, while 56.57% (n=56) have not.

In response to a question asking what factors would increase their likelihood of discussing psychiatric genetics with patients, 61.96% (n=57) selected learning more about psychiatric genetics, 53.26% (n=49) selected having more access to patient resources, 57.61% (n=53) selected more information about evidence-based practice of genetic counseling, and 18.48% (n=17) described other factors, including if they were in a position to have referrals for psychiatric conditions, more time to address it in sessions, more conclusive evidence of psychiatric genetics, patient questions, support from their boss, relevance to their clinic, more opportunity to practice

psychiatric genetic counseling, whether testing for psychiatric conditions would change medical management, patient interest, and more awareness of testing and screening options.

Fisher's exact tests were performed to determine whether demographic factors (year of graduation, gender, specialty, region, attending a training program that addressed psychiatric genetics) were significantly associated with provider practices (having seen a patient whose primary indication was a psychiatric condition, having referred a patient to a psychiatric genetic counselor, having disclosed secondary findings related to a psychiatric condition, having ordered genetic testing primarily for a psychiatric condition, and attending a training program that addressed psychiatric genetics).

Year of graduation and having referred a patient to a psychiatric genetic counselor were significantly associated ( $p=0.022$ ). The association of year of graduation with attending a training program that addressed psychiatric genetics approached significance ( $p=0.051$ ). Specialty and having ordered genetic testing for a psychiatric condition were also significantly associated ( $p=0.005$ ), as were having attended a training program that addressed psychiatric genetics and disclosing secondary results related to psychiatric genetic counseling ( $p=0.046$ ). (Table 7).

**Table 7: Associations Between Demographic Factors and Psychiatric Genetics Practices**

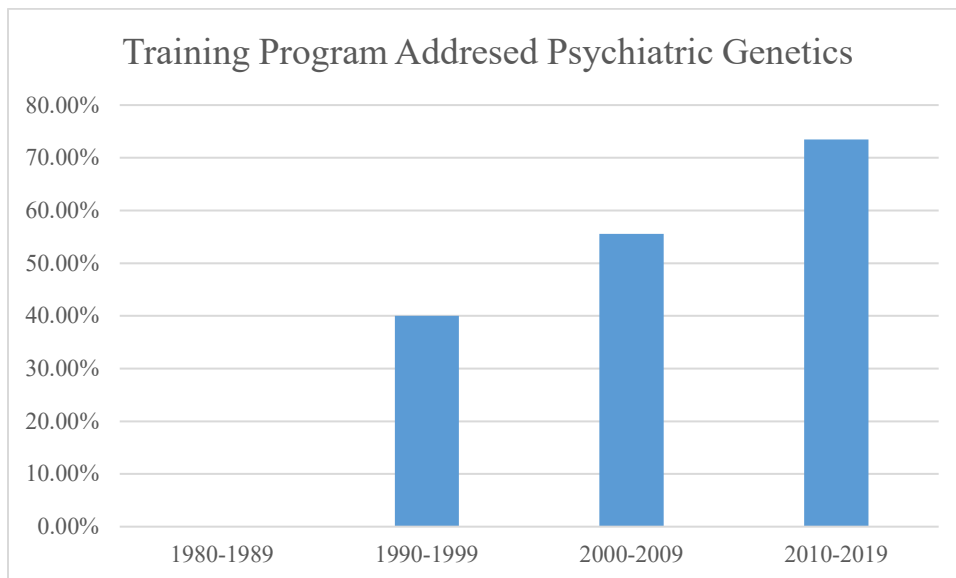
	<b>Seen a patient whose 1° indication psychiatric condition</b>	<b>Referred patient to psychiatric GC</b>	<b>Disclosed 2° finding of psychiatric condition</b>	<b>Tested for psychiatric condition</b>	<b>Psychiatric genetics taught in program</b>
	P-Value	P-Value	P-Value	P-Value	P-Value
<b>Year of Graduation</b>	0.18	0.022*	0.37	0.189	0.051
<b>Gender</b>	0.718	0.214	1	1	0.596
<b>Region</b>	0.296	0.218	0.197	0.093	0.248
<b>Specialty</b>	0.36	0.068	0.274	0.005*	0.307
<b>Psychiatric genetics taught in program</b>	0.53	0.717	0.046*	0.512	N/A

\*=p<0.05

Assessing the significant associations, Table 8 indicates the percentage of individuals who have performed certain practices given their specialty, graduation year, and psychiatric genetic counseling training. Based on this data, the genetic counselors with the highest likelihood of having ordered genetic testing specifically for a psychiatric condition are those who work in Adult clinics (67%, n=2), those with the highest likelihood of having referred a patient to a psychiatric genetic counselor are those who graduated in the 1980s (50%, n=1), and those with the highest likelihood of having disclosed secondary findings related to psychiatric conditions are those who don't remember whether their training program addressed psychiatric genetics (38%, n=3/8). The true significance of these associations is suspect due to the low number of respondents in different demographic categories. The chance of having been through a training program that addressed psychiatric illnesses steadily increased from zero if one graduated 1980-1989, 40% if one graduated 1990-1999, 56% if one graduated 2000-2009, and 73% if one graduated 2010-2019. (Figure 5)

**Table 8: Psychiatric Genetics Practices Given Demographic Category**

	Has ordered testing		n=	
<b>Psychiatric</b>	0.00%		0/2	
<b>Cancer</b>	5.00%		1/20	
<b>Prenatal</b>	0.00%		0/30	
<b>Pediatric</b>	19.05%		4/21	
<b>Adult</b>	66.67%		2/3	
<b>Cardiology</b>	50.00%		1/2	
<b>General</b>	33.33%		2/6	
<b>Other</b>	0.00%		0/6	
	Has referred to a psychiatric GC	n=	Training program addressed psychiatric genetics	n=
<b>1980-1989</b>	50.00%	½	0.00%	0/2
<b>1990-1999</b>	0.00%	0/5	40.00%	2/5
<b>2000-2009</b>	33.00%	3/9	55.56%	5/9
<b>2010-2019</b>	6.20%	5/81	73.49%	61/83
	Has disclosed secondary findings		n=	
<b>Received Training</b>	9.00%		6/64	
<b>No</b>	22.00%		5/23	
<b>Don't Remember</b>	38.00%		3/8	



**Figure 5: Likelihood of Training Program Addressing Psychiatric Genetics by Graduation Decade**



Fisher’s exact test was performed to evaluate the relationships between demographic factors and agreement with statements about confidence. The association between decade of graduation and agreement with the statement “I feel confident in my understanding of psychiatric genetics” was significant ( $p=0.004$ ), as was the association between gender and agreement with that statement ( $p=0.047$ ). No other associations with that phrase reached significance. None of the variables (gender, year of graduation, region, specialty, or having attended a training program that addressed psychiatric genetics) were significantly associated with agreement with the statement “I feel confident I could explain psychiatric genetics to a patient. (Table 9)

**Table 9: Association of Demographic Factors with Confidence**

	<b>I feel confident I could effectively explain psychiatric genetics to a patient</b>	<b>I feel confident in my understanding of psychiatric genetics</b>
	P-Value	P-Value
<b>Year of Graduation</b>	0.368	0.004*
<b>Gender</b>	0.41	0.047*
<b>Region</b>	0.166	0.389
<b>Specialty</b>	0.727	0.761
<b>Psychiatric genetics taught in training program</b>	0.14	1

\*= $p<0.05$

The significant relationships between decade of graduation and confidence, and between gender and confidence, were examined more closely. (Table 10) 70% of genetic counselors who graduated between 2010 and 2019 said they “Somewhat” or “Strongly Agree” that they felt confident in their understanding of psychiatric genetics. Women were more likely to agree that they felt confident in their understanding (77.50%) than men (25%).

**Table 10: Agreement with the statement “I feel confident in my understanding of psychiatric genetics”**

<b>Year of Graduation</b>	<b>Somewhat Agree/Strongly Agree</b>	<b>n=</b>
1980-1989	50.00%	1/2
1990-1999	60.00%	3/5
2000-2009	62.50%	5/8
2010-2019	70.00%	56/80
<b>Gender</b>		<b>n=</b>
Female	77.50%	62/80
Male	25.00%	1/4
Other	100.00%	1/1
Prefer not to say	100.00%	1/1

### **3.4 Discussion**

#### **3.4.1 Practice**

The majority of participants in this study (68.69%) have never seen a patient for a primary indication of a psychiatric condition. Few have referred patients to psychiatric genetic counselors, disclosed secondary findings related to psychiatric conditions, or ordered genetic tests for psychiatric conditions. This finding corresponds with Hoop et al.’s survey of 45 psychiatrists that few healthcare professionals have referred patients to psychiatric genetic counseling.<sup>92</sup> These low frequencies may reflect the dearth of psychiatric genetic counselors to be referred to and the absence of guidelines recommending genetic testing for psychiatric genetic counseling or how to interpret genetic test results related to psychiatric disorders. 41.9% of participants in this survey have ordered a genetic test for ASD, followed by dementia, ADD/ADHD, then depression, anxiety, and schizophrenia. The high proportion of respondents who have ordered tests for ASD may be due to the presence of more guidelines regarding genetic testing and results for ASDs and may also be influenced by parents requesting or pushing for genetic testing. The International

Society of Psychiatric Genetics has issued guidelines supporting the utility of microarrays in children with ASD or other neurodevelopmental disorders but has not come to a consensus on microarrays for adult-onset psychiatric disorders.<sup>69</sup>

Most participants said they sometimes ask about personal or family histories of psychiatric conditions, and if those are present, sometimes discuss this with the patient. Respondents were more likely to discuss psychiatric personal or family histories if present than to ask about psychiatric personal or family histories. This may be due to genetic counselors tailoring sessions toward individual patients and what is relevant to their indication and history, rather than asking the same questions of every patient. In addition, counselors are more likely to ask about psychiatric conditions when getting personal history information than family history. It is possible this is due to perceptions that personal histories of psychiatric conditions are more relevant, which could indicate a lack of appreciation for the heritability of psychiatric disorders. This aligns with Moldovan et al.'s recent 2019 study, which found that across the world, most genetic counselors only discuss psychiatric genetics if it is brought up by the patient.<sup>94</sup> This may be due to genetic counselors tailoring sessions toward individual patients and what is relevant to their indication and history, rather than asking the same questions of every patient. In addition, counselors are more likely to ask about psychiatric conditions when getting personal history information than family history. It is possible this is due to perceptions that personal histories of psychiatric conditions are more relevant, which could indicate a lack of appreciation for the heritability of psychiatric disorders.

NSGC's online course "Psychiatric Genetics across Genetic Counseling Practice Settings" advises on how to discuss psychiatry during a genetic counseling session and provides case examples for practice, as well as discussing testing options.<sup>129</sup> Without concrete guidelines,

counselors are left to make their own assessments of psychiatric genetic counseling practices, such as when or if to order genetic testing, how and where to refer patients to psychiatric genetic counselors, and how to discuss risks. The genetic counselors in this study preferred discussing qualitative risk information (57.9%) over quantitative risk estimates (5.27%). Many of the respondents (29.47%) provide a combination of qualitative and quantitative risk, and they may tailor the risk discussion based on the patients' questions and interest. Counselors may be more comfortable avoiding specific numbers because information about recurrence risks, polygenic risk scores, or genetic testing results is not yet concrete.

The importance of relevance to the patient's indication, as noted in responses to other survey questions, is a driving factor in decisions to ask about and discuss histories of psychiatric conditions, order genetic testing, and discuss psychiatric genetics with patients in general. This aligns with genetic counselors' training to tailor sessions to individual patients.

### **3.4.2 Confidence/Education**

The majority of respondents agreed that they felt confident in their understanding of psychiatric genetics and their ability to effectively explain it to patients. Recent graduates and women were the most likely to feel confident in their understanding, with 70% of graduates from 2010-2019 agreeing they feel confident compared to approximately 50% of graduates from 1980-1989. Although the association between gender and confidence was significant, the presence of only four male participants may have skewed the analysis. Higher confidence in recent graduates, who are also more likely to have received training in psychiatric genetics, aligns with the idea that more frequent instruction about psychiatric genetic counseling, practice, and access to patient resources had significant impacts on preparedness for psychiatric genetic counseling, as reported

by Low et al. in 2018.<sup>17</sup> Overall, however, the high percentage of confident respondents contrasts with the low percentage of respondents who always discuss psychiatric genetics with their patients. This discrepancy may be due to the common tendency for individuals to overestimate their knowledge and confidence.<sup>145</sup>

Most participants indicated their genetic counseling training programs provided information about psychiatric genetic counseling, usually by lecture, followed by conferences or seminars, clinical rotations, then extra-curricular or other methods. Active, involved experiences were shown to be particularly helpful by Low et al.;<sup>17</sup> however, participants in this thesis survey did not indicate much hands-on practice or experience with psychiatric genetic counseling in their training programs, although three respondents did say they had patient simulations involving psychiatric genetics, and respondents who graduated 2010-2019 were the only cohort to report learning information about psychiatric genetics through extra-curricular activities and conferences or seminars, as well as several (n=9) through clinical rotations. Participants' overall likelihood to have learned about psychiatric genetics increased over time, possibly because more genetic counseling programs have adjusted their curricula to reflect the increase in awareness and information about psychiatric genetics.

#### **3.4.2.1 Resources**

Respondents most frequently preferred journal articles, conferences or seminars, and online courses to stay up to date on general and psychiatric genetic information. These information sources may be preferred due to peer-review, production by a group of experts, and focus on factual information, rather than opinions. Email listservs and discussion with peers were not as popular for psychiatric genetics as general genetics. Perhaps this is due to fewer emails addressing psychiatric genetics and colleagues being unfamiliar with it. People were more likely to choose

online courses and podcasts, radio, and television for information on psychiatric genetics than for information on general genetics. This may be due to the recent growth of the field, as counselors may want to take online courses to supplement knowledge of psychiatric genetics that may not have been presented in their training programs or addressed since then. The increased preference for podcasts, radio, and television may be due to high media coverage of new advances in the field of psychiatric genetics.

Some of the information respondents said they would find beneficial, such as case studies, associations between psychiatric conditions and other indications, and studies of the utility and efficacy of psychiatric genetic counseling, are available, while other information, like recurrence risks, polygenic risk scores, and pharmacogenetics is in the process of being researched and fine-tuned to be useful for clinical practice. These selections of information reflect the 61.96% who said learning more about psychiatric genetics would increase their likelihood of discussing psychiatric genetics with patients and the 57.61% who selected information about evidence-based practice of psychiatric genetic counseling. Access to patient resources and ability to refer patients to psychiatric genetic counselors, more time available in session, practice to become more familiar with psychiatric genetic counseling, applicability to their patients, and knowledge about testing and screening options are important factors to consider if the field of psychiatric genetic counseling is to grow. Time constraints are a common barrier to adoption of new practices in healthcare across professions.<sup>17,128</sup>

Physicians' decisions about practices have been showed to be influenced by perceptions of the purpose of those practices and explicit interest from patients.<sup>127</sup> Some of the genetic counselors of this study expressed similar concepts, by tailoring their discussions of psychiatric genetics and risk based on patients asking questions and expressing interest. Participants also expressed their

opinions that psychiatric genetic counseling may not be widely applicable or adopted until more clinically relevant information is available, such as new genetic tests, more concrete risk estimates, and pharmacogenetics information, which demonstrates that perceptions of management versus psychosocial uses of psychiatric genetic counseling may affect practice.<sup>128</sup>

Relevance to the patients' primary indication was the factor with the most influence on decisions to order genetic testing for psychiatric conditions, followed by current evidence for psychiatric genetic counseling. Confidence mainly had a moderate influence, as well as assessment of the patient's comfort discussing mental health. The counselors' level of comfort discussing mental health was ranked with the least influence on testing decisions.

### **3.4.3 Study Limitations**

This study had a low response rate and small sample size, and therefore may not be fully representative of all members of NSGC. The differences in distribution patterns, particularly in large overrepresentation of recent graduates and the discrepancies in specialty distribution, may have impaired data analysis. It is possible that recent graduates are more inclined to participate in the student surveys sent through NSGC because they were recently in the position of sending surveys or otherwise gathering data for their own theses. Additionally, with the field of genetic counseling growing, training programs are adapting to accept more students, which in turn leads to more graduates. The over- and under-representations of specialties may be related to random sampling with a small sample size.

Selection bias is another possibility with use of surveys; genetic counselors who are interested in psychiatric genetics may have been more likely to participate, and those with higher interest and awareness may be more likely to perform psychiatric genetic counseling practices like

referrals to psychiatric genetic counselors or ordering genetic tests, and may feel more confident in their knowledge due to their interest. Genetic counselors without familiarity or interest in psychiatric genetics could have been less likely to respond to the survey. This type of selection bias could have led to overestimation of confidence and frequency of psychiatric genetic counseling practices. Another limitation is the reliance on self-reported practices, with inaccurate memories skewing reports of frequency, or answering in ways they thought they should, which could also overestimate frequency of genetic counseling practices.

#### **3.4.4 Future Directions**

Comprehensive evaluation of how many patients with primary indications of psychiatric conditions are seen by genetic counselors in other specialties, how often patients present with a different indication but reveal personal or family histories of psychiatric conditions, how often testing incidentally identifies variants related to psychiatric conditions, and other measures of practice will be important to assess the current state of psychiatric genetic counseling. With a better idea of what is currently being practiced, further studies can then assess where problems lie and what interventions may be beneficial in optimizing patient care. Current data suggests that the way training programs teach about psychiatric genetic counseling, access to provider and patient resources, experience with individuals who have mental illness, access to journal articles, conferences, and online courses or webinars could be places to focus on for improved and increased sharing of psychiatric genetics information. Determining how best to make these improvements is an important future direction. For example, a conference lecture or panel designed to attract genetic counselors who are not already familiar with psychiatric genetic counseling may be an efficient way to introduce counselors to the resources that are currently available, as well as



invite discussion of what methods and practices other genetic counselors are currently using or find useful. Increasing the awareness of psychiatric genetic counseling is an important first step in growing the field.

### **3.5 Conclusion**

Psychiatric genetic counseling can provide knowledge and understanding to patients and their families about their mental health issues and risks, as well as psychosocial support to relieve guilt, shame, blame, and fear surrounding psychiatric disorders. Stigma surrounding mental illness is often a barrier to individuals receiving care as well; because studies have shown exposure to mental illness is beneficial in reducing stigma, the trend of increasing training about psychiatric genetics in genetic counseling programs is promising. If more genetic counselors become comfortable with mental illness, patient care will improve, even beyond the field of psychiatric genetic counseling. While genetic counselors currently provide counseling on multiple genetic conditions that can include mental illness as one of multiple components, as more information about psychiatric genetics is discovered and translated into clinical use, such as polygenic risk scores and pharmacogenetic tests, genetic counselors will need to become familiar with asking questions about psychiatric history, discussing mental illness, interpreting pedigrees with psychiatric conditions, ordering and screening options, how and where to refer patients to psychiatrists, psychiatric genetic counselors, or other healthcare providers, and resources for patients. A goal of this study was to assess how often these practices are currently performed, and the results show that the majority of responding genetic counselors have not seen patients for psychiatric conditions, disclosed secondary findings related to psychiatric conditions, referred a

patient to a psychiatric genetic counselor, or ordered genetic testing for a psychiatric condition. Some genetic counselors are hesitant to perform psychiatric genetic counseling because of time limitations, unawareness of patient resources and referral options, not viewing psychiatric genetics as relevant to their clinic and patients, and not knowing how it could affect medical management.

Because these practices are relatively new and many current genetic counselors may not have learned about psychiatric genetic counseling in their training programs, it is important that counselors have resources to learn more about psychiatric genetics and ways to incorporate it into their practices. This study revealed that genetic counselors would be most interested in journal articles, conferences or seminars, and online courses to receive this information. Additional studies of widespread psychiatric genetic counseling practices in nonpsychiatric genetics clinics could help develop useful resources about psychiatric genetic counseling for providers and patients.

#### 4.0 Public Health Significance

A core function of public health is assurance, and this study assesses current practices of genetic counselors in relation to psychiatric genetics and identifies gaps of care in order to ensure that the workforce is competent in psychiatric genetics. It also investigates what factors influence those practices, as well as genetic counselors' confidence in knowledge. By determining how genetic counseling training programs, educational resources, and other factors affect counselors' delivery of psychiatric genetic counseling services, interventions to standardize practices and improve knowledge can be developed. These interventions can improve provision of and access to care for individuals with mental illnesses and their families.

The methods of resource development based on providers' feedback and interest are applicable to many areas of health, and regular updates and resource development are key parts of maintaining knowledge for providers and health literacy for communities.<sup>146</sup> Guidelines for practice and training programs involve policy development, another core function of public health. National organizations such as the National Society of Genetic Counselors, American Society of Human Genetics, American Board of Genetic Counseling, and others should continue publishing statements, recommendations, updates, and other communications to help providers remain up to date. The American Psychiatric Association encourages genetic counseling for individuals with bipolar disorder, and the International Society of Psychiatric Genetics has published recommendations for clinical use of genetic testing for psychiatric disorders.<sup>55,69</sup> Ensuring that government policies and insurance companies reflect the current state of psychiatric genetics and psychiatric genetic counseling is also essential. Funding for research into clinical applications of psychiatric genetics, instituting specialized psychiatric genetic counseling clinics, and campaigns

to increase awareness of psychiatric genetic counseling services are vital tools to encourage adoption of practices and learning about psychiatric genetics will be necessary as psychiatric genetic counseling becomes more widespread and in demand. Evaluations of methods and outcomes of psychiatric genetic counseling in dedicated clinics as well as cancer, prenatal, pediatric, and other settings will provide assurance that counselors are using consistent, complementary data, patient resources, and strategies to optimize patient care.

## Appendix A: IRB Approval Letter

### University of Pittsburgh Institutional Review Board

Human Research Protection Office  
3500 Fifth Avenue, Suite 106  
Pittsburgh, PA 15213  
Tel (412) 383-1480  
www.hrpo@pitt.edu

### APPROVAL OF SUBMISSION (Exempt)

Date:	June 7, 2019
IRB:	STUDY19050028
PI:	Kaitlin Sullivan
Title:	Addressing psychiatric disorders in genetic counseling

The Institutional Review Board reviewed and approved the above referenced study. The study may begin as outlined in the University of Pittsburgh approved application and documents.

#### Approval Documentation

Review type:	Initial Study
Approval Date:	6/7/2019
Exempt Category:	(2)(ii) Tests, surveys, interviews, or observation (low risk), (2)(i) Tests, surveys, interviews, or observation (non-identifiable)

Approved Documents:	<ul style="list-style-type: none"><li>• Survey Exemption Worksheet, Category: IRB Protocol;</li><li>• Intro Script, Category: Recruitment Materials;</li><li>• Survey, Category: Data Collection;</li></ul>
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As the Principal Investigator, you are responsible for the conduct of the research and to ensure accurate documentation, protocol compliance, reporting of possibly study-related adverse events and unanticipated problems involving risk to participants or others. The HRPO Reportable Events policy, Chapter 17, is available at <http://www.hrpo.pitt.edu/>.

Clinical research being conducted in an UPMC facility cannot begin until fiscal approval is received from the UPMC Office of Sponsored Programs and Research Support (OSPARS).

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, [Carolyn Ivanusic](#).

*Please take a moment to complete our [Satisfaction Survey](#) as we appreciate your feedback.*

## **Appendix B: Survey**

### **Psychiatric Disorders**

My name is Kaitlin Sullivan, and I am currently a genetic counseling student at the University of Pittsburgh. I would like to invite you to participate in this research study that aims to evaluate how genetic counselors address psychiatric disorders and identify methods to increase genetic counselors' familiarity with psychiatric genetics. Psychiatric genetics is the study of how genetics relate to the development of psychiatric disorders. To assess this information, we will be surveying genetic counselors (clinical and non-clinical) with a brief (approximately 10 minute) survey that includes questions about practices and opinions regarding psychiatric genetic counseling, as well as limited demographic information. It is anonymous, and your responses are not identifiable. The information that you give in the study will be handled confidentially. This survey is part of a Master's in genetic counseling thesis project.

Your participation in the study is completely voluntary. You may skip any question that you feel uncomfortable answering. You are free to exit the survey at any time. If you exit the survey before completing and submitting it, you may return to it at a later time.

This survey is open to any current genetic counselor. There are no anticipated risks in this study. There are no direct benefits to you for participating in this research study. The study may help us develop resources in the future to enhance genetic counselors' knowledge of and comfort with psychiatric genetic counseling. This study was approved as an exempt study by the University of Pittsburgh IRB, Study #19050028.

Thank you for taking the time to consider this study.

**If you have questions, please contact:**

Kaitlin Sullivan

Kms335@pitt.edu

Department of Human Genetics

University of Pittsburgh

130 DeSoto St

Pittsburgh, PA 15261

In what year did you graduate from a genetic counseling graduate program?

- 2019
- 2010-2018
- 2000-2009
- 1990-1999
- 1980-1989
- 1971-1979

What is your gender?

- Male
- Female
- Other
- Prefer not to answer

In what region are you located?

- Region I (CT, MA, ME, NH, RI, VT, Canadian Maritime Provinces)
- Region II (DC, DE, MD, NJ, NY, PA, VA, WV, Quebec, Puerto Rico, Virgin Islands)
- Region III (AL, FL, GA, KY, MS, NC, SC, TN)
- Region IV (AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, SD, WI, Ontario)
- Region V (AZ, CO, MT, NM, TX, UT, WY, Alberta, Manitoba, Saskatchewan)
- Region VI (AK, CA, HI, NV, OR, WA, British Columbia)

What is your primary area of specialty?

- Psychiatric
- Cancer
- Prenatal
- Pediatric
- Preconception
- Adult
- Cardiology
- Specialty disease (please specify): \_\_\_\_\_
- General
- Laboratory
- Education
- Other (please specify): \_\_\_\_\_
- N/A – I am not currently practicing as a genetic counselor



*Skip To: Q14 If What is your primary area of specialty? = N/A – I am not currently practicing as a genetic counselor*

*Skip To: Q14 If What is your primary area of specialty? = Laboratory*

*Skip To: Q6 If What is your primary area of specialty? = Psychiatric*

Have you ever seen a patient whose primary indication was a psychiatric condition?

- Yes
- No

When gathering personal history information, how often do you ask about psychiatric conditions?

- Always
- Sometimes
- Never

When gathering family history information, how often do you ask about psychiatric conditions?

- Always
- Sometimes
- Never

If a patient has a personal or family history of psychiatric conditions, how often do you discuss this with the patient?

- Always
- Sometimes
- Never

*Skip To: Q10 If a patient has a personal or family history of psychiatric conditions, how often do you discuss... = Never*

When discussing psychiatric disorders, how do you present risk information?

- I provide quantitative risk/recurrence numbers
- I provide qualitative risk information
- I provide both quantitative and qualitative risk information
- I provide other information (please specify): \_\_\_\_\_

Have you ever referred a patient to a psychiatric genetic counselor?

- Yes
- No

Have you ever disclosed secondary findings related to a psychiatric condition when returning results to a patient?

- Yes
- No

Have you ever ordered genetic testing specifically for a psychiatric condition?

- Yes
- No

For which conditions have you ordered genetic testing? (Select all that apply)

- Depression
- Anxiety
- ADD/ADHD
- Schizophrenia/schizoaffective disorder
- Psychosis
- Bipolar disorder
- Personality disorder
- Alcohol/substance abuse
- Eating disorder
- Autism spectrum disorder
- Dementia
- Other: \_\_\_\_\_
- None of the above

To what degree do the following factors play a role in your decision whether or not to discuss psychiatric conditions in session?

	No Influence	Low Degree	Moderate Degree	High Degree
Relevance to the patient's primary indication	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Confidence in my knowledge of psychiatric genetics	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Amount of current evidence for psychiatric genetic counseling	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Level of comfort talking about mental health	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Assessment of the patient's level of comfort talking about mental health	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Other (please specify):	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

To what level do you agree with the following statements:

	Strongly Disagree	Somewhat Disagree	Neither agree nor disagree	Somewhat agree	Strongly Agree
I feel confident in my understanding of psychiatric genetics	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I feel confident I could effectively explain the genetics of psychiatric conditions to a patient	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Did your genetic counseling training program's curriculum include information about genetic counseling for psychiatric conditions?

- Yes
- No
- I don't remember

*Skip To: Q17 If Did your genetic counseling training program's curriculum include information about genetic couns... = No*

*Skip To: Q17 If Did your genetic counseling training program's curriculum include information about genetic couns... = I don't remember*

How was information about genetic counseling for psychiatric conditions provided?  
(Select all)

- Classes
- Clinical rotations
- Extra-curricular activities
- Conferences or seminars
- Other (please specify): \_\_\_\_\_

What resources do you use to stay current on information about genetic counseling in general? (Select all that apply)

- Journal articles
- Conferences or seminars
- Blogs or social media (Facebook, Twitter, Instagram)
- Podcasts, radio, or television
- Email listservs from professional organizations
- Discussion with colleagues
- Online courses or webinars
- Other (please specify): \_\_\_\_\_
- None of the above

What types of resources would you find most helpful to learn about psychiatric genetics?  
(Select all that apply)

- Journal articles
- Conferences or seminars
- Blogs or social media (Facebook, Twitter, Instagram)
- Podcasts, radio, or television
- Email listservs from professional organizations
- Discussion with colleagues
- Online courses or webinars
- Fact sheets or reference lists
- Other (please specify): \_\_\_\_\_
- None of the above

What types of information about psychiatric genetics would you find most useful in your practice? (Select all that apply)

- Recurrence risks
- Pharmacogenetics
- Polygenic risk scores
- Case studies
- Associations between psychiatric conditions and other patient indications (i.e. genetic syndromes, neurodevelopmental disorders)
- Studies of psychiatric genetic counseling utility and efficacy

Other: \_\_\_\_\_

Are you aware of NSGC's online course "Psychiatric Genetics across Genetic Counseling Practice Settings?"

- I have taken this course
- I am aware of this course, but have not taken it
- No

In the last year, have you attended a lecture, panel, or other speaking event (at a conference or otherwise) regarding psychiatric genetics?

- Yes
- No

What factors would increase your likelihood discussing psychiatric genetics with patients?  
(Select all that apply)

- Learning more about psychiatric genetics
- Having access to more patient resources
- More information about evidence-based practice of psychiatric genetic counseling
- Other: \_\_\_\_\_
- None of the above

Optional: How do you see psychiatric genetic counseling being incorporated into genetic counseling sessions in the future?

\_\_\_\_\_



## Bibliography

1. Austin J, Semaka A, Hadjipavlou G. Conceptualizing genetic counseling as psychotherapy in the era of genomic medicine. *Journal of genetic counseling*. 2014;23(6):903-909.
2. Austin JC, Honer WG. The potential impact of genetic counseling for mental illness. *Clinical genetics*. 2005;67(2):134-142.
3. Austin JC, Honer WG. Psychiatric genetic counselling for parents of individuals affected with psychotic disorders: a pilot study. *Early intervention in psychiatry*. 2008;2(2):80-89.
4. Costain G, Esplen MJ, Toner B, et al. Evaluating genetic counseling for individuals with schizophrenia in the molecular age. *Schizophrenia bulletin*. 2014;40(1):78-87.
5. Administration SAaMHS. Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health. In: Services USDoHaH, ed2018.
6. Administration SS. Annual Statistical Report on the SSDI Program, 2017. 2017.
7. Administration SS. Annual Statistical Report on the SSDI Program, 2010. 2010.
8. Dobson AE-G, A.; Pal, S.; Heath, S.; DaVanzo, J. E. *Projecting the Supply and Demand for Certified Genetic Counselors: A Workplace Study*. Vienna, VA2016.
9. Cichon S, Craddock N, Daly M, et al. Genomewide association studies: history, rationale, and prospects for psychiatric disorders. *The American journal of psychiatry*. 2009;166(5):540-556.
10. Egeland JA, Gerhard DS, Pauls DL, et al. Bipolar affective disorders linked to DNA markers on chromosome 11. *Nature*. 1987;325(6107):783-787.
11. Johnson EC, Border R, Melroy-Greif WE, de Leeuw CA, Ehringer MA, Keller MC. No Evidence That Schizophrenia Candidate Genes Are More Associated With Schizophrenia Than Noncandidate Genes. (1873-2402 (Electronic)).
12. Collins AL, Kim Y, Sklar P, O'Donovan MC, Sullivan PF. Hypothesis-driven candidate genes for schizophrenia compared to genome-wide association results. *Psychological medicine*. 2012;42(3):607-616.
13. Olfson M, Blanco C, Wang S, Laje G, Correll CU. National Trends in the Mental Health Care of Children, Adolescents, and Adults by Office-Based PhysiciansNational Trends in Mental Health CareNational Trends in Mental Health Care. *JAMA psychiatry*. 2014;71(1):81-90.
14. Chiu M, Gatov E, Vigod SN, et al. Temporal Trends in Mental Health Service Utilization across Outpatient and Acute Care Sectors: A Population-Based Study from 2006 to 2014. 2018;63(2):94-102.
15. Mechanic DB, S. Treatment Of People With Mental Illness: A Decade-Long Perspective. 2004;23(4):84-95.
16. Hippman C, Ringrose A, Inglis A, et al. A pilot randomized clinical trial evaluating the impact of genetic counseling for serious mental illnesses. *The Journal of clinical psychiatry*. 2016;77(2):e190-198.
17. Low A, Dixon S, Higgs A, Joines J, Hippman C. Training to Provide Psychiatric Genetic Counseling: How Does It Impact Recent Graduates' and Current Students' Readiness to Provide Genetic Counseling for Individuals with Psychiatric Illness and Attitudes towards this Population? *Journal of genetic counseling*. 2018;27(1):301-311.
18. Celebrating 175 Years. 2019; <https://www.psychiatry.org/psychiatrists/meetings/annual-meeting/about/175th-anniversary>.
19. Propping P. The biography of psychiatric genetics: From early achievements to historical burden, from an anxious society to critical geneticists. 2005;136B(1):2-7.
20. Russell Schachar.
21. Psychiatry Do. First Contact Assessment Service.

22. Sullivan PF, Agrawal A, Bulik CM, et al. Psychiatric Genomics: An Update and an Agenda. *The American journal of psychiatry*. 2018;175(1):15-27.
23. Buchholz V, Kotsiari A Fau - Bleich S, Bleich S Fau - Frieling H, Frieling H. [Nature meets nurture: the importance of epigenetics for the aetiology of psychiatric diseases]. (1439-3522 (Electronic)).
24. Borg J, Cervenka S, Kuja-Halkola R, et al. Contribution of non-genetic factors to dopamine and serotonin receptor availability in the adult human brain. (1476-5578 (Electronic)).
25. Weaver IC. Integrating early life experience, gene expression, brain development, and emergent phenotypes: unraveling the thread of nature via nurture. (0065-2660 (Print)).
26. Rüdin EJZfdgNuP. Einige Wege und Ziele der Familienforschung, mit Rücksicht auf die Psychiatrie. 1911;7(1):487.
27. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. *The American journal of psychiatry*. 2000;157(10):1552-1562.
28. Kallmann FJ. The genetic theory of schizophrenia; an analysis of 691 schizophrenic twin index families. *The American journal of psychiatry*. 1946;103(3):309-322.
29. Sullivan PF, Kendler Ks Fau - Neale MC, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. 2003(0003-990X (Print)).
30. Johansson V, Kuja-Halkola R, Cannon TD, Hultman CM, Hedman AM. A population-based heritability estimate of bipolar disorder - In a Swedish twin sample. *Psychiatry research*. 2019;278:180-187.
31. Tick B, Bolton P, Happe F, Rutter M, Rijdsdijk F. Heritability of autism spectrum disorders: a meta-analysis of twin studies. *Journal of child psychology and psychiatry, and allied disciplines*. 2016;57(5):585-595.
32. John M. Hettema, M.D., Ph.D. , Michael C. Neale, Ph.D. , and, Kenneth S. Kendler, M.D. A Review and Meta-Analysis of the Genetic Epidemiology of Anxiety Disorders. 2001;158(10):1568-1578.
33. Richard Border, M.A. , Emma C. Johnson, Ph.D. , Luke M. Evans, Ph.D. , et al. No Support for Historical Candidate Gene or Candidate Gene-by-Interaction Hypotheses for Major Depression Across Multiple Large Samples. 2019;176(5):376-387.
34. Psychiatric GCCC, Cichon S, Craddock N, et al. Genomewide association studies: history, rationale, and prospects for psychiatric disorders. *The American journal of psychiatry*. 2009;166(5):540-556.
35. Sklar P. Linkage analysis in psychiatric disorders: the emerging picture. *Annual review of genomics and human genetics*. 2002;3:371-413.
36. Ng MYM, Levinson DF, Faraone SV, et al. Meta-analysis of 32 genome-wide linkage studies of schizophrenia. *Molecular psychiatry*. 2008;14:774.
37. Rüdin E. *Studien über Vererbung und Entstehung geistiger Störungen. 1. Zur Vererbung und Neuentstehung Der Dementia Praecox*. Springer; 1916.
38. Wray NR, Ripke S, Mattheisen M, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature genetics*. 2018;50(5):668-681.
39. Prata DP, Costa-Neves B, Cosme G, Vassos E. Unravelling the genetic basis of schizophrenia and bipolar disorder with GWAS: A systematic review. *Journal of psychiatric research*. 2019;114:178-207.
40. Vornholt E, Luo D, Qiu W, et al. Postmortem brain tissue as an underutilized resource to study the molecular pathology of neuropsychiatric disorders across different ethnic populations. *Neuroscience and biobehavioral reviews*. 2019;102:195-207.
41. Subramanian A, Tamayo P, Mootha VK, et al. Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles. 2005;102(43):15545-15550.

42. Srivastava A, Singh P, Gupta H, et al. Systems Approach to Identify Common Genes and Pathways Associated with Response to Selective Serotonin Reuptake Inhibitors and Major Depression Risk. *International journal of molecular sciences*. 2019;20(8).
43. Darby MM, Yolken RH, Sabunciyan S. Consistently altered expression of gene sets in postmortem brains of individuals with major psychiatric disorders. *Translational psychiatry*. 2016;6:e890.
44. Levy RJ, Xu B, Gogos JA, Karayiorgou M. Copy Number Variation and Psychiatric Disease Risk. In: Feuk L, ed. *Genomic Structural Variants: Methods and Protocols*. New York, NY: Springer New York; 2012:97-113.
45. Kirov G. CNVs in neuropsychiatric disorders. *Human molecular genetics*. 2015;24(R1):R45-49.
46. Schneider M, Debbané M, Bassett AS, et al. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *The American journal of psychiatry*. 2014;171(6):627-639.
47. Xu B, Woodroffe A, Rodriguez-Murillo L, et al. Elucidating the genetic architecture of familial schizophrenia using rare copy number variant and linkage scans. 2009;106(39):16746-16751.
48. Tomassi S, Tosato S. Epigenetics and gene expression profile in first-episode psychosis: The role of childhood trauma. *Neuroscience and biobehavioral reviews*. 2017;83:226-237.
49. Klengel T, Binder EB. Epigenetics of Stress-Related Psychiatric Disorders and Gene x Environment Interactions. *Neuron*. 2015;86(6):1343-1357.
50. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science (New York, NY)*. 2003;301(5631):386-389.
51. Vorstman JAS, Parr JR, Moreno-De-Luca D, Anney RJL, Nurnberger JI, Jr., Hallmayer JF. Autism genetics: opportunities and challenges for clinical translation. *Nature reviews Genetics*. 2017;18(6):362-376.
52. Finucane B, Challman TD, Martin CL, Ledbetter DH. Shift happens: family background influences clinical variability in genetic neurodevelopmental disorders. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2016;18(4):302-304.
53. Leblond CS, Cliquet F, Carton C, et al. Both rare and common genetic variants contribute to autism in the Faroe Islands. *npj Genomic Medicine*. 2019;4(1):1.
54. Grove J, Ripke S, Als TD, et al. Identification of common genetic risk variants for autism spectrum disorder. *Nature genetics*. 2019;51(3):431-444.
55. Association AP. *Autism Spectrum Disorders*. 5th ed. Arlington, VA 2013.
56. Finucane B, Myers SM. Genetic Counseling for Autism Spectrum Disorder in an Evolving Theoretical Landscape. *Current genetic medicine reports*. 2016;4:147-153.
57. Chaste P, Klei L, Sanders SJ, et al. A genome-wide association study of autism using the Simons Simplex Collection: Does reducing phenotypic heterogeneity in autism increase genetic homogeneity? *Biological psychiatry*. 2015;77(9):775-784.
58. Gonzalez-Mantilla AJ, Moreno-De-Luca A, Ledbetter DH, Martin CL. A Cross-Disorder Method to Identify Novel Candidate Genes for Developmental Brain Disorders. *JAMA psychiatry*. 2016;73(3):275-283.
59. Austin JC, Palmer CG, Rosen-Sheidley B, Veach PM, Gettig E, Peay HL. Psychiatric disorders in clinical genetics II: Individualizing recurrence risks. *Journal of genetic counseling*. 2008;17(1):18-29.
60. Peay HL, Veach PM, Palmer CG, Rosen-Sheidley B, Gettig E, Austin JC. Psychiatric disorders in clinical genetics I: Addressing family histories of psychiatric illness. *Journal of genetic counseling*. 2008;17(1):6-17.
61. Jokiranta-Olkoniemi E, Cheslack-Postava K, Sucksdorff D, et al. Risk of Psychiatric and Neurodevelopmental Disorders Among Siblings of Proband With Autism Spectrum Disorders. *JAMA psychiatry*. 2016;73(6):622-629.

62. Witt SH, Streit F, Jungkunz M, et al. Genome-wide association study of borderline personality disorder reveals genetic overlap with bipolar disorder, major depression and schizophrenia. *Translational psychiatry*. 2017;7(6):e1155.
63. Foo JC, Streit F, Treutlein J, et al. Shared genetic etiology between alcohol dependence and major depressive disorder. *Psychiatric genetics*. 2018;28(4):66-70.
64. Ripke S, Wray NR, Lewis CM, et al. A mega-analysis of genome-wide association studies for major depressive disorder. *Molecular psychiatry*. 2013;18(4):497-511.
65. Oliver D, Radua J, Reichenberg A, Uher R, Fusar-Poli P. Psychosis Polyrisk Score (PPS) for the Detection of Individuals At-Risk and the Prediction of Their Outcomes. *Frontiers in psychiatry*. 2019;10:174.
66. Barnett JH, Smoller JW. The genetics of bipolar disorder. *Neuroscience*. 2009;164(1):331-343.
67. Palk AC, Dalvie S, de Vries J, Martin AR, Stein DJ. Potential use of clinical polygenic risk scores in psychiatry - ethical implications and communicating high polygenic risk. *Philos Ethics Humanit Med*. 2019;14(1):4.
68. de Jong S, Diniz MJA, Saloma A, et al. Applying polygenic risk scoring for psychiatric disorders to a large family with bipolar disorder and major depressive disorder. *Commun Biol*. 2018;1:163-163.
69. Genetics ISoP. *Genetic Testing Statement*. TN2019.
70. Musliner KL, Mortensen PB, McGrath JJ, et al. Association of Polygenic Liabilities for Major Depression, Bipolar Disorder, and Schizophrenia With Risk for Depression in the Danish Population Association of Polygenic Liabilities With Risk for Depression in the Danish Population Association of Polygenic Liabilities With Risk for Depression in the Danish Population. *JAMA psychiatry*. 2019;76(5):516-525.
71. Group W. *The Precision Medicine Initiative Cohort Program - Building a Research Foundation for 21st Century Medicine*. National Institute of Health;2015.
72. All of Us Research Program. 2019; [allofus.nih.gov](http://allofus.nih.gov).
73. Jukic MM, Smith RL, Haslemo T, Molden E, Ingelman-Sundberg M. Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. *The lancet Psychiatry*. 2019;6(5):418-426.
74. Veldic M, Ahmed AT, Blacker CJ, et al. Cytochrome P450 2C19 Poor Metabolizer Phenotype in Treatment Resistant Depression: Treatment and Diagnostic Implications. *Frontiers in pharmacology*. 2019;10:83.
75. Serretti A. The Present and Future of Precision Medicine in Psychiatry: Focus on Clinical Psychopharmacology of Antidepressants. *Clinical psychopharmacology and neuroscience : the official scientific journal of the Korean College of Neuropsychopharmacology*. 2018;16(1):1-6.
76. Fabbri C, Corponi F, Souery D, et al. The Genetics of Treatment-Resistant Depression: A Critical Review and Future Perspectives. *The international journal of neuropsychopharmacology*. 2019;22(2):93-104.
77. Lister JF. Pharmacogenomics: A focus on antidepressants and atypical antipsychotics. 2016;6(1):48-53.
78. Hirschtritt ME, Besterman AD, Ross DA. Psychiatric Pharmacogenomics: How Close Are We? *Biological psychiatry*. 2016;80(8):e63-e65.
79. Hicks JK, Swen JJ, Thorn CF, et al. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. *Clinical pharmacology and therapeutics*. 2013;93(5):402-408.
80. Fabbri C, Zohar J, Serretti A. Pharmacogenetic tests to guide drug treatment in depression: Comparison of the available testing kits and clinical trials. *Progress in neuro-psychopharmacology & biological psychiatry*. 2018;86:36-44.
81. Gross T, Daniel J. Overview of pharmacogenomic testing in clinical practice. *The mental health clinician*. 2018;8(5):235-241.

82. Pan LA, Martin P, Zimmer T, et al. Neurometabolic Disorders: Potentially Treatable Abnormalities in Patients With Treatment-Refractory Depression and Suicidal Behavior. *The American journal of psychiatry*. 2017;174(1):42-50.
83. Zai CC, Tiwari AK, Zai GC, Maes MS, Kennedy JL. New findings in pharmacogenetics of schizophrenia. *Current opinion in psychiatry*. 2018;31(3):200-212.
84. Pisanu C, Heilbronner U, Squassina A. The Role of Pharmacogenomics in Bipolar Disorder: Moving Towards Precision Medicine. *Molecular diagnosis & therapy*. 2018;22(4):409-420.
85. Zwicker A, Fabbri C, Rietschel M, et al. Genetic disposition to inflammation and response to antidepressants in major depressive disorder. *Journal of psychiatric research*. 2018;105:17-22.
86. Roberts S, Wong CCY, Breen G, et al. Genome-wide expression and response to exposure-based psychological therapy for anxiety disorders. *Translational psychiatry*. 2017;7(8):e1219.
87. Turlington L, Moldin SJAJHG. Assessing the demand for psychiatric genetic counseling. 1994;55:A144.
88. Finn CT, Smoller JW. Genetic counseling in psychiatry. *Harvard review of psychiatry*. 2006;14(2):109-121.
89. Phelan JC, Yang LH, Cruz-Rojas R. Effects of attributing serious mental illnesses to genetic causes on orientations to treatment. *Psychiatric services (Washington, DC)*. 2006;57(3):382-387.
90. Lyus VL. The importance of genetic counseling for individuals with schizophrenia and their relatives: potential clients' opinions and experiences. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2007;144b(8):1014-1021.
91. Hunter MJ, Hippman C, Honer WG, Austin JC. Genetic counseling for schizophrenia: a review of referrals to a provincial medical genetics program from 1968 to 2007. *American journal of medical genetics Part A*. 2010;152a(1):147-152.
92. Hoop JG, Roberts LW, Hammond KA, Cox NJ. Psychiatrists' attitudes, knowledge, and experience regarding genetics: a preliminary study. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2008;10(6):439-449.
93. Inglis A, Koehn D, McGillivray B, Stewart SE, Austin J. Evaluating a unique, specialist psychiatric genetic counseling clinic: uptake and impact. *Clinical genetics*. 2015;87(3):218-224.
94. Moldovan R, McGhee KA, Coviello D, et al. Psychiatric genetic counseling: A mapping exercise.0(0).
95. Hoell C, Pan V, Bucheit L, et al. *Demographics & Methodology*. Chicago: National Society of Genetic Counselors;2019.
96. Hippman C, Lohn Z, Ringrose A, Inglis A, Cheek J, Austin JC. "Nothing is absolute in life": understanding uncertainty in the context of psychiatric genetic counseling from the perspective of those with serious mental illness. *Journal of genetic counseling*. 2013;22(5):625-632.
97. Moldovan R, Pinte S, Austin J. The Efficacy of Genetic Counseling for Psychiatric Disorders: a Meta-Analysis. *Journal of genetic counseling*. 2017;26(6):1341-1347.
98. Semaka A, Austin J. Patient perspectives on the process and outcomes of psychiatric genetic counseling: An "Empowering Encounter". *Journal of genetic counseling*. 2019.
99. Inglis A, Morris E, Austin J. Prenatal genetic counselling for psychiatric disorders. *Prenatal diagnosis*. 2017;37(1):6-13.
100. Costain G, Esplen MJ, Toner B, Hodgkinson KA, Bassett AS. Evaluating genetic counseling for family members of individuals with schizophrenia in the molecular age. *Schizophrenia bulletin*. 2014;40(1):88-99.
101. Peay HL, Hooker GW, Kassem L, Biesecker BB. Family risk and related education and counseling needs: perceptions of adults with bipolar disorder and siblings of adults with bipolar disorder. *American journal of medical genetics Part A*. 2009;149a(3):364-371.
102. Peay HL, Rosenstein DL, Biesecker BB. Parenting with bipolar disorder: coping with risk of mood disorders to children. *Social science & medicine (1982)*. 2014;104:194-200.

103. Dar-Nimrod I, Heine SJ. Genetic essentialism: on the deceptive determinism of DNA. *Psychological bulletin*. 2011;137(5):800-818.
104. Lebowitz MS, Ahn WK, Nolen-Hoeksema S. Fixable or fate? Perceptions of the biology of depression. *Journal of consulting and clinical psychology*. 2013;81(3):518-527.
105. Hercher L, Bruenner G. Living with a child at risk for psychotic illness: the experience of parents coping with 22q11 deletion syndrome: an exploratory study. *American journal of medical genetics Part A*. 2008;146a(18):2355-2360.
106. Austin JC, Smith GN, Honer WG. The genomic era and perceptions of psychotic disorders: genetic risk estimation, associations with reproductive decisions and views about predictive testing. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2006;141b(8):926-928.
107. Austin J. Clinical Setting: The Role of Psychiatric Genetic Counseling. *Psychiatric Times*. 2018;35(3).
108. Vorderstrasse AA, Ginsburg GS, Kraus WE, Maldonado MC, Wolever RQ. Health coaching and genomics-potential avenues to elicit behavior change in those at risk for chronic disease: protocol for personalized medicine effectiveness study in air force primary care. *Global advances in health and medicine*. 2013;2(3):26-38.
109. Dar-Nimrod I, Cheung BY, Ruby MB, Heine SJ. Can merely learning about obesity genes affect eating behavior? *Appetite*. 2014;81:269-276.
110. Ahn WK, Lebowitz MS. An experiment assessing effects of personalized feedback about genetic susceptibility to obesity on attitudes towards diet and exercise. *Appetite*. 2018;120:23-31.
111. Aspinwall LG, Taber JM, Leaf SL, Kohlmann W, Leachman SA. Melanoma genetic counseling and test reporting improve screening adherence among unaffected carriers 2 years later. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2013;22(10):1687-1697.
112. Aspinwall LG, Stump TK, Taber JM, Kohlmann W, Leaf SL, Leachman SA. Impact of melanoma genetic test reporting on perceived control over melanoma prevention. *Journal of behavioral medicine*. 2015;38(5):754-765.
113. Cameron LD, Marteau TM, Brown PM, Klein WM, Sherman KA. Communication strategies for enhancing understanding of the behavioral implications of genetic and biomarker tests for disease risk: the role of coherence. *Journal of behavioral medicine*. 2012;35(3):286-298.
114. Marteau T, Senior V, Humphries SE, et al. Psychological impact of genetic testing for familial hypercholesterolemia within a previously aware population: a randomized controlled trial. *American journal of medical genetics Part A*. 2004;128a(3):285-293.
115. Network NCC. Colon Cancer (Version 2.2019).
116. Umlauf MG, Shattell M. The ecology of bipolar disorder: the importance of sleep. *Issues in mental health nursing*. 2005;26(7):699-720.
117. Wied C. Stress in schizophrenia: An integrative view. *European journal of pharmacology*. 2000;405:375-384.
118. Mayer JS, Hees K, Medda J, et al. Bright light therapy versus physical exercise to prevent comorbid depression and obesity in adolescents and young adults with attention-deficit / hyperactivity disorder: study protocol for a randomized controlled trial. *Trials*. 2018;19(1):140.
119. Vallersnes OM, Dines AM, Wood DM, et al. Psychosis associated with acute recreational drug toxicity: a European case series. *BMC psychiatry*. 2016;16:293.
120. Know the Warning Signs. 2019; <https://www.nami.org/learn-more/know-the-warning-signs>.
121. Prevention and Early Intervention in Mental Health. 2019; <https://www.mentalhealthamerica.net/issues/prevention-and-early-intervention-mental-health>.
122. McGorry PD, Killackey EJ. Early intervention in psychosis: a new evidence based paradigm. *Epidemiologia e psichiatria sociale*. 2002;11(4):237-247.
123. McGorry PD, Yung AR. Early intervention in psychosis: an overdue reform. 2003;37(4):393-398.

124. German A, Johnson L, Ybarra G, Warholak T. Assessment of pharmacists' self-reported preparedness to provide pharmacotherapy services to individuals with psychiatric disorders. *The mental health clinician*. 2018;8(1):1-6.
125. Leach E, Morris E, White HJ, Inglis A, Lehman A, Austin J. How do Physicians Decide to Refer Their Patients for Psychiatric Genetic Counseling? A Qualitative Study of Physicians' Practice. *Journal of genetic counseling*. 2016;25(6):1235-1242.
126. Phokeo V, Sproule B, Raman-Wilms L. Community pharmacists' attitudes toward and professional interactions with users of psychiatric medication. *Psychiatric services (Washington, DC)*. 2004;55(12):1434-1436.
127. Heinlen C, Hovick SR, Brock GN, Klamer BG, Toland AE, Senter L. Exploring genetic counselors' perceptions of usefulness and intentions to use refined risk models in clinical care based on the Technology Acceptance Model (TAM). *Journal of genetic counseling*. 2019;28(3):664-672.
128. Finn CT, Wilcox MA, Korf BR, et al. Psychiatric genetics: a survey of psychiatrists' knowledge, opinions, and practice patterns. *The Journal of clinical psychiatry*. 2005;66(7):821-830.
129. Counselors NSoG. Psychiatric Genetics across Genetic Counseling Practice Settings Online Course. 2017.
130. Achieving Precision Psychiatry. Paper presented at: World Congress of Psychiatric Genetics2019; Los Angeles, CA.
131. Edwards A, Gray J, Clarke A, et al. Interventions to improve risk communication in clinical genetics: systematic review. *Patient education and counseling*. 2008;71(1):4-25.
132. Nurnberger JI, Jr., Austin J, Berrettini WH, et al. What Should a Psychiatrist Know About Genetics? Review and Recommendations From the Residency Education Committee of the International Society of Psychiatric Genetics. *The Journal of clinical psychiatry*. 2018;80(1).
133. Counselors NSoG. Making Sense of Your Genes: A Guide to Genetic Counseling. 2008:11-12.
134. Cook DA, Garside S, Levinson AJ, Dupras DM, Montori VM. What do we mean by web-based learning? A systematic review of the variability of interventions. 2010;44(8):765-774.
135. Cook DA, Levinson AJ, Garside S, Dupras DM, Erwin PJ, Montori VM. Internet-based learning in the health professions: a meta-analysis. *Jama*. 2008;300(10):1181-1196.
136. Lam-Antoniades M, Ratnapalan S, Tait G. Electronic continuing education in the health professions: An update on evidence from RCTs. 2009;29(1):44-51.
137. Maio V, Belazi D, Goldfarb NI, Phillips AL, Crawford AG. Use and effectiveness of pharmacy continuing-education materials. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists*. 2003;60(16):1644-1649.
138. De Leo G, LeRouge C, Ceriani C, Niederman F. Websites most frequently used by physician for gathering medical information. *AMIA Annu Symp Proc*. 2006;2006:902-902.
139. Grierson LEM, Barry M, Kapralos B, Carnahan H, Dubrowski A. The role of collaborative interactivity in the observational practice of clinical skills. 2012;46(4):409-416.
140. Robertson MK, Umble KE, Cervero RM. Impact studies in continuing education for health professions: update. *The Journal of continuing education in the health professions*. 2003;23(3):146-156.
141. Thomson O'Brien MA, Freemantle N, Oxman AD, Wolf F, Davis DA, Herrin J. Continuing education meetings and workshops: effects on professional practice and health care outcomes. *The Cochrane database of systematic reviews*. 2001(2):Cd003030.
142. Forsetlund L, Bjorndal A, Rashidian A, et al. Continuing education meetings and workshops: effects on professional practice and health care outcomes. *The Cochrane database of systematic reviews*. 2009(2):Cd003030.
143. Durham L, Papanna R, Stevens B, et al. The utilization of prenatal microarray: A survey of current genetic counseling practices and barriers. *Prenatal diagnosis*. 2019;39(5):351-360.
144. LLC S. Stata Statistical Software: Release 16. In. College Station, TX2016.

145. Kruger J, Dunning D. Unskilled and unaware of it: how difficulties in recognizing one's own incompetence lead to inflated self-assessments. *Journal of personality and social psychology*. 1999;77(6):1121-1134.
146. Desalvo K, Wang C, Harris A, Auerbach J, Koo D, O'Carroll P. Public Health 3.0: A Call to Action for Public Health to Meet the Challenges of the 21st Century. 2017.